TECHNICAL REPORT

Cost-effectiveness analysis of programmatic screening strategies for latent tuberculosis infection in the EU/EEA

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Contents

Figures

Tables

Abbreviations

CXR	Chest X-ray
EEA	European Economic Area
EPTB	Extrapulmonary tuberculosis
EU	European Union
FOI	Force of infection
GDP	Gross domestic product
ICER	Incremental cost-effectiveness ratio
IGRA	Interferon gamma release assay
KNCV	KNCV Tuberculosis Foundation
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
PPP	Purchasing power parity
PTB	Pulmonary tuberculosis
QALY	Quality adjusted life years
RIVM	Dutch National Institute of Public Health and the Environment
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organization
XDR TB	Extensively drug-resistant tuberculosis
YLL	Years of life lost

Glossary

Active tuberculosis	A disease that is caused by *Mycobacterium tuberculosis* or other members of the *Mycobacterium tuberculosis* complex in any part of the body, and that is in an active state, characterised by signs or symptoms of disease [1,2].
Cost-effectiveness analysis	A type of economic evaluation that assesses the gains in health relative to the costs of different health interventions [3].
Directly observed therapy	An approach which seeks to improve the adherence of people to tuberculosis treatment by having health workers, family members, or community members directly observing the taking of anti-tuberculosis drugs [4].
Force of infection	Per capita rate at which susceptible people contract infection [5].
Incremental cost-effectiveness ratio	A cost per unit health effect achieved by using a particular health intervention [6]. It represents the additional cost of one unit of outcome gained by one strategy compared with another [7].
Latent tuberculosis infection	State of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifest active tuberculosis. Persons with latent tuberculosis infection are not infectious and cannot spread tuberculosis infection to others [8].
Migrant	First-generation migrants (including refugees and asylum seekers) from middle and high TB-endemic countries, i.e. with TB incidence of >50/100 000.
Purchasing power parity	A measure of the total amount of goods and services that a single unit of a country's currency can buy in another country [9].
Quality adjusted life year (QALY)	"A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life lived in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance" [10].
Tuberculosis	'Tuberculosis' refers to clinically, bacteriologically, histologically and/or radiologically active disease [4].
Years of life lost	Summary measure of premature mortality in the population. It is calculated by multiplying the number of deaths by the standard life expectancy at the age at which death occurs[11].

Executive summary

Background

The elimination of tuberculosis (TB) in Europe will require the management of latent tuberculosis infection (LTBI) in key populations. Management of LTBI requires the identification and adequate treatment of infected people. It is currently unknown how screening and treatment of key populations should be best organised to have the highest impact with the available resources.

Objective

The objective of this project was to assess the cost-effectiveness of selected LTBI screening and treatment strategies for various cohorts of key population groups in four selected European Union, low TB burden countries: the Netherlands, the Czech Republic, Portugal, and Spain.

Methods

A deterministic TB transmission model was used to predict the impact of different LTBI screening and treatment strategies for the following risk-groups considered for programmatic LTBI control: first generation migrants from TB high-endemic countries, people who inject drugs/homeless people (PWID/homeless people) and prisoners. The LTBI screening strategies investigated were tuberculin skin test (TST), interferon gamma release assay (IGRA), and a two-step TST/IGRA strategy. In addition, cohort versions of the same model were used to predict the impact of programmatic LTBI screening in cohorts of people with

- a temporarily increased risk of infection (healthcare workers, travellers to TB high-endemic countries, and contacts of TB patients)
- an increased risk of disease following infection (immunocompromised people, such as HIV-patients)
- different cohorts of migrants (from low-endemic and high-endemic countries).

The cost-effectiveness of LTBI screening strategies was expressed as an incremental cost-effectiveness ratio, which was calculated by dividing the cost difference (incremental costs) between the strategies of interest and the baseline (current policy), with the burden difference (effectiveness of the screening). The TB burden was expressed in quality adjusted life years, which includes averted TB disease and life years lost. The costs were analysed from both the healthcare and societal perspective. Healthcare costs included all testing, screening, and treatment costs, as well as costs associated with hospitalisation and contact tracing for TB patients. Societal costs included out-of-pocket payments for travel, and societal costs due to productivity loss. Arbitrary willingness-to-pay thresholds (2 x per capita GDP) were chosen per country in order to determine whether a strategy was cost-effective. Sensitivity analysis was done for different levels of screening coverage, as well as different cost values.

Results

From the healthcare perspective results from the model showed that, regardless of the population group at risk, LTBI screening is most cost-effective when done using TST, and if positive, followed by IGRA. From the societal perspective, using only IGRA or TST/IGRA is the most cost-effective option, as it requires one visit for the testing. LTBI screening for migrants at entry was cost-effective in all four countries. The cost-effectiveness of screening migrants increased when the TB incidence in the country of origin was higher. However, it was dominated by all other strategies in countries with relatively low in-migration rates (the Czech Republic and Portugal), while it was comparable with LTBI screening for the PWID/homeless people group in countries with high immigration rates (the Netherlands and Spain). The most cost-effective targeting strategy is screening migrant prisoners for LTBI at the moment of incarceration. Furthermore, it was shown that LTBI screening for healthcare workers and travellers is not cost-effective, except when these populations are exposed to extremely high transmission risk. LTBI screening for immunocompromised patients only seems cost-effective for migrant patients, or for low-risk native patients in countries with a relatively high TB burden. A one-time screening provides the best value for money. Finally, LTBI screening for TB contacts seems to be cost-effective, because of their extremely high temporary exposure to infection.

Conclusions

In conclusion, programmatic LTBI screening in general is a cost-effective policy option for the four European countries studied. Both LTBI screening for migrants at entry, LTBI screening for prisoners and LTBI screening for people who inject drugs/homeless people is cost-effective. LTBI screening for travellers and healthcare workers is only cost-effective under extremely high levels of increased risks for transmission. LTBI screening for immunocompromised patients is only cost-effective for migrants and for low-risk native patients in the European countries studied with a relatively high TB burden. Finally, LTBI screening for TB contacts is cost-effective in the four countries.

Assumptions made in the quantification of the models (e.g. size and importance of the main risk groups, particularly the people who inject drugs/homeless people and prison populations), might have determined to some extent the conclusions reached. However, the main findings on the cost-effectiveness of the strategies are robust to reasonable changes in these assumptions.

1. Background

Tuberculosis (TB) is a bacterial infectious disease caused by *Mycobacterium tuberculosis*. Following exposure to *M. tuberculosis*, some people eliminate the bacillus by innate or acquired immune response. Others develop latent infection with *M. tuberculosis* (LTBI), a state in which the host immune system controls the replication of the bacillus to the extent that the progression to TB is prevented [12,13]. Given that a quarter of the world population is estimated to be infected with *M. tuberculosis*, there is a huge reservoir for subsequent progression to TB [14].

In high-income countries, TB is primarily prevalent among risk groups (persons who are at a higher risk of progression to active disease) as a result of reactivation of LTBI [15]. Therefore, the control of LTBI is an important step towards TB elimination, a fact that was acknowledged in the *End TB* strategy adopted by the 67th World Health Assembly in May 2014 [16,17]. In some high-income countries, TB is controlled by identifying and offering treatment to people with LTBI [18-20] in addition to case detection and treatment. The World Health Organization (WHO) recently added a conditional recommendation for systematic testing and treatment of LTBI in low TB burden countries [21]. Key population groups in this recommendation included migrants, people who inject drugs/homeless people (PWID/homeless people) and prisoners.

Diagnosis of LTBI is challenging as people with LTBI are asymptomatic and no living mycobacteria can be extracted [22]. For over a century, the tuberculin skin test (TST) was the only available test for LTBI. Since the early 2000s interferon gamma release assays (IGRA) have been developed to improve the diagnosis of LTBI. The diagnosis is based on measurement of the adaptive immune response against *M. tuberculosis*. Once LTBI has been identified, LTBI treatment can halt the progression to TB in most infected people [23,24]. However, initiation, adherence and completion rates of LTBI treatment are often low and differ between treatment regimens and risk groups [25-27].

Management of LTBI requires the identification of infected people and adequate treatment of those identified. Migrants and other risk groups have been identified as relevant target groups for TB elimination activities. In some migrant groups a high proportion of people test positive for LTBI, and migrant groups may thus benefit from programmatic management of LTBI.

In 2013, the European Centre for Disease Prevention and Control (ECDC) initiated a comprehensive assessment of different components that could be integrated into national TB control strategies with the purpose of reducing LTBI in the European Union/European Economic Area (EU/EEA) region. As part of this assessment, a workshop was held in September 2013 with representatives from EU/EEA Member States and Candidate Countries as well as additional stakeholders in the field of TB. The workshop resulted in the identification of key areas/research topics that needed further attention in the assessment [28]. The main components identified were: i) groups at risk, ii) diagnosis, iii) treatment and iv) programme control of LTBI. For these components, the scientific evidence was collected using literature reviews. Subsequently, a new TB transmission model was constructed as a tool to assess the contribution of these components towards TB elimination. This mathematical model was the basis for cost-effectiveness analyses to assess the economic effects of selected LTBI screening strategies. The methodology and results of the cost-effectiveness analyses are presented in this report.

Scope and objectives

This report is part of a series of technical documents describing the collection, synthesis and appraisal of the available information on specific measures for prevention, identification and treatment of LTBI, analysed from the perspective of national TB control programmes. The long-term goal of this approach is to contribute to the attainment of the End TB Strategy target of 90% reduction of TB incidence and 95% reduction of TB mortality by 2035 [16].

The objective of this technical report is to assess the cost-effectiveness of selected LTBI screening strategies for specific key populations for low TB burden countries.

Outline of this report

Chapter 2 describes the methods and analysis approach used in this report. The cost-effectiveness analysis built upon a deterministic transmission model described in a separate report. Chapter 3 presents the results on the costs, effects, and cost-effectiveness of targeted LTBI screening strategies in the Netherlands, Czech Republic, Portugal, and Spain. The results comprise i) population-based cost-effectiveness analysis for first generation migrants, PWID/homeless people, and prisoners; and ii) cohort-based analysis for health care workers, HIV-patients or otherwise immunocompromised people, long-term travellers, contacts, and migrants from different endemic settings. Chapter 4 discusses the main findings and Chapter 5 summarises the general conclusions of the report.

2. Methods

A deterministic TB transmission model, including both population-based and cohort-based analyses was used to determine the cost-effectiveness of different LTBI screening and treatment strategies for a wide range of risk groups. Country-specific estimates of unit costs were used in the cost-effectiveness analysis. The model was run for a number of population groups that are continuously, or for some time part of one of the risk groups considered for programmatic LTBI control interventions. The underlying mathematical model is described in detail in the related modelling report [29]. A brief description is given below.

In order to adequately capture the benefits of an intervention for infectious diseases, incorporating the health benefits through reduced transmission is essential when examining interventions targeted at risk groups that drive transmission. For TB, these groups are first-generation migrants from TB endemic countries, PWID/homeless people, and prisoners. For these groups, the cost-effectiveness of LTBI screening strategies is evaluated using the TB transmission model. Other risk groups, such as immunocompromised patients or healthcare workers, are at risk for contracting and developing TB, but do not contribute substantially to transmission. Therefore, the cost-effectiveness of LTBI screening strategies in these subgroups is evaluated by using cohort versions of the model rather than the complete population-based transmission model.

2.1 Screening strategies

The full cascade of algorithms for screening is given in Figure 1. A range of different screening strategies were proposed for different population groups, and the following screening algorithms were considered:

- **TST:** if TST is positive, it is followed by chest x-ray (CXR). If CXR is normal, LTBI treatment is started. If CXR shows abnormalities, this leads to TB treatment after confirmation tests (culture). If confirmatory test is negative, LTBI treatment is started. To prevent missing active pulmonary TB (PTB), people are also asked for symptoms.
- **IGRA:** if IGRA is positive, it is followed by CXR. If CXR is normal, LTBI treatment is started. If CXR shows abnormalities, TB treatment is started after confirmation tests (culture). LTBI treatment is started if confirmatory test is negative, to prevent missing active PTB, people are also asked for symptoms.
- **TST/IGRA:** if TST is positive, it is followed by IGRA. If IGRA is positive, it is followed by CXR. If CXR is normal, LTBI treatment is started. If CXR shows abnormalities, TB treatment is started after confirmation tests (culture). To prevent missing active PTB, people are also asked for symptoms.

The sensitivity and specificity of all tests in the different disease stages specified for this analysis are described in detail in the modelling report, and schematic overviews are given in supplementary Figures A1.1 to A1.4.

With these different algorithms, screening strategies were simulated in the different subpopulations as follows:

- Entry screening of migrants from TB high-endemic countries
- Screening of prisoners at the moment of incarceration (further subdivided by prisoners from TB endemic countries and native prisoners)
- Periodic screening of PWID/homeless people populations (annual or triennial screening)
- A combination of the three strategies above.

Table 1 gives an overview of the coverage assumptions for each of the target groups. For comparison purposes, these were kept similar across countries and test (i.e. CXR, TST, IGRA, and TST/IGRA). Details on underlying assumptions can be found in the mathematical modelling report [29].

Baseline: for each country, a baseline was considered which represents the current policy. Country specific baselines are described below:

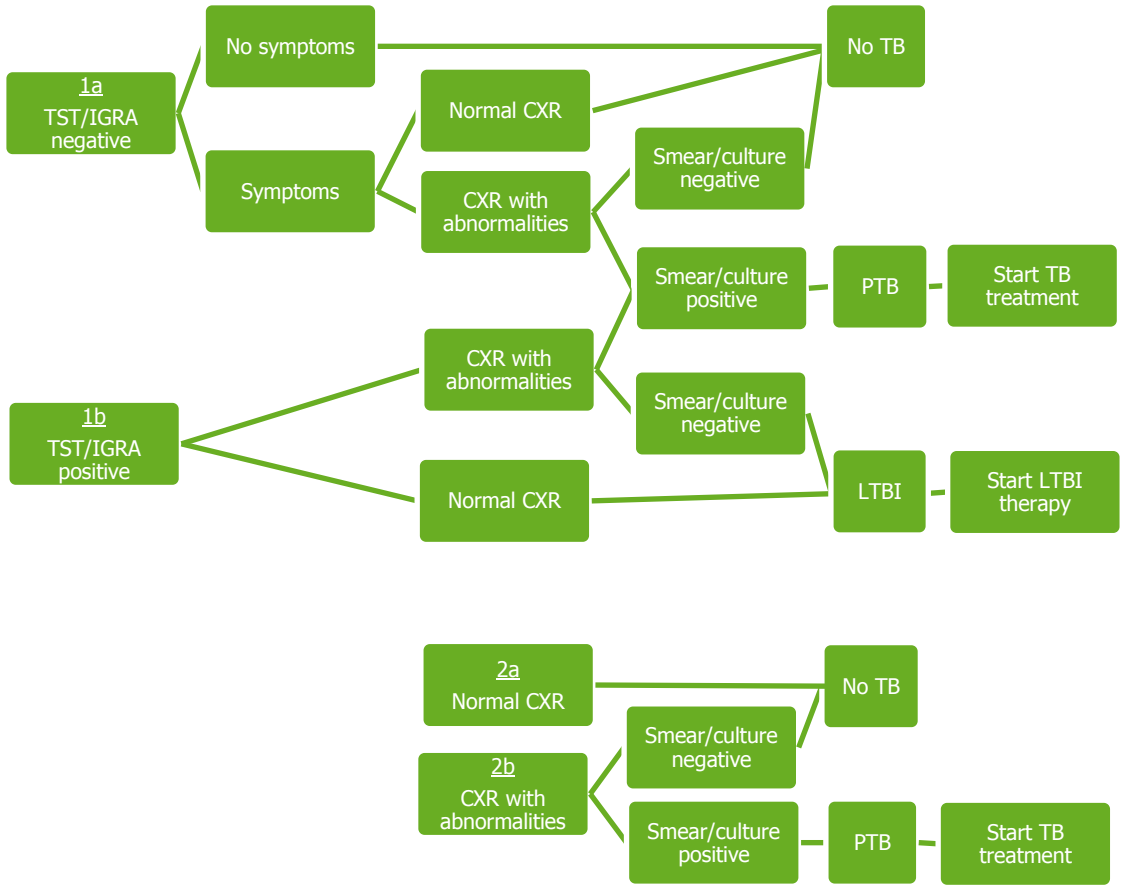
- Netherlands: CXR for migrants at entry, and migrant and PWID/homeless people prisoners at incarceration. Because of the difficulty in identifying PWID/homeless people accurately, screening by CXR of all native prisoners was assumed in the analyses, at a slightly reduced coverage (90%).
- Czech Republic: CXR for migrants at entry, and prisoners at incarceration.
- Portugal: CXR for prisoners at incarceration.
- Spain: TST followed by CXR to detect active PTB for migrants, and TST followed by LTBI treatment for prisoners at incarceration.

Table 1. Coverage of tuberculosis and latent tuberculosis infection screening strategies and proportion successfully treated after positive test result

Target group	Coverage	Treatment started and successful	
		LTBI	TB
Within transmission model: Migrants at entry	80%	60%	95%
Migrant prisoners	100%	70%	80%
Native prisoners	90%	80%	80%
PWID/homeless people – triennial	70%	60%	90%
PWID/homeless people – annual	50%	60%	90%
Within cohort model: Migrants at entry	80%	60%	95%
Healthcare workers	100%	100%	100%
TB contacts (realistic)	90%	70%	90%
Travellers (realistic)	50%	70%	90%
Travellers/TB contacts (perfect)	100%	100%	100%
Immunocompromised	90%	70%	90%

LTBI= latent TB infection, TB= tuberculosis
The proportions on treatment success reflect the proportion of people that successfully complete treatment. In order to incorporate the costs for those who do not complete treatment, an additional cost of 0.5 x LTBI treatment cost was added for the proportion not completing treatment.

Figure 1. Flow diagram of the cascade of possible test outcomes and testing sequences



CXR= chest X-ray, LTBI= latent TB infection, PTB= pulmonary TB, IGRA= interferon gamma release assay, TB= tuberculosis, TST= tuberculin skin test. The boxes 'No TB', 'PTB', and 'LTBI' in the second column from the right represent the diagnosis of the person as a result of the tests with their own sensitivity and specificity, and do not necessarily reflect the actual disease stage of the individual. Smear/culture is indicated as a combined test, since usually both are done, but the sensitivity and specificity of culture was used in the model.

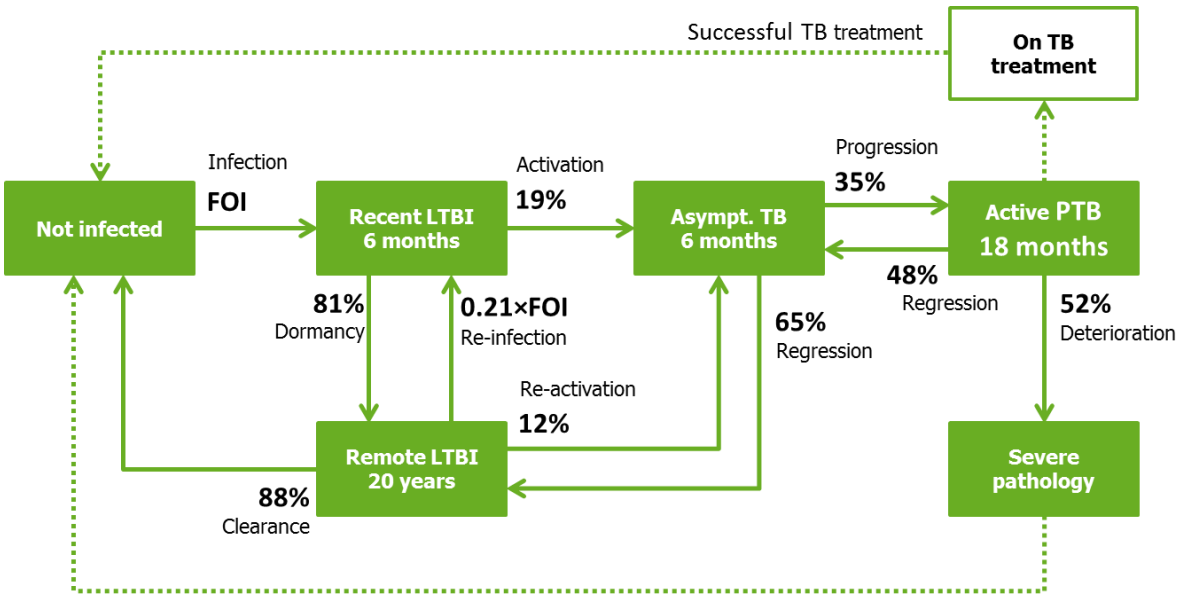
2.2 Models

TB transmission model

The deterministic TB transmission model was used to calculate the cost-effectiveness of LTBI screening interventions in high-risk populations that are relevant to overall TB transmission in EU settings (migrants, PWID/homeless people and prisoners). Without LTBI treatment, those with TB infection follow the natural history of infection and disease as shown in Figure 2. People in the transmission model can move forwards and backwards through a series of compartments (mathematically defined compartments related to health stages) which represent the natural history of TB infection: not infected (i.e. susceptible), recent LTBI, remote LTBI, asymptomatic TB, PTB, and severe pathology (i.e. hospitalised, and in some cases leading to death due to TB). Asymptomatic TB, also known as subclinical TB, is an infectious stage of the disease with mild or no symptoms. In contrast, LTBI is an asymptomatic and non-infectious stage [30]. Extrapulmonary TB (EPTB) is not included since its contribution to transmission is negligible. However, for the cost-effectiveness analysis, the EPTB burden was estimated to arrive at the total TB burden by applying country and population specific EPTB:PTB ratios (see 3.2 for more details). A full description of the model is given in the accompanying modelling report [31].

Schematic representations of the health stages and probabilities to test positive with CXR, TST, and IGRA, as well as for culture are illustrated in Figures A1.1 to A1.4 of Appendix 1. Based on the outcomes of these tests, people can be eligible for uptake of TB treatment (i.e. positive for CXR, smear, or culture) and LTBI treatment (i.e. positive for IGRA or TST but not for CXR, smear or culture). People can also be treated following self-reporting, but before treatment they need to be confirmed with CXR, smear and culture. The average duration until self-reporting was assumed to be three months after the onset of symptoms in the Netherlands. However, for the PWID/homeless people group a longer duration was assumed (six months), while prisoners are subject to more frequent check-ups resulting in rapid detection of TB (after one month). In order to explain the currently higher incidence of TB in the other countries, as a result of less extensive and/or a shorter history of TB control efforts, these durations were assumed to be one month longer in the Czech Republic, Portugal, and Spain. Finally, the specificity of TST and IGRA is not 100% for PTB. Therefore, when patients present with TB-like symptoms, CXR and smear/culture are still performed even when TST and/or IGRA are negative. For all countries, LTBI treatment was assumed to consist of three months isoniazid and rifampicin.

Figure 2. Schematic overview of the model for the natural history of tuberculosis infection and disease



Asympt=asymptomatic, FOI= force of infection, LTBI= latent tuberculosis infection, PTB= pulmonary tuberculosis, TB= tuberculosis.
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. People with remote LTBI can get reinfected, but at 21% of the rate for not infected susceptible people, due to some degree of immunity. Durations and proportions given for PTB are assuming no treatment will take place. Severe pathology does not have a specific duration as it is included as a flow through which people immediately return to not infected. The number of times severe pathology occurs are only counted for burden calculations, and hospitalisation and death are proportionally related to the flow through severe pathology (see Chapter 2.4).

The transmission model simulates four key population groups: general population; migrant population; PWID/homeless people; and prisoners. The general population in the model concerns all people born in the country of interest, and also includes second and third generation migrants from high incidence countries, and all migrants from low incidence countries.

The migrant population is defined as all first-generation migrants (including refugees and asylum seekers) from middle and high TB-endemic countries, i.e. with TB incidence of >50/100 000 (WHO global TB report 2015 [32]). The TB burden of migrants at entry was quantified for each country separately, and is explained in more detail in the modelling report [31]. In short, data from Erkens et al [33] on the yield of entry screening with CXR of migrants were used to quantify the force of infection (FOI) experienced by the average migrant in the country of origin in order to reproduce the CXR yield at entry. The data provided by Erkens are only for the Netherlands, and migrant cohorts in the other countries were likely to be different compared with the Netherlands in terms of their TB burden. Therefore, the data were corrected to arrive at country specific CXR yields as follows:

- for each country, the top 10 countries of origin were determined (based on number of migrants) for migrants from a country with a TB incidence of at least 50/100 000
- the weighted average TB incidence in the country of origin was determined using the average incidence in each of the top 10 countries and the number of migrants from each of these countries
- the proportional difference of the weighted average TB incidence was calculated in the Czech Republic, Portugal, and Spain compared with the Netherlands
- the expected yield of CXR at entry in the Czech Republic, Portugal, and Spain was corrected using this proportional difference, and quantified the TB burden in the migrants for these countries accordingly.

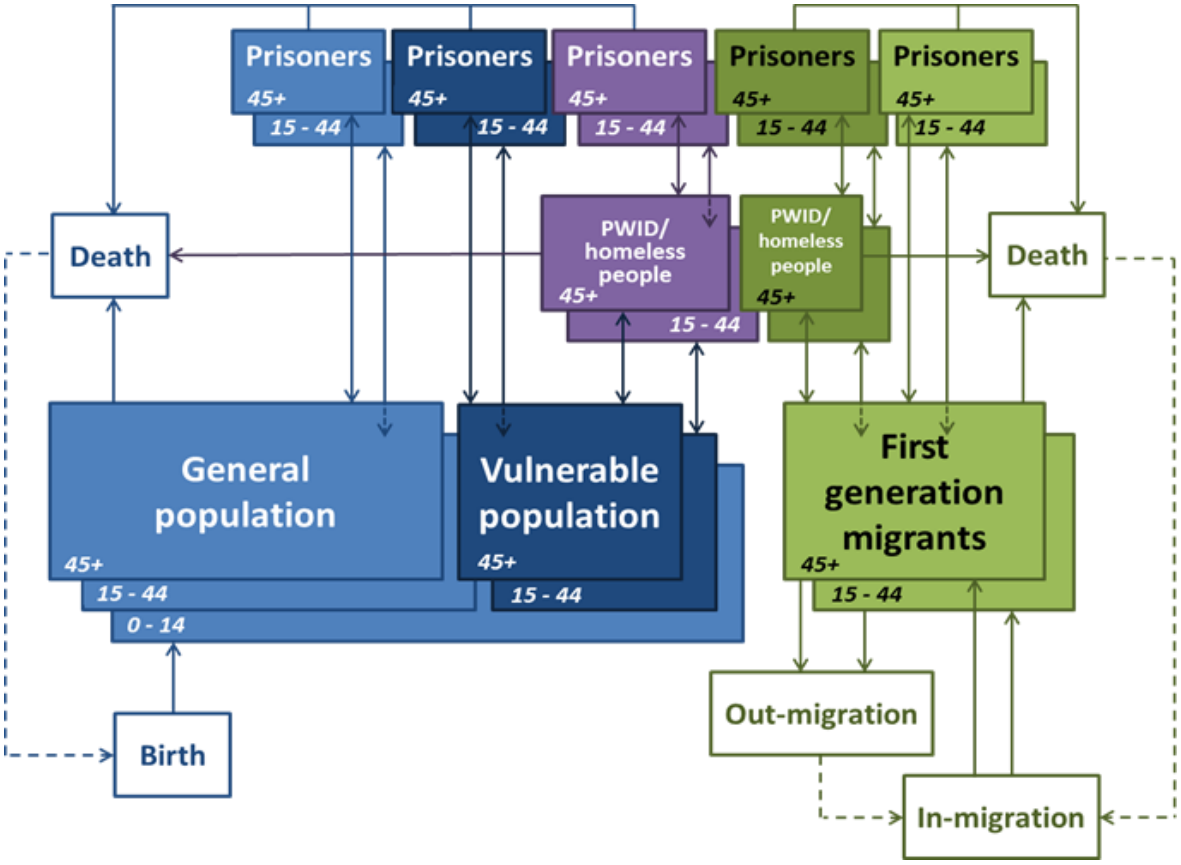
The weighted average TB incidence in the country of origin was 177.6/100 000 for migrants in the Netherlands; 106.7/100 000 for migrants in the Czech Republic; 178.2/100 000 for migrants in Portugal, and 93.5/100 000 for migrants in Spain. In the cohort-based approach, the cost-effectiveness of LTBI screening in specific cohorts of migrants with different levels of TB incidence in the country of origin (ranging from 50/100 000 to 300/100 000; see section 'cohort models' below) was also examined.

PWID/homeless people come from both the general population and the migrant population. In the general population, a distinction was made between 'vulnerable population' and 'general population'. The vulnerable population is exactly the same as the general population, with the only difference being that these people can move to the PWID/homeless people group. People are part of the PWID/homeless people population for some time (here: average of five years) and may move back to the general population.

Prisoners can come from the general population, from the PWID/homeless people population, or from the migrant populations. They stay in prison for some time (here: average of three months) and after release become part of the population groups they originally came from. Members of the PWID/homeless people group have a substantially higher chance of going to prison. Figure 3 shows the specific population groups that are considered for LTBI screening in this study, in particular migrants that can be screened at entry to a European country, the PWID/homeless people groups that can be screened at regular intervals, and prisoners at incarceration. The model is described in detail in the modelling report [31], and was tuned to the situation in the chosen European countries: the Netherlands, Czech Republic, Portugal, and Spain regarding sizes of risk-groups and their PTB incidences, when available.

Table 2 gives an overview of the population composition and PTB burden for the four countries in the analyses. The choices made and their justifications are described in the modelling report [31]. Some important differences can be observed between the countries. For instance, Portugal has a relatively large PWID/homeless people population, nearly 1% of the total population, while Spain has a relatively small PWID/homeless people population (0.08% of the total population). This substantial difference was reported by the country experts, but may likely reflect differences in definitions of people who inject drugs and those that are homeless. Furthermore, the Netherlands and Spain have a relatively large population of migrants from high-endemic countries, whereas these populations in the Czech Republic and Portugal are about twice as small. It is also important to note that the model simulates a steady state TB epidemic, yet TB incidence in the countries of interest has been declining over the past years. This is reflected in the difference in the distribution of total TB cases over the 15–44 and 45+ age groups in natives compared with the data (Table 3; see modelling report for more explanation) [31].

Figure 3. Population groups and their interactions in the tuberculosis transmission model



The vulnerable population reflects 30% of the general population from which PWID/homeless people come from. This way they have an increased risk of acquiring LTBI during a temporary period of stay in the PWID/homeless people group, but i people in the vulnerable population are exactly the same as the rest of the general population regarding any other aspect of TB transmission and control. Prisoners can come from any population group, and after their incarceration they return to the group they came from. To keep the population at a steady state it was assumed that deaths in the general population are replaced by an equal number of births. Similarly, deaths and out-migration of first generation migrants are replaced by the same number of new migrants. The model distinguished three age groups: 0–14 (only general population), 15–44 and 45+ years. The relatively low number of first generation migrants in the age group 0–14 was added to the 15–44 year group (not indicated as such).

Table 2. Overview of key epidemiological values for modelling tuberculosis and latent tuberculosis infection control in European Union countries

	Netherlands	Czech Republic	Portugal	Spain
Population sizes (%)				
Natives	95.85	97.60	98.00	95.03
Migrants from high-endemic countries	4.15	2.40	2.00	4.97
Subgroups among both natives and migrants:				
PWID/homeless people	0.23	0.46	0.94	0.08
Prisoners	0.07	0.19	0.12	0.11
Proportion of prisoners from PWID/homeless people (%)	24	37	12	10
PTB cases (per 10 million total population)				
Natives	176	515	1 907	746
Migrants from high-endemic countries	165	69	157	219
Total population	341	583	2 065	964
Subgroups among both natives and migrants				
PWID/homeless people	15	42	255	18
Prisoners	10	51	35	18
Annual PTB incidence (per 100 000 in the population group)				
Natives	2	5	19	8
Migrants from high-endemic countries	40	29	79	44
PWID/homeless people	67	91	272	220
Prisoners	159	262	301	163

N/A=not available, PTB= pulmonary tuberculosis.
Natives concern anyone born in the country, including second generation migrants as well as migrants from non-screening countries (i.e. TB incidence <50 per 100 000).

Table 3. Total number of annual pulmonary tuberculosis cases by population group and age group, model versus data

	Netherlands		Czech Republic		Portugal		Spain	
	Data	Model	Data	Model	Data	Model	Data	Model
Natives								
0–14	11	13	3	16	40	65	278	138
15–44	127	149	134	293	1 017	988	1455	1766
45+	155	131	406	232	957	961	1731	1560
Total*	**293**	**293**	**542**	**542**	**2 014**	**2 014**	**3 463**	**3 463**
Migrants								
15–44	202	204	61	54	117	133	821	858
45+	73	71	12	19	49	33	195	159
Total*	**274**	**275**	**72**	**72**	**166**	**166**	**1 017**	**1 017**

**Due to rounding, some totals may not correspond with the sum of the separate figures.*
Data are averages over the period 2005–2014 for the Netherlands, the Czech Republic and Portugal; for Spain data from 2010–2014 were used. Although the TESSy database provided data from 2007–2014 for Spain, the years 2007 to 2009 were excluded due to high numbers of missing country of origin information. Furthermore, in the data used for Portugal and Spain, many case notifications had a missing country of birth. These were distributed over migrants and natives according to the distribution found in cases with country of birth. The model was tuned to only fit the total number of PTB cases. For the native population, the number of PTB cases aged 45+ years is to some extent underestimated, whereas it is overestimated for those aged 15–44 years. This is particularly the case for the Czech Republic which has experienced a substantial decrease in the TB epidemic over past decades, leading to a relatively high number of those aged 45+ years with (remote) LTBI from past infection that may eventually re-activate. In the discussion, it is explained how this model limitation may affect predictions. Estimates for migrants are more in balance with data, and country-specific differences between age groups may reflect different flows of younger and older migrants coming and leaving the EU country. Finally, the small number of TB cases reported in migrants aged younger than 15 years were included in the 15–44 age group. Information on prisoners and PWID/homeless people groups as well as the fit of the model to the observed data can be found in the modelling report [31].

Cohort models

Different cohort models were derived from the same transmission model to calculate the cost-effectiveness of LTBI screening in high-risk populations that do not substantially contribute to overall transmission in EU countries: immunocompromised patients (i.e. transplant patients or HIV infected patients); long-term travellers; TB contacts; and healthcare workers. The cohort model is an adaptation of the transmission model and works as follows. Based on the output of the transmission model, cohort-specific distribution of TB and LTBI was determined at the start (e.g. at the start of a career as a healthcare worker), and applied as a fixed model-derived force of infection (FOI) representing the risk for infection in the group of interest (usually the low-risk natives). The model was run with proportional increases of the FOI or rates of activation (both from recent and remote LTBI) in each specific cohort. By doing so, the increased risk for TB infection or disease, which makes the cohort of interest special, could be reproduced. For instance, travellers to high endemic countries will be subject to a temporarily increased FOI, while immunocompromised patients will have higher activation. Furthermore, all in- and –outflow in the cohort models is disabled, and the model follows the same cohort over a period of 20 years. Below the simulation of each cohort is described.

Healthcare workers: Healthcare workers were simulated in the model as a cohort of low-risk natives, who experience a higher FOI because of their job. A cohort was simulated in which the initial TB stage distribution was the same as for low-risk natives in the transmission model, and then the effects of LTBI screening strategies were explored under incrementally increased FOIs, and for different screening intervals. This was only explored in the Netherlands and Portugal, as these respectively have the lowest and highest TB incidence in this analysis. TB incidence in Spain and the Czech Republic are in between. Furthermore, coverage and LTBI treatment completion rates were assumed to be 100% for this specific cohort.

Travellers and TB contacts: Travellers and TB contacts were simulated in a similar fashion to healthcare workers, with the difference that the higher FOI is only experienced for a short period of time (three months), and screening takes place shortly after this period of higher exposure. Again, different ranges of increased FOIs and coverage levels were explored, and these cohorts were developed for the Netherlands and Portugal. Travellers and TB contacts were taken together, as the underlying exposure mechanism (increased FOI for a short period) and the screening approach (screening after experiencing the increased FOI) is the same. The FOI multipliers in the Portuguese cohorts were divided by a factor of 10 as low-risk natives in the Netherlands experience a FOI approximately 10 times lower compared with Portugal. The FOI experienced by travellers in the destination country or by TB contacts is the same regardless of country of origin (i.e. Portugal or the Netherlands).

Immunocompromised patients: Two cohorts of immunocompromised patients were simulated, one for natives and one for migrants. The cohorts were as a population originating from low-risk natives or low-risk migrants, but with an increased rate of activation due to the underlying immune-compromising morbidity (e.g. HIV or transplant patients). Different rates of increased activation were explored (three, six, and nine times increased rates of activation, both from recent and remote LTBI, compared with those for the general population), and different screening intervals for both cohorts. Again, cohorts were developed for the Netherlands and Portugal.

2.3 Extrapulmonary tuberculosis

The models do not explicitly simulate the progression of LTBI to EPTB as EPTB is not relevant for transmission. However, EPTB does contribute substantially to the overall TB burden, and therefore needs to be included in the cost-effectiveness analyses. EPTB was incorporated by estimating the ratio of PTB:EPTB cases by country, age group, and migrant status (first generation migrant versus native). Absolute numbers of reported PTB and EPTB cases were obtained from ECDC directly (ECDC TESSy database), and Table 4 gives an overview of the absolute numbers and resulting EPTB/PTB ratios. In order to calculate both costs and burden associated with EPTB, these ratios were applied to PTB burden, number of PTB treatments, PTB hospitalisations, and PTB mortality.

Table 4. Extrapulmonary tuberculosis/pulmonary tuberculosis ratios

Age categories in included countries	PTB cases	EPTB cases	EPTB/PTB ratio
Netherlands			
Native			
0–14 years	113	210	1.86
15–44 years	1 267	600	0.47
45+ years	1 547	849	0.55
Migrants			
15–44 years	2 017	1 954	0.97
45+ years	727	721	1.00
Czech Republic			
Native			
0–14 years	25	17	0.68
15–44 years	1 335	119	0.09
45+ years	4 056	788	0.19
Migrants			
15–44 years	606	123	0.20
45+ years	115	31	0.27
Portugal			
Native			
0–14 years	404	226	0.56
15–44 years	10 166	2 237	0.22
45+ years	9 570	3 541	0.37
Migrants			
15–44 years	1 171	410	0.35
45+ years	491	142	0.29
Spain			
Native			
0–14 years	1 298	341	0.26
15–44 years	6 268	1 707	0.27
45+ years	7 930	3 343	0.42
Migrants			
15–44 years	2 435	1 425	0.59
45+ years	549	332	0.60

EPTB= extrapulmonary tuberculosis; PTB = pulmonary tuberculosis
Cases are dispayed as total numbers for the period 2005–2014 (and 2010–2014 for Spain). The unknown EPTB/PTB cases were assumed to be distributed the same over PTB and EPTB as for those with a known location. Note that only migrants recorded as coming from medium- and high-endemic countries (TB incidence of >50/100 000) were included here, cases with missing country of birth information were assumed to be equally distributed as cases with information on country of birth. The few cases in migrants below 15 years of age were included in the 15–44 years group.

2.4 Cost data

Unit cost data for all components of TB and LTBI control were collected following the WHO-CHOICE approach[i], which consists of the following:

- An 'ingredient approach' to costing analysis which separates the reporting of prices and quantities of TB interventions. This allows the generalisation of cost estimates across countries. Purchasing power parities (PPPs) were applied to extrapolate costs from one country to another.
- Estimation of both patient costs and program costs of TB interventions. The latter type of cost is often ignored in economic analysis but may make up a significant amount of the total cost.
- The analysis followed the principles of 'generalised cost-effectiveness analysis', which implies the comparison of a current and new/hypothetical programme against a scenario representing the absence of any TB control – this allows insights in the cost-effectiveness of the current programme.

i World Health Organization. Cost effectiveness and strategic planning (WHO-CHOICE). Available from: http://www.who.int/choice/en/

- Discounting of costs and effects, both were discounted at a rate of 3% in the base-case analysis. Costs were collected from both the healthcare perspective (only costs incurred by the healthcare system) and societal perspective (costs incurred by the healthcare system, individual patients, and society).

Country-specific data were collected in the same way as epidemiological data in the modelling report. However, it was hard to determine precisely which components were included in specific cost estimates supplied by the countries. Thus, the cost estimates derived from these data had poor quality. Consequently, it was more reliable to standardise cost estimates to one country, and translate these using PPP for other countries. The Netherlands has an extensive TB control programme and served as a reference for calculating costs for other European countries. A comparison between country-specific unit costs obtained through PPP conversions and obtained through country consultations is given in the section 'Validation of PPP conversions' at the end of Chapter 2.3.

Healthcare costs

For calculating healthcare costs, programmatic TB control was categorised into the following activities:

- screening
- LTBI treatment
- TB treatment
- contact tracing
- directly observed treatment
- hospitalisation

In order to screen PWID/homeless people, the cost of identifying and enrolling these people ('outreach') was added into the screening programme, based on in-depth interviews of staff from municipal health services in Amsterdam and Rotterdam, who had experience with these activities[ii]. Costs for three LTBI regimens (3-month isoniazid plus rifampicin, 6-month isoniazid and 4-month rifampicin) have been included in the tables for reference, but 3-month isoniazid plus rifampicin is mainly used in the calculations since all have equal effectiveness and 3-month isoniazid plus rifampicin is the cheapest [24]. For the treatment activities, a distinction was made between traded goods (medicines) and non-traded goods (all other items). It is assumed that medicines can be purchased throughout the whole of the 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 were based on 2016. Table 5 gives an overview of all unit cost data collected. 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 given quantities are specific to national programmes, and were therefore adjusted by country according to local guidelines or practice, after consultation of the ECDC contact person in the country.

The costs of severe side-effects were ignored, as they are negligibly small. An estimated 0.01% of those that start treatment will have severe side-effects requiring hospitalisation [34,35]. Assuming the average duration of hospitalisation 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 one EUR. In addition, in rare instances of severe side-effects, liver transplantation might be needed. No data were found on the frequency of liver transplantation due to TB treatment side-effects. Thus, an extreme scenario was assumed in which 10% of those hospitalised would require transplantation (at a cost per transplantation of EUR 100 000 to 200 000). Yet, it was estimated that the additional costs per TB treatment would be about one to two EUR per TB treatment, which is less than 0.5% of the current unit cost of TB treatment (see Table 5).

[ii] Acknowledgements to Peter Kouw and Annet Reusken from GGD Amsterdam and Rob van Hest from GGD Rotterdam, the Netherlands

Table 5. Prices per item and the quantity provided under the different activities of tuberculosis control for the Netherlands in 2016

Activity	Price (EUR)	Quantity	Notes / references
Screening:			Tuberculin skin test and Chest X-ray;[36] Interferon gamma release assay: average of cost charged by 25 laboratories in the Netherlands (KNCV[iii]). Culture [37] For all the above consultation cost was included as applicable.
Tuberculin skin test	47.55	1	
Interferon gamma release assay	91.41	1	
Chest X-ray	62.66	1	
Culture	52.05	1	
Outreach screening PWID/homeless people per hour	76.00	2	Based on in-depth interview with the Public Health Service (GGD) Amsterdam and Rotterdam
Latent tuberculosis infection treatment:			
3-month isoniazid plus rifampicin*	157.06	1	[38]
6-month isoniazid	69.40	1	
4-month rifampicin alone	126.62	1	
Start consultation physician	54.26	1	[39]
Monthly physician consultation	27.13	2-5**	
Monthly nurse support	19.00	3-6**	
Chest X-ray	43.66	3	
Aspartate aminotrasnferase and alanine aminotrasnferase	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	[38]
2HRZE + 4HR (multidrug-resistant TB)*	17 369.95	1	
Start consultation	54.26	1	[39]
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	

[iii] Acknowledgements Ineke Spruijt, KNCV Tuberculosis Foundation

Activity	Price (EUR)	Quantity	Notes / references
Contact tracing:			
Fixed, per contact investigation	2 150.00	1	
Variable, per contact screened	135.57	14	Based on average 14 people investigated per contact investigation in the Netherlands
Directly observed treatment:			[37]
For normal tuberculosis treatment	330.00	1	
For multidrug/extensively drug–resistant tuberculosis treatment	1 647.00	1	
Hospitalisation:			[40] and update [41] (average hospitalization time was 1.9 weeks, when subtracting MDR TB patients 1.5 weeks). Updated with bedcosts from reference [42]
For normal tuberculosis patient (per week)	4 228.00	1.5	
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)*

Finally, to adjust for the cost level for an individual country, the purchasing power parity (PPP) of that country was applied to the prices, with the Netherlands being the reference value 1.00 [43]. Purchasing power parity takes into account the relative cost 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 [44]. 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 (as provided by ECDC contact persons in countries). Costs for non-traded goods were derived by calculating the price times the quantity times the PPP ($p \times q \times PPP$). The information is managed in an Excel spreadsheet, which forms the basis for a TB unit cost calculation tool (Appendix 3). The results of the cost calculation for each of the four countries are given in Table 6a. Even though the shortest treatment regimen is 3-month isoniazid and rifampicin, the question was also asked whether the cost-effectiveness of some strategies would change if alternative regimen were used, since countries may choose to use these over 3-month isoniazid and rifampicin for various reasons. Costs and characteristics of these alternative treatment regimens are given in Table 6b.

Societal costs

Societal costs were considered as the productivity loss of TB patients attending treatment or being hospitalised, and for people being screened. In addition, the travel costs incurred by patients attending treatment and people attending screening were calculated. People are assumed to have lost productivity when they:

- have TB disease (two months) [45]
- are hospitalised (country specific durations on top of two months due to TB)
- attend screening interventions (0.5 days)
- die due to TB (calculated as the average number of years until pension).

As TB disproportionally affects people of lower socioeconomic status in the selected countries, the average income generated by the lowest quintile for each country was used to determine the societal costs of productivity loss due to TB. Data from the World Bank was used to determine the income share of the lowest quintile for each country [46], and the monetary equivalent was calculated using the per capita gross domestic product (GDP) (data World Bank 2015, [47]). For instance, in the Netherlands the average GDP per capita is USD 44 433. However, the lowest income quintile generates about 9% of the total economic output of the country. The per-capita GDP of the lowest quintile is then calculated as (9% x USD 44 433)/0.20 = USD 19 706. An exchange rate of 1.12296 USD/EUR was used[iv].

iv Exchange rates as of 2 October 2016, available from: http://www.xe.com/currencytables/?from=USD&date=2016-10-02

Finally, the costs incurred for travel were calculated by multiplying the average distance to a hospital with the average cost of public transportation. Information was only available for the Netherlands (7 KM;[42,48]). The average distance to the hospital was assumed to be similar for all countries, and the average cost of public transport per kilometre were corrected using PPP corrections. The average distance to a health facility is likely to be different for each country. However, the distance is determined by many factors such as size, population density, urbanisation, and infrastructural organisation of the country. The only other two European countries with data were France (average distance is 5 KM) and Germany (average distance is 8 KM) [17]. One trip was counted for each screening test, but two trips for TST. In addition, a trip was assumed for each consultation when receiving TB or LTBI treatment. Finally, no travel and productivity costs were assumed for screening in prisons, yet productivity loss due to disease and treatment in prison was included, as prisoners are often released before they finished treatment. An overview of the societal costs due to productivity loss is given in Table 7. For the cohort-based analysis regarding healthcare workers, travel costs were assumed to be half that of the rest of the population, as many healthcare workers will already be at a facility where they can be screened due to their job.

Table 6a. Unit costs of the different activities of tuberculosis control for the Netherlands, the Czech Republic, Portugal, and Spain in year 2016

Activity	Netherlands	Czech Republic	Portugal	Spain
Purchasing power parity	1.00	0.59	0.75	0.82
Screening				
Tuberculin skin test	EUR 47.55	EUR 28.14	EUR 35.49	EUR 38.98
Interferon gamma release assay	EUR 91.41	EUR 54.09	EUR 68.22	EUR 74.93
Chest X-Ray	EUR 62.66	EUR 37.08	EUR 43.00	EUR 51.36
Culture	EUR 52.05	EUR 30.80	EUR 38.84	EUR 42.66
Outreach PWID/homeless people	EUR 152.00	EUR 89.94	EUR 113.43	EUR 124.59
LTBI treatment				
3-month isoniazid plus rifampicin	EUR 461.60	EUR 311.43	EUR 319.16	EUR 374.19
6-month isoniazid	EUR 520.37	EUR 336.25	EUR 405.94	EUR 439.05
4-month rifampicin alone	EUR 481.31	EUR 336.50	EUR 391.31	EUR 417.35
TB (non-MDR) treatment [b]	EUR 1 414.16	EUR 1 194.70	EUR 981.68	EUR 1 159.64
TB (MDR) treatment [b]	EUR 18 273.11	EUR 18 053.65	EUR 17 840.63	EUR 18 018.59
(% MDR)	1.16%	1.08%	0.94%	0.94%
Contact tracing [c] (Average size)	EUR 4 048.00 (n=14)	EUR 2 074.39 (n=10)	EUR 2 515.03 (n=9)	EUR 2 651.29 (n=8)
Directly observed treatment				
Normal TB treatment (Frequency)	EUR 330.00 (20%)	N/A [a]	EUR 246.27 (75%)	EUR 270.49 (15%)
MDR/XDR treatment (Frequency)	EUR 1 647.00 (50%)	N/A [a]	EUR 1 229.10 (100%)	EUR 1 350.00 (10%)
Hospitalisation				
Normal TB patient (Average duration)	EUR 6 341.50 (1.5 weeks)	EUR 25 015.76 (10 weeks) [a]	EUR 7 887.43 (2.5 weeks)	EUR 6 930.60 (2 weeks)
MDR/XDR TB patient (Average duration)	EUR 39 491.96 (16 weeks)	EUR 38 946.71 (26 weeks) [a]	EUR 30 227.30 (16 weeks)	EUR 22 825.32 (11 weeks)

LTBI= latent tuberculosis infection; MDR TB= multidrug-resistant tuberculosis; TB= tuberculosis; XDR TB= extensively drug resistant tuberculosis.

Average size of contact tracing, frequency of directly observed treatment, and average duration of hospitalisation, as well as the number of tests and consultations during TB and LTBI treatment, were obtained from the ECDC contact persons in the country.

[a] In the Czech Republic, each TB case is treated during hospitalisation by law, so all treatments are directly observed.

[b] Treatment includes microscopy and culture confirmatory tests. % MDR obtained from ECDC database (TESSy).

[c] In all four countries, contact tracing is usually performed for all self-reported pulmonary TB cases (100% assumed in the model).

Frequencies between brackets on contact tracing and hospitalisation have been used in the cost calculated mentioned above these frequencies; while for directly observed treatment the frequencies mentioned are applied to the actual numer of TB patients.

Table 6b. Assumptions on alternative latent tuberculosis infection treatment regimens for the Netherlands*

LTBI treatment	Cost treatment (EUR)	LTBI treatment combined start and completion in migrants at entry**/migrant prisoners/native prisoners/ PWID/homeless people
3-month isoniazid plus rifampicin (standard)	461.60	60% / 70% / 80% / 60%
6-month isoniazid	520.37	50% / 60% / 70% / 50%
4-month rifampicin alone	481.31	55% / 65% / 75% / 55%

LTBI= latent tuberculosis infection.
** Coverage, treatment efficacy/effectiveness and adverse events are assumed to be similar [24]*
*** Assumed 5% and 10%-points decrease in 4-month rifampicin alone and 6-month isoniazid, respectively, in absence of more detailed data [24].*

Table 7. Overview of societal unit costs due to productivity loss and travel

	Netherlands	Czech Republic	Portugal	Spain
Productivity loss				
Income share lowest quintile	9%	10%	6%	6%
Per capita GDP (USD)	USD 44 433	USD 17 231	USD 19 229	USD 25 831
Per capita income generated by lowest quintile (annual USD)	USD 19 706	USD 8 228	USD 6 201	USD 7 439
Per capita income generated by lowest quintile (annual EUR)	EUR 17 548	EUR 7 327	EUR 5 522	EUR 6 625
Travel costs				
Average distance to health facility (KM, kilometres)	7 KM	7 KM	7 KM	7 KM
Average travel costs per kilometre (EUR)	EUR 0.19	EUR 0.11	EUR 0.14	EUR 0.16
Travel costs per trip to facility (EUR)	EUR 2.66	EUR 1.57	EUR 1.99	EUR 2.18

GDP = gross domestic product.
Data on productivity loss were derived from the World Bank. Data on travel costs were derived for the Netherlands [49], and corrected with PPP corrections to arrive at estimates for the other countries.

Validation of PPP conversions

Each of the four countries were asked to provide unit costs of screening (CXR, IGRA, TST, and confirmation tests), treatment (TB, LTBI, directly observed treatment, side effects), and contact investigation. In the Netherlands, the KNCV Tuberculosis Foundation provided a detailed overview of the current unit costs and quantities (Table 5). Unfortunately, the Czech Republic, Portugal and Spain only provided a limited amount of data. In addition, data that were provided proved hard to interpret, as it was sometimes unclear what the precise components were in the provided cost-estimates (e.g. for cost of treatment it could not be determined 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 were used, and correct data using PPP conversions was used for the other countries. After doing so, Spain, Portugal and the Czech Republic were 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 6. As estimates were received from the Czech Republic, Spain and Portugal for some of the requested unit costs, a comparison between the PPP method and the data provided could be performed. The results are summarised in Table 8, and the most significant discrepancies are discussed in the footnotes.

Table 8. Validation of unit cost, purchasing power parity method compared with data provided by Spain, Portugal and the Czech Republic

	Spain (expert)	Spain (PPP)	Portugal (expert)	Portugal (PPP)	Czech Republic (expert)	Czech Republic (PPP)
Screening						
CXR	EUR 17 [a]	EUR 51	EUR 43 [a]	EUR 47	EUR 19 [a]	EUR 37
IGRA	EUR 54-66	EUR 75	EUR 50	EUR 68	EUR 56 [b]	EUR 54
TST	EUR 19	EUR 39	EUR 15	EUR 35	EUR 56 [b]	EUR 28
Treatment						
TB	EUR 870	EUR 1 060	EUR 140 [c]	EUR 982	EUR 144 [c]	EUR 1 195
LTBI 3–month isoniazid and rifampicin	EUR 400	EUR 374	EUR 91 [c]	EUR 319	EUR 146	EUR 311
Directly observed treatment	EUR 3 090 [d]	EUR 270	unknown	EUR 246	N/A [e]	N/A [e]

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 cost 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] The aggregate price was provided.
[c] These values probably reflect only the cost for medication, not additional consultations / tests performed, and Czech Republic reported that most test are done 7 times for regular TB treatment, where other countries do these only 1-6 times.
[d] This value probably included hospitalisation costs.
[e] All pulmonary TB cases in the Czech Republic are hospitalised; therefore, DOT does not concern additional costs.
Amounts are rounded to whole EUR.

2.5 Burden estimates

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 [50]. In order to calculate the burden of TB morbidity, the number of person-years lived with TB was multiplied by 0.331. A year of life lost due to death corresponds with one QALY loss. Because the cost-effectiveness analysis was performed for the key transmission groups in the transmission model, the effects of prevented PTB on transmission are incorporated into these estimates. In the cohort model, the transmission effects were not considered.

Country-specific assumptions were made on the rates of hospitalisation and mortality due to TB disease (see Table 9 for an overview). Country-specific data on hospitalisation rates for TB were obtained for all four countries from ECDC TB contact persons or the literature, and country-specific TB mortality rates for all countries were obtained from WHO (WHO Global TB report 2015). These mortality data roughly compare with the mortality rates from the ECDC/WHO report on TB surveillance in Europe [51], yet the latter excluded TB mortality with HIV as an underlying cause [18]. In the model, people with active PTB can be successfully treated either through self-reporting or screening. Depending on the duration until treatment, people can progress to so-called severe pathology (see Figure 1, described in detail in the modelling report). For hospitalisation, it was assumed that all people with severe pathology will be hospitalised, and a country-specific rate was added where people who self-report without severe pathology are hospitalised to reproduce the country hospitalisation rates. In the Czech Republic, all people with PTB are hospitalised. This is reflected in the high proportion of people with self-reported TB being hospitalised in the country, yet it is not 100% of those cases as not all EPTB cases are hospitalised. The value of 96.9% was chosen in order to arrive at the overall hospitalisation rate data from the Czech Republic.

For mortality, it was assumed that only people with severe pathology can die due to TB. Country-specific rates of mortality during severe pathology were applied to arrive at mortality rates as reported by the GBD. Consistent with data, a four times higher probability of dying due to severe pathology was assumed in people aged 45+ [52]. Mortality in the age group 45+ in the Czech Republic had to slightly exceed 100% in order to be able to reproduce the observed TB mortality in the country. This can be explained by the fact that recent rapid declines in TB due to improved control were not incorporated into the model. Thus, the model was not able to properly reproduce the age distribution in the number of reported PTB cases in the country. A more detailed discussion on this topic can be found in Chapter 4 and in the modelling report.

In order to calculate the number of years of life lost (YLL) due to mortality, country-specific life tables were obtained (Sources: Netherlands [53]; Czech Republic [54]; Portugal [55]; Spain [56]), and the average age was determined in each of the three age groups using population composition data from the United Nations World Population Prospects [57]. 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 0–14 and 15–44 years. Mortality rates due to TB were about four times higher in the 45+ age group [52], and the excess mortality compared with 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 [58]. 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, it was assumed that 75% of those dying due to TB in the age group 45+ had a remaining life-expectancy of one year, and 25% had a remaining life-expectancy similar to the average person in the age group. Finally, the number of years of work lost (YWL) due to TB mortality were estimated for societal cost calculations by subtracting the difference between the age at pension and the total life-expectancy from the remaining life-expectancy. The age at pension is 67 in the Netherlands and Spain, 66 in Portugal, and 65 in the Czech Republic. For all countries, the average age at which people start working was assumed to be 20 years. Table 9 shows the resulting proportions in those hospitalised and dying, and the YLL and YWL due to TB mortality in the four countries.

All numbers of people self-reporting with and without severe pathology in the model are multiplied with PTB:EPTB ratios (see chapter 2.3) in order to arrive at the total TB burden. Hospitalisation and mortality reported here thus reflect PTB and EPTB combined, and were compared with data about total TB hospitalisation and mortality.

Table 9. Hospitalisation, mortality, years of life lost, and years of work lost due to tuberculosis

	Netherlands	Czech Republic	Portugal	Spain
Hospitalisation				
Screen-detected PTB	0.0%	100.0%	0.0%	0.0%
Self-reported TB	13.0%	97.1%	14.3%	60.4%
Severe pathology TB	100.0%	100.0%	100.0%	100.0%
Corresponding TB hospitalisation rate per 100 000 [59,60]	**1.2**	**6.5**	**7.1**	**8.6**
Proportion of people with severe pathology dying				
0–14	12.8%	26.8%	16.2%	13.8%
15–44	12.8%	26.8%	16.2%	13.8%
45+	51.2%	107.2%	64.8%	55.2%
Corresponding TB death rate per 100 000 population [32]	**0.16**	**0.56**	**1.6**	**0.64**
Years of life lost due to TB mortality				
0–14	74.70	71.98	73.33	75.95
15–44	51.97	48.40	49.73	51.24
45+	6.29	5.77	5.91	6.37
Years of work lost due to TB mortality				
0–14	47.00	45.00	46.00	47.00
15–44	37.23	33.72	35.14	35.41
45+	5.04	2.52	2.73	4.40

PTB= pulmonary tuberculosis; TB= tuberculosis.
For calculating years of work lost, we applied the following pension age: 67 in the Netherlands and Spain; 66 in Portugal; and 65 in Czech Republic. People are assumed to start working at an average age of 20 years.

2.6 Cost-effectiveness analysis

The cost-effectiveness of LTBI screening 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). An ICER was calculated for both the healthcare and societal perspective. Arbitrary willingness-to-pay thresholds (2 x per capita GDP) were chosen per country in order to determine whether a strategy was cost-effective, which corresponds to the current value of EUR 80 000 as a threshold in the Netherlands. The corresponding willingness-to-pay thresholds for the other countries were: 35 000 EUR/QALY for the Czech Republic; 40 000 EUR/QALY for Portugal; and 50 000 EUR/QALY for Spain. 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. In order to more directly compare strategies, the total incremental costs were plotted against the total incremental effects in a traditional cost-effectiveness plot.

A line of optimal expansion was drawn based on calculating the ICER for the next most effective screening option. Strategies connected with this line are dominant over all other strategies. This was done for both the healthcare and societal perspective.

The time horizon for all cost-effectiveness analyses is 20 years. Costs and effects are discounted at 3% annually.

2.7 Sensitivity analyses

The importance and contribution of the different risk groups to the overall TB epidemic in the country of interest is different for each of the four countries. This makes the comparison of cost-effectiveness of strategies across the countries an important sensitivity analysis of the importance of the different risk groups. For instance, the Netherlands and Spain have relatively large rates of immigration from high-endemic countries, whereas the Czech Republic and Portugal have lower rates. In addition, Spain has the smallest PWID/homeless people population, while Portugal has the largest population. However, PTB incidence in the PWID/homeless people group is highest in Spain and Portugal, and lower in the Netherlands and the Czech Republic. In order to reproduce the data on TB by risk group, the different countries contain different combinations of high-risk groups and their interactions. Because all risk groups in the transmission model interact dynamically, changing the size or transmission in one of the groups will affect the entire fit of the model. Further, comparisons of the main results would be impossible if systematic changes would be made in individual parameters on these aspects.

For the base-case screening options, coverage rates of 50% and 70% were assumed for annual and triennial screening of PWID/homeless people groups, respectively. As no data exists on the expected coverage, the coverage for annual screening varied between 20% and 70%; and between 40% and 90% for triennial screening.

Finally, in order to determine the importance of all cost assumptions in the analyses, the contribution of each cost item to the incremental costs of one strategy is presented for each country. The intervention chosen was TST/IGRA for all risk groups, as this is one of the most expensive but still cost-effective strategies, and because of this it demonstrates the importance of different cost-items, and indicates how and to what extent uncertainty of a certain cost-assumption might influence the predicted cost-effectiveness of a certain intervention.

3. Results

3.1 Transmission model

Tables 10 to 13 show the cost, effects, and ICER for all screening strategies in the Netherlands, the Czech Republic, Portugal, and Spain, respectively. The most cost-effective screening algorithm is TST/IGRA from the healthcare perspective, and either TST/IGRA or IGRA from the societal perspective. For all countries, screening migrants at entry was the least cost-effective LTBI screening strategy, except for Spain. This can be explained by the difference in the baseline strategy. Spain currently screens migrants at entry with TST followed by a confirmatory CXR to detect active TB, and already screens prisoners at incarceration with TST, followed by LTBI treatment if positive. Nevertheless, entry screening for migrants met the criteria of being cost-effective for all countries.

The most effective strategies in reducing QALY loss due to TB were screening of PWID/homeless people populations annually in Portugal (Table 12), and targeting all risk groups in the Netherlands (Table 10), the Czech Republic (Table 11), and Spain (Table 13). Furthermore, screening prisoners at incarceration with IGRA or TST/IGRA compared with the current baseline will result in a net QALY loss in Spain due to the current baseline of TST screening for prisoners in the country. The incremental costs from the healthcare perspective are highest when screening the PWID/homeless people population annually in the Czech Republic (Table 11) and Portugal (Table 12), and when screening all risk groups in the Netherlands (Table 10) and Spain (Table 13). In the Czech Republic, profound cost-savings occur even in the healthcare perspective (Table 11), which can be explained by the fact that all TB patients in the Czech Republic are hospitalised, making it extremely beneficial to prevent a TB case through LTBI screening. Figure 4 shows the incremental costs and effects of all strategies and all countries for the healthcare perspective. Screening of migrants at entry is dominated by all other strategies in all the countries, except for the Netherlands, where entry screening of migrants is on par with screening of PWID/homeless people populations. In addition, screening PWID/homeless people groups is the most dominant strategy in Portugal, while screening all risk groups is the most dominant strategy in the Netherlands, the Czech Republic, and Spain. Furthermore, for all targeting strategies, screening with TST/IGRA is the most cost-effective option, followed by TST alone. IGRA is dominated by the other two in all countries except Portugal. Finally, IGRA and TST/IGRA strategies for prisoners in Spain result in negative QALYs averted, because the strategies are compared with a baseline of TST screening, which is a slightly more sensitive test.

Figure 5 shows the incremental costs and effects of all strategies and all countries from the societal perspective. When including the societal costs, the order of targeting strategies in all countries is largely maintained. However, using IGRA is now more cost-effective compared with TST or TST/IGRA, as IGRA testing results in relatively less false positives and LTBI overtreatment, and the societal costs for undergoing LTBI treatment (travel and productivity loss) are lower compared with TST (which requires two visits to a health facility).

Table 14 shows that LTBI treatment with 3-month isoniazid plus rifampicin is the most cost-effective option when compared with 6-month isoniazid or 4-month rifampicin. However, choosing an alternative regimen did not substantially change the cost-effectiveness of the evaluated strategies, and all are still below the willingness-to-pay threshold from the healthcare perspective.

Figure 6 shows the impact of alternative coverage assumptions on the incremental costs and effects of annual and triennial screening of the PWID/homeless people group from the healthcare perspective. The results show that, regardless of coverage assumptions, triennial screening is more cost-effective than annual screening, as costs are lower with similar QALY gains for triennial screening. In addition, it was observed that with higher coverage levels, the QALY gains per additional investment decreases. This effect is even more profound in the societal perspective (Figure 7), as the large number of screening tests required to achieve high coverage levels result in large rates of productivity loss due to attending screening.

Table 10. Costs, effects, and cost-effectiveness over a period of 20 years for different LTBI screening strategies per 10 000 people in the Netherlands, for the healthcare and societal perspective

			Healthcare perspective			Societal perspective		
	Total QALY	QALY gained	Total costs (EUR)	Incremental costs (EUR)	ICER*	Total costs (EUR)	Incremental costs (EUR)	ICER*
Baseline	5.90	N/A	81 058	N/A	N/A	189 185	N/A	N/A
Migrants at entry								
TST	5.23	0.67	113 076	32 018	47 994	253 703	64 518	96 713
IGRA	5.28	0.62	105 976	24 918	40 380	222 291	33 106	53 650
TST/IGRA	5.36	0.54	101 175	20 117	37 464	230 667	41 483	77 255
Migrant prisoners								
TST	5.74	0.16	86 094	5 035	32 039	196 445	7 260	46 194
IGRA	5.75	0.15	82 904	1 846	12 474	189 953	768	5 189
TST/IGRA	5.77	0.13	82 478	1 420	10 673	189 532	347	2 612
All prisoners								
TST	5.55	0.35	90 269	9 211	26 020	203 742	14 557	41 122
IGRA	5.57	0.33	93 952	12 894	38 555	200 512	11 327	33 869
TST/IGRA	5.60	0.30	80 837	-222	*Dominant*	185 867	-3318	*Dominant*
PWID/homeless people (Triennial–70% coverage)								
TST	5.37	0.53	101 608	20 550	38 566	214 637	25 452	47 766
IGRA	5.38	0.52	102 187	21 128	40 554	208 886	19 701	37 814
TST/IGRA	5.40	0.50	98 966	17 907	35 975	209 816	20 631	41 447
PWID/homeless people (Annual–50% coverage)								
TST	5.25	0.65	124 647	43 589	66 989	248 703	59 518	91 468
IGRA	5.26	0.64	125 361	44 302	68 937	236 178	46 993	73 124
TST/IGRA	5.27	0.63	118 697	37 638	60 119	237 417	48 232	77 040
All risk groups								
TST	4.59	1.31	143 926	62 868	47 876	298 134	108 950	82 968
IGRA	4.65	1.25	140 506	59 447	47 554	256 523	67 338	53 866
TST/IGRA	4.76	1.14	119 206	38 148	33 327	250 638	61 453	53 686

ICER=Incremental cost effectiveness ratio, IGRA= interferon gamma release assay; LTBI= latent tuberculosis infection, N/A = not applicable, QALY= quality adjusted life years; TST= tuberculin skin test.
**Due to rounding, exact ICERs might not be reproduced from given QALY and cost.*

Table 11. Costs, effects, and cost-effectiveness over a period of 20 years for different LTBI screening strategies per 10 000 people in Czech Republic, for the healthcare and societal perspective

			Healthcare perspective			Societal perspective		
	Total QALY	QALY gained	Total costs (EUR)	Incremental costs (EUR)	ICER	Total costs (EUR)	Incremental costs (EUR)	ICER
Baseline	15.03	N/A	314 223	N/A	N/A	403 385	N/A	N/A
Migrants at entry								
TST	14.68	0.35	315 932	1710	4 847	410 505	7 120	20 187
IGRA	14.71	0.33	315 394	1172	3 590	405 193	1 808	5 540
TST/IGRA	14.75	0.28	313 096	-1127	*Dominant*	405 843	2 458	8 653
Migrant prisoners								
TST	14.57	0.46	311 545	-2678	*Dominant*	400 802	-2 583	*Dominant*
IGRA	14.60	0.43	309 145	-5078	*Dominant*	396 455	-6 929	*Dominant*
TST/IGRA	14.64	0.39	308 721	-5501	*Dominant*	396 112	-7 273	*Dominant*
All prisoners								
TST	12.43	2.60	289 213	-25010	*Dominant*	376 836	-26 548	*Dominant*
IGRA	12.54	2.49	294 585	-19637	*Dominant*	373 828	-29 556	*Dominant*
TST/IGRA	12.75	2.28	274 051	-40172	*Dominant*	351 978	-51 406	*Dominant*
PWID/homeless people (Triennial–70% coverage)								
TST	12.22	2.81	298 426	-15796	*Dominant*	383 000	-20 385	*Dominant*

			Healthcare perspective			Societal perspective		
IGRA	12.28	2.75	299 957	-14266	*Dominant*	379 554	-23 830	*Dominant*
TST/IGRA	12.40	2.63	297 799	-16424	*Dominant*	381 287	-22 098	*Dominant*
PWID/homeless people (Annual–50% coverage)								
TST	11.63	3.41	317 219	2996	880	409 134	5 750	1 688
IGRA	11.67	3.37	318 523	4300	1 277	399 781	-3 604	*Dominant*
TST/IGRA	11.75	3.29	311 574	-2648	*Dominant*	399 793	-3 591	*Dominant*
All risk groups								
TST	10.98	4.05	301 892	-12330	*Dominant*	399 227	-4 158	*Dominant*
IGRA	11.08	3.95	306 438	-7784	*Dominant*	384 981	-18 404	*Dominant*
TST/IGRA	11.26	3.78	278 276	-35946	*Dominant*	361 335	-42 050	*Dominant*

ICER= Incremental cost effectiveness ratio; IGRA= interferon gamma release assay; N/A = not applicable; QALY= quality adjusted life years; TST= tuberculin skin test

Table 12. Costs, effects, and cost-effectiveness over a period of 20 years for different LTBI screening strategies per 10 000 people in Portugal, for the healthcare and societal perspective

			Healthcare perspective			Societal perspective		
	Total QALY	QALY gained	Total costs (EUR)	Incremental costs (EUR)	ICER	Total costs (EUR)	Incremental costs (EUR)	ICER
Baseline	44.01	N/A	242 251	N/A	N/A	430 533	N/A	N/A
Migrants at entry								
TST	43.29	0.72	266 143	23 892	33 083	464 384	33 851	46 874
IGRA	43.32	0.68	262 878	20 627	30 209	455 240	24 707	36 185
TST/IGRA	43.39	0.62	260 388	18 137	29 290	455 995	25 462	41 119
Migrant prisoners								
TST	43.72	0.29	246 312	4 060	13 885	435 233	4 700	16 074
IGRA	43.74	0.27	244 034	1 782	6 580	431 837	1 304	4 813
TST/IGRA	43.77	0.24	243 850	1 599	6 801	431 700	1 167	4 964
All prisoners								
TST	42.37	1.63	262 691	20 439	12 506	454 883	24 350	14 899
IGRA	42.49	1.51	260 801	18 550	12 257	446 672	16 139	10 664
TST/IGRA	42.69	1.31	246 713	4 462	3 396	432 129	1 596	1 214
PWID/homeless people (Triennial–70% coverage)								
TST	32.99	11.02	280 885	38 634	3 507	447 056	16 522	1 500
IGRA	33.22	10.79	276 743	34 492	3 197	432 177	1 644	152
TST/IGRA	33.69	10.32	271 626	29 375	2 847	434 951	4 418	428
PWID/homeless people (Annual–50% coverage)								
TST	30.43	13.58	351 970	109 719	8 078	529 226	98 693	7 267
IGRA	30.57	13.44	339 169	96 917	7 214	492 391	61 858	4 604
TST/IGRA	30.90	13.11	326 015	83 764	6 389	492 577	62 044	4 732
All risk groups								
TST	31.41	12.59	326 839	84 587	6 716	509 534	79 001	6 272
IGRA	31.72	12.29	316 085	73 833	6 007	475 104	44 571	3 626
TST/IGRA	32.32	11.69	293 892	51 640	4 417	463 153	32 620	2 790

ICER=Incremental cost effectiveness ratio; IGRA= interferon gamma release assay, LTBI= latent TB infection, N/A = not applicable, QALY= quality adjusted life years, TST= tuberculin skin test

Table 13. Costs, effects, and cost-effectiveness over a period of 20 years for different LTBI screening strategies per 10 000 people in Spain, for the healthcare and societal perspective

			Healthcare perspective			Societal perspective		
	Total QALY	QALY gained	Total costs (EUR)	Incremental costs (EUR)	ICER	Total costs (EUR)	Incremental costs (EUR)	ICER
Baseline	20.87	N/A	222 011	N/A	N/A	356 590	N/A	N/A
Migrants at entry								
TST	20.17	0.70	238 531	16 520	23 596	377 826	21 236	30 332
IGRA	20.22	0.65	239 424	17 413	26 868	367 901	11 311	17 453
TST/IGRA	20.30	0.56	229 528	7 517	13 317	364 869	8 279	14 668
Migrant prisoners								
TST	20.87	N/A*	222 011	N/A*	N/A*	356 590	N/A*	N/A*
IGRA	20.90	-0.03	219 124	-2 887	95 349	351 790	-4 799	158 492
TST/IGRA	20.95	-0.08	217 713	-4 298	52 663	350 441	-6 149	75 340
All prisoners								
TST	20.87	N/A*	222 011	N/A*	N/A*	356 590	N/A*	N/A*
IGRA	20.96	-0.09	224 069	2 058	*Dominated*	353 233	-3 356	35 429
TST/IGRA	21.13	-0.26	208 006	-14 006	54 079	336 688	-19 901	76 844
PWID/homeless people (Triennial–70% coverage)								
TST	19.96	0.91	222 826	815	892	354 483	-2 107	*Dominant*
IGRA	19.97	0.90	222 423	412	459	352 998	-3 591	*Dominant*
TST/IGRA	20.01	0.86	221 924	-88	*Dominant*	353 276	-3 313	*Dominant*
PWID/homeless people (Annual–50% coverage)								
TST	19.78	1.09	228 808	6 797	6 260	361 490	4 901	4 514
IGRA	19.79	1.08	227 874	5 863	5 447	358 280	1 691	1 571
TST/IGRA	19.81	1.05	226 445	4 433	4 203	358 139	1 549	1 469
All risk groups								
TST	19.26	1.61	239 337	17 326	10 738	375 706	19 116	11 847
IGRA	19.37	1.50	241 701	19 690	13 103	360 540	3 950	2 629
TST/IGRA	19.56	1.31	214 518	-7 493	*Dominant*	340 105	-16 484	*Dominant*

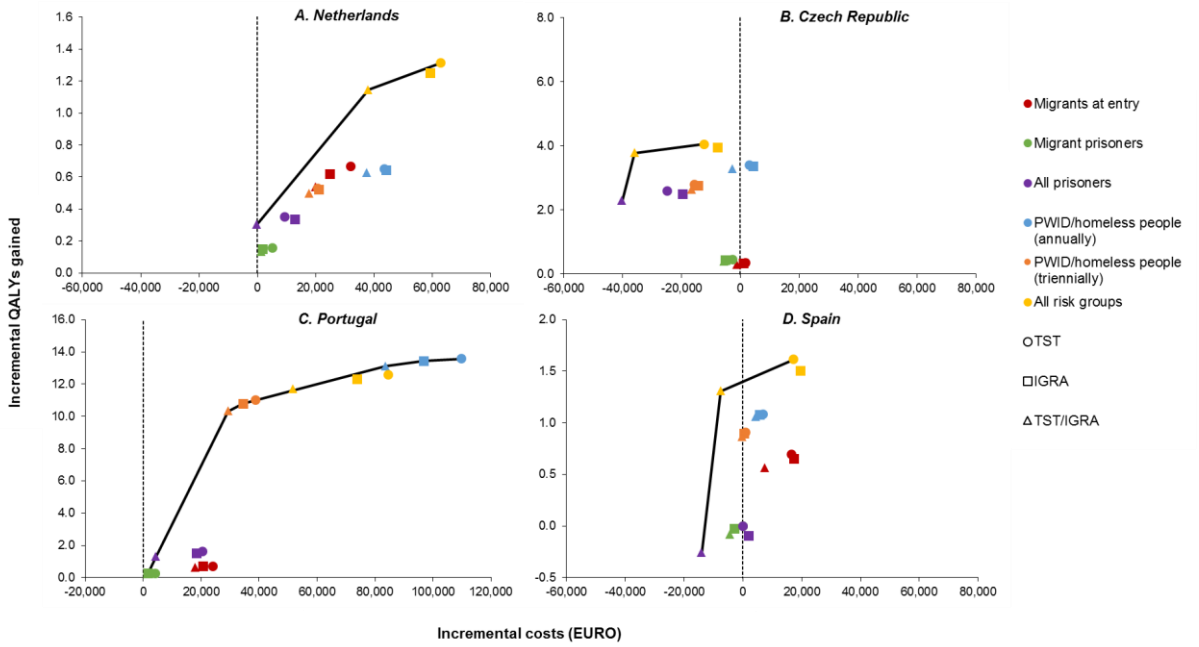
**In Spain, TST screening followed by LTBI screening for prisoners at incarceration is already part of the current policy. ICER=Incremental cost effectiveness ratio; IGRA= interferon gamma release assay, LTBI= latent TB infection, N/A = not applicable, QALY= quality adjusted life years, TST= tuberculin skin test*

Table 14. Costs, effects, and cost-effectiveness over a period of 20 years for selected* LTBI screening strategies per 10 000 people in the Netherlands, for the healthcare and societal perspective; for three alternative treatment strategies

			Healthcare perspective			Societal perspective		
	Total QALY	QALY gained	Total costs (EUR)	Incremental costs (EUR)	ICER	Total costs (EUR)	Incremental costs (EUR)	ICER
Baseline	5.90		81 058			189 185		
3-month isoniazid plus rifampicin								
Migrants at entry								
TST/IGRA	5.36	0.54	101 175	20 117	37 464	230 667	41 483	77 255
All risk groups								
TST/IGRA	4.76	1.14	119 206	38 148	33 327	250 638	61 453	53 686
6-month isoniazid								
Migrants at entry								
TST/IGRA	5.46	0.44	102 754	21 696	49 004	232 963	43 778	98 882
All risk groups								
TST/IGRA	4.88	1.02	121 253	40 195	39 310	253 833	64 648	63 224
4-month rifampicin								
Migrants at entry								
TST/IGRA	5.41	0.49	101 676	20 618	42 092	231 527	42 342	86 443
All risk groups								
TST/IGRA	4.82	1.08	119 895	38 836	35 825	251 893	62 708	57 845

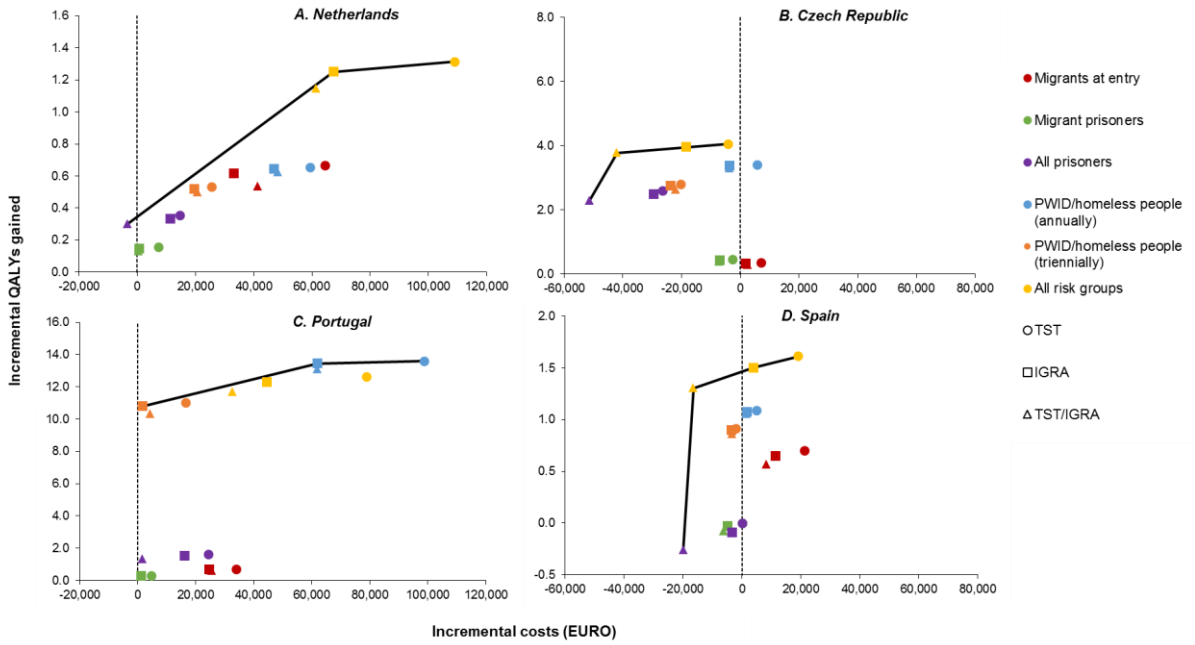
ICER=Incremental cost effectiveness ratio; IGRA= interferon gamma release assay, LTBI= latent TB infection, N/A = not applicable; QALY= quality adjusted life year, TST= tuberculin skin test,
**TST/IGRA screening was chosen since it is currently applied in many settings. Migrants were chosen as the largest risk group.*

Figure 4. Incremental costs and effects of different LTBI screening strategies in (A) the Netherlands, (B) the Czech Republic, (C) Portugal, and (D) Spain from the healthcare perspective



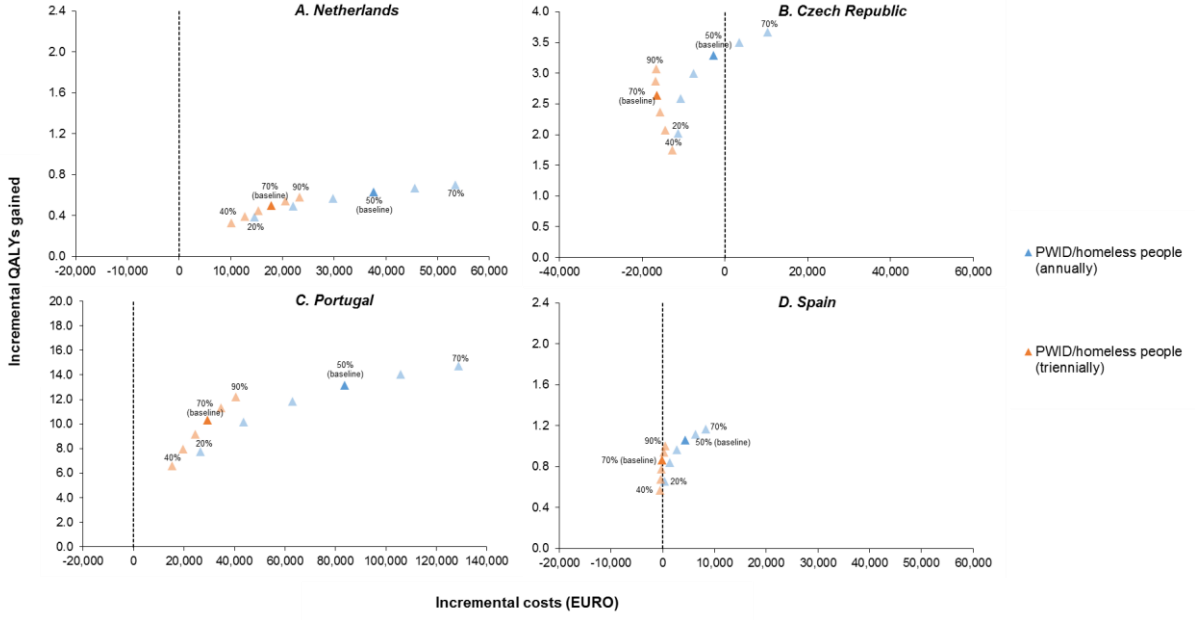
IGRA= interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test.
Results are cumulative incremental costs and QALY gains over a 20-year period and in a population of 10 000 people, compared with the baseline of continuation of the current policy. Colours distinguish between targeting strategies, while shapes distinguish between LTBI testing methods. The dots that are connected with the black line give the most cost-effective strategies for each country; these strategies dominate the others. Costs and effects are discounted at 3% annually.

Figure 5. Incremental costs and effects of different LTBI screening strategies in (A) the Netherlands, (B) the Czech Republic, (C) Portugal, and (D) Spain from the societal perspective



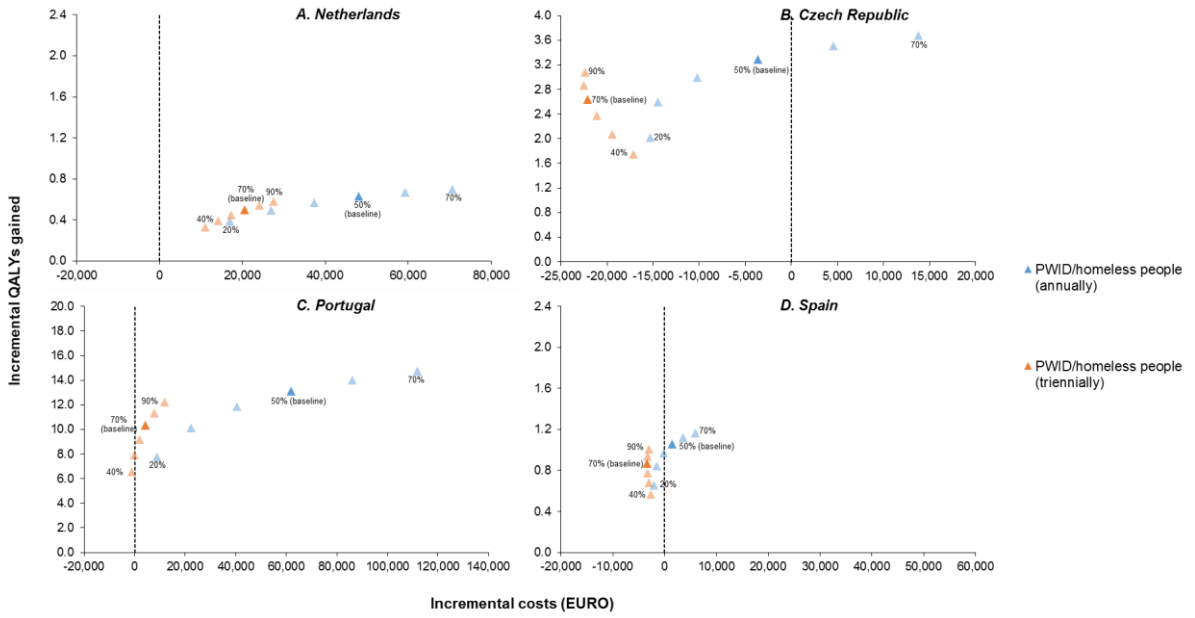
IGRA= Interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test.
Results are cumulative incremental costs and QALY gains over a 20-year period and in a population of 10 000 people, compared with the baseline of continuation with the current policy. Colours distinguish between targeting strategies, while shapes distinguish between LTBI testing methods. The dots that are connected with the black line give the most cost-effective strategies for each country; these strategies dominate the others. Costs and effects are discounted at 3% annually.

Figure 6. Impact of coverage on the incremental costs and effects of annual and triennial screening of PWID/homeless people for LTBI, healthcare perspective



QALY= quality adjusted life year.
Screening is performed using a combination of TST and IGRA, for both strategies. Incremental costs and effects are compared with a baseline of no screening of PWID/homeless people populations. The default values represent the scenarios included in the main cost-effectiveness analyses. Coverage ranges of 20% to 70% were examined for annual screening, and 40% to 90% for triennial screening. Coverage was increased in steps of 10%. Baseline = coverage level used in the base-case analyses.

Figure 7. Impact of coverage on the incremental costs and effects of annual and triennial screening of PWID/homeless people for latent tuberculosis infection, societal perspective



QALY= quality adjusted life year.
Screening is performed using a combination of TST and IGRA, for both strategies. Incremental costs and effects are compared with a baseline of no screening of PWID/homeless people populations. The default values represent the scenarios included in the main cost-effectiveness analyses. Coverage ranges of 20% to 70% were examined for annual screening, and of 40% to 90% for triennial screening. Coverage was increased in steps of 10%. Baseline = coverage level used in the base-case analyses

3.2 Cohorts

Migrant cohorts

Figure 8 shows the incremental cost-effectiveness ratio of LTBI screening strategies in migrant cohorts, with different endemicity levels in the country of origin. Compared with a willingness-to-pay threshold of two times the country GDP, LTBI screening for migrants at entry is cost-effective, except for migrants from relativity low-endemic countries (TB incidence <50/100 000) in the Netherlands, the Czech Republic, and Spain; while LTBI screening for migrants at entry is only cost-effective for migrants in Portugal with very high TB incidence in the country of origin (>300/100 000). Figure 8 also shows that the choice of baseline is a critical aspect in the CEA. For instance, LTBI screening for migrants in the Netherlands with a TB incidence of 100/100 000 is cost-effective when compared with the baseline of CXR screening (left panels in Figure 8), but no longer cost-effective when compared with no screening (right panels in Figure 8). Therefore, comparing with a baseline of no screening increases the ICERs. For the current country averages and migrants from high-endemic countries, the contrast is less profound. The exception is Spain, where the current policy consists of TST screening followed by CXR to detect active TB. Compared with this baseline, LTBI screening is cost-effective for the current average migrant cohort in Spain, but not when LTBI screening is compared with doing nothing (table A2.1). Finally, it is important to note that the cohort model does not incorporate prevented secondary infections. When compared with the transmission model, ICERs for the cohort-based approach are about 20% to 40% higher compared with the same strategies evaluated in the transmission model (e.g. in the Netherlands TST screening for migrants had an ICER of 47 994 EUR/QALY, and in the cohort model this was 58 452 EUR /QALY in the cohort model). Therefore, if prevented secondary cases were taken into account, ICERs for screening migrants from the different categories in the cohort model would be 20% to 40% lower.

Healthcare workers

Figure 9 shows the incremental costs and effects of LTBI screening for healthcare workers in the Netherlands and Portugal for different FOIs and screening intervals. Even under unrealistically high relative FOIs (i.e. 30 times higher than the model-derived FOI value for low-risk natives at equilibrium), LTBI screening for healthcare workers is not cost-effective in the Netherlands, while it is only cost-effective when assuming a relative FOI of 10 or 30 times higher than the model-derived FOI value for low-risk natives at equilibrium in Portugal. In comparison, a study by Baussano et al [61] showed that healthcare workers have an incidence rate ratio of about 2.4 compared with non-healthcare workers, which would correspond roughly with the scenario of three times higher FOI. A detailed overview of the results can be found in the Appendices (Table A2.2).

Travellers and TB contacts

Figure 10 shows the incremental costs and effects of LTBI screening for cohorts with a short-term increased level of exposure, i.e. travellers and TB contacts, in the Netherlands and Portugal. For travellers, LTBI screening is only cost-effective when the FOI in the destination country is at least 300 times the FOI of the Netherlands. As a reference, an FOI of 200 times that in the Netherlands or 20 times in Portugal is comparable to that in high-endemic countries with a TB incidence of 300 per 100 000. Therefore, LTBI screening for travellers is only likely to be cost-effective for extremely high-endemic settings, such as healthcare settings in high endemic countries (see Table A2.3 for more details).

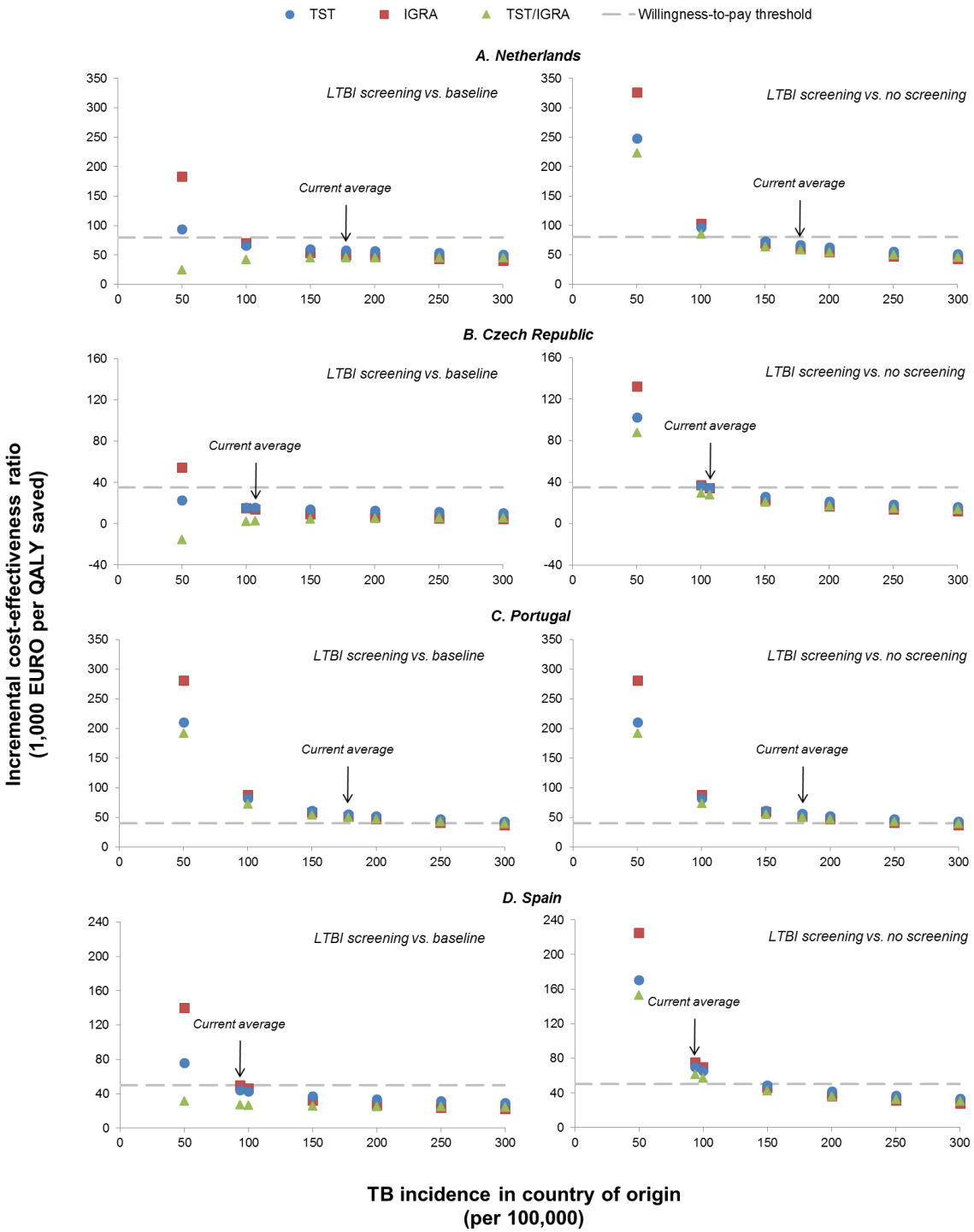
In contrast, LTBI screening for TB contacts is cost-effective in both countries, as the situations with a 100 fold (for Portugal) or 1 000 fold (for the Netherlands) increased FOI during three months are substantially higher than the willingness-to-pay threshold (Figure 10). For TB contacts this increased transmission risk may be even higher than that. A systematic review by Fox et al [62] showed that the prevalence of LTBI among contacts was about 28% in high-income countries, while the prevalence of LTBI in the general population in the Netherlands was about 1.5% in the model. Under the FOI in the general population, it takes about 40 years to accrue an LTBI prevalence of 1.5% (the average prevalence in the Netherlands), while it takes about three months (the average duration of PTB) to accrue a prevalence of 28%–1.5% = 26.5% in TB contacts. This requires an FOI that is about (26.5%/3 months)/(1.5%/40 years) ≈ 3 000 times higher compared with the FOI for the general population in the Netherlands.

Alternatively, there are about 300 PTB cases in the Netherlands each year over a total population of 16 million. As contact tracing comprises of approximately 14 contacts per case (data obtained through country consultations, see chapter 2.3), the total number of contacts in the Netherlands would be 300 x 14 = 4 200, corresponding to 3 x 4 200 = 12 600 person-months of exposure. If 20% of all PTB cases in the Netherlands (i.e. 60 cases) are caused by TB contacts, this corresponds to an incidence of 60/12 600 person-months, while this is about (300 / 12)/16 million person-months for the general population, i.e. again about 3 000 times higher.

Immunocompromised patients

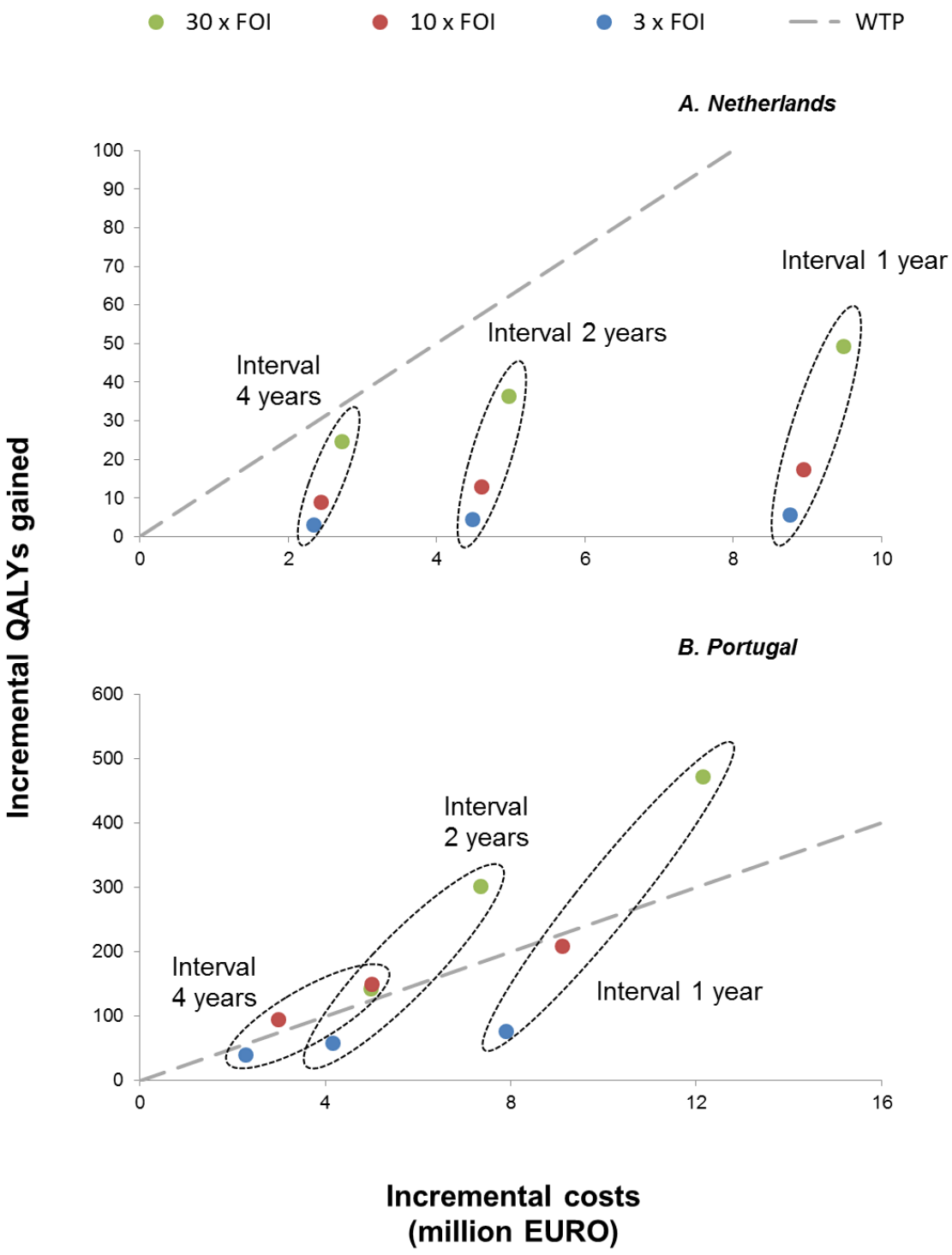
Figure 11 shows the incremental costs and effects of LTBI screening for a cohort of immunocompromised patients in the Netherlands and Portugal. The results show that whether or not LTBI screening is cost-effective for immunocompromised natives depends largely on the background risk of being LTBI positive. For instance, low-risk natives in the Netherlands have a relatively low LTBI prevalence, and LTBI screening for immunocompromised patients among this population does not seem to be cost-effective. However, low-risk natives in Portugal have a higher prevalence, and LTBI screening does seem to be borderline cost-effective for this population. For migrants from TB endemic countries, LTBI screening in immunocompromised patients always seems to cost-effective, especially if activation is six or more times higher compared with healthy low-risk natives. Heterogeneity in the prevalence of immunocompromised patients and TB incidence from countries of origin might make the screening even more cost-effective, as migrants with HIV are more like to come from countries with relatively high TB levels (e.g. countries in Southern and Eastern Africa). See Table A2.4 for a detailed overview.

Figure 8. Incremental cost-effectiveness of screening migrants at entry, calculated from a cohort-based approach



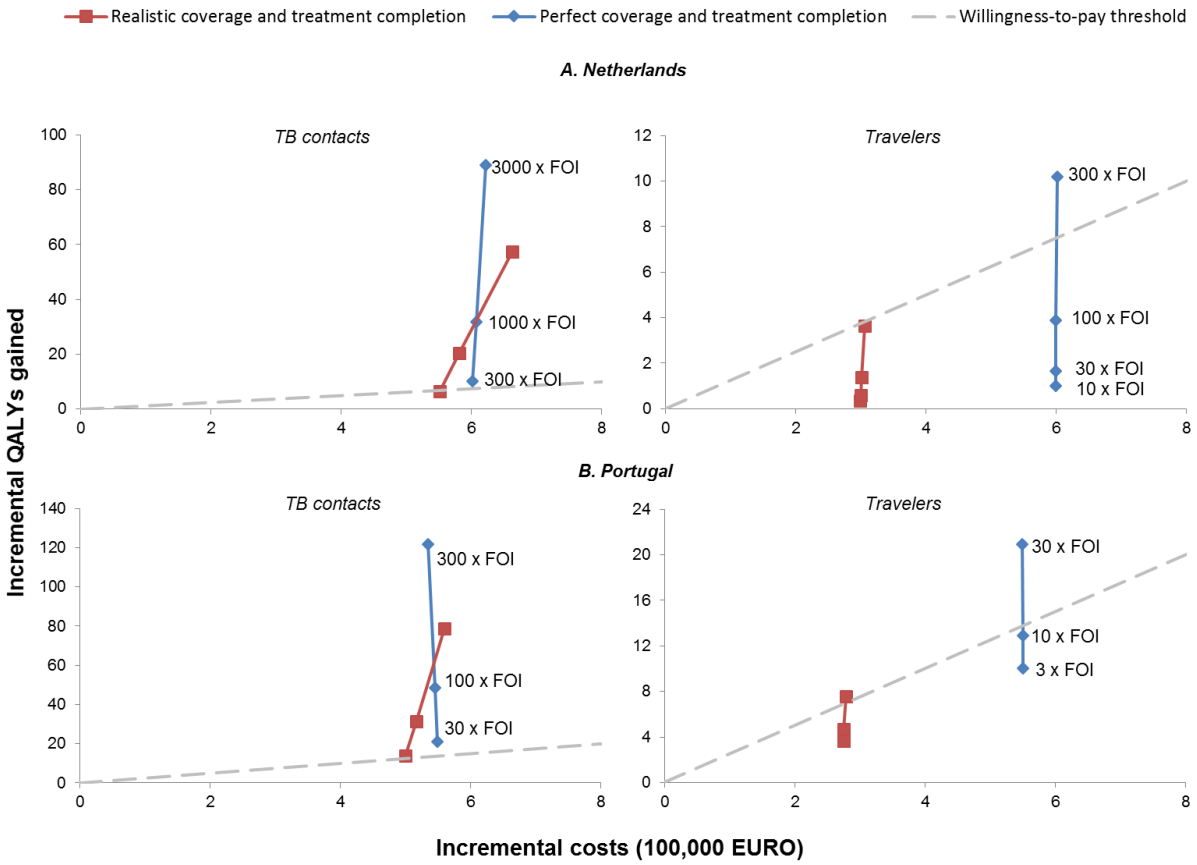
IGRA= Interferon gamma release assay, LTBI= latent tuberculosis infection, QALY= quality adjusted life years, TST= tuberculin skin test The left panels show the ICER compared with the current policy baseline of CXR in the Netherlands and the Czech Republic, TST followed by CXR to detect active TB in Spain, and nothing in Portugal. The right panels show the ICER compared with no screening. The horizontal axes from left to right represent different cohorts of migrants, with increasing levels of endemicity in the country of origin. Results are based on a cohort of 10 000 people, followed up over 20 years. Current average = average TB incidence in country of origin of all migrants entering the Netherlands, the Czech Republic, Portugal, and Spain respectively. Willingness-to-pay thresholds: 80 000 EUR /QALY in the Netherlands; 35 000 EUR/QALY in Czech Republic; 40 000 EUR /QALY in Portugal; and 50 000 EUR /QALY in Spain.

Figure 9. Incremental costs and effects of LTBI screening in a cohort of healthcare workers in the Netherlands and Portugal



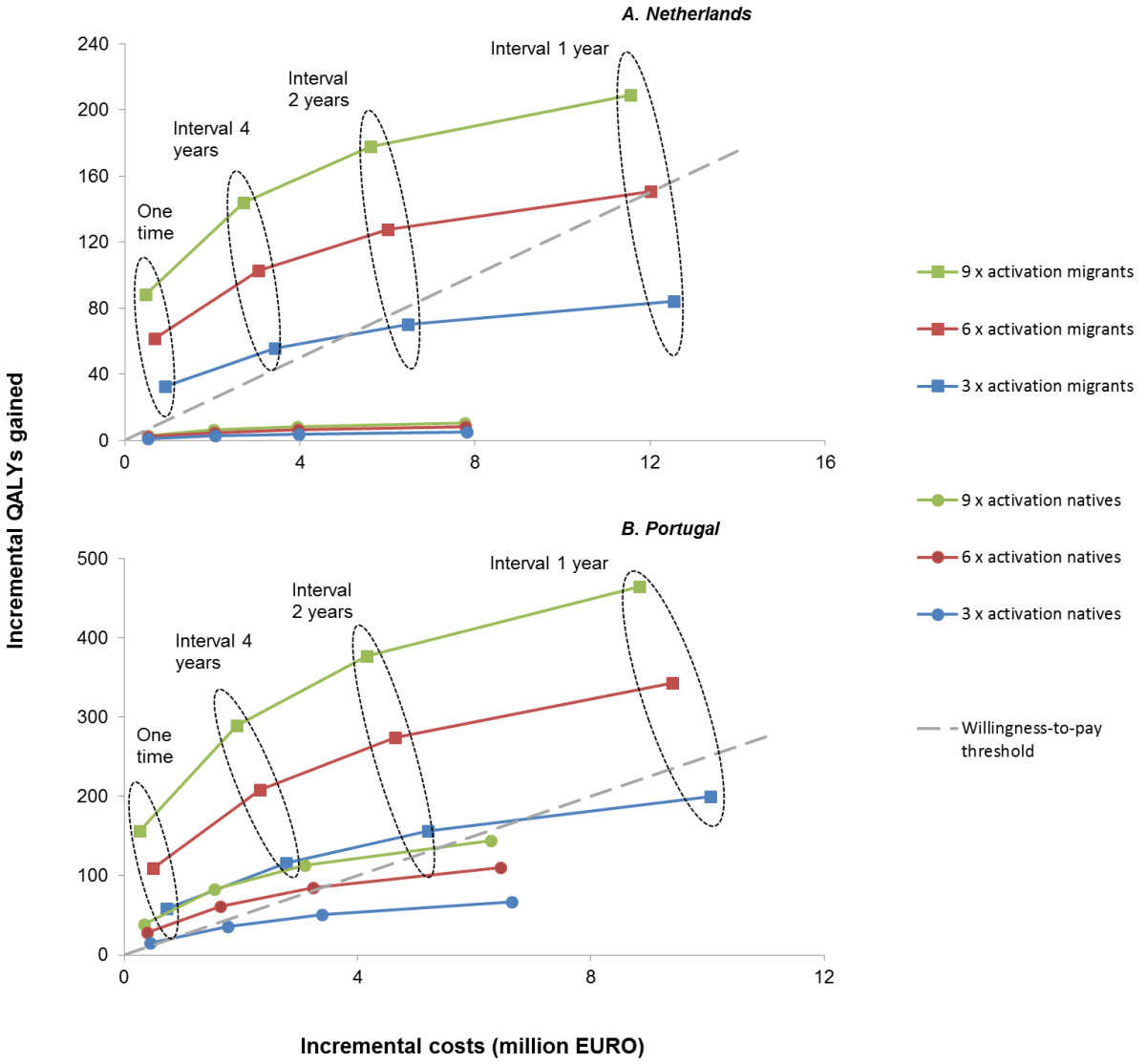
FOI= force of infection, QALY= quality adjusted life year, WTP= willingness-to-pay.
The healthcare worker cohort was generated as a cohort of low-risk natives that is subject to a higher force-of-infection compared with other low-risk natives. The colours represent different FOI levels, and the order of the points from left to right represent decreasing screening intervals. The dashed grey line represents the willingness-to-pay thresholds; points above that line indicate cost-effective strategies, points below the line are not cost-effective. Results are based on a cohort of 10 000 people, followed-up over 20 years. See Table A2.2 for more details. Willingness-to-pay the Netherlands = 80 000 EUR /QALY; willingness-to-pay Portugal = 40 000 EUR /QALY.

Figure 10. Incremental costs and effects of LTBI control in TB contacts and travellers in the Netherlands and Portugal, for different force of infection



FOI= force of infection, QALY= quality adjusted life year, TB= tuberculosis
Colours distinguish between different scenarios of coverage and treatment uptake. Realistic coverage and uptake represents 90% coverage, 70% LTBI treatment completion and 90% TB treatment completion for TB contacts, and 50%, 70%, and 90% respectively for travellers. Perfect coverage and uptake represents 100% coverage and treatment completion. The points on each line represent incrementally increased FOIs compared with the FOI in low-risk natives in the Netherlands and Portugal. Note that a FOI of 200 times that in the Netherlands or 20 times in Portugal is comparable with that in high-endemic countries with a TB incidence of 300 per 100 000. The dashed grey line represents the willingness-to-pay threshold of 2 x the per capita GDP (80 000 EUR for the Netherlands, 40 000 EUR for Portugal); points above that line indicate cost-effective strategies, points below the line are not cost-effective. Results are based on a cohort of 10 000 people, followed-up over 20 years. See Table A2.3 for more details.

Figure 11. Incremental costs and effects of LTBI screening among immunocompromised patients for different activation assumptions and stratified by migrant status in the Netherlands and Portugal



QALY= quality adjusted life year
The colours represent alternative assumptions regarding higher activation rates due to the underlying morbidity, while the lines indicate incrementally decreasing screening intervals. Squares represent migrant patients, dots represent native patients. The dashed grey line represents the willingness-to-pay threshold of 2 x the per capita GDP in the Netherlands and Portugal; points above that line indicate cost-effective strategies, points below the line are not cost-effective. Results are based on a cohort of 10 000 people, followed-up over 20 years. See Table A2.4 for more details.

3.3 Sensitivity analyses

The results from the country comparison show that, above all else, these results are sensitive to assumptions made regarding the sizes and interactions between the population groups in the transmission model. For instance, the Netherlands has the largest migrant population of the four countries, and this is reflected in the cost-effectiveness analyses, as migrant screening at entry is substantially more expensive, and results in more health gains in the Netherlands compared with other countries. In addition, the relative contribution of the PWID/homeless group to the prison population in each country determines the effectiveness of screening of prisoners at incarceration. In the Czech Republic, where the proportion of prisoners coming from the PWID/homeless people group is highest, the largest effects of screening can be seen in terms of QALY gains, while screening prisoners in Spain has very limited impact. Table 1 in Chapter 2.1 gives an overview of the relative sizes, PTB cases, and corresponding PTB incidence in the model for the four countries, while Table 2 in Chapter 2.1 shows the total number of PTB cases for natives and migrants by age group.

It is important to note that, even though the sizes and interactions of the different groups within the four countries differ substantially, LTBI screening is cost-effective for all groups and situations, and our results are therefore robust to reasonable regarding differences in sizes and interactions of the at-risk populations.

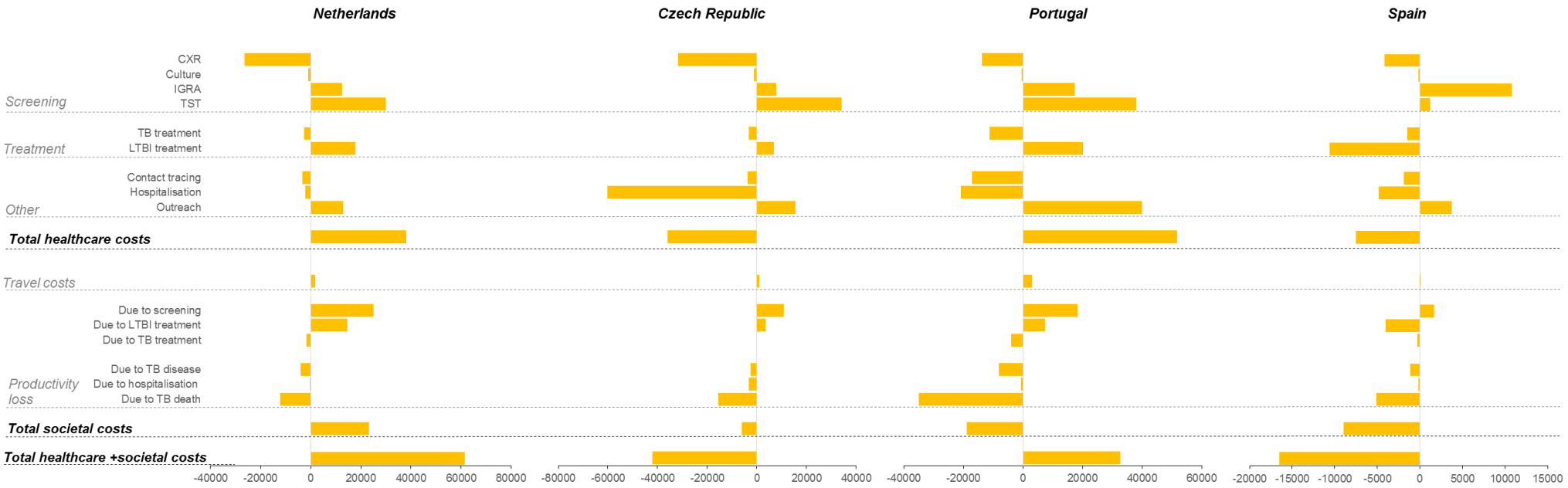
The explorations with alternative start and completion rates of LTBI treatment (Table 14), different coverages of PWID/homeless screening strategies (Figures 6 and 7), as well as varying FOI levels (Figures 9 and 10), can also be considered as sensitivity analyses. The analysis in Table 14 can further be seen as a crude attempt to relate a relatively short LTBI treatment regime (e.g. 3-month isoniazid plus rifampicin) to a possibly more effective one with higher costs involved. Treatment with only rifampicin for four months could be one of those alternative strategies, yet studies have shown that the uptake, compliance, and health outcome of 3-month isoniazid plus rifampicin and 4-month rifampicin alone are similar [24]. Therefore, the preference should simply be given to the cheapest option in this comparison, which is 3-month isoniazid plus rifampicin. The modelling report contains more sensitivity analyses regarding assumptions on durations of natural history compartments and the rates between them.

Figure 12 shows the breakdown of all incremental costs for the strategy of TST/IGRA for all risk groups, by country. The figure shows the importance of the incremental costs of each component in contributing to the overall healthcare and societal costs of the strategy. A negative value means that there are cost savings regarding that component compared with the baseline, while a positive value means that there is an investment need. For instance, there are cost savings for CXR, as the implemented TST/IGRA screening strategy replaces existing CXR strategies, so the number of CXRs performed, and hence the costs of those CXRs, reduces substantially. As expected, most investment needs from the healthcare perspective are required in TST testing and LTBI treatment, hence our results are sensitive to cost assumptions on TST tests and LTBI treatment. A 50% reduction in unit costs for TST and LTBI treatment would significantly reduce healthcare costs and thus the ICER, while similar changes in other prices are unlikely to have a large effect.

Figure 12 particularly shows that these results are sensitive to assumptions in the baseline. For instance, in the Czech Republic, all patients diagnosed with PTB are required to be hospitalised. Prevented cases of TB due to LTBI screening result in prevented hospitalisations. Thus, a disproportionally large amount of cost savings is observed in the Czech Republic. From the societal perspective, productivity loss due to attending screening and receiving treatment resulted in the highest investment costs, while cost savings were most profound in productivity loss due to TB mortality. Furthermore, in Spain, cost savings occur for LTBI treatment compared with the baseline. This can be explained by the fact that Spain already performs LTBI screening for prisoners at incarceration using TST. TST is far less specific compared with IGRA, and using TST/IGRA compared with TST alone substantially reduces the LTBI treatment need for prisoners.

Furthermore, it can also be judged from Figure 12 which aspects play a minimal role in the overall outcome. For example, travel costs are negligible compared with the productively loss that is associated with consultations for screening. This justifies the decision not to aim for very precise country-specific assessments of distances to health facilities, after these turned out to be difficult to obtain.

Figure 12. Incremental costs of all components for the strategy of tuberculosis skin test/interferon gamma release assay screening for all risk groups for a population of 10 000 people and over a 20-year period



CXR= chest X-ray, IGRA= interferon gamma release assay, LTBI= latent TB infection, TB= tuberculosis, TST= tuberculin skin test.
Costs are incremental to the country specific baseline (current policy).

4. Discussion

A dynamic transmission model has been developed for TB control in European settings, which simulates TB transmission in four key populations: the general (native) population, first generation migrants from TB endemic countries, prisoners, and PWID/homeless people populations. The model was used to estimate the cost-effectiveness of LTBI screening in four European countries: the Netherlands, the Czech Republic, Portugal, and Spain. For all countries, screening PWID/homeless people was the dominant strategy, and for most countries (the Netherlands, the Czech Republic, and Spain) this was done in combination with screening the other risk groups. In addition, we found that LTBI screening for migrants at entry was dominated by all other strategies in countries with relatively low in-migration rates (the Czech Republic and Portugal), while it was comparable with the PWID/homeless group in countries with high immigration rates (the Netherlands and Spain). From the healthcare perspective, using TST followed by IGRA was the most cost-effective screening strategy in all countries. From the societal perspective, screening with TST followed by IGRA or IGRA alone were the most cost-effective strategies in all countries. Furthermore, LTBI screening for healthcare workers and travellers is only cost-effective when these populations are exposed to extremely (perhaps unrealistically) high transmission risks. In addditon, LTBI screening for immunocompromised patients only seems cost-effective for migrants, especially for a one-time screening. Finally, LTBI screening for TB contacts seems to be highly cost-effective.

TST versus IGRA

Using TST followed by IGRA was the most cost-effective screening strategy from the healthcare perspective. This is similar to what was found in most studies in a review on cost-effectiveness of screening with TST versus IGRA versus 2-step [63]. In Canada, using Markov modelling and a cost-minimisation analysis, it was found that screening for LTBI, with TST or IGRA is cost-effective only if the risk of disease is high [64].

LTBI screening for migrants

LTBI screening for migrants at entry was found to be cost-effective. Other cost-effectiveness studies use a wide variety of methodologies giving a variety of results therefore making it difficult to compare [65,66]. Remarkably, only a few used QALYs [67]. One systematic review reported that diagnosing LTBI that progresses to active TB with TST (≥5mm) appears to be cost-effective in recent arrivals [68]. In contrast, a second systematic review concluded that screening adult immigrants with an IGRA appears to be moderately cost-effective [65]. After these reviews, three more recent studies found the following: in Belgium, screening migrants and asylum seekers at entry is less cost-effective compared with doing contact investigation and screening in prison [69]. In Norway, the cost-effectiveness of screening migrants for LTBI was higher than screening them for PTB [70]. A study in the UK found that screening migrants in language classes was cost-effective, and that the cost per case averted increased with higher TB incidence in country of origin [71], confirming our results from the cohort based analysis that screening migrants with a higher incidence in the country of origin is more cost-effective.

LTBI screening for prisoners and PWID/homeless people groups

The most important critical assumptions in the model that have an effect on the predicted impact and cost effectiveness of LTBI screening, are the assumptions on the size, interactions, and TB incidence in the various subgroups of the model. When quantifying the model, the data on size of risk groups and TB cases among those risk groups was reproduced. However, a one-on-one translation between the model and the data may not necessarily be correct, especially for the PWID/homeless people group. As these are often hard-to-reach populations which may require specific approaches, it is difficult to say whether the data used accurately describes the group of interest in the model, and the cost of reaching such groups ensuring compliance to screening procedures and treatment are highly variable and vary by setting. Therefore, results should be interpreted with caution and pilots of screening of PWID/homeless groups should be done before countrywide implementation. Nevertheless, it is important to note that, even with big differences in the size of the PWID/homeless people group between countries, LTBI screening for this group was cost-effective in all countries, suggesting that the model's predictions are relatively robust to reasonable alternative assumptions about size and interactions of the risk groups. It might be more cost-effective to limit screening of prisoners and the PWID/homeless group to outbreak situations, when screening would actually be expanded contact investigation.

LTBI screening for contacts, healthcare workers and travellers

Our findings on LTBI screening for contacts are in agreement with earlier models which show this approach is cost-effective, since exposure and the risk of breakdown shortly after infection is high[63]. Only a few studies have reviewed cost-effectiveness of screening healthcare workers and found it was not cost-effective [63,72]. Similarly, few studies were found on cost-effectiveness of screening travellers and reported high cost per averted case, but still considered this cost-effective [73,74].

LTBI screening for immunocompromised patients

LTBI screening and LTBI treatment for all people living with HIV and other immunocompromised patients was found to be cost-effective in only first-generation migrants from high-endemic countries (TB incidence of >50/100 000). In contrast, a systematic review concluded that screening people living with HIV with a TST appears to be highly cost-effective [65]. Another systematic review reported that using IGRA (negative result with QuantiFERON-TB Gold-InTube) followed by TST (≥5 mm) for diagnosing LTBI that progresses to active TB appears to be cost-effective in the immunocompromised population [68]. To a large extent, whether or not LTBI screening is cost-effective for immunocompromised patients depends on the prevalence of LTBI in the population. For instance, our results did show that LTBI control for immunocompromised, low-risk natives in Portugal, a country with substantially more TB than the Netherlands, is a cost-effective policy.

Current country baseline

Important aspects that determine the cost-effectiveness of LTBI screening are the current baseline and other TB control policies such as hospitalisation. For instance, in the Czech Republic, all TB patients are hospitalised. The consequence of this is that TB treatment is disproportionally expensive, which makes preventing TB through LTBI screening much more cost-effective than for other countries. In fact, most LTBI screening strategies in the Czech Republic even result in cost savings because of this effect. Furthermore, when comparing LTBI control with CXR in migrants from relatively low-endemic TB countries (TB incidence of 50/100 000), this strategy seems cost-effective. This can largely be explained by the fact that an expensive CXR is replaced by a relatively cheap LTBI test. When comparing with a baseline of no CXR, LTBI screening in low-endemic migrants is often not cost-effective.

Costing

The cost of screening might have been overestimated since the tariffs set by the Dutch Health Care Authority (NZA) were used. These tariffs are jointly agreed upon by primary healthcare facilities and insurance companies [48]. When screening is applied on a larger scale these costs might become less, even more when screening for LTBI would be combined with that for other diseases. Furthermore, unit costs derived from the Netherlands were translated into estimates for the other countries using PPP. This might not necessarily be correct, as costs are also determined by many other factors, such as healthcare policies and insurance schemes, which is another reason to interpret country-specific outcomes with caution.

Transmission versus cohort based model

Most of the CEAs, except for the special cohorts, were performed using a deterministic TB transmission model, and are population-based cost-effectiveness estimates. This approach has both strengths and weaknesses compared with cohort-based cost-effectiveness. By directly incorporating all transmission effects of a screening strategy, the accrued benefits of averted secondary infections could be accounted for. This approach is less conservative than other models [75]. However, because the model only simulates three age-groups, the number of life-years saved due to a prevented TB death could not be accurately calculated. Similarly, the costs and effects on transmission of targeting other at-risk populations (i.e. immunocompromised patients, long-term travellers, and healthcare workers) was not determined as these groups were not included in the deterministic model. They are however considered to contribute little to overall transmission. Yet, the cost-effectiveness of LTBI screening in long-term travellers and healthcare workers was determined through a cohort-based approach.

It was reassuring that the ICERs resulting from screening migrants at entry turned out to be of the same order of magnitude for the population-based (Tables 10–13, and Figures 4 and 5) and cohort-based approach (Figure 8 and Table A1.1) of our cost-effectiveness analysis. On the one hand the impact of screening in the cohort-based approach is underestimated as the reduced transmission and averted secondary cases are not considered. However, on the other hand, the cohort-based approach considers the effect of a single-entry screening for the full 20-year period, whereas the population-based approach concerns ongoing screening of incoming migrants, of which the screening investments of those entering shortly before the time horizon will not have lead to their full yield. Nevertheless, it was found that the ICER of comparable screening strategies in the cohort model were about 20% to 40% higher compared with the transmission model, suggesting that the latter is of lesser importance.

Declining TB epidemic

The analyses are based on a model that simulates a TB epidemic in a steady state (equilibrium), yet the TB epidemics in the countries modelled are currently declining. This is reflected in the distribution of PTB cases over the different age groups in natives in the model compared with the data. For all countries, the total number of TB cases among native people were accurately reproduced. However, the distribution across age groups was only reproduced for Portugal (see Table 2). In a declining epidemic, the distribution of TB is expected to shift towards more TB in older people, as latent TB infection that was acquired in a period of higher transmission activates. The largest discrepancies between the data can be seen in the Czech Republic, where the decline in TB is also the strongest. In Portugal, TB incidence is still at a relatively high level, and therefore the effects of the declining incidence on the age distribution in cases is not yet clearly visible. Hence the model did reproduce the age distribution in Portugal well. Because the number of cases were slightly overestimated in younger populations, the cost-effectiveness of LTBI screening might be slightly overestimated as well. Also, with a declining overall trend in TB incidence, there is relatively less TB burden and high costs for treatment and hospitalisation to avert in the future, which further reduces the cost-effectiveness. It is likely that the effects of the declining trends on the predictions will be limited because of the relatively short timeframe of the analyses (20 years). As a next step, it would be worthwhile to further develop the model into an age-structured variant, which would take into account historic trends and their consequences. However, obtaining proper information (and data) about the many different reasons for the country-specific decreases in TB incidence over the past decades, and translating this information into correct parameter values, will be challenging.

5. Conclusions

In conclusion, LTBI screening in general is a cost-effective policy option for the four European countries studied (the Netherlands, the Czech Republic, Portugal and Spain), and this is likely to be generalisable to other European countries with similar profiles. In the four countries considered in the study, LTBI screening for migrants at entry, LTBI screening for prisoners, and LTBI screening for the homeless and people who inject drugs is cost-effective, with a willingness-to-pay threshold of 2 x per capita GDP. LTBI screening for travellers and healthcare workers is only cost-effective when under extremely high levels of increased risks for transmission. LTBI screening for immunocompromised patients is only cost-effective for migrants and for low-risk native patients in European countries with a relatively high TB burden. Finally, LTBI screening for TB contacts is cost-effective. These conclusions depend to some extent on the choices made regarding the size and importance of the main risk groups, particularly the PWID/homeless people and prison populations, in the quantification of the models. However, the main findings regarding whether strategies are cost-effective are robust to reasonable changes in these assumptions.

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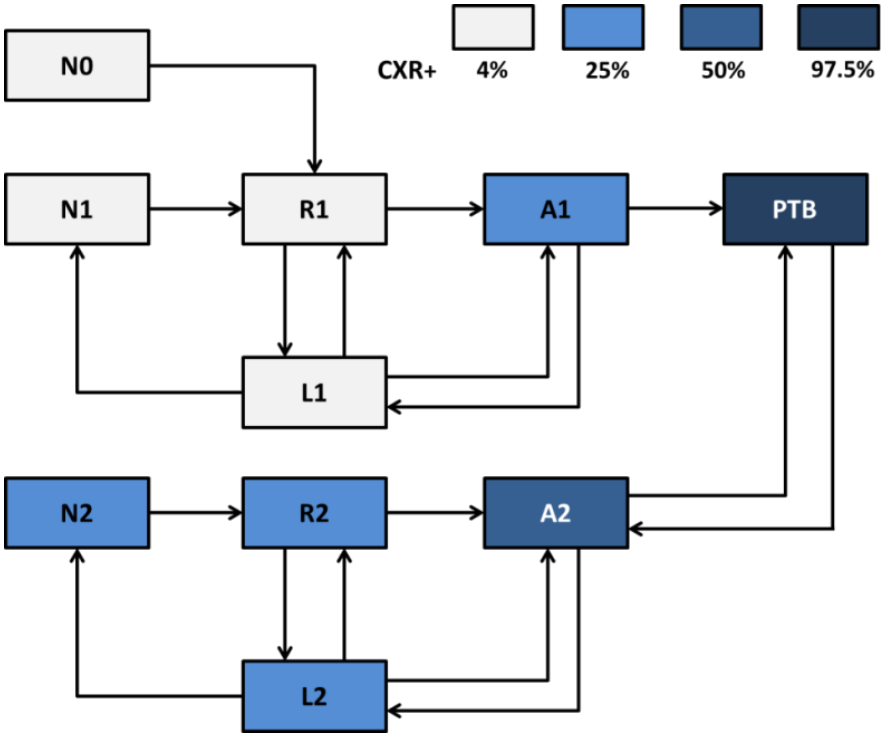
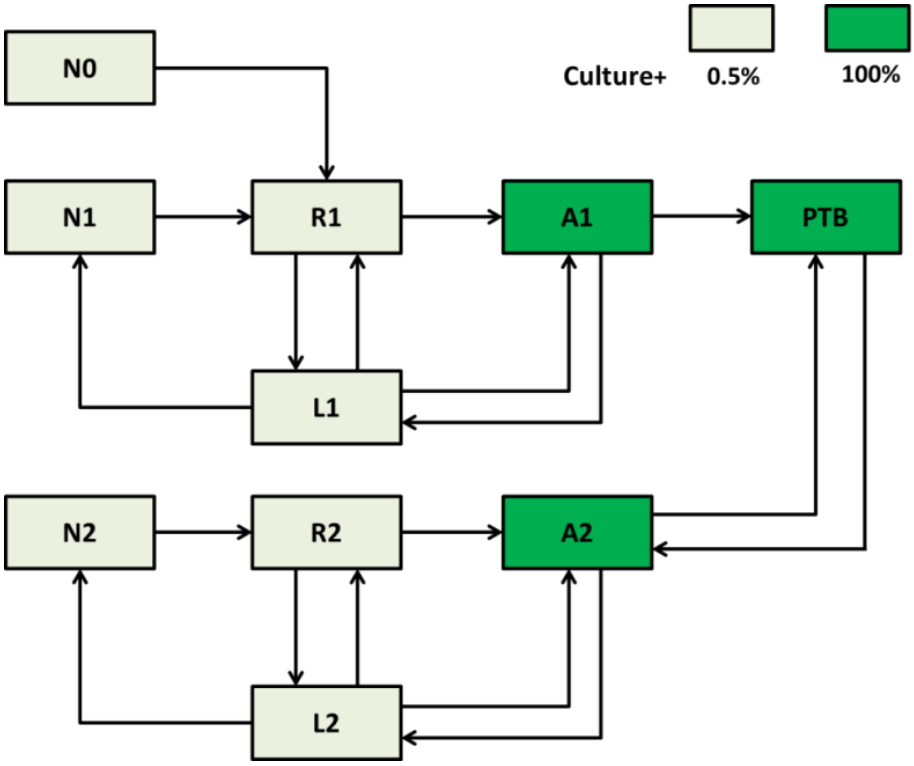
Appendix 1. Diagnostic characteristics

Figure A1.1. Schematic representation of the probability to be tested positive with chest X-ray for people with different history of tuberculosis infection or disease



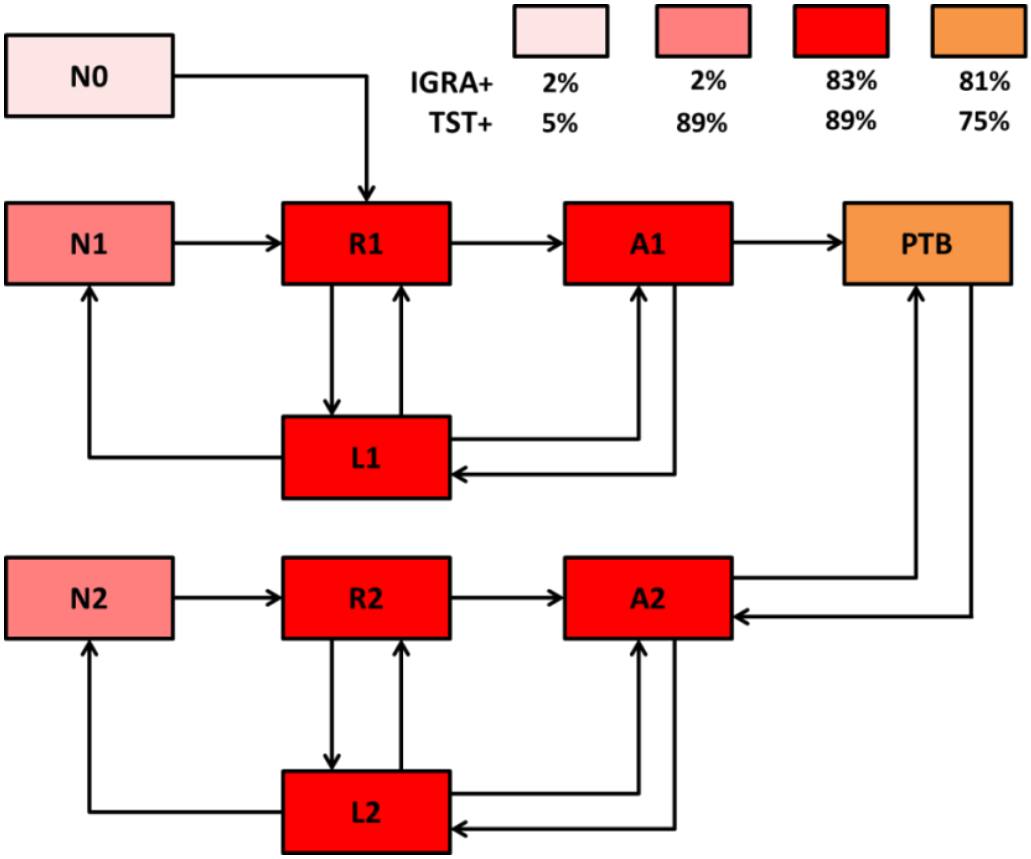
A= asymptomatic TB; CXR= chest X-ray; PTB= active pulmonary TB; N= not infected; R= recent latent tuberculosis infection; L= late (remote) latent tuberculosis infection.
The numbers reflect history with TB infection and disease as follows: 0= no experience; 1= having been infected; 2= having had TB disease. The structure of the model is equal to figure 1, apart from the severe pathology state, which is not shown here.

Figure A1.2. Schematic representation of the probability to test positive with culture for people with different history of tuberculosis infection or disease



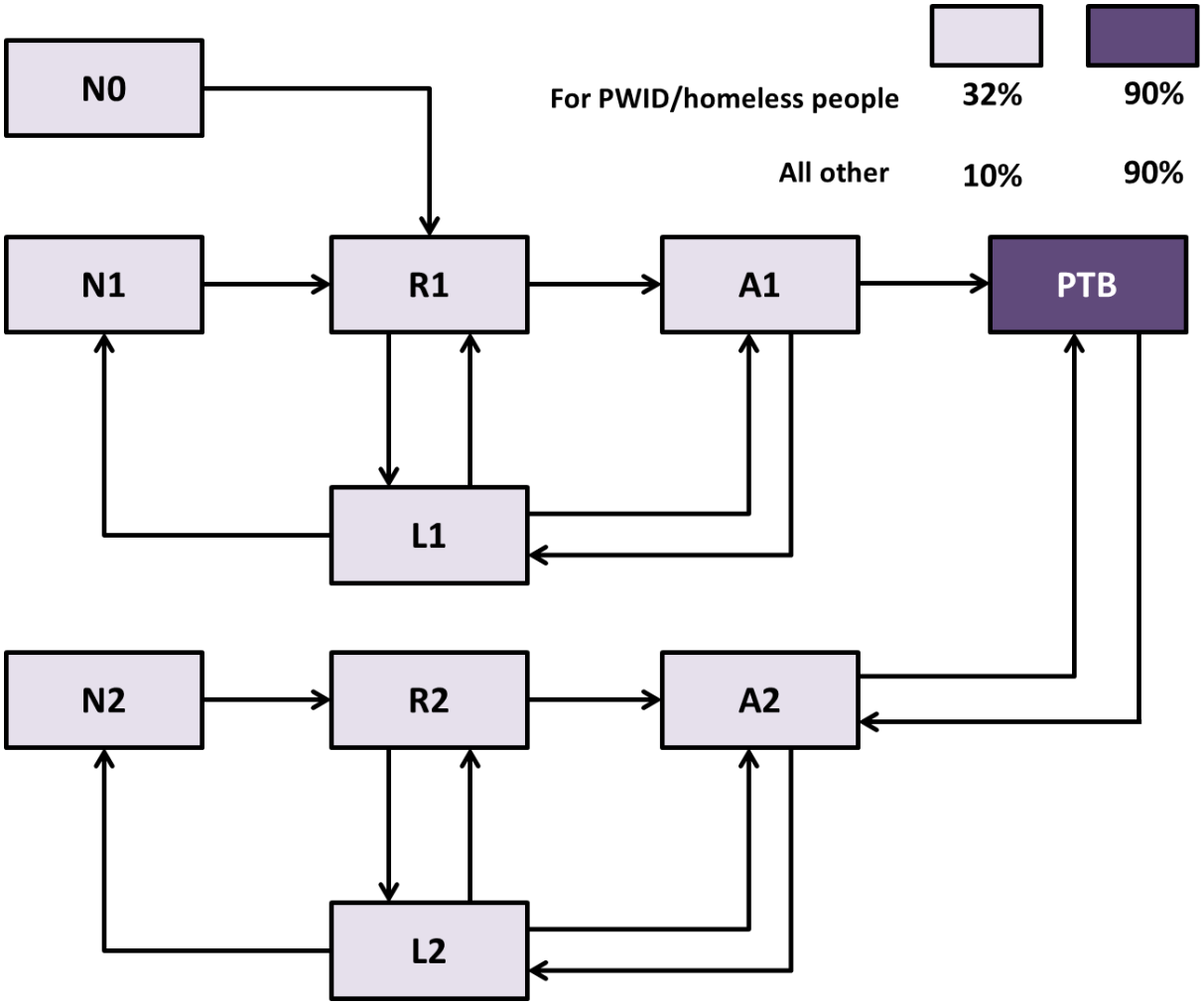
A= asymptomatic TB; PTB= active pulmonary TB; N= not infected; R= recent latent tuberculosis infection; L= late (remote) latent tuberculosis infection. The numbers reflect history with TB infection and disease as follows: 0: no experience; 1: having been infected; 2: having had TB disease. The structure of the model is equal to Figure 1, apart from the severe pathology state, which is not shown here.

Figure A1.3. Schematic representation of the probability to be tested positive with tuberculin skin test or interferon gamma release assay for people with different history of tuberculosis infection or disease and having had BCG vaccination



A= asymptomatic TB; IGRA= interferon gamma release assay; PTB= active pulmonary TB; N= not infected; R= recent latent tuberculosis infection; L= late (remote) latent tuberculosis infection; TST= tuberculin skin test.
The numbers reflect history with TB infection and disease as follows: 0: no experience; 1: having been infected; 2: having had TB disease. The structure of the model is equal to figure 1, apart from the severe pathology state, which is not shown here.

Figure A1.4 Schematic representation of the probability to report symptoms (suspicious for tuberculosis) for people with different history of tuberculosis infection or disease



A= asymptomatic TB; PTB= active pulmonary TB; N= not infected; R= recent latent tuberculosis infection; L= late (remote) latent tuberculosis infection. The numbers reflect history with TB infection and disease as follows: 0: no experience; 1: having been infected; 2: having had TB disease. The structure of the model is equal to figure 1, apart from the severe pathology state, which is not shown here. This is a standard part of any LTBI-control strategy, to increase the probability of detecting PTB cases, which are not always identified by IGRA and/or TST.

Appendix 2. Detailed results from cohort-based cost-effectiveness analyses

Table A2.1. Detailed costs, effects, and cost-effectiveness results for latent tuberculosis infection screening in migrant cohorts by endemicity of the country of origin

Netherlands								
TB incidence in country	**Average**	**177.6**	**50**	**100**	**150**	**200**	**250**	**300**
Total QALY loss								
No screening		68.18	19.29	38.52	57.66	76.66	95.41	113.77
Baseline screening		62.99	18.65	36.09	53.45	70.68	87.66	104.25
TST		44.04	16.32	27.22	38.08	48.84	59.46	69.84
IGRA		45.43	16.49	27.87	39.20	50.44	61.53	72.37
TST/IGRA		47.63	16.76	28.91	40.99	52.98	64.81	76.38
Total healthcare costs								
No screening		EUR 504 ,687	EUR 166 214	EUR 299 426	EUR 431 934	EUR 563 279	EUR 692 772	EUR 819 419
Baseline screening		EUR 1 004 047	EUR 683 593	EUR 809 709	EUR 935 168	EUR 1 059 512	EUR 1 182 ,057	EUR 1 301 809
TST		EUR 2 112 015	EUR 903 550	EUR 1 397 990	EUR 1 866 149	EUR 2 303 738	EUR 2 705 676	EUR 3 066 306
IGRA		EUR 1 870 527	EUR 1 080 426	EUR 1 391 340	EUR 1 700 752	EUR 2 007 107	EUR 2 308 050	EUR 2 600 142
TST/IGRA		EUR 1 704 776	EUR 730 335	EUR 1 118 200	EUR 1 498 615	EUR 1 869 206	EUR 2 226 707	EUR 2 566 761
ICER (with no screening)								
Baseline (CXR)		EUR 96 226	EUR 809 716	EUR 210 358	EUR 119 604	EUR 82 937	EUR 63 117	EUR 50 708
TST		EUR 66 571	EUR 247 944	EUR 97 265	EUR 73 227	EUR 62 562	EUR 55 986	EUR 51 152
IGRA		EUR 60 025	EUR 326 190	EUR 102 580	EUR 68 740	EUR 55 071	EUR 47 672	EUR 43 015
TST/IGRA		EUR 58 406	EUR 222 884	EUR 85 180	EUR 63 996	EUR 55 162	EUR 50 134	EUR 46 741
ICER (with baseline)								
TST		EUR 58,452	EUR 94 206	EUR 66 331	EUR 60 538	EUR 56 980	EUR 54 026	EUR 51 274
IGRA		EUR 49 330	EUR 183 401	EUR 70 769	EUR 53 722	EUR 46 831	EUR 43 090	EUR 40 720
TST/IGRA		EUR 45 627	EUR 24 704	EUR 42 926	EUR 45 219	EUR 45 768	EUR 45 729	EUR 45 387
Czech Republic								
TB incidence in country	**Average**	**106.7**	**50**	**100**	**150**	**200**	**250**	**300**
Total QALY loss								
No screening		58.09	27.19	54.45	81.60	108.54	135.13	161.17
Baseline screening		54.35	26.29	51.04	75.68	100.12	124.23	147.79
TST		40.50	22.98	38.44	53.83	69.09	84.15	98.88
IGRA		41.52	23.22	39.36	55.43	71.37	87.09	102.47
TST/IGRA		43.13	23.61	40.82	57.97	74.98	91.75	108.17
Total healthcare costs								
No screening		EUR 1 002805	EUR 513 104	EUR 945 093	EUR 1 374 845	EUR 1 800 854	EUR 2 220 866	EUR 2 631 624
Baseline screening		EUR 1 390 328	EUR 870 125	EUR 1 329 006	EUR 1 785 777	EUR 2 238 946	EUR 2 686 274	EUR 3 124 513
TST		EUR 1 607 332	EUR 945 911	EUR 1 530 410	EUR 2 096 093	EUR 2 639 372	EUR 3 155 793	EUR 3 640 055
IGRA		EUR 1 567 057	EUR 1 038 302	EUR 1 504 718	EUR 1 969 058	EUR 2 429 558	EUR 2 883 561	EUR 3 327 195
TST/IGRA		EUR 1 419 269	EUR 829 024	EUR 1 349 902	EUR 1 865 071	EUR 2372,235	EUR 2 868 125	EUR 3 348 228
ICER (with no screening)								
Baseline (CXR)		EUR 103 407	EUR 397 310	EUR 112 534	EUR 69 446	EUR 52 063	EUR 42 688	EUR 36 840
TST		EUR 34 366	EUR 102 659	EUR 36 552	EUR 25 972	EUR 21 257	EUR 18 338	EUR 16 189
IGRA		EUR 34 038	EUR 132 189	EUR 37 085	EUR 22 706	EUR 16 913	EUR 13 794	EUR 11 850
TST/IGRA		EUR 27 824	EUR 88 061	EUR 29 709	EUR 20 747	EUR 17 024	EUR 14 921	EUR 13 521
ICER (with baseline)								
TST		EUR 15 675	EUR 22 845	EUR 15 982	EUR 14 200	EUR 12 903	EUR 11 714	EUR 10 541
IGRA		EUR 13 775	EUR 54 701	EUR 15 045	EUR 9 050	EUR 6 628	EUR 5 312	EUR 4 472
TST/IGRA		EUR 2 579	EUR 15 285	EUR 2 046	EUR 4 477	EUR 5 300	EUR 5 600	EUR 5 646
Portugal								
TB incidence in country	**Average**	**178.2**	**50**	**100**	**150**	**200**	**250**	**300**
Total QALY loss								
No screening		95.74	53.58	70.09	86.53	102.86	118.99	134.81

	Baseline screening		95.74	53.58	70.09	86.53	102.86	118.99	134.81
	TST		74.85	51.02	60.35	69.65	78.87	87.97	96.90
	IGRA		76.02	51.16	60.90	70.59	80.20	89.70	99.01
	TST/IGRA		77.88	51.39	61.76	72.09	82.35	92.47	102.39
Total health care costs									
	No screening		EUR 442 875	EUR 257 600	EUR 330 192	EUR 402 425	EUR 474 076	EUR 544 813	EUR 614 156
	Baseline screening		EUR 442 875	EUR 257 600	EUR 330 192	EUR 402 425	EUR 474 076	EUR 544 813	EUR 614 156
	TST		EUR 1 615 688	EUR 796 692	EUR 1 130 922	EUR 1 446 862	EUR 1 741 568	EUR 2 011 577	EUR 2 253 057
	IGRA		EUR 1 460 723	EUR 936 679	EUR 1 142 019	EUR 1 346 394	EUR 1 548 776	EUR 1 747 609	EUR 1 940 620
	TST/IGRA		EUR 1 339,651	EUR 678 360	EUR 940 782	EUR 1 197 825	EUR 1 447 851	EUR 1 688 630	EUR 1 917 202
ICER (with no screening)									
	Baseline (No screening)		*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
	TST		EUR 56 136	EUR 210 337	EUR 82 254	EUR 61 862	EUR 52 840	EUR 47 294	EUR 43 224
	IGRA		EUR 51 592	EUR 280 562	EUR 88 309	EUR 59 207	EUR 47 445	EUR 41 070	EUR 37 047
	TST/IGRA		EUR 50 200	EUR 191 970	EUR 73 349	EUR 55 096	EUR 47 478	EUR 43 134	EUR 40 191
ICER (with baseline)									
	TST		EUR 56 136	EUR 210 337	EUR 82 254	EUR 61 862	EUR 52 840	EUR 47 294	EUR 43 224
	IGRA		EUR 51 592	EUR 280 562	EUR 88 309	EUR 59 207	EUR 47 445	EUR 41 070	EUR 37 047
	TST/IGRA		EUR 50 200	EUR 191 970	EUR 73 349	EUR 55 096	EUR 47 478	EUR 43 134	EUR 40 191
Spain									
TB incidence in country		**Average**	**93.5**	**50**	**100**	**150**	**200**	**250**	**300**
Total QALY loss									
	No screening		66.83	47.15	69.77	92.30	114.68	136.78	158.45
	Baseline screening		64.24	46.40	66.90	87.33	107.61	127.63	147.22
	TST		54.81	43.65	56.48	69.24	81.92	94.43	106.68
	IGRA		55.50	43.85	57.23	70.56	83.78	96.84	109.63
	TST/IGRA		56.59	44.17	58.44	72.65	86.76	100.69	114.33
Total health care costs									
	No screening		EUR 538 624	EUR 383 142	EUR 561 690	EUR 737 752	EUR 910 474	EUR 1 078 695	EUR 1 240 878
	Baseline screening		EUR 958 084	EUR 770 200	EUR 985 813	EUR 1 196 089	EUR 1 399 729	EUR 1 595 048	EUR 1 779 944
	TST		EUR 1 378 004	EUR 979 635	EUR 1 436 051	EUR 1 869 225	EUR 2 275 237	EUR 2 649 425	EUR 2 986 562
	IGRA		EUR 1 394 638	EUR 1 126 270	EUR 1 434 531	EUR 1 739 668	EUR 2 039 979	EUR 2 333 010	EUR 2 615 328
	TST/IGRA		EUR 1 165 112	EUR 840 335	EUR 1 213 125	EUR 1 577 919	EUR 1 932 339	EUR 2 273 178	EUR 2 596 239
ICER (with no screening)									
	Baseline (TST)		EUR 161 850	EUR 512 775	EUR 148 011	EUR 92 225	EUR 69 234	EUR 56 402	EUR 47 989
	TST		EUR 69 832	EUR 170 501	EUR 65 786	EUR 49 077	EUR 41 661	EUR 37 086	EUR 33719
	IGRA		EUR 75 518	EUR 225 243	EUR 69 639	EUR 46 084	EUR 36 564	EUR 31 406	EUR 28 153
	TST/IGRA		EUR 61 151	EUR 153 320	EUR 57 507	EUR 42 759	EUR 36 602	EUR 33 092	EUR 30 718
ICER (with baseline)									
	TST		EUR 44 538	EUR 76 335	EUR 43 186	EUR 37 220	EUR 34 077	EUR 31 759	EUR 29 765
	IGRA		EUR 49 928	EUR 139 942	EUR 46 412	EUR 32 411	EUR 26 874	EUR 23 972	EUR 22 225
	TST/IGRA		EUR 27 051	EUR 31 491	EUR 26 861	EUR 26 012	EUR 25 543	EUR 25 171	EUR 24 819

CXR=chest X-ray, ICER=Incremental cost effectiveness ratio, IGRA= interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test; TB= tuberculosis.

See Figure 8 for a graphical representation of part of the table.

Table A2.2. Detailed costs, effects, and cost-effectiveness results for latent tuberculosis infection screening in healthcare worker cohorts by screening interval and force of infection for the Netherlands and Portugal

Netherlands		3 x FOI		10 x FOI		30 x FOI	
FOI per month (x100)		**0.00543**		**0.01810**		**0.05431**	
		QALY loss	**HC costs (EUR)**	**QALY loss**	**HC costs (EUR)**	**QALY loss**	**HC costs (EUR)**
Strategy	*Interval*						
None	1	7.88	64 189	23.90	195 182	68.35	558 337
None	2	8.17	66 388	25.15	204 711	72.20	587 563
None	4	8.42	68 367	26.20	212 865	75.21	610 889
TST	1	1.63	12 600 054	5.12	13 502 715	15.06	15 991 373
TST	2	3.28	6 444 825	10.71	6 976 800	31.82	8 446 217
TST	4	4.86	3 374 508	15.99	3 735 404	47.46	4 734 156
IGRA	1	1.78	15 725 748	5.60	15 872 357	16.48	16 289 646
IGRA	2	3.44	8 054 109	11.22	8 226 826	33.30	8 716 891
IGRA	4	5.00	4 221 897	16.39	4 415 437	48.59	4 961 552
TST/IGRA	1	2.05	8 824 864	6.47	9 143 978	19.04	10 036 173
TST/IGRA	2	3.72	4 543 538	12.10	4 808 656	35.87	5 552 445
TST/IGRA	4	5.23	2 405 051	17.08	2 649 130	50.53	3 332 985
Portugal		**3 x FOI**		**10 x FOI**		**30 x FOI**	
FOI per month (x100)		**0.05681**		**0.18938**		**0.56815**	
		QALY loss	**HC costs (EUR)**	**QALY loss**	**HC costs (EUR)**	**QALY loss**	**HC costs (EUR)**
Strategy	*Interval*						
None	1	100.92	489 212	285.74	1 386 542	692.55	3 347 070
None	2	104.57	505 611	299.79	1 448 919	724.01	3 483 041
None	4	107.59	519 500	308.54	1 488 418	726.62	3 490 521
TST	1	19.64	15 295 758	60.73	20 476 139	174.86	31 052 251
TST	2	41.12	8 011 136	132.27	11 135 836	379.80	17 700 776
TST	4	62.77	4 420 732	201.69	6 618 806	562.96	11 361 133
IGRA	1	21.41	12 232 400	66.37	13 294 267	190.68	16 211 373
IGRA	2	43.12	6 593 610	138.33	7 839 749	395.14	11 158 429
IGRA	4	64.42	3 795 515	205.98	5 176 982	570.47	8 666 507
TST/IGRA	1	24.70	8 386 247	76.79	10 487 665	219.78	15 478 131
TST/IGRA	2	46.69	4 649 173	149.07	6 446 322	422.12	10 826 525
TST/IGRA	4	67.29	2 794 757	213.47	4 466 457	583.79	8 461 275

FOI= force of infection, HC= health care; IGRA= interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test.
See figure 9 for a graphical representation.

Table A2.3. Detailed costs, effects, and cost-effectiveness results for latent tuberculosis infection screening in traveller and tuberculosis contact cohorts by screening interval, force of infection, and duration of exposure for the Netherlands and Portugal

Netherlands				
Perfect (100%, 100%, 100%)			**Incremental**	
FOI multiplier			QALYs	Costs (EUR)
10	**0.01810**			
None	3.67	EUR 29 547		
TST	2.48	EUR 854 664	1.19	825 117
IGRA	2.55	EUR 1 104 284	1.12	1 074 737
TST/IGRA	2.67	EUR 628 491	1.00	598 944
30	**0.05431**			
None	4.60	EUR 36 641		
TST	2.64	EUR 860 705	1.96	824 065
IGRA	2.77	EUR 1 110 559	1.83	1 073 919
TST/IGRA	2.96	EUR 635 749	1.64	599 108
100	**0.18103**			
None	7.84	EUR 61 408		
TST	3.22	EUR 881 800	4.62	820 391
IGRA	3.52	EUR 1 132 472	4.33	1 071 063
TST/IGRA	3.97	EUR 661 088	3.87	599 680
300	**0.54308**			
None	17.04	EUR 131 660		
TST	4.85	EUR 941 638	12.18	809 979
IGRA	5.64	EUR 1 194 629	11.39	1 062 969
TST/IGRA	6.86	EUR 732 966	10.18	601 306
1000	**1.81028**			
None	48.46	EUR 371 655		
TST	10.45	EUR 1 146 129	38.00	774 474
IGRA	12.92	EUR 1 407 031	35.53	1 035 377
TST/IGRA	16.71	EUR 978 557	31.74	606 903
3000	**5.43083**			
None	131.95	EUR 1 009 468		
TST	25.39	EUR 1 690 132	106.56	680 664
IGRA	32.32	EUR 1 971 978	99.63	962 511
TST/IGRA	42.95	EUR 1 631 585	89.01	622 117
Realistic for travel (50%, 70%, 90%)				
10	**0.01810**			
None	3.67	EUR 29 547		
TST	3.24	EUR 423 288	0.43	393 741
IGRA	3.27	EUR 560 159	0.40	530 612
TST/IGRA	3.31	EUR 328 669	0.36	299 122
30	**0.05431**			
None	4.60	EUR 36 641		
TST	3.90	EUR 430 376	0.70	393 735
IGRA	3.94	EUR 567 317	0.66	530 677
TST/IGRA	4.01	EUR 336 261	0.59	299 620
100	**0.18103**			
None	7.84	EUR 61 408		
TST	6.18	EUR 455 122	1.66	393 713
IGRA	6.29	EUR 592 311	1.55	530 903
TST/IGRA	6.45	EUR 362 768	1.39	301 359
300	**0.54308**			
None	17.04	EUR 131 660		
TST	12.67	EUR 525 312	4.37	393 652
IGRA	12.95	EUR 663 207	4.09	531 547
TST/IGRA	13.38	EUR 437 953	3.66	306 293

Netherlands				
Realistic for contacts (90%, 70%, 90%)				
300	**0.54308**			
None	17.04	EUR 131 660		
TST	9.18	EUR 840 234	7.86	708 574
IGRA	9.68	EUR 1 088 444	7.36	956 784
TST/IGRA	10.46	EUR 682 988	6.58	551 328
1000	**1.81028**			
None	48.46	EUR 371 655		
TST	23.94	EUR 1 079 884	24.52	708 230
IGRA	25.52	EUR 1 332 420	22.94	960 765
TST/IGRA	27.94	EUR 953 335	20.51	581 681
3000	**5.43083**			
None	131.95	EUR 1 009 468		
TST	63.20	EUR 1 717 010	68.75	707 542
IGRA	67.62	EUR 1 980 989	64.33	971 521
TST/IGRA	74.43	EUR 1 671 909	57.52	662 441

Portugal				
Perfect (100%, 100%, 100%)			**Incremental**	
FOI multiplier			QALYs	Costs (EUR)
1	**0.01894**			
None	42.67	EUR 205 626		
TST	31.80	EUR 1 025 312	10.87	819 687
IGRA	32.44	EUR 1 059 406	10.23	853 781
TST/IGRA	33.46	EUR 756 634	9.21	551 009
3	**0.05681**			
None	43.86	EUR 211 010		
TST	32.01	EUR 1 029 484	11.85	818 475
IGRA	32.72	EUR 1 063 943	11.14	852 934
TST/IGRA	33.83	EUR 761 895	10.03	550 885
10	**0.18938**			
None	48.02	EUR 229 807		
TST	32.75	EUR 1 044 049	15.27	814 243
IGRA	33.68	EUR 1 079 784	14.34	849 978
TST/IGRA	35.14	EUR 780 260	12.88	550 454
30	**0.56815**			
None	59.80	EUR 283 106		
TST	34.85	EUR 1 085 353	24.95	802 247
IGRA	36.41	EUR 1 124 705	23.39	841 599
TST/IGRA	38.83	EUR 832 339	20.97	549 233
100	**1.89383**			
None	100.01	465 008		
TST	42.03	EUR 1 226 361	57.98	761 353
IGRA	45.73	EUR 1 278 048	54.27	813 040
TST/IGRA	51.45	EUR 1 010 097	48.56	545 089
300	**5.68150**			
None	206.55	EUR 947 002		
TST	61.14	EUR 1 600 369	145.42	653 367
IGRA	70.52	EUR 1 684 664	136.04	737 662
TST/IGRA	84.94	EUR 1 481 298	121.61	534 296
Realistic for travel (50%, 70%, 90%)				
1	**0.01894**			
None	42.67	EUR 205 626		

Portugal				
TST	38.71	EUR 591 317	3.96	385 691
IGRA	38.94	EUR 627 077	3.73	421 452
TST/IGRA	39.30	EUR 479 881	3.37	274 255
3	**0.05681**			
None	43.86	EUR 211 010		
TST	39.55	EUR 596 518	4.31	385 509
IGRA	39.80	EUR 632 414	4.06	421 404
TST/IGRA	40.20	EUR 485 534	3.67	274 525
10	**0.18938**			
None	48.02	EUR 229 807		
TST	42.48	EUR 614 677	5.54	384 870
IGRA	42.81	EUR 651 046	5.21	421 239
TST/IGRA	43.33	EUR 505 272	4.69	275 465
30	**0.56815**			
None	59.80	EUR 283 106		
TST	50.79	EUR 666 168	9.01	383 062
IGRA	51.34	EUR 703 878	8.45	420 771
TST/IGRA	52.21	EUR 561 239	7.59	278 133
Realistic for contacts (90%, 70%, 90%)				
30	**0.56815**			
None	59.80	EUR 283 106		
TST	43.59	EUR 972 618	16.21	689 511
IGRA	44.58	EUR 1 040 495	15.22	757 388
TST/IGRA	46.13	EUR 783 745	13.67	500 639
100	**1.89383**			
None	100.01	EUR 465 008		
TST	62.48	EUR 1 143 426	37.53	678 418
IGRA	64.84	EUR 1 219 533	35.16	754 526
TST/IGRA	68.50	EUR 982 033	31.50	517 026
300	**5.68150**			
None	206.55	EUR 947 002		
TST	112.56	EUR 1 596 156	93.99	649 154
IGRA	118.56	EUR 1 694 024	87.99	747 023
TST/IGRA	127.80	EUR 1 507 456	78.75	560 454

FOI= force of infection, IGRA= interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test. The percentages in the headings reflect coverage and proportions successful LTBI treatment and TB treatment. See Figure 10 for a graphical representation.

Table A2.4. Detailed costs, effects, and cost-effectiveness results for LTBI screening cohorts of immunocompromised patients by screening interval and activation multiplier for natives and migrants in the Netherlands

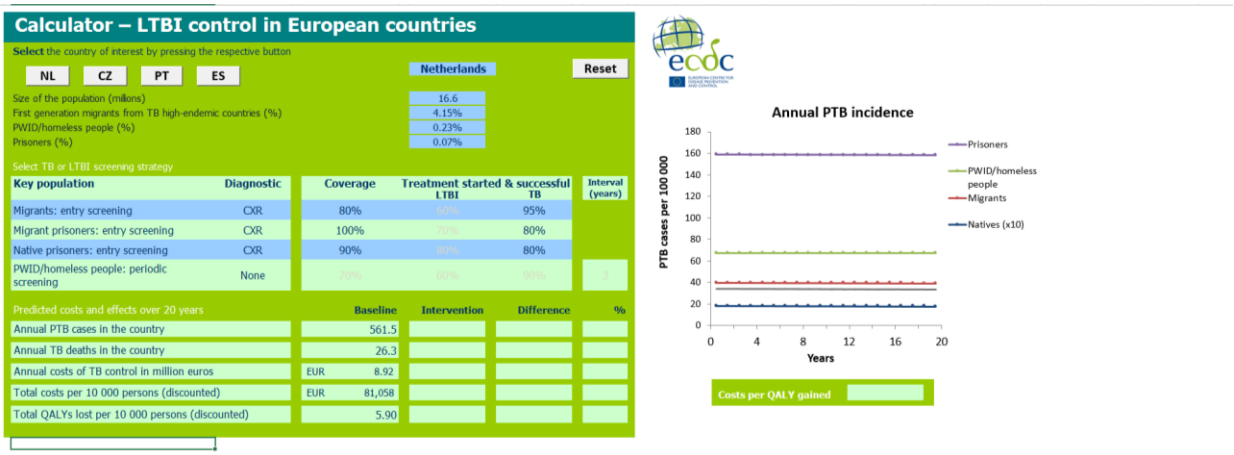
Netherlands	Interval of 1 year		Interval of 2 years		Interval of 4 years		One time	
	QALYs	Costs (EUR)	QALYs	Costs (EUR)	QALYs	Costs(EUR)	QALYs	Costs(EUR)
3 x activation natives	7.62	61 820	7.62	61 820	7.62	61 820	7.62	61 820
TST	2.31	10 573 605	3.52	5 398 707	4.60	2 815 559	6.18	763 641
IGRA	2.42	13 959 395	3.64	7 139 167	4.71	3 730 035	6.27	1 010 396
TST/IGRA	2.61	7 872 054	3.84	4 040 170	4.91	2 124 428	6.41	594 056
6 x activation natives	12.19	98 937	12.19	98 937	12.19	98 937	12.19	98 937
TST	3.54	10 585 231	5.36	5 414 582	7.00	2 835 640	9.59	791 641
IGRA	3.70	13 970 870	5.54	7 154 781	7.20	3 749 992	9.75	1 038 984
TST/IGRA	3.99	7 884 191	5.86	4 056 665	7.53	2 145 487	10.01	623 557
9 x activation natives	15.68	127 242	15.68	127 242	15.68	127 242	15.68	127 242
TST	4.38	10 593 035	6.60	5 425 254	8.66	2 849 471	12.05	811 854
IGRA	4.57	13 978 574	6.83	7 165 346	8.93	3 763 848	12.28	1 059 719
TST/IGRA	4.93	7 892 362	7.24	4 067 941	9.38	2 160 280	12.64	645 102
3 x activation migrants	111.19	896 613	111.19	896 613	111.19	896 613	111.19	896 613
TST	23.19	31 482 933	36.04	16 212 416	49.27	8 631 563	71.98	2 691 446
IGRA	24.46	14 920 346	37.79	8 127 622	51.53	4 725 723	74.51	1 928 422
TST/IGRA	26.84	13 440 363	40.92	7 369 853	55.38	4 325 020	78.39	1 811 188
6 x activation migrants	193.45	1 558 983	193.45	1 558 983	193.45	1 558 983	193.45	1 558 983
TST	36.53	31 607 351	57.33	16 394 406	79.62	8 882 127	119.55	3 079 660
IGRA	38.60	15 045 468	60.41	8 311 227	83.79	4 981 449	124.34	2 334 630
TST/IGRA	42.55	13 576 729	65.93	7 571 479	90.88	4 606 103	131.71	2 245 100
9 x activation migrants	263.69	2 122,681	263.69	2 122 681	263.69	2 122 681	263.69	2 122 681
TST	46.66	31 701 134	73.76	16 534 022	103.66	9 079 886	158.16	3 394 148
IGRA	49.41	15 140 290	78.02	8 453 454	109.58	5 185 032	165.02	2 665 456
TST/IGRA	54.66	13 681 077	85.68	7 729 852	119.60	4 832 595	175.57	2 601 090
Portugal	**Interval of 1 year**		**Interval of 2 years**		**Interval of 4 years**		**One time**	
	QALYs	Costs (EUR)	QALYs	Costs (EUR)	QALYs	Costs(EUR)	QALYs	Costs(EUR)
3 x activation natives	99.54	481 065	99.54	481 065	99.54	481 065	99.54	481 065
TST	28.53	11 433 351	44.93	5 952 507	59.79	3 241 490	81.20	1 123 403
IGRA	29.81	10 788 824	46.36	5 746 388	61.25	3 228 055	82.33	1 191 115
TST/IGRA	32.29	7 125 106	48.98	3 878 045	63.79	2 255 077	84.09	931 345
6 x activation natives	159.34	770 046	159.34	770 046	159.34	770 046	159.34	770 046
TST	43.60	11 521 314	68.27	6 074 513	91.02	3 397 716	126.04	1 342 966
IGRA	45.49	10 876 009	70.50	5 866 952	93.51	3 383 882	128.13	1 415 154
TST/IGRA	49.19	7 217 257	74.63	4 005 342	97.82	2 419 325	131.36	1 162 318
9 x activation natives	205.15	990 961	205.15	990 961	205.15	990 961	205.15	990 961
TST	53.77	11 580 246	84.00	6 156 465	112.56	3 505 255	158.47	1 501 707
IGRA	56.06	10 934 432	86.89	5 948 462	115.95	3 492 012	161.42	1 577 909
TST/IGRA	60.61	7 279 185	92.22	4 092 293	121.78	2 534 662	165.97	1 331 289
3 x activation migrants	282.43	1 360 567	282.43	1 360 567	282.43	1 360 567	282.43	1 360 567
TST	72.41	25 894 715	114.48	13 541 037	154.07	7 447 143	213.27	2 721 735
IGRA	75.83	11 723 762	118.62	6 729 341	158.73	4 231 946	217.60	2 135 111
TST/IGRA	82.45	11 416 757	126.19	6 566 231	166.76	4 134 986	224.31	2 092 343
6 x activation migrants	470.43	2 265 415	470.43	2 265,415	470.43	2 265 415	470.43	2 265 415
TST	111.59	26 123 059	176.55	13 864 598	239.53	7 873 002	340.10	3 341 066
IGRA	116.84	11 951 416	183.40	7 051 825	247.88	4 660 805	348.39	2 773 052
TST/IGRA	127.12	11 659 681	195.98	6 911 193	262.25	4 593 650	361.19	2 758 979
9 x activation migrants	623.26	2 998 780	623.26	2 998 780	623.26	2 998 780	623.26	2 998 780
TST	139.16	26 282 487	220.61	14 093 029	301.88	8 182 725	436.75	3 812 480
IGRA	145.77	12 110 793	229.78	7 281 487	313.58	4 975 682	448.68	3 261 544
TST/IGRA	158.82	11 830 863	246.63	7 160 169	333.62	4 935 114	467.08	3 273 796

IGRA= Interferon gamma release assay, QALY= quality adjusted life year, TST= tuberculin skin test .See figure 11 for a graphical representation.

Appendix 3. Calculator – LTBI control in European countries

A user-friendly tool has been developed, based on the transmission model, and inspired by the earlier developed calculator of TB among migrants (Erasmus MC for ECDC, 2008). It is called the ECDC Calculator - LTBI control in European countries. With this tool, users can tune certain key characteristics describing the particularities of the TB epidemiology and options with regards to LTBI screening and treatment in particular populations of a European country. Figure A4.1 gives a screen shot. This tool takes into account prevented secondary cases and interaction between population groups, which other tools do not since they are based on simple relative risks.

Figure A4.1. Screen shot of the first draft of a working user-friendly tool



The completed tool can be used to estimate annual PTB incidences over a 20 year period, and to predict the costs and effects of different LTBI control strategies

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