TECHNICAL REPORT

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Abbreviations

BCG	Bacillus Calmette–Guérin
CXR	Chest X-ray
EEA	European Economic Area
EPTB	Extrapulmonary tuberculosis
EU	European Union
FOI	Force of infection
HIV	Human immunodeficiency virus
IGRA	Interferon gamma release assay
KNCV	KNCV Tuberculosis Foundation
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
PWID	People who inject drugs
PTB	Pulmonary tuberculosis
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

Glossary

Active tuberculosis	A disease that is caused by *Mycobacterium tuberculosis* or other members of the *Mycobacterium tuberculosis* complex family in any part of the body and that is in an active state, characterised by signs or symptoms of disease [1,2].
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 [3].
Force of infection	Per capita rate at which susceptible people contract infection [4].
Immigrant	A person who moves to a country other than his/her usual residence for a period of at least a year so that the country of destination effectively becomes his/her country of usual residence [5].
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 [6].
Migrant	First-generation migrants (including refugees and asylum seekers) from middle and high TB-endemic countries, i.e. countries with TB incidence of >50/100 000. 'First generation' refers to migrants who were born abroad, irrespective of naturalisation status.
Tuberculosis	'Tuberculosis' refers to clinically, bacteriologically, histologically and/or radiologically active disease [3].

Executive summary

Background

Elimination of tuberculosis (TB) requires the management of latent tuberculosis infection (LTBI) in key populations. Thus, people with LTBI need to be diagnosed and treated with appropriate regimens. It is unknown how different screening and treatment strategies of key populations affect TB transmission and progress toward elimination.

Objective

The objective of this project was to estimate the potential of various LTBI screening and treatment strategies in reducing transmission and to assess their contribution in moving towards elimination of TB in Europe.

Methods

A novel, comprehensive, deterministic TB transmission model for four European Union countries (the Netherlands, the Czech Republic, Portugal and Spain) was developed. The selected countries were used as examples for other low-incidence countries/settings in order to pilot-test the model. This model accounts for transmission within and between the general population and different key population groups (i.e. migrants from TB high-endemic countries, homeless people, people who inject drugs, and prisoners). The TB natural history is characterised by two stages of LTBI (recent and remote), asymptomatic TB, and active pulmonary TB. Infected people can progress and regress between the different stages, depending on transition rates. The different stages correspond to different chances after a positive chest X-ray (CXR), tuberculin skin test (TST), interferon gamma release assays (IGRA), and culture. Transmission is governed by infection rates within and between population groups, as well as an external force-of-infection due to travel to endemic countries. The quantified model was used for four representative countries (the Netherlands, the Czech Republic, Portugal, and Spain) as a pilot to predict the impact of different strategies to screen for LTBI and provide preventive treatment to those testing positive. The model assumes equilibrium situations, both regarding the dynamics of population groups and transmission within and between these groups. The 4% annual decreasing trend in notified TB incidence observed in the Netherlands was used to assess the long-term impact of LTBI screening strategies.

Results

Outcomes are expressed as trends in pulmonary TB incidence and LTBI prevalence for the total population as well as for different population groups. Screening and treatment for LTBI in people who inject drugs (PWID) and homeless people usually results in the steepest decrease in pulmonary TB incidence, followed by screening prisoners or migrants from high-endemic countries at entry. With a combination of screening and treatment for LTBI in all three key population groups, the incidence of pulmonary tuberculosis (PTB) could be reduced by 15 to 45%, over a period of 20 years, depending on the country. In all countries analysed and for all strategies, the impact is slightly better for screening with TST than with IGRA, due to a slightly higher sensitivity of the test. These findings build upon very optimistic assumptions, including maximum coverage, no imported infections due to travel and migration, and applying an additional 4% annual decrease. According to the model, the elimination threshold of a TB incidence of <1/1 000 000 will only be achieved about 50 years after implementation of LTBI screening of at-risk groups for all countries studied. The predicted number of (averted) pulmonary TB cases does not change significantly when using reasonable alternative parameter values in the sensitivity analysis.

Conclusions

This is the first TB transmission model that includes various interacting risk and age groups in low-incidence settings. The findings obtained from the model indicate that the World Health Organization's TB elimination target cannot be achieved by 2050 using LTBI screening as the sole control strategy for the disease. This is largely due to the remaining presence of LTBI in the population, including the general population and migrants already residing in the country of interest. Neither the general population nor migrants are currently considered for LTBI screening since their infection may have been acquired a long time ago and has a low risk of progressing to active disease. LTBI screening shows more potential for people who inject drugs/homeless people and prisoners than for new migrants from high-endemic countries. A high coverage of screening and completion of treatment are important to further increase effectiveness of LTBI control. Better diagnostic tests and shorter LTBI treatment would be welcomed as well, but to ensure that the reservoir of LTBI eventually disappears from the population, dedicated screening and more time is needed.

1 Background

Introduction

About one fourth of the world population is infected with *Mycobacterium tuberculosis* and has so-called latent tuberculosis infection (LTBI) [7]. Most of those people never develop active disease, but about 10% do and then become an important source of ongoing transmission [8]. The control of LTBI is an important step towards tuberculosis (TB) elimination. This has been acknowledged in the End TB strategy adopted by the 67th World Health Assembly in May 2014 [9]. In many high-income countries, in addition to case detection and treatment, TB is controlled by identifying and offering preventive treatment to people who are latently infected with *M. tuberculosis* [10–14]. These are often contacts of TB patients, belong to underserved populations or have co-morbidities such as HIV. The World Health Organization (WHO) added in 2015 a conditional recommendation for systematic testing and treatment of LTBI in low TB burden countries for other key population groups [15]. These groups include migrants, PWID/ homeless people, and prisoners[1]. There is limited knowledge about the effects of screening and preventive therapy for different key population groups on TB transmission dynamics and possible elimination in low income countries, and modelling can help to assess this [13].

Many mathematical models have tried to assess the effect of treatment for LTBI and other TB control interventions on the TB epidemic [16-23]. Most of them were developed for low income, high-TB-incidence countries [17-19,22]. Only a few models assessed the effects of diagnosis and treatment for LTBI in low-TB- incidence countries, as was shown in a 2015 systematic review [24]. Simple models for Canada and Australia analysed LTBI treatment in a cohort of migrants, but did not take into account transmission and interaction with the general population [25,26]. A more sophisticated model for the USA considered these aspects and split LTBI into an early stage with high risk of progression to active disease and a late stage with low risk of progression [27]. All models concluded that treatment for LTBI for migrants would substantially contribute to reducing TB incidence and reaching TB elimination [25-27]. The models from the USA and Australia reported that LTBI treatment for migrants alone would not be enough to eliminate TB in low-incidence countries. None of the models took into account interactions with other key population groups and possible effects of screening and treating other key population groups.

In addition to the groups included in the cited modelling studies, prisoners are an important risk group contributing to the TB epidemic in Europe [28-30]. In addition, homeless people and people who inject drugs (PWID) are at increased risk for TB due to immunologic, socio-economic and access factors [31-33]. It is important to assess the contributions of interventions towards reducing transmission and disease elimination related to LTBI in all these groups.

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 [34]. 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 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). 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 [35]. The main components identified were: i) groups at risk, ii) diagnosis, iii) treatment and iv) programmatic control of LTBI. For these components, a scientific evidence base was collected (based on literature reviews). Subsequently, a new TB transmission model was constructed as a tool to assess the contribution of these components towards TB elimination. The present report describes the methodology and quantification of this TB transmission model.

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 the 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 targets: a 90% reduction of TB incidence and a 95% reduction of TB mortality by 2035 [9].

[1] The term 'key populations' covers migrants, prisoners, PWID and homeless people. The term is also used by WHO in the End TB strategy.

The objective of this technical report is to evaluate the contribution of certain LTBI control strategies on TB transmission and towards TB elimination in low-TB-incidence settings. Hence, a comprehensive deterministic TB transmission model was developed. This model contains different interrelated risk groups that are relevant for TB transmission, i.e. first-generation migrants from TB-endemic countries, PWID and homeless people, prisoners, and the general population. The model focusses only on active pulmonary TB because extrapulmonary TB (EPTB) is usually not contagious. Possible LTBI control strategies include different screening algorithms to detect LTBI cases among specific populations which will them receive LTBI treatment.

This mathematical model is also the basis of cost-effectiveness analyses to assess the economic effects of LTBI control strategies. The methodologies and results of the cost-effectiveness analyses are described in a separate report [36].

Outline of this report

Chapter 2 describes the methodology of the mathematical modelling. The deterministic transmission model developed in this report has also been used in a cost-effectiveness analysis described in a separate report [37].

Chapter 3 summarises the results on LTBI control interventions for the selected risk groups.

Chapter 4 discusses the main findings, strengths and limitations of the model whereas Chapter 5 presents the general conclusions of this report.

2 Methods

2.1 Model structure and quantification

A novel deterministic model for TB transmission was developed using available data from four European countries[2]: the Netherlands, the Czech Republic, Portugal, and Spain. The selected countries were used as examples for other low-incidence countries/settings in order to pilot-test the model. The model accounts for transmission within and between the general population and different key populations. Most model predictions were made for a 20-year period. However, a long-term prediction of 50 years was also included to assess to which extent the WHO elimination threshold of <1 per million may be reached.

The deterministic transmission model was developed in Microsoft Excel 2010. A one-month time step was deemed adequate to reproduce all dynamic processes, given the shortest average durations considered in the modelling, i.e. three months for the average prison stay and six months for the average duration of recent LTBI and asymptomatic TB (see below). For every month, all transitions regarding demography and movement between population groups, including screening at entry where applicable, were carried out first, followed by all transitions regarding progression and regression of LTBI and TB, including treatment after self-reporting.

The model development and fitting procedures covered the following steps:

- Modelling the natural history of TB infection and disease.
- Fitting transition rates concerning progression and regression of PTB and asymptomatic TB.
- Fitting transition rates concerning activation of recent LTBI and reactivation of remote LTBI.
- Assumptions about diagnostic testing.
- Adapting the model to data based on entry screening of migrants.
- Size of, and interaction between, key population groups in European countries.
- Modelling TB transmission in European countries.

Appendices 1 to 7 provide background information of these successive steps. The general modelling plans and a first version programmed in the R software environment were reviewed by two external modelling experts.

Parameters were quantified based on information found in the following sources:

- Literature included in the scientific evidence base that was collected from literature reviews relevant for the LTBI guidance.
- Critical country and risk group specific data about TB epidemiology were obtained from ECDC/WHO [38].
- Data for 2005–2014 from The European Surveillance System (TESSy), provided by the Netherlands, Portugal, Spain and the Czech Republic and released by ECDC.
- Additional data were requested from TB experts in the four countries through a questionnaire and regular contact with country representatives who answered additional questions and collected the data for their country (Appendix 8). These data also included a listing of major TB-endemic countries where migrants/asylum seekers have come from, the annual number of TB cases among migrants/asylum seekers from the listed countries, estimated number of TB cases. Also included were the numbers of homeless people and PWID, the number of prisoners per inhabitants (last 10 years), the annual number of new TB cases among prisoners (on admission to prison and/or during stay in prison). Requested national data could not always be provided, and some assumptions had to be made.
- Additional specific literature (database searches such as PubMed).
- Discussion with TB experts, modelling experts and (former) team members[3].

2.1.1 Modelling natural history of TB infection and disease

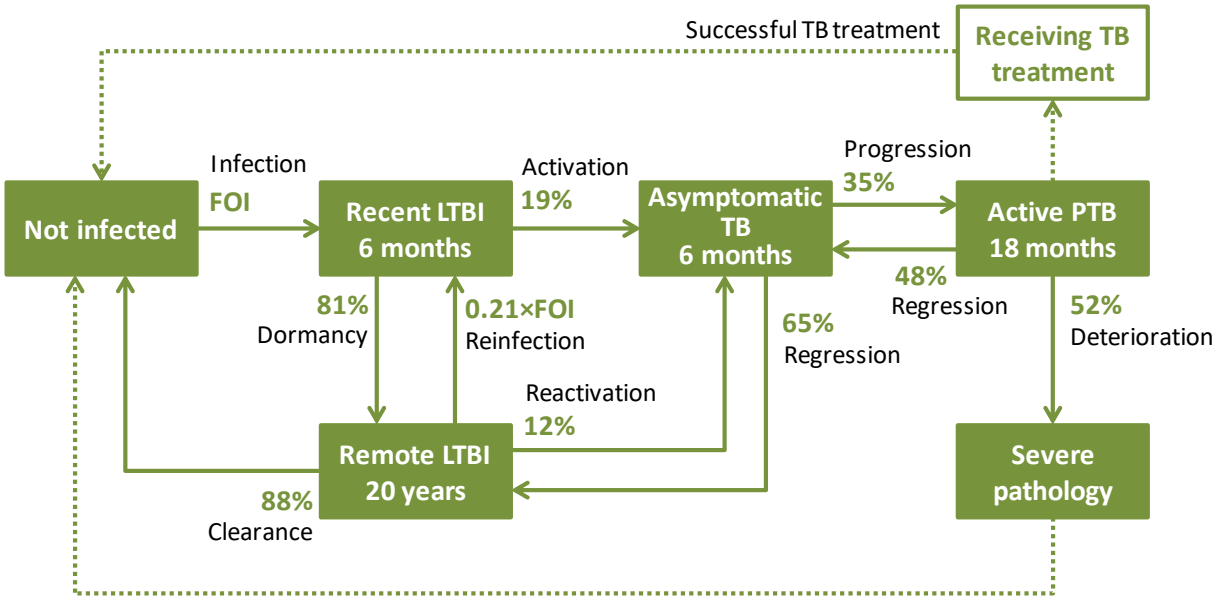
People in the model can move in and out of several compartments (mathematically defined compartments related to health stages) that represent the natural history of TB infection: not infected (i.e. susceptible), recent LTBI, remote LTBI, asymptomatic TB (i.e. infectious TB with mild or no symptoms), active pulmonary TB (PTB), and severe pathology (i.e. hospitalised, sometimes leading to death due to TB) (Figure 1). People in the 'not infected' category have never been in contact with *M. tuberculosis* before or completely cleared a previous infection. Extrapulmonary TB (EPTB) is not included in the model because it does not play a significant role in transmission. The structure of the natural history model is partly based on the outcome of different diagnostic tests. In particular, the decision to include a compartment for asymptomatic TB is based on the fact that several people had a positive

[2] EU/EEA Member States and candidate countries are referred to as 'Europe' or 'European countries'.

[3] Martien Borgdorff, Rui Cai, Frank Cobelens, Luc Coffeng, Connie Erkens, Jan Hontelez, Frank van Leth, Christiaan Mulder, Nico Nagelkerke, Jan Hendrik Richardus, Tom Sumner, Joost Vanhommerig, Jesse Verdier, Suzanne Verver, Sake de Vlas, Marije Vonk Noordegraaf, and Gerard de Vries (in alphabetical order.)

chest X-ray before developing active PTB. Furthermore, the process of clearance of remote LTBI is assumed to be linked to the test results (IGRA versus TST): after clearance, TST results will be positive but IGRA results will be negative, reflecting the process of waning.

Figure 1. Schematic overview of the model for the natural history of tuberculosis infection and disease



FOI = force of infection, LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis, TB = tuberculosis
The duration given in the graph for each compartment indicates the assumed average duration that an individual spends in a certain health stage. The percentages indicate the proportion of cases that move to another health stage when leaving a compartment. People with remote LTBI can get reinfected but due to some degree of immunity, the rate of reinfection is significantly below the rate for uninfected susceptible people (79% lower compared to those infected for the first time). Durations and proportions given for PTB are based on the assumption that no treatment will take place (see Table A2-3 in Appendix 2 for values in the presence of treatment). Severe pathology is included as an absorbing state (cohort model) or as a flow through which people immediately return to 'uninfected' (transmission model).
Similarly, cases with PTB return to uninfected after self-reporting and successful TB treatment. Hospitalisation and death due to TB are proportionally related to the flow through severe pathology (only used for the cost-effectiveness analyses).

Appendix 1 presents the underlying mathematical formulas (differential equations) for modelling the natural history of TB, including a differentiation of the compartments to reflect history of previous TB as follows: (0) naive, (1) having had LTBI, or (2) having had PTB. This differentiation is relevant for modelling the outcomes of diagnostic testing. In particular, chest X-ray may identify past PTB, and TST detects cleared LTBI. Infected people can progress and regress between the different stages in accordance with transition rates (or corresponding durations and probabilities, Figure 1) which are a result of assumptions and/or fitting (further explained in Sections 2.1.2 and 2.1.3, with details in Appendices 2 and 3). The duration (sojourn time) in a compartment is the reciprocal of the sum of the rates of progression or regression from that same compartment.

In the model, people are infected by a force of infection (FOI, i.e. the annual rate of TB infection), depending on the TB situation in the country where they reside and the key populations they belong to. This makes FOI a function of time, with a fixed value only when the system is in equilibrium. It is assumed that people with remote LTBI can get reinfected, but at a lower rate than uninfected susceptible people due to some degree of immunity. Note that reinfection is included as a movement from remote LTBI to recent LTBI, which makes it more likely to develop active TB. This reduced rate of reinfection due to immunity was based on the findings of several studies. In particular, Andrews et al. (2012) showed that the average risk of progression to active TB following reinfection is about 79% lower compared to those infected for the first time [39]. Following this observation, the rate to move from remote LTBI to recent LTBI was assumed to be 21% of the rate of fully susceptible people to move from uninfected to recent LTBI, based on the same FOI.

However, the actual value may be different. In the UK, previous infection was found to impart only 41% protection against disease subsequent to reinfection among adults (age > 20), and little protection against reinfection [40]. In addition, using data from the Netherlands, it was estimated that the degree of protection against pulmonary tuberculosis arising from a recent reinfection conferred by a distant primary infection was 63 per cent for males and 81 per cent for females [41]. Further details about how the FOI is constructed (transmission parameters, proportion of infectious people in each group, travel to high-endemic countries) are given in Section 2.1.7.

The general structure of the natural history model and the durations of the different compartments were discussed during a consultation meeting involving 41 Dutch TB epidemiologists, TB control experts and modellers (The Hague, 30 October 2012) [42]. The duration of PTB (without treatment) was set at 18 months. The durations of asymptomatic TB and recent LTBI were set at six months each, making the total duration from infection to PTB (without any regression) 12 months on average. All durations were based on the views of TB experts in individual consultations and at the expert meeting mentioned above.

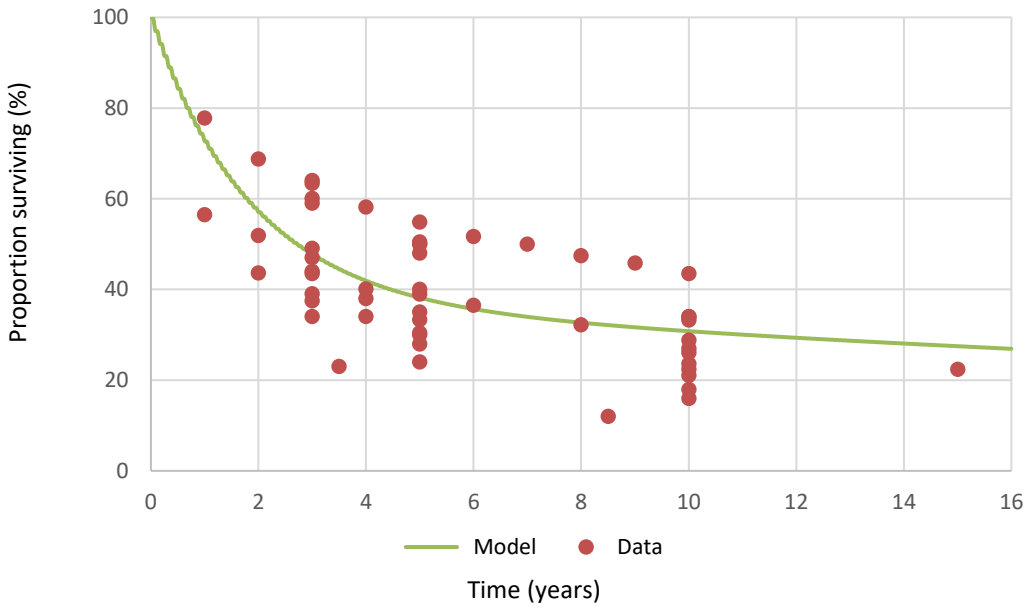
The duration of remote LTBI excluding reinfection was set at 20 years. This 20-year duration (on average) of remote LTBI (i.e. annual rate of leaving this stage = 0.05) is largely synonymous with lifelong. However, some people with remote LTBI will experience reactivation of their disease as a result of the competing rate of (natural) death and the rate of leaving this stage. The term 'LTBI reactivation' was used to indicate activation after remote infection in order to distinguish it from activation after a recent infection.

To give an example: for a healthy and relatively young individual in the compartment 'remote LTBI' with an annual death rate of 0.01, the probability of leaving this stage within the next 15 years is: 1-exp(-(0.05+0.01)×15) = 59%, assuming exponential durations (i.e. given the deterministic compartmental modelling approach , i.e. mathematically defined compartments related to health stages). Of those leaving the stage, 0.05/(0.05+0.01) = 83% will do so not because of death but because of other reasons, and 12% will move on to asymptomatic TB. Of these 12%, 35% will eventually develop active PTB. Thus, a total of about 2% (59% × 83% × 12% × 35% = about 2%) will experience reactivation of their disease from remote LTBI. However, those 65% that regress from asymptomatic TB back to remote LTBI can again experience reactivation of their disease to full-blown pulmonary tuberculosis, accounting for another chance of about 0.5%. This results in a 2.5% long-term reactivation of disease from remote LTBI if calculated together with the short-term activation from recent LTBI. The overall pattern of activation after infection is discussed further in Section 2.1.3.

2.1.2 Fitting transition rates for progression and regression of TB disease

The probabilities of deteriorating from PTB to severe pathology (or reversely: regressing to asymptomatic TB) and progressing from asymptomatic TB to PTB (or reversely: regressing to remote LTBI) in the natural history model (Figure 1) were fitted to historical data on the survival of PTB cases in the absence of treatment as reviewed by Tiemersma et al. [43] and studies mentioned by Berg et al. [44]. Table A2-1 in Appendix 2 shows the observations from each of these studies, and Figure 2 depicts the best-fitting trend. This trend was fitted by starting a cohort of people with PTB and following it for 15 years. The annual background mortality (not due to TB) was set to be 2%, which is consistent with an average survival of 50 years, crudely corresponding to the risk of dying for the study populations at that time. Any person deteriorating from PTB to severe pathology (i.e. not all PTB patients) was assumed to have died from TB, as no chemotherapy was available at that time.

Figure 2. Fitting the model to pre-treatment era survival data from cases with pulmonary tuberculosis



People moving to severe pathology were assumed to have died, irrespective of their cause of death. Data points (n = 54) and their sources are presented in Table A2-1.

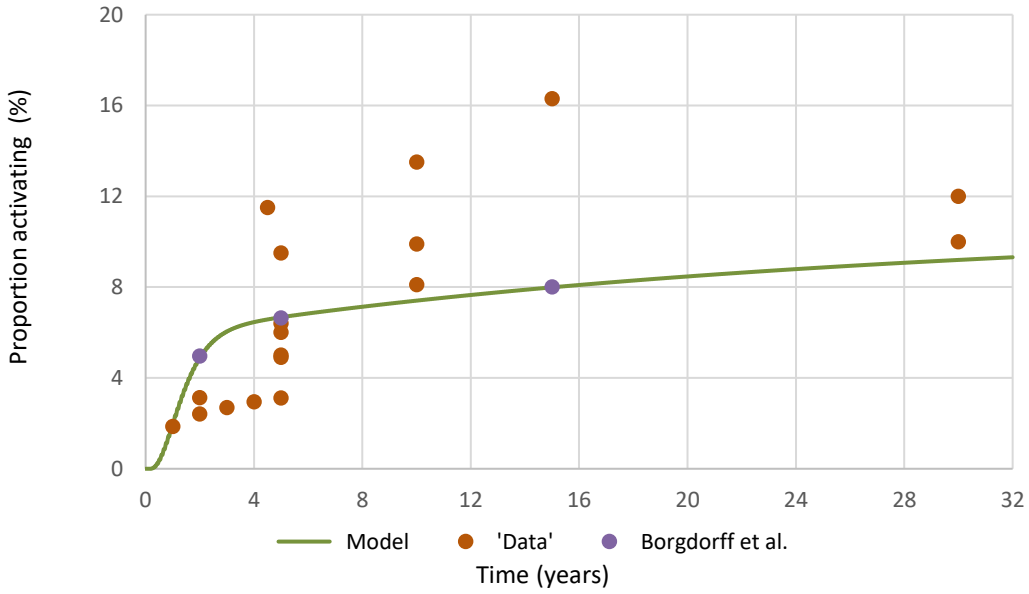
Given the selected PTB stage duration of 18 months, the resulting best-fitting trend to available data in Figure 2 corresponds to about half (52%) of the people developing severe pathology. Thus, the other half (48%) in the PTB stage not on treatment will regress to asymptomatic TB, after which they may return to PTB or recover spontaneously. For asymptomatic TB (assuming a duration of six months), the resulting proportion (re-)progressing to PTB is 35%, so 65% will regress back to remote LTBI. Table A2-3 shows that these proportions are not affected much by the assumed background mortality, given that reasonable values are assumed.

In the remainder of this report, (most) people with PTB are considered to self-report and receive successful treatment. However, for those not receiving treatment, it is assumed that when leaving the compartment, the division of 52% moving to severe pathology and 48% to asymptomatic TB will still hold. Table A2-3 gives a complete overview of the rates and proportions of cases moving to self-reporting/treatment, severe pathology and asymptomatic TB, for all overall durations of PTB assumed in this report.

2.1.3 Fitting transition rates for activation of recent and remote LTBI

A critical component of any modelling study about the impact of LTBI control is to properly reproduce the progression from LTBI to active PTB because the studied interventions are designed to prevent both activation and further TB transmission. Figure 1 shows that in this model, after infection, people first move to recent LTBI, a health state with a selected average duration of six months. Those with recent LTBI can progress to asymptomatic TB (19%), but most (81%) eventually move to remote LTBI, a process called dormancy. Remote LTBI is a health state that in the model lasts for an average of 20 years, after which 12% reactivate to asymptomatic TB, and the remaining 88% clear the infection. Figure 3 explains how these proportions were derived from fitting to data on activation after recent infection.

Figure 3. Fitting the model to available information about tuberculosis activation after recent infection



The curve followed the general findings of Borgdorff et al. (2011) [45], assuming that 8% of all LTBI cases will activate after 15 years, resulting in a lifetime activation rate of about 10% overall. Data points for comparison are listed in Table A3-1. The trend crudely follows the general idea of about 50% of activations occurring rapidly (i.e. within about two years) and another 50% later in life. In the model, the early activations are due to those activating from recent LTBI, the late activations result from reactivation from remote LTBI. The continuous line in the above figure shows the trend in proportions reactivating as described in Figure 1. The shape of the curve indicates the durations of recent and remote LTBI.

The probabilities of progressing from recent LTBI to asymptomatic TB ('activation' in Figure 1) and progressing from remote LTBI to asymptomatic TB ('reactivation' in Figure 1) were fitted to best reproduce the findings of Borgdorff et al. (2011). Borgdorff's study is based on patients whose *M. tuberculosis* isolates had identical DNA fingerprints and who were interviewed to identify epidemiological links between cases [45]. Borgdorff et al. concluded that of those developing PTB within 15 years, 83% did so within five years, and 62% within two

years[4] [45]. The number of diagnosed PTB cases over time was fitted by starting a cohort of recent LTBI, with patients progressing through the model with preset durations for each compartment: six months for recent LTBI and 20 years for remote LTBI. In the model, diagnosed TB cases were interpreted as either self-reporting or moving to severe pathology (absorbing stages). This means that people diagnosed with PTB were assumed not to return to earlier health stages of the model and hence could not be counted twice. The rate of natural mortality was set at 0% because the study by Borgdorff et al. (2011) already corrected for mortality by censoring [45]. Furthermore, the rate of self-reporting was set so that the average duration in PTB was four months. For comparison, Figure 3 also shows the outcomes of several other studies on the risk of activation after recent infection (see Table A3-1), but these studies showed a wide variation and often focussed on children (with a lower risk of activation to PTB) or migrants (with a high risk of previous infection). Table A3-2 shows to which extent the fitted proportions depend on the chosen background mortality and the duration of PTB.

Alternative rates of (re-)activation were also considered, as these are known to vary between age groups and risk groups. Table A3-3 gives an overview of all activation and reactivation rates used in this report. The data and the resulting rates of (re-)activation in Figure 3 are assumed to be illustrative of healthy people in the age group 15–44 years (young adults and adults). For children below 15 years of age, the rates of activation (both from recent and remote LTBI) were arbitrarily set at 25% of the values for adults because children have a substantially lower risk of progression to PTB disease [46-48]. Note that activation only includes the process leading to PTB, not EPTB (lymph node TB is relatively common among infected young children). The rate of activation in the age group 45 years and above was assumed to be 75% of the 15–44-years age group in order to account for the observation that in the Netherlands persons with LTBI aged 25–44 years had a 1.3 times higher chance of developing TB than those aged 45 years and above [49]. However, a study in Denmark reported that TST-positive people in the age group 15–44 years developed active PTB approximately twice as often as those in the age group 45 years and above [50,51]. By contrast, a modelling study from the United Kingdom suggested that those infected at age 20, 40 or 60 have a similar risk of developing active disease during their lifetime; the risk is 20–30% lower for those infected at age 70 because of higher mortality [40]. All in all, a 75% (re-)activation rate in those aged 45 years and above relative to those in the 15–44-years age group was considered a reasonable estimate.

Furthermore, activation is also likely to depend on a person's general health condition. Therefore, the rates of (re-) activation for PWID and homeless people (see Section 2.1.6) were assumed be two times (200%) higher, among the 15–44-years age group, based on their generally poor health. Table A3-3 gives more details about the activation and reactivation rates used in this report.

2.1.4 Assumptions about diagnostic testing

In order to relate the natural history model to data, it is essential to translate the modelled 'truth' correctly to the 'reality' of observations, including imperfect sensitivities and specificities, and thus the risk of false-negative and false-positive test results. Consequently, for each compartment of the natural history model (Figure 1), the probability of obtaining a positive test result test was estimated and assumed for each test method. This also took into account the possibility of a false-positive result due to <100% specificity.

An accurate mathematical model should be able to accommodate the outcome of chest X-rays (CXR), repeated cultures (or smears) for confirmation, as this is the way that most data on PTB are obtained. To model the outcome of CXR testing correctly, it is necessary to include a history component because people who had PTB may have remaining lesions suspicious of active TB, which requires further testing. In addition, people who do not have active PTB may have a positive CXR because of earlier lesions. In the model, these people are accounted for in the asymptomatic TB stage. Cases with asymptomatic TB are assumed to have positive cultures but negative AFB sputum smear results and can crudely be seen as smear-negative pulmonary TB cases.

Furthermore, the model should properly take into account the tests specific for LTBI diagnosis, i.e. TST (positive if ≥10 mm), IGRA, and IGRA after a positive TST. Again, a history component is required because those who had an infection but cleared it (either spontaneously or through treatment), may still test positive due to an ongoing immunity reaction (TST), or, with a smaller probability, due to a waning effect over time (IGRA). Figure A1-1 shows the same model as Figure 1, but with an added history component.

The sensitivity and specificity of each of the mentioned tests is summarised in Table 1 and shown in relation to the different health stages in Appendix 1. Cross reactivity of bacillus Calmette–Guérin (BCG) vaccination with TST is not included because most migrant populations originate from countries where BCG vaccination is only given at birth [52] and will thus have limited effect on the TST [53]. Note that all tests also have false-positive test results due to imperfect specificity. Culture is used in this model as the gold standard and assumed to have 100% specificity. The probability to report symptoms of active PTB has also been included. Most LTBI screening strategies ask for

[4] Borgdorff et al. (2011) also concluded that 45% of those who develop reactivation TB disease after 15 years did so within one year. This observation was not considered for this report because Borgdorff's retrospective study did not allow for making short-term estimates.

symptoms in order to avoid missing cases of active PTB, as both TST and IGRA do not have 100% sensitivity for this stage. The specificity of screening for symptoms is assumed to be lower for PWID and homeless people to reflect the generally poorer health condition of this population.

Graphical representations of the assumptions regarding all testing results used are given in Figures A4-1, A4-2, A4-3 and A4-4.

Table 1. Diagnostic parameters: different tests for active pulmonary tuberculosis and latent tuberculosis infection

Diagnostic parameter	Value / range	Chosen value	Source(s)
TST sensitivity in those with LTBI or past LTBI [b]	89%	89%	[54,55]
TST sensitivity in those with active TB	70 – 82%	75%	[55-57]
TST specificity [c]	92 – 98%	95%	[55,57]
IGRA sensitivity in those with LTBI	83 – 84%	83%[a]	[58,59]
IGRA sensitivity in those with active TB	81 – 82%	81%	[55-57]
IGRA specificity	98 – 99.4%	98%	[54-56,58]
CXR positivity in those with a history of PTB	10.5%–40%	25%	[60,61]
CXR sensitivity in those with active TB [f]	97.5%	97.5%	[57,62,63]
CXR positivity in those with asymptomatic TB	Unknown	25%	Assumption
CXR positivity among people with a recent TB episode	Unknown	50%	Assumption
CXR specificity [f]	75.4% – 97.7%	96%	[62,64,65]
Culture sensitivity after CXR	90%	100%[d]	[62,63]
Culture specificity after CXR	96–100%	99.5%[d]	[66-68]
Symptom screening sensitivity for active TB [e]	77%	90%[g]	[62]
Symptom screening specificity for active TB [e]	68%	90%, 68%[g]	[62]

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

These values should be interpreted as follows for the model (see Figures A4-1–A4-4): sensitivity is proportion positive in the group with disease; specificity is 1 minus the proportion positive in those without the disease.

[a] *20% for those who had TB before, to allow for waning [59].*

[b] *Positive predictive value for TST was 1–7% for TST and 0–13% for IGRA. Negative predictive value was 92–100% for TST and 88–100% for IGRA [156]. A recently published review in children, immunocompromised people and migrants, found that cumulative TB incidence rate after positive TST or IGRA were similar but the reviewed studies had several limitations [69]. Both reviews do not give sensitivity and specificity.*

[c] *A middle value was chosen to take into account positive TSTs due to non-tuberculous mycobacteria.*

[d] *Minimum of two cultures; assuming use of confirmatory tests and no-cross contamination because of continuous improvement of laboratory procedures.*

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

[f] *Values for 'any abnormalities' on CXR were chosen to have high sensitivity. Nationwide prevalence surveys in high-risk countries reported a CXR specificity of 75.4% [62]. An older study reported 97.7% CXR specificity in migrants in the Netherlands [64]; a more recent report cited 95.0% [65].*

[g] *The only specificity value used comes from a review including homeless people since the review is based on populations in countries with high TB incidence [62]. For all other groups, which are healthier, 90% was used.*

2.1.5 Adapting the model to data on entry screening of migrants

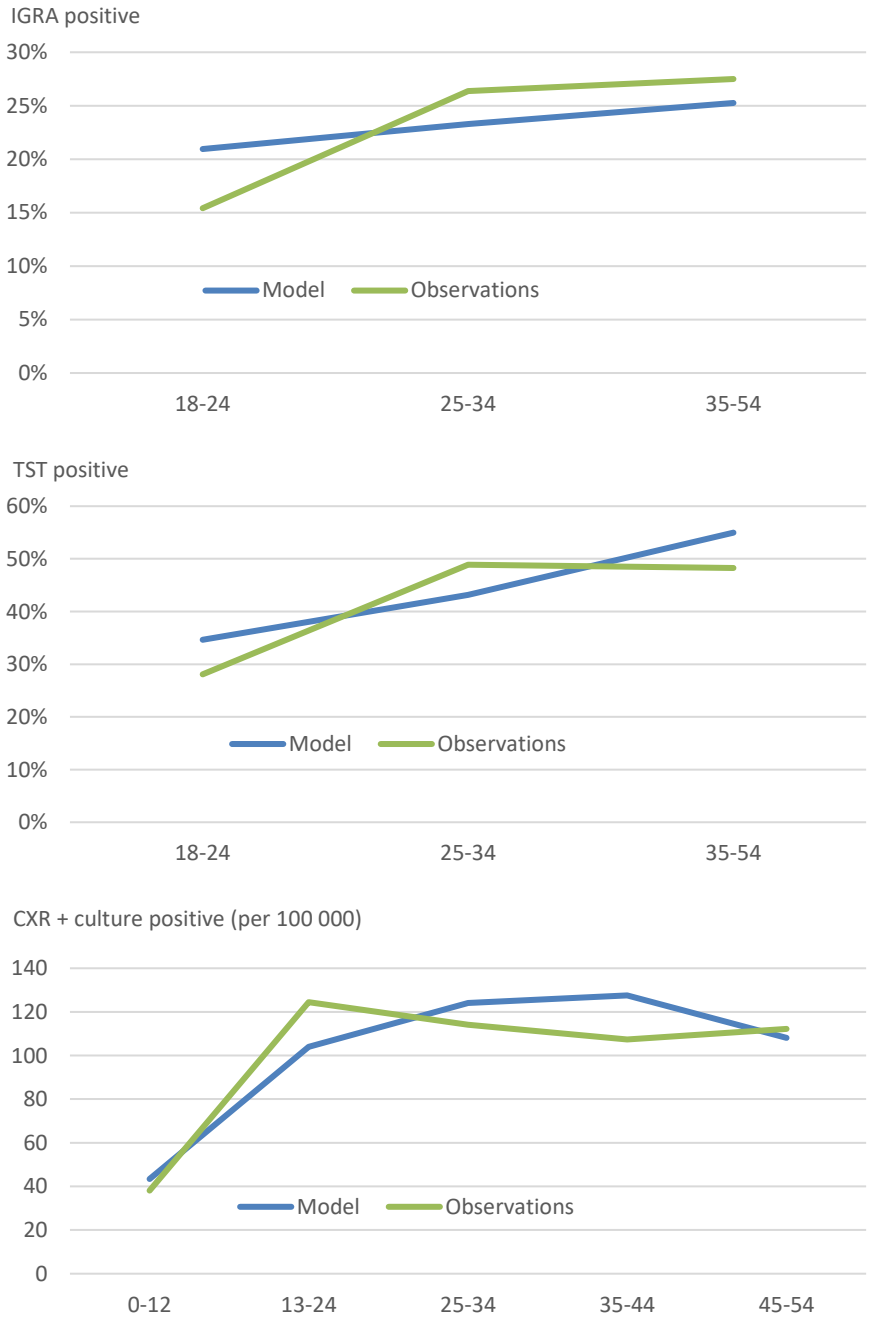
The quantified natural history model mentioned above, together with assumptions regarding diagnostic testing, was used to fit to Dutch data on TB (CXR) and LTBI (IGRA and TST) obtained from migrants from high-endemic countries (i.e. countries with a total TB incidence >50 cases per 100 000 population) which were screened at entry. Key values came from two relatively recent studies. The first study was conducted by the KNCV Tuberculosis Foundation and reported on migrants from countries with an incidence >50/100 000 (WHO estimate) who entered the Netherlands between 2005 and 2010 [65], updating the data previously published by Erkens et al. [64]. These data were used to calculate that of 84 166 migrants, 93 had a positive CXR and a positive culture for bacteriological confirmation, i.e. 11.05 per 10 000 [65]. In the same study, 5 937 of 117 389 migrants had an abnormal CXR (506 per 10 000), requiring further testing with culture [65]. The second study, by Mulder et al. (2012), reported that 23.4% of the migrants that came to the Netherlands from high-endemic countries had a positive IGRA result (raw data obtained from Mulder to select migrants from countries with WHO-estimated incidence > 50/100 000) [70]. In addition, Mulder also found that 42.9% of all migrants had a positive TST reaction following entry screening (this excludes migrants from Europe and the Americas). This information was also used for fitting [71].

The average TB incidence of the 10 TB-endemic countries with the most resident migrants in each EU/EEA pilot countries was used to calculate an average FOI value. The FOI and the tendency of PTB cases to travel (relative to all other people) were fixed in order to obtain 23.4% migrants with positive IGRA results, 42.9% with a positive TST, and 0.11% with positive CXR and culture. The same age distributions as in the studies by Erkens and Mulder were applied. Further, the average duration of PTB (until treatment) was assumed to be four months in the country

of origin. This duration (for reference: three or four months were used for European countries, see Section 2.1.7) may very well reflect the average situation in high TB-endemic countries [72,73].

Figure 4 shows that the observed overall proportions of those with a positive IGRA, TST and CXR/culture could very well be reproduced, including the crude trends with age. The corresponding estimates of the two tuned parameters are: FOI = 0.02 per year; PTB cases: 56% tendency to migrate relative to the rest of the population. It is reassuring that the model resulted in 451 cases per 10 000 population with an abnormal CXR, which is relatively close to the reported value of 506 cases per 10 000 population. In addition, the model-predicted proportion of all CXR/culture-positive cases having symptoms is 31%, which is almost the same as the observation that only one-third of migrant TB patients reported symptoms during entry screening [74].

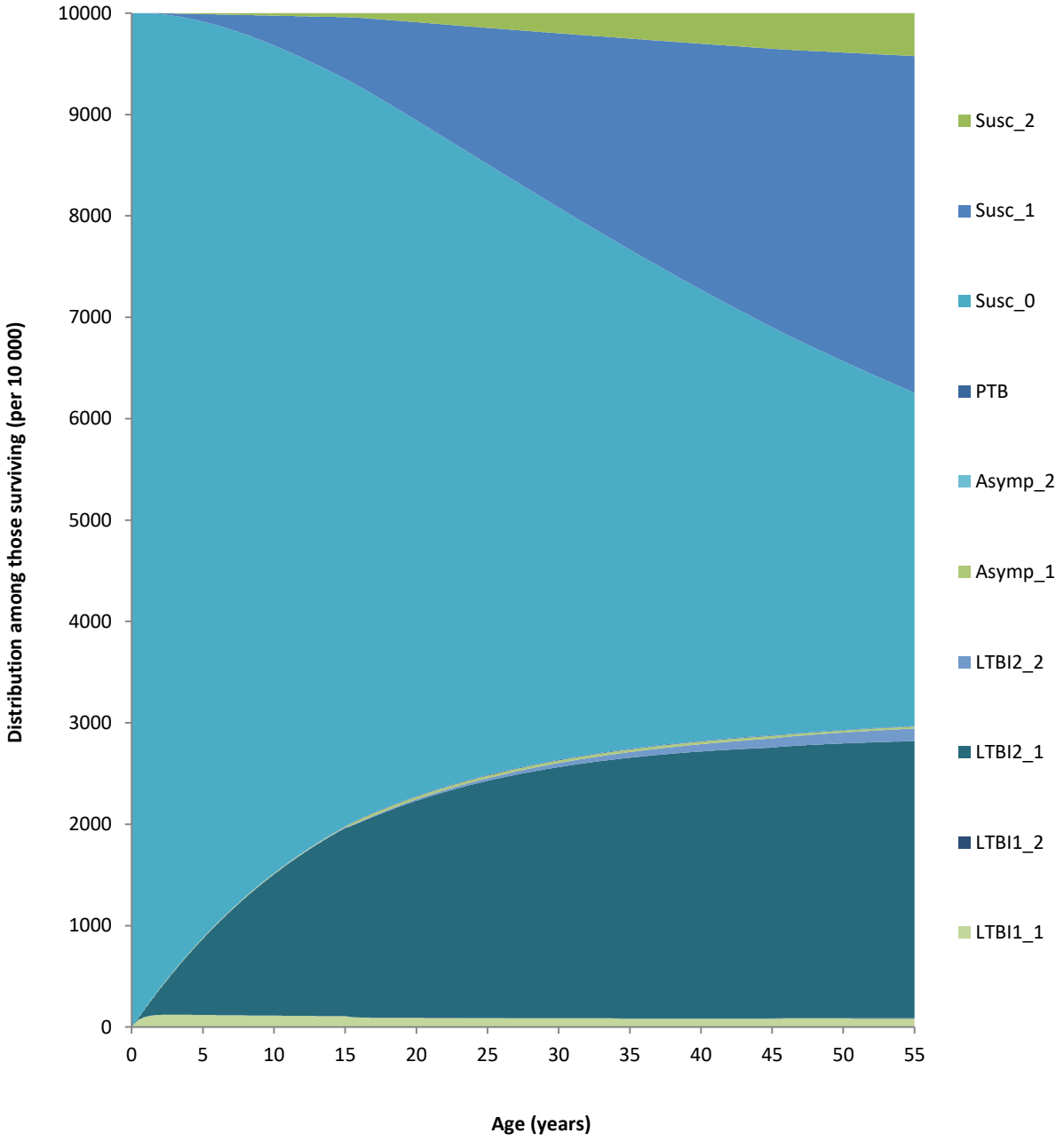
Figure 4. Fitting the natural history model to data from migrants to the Netherlands; migrants from high-endemic countries after entry screening; different age groups



CXR = chest X ray; IGRA = interferon gamma release assays; TST = tuberculin skin test.
Please refer to the main text for further explanations on the fitting procedure. Supplementary Figures A4-1, A4-2, and A4-3 give the assumptions on proportions for those with positive CXR, culture and IGRA.

Figure 5 shows the distribution of natural history stages for migrants as a function of age. Table A5-1 presents how the average TB incidence for the 10 TB-endemic countries with the most migrants to the Netherlands was used to also arrive at distributions across natural history stages for migrants to the Czech Republic, Portugal and Spain (in the absence of comparably detailed data), to be used in section 2.1.7 to model the presence of PTB and LTBI among migrants to all four pilot European countries.

Figure 5. Distribution of natural history stages by age among migrants during their time in the country of origin; only migrants to the Netherlands; does not include those who died (by all causes of death)



Asymp = asymptomatic tuberculosis; LTBI = latent tuberculosis infection; LTBI1 = recent latent tuberculosis infection; LTBI2 = remote (late) latent tuberculosis infection; T PTB = active pulmonary tuberculosis; Susc = not infected.
Numbers reflect the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease. This distribution is the result of the best-fitting FOI of 0.02 per year, together with a fitted 56% tendency of PTB cases to travel, both for a chosen average PTB duration of four months (until treatment). Using this distribution across TB/LTBI stages and the distribution of migrants across the age groups 15–44 years (95%) and 45 years and above (5% in 45–55-year-olds) results in exactly the same overall proportion of people with a positive IGRA, TST and CXR/culture as recently reported for the Netherlands (see Figure 4).

2.1.6 Size and composition of key population groups in Europe

ECDC and TB experts [75,76] suggested several key population groups for programmatic LTBI control: HIV patients, migrants, refugees, prisoners, homeless people, PWID, healthcare workers, travellers to countries with high TB incidence, immunocompromised patients, and TB contacts.

In the TB transmission model, TB spread is simulated for four key population groups, taking into account different risks of infection within each population group and interactions between the groups (Figure 6):

- General population
- First-generation migrants (including refugees and asylum seekers) from TB high-endemic countries
- A combined population of PWID and homeless people
- Prisoners

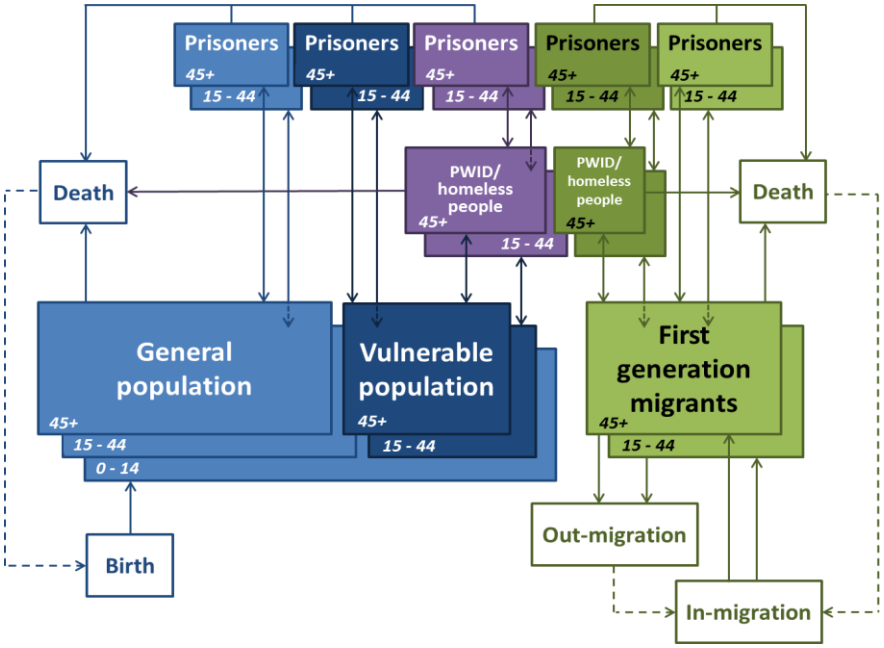
The migrants, prisoners and PWID/homeless people were eventually chosen because an LTBI intervention targeted at these population groups is likely to have an effect on TB transmission in the population as a whole. Other risk groups are considered in the cost-effectiveness report, but on the basis of a cohort version of the same transmission model.

An essential characteristic of the model is that the system is assumed to be in equilibrium when fitting to data, and the population groups are assumed to remain in equilibrium when making predictions regarding different LTBI screening strategies. The approach to fitting the population subgroups is outlined below. A complete overview of the resulting size and distribution of the key populations for each country is given in Table 2.

Demography

The model takes into account age by distinguishing three age groups: 0–14, 15–44 and 45 years and above (Figure 6). People of the general population stay in the age group 0–14 years for a slightly shorter time than 15 years to arrive at a stable number of people in this age group, compensating for the declining birth rates in European countries. Those in the age group 15–44 years are preset to stay there for on average of 30 years, and those in the age group 45 years and above stay for an average of 30 to 40 years, depending on the life expectancy in the country considered. Death (due to other causes than TB) is assumed to play a role only for the age group 45 years and above. All deaths among natives (i.e. general population and native key population groups) are replaced by new births to the general population, and all deaths of migrants plus those out-migrating are replaced by new migrants, so that the size of the population remains constant over time. Information about the size of the overall population in the four countries and the distribution across age groups was obtained from Eurostat [77].

Figure 6. Schematic overview of the population groups included in the tuberculosis transmission model



Numbers refer to age groups. In the general population, deaths are replaced by births to obtain model equilibrium. Similarly, out-migrations and deaths among migrants are replaced by in-migrations. The vulnerable population is not a separate key population, but represented by 30% of the general population who are vulnerable to become, for the purposes of this model, homeless people or PWID. This subgroup was added only for modelling purposes and does not differ from the rest (70%) of the general population.

General population

General population refers to all people born in the country and therefore includes second and third-generation migrants. Migrants from low TB-endemic countries (e.g. other EU-countries) are considered part of this group. The vulnerable population is set at 30% of the general population. These 30% can – for a certain period – become part of the group of PWID/homeless people. This implies that people in the vulnerable population may have acquired LTBI because of a history of being homeless or injecting drugs (which carries a relatively high risk of infection), whereas the rest of the general population only experienced very low transmission rates. By using a smaller group from which PWID and homeless people are recruited, some people may repeatedly be part of this high-risk group – a well-known heterogeneity in real life. The vulnerable population from which PWID and homeless people are recruited is assumed to be 30% of the overall general population. People in the vulnerable population and the rest of the general population are equal in all other aspects of TB transmission and control.

Migrants

The migrant population consists of first-generation migrants and asylum seekers from high TB-endemic countries that may be considered a priority for TB and LTBI control by any European country. For the Netherlands, this group refers to immigrants from countries with a WHO-estimated TB incidence > 50/100 000 [78] (high-endemic countries), including refugees. The same definition was applied to the other countries. In the model, 95% of all migrants who migrated to a European country are aged 15–44 years, and 5% were part of the 45+ group. Migrant children were not included as a group, since they constitute a very small group and are responsible for less than 5% of all TB cases and therefore hardly contribute to transmission. The few migrating children and possible PTB cases in this group are included in the age group 15–44 years.

An important aspect of TB and LTBI control in the migrant population is the inflow and outflow of migrants, as PTB and LTBI can be picked up through entry screening. With a high rate of in-migration, more migrants need to be screened, leading to many PTB and LTBI cases identified. If there is a high rate of out-migration, the missed LTBI cases are relatively less important because activation would then occur when the migrant has already left Europe.

Figure 7 shows how the model was quantified to reproduce the trend observed in the Netherlands (proportion of migrants staying in the country as a function of time since arrival). The associated immigration (to keep the migrant population in equilibrium over time) was close to the observed data as well (see Figure 7). The same rates were used for the Czech Republic. For Portugal, a higher emigration rate needed to be assumed to arrive at the observed rate of immigration, whereas it was somewhat lower for Spain.

Combined high-risk group (PWID and homeless people)

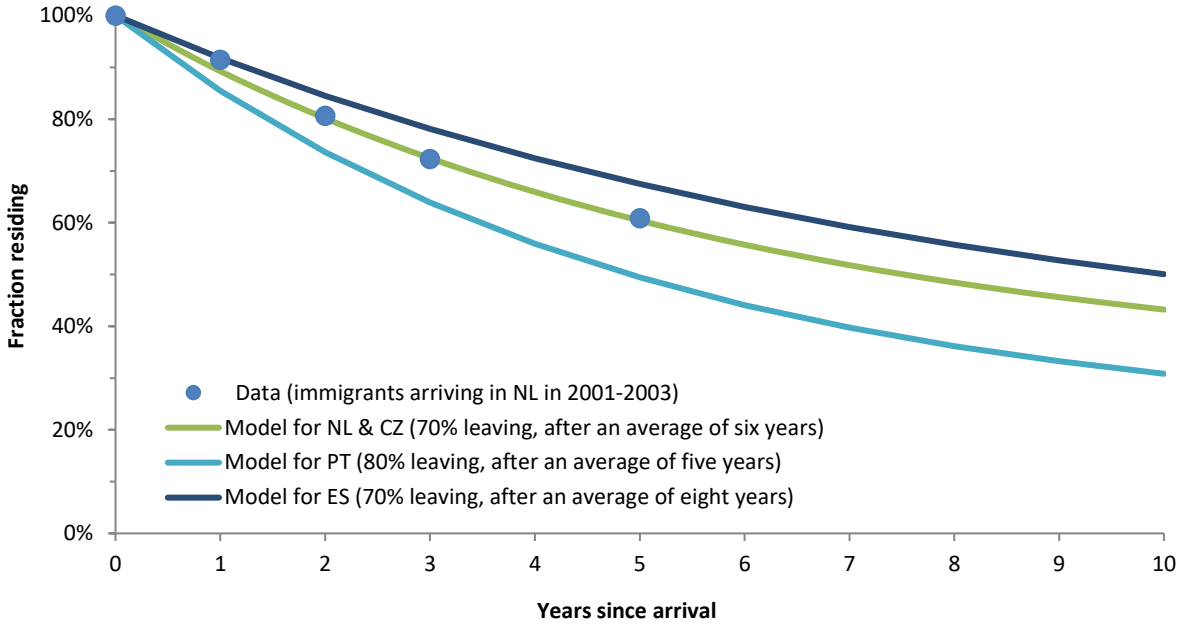
For the purposes of this model, homeless people and PWID were included in a single high-risk group. These people mainly originate from the general native population (in the model, recruitment is only from 30% of the population designated as vulnerable population), but it is possible for migrants to move to this group. A dedicated vulnerable group was not included in the first-generation migrant population, because LTBI is already widely spread among migrants – a result of transmission in the country of origin. People stay in the PWID/homeless population for an amount of time and then move back to the general population (i.e. vulnerable) or the migrant population they came from. PWID and homeless people are assumed to have a life expectancy ten years shorter than the rest of the population, based on data from the Netherlands [79,80].

The size of this population is notably difficult to assess, as the considered subgroups overlap. In addition, it is also likely that several PWID and homeless people are missed in attempts to estimate the size of this hard-to-reach population. There are considerable differences in the estimated sizes of this group for the four countries (see Table A6-1). In addition, the average duration of stay in the PWID/homeless population is difficult to estimate. Based on limited data from the Netherlands, a duration of five years was estimated, which was used for all four countries. This duration originated from the following observations regarding the homeless and PWID:

- The mean duration of homelessness is about 3.5 years, which can be calculated (after accounting for selection bias) from the following cross-sectional distribution of reported durations of homelessness: for one-third, the duration of homelessness is <1 year; for another one-third, the duration of homelessness is 1–5 years; for the last one-third, the duration of homelessness is > 5 years [81]
- PWID: assumed duration of 10 years, loosely based on data from the Amsterdam PWID cohort [82]

Age distribution in groups with high risk was taken from a report about homeless people in the Netherlands (2010–2012 data): 60.3% are between 18 and 44 years of age, and 39.7% are 45 years of age or above 45+ [81]. The corresponding relative durations (or inverse rates) for young adults vs. older adults becoming homeless or injecting drugs in the Netherlands were also used for the other three countries (due to lack of country-specific data on the age distribution of homeless people and PWID).

Figure 7. Pattern of emigration of first-generation migrants used in the model



CZ = Czech Republic; NL = Netherlands; PT = Portugal; ES = Spain

The trend for the Netherlands was based on Dutch data on migrants who arrived between 2001 and 2003 in the Netherlands. The fraction of migrants that stayed in the Netherlands was calculated as a function of years since entry into the country. The observed trend (circles) can be reproduced by assuming that 30% of newly arriving migrants will never leave the country and that 70% leave the country after an average of six years. The corresponding immigration rate (to keep the population in equilibrium) is 19.7 per 10 000 population per year, which is close to the average of 20.4 per 10 000 over the past 10 years (www.cbs.nl [153]). For Spain, a slightly lower emigration rate (70% leave the country, after an average stay of eight years) was necessary to result in an immigration rate close to the data (29.3 predicted vs. 29.0 observed) (Instituto Nacional de Estadística (INE), Spain, 2015 [154]). For the Czech Republic, no data were available, which is why the same trend was used as for the Netherlands. For Portugal, a higher rate of emigration was used (80% leave the country, after an average stay of five years), in order to match the observed immigration of 15.1 per 10 000 (Instituto Nacional de Estadística (INE), Portugal, 2014 [155]) with the model (14.2 per 10 000).

Prisoners

Prisoners can come from any population group, and they most likely return to the population group they came from after release from prison. The parameters for this group are chosen to fit the actual size of the prison population in each country.

Data on the age distribution of prisoners were only available for the Netherlands (2010–2014: 15–44 years of age: 77.6%; 45 years of age and above: 22.4%). The mean length of a prison stay in the Netherlands is 93 days (i.e. about three months, median 20 days) [83,84]. Due to lack of data from other countries, a duration of about three months (0.25 years) was used for all the countries in the analyses.

Overview of risk group quantifications

Table 2 gives a complete overview of the size and composition of the risk groups for each country that were used in the analysis. All totals – as available from data – are summarised in Table A6-1. Table A6-2 gives a complete overview of all country-specific parameters that correspond to the values in Table 2. If no data were available on the number of people in risk groups in the 15–44-year age group versus the age group 45 years and above, relative durations from the Netherlands were used (see footnotes for Table A6-2). The model structure was flexible enough to exactly reproduce all available data on the size of risk groups. In addition, the flow of incoming immigrants was closely matched by the model as described in Figure 7. See also Table 2 (note D). Other flows were unknown or not considered in detail and were roughly based on (observed) group size and (assumed) average duration, assuming that the system is in equilibrium.

Table 2. Overview of country-specific quantifications regarding size and composition of the key population groups (per 10 000 population) used in the model

	Netherlands	Czech Republic	Portugal	Spain
Age distribution of native population [A]				
• 0–14 years	1 750	1 436	1 471	1 484
• 15–44 years	3 721	4 146	3 797	3 931
• 45+ years	4 114	4 179	4 533	4 088
Age distribution of first-generation migrants from high-endemic countries [B]				
• 15–44 years	245	149	152	403
• 45+ years	170	90	48	93
Percentage of first-generation migrants from high-endemic countries				
• among the general population [C]	4.2%	2.4%	2.0%	5.0%
• Annual in-migration [D]	19.7	11.5	14.2	29.3
Distribution of PWID/homeless group [E]				
• From general native population, 15–44 years	11.3	25.3	48.6	3.8
• From general native population, 45+ years	7.9	16.3	36.6	2.5
• From migrant population, 15–44 years	2.5	3.0	6.4	1.3
• From migrant population, 45+ years	1.2	1.4	2.0	0.4
Percentage of the population in PWID/homeless group [F]	0.23%	0.46%	0.94%	0.08%
Distribution of prison population [G]				
• From general native population, 15–44 years	4.56	14.33	8.23	7.25
• From general native population, 45+ years	1.34	3.67	2.74	2.12
• From migrant population, 15–44 years	0.57	1.19	0.68	1.48
• From migrant population, 45+ years	0.10	0.18	0.07	0.11
Percentage of the population in prison [H]	0.07%	0.19%	0.12%	0.11%
• Percentage of prisoners who are first-generation migrants [J]	10%	7%	6%	14%
• Percentage of prisoners from PWID/homeless group [K]	24%	37%	12%	10%

Values were as much as possible based on data (see Table A6-1 for population totals) or are a result of parameters derived from other countries. Table A6-2 gives a complete overview and justification of all country-specific parameters that correspond to the values in this table. The number of people in the native population and first-generation migrants add up to 10 000. PWID, homeless people and prisoners are subgroups.

A *Consistent with country-specific demographic data [77]. Here, native means not born in a high-endemic country (i.e. a WHO-estimated TB incidence >50/100 000).*

B *This value reflects country-specific demographic data on first-generation migrants from high-endemic countries (Table A6-1). Table A5-1 (see first footnote) lists all major countries with a substantial number of migrants. The distribution across age groups was based on actual data for the Netherlands and Spain. For Portugal and the Czech Republic, no age distribution was available. For Portugal, age distribution was available for some countries of origin (China, India, Macau, Pakistan, East Timor, South Africa, Angola, Bangladesh, Cape Verde, Guinea, Guinea-Bissau, Morocco, Mozambique, Senegal, Sao Tome & Principe, Ukraine and Russia). For the Czech Republic, the Netherlands' migrant age distribution was used.*

C *Consistent with country-specific data (Table A6-1).*

D *Based on country-specific data (Table A6-1), with the exception of the Czech Republic, for which the same emigration rates as for the Netherlands were used.*

E *Data on the distribution of PWID/homeless people was only available for the Netherlands (15–44 years of age: 60.3%, 45+ years: 39.7%), as was information on the percentage of natives vs. migrants (85% vs. 15%) [81,82,85]. Among the homeless, 25% were migrants [81]. Among PWID, 21.4% were migrants [86]. As these figures include all migrants, it was assumed that 15% were from high-TB-incidence countries [81]. The same relative parameters of moving into a high-risk group were used for the other three countries.*

F *Based on data on homeless people and PWID (Table A6-1).*

G *Data on the distribution of prisoners over both age groups was only available for the Netherlands [83,84]. The same relative parameters for moving to prison were used for the other three countries.*

H *Consistent with country-specific data (Table A6-1).*

J *Values reflect the size of the first-generation migrant population (see also C). The value for the Netherlands is a good approximation of the available data (10% of all prisoners are migrants from high-endemic countries) [83,84]. In Spain, 27% of prisoners were reported to be migrants [156]; it was assumed that 15% are from high-incidence countries. No data could be found for the other countries.*

K *The value for the Netherlands reflects a very crude estimate from data (12% of prisoners use opiates [87]; unknown proportion of prisoners is homeless [81]; total estimate: 24%). See section below on 'Interactions between risk groups' for further explanation.*

Interactions between risk groups

Based on limited data, it was crudely estimated that 24% of the prisoners came from the PWID/homeless group in the Netherlands [81,87]. Reproducing this proportion required a very high relative tendency of the PWID/homeless group (100 times the tendency of other groups) to go to prison in the model. This value was also used for the Czech Republic and Spain. For Portugal, the PWID/homeless group was assumed to be less concentrated, and a much lower relative tendency to go to prison (10 times the tendency of other groups) was used. Only then, the PTB incidence in PWID/homeless peoples and prisoners could be reproduced, in accordance with the data from

Portugal (see also Chapter 3.1). As a result, the proportion of prisoners coming from the PWID/homeless group in the model varies substantially between countries, from 10% (Spain) to 37% (Czech Republic) (Table 2, note K). No sensitivity analysis for these proportions was performed because no data could be obtained from the ECDC TB contact persons.

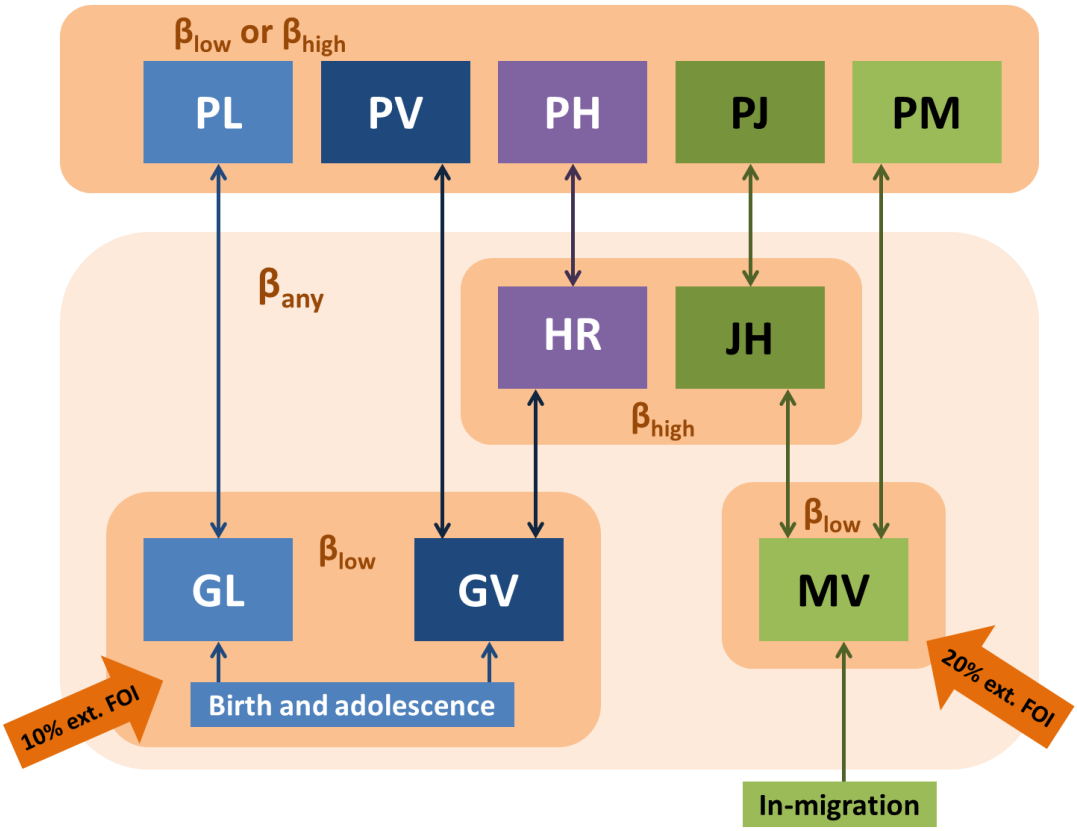
For the Netherlands, about 10% of prisoners were estimated to originate from the migrant group (high-TB-endemic countries) [83,84]. This could be reproduced by applying a prison stay that was 0.8 times shorter for migrants compared with low-risk natives. This assumption was also used for the Czech Republic. For Spain, it was necessary to assume a prison stay that was 0.6 times shorter for migrants compared with low-risk natives in order to approximately arrive at the observed 15% of prisoners originating from the migrant group. The same assumption was applied to the value for Portugal.

2.1.7 Modelling TB transmission in European countries

The previous section addressed modelling the number of people in each risk group (i.e. the denominators), whereas this section focusses on the numerators by documenting how TB transmission within and between the various groups was modelled. By combining the two, we arrive at the PTB incidence per risk group, expressed here as the annual number of PTB cases per 100 000 population. Table A7-1 provides an overview of PTB cases in the four pilot countries.

For each European country, TB transmission was simulated for the following population groups: general native population (including a vulnerable group), first-generation migrants from high-endemic countries, PWID/homeless group, and prisoners. Each infectious individual (i.e. someone with PTB) can infect members of his own group and members of the population as a whole (with the exception of prisoners). Prisoners are assumed to cause transmission only within their facility. Figure 8 gives a graphical illustration of the transmission processes.

Figure 8. Schematic representation of transmission between groups



*The compartments reflect the same population groups as shown in Figure 6, but without indicating age groups. The population groups are: **GL** (general native population, low-risk), **GV** (general native population, vulnerable), **HR** (PWID/homeless group from the general native population), **MV** (migrants, vulnerable), **JH** (PWID/homeless group from the migrant population), **PL** (prisoners from GL), **PV** (prisoners from GV), **PH** (prisoners from HR), **PM** (prisoner from MV), and **PJ** (prisoners from JH).*

The shaded fields indicate how transmission is assumed to be concentrated in parts of the population (dark brown) and in the population as a whole, excluding prisoners (light brown). These parts of the population reflect the different population groups addressed in this analysis: natives, first-generation migrants, PWID/homeless group and prisoners. The beta values indicate the choice of transmission parameter used within each population group. The general native population and migrants also experience an external force of infection ('ext. FOI') to reflect the introduction of additional infections (i.e. infections acquired outside of Europe) due to travel to high-endemic countries. It is assumed that this external FOI is more relevant for migrants than the native population.

Transmission parameters

The transmission parameter β reflects the number of infections per month in a susceptible population, combining both contact rate and transmission probability in one parameter. In the formula below, β_{own} was used as the transmission parameter determining the rate of being infected by a person of one's own group. Here, a group means a combination of population (risk) group and age group. Similarly, β_{any} determines the rate of being infected by a person with PTB from any risk group, except prisoners, but including his/her own group. Mixing is assumed to be homogenous, irrespective of risk group or age group.

$$\frac{dN_i}{dt} = -N_i.FOI_i = -N_i.\left(\beta_{own} \cdot \frac{\sum_j PTB_j}{\sum_j Total_j} + \beta_{any} \cdot \frac{\sum_k PTB_k}{\sum_k Total_k}\right)$$

where N_i = not infected in subgroup i; subgroup i is part of the combined (risk) group j, which in turn is part of the whole population, which consists of all (risk) groups k (but not prisoners). Thus, $i \in j$ and $j \in k$, except for prisoners. The part between brackets is the FOI that susceptible people in group i experience. This (internal) FOI was increased by 10% (for the native general population) and 20% (for migrants) to represent the introduction of infection due to travel to high-burden countries (not shown in the formula). This formula is also used to model reinfection of remote LTBI cases, but at 21% of the level for fully susceptible (i.e. not infected) people N_i to reflect some degree of immunity [39].

For migrants and natives, it was assumed that β_{own} was similar, because migrants and natives have similar transmission patterns (see fingerprint studies from the Netherlands and Spain [88-91]. It was named β_{low} to distinguish it from the parameter for infectious PWID/homeless people, where β_{high} was used. It was initially considered to offer a choice between values β_{low} and β_{high} for prisoners, depending on placement in a single cell or cell sharing. It was eventually decided to only use β_{low} because prison conditions in the selected four Member States are believed to offer a relative generous amount of private space.

This approach resulted in three free transmission parameters (β_{low}, β_{high} and β_{any}) to reproduce the country-specific TB incidence values over the past 10 years. More free parameters would not be possible because they should not exceed the number of reproducible PTB incidences, i.e. four for the Netherlands and Portugal, three for Spain (where no PTB data are available for the PWID/homeless group) and the Czech Republic (where no PTB data are available for prisons). All missing values are highlighted in Table 4.

After exploring the transmission model it was concluded that the estimated value of β_{low} is largely determined by the number of PTB cases among migrants who have already stayed longer in the country, in addition to the PTB cases which were already detected during entry screening of migrants. Subsequently, parameter β_{any} is determined by the number of PTB cases in the general native population. Finally, β_{high} mainly relates to the number of PTB cases in the PWID/homeless group, but – especially for the Netherlands and the Czech Republic – to the number of PTB cases among prisoners, as many of them are recruited from PWID/homeless people. For the Czech Republic and Spain, where no data were available for the PWID/homeless group, parameter β_{high} was largely based on the fit of the PTB incidence among prisoners.

Other processes relevant for transmission

Another important aspect for modelling the number of PTB cases is screening. In the short run, screening leads to an increase in the number of detected cases. In the long run, it will lead to a decrease in transmission and a reduction in PTB cases (not necessarily in the same groups as the ones screened). All four countries were therefore asked about their current screening policies. Recently, policies changed. The Netherlands, the Czech Republic and Spain (only in Barcelona) have started pilot screening for LTBI with IGRA among migrants and other high-risk groups. For modelling purposes, the policies applied over the last 10 years were most relevant because they directly influenced the number of reported PTB cases. Table A7-2 gives an overview of the baseline screening policies included in the model. The assumed coverage levels and the proportions of people who successfully completed TB treatment per screened risk group (if applicable) are equal to those in Table 5 and are discussed in more detail in Chapter 2.2.

An external FOI was assumed for people living in a European country but travel to medium- and high-TB-incidence countries. This assumption was based on findings from studies on travellers [92-94]. The external FOI was

arbitrarily assumed to be 20% of the overall FOI for migrants, and 10% of the overall FOI for the native population. This overall FOI was derived at by dividing the calculated internal FOI values (based on transmission within the country as expressed by the equation above) for migrants by 0.8, and those for natives by 0.9 (FOI/0.8 is the same as 1.25xFOI overall; of which 0.25xFOI = 20% external and 1xFOI = 80% internal). In order to make predictions, the corresponding external FOI was considered a fixed value, and an annual 1.5% reduction was assumed, consistent with a similar worldwide decline in incidence, as reported by WHO [95].

Two important decisions remained to be made before TB transmission could be properly modelled. First, it was necessary to make assumptions on how long infectious people are able to infect others. In terms of the mathematical model used, this means: how long does a person remain in the PTB compartment (compartment is usually left due to self-reporting followed by treatment)? There are a number of studies about patient's (until self-reporting) and doctors' delay (until receiving proper treatment). However, these studies are of limited value because of their poor quality due to bias, lack of information about key populations, and low-incidence settings [73]. Data on patient's/doctor's delay were therefore taken from the Netherlands [96] and supplemented by educated guesses.

Even if the assumed durations of PTB are not fully correct, the effect on the modelling outcomes is limited, as the (unmeasurable) transmission parameters β will to some extent compensate for it. Basically, it is the person-months with PTB times β that determine the risk of TB transmission. If PTB is assumed to last longer, the corresponding value of β will become lower, and vice versa. Only one of the two can be estimated, the other one needs to be fixed. Thus, the β values were estimated and the values for PTB duration were preset. Related to this, (the few) PTB cases with severe pathology were assumed not to infect others. Similarly, cases identified through self-reporting or screening were assumed to be non-infectious during the first weeks of treatment. This is based on the assumption that a patient's infectiousness diminishes rapidly once effective treatment is initiated. Patients may transmit to a limited number of healthcare workers, but it is unlikely that they will become a critical source of transmission to the rest of the population.

Crudely based on Dutch data on delay, a PTB duration of three months was used for most people with disease [96]. For people in the PWID/homeless groups, disease duration will most likely be longer; consequently, a duration of six months was used. Quite the reverse, the duration of PTB is likely much shorter for prisoners (set to one month in the model), as they are under continuous observation and a well-known risk group for TB infection.

PTB durations were assumed to be one month longer for all risk groups in the other three countries, as explained above. This merely reflects the fact that the Netherlands has a longer history of successful TB control, so that this assumption could be used to account to some extent for the lower TB incidences in the country. Table A2-3 gives an overview of the durations of stay in the PTB stage that were assumed in this report; the table also lists the corresponding rates and proportions for leaving the PTB compartment.

Resulting fits to PTB incidence data

Table 3 shows the best-fitting β values as well as the resulting FOI per month at equilibrium for all four countries. It shows that in Portugal and Spain the FOI are higher than in the Netherlands and the Czech Republic, which was expected since PTB incidence is higher in Portugal and Spain. Furthermore, the FOI for migrants in Portugal is much higher than for other countries. This can be explained by the fact that PTB incidence among migrants in Portugal is relatively high, compared with the other three countries. Migrants in Spain or the Netherlands, on the other hand, mostly come from countries which do not have a particularly high TB incidence (Table A5-1).

Table 4 shows the fit of the model to the observed average annual number of new PTB cases over the past 10 years (only data for five years were available for Spain). With the three free β parameters it was possible to exactly tune the model to the observed total numbers of PTB cases that were available from the data.

With regard to the native population, the number of PTB cases in people 45 years of age and older is to some extent underestimated, whereas it is overestimated for in the age group 15–44 years. This is particularly the case for the Czech Republic which has experienced a substantial reduction in TB cases over the recent years, leading to a relatively high proportion of people 45 years of age and older with (remote) LTBI from past infection that may eventually reactivate to TB disease. Estimates for migrants are more in balance with the data. Also, some country-specific differences between age groups reflect different flows of migrants coming to and from Europe.

Table 3. Fitted values for the transmission parameters (beta) and the corresponding force of infection values for key population groups

	Nether-lands	Czech Republic	Portugal	Spain
Transmission parameters				
β_{any}	1.09	1.34	1.12	0.73
β_{low}	0.93	0.68	0.90	1.61
β_{high}	1.75	1.91	1.54	2.47
FOI per month (× 10 000)				
• Natives	0.18	0.49	1.89	0.90
• Migrants	1.43	1.19	4.53	3.82
• PWID/homeless people	7.75	13.66	33.38	42.15
• Prisoners	0.29	0.62	0.95	0.94

FOI = force of infection.
FOI values only concern the equilibrium situation; values will change (become smaller) due to interventions.

Table 4. 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	11.3	12.7	2.5	16.2	40.4	65.2	277.7	137.6
• 15–44	126.7	148.6	133.5	293.3	1 016.6	988.4	1 454.8	1 765.5
• 45+	154.7	131.4	405.6	232.0	957.0	960.8	1 730.6	1 560.0
Total natives	292.7	292.8	541.6	541.6	2 014.0	2 014.4	3 463.1	3 463.1
First-generation migrants from high-endemic countries								
• 15–44	201.7	203.9	60.6	53.5	117.1	133.2	821.5	857.6
• 45+	72.7	70.7	11.5	18.6	49.1	33.1	195.2	159.0
Total migrants	274.4	274.6	72.1	72.1	166.2	166.3	1016.7	1016.7
Total population	567.1	567.4	613.7	613.7	2 180.2	2 180.7	4 479.8	4 479.8
PWID/homeless people*								
• 15–44	12.0	14.5	N/A	23.4	182.6	152.6	N/A	43.4
• 45+	12.2	11.3	N/A	20.4	85.6	116.5	N/A	38.5
Total PWID/homeless people	24.2	25.7	43.8	43.8	268.2	269.1	**N/A**	81.8
Prisoners								
• 15–44	17.9	14.1	N/A	43.4	29.4	30.1	N/A	68.6
• 45+	3.3	3.2	N/A	10.0	9.6	7.1	N/A	14.2
Total prisoners	21.2	17.3	**N/A**	53.4	39.0	37.2	82.8	82.8

N/A = no data available.
*The model was tuned to fit the available total number of PTB cases in each group (light green overlay) by varying the beta parameters (see Table 3 for values). Missing total values are given in **bold**.*
** Details for PWID/homeless group, see Table A7-1. PTB patients in PWID/homeless group who are in prison were excluded from the PWID/homeless group to avoid double counting. This was only possible for the Netherlands.*
Data sources are described in Appendix 9.

2.2 Model application and outcomes

All predictions made by the model started from equilibrium situations, as derived when fitting the data to the observed PTB incidences (details in in Chapter 2.1).

2.2.1 LTBI screening strategies

All modelled LTBI control options refer to the LTBI screening of risk groups and the subsequent treatment of those found positive. The following aspects were modelled:

- Entry screening of migrants from high-endemic countries, including asylum seekers.
- Entry screening of prisoners (all prisoners or only prisoners who were migrants from high-endemic countries).

- Periodic screening – annually or every three years – of the PWID/homeless group. 'Annually' was chosen because this is a common screening interval; 'triennial' (every three years) was selected as a reasonable alternative if there are no other reasonable screening options.
- A combination of the three strategies above.

The model was used to estimate the effect of three screening strategies (IGRA, TST, and IGRA after TST) in comparison with continued baseline screening as practiced in the four Member States in the last 10 years. Baseline screening always refers to CXR followed by culture for confirmation, with the exception of migrant screening in Spain where CXR screening is only performed to those testing positive with TST (see Table A7-2).

The model takes into account the following diagnostic tests for LTBI screening:

- TST: If TST is positive, it is followed by CXR. TST detects LTBI, asymptomatic TB, and PTB. Leads to LTBI treatment if CXR is normal. If CXR shows abnormalities, this leads to TB treatment after confirmation tests (culture). If confirmatory test is negative, LTBI treatment is started.
- IGRA: If IGRA is positive, it is followed by CXR. IGRA detects LTBI, asymptomatic TB and PTB. Leads to LTBI treatment if CXR is normal. If CXR shows abnormalities, TB treatment is started after confirmation tests (culture). If confirmatory test is negative, LTBI treatment is started.
- IGRA if TST is positive: If TST is positive, it is followed by IGRA; if IGRA is positive, it is followed by CXR. TST followed by IGRA detects LTBI, asymptomatic TB, and PTB. If CXR is normal, LTBI treatment is started. If CXR shows abnormalities, TB treatment is started after confirmation tests (culture). If confirmatory test is negative, LTBI treatment is started.

Symptom screening always takes place at the same time as LTBI screening (TST and/or IGRA), as recommended by WHO [15]. This ensure that those with PTB (but not those with asymptomatic TB) can be detected when their LTBI test is false negative. Figure A4-5 gives a complete overview of the possible test outcomes and testing sequences.

It should be noted that PTB patients detected by screening will be only registered in connection with the risk group for which the screening was conducted, i.e. a person from the PWID/homeless group screened in prison and diagnosed with TB will be registered as 'prisoner detected by screening' and not as a 'PWID/homeless person detected by screening'.

2.2.2 TB and LTBI treatment

TB treatment is offered to all people diagnosed with active PTB. In this report, all people starting TB treatment are assumed to be cured. Taking into account death, drop-out and loss to follow-up would not have significantly influenced the modelling results regarding transmission. These factors, as well as increased treatment costs due to MDR/XDR, have been taken into account in the 2017 cost-effectiveness report [37].

LTBI treatment with three months of rifampicin and isoniazid is offered to those who are diagnosed with LTBI. Other regimens are included in the cost-effectiveness report but not covered in the model because the effectiveness of different LTBI regimens is similar [97]. As a result of LTBI treatment, all people with LTBI (both recent and remote) will be cured and move to the 'not infected' state (see Figure 1). For asymptomatic TB cases it was assumed that LTBI treatment cures 50% while 50% stay in the asymptomatic TB compartment. People with PTB that receive LTBI treatment (e.g. because of a false-negative CXR after they had a positive TST or IGRA) will stay in the same compartment because LTBI treatment is usually not a proper treatment for TB disease.

2.2.3 Coverage and treatment completion

Table 5 shows assumed coverages and treatment success for different scenarios. Currently, these values are standardised across countries due to insufficient data. The Excel tool (Appendix 10) allows for varying these values. The Netherlands and Spain confirmed almost complete coverage of screening among prisoners; 80% of all migrants were screened for TB in the Netherlands [64,65]. The coverage for the screening of native prisoners was assumed to be 90%. This is slightly lower than the screening coverage for prisoners with a migrant background.

2.2.4 Outcomes

Outcomes are expressed as annual PTB incidence and LTBI prevalence, both for the total population and for the different population groups, over a 20-year horizon. The population trends were extended to 50 years to assess the probability of reaching a TB incidence below the elimination threshold (annual TB incidence of one case per million population). In order to account for the fact that the model does not include the current decreasing trends in TB incidence, an artificial 4% annual reduction was added to the predicted best-case scenario, based on the trend in the Netherlands. This scenario combines the screening of all risk groups, assuming 100% coverage and 100% treatment success, and assumes that there are no LTBI infections through travelling to high-endemic countries (i.e. external FOI = 0).

Table 5. Screening strategy for latent tuberculosis infection: assumed screening coverages, treatment initiations and completion rates

Population group	Assumed screening coverage	Literature on LTBI treatment initiation rate	Literature on LTBI treatment completion rate	Assumed combined LTBI treatment, started and completed [a]	Assumed TB treatment, started and completed [b]
Migrants (MV) at the point of entry	80% [c]	23–97%	7–86%	60%	95%
Migrant prisoners (PM, PJ) at the point of entry	100%	7–90%	4–100%	70%	80%
Native prisoners (PL, PV, PH) at the point of entry	90%	As above	As above	80%	80%
PWID/homeless, (HR, JH) every three years	70%	38–91%[d]	23–89%[#]	60%	90%
PWID/homeless, (HR, JH) annually	50%	As above	As above	60%	90%

Abbreviations: LTBI = latent tuberculosis infection; TB = tuberculosis.

***GL** (general native population, low-risk), **GV** (general native population, vulnerable), **HR** (PWID/homeless group from the general native population), **MV** (migrants, vulnerable), **JH** (PWID/homeless group from the migrant population), **PL** (prisoners from GL), **PV** (prisoners from GV), **PH** (prisoners from HR), **PM** (prisoner from MV), and **PJ** (prisoners from JH).*

[a] *Data available for migrants at the point of entry in the Netherlands [98] and from a review by Sandgren et al. [76]. Prospective and retrospective data from Sandgren et al.; data on short and long regimens are also from Sandgren et al.: short regimens ≤4 months, long regimens >4 months (data on short regimens were not always available).*

[b] *Based on expert opinion because data for key population groups were not available.*

[c] *Actual coverage was 75% among regular migrants and 95% for asylum seekers. A value of 80% was assumed because the number of regular migrants exceeds the number of refugees, and undocumented migrants had to be taken account of. See [64,65].*

[d] *Combination of homeless people and PWID.*

2.3 Overview of parameters and sources

The complexities of this model make it necessary to use a large number of parameters. The majority of these parameters have to be quantified for each of the four pilot countries.

Parameters have already been presented in the seven sections of Chapter 2.1 and the seven corresponding appendices, including data sources and the reasoning behind their quantification.

Parameters of the model and their location in the text

Natural history: Figure 1 for general values and Tables A2-3 and A3-3 for age, country- and risk group-specific quantifications

Diagnostics: Figures A4-1, A4-2, A4-3 and A4-4, with sources in Table 1

Risk groups: Table A6-2, with explanations in the notes

Transmission: Table 3 (only beta values are parameters)

The above parameters are also included in the sensitivity analysis described in Chapter 3.

As the model described in this report does not include TB deaths, hospitalisations and extrapulmonary TB (EPTB), quantifications for these aspects are not provided. However, for the cost-effectiveness analyses in the corresponding cost-effectiveness report [37], these aspects have been related to the same natural history processes as described here. The cost-effectiveness report demonstrates how TB deaths and hospitalisations are related to the incidence of severe pathology. The report also contains a table on the interconnection of EPTB, the number of (self-reported) PTB cases and the PTB burden.

Other aspects not covered in this report are MDR/XDR TB and the consequences of HIV infection. These aspects are assumed to play only a minor role in the transmission of TB in European countries. However, the high costs of MDR/XDR TB treatment and the accelerated activation of LTBI in HIV-infected patients was taken into account in the cost-effectiveness analysis.

2.4 Sensitivity analysis

The sensitivity of model predictions to alternative values was determined for all parameters of the model. For each parameter (see Chapter 2.3), the value was univariately multiplied with 4/5th and 5/4th to produce lower and higher estimates and thus determined the resulting predicted total number of PTB cases over 20 years in baseline

levels (no LTBI screening) and the proportion of PTB cases averted over 20 years through LTBI screening (TST/IGRA for all risk groups). The same baseline equilibrium situation at time t = 0 was used for the alternative calculations.

For some of the important parameters in the sensitivity analysis with values that cause opposite effects on the predicted impact of LTBI screening, the above analyses were repeated with a combination of the two parameters (i.e. bi-variate sensitivity analysis). For the most part, this meant that two parameters were combined (one parameter multiplied by 4/5th, the other by 5/4th). These analyses were performed only for the Netherlands and Portugal because these countries showed contrasting epidemics with regard to the PWID/homeless group and, to a lesser extent, the size of the first-generation migrant population. Also, only these two countries provided complete data on total group sizes and PTB cases.

The impact of alternative scenarios in coverage and LTBI treatment uptake for all target groups (migrants at the point of entry, migrant prisoners at incarceration, native prisoners at incarceration, and PWID/homeless population) on the proportion of infections averted over 20 years of LTBI screening was also examined. The uptake of LTBI treatment varied from 50% to 90% (in increments of 10%), and the screening coverage ranged from 60% to 100% (for migrants and prisoners) and from 50% to 90% for triennial screening of the PWID/homeless population. All scenarios consisted of TST/IGRA for the specific target group and were developed for the Netherlands and Portugal.

3 Results

3.1 Goodness of fit and validation

Even though the comprehensive model presented in this report is rather complex, a large majority of parameters could be quantified with independent data sources. Several times, expert opinions had to be used and in a few instances arbitrary choices were necessary. In the end, only the three transmission parameters β remained as free parameters; these free parameters were tuned to reproduce the observed PTB incidences in the four risk groups in each of the four countries. It was thus possible to exactly reproduce these numbers (Table 4).

3.1.1 Uncertainty about PWID/homeless group

Table 6 shows that annual PTB incidence in prisoners in the Netherlands is very high (159 cases per 100 000 population) compared with the levels in the rest of the population and in the general PWID/homeless group (67 cases per 100 000 population). As most reported PTB cases in prison are detected during entry screening, it is necessary to view a large proportion of prisoners coming as part of the PWID/homeless group, which is also supported by data [81]. The tendency of participants of the PWID/homeless group to go to prison was therefore increased by a factor of 100, which resulted in a good fit of the data for prisoners and PWID/homeless people (Table 4). The same factor was used for the Czech Republic and Spain.

Table 6. Overview of key epidemiological values for modelling tuberculosis and latent tuberculosis infection control in European 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 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 group (%)	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 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' refers to anyone born in the country, including second-generation migrants and migrants from low-incidence countries (i.e. TB incidence <50 per 100 000).

For Portugal, an approach based on key epidemiological data was used. In Portugal, PTB incidence for prisoners is twice as high as in the Netherlands, but incidence rates in some of the main groups going to prison are much higher. For natives, for example, the incidence rate is 10 times higher in Portugal, and for PWID/homeless people it is four times higher. This situation can only be reproduced by having a lower percentage of the PWID/homeless population go to prison. PTB incidences were fitted in both risk groups (prisoners and PWID/homeless people) by choosing a tendency factor of 10 for Portugal.

3.1.2 Equilibrium situation versus declining trends

An important concession was the assumption that the system is in equilibrium, even though all four countries currently experience rather strong decreases in TB incidence (see Figure A7-1). This is a common simplification in many modelling studies of infectious disease transmission and control: epidemiological data are only needed for a relatively short period, and no information is required on the history of interventions over the past decades. Given the limited availability of historical data (past 10 years), it was decided to not make the modelling even more complex by looking further in the past.

Table 4 shows that PTB incidences could be exactly reproduced at the risk-group level. This was not the case for PTB distribution in natives across all age groups. Data show that 53% (155/293) of native-born Dutch citizens with PTB are in the 45+ age group, while the model predicts only 45% in this age group (131/293). This

underestimation of PTB in older adults is most striking for the Czech Republic. By contrast, the fit for Portugal is very good (48% of PTB in the age group 45+ for both data and model), but the model still tends to underestimate PTB among older native populations, especially in countries with an established TB programme. This can easily be explained by the fact that TB transmission was more common when this age group was young. Many of them have LTBI infections that date back many decades and can result in PTB due to reactivation.

Figure A8-1 shows an attempt to reproduce a declining trend observed in the Netherlands. As a starting point, higher (equilibrium) values were used: longer PTB duration (until treatment) or higher transmission rates (e.g. due to poorer hygienic and nutritional conditions and no contact investigations). As a result, the model showed a higher proportion of PTB among the age group 45+. It was not possible to reproduce the speed of the declining trend that is currently observed in the Netherlands. This can be explained by the fact that the model does not include a very detailed age structure. Only three age groups are included, with death as a fourth compartment to move to (exponential distribution). Existing LTBI will therefore not disappear as rapidly from the population as in an age-structured or individual-based model where people can reach a maximum age of, for example, 90 years. This is another aspect that requires further research.

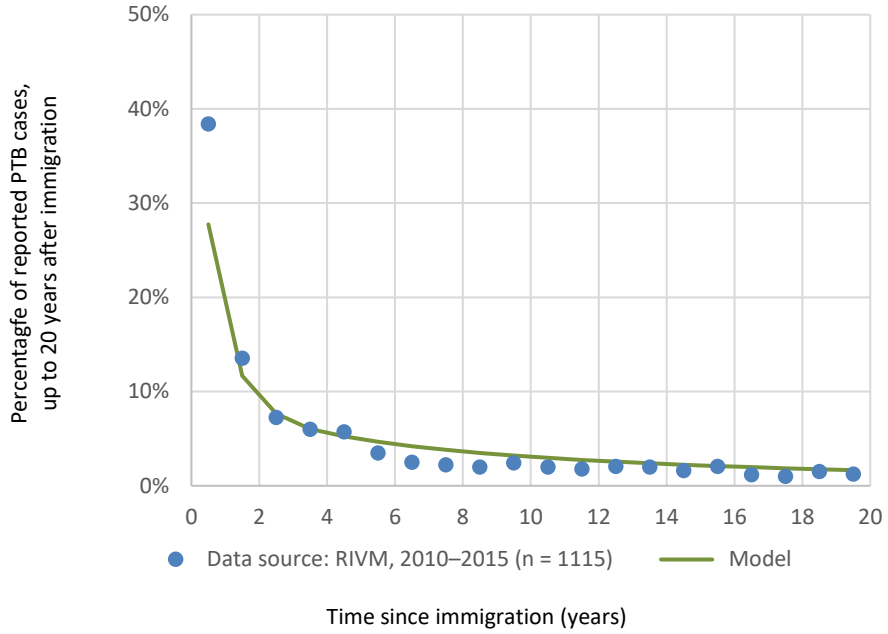
3.1.3 Validation of the model

There are a number of observations that have helped increase confidence in the model. First of all, after fitting the natural history parameters and determining the diagnostic parameters from data, tuning a fixed FOI and the tendency of PTB cases to migrate made it possible to exactly reproduce the proportions of TB-positive migrants detected during entry screening (positive IGRA, TST and CXR/culture) for the Netherlands (Figure 4). In addition, the model predictions were in concordance with independent data about the proportion of migrants with CXR abnormalities and the proportion of TB cases that report symptoms.

The model also receives validation from studies about LTBI prevalence in risk groups in different countries. Two studies reported that 30% of migrants in Spain had a positive TST [99,100]. The distribution across LTBI stages calculated for Spain was estimated at 22%, based on the 10 TB-endemic countries with the most migrants to Spain (see Table A5-1). This could mean that the assumptions on the sensitivity and specificity of TST are not fully correct, or that the incidence of LTBI in the (migrant) population is higher than assumed by the model. It is also possible that migrants with TB symptoms and a higher risk of LTBI are more likely to participate in these studies.

Further validation of the model comes from comparing model-predicted patterns of PTB incidence among first-generation migrants from high-endemic countries since arriving in the Netherlands. Data on migrant PTB cases by time since immigration were obtained from RIVM (Dutch Institute for Public Health and the Environment). Figure 9 shows that the pattern predicted by the model is rather similar to these data, supporting the assumptions on the duration of LTBI, the associated estimated rates of activation and reactivation, and TB transmission among migrants. The difference in the percentage of PTB cases detected in the first year (of a total of 20 years) is likely due to the fact that the Netherlands offers voluntary follow-up screening for migrants, which has not been accounted for in the model.

Figure 9. Fitting the model to pulmonary tuberculosis cases in first-generation migrants from high-endemic tuberculosis countries to the Netherlands



PTB = pulmonary tuberculosis, TB = tuberculosis.
Source: Data obtained from RIVM.

3.2 Predicted impact of different LTBI screening strategies

3.2.1 Impact at population level

Figure 10 presents the trends in annual PTB incidence (left panel) and LTBI prevalence (right panel) in the total population over 20 years of LTBI screening in different risk groups and with varying diagnostics. The corresponding proportional changes in annual PTB incidence after 20 years are summarised in Table 7. The country-specific baseline interventions represent a continuation of the screening policies of the last 10 years. All interventions are based on screening for TB disease with CXR, followed by culture for confirmation (see overview in Table A7-2).

The effects of LTBI screening in one particular risk group are relatively modest when looking at the population as a whole. The effect on annual PTB incidence is always similar or somewhat larger than on LTBI prevalence, except during entry screening. This delay can be explained by the fact that averted secondary infections due to reduced transmission also reduce the number of rapid activations of recent LTBI in the short term, but the overall proportion of people with LTBI (most of whom have remote LTBI) will only be affected by continued long-term screening. Only if focussing on all groups in combination, a more substantial impact of LTBI screening can be obtained. The slightly declining baseline trend is due to the assumed 1.5% annual decline in the external FOI (see Section 2.1.7 under subheading 'Other processes relevant for transmission').

The impact of targeted LTBI screening on the PTB epidemic in the total population (i.e. proportional change in annual PTB incidence) differs between countries due to differences in population composition (Figures 10 and 11, Table 7). In the Netherlands, for example, entry screening of migrants is more effective (17–20% reduction in annual PTB incidence), while screening PWID/homeless groups is most effective in Portugal (35–37% reduction in annual PTB incidence) and Spain (11–12% reduction in annual PTB incidence). In the Czech Republic, screening PWID/homeless groups (31–32% reduction in annual PTB incidence) is nearly as effective as screening of prisoners (33–35% reduction in annual PTB incidence). For Portugal and the Czech Republic, screening PWID/homeless groups is favourable because of the relatively large size of the risk groups and their more intense interaction with the rest of the population, both through transmission and PWID/homeless people returning to the low-risk groups. LTBI screening of prisoners in the Czech Republic is effective because of the assumed relatively high representation of PWID/homeless people in prison.

LTBI entry screening of migrants is effective in all countries, but does not have a very strong effect for the population as a whole because it does not extend to first-generation migrants who have already lived in the country for some time. Migrants who already live in the country are a demographically relatively stable group, with emigration or death the main drivers for change. Another reason for the slowdown in the decreasing trend in LTBI

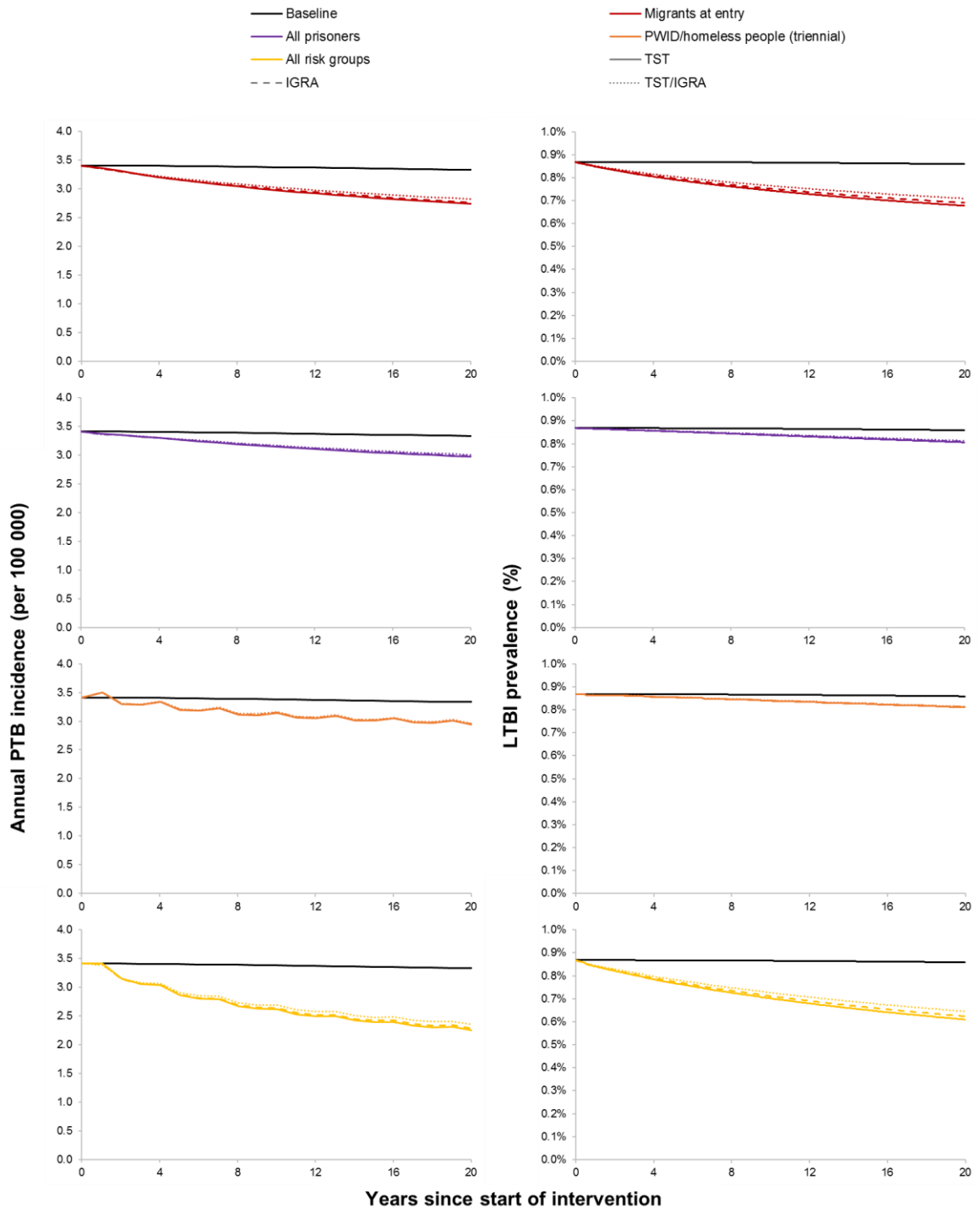
is transmission due to reactivation in people with remote LTBI. Only in the Netherlands, the impact of screening migrants is comparable to the impact of screening prisoners and PWID/homeless groups, because of the country's relatively large migrant population; this leads to more indirect effects due to averted transmission/averted secondary cases in the native population.

Another important finding is that the effect of screening with TST is always slightly higher than with IGRA, while using TST followed by IGRA is the least effective strategy. This can be explained by the fact that TST has a somewhat higher sensitivity than IGRA (Table 1). (Some figures below only show the effects for LTBI screening with TST).

With a combination of screening and treatment for LTBI in all three key population groups, PTB incidence could be reduced by 15%–45%, depending on the country. The impact is smallest for Spain, which can be explained by its presumed relatively small PWID/homeless group, in combination with the fact that migrants to Spain come from countries with a relatively low TB incidence. In all countries, the impact is slightly better when TST is used instead of IGRA.

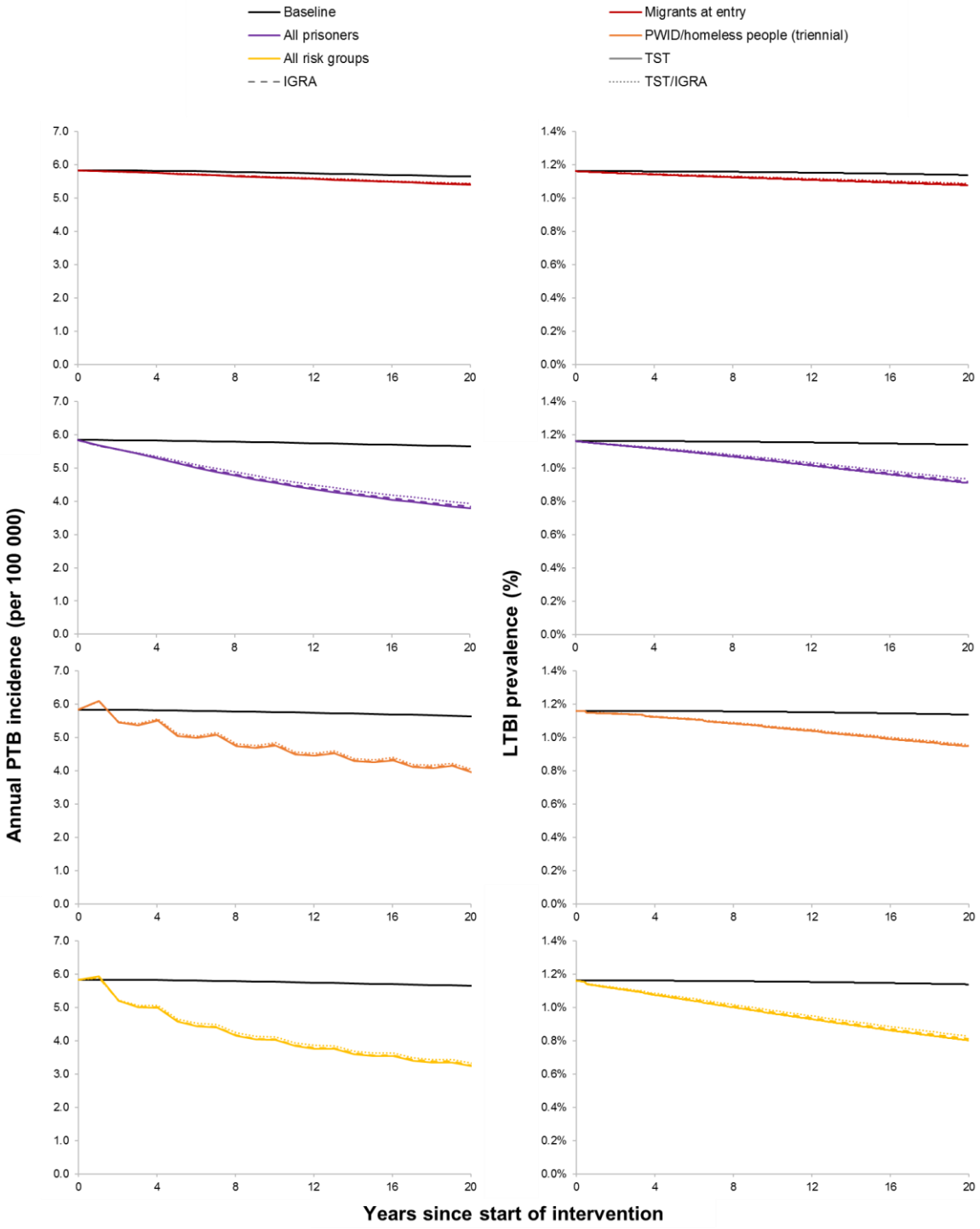
Figures 10a–d. Annual pulmonary tuberculosis incidence (left-hand panels) and latent tuberculosis infection prevalence (right-hand panels) for different diagnostic methods and different screening strategies for latent tuberculosis infection

Figure 10a. Netherlands: population level impact of screening strategies for latent tuberculosis infection



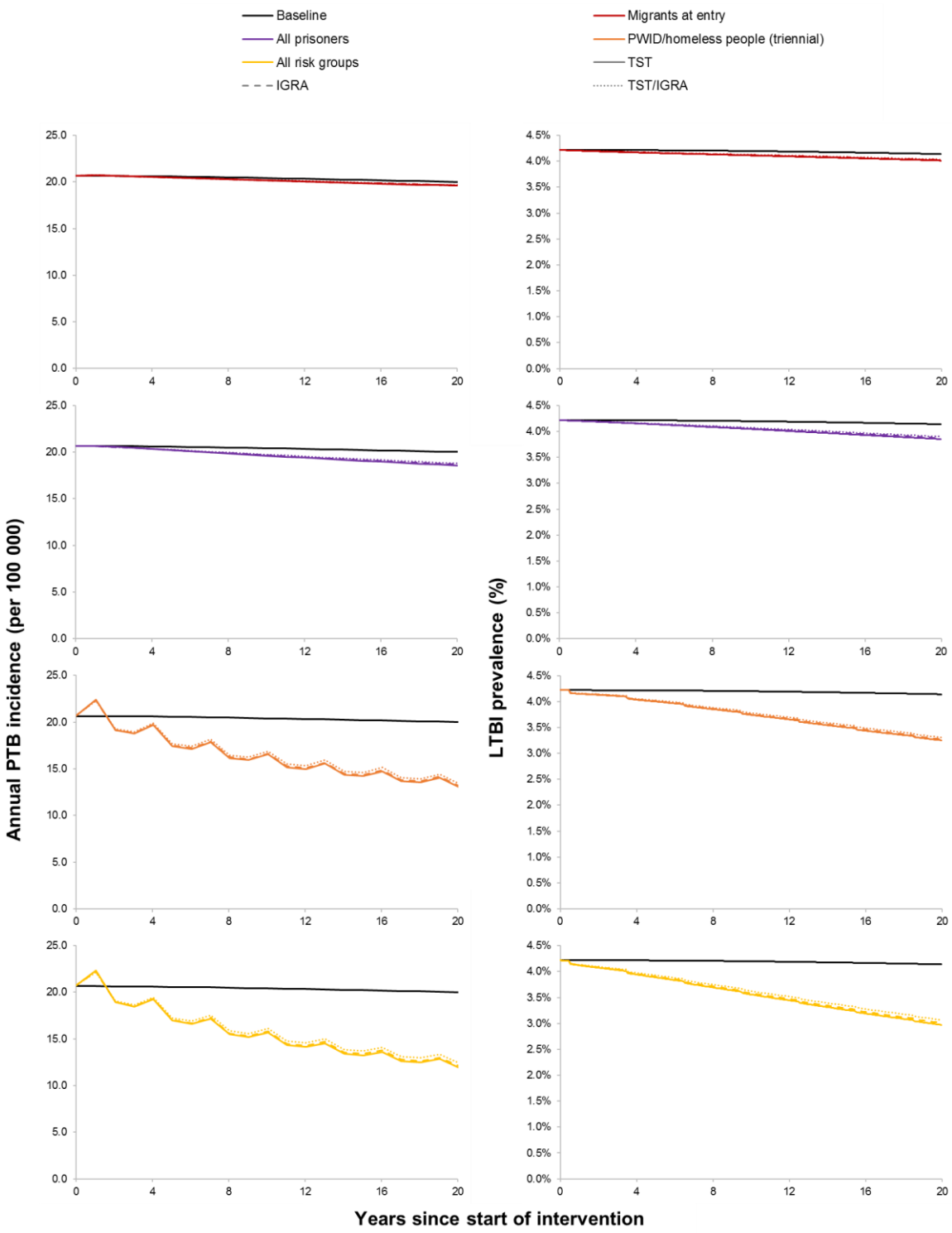
IGRA = interferon gamma release assay; LTBI = latent TB infection. Triennial = screening every three years; TST = tuberculin skin test; TST/IGRA = positive TST followed by IGRA.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 10b. Czech Republic: population-level impact of screening strategies for latent tuberculosis infection



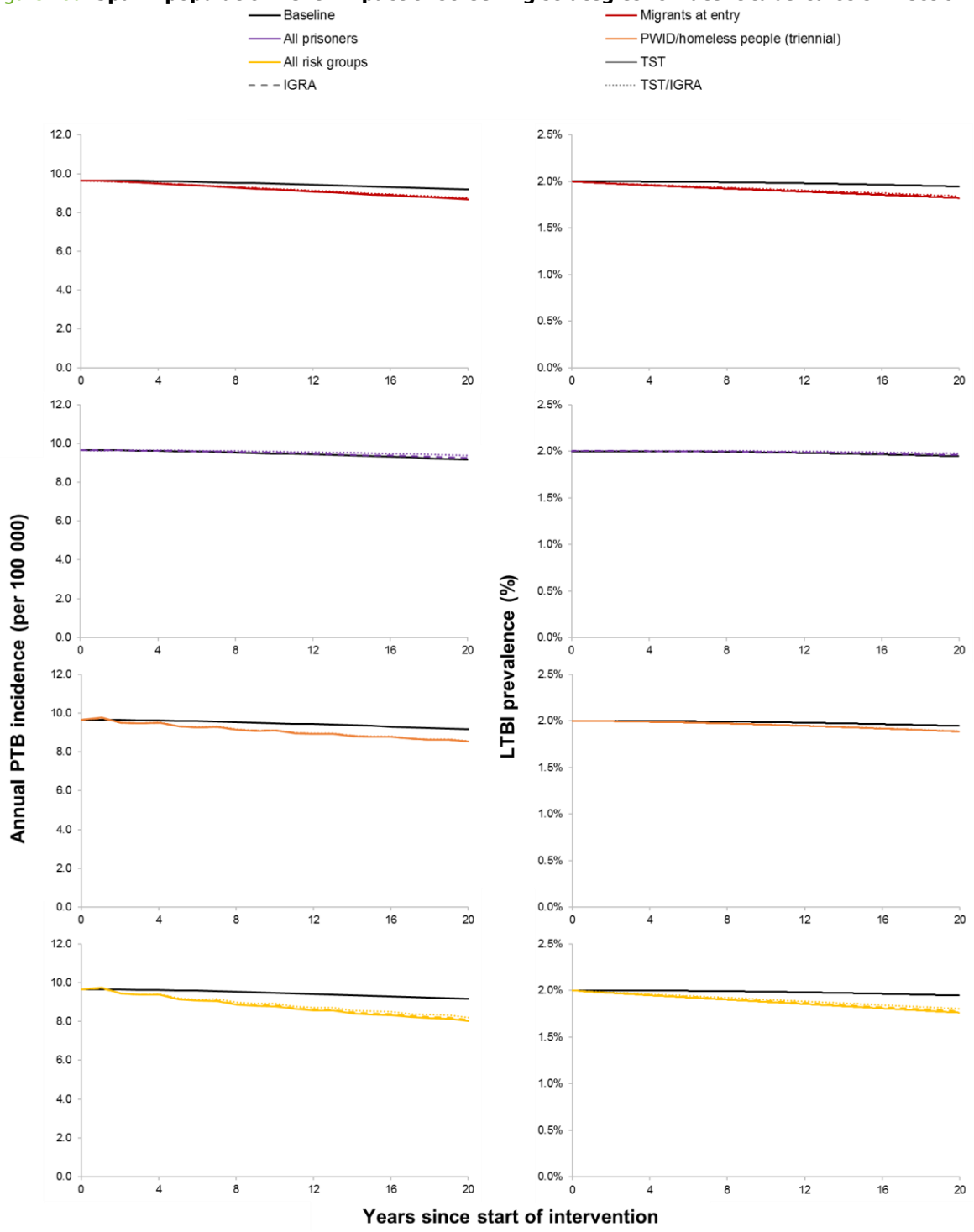
IGRA = interferon gamma release assay; LTBI = latent TB infection. Triennial = screening every three years; TST = tuberculin skin test; TST/IGRA = positive TST followed by IGRA.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 10c. Portugal: population-level impact of screening strategies for latent tuberculosis infection



IGRA = interferon gamma release assay; LTBI = latent TB infection. Triennial = screening every three years; TST = tuberculin skin test; TST/IGRA = positive TST followed by IGRA.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 10d. **Spain: population-level impact of screening strategies for latent tuberculosis infection**



IGRA = interferon gamma release assay; LTBI = latent TB infection. Triennial = screening every three years; TST = tuberculin skin test; TST/IGRA = positive TST followed by IGRA.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Table 7. Proportional change in annual pulmonary tuberculosis incidence after 20 years

LTBI screening strategy	Netherlands	Czech Republic	Portugal	Spain
LTBI entry screening of migrants:				
• TST	19.7%	7.5%	5.1%	10.0%
• IGRA	18.9%	7.2%	5.0%	9.7%
• IGRA after TST	17.2%	6.8%	4.8%	9.2%
LTBI screening for all prisoners at incarceration:				
• TST	12.9%	35.0%	10.0%	NA*
• IGRA	12.5%	34.3%	9.6%	4.1%
• IGRA after TST	11.8%	32.6%	8.9%	2.7%
LTBI screening for PWID/ homeless people; every three years:				
• TST	13.7%	32.1%	36.7%	11.6%
• IGRA	13.5%	31.6%	36.1%	11.5%
• IGRA after TST	13.1%	30.7%	34.9%	11.3%
Combination: all groups TST	34.0%	44.7%	42.1%	16.7%
Combination: all groups IGRA	33.1%	44.2%	41.4%	16.1%
Combination: all groups IGRA after TST	31.2%	43.1%	39.8%	14.8%

Note: Screening of specific key population groups and keeping all other groups at current policy.
IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; NA = not applicable; TST = tuberculin skin test.
** In Spain, TST screening of prisoners is part of the current policy; no policy change expected.*

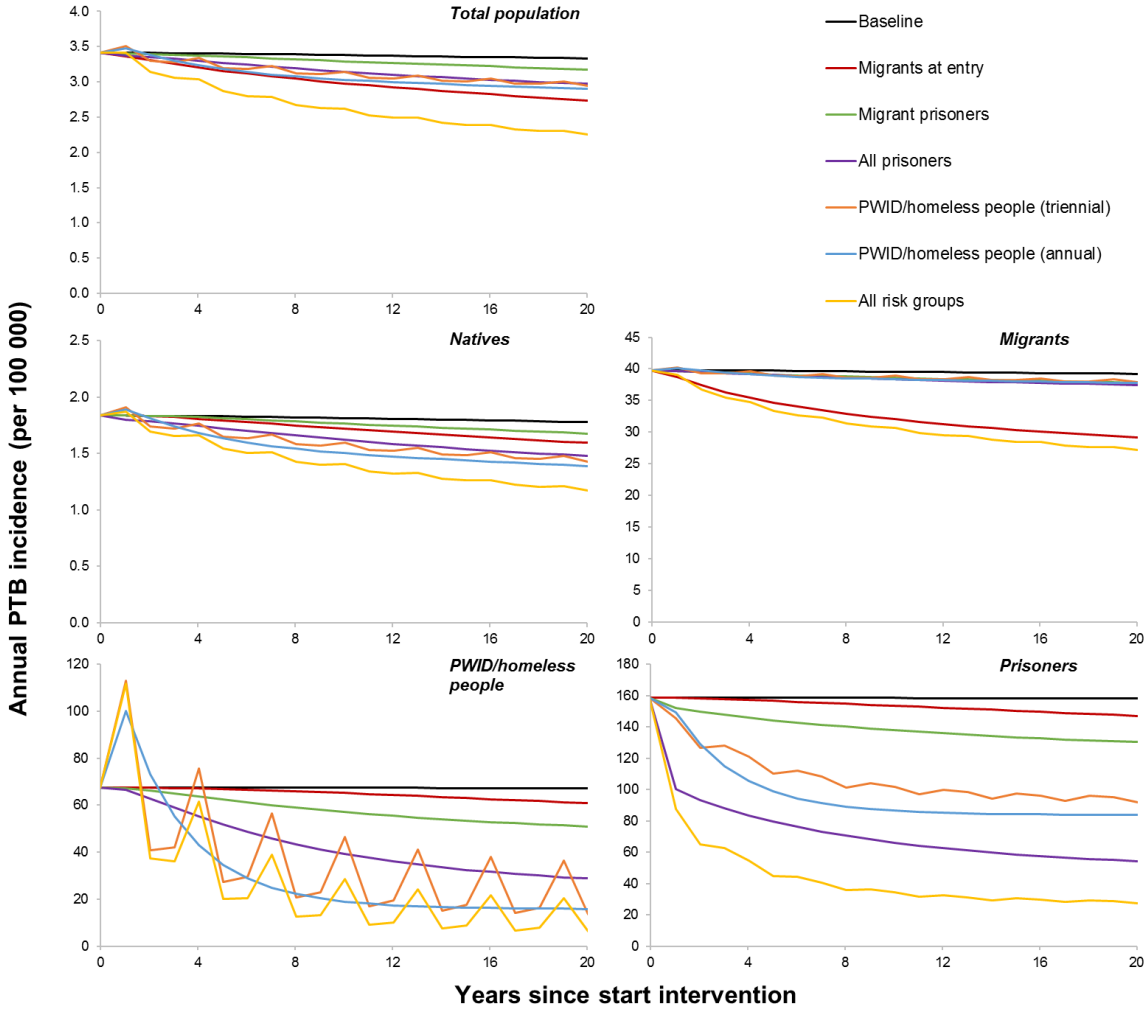
3.2.2 Impact on population groups

Figure 11 shows PTB incidence in different population groups after TST screening and preventive therapy for different key population groups. In general, maximum effectiveness is achieved by first screening PWID/homeless groups (annually), then prisoners, and, finally, by entry screening migrants. For all countries, annual screening of PWID/homeless groups is more effective than triennial screening, even if coverage is lower (50% vs. 70%). This can be explained by the fact that annual screenings reach more people from PWID/homeless groups, given their average five-year retention in the PWID/homeless group. Graphs visualising triennial screening (or a combination including triennial screenings) show typical saw shape triangles, with a repeated sharp increase due to PTB cases detected by screening at specific time points (due to the use of CXR for those with a positive TST or IGRA, or those who report symptoms), followed by a rapid decrease until the next screening round. Obviously, screening all prisoners is more effective than only screening prisoners with a migrant background. Figure 11 also confirms that screening prisoners has a high impact on PWID/homeless groups.

Figure 12 shows the corresponding trends for LTBI prevalence in risk groups. Annual screening and LTBI treatment of the modelled PWID/homeless group also results in saw shape triangles. This is due to the fact that the model produces monthly outcomes on LTBI prevalence, whereas PTB incidences (Figure 11) are calculated annually. As was to be expected, LTBI prevalence drops most significantly in the prison population, especially when doing screening at incarceration, due to the rapid turnover in this population (average prison stays are about three months). This effect cannot be seen in Spain, since in Spain the current policy already includes screening of prisoners with TST at admission. However, after an initial fast drop in the first two years, LTBI prevalence in prison does not decrease much further, because LTBI prevalence in the rest of the population (where most prisoners come from) also largely remains the same.

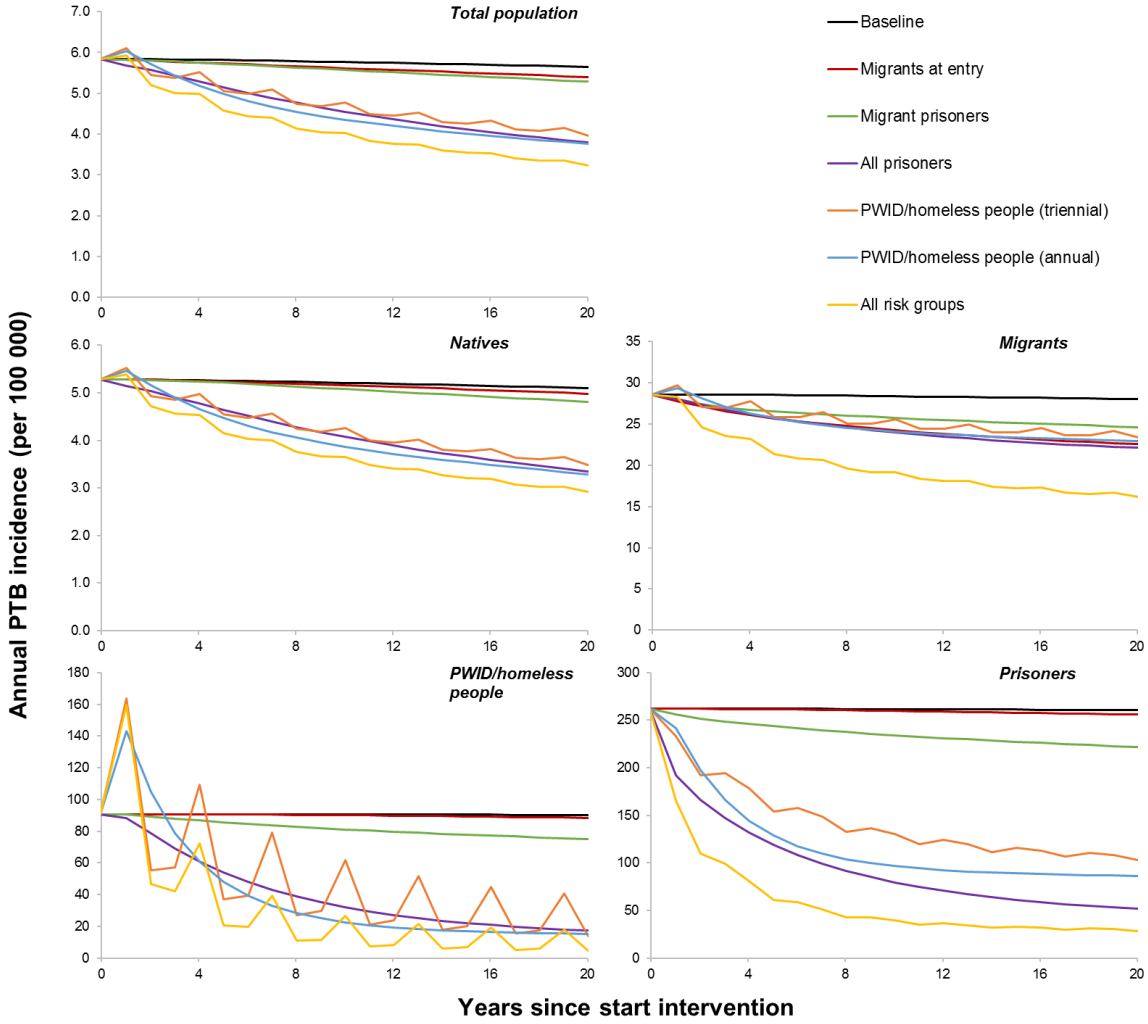
Figures 11a–11d. Impact of tuberculin skin test screening on pulmonary tuberculosis incidence for different screening strategies by risk group in four countries

Figure 11a. Netherlands: impact of screening strategies for latent tuberculosis infection on pulmonary tuberculosis incidence in different population groups



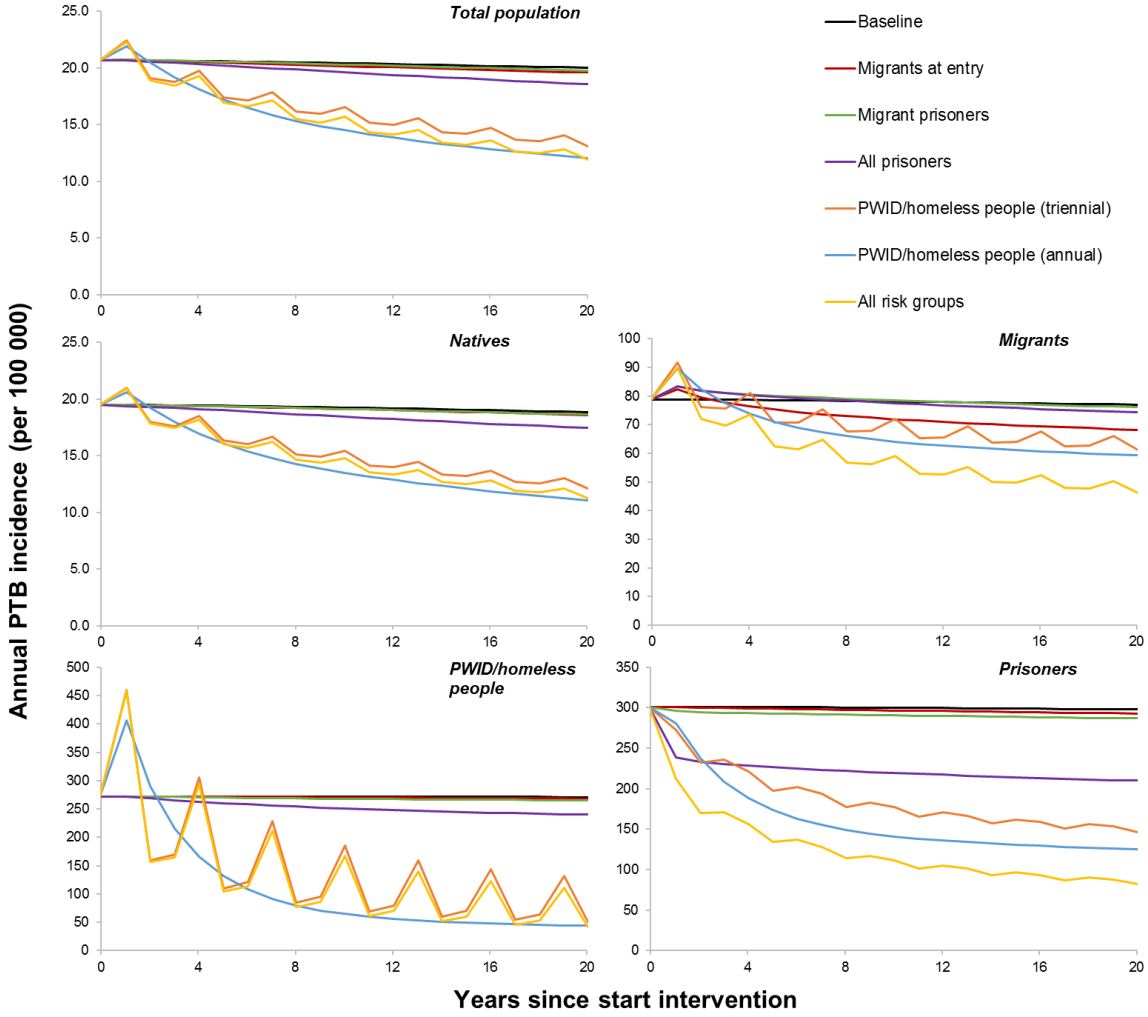
LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 11b. Czech Republic: impact of screening strategies for latent tuberculosis infection on pulmonary tuberculosis incidence in different population groups



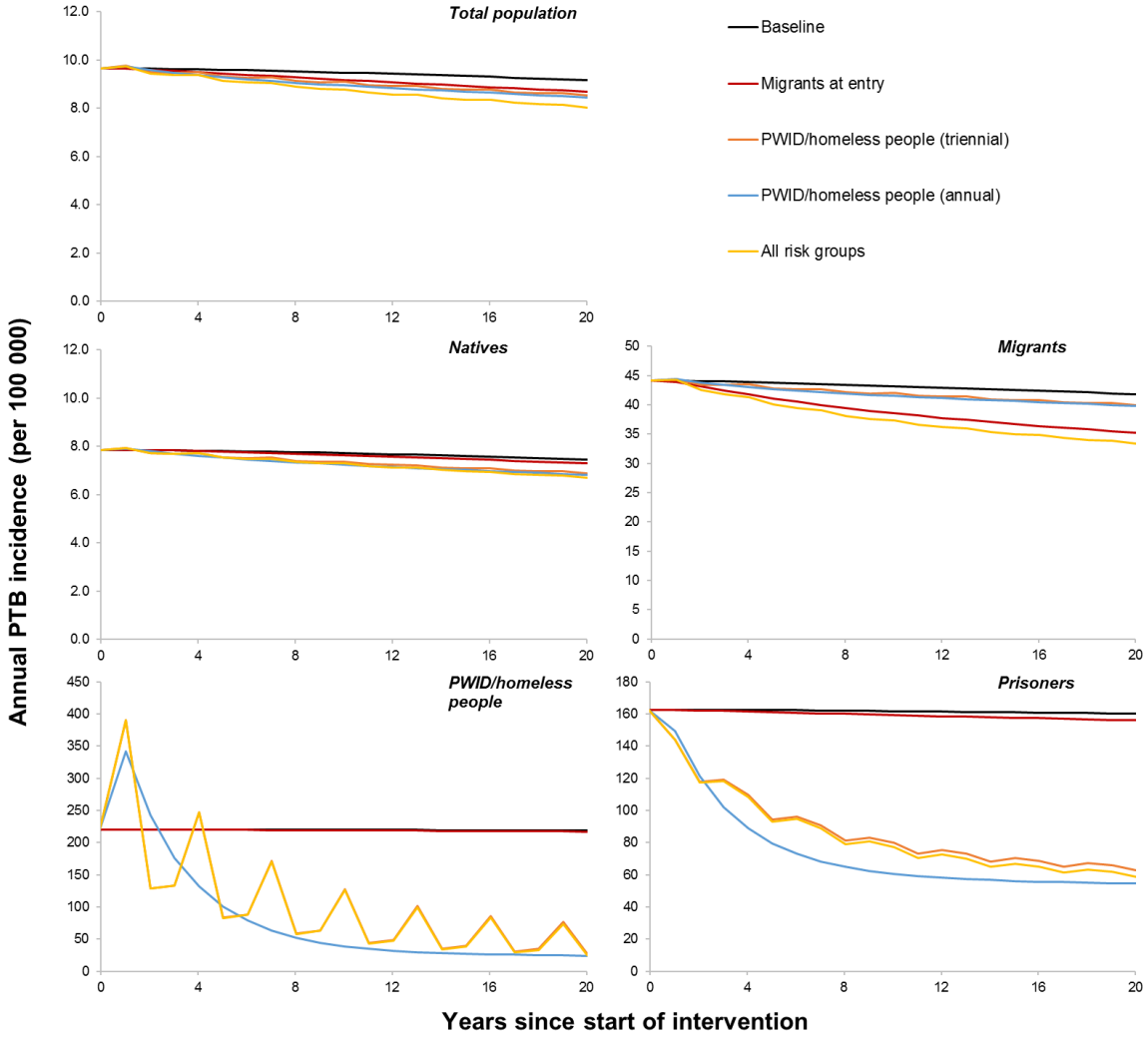
LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 11c. Portugal: impact of screening strategies for latent tuberculosis infection on pulmonary tuberculosis incidence in different population groups



LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

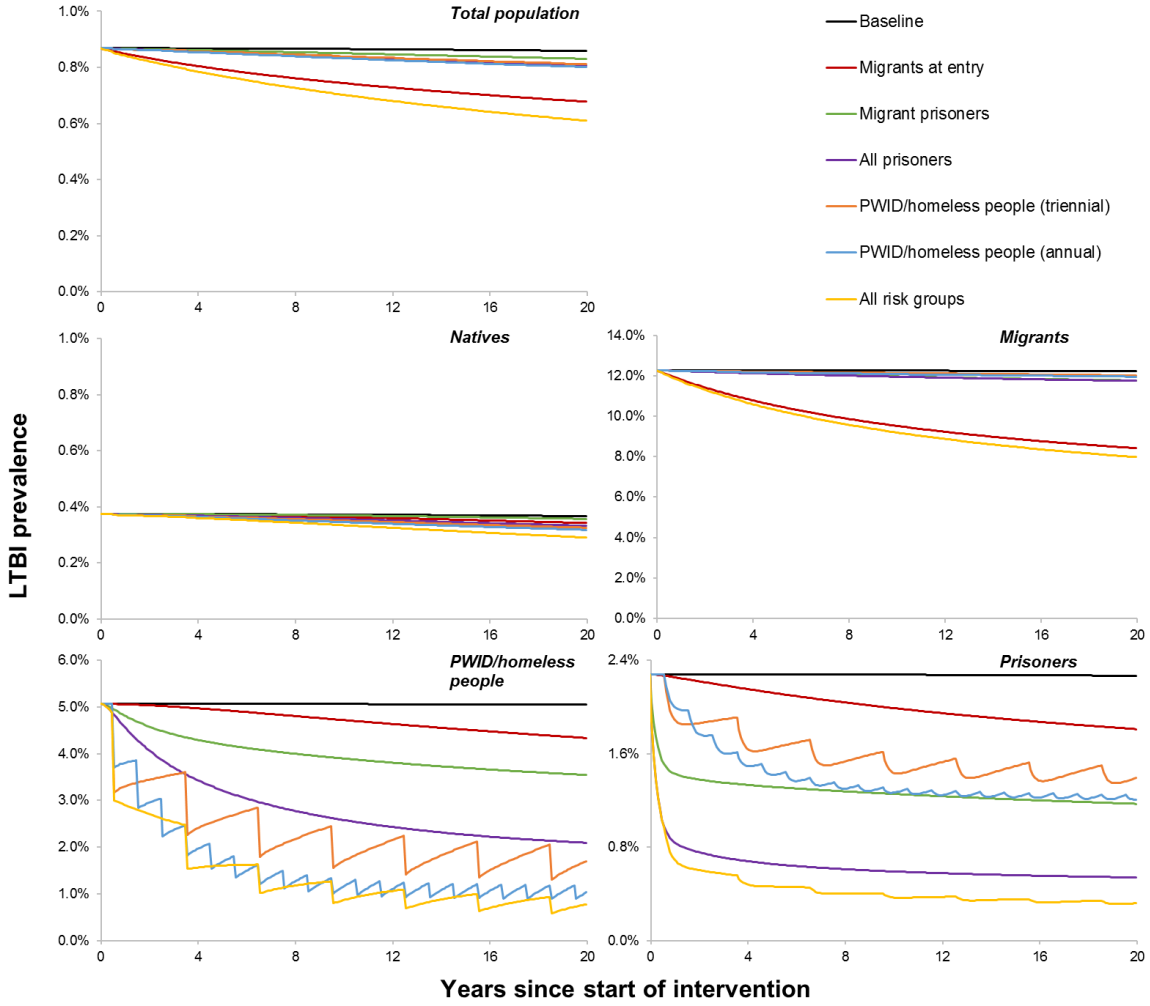
Figure 11d. Spain: impact of screening strategies for latent tuberculosis infection on pulmonary tuberculosis incidence in different population groups



LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

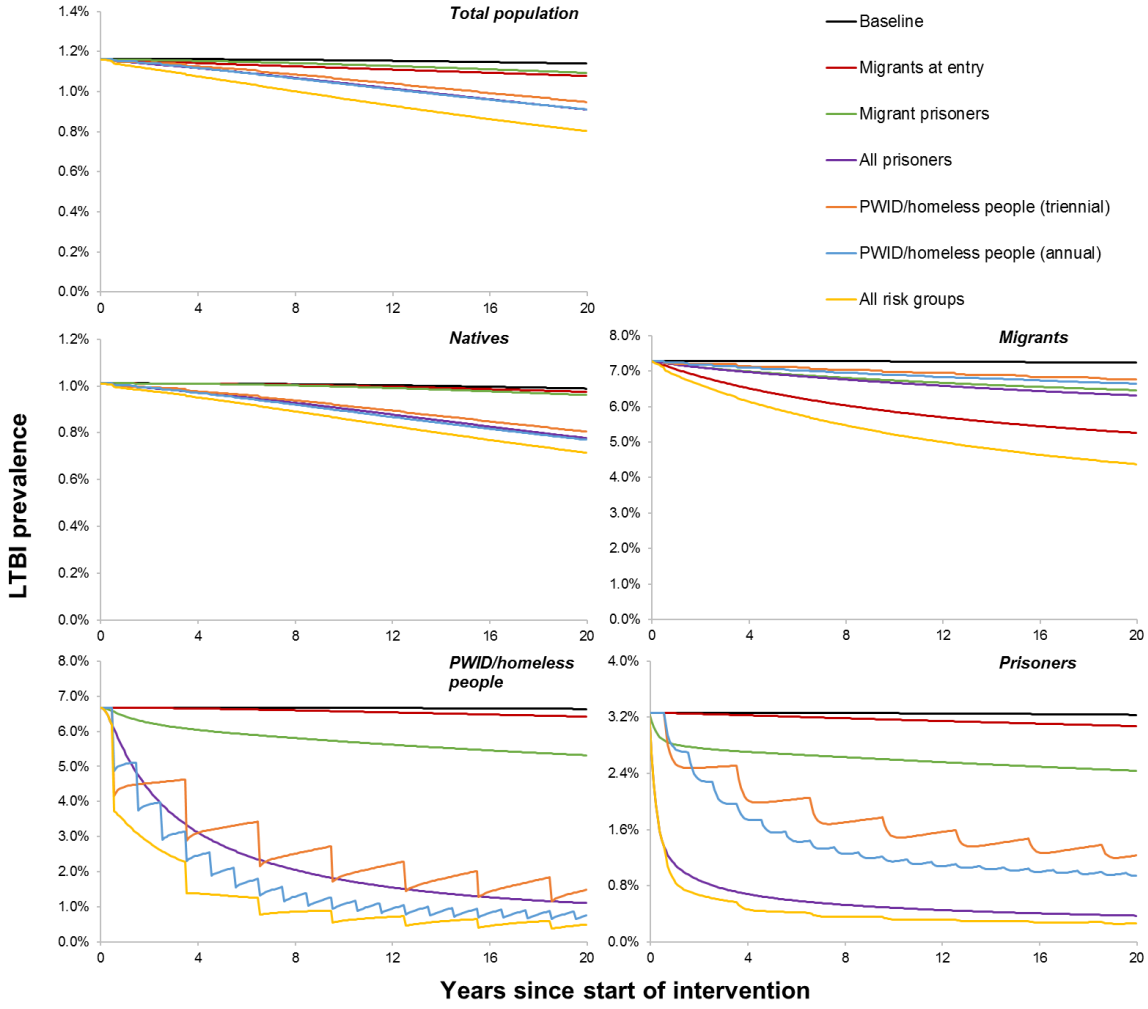
Figures 12a–12d. Impact of tuberculin skin test screening on latent tuberculosis infection prevalence for different screening strategies; by risk group in four countries

Figure 12a. Netherlands: impact of screening strategies for latent tuberculosis infection on latent tuberculosis infection prevalence in different population groups



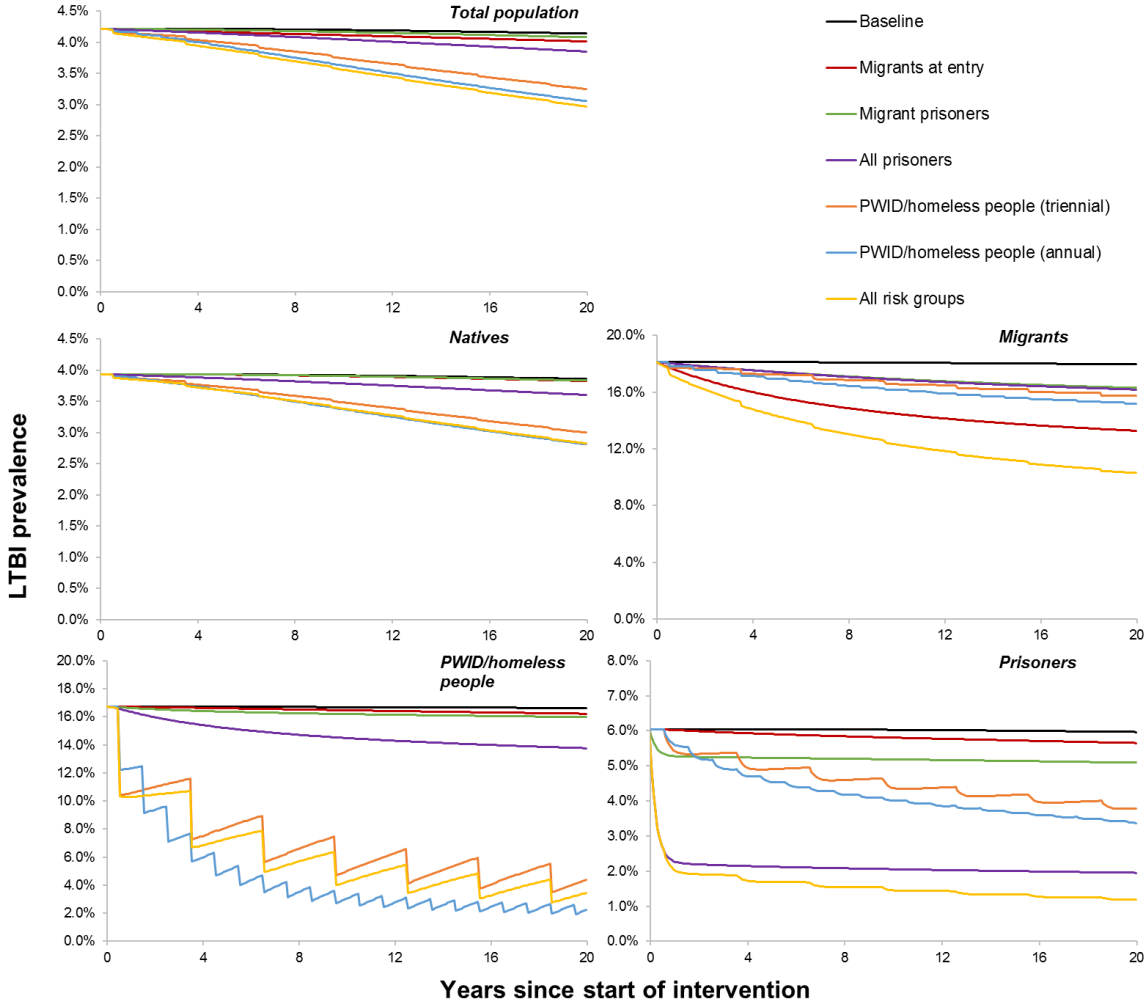
LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 12b. Czech Republic: impact of screening strategies for latent tuberculosis infection on latent tuberculosis infection prevalence in different population groups



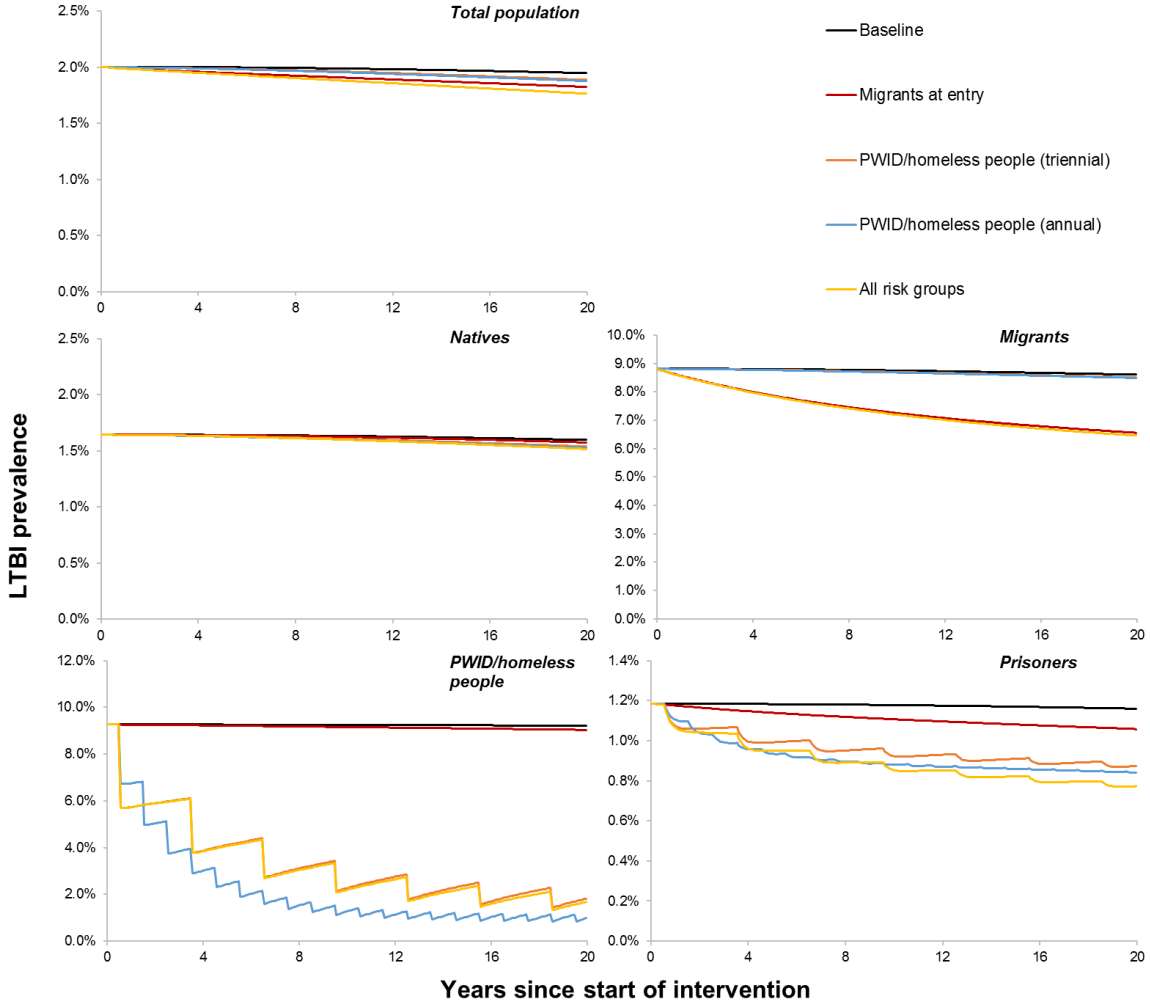
LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 12c. Portugal: impact of screening strategies for latent tuberculosis infection on latent tuberculosis infection prevalence in different population groups



LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

Figure 12d. Spain. Impact of screening strategies for latent tuberculosis infection on latent tuberculosis infection prevalence in different population groups



LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; triennial = screening every three years.
Migrants = migrants from medium- and high-incidence countries (WHO-estimated TB incidence >50 cases per 100 000 population).
The coloured lines indicate which groups are screened for LTBI. The effect shown is the effect on the total population.

3.2.3 Long-term population impact and the prospect of elimination

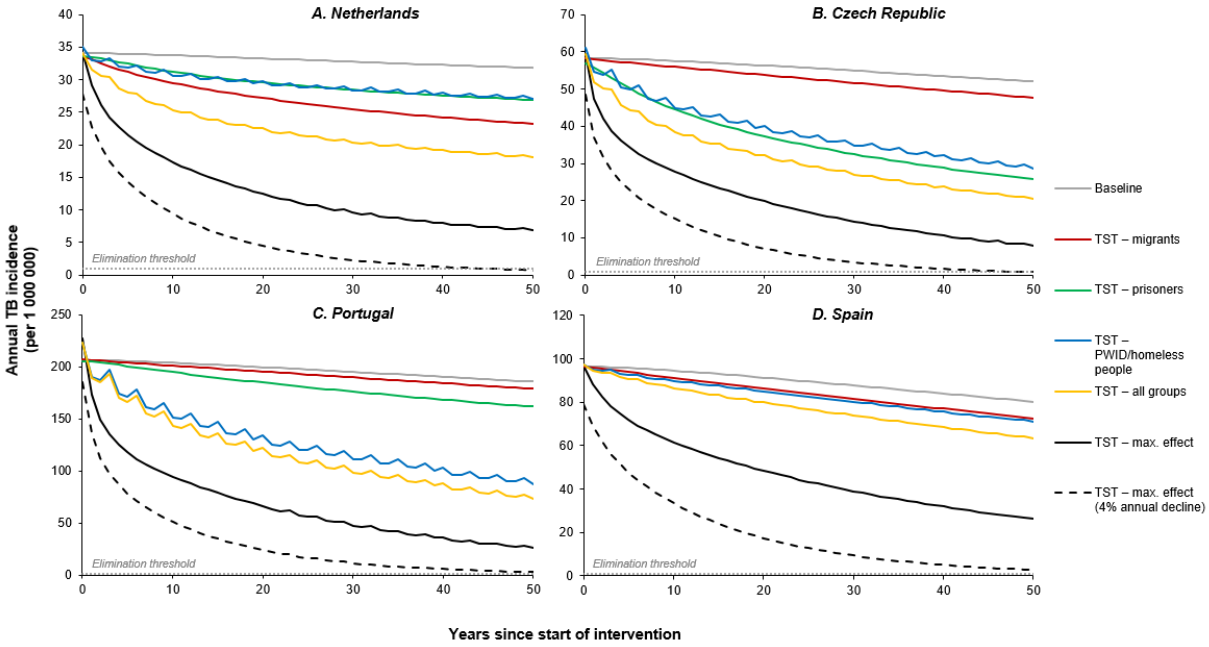
Trends in TB incidence and LBTI prevalence in the four countries were also examined over a period of 50 years of LTBI screening to determine whether elimination is possible within this timeframe. The only trends reported are on TST strategies, as TST was slightly more effective in reducing PTB incidence than IGRA or TST followed by IGRA. A scenario was added in which all strategies reach 100% coverage, infections due to travel were eliminated (i.e. external FOI is set at 0), and all diagnosed cases have a treatment success rate of 100%. An additional scenario included a superimposed annual decline of 4% in the TB burden, as many countries experience a declining trend. Declining trends in PTB case notification rates between 2005 and 2014 are illustrated in Figure A7-1: -4.1% (Netherlands), -7.8% (Czech Republic), -5.5% (Portugal), -11.6% (Spain, five-year trend) [38]. The rate for the Netherlands is expected to be representative of what countries may experience in the coming years, as all of them will have benefitted from a successful TB programme by then.

Figure 13 shows that – even with the assumptions of maximum coverage, maximum effectiveness an no travel-related TB – none of the four countries will reach the WHO elimination threshold of a TB incidence of <1/1 000 000. This is due to further transmission and a substantial proportion of LBTI in the low-risk population, which will eventually result in activation. Only when combining the current declining trend with the maximum optimistic scenario, the threshold is reached. It should, however, be noted that these results are from a deterministic model; studying disease elimination based on exponential durations over such a long time frame is difficult, as the model does not take into account the mortality of specific cohorts. For example, there will always be some level of LBTI prevalence among migrants – despite full screening coverage – due to the prevalence of LTBI among elderly migrants already in the country (see also Chapter 3.1). Furthermore, the predictions in Figure 13 only take into account trends in PTB, whereas the WHO threshold for TB elimination includes PTB and EPTB, making it even more unlikely that the indicated threshold will be reached.

Figure 13 also shows that the long-term effects on PTB incidence differ substantially between countries. In the model for the Netherlands, prisoners and PWID/homeless groups both show a similar decline over 50 years; screening migrants doubles this decline. In the Czech Republic and Portugal, the effect of screening prisoners and PWID/homeless groups has a much larger effect than screening migrants. In Portugal, screening PWID/homeless groups has a larger effect than screening prisoners, which can be explained by the assumed relatively lower tendency of PWID/homeless people in Portugal to go to prison (10 vs. 100 in the other countries) (see also Section 2.1.6 and Chapter 3.1).

Figure 14 gives the 50-year trends for LTBI prevalence in the total population, as the result of different LTBI screening strategies. It was not possible to conduct a real validation of the current LTBI prevalence, apart from some small studies in special groups. Thus, it is uncertain whether these quantifications are close to reality. However, the relative reductions still provide interesting outcomes to help understand the importance of the various population subgroups and the effects of LTBI screening on LTBI prevalence levels. Clearly, the LTBI patterns are largely the same as for PTB incidence, but are less irregular in PWID/homeless groups due to fact that screening immediately leads to a decrease in numbers. The screening of migrants in the Netherlands has a relatively bigger impact than would be expected from PTB incidence trends, which is due to the relatively large population that immigrated from countries with a relatively high TB incidence.

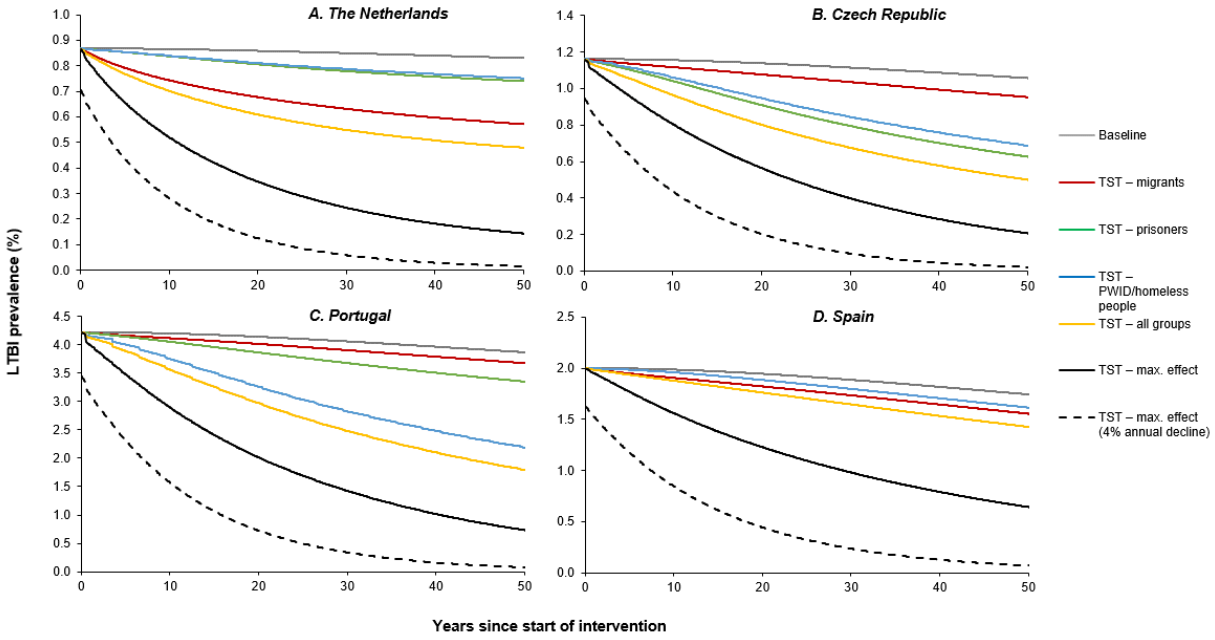
Figure 13. Annual tuberculosis incidence for different tuberculin skin test screening strategies in different risk groups in the Netherlands, the Czech Republic, Portugal, and Spain, over a period of 50 years



LTBI = latent tuberculosis infection; TB = tuberculosis; TST = tuberculosis skin test.

The baseline represents a continuation of the current policy in each country. TST – migrants (red line) = TST entry-screening of all migrants from TB-endemic countries; TST – prisoners (green line) = TST screening of all prisoners at the moment of incarceration; TST – PWID/homeless people (blue line) = triennial screening of PWID/homeless populations; TST – all groups (yellow line) = combination of the targeting strategies mentioned above; maximum effect scenario (black line) = all strategies have 100% coverage, infections due to travel are eliminated (i.e. external FOI is set at 0), and all diagnosed cases have a treatment success rate of 100%. An additional scenario which includes an annual decline of 4% in the TB burden (dashed black line) was used, as many countries experience a declining trend. The dashed line starts at a lower level because the 4% decline was already assumed to be present in the 10 years before the introduction of the interventions explored by the model. All trends are related to the elimination threshold of <1 per million per year.

Figure 14. Latent tuberculosis infection prevalence in the general population over a 50-year period, by screening strategy for latent tuberculosis infection, for the Netherlands, the Czech Republic, Portugal, and Spain



LTBI = latent tuberculosis infection; TB = tuberculosis; TST = tuberculosis skin test.
The baseline represents a continuation of the current policy in each country. TST – migrants (red line) = TST entry-screening of all migrants from TB-endemic countries; TST – prisoners (green line) = TST screening of all prisoners at the moment of incarceration; TST – PWID/homeless (blue line) = triennial screening of PWID/homeless populations such as homeless people and people who inject drugs; TST – all groups (yellow line) = combination of all targeting strategies mentioned above; Maximum effect scenario (black line) = all strategies have 100% coverage, infections due to travel are eliminated (i.e. external FOI is set at 0), and all diagnosed cases have a treatment success rate of 100%.
An additional scenario which includes an annual decline of 4% in the TB burden (dashed black line) was used, as many countries experience a declining trend. The dashed line starts at a lower level because the 4% decline was already assumed to be present in the 10 years before the introduction of the interventions explored by the model.

3.3 Results of the sensitivity analysis

Sensitivity analyses were only conducted for the Netherlands and Portugal, as these countries showed contrasting epidemics regarding the role of the PWID/homeless group and, to a lesser extent, the size of the first-generation migrant population. Also, only the Netherlands and Portugal supplied complete data on total group sizes and the number of PTB cases per group. This report focuses on the following overall outcomes: 1) cumulative number of PTB cases per 100 000 population over 20 years without LTBI screening (but with CXR screening); 2) the relative reduction (expressed as a percentage) in PTB cases averted over 20 years of LTBI screening with TST/IGRA. For the Netherlands, this amounts to 68 PTB cases, 21% of which can be averted by this strategy. For Portugal, 404 PTB cases are diagnosed, and 22% can be averted.

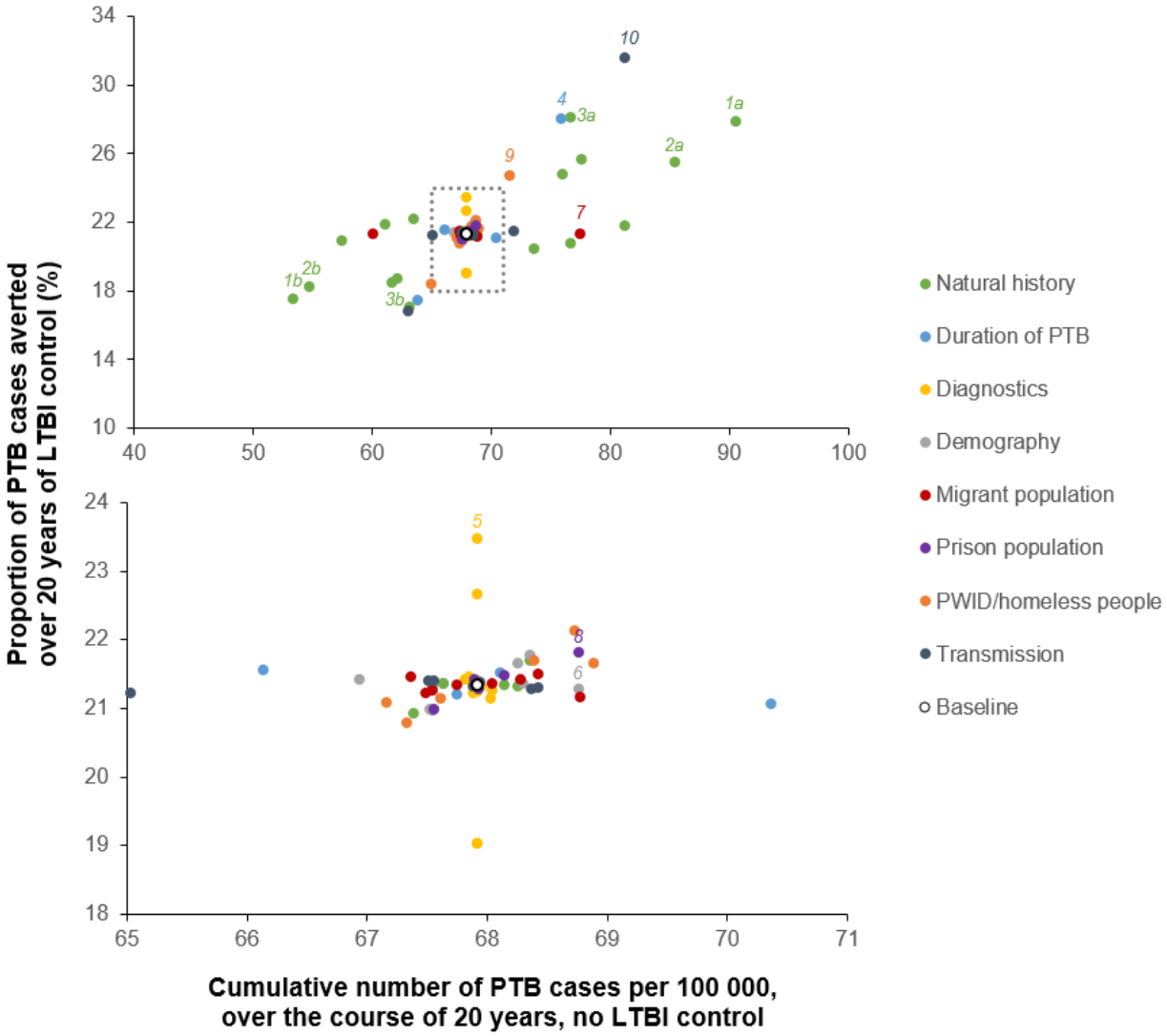
Figures 15 and 16 show the impact of alternative parameter values for all parameters in the model (see Chapter 2.3 for a listing) on the predicted baseline PTB cases in absence of LTBI screening. For both the Netherlands and Portugal, most of the alternative parameter values have very limited impact on the predicted reduction in PTB cases. For the Netherlands, the predicted reduction is 20%–22% for 80% of the alternative parameter values, compared with a 21% reduction (bottom graph, Figure 15). Similarly, 80% of the alternative values for parameters for Portugal result in a reduction of 20%–24%, compared with a 22% reduction (bottom graph, Figure 16).

Model predictions were most sensitive to changes in the natural history parameters (green dots), especially for the progression rate from asymptomatic TB to PTB (numbers 1a and 1b) and the regression rate from asymptomatic TB to remote LTBI (2a and 2b). Increasing or decreasing those parameters results in relatively more or less PTB, and therefore higher or lower rates of transmission. Changing these parameters also substantially changes the predicted total number of PTB cases in the absence of LTBI screening, thus making the model calculations no longer resembling the situation in the Netherlands and Portugal. However, when we combined two opposing parameters, the predicted impact of LTBI screening returned to resembling the baseline (Figure A10-2).

In addition, changes to the parameters for the PWID/homeless population, particularly the relative activation rate (number 3 in Figures 15 and 16), the duration of PTB in PWID/homeless people (number 4), the time of retention in the PWID/homeless group (number 9), and the β value for PWID/homeless people (number 10) all have a relatively large impact on the predicted effects of LTBI screening. This highlights the importance of further research to adequately assess the quality of the data against which the model was quantified and to gain more insight into the size and importance of the PWID/homeless group in the overall epidemic.

Figure 17 shows the 20-year incidence reduction in PTB under alternative scenarios of LTBI treatment uptake for the different target populations in the four countries. As expected, the predicted impact of LTBI screening increases with increasing levels of LTBI treatment uptake. In addition, the graphs clearly reflect the relative size and importance of the risk groups in the overall epidemic. In Portugal and the Czech Republic, the PWID/homeless population is relatively larger, while the migrant population is smaller compared with the Netherlands. Therefore, the impact of LTBI screening in PWID/homeless groups is much more substantial in Portugal and the Czech Republic, while LTBI control for migrants is relatively less effective compared with the Netherlands. Spain obviously has a negative impact of screening prisoners at low LTBI treatment uptake, since they are already screened with TST under the current policy, assuming an 80% LTBI uptake. The relative importance of risk groups is also reflected in the impact of alternative scenarios of coverage of LTBI screening (Figure 18).

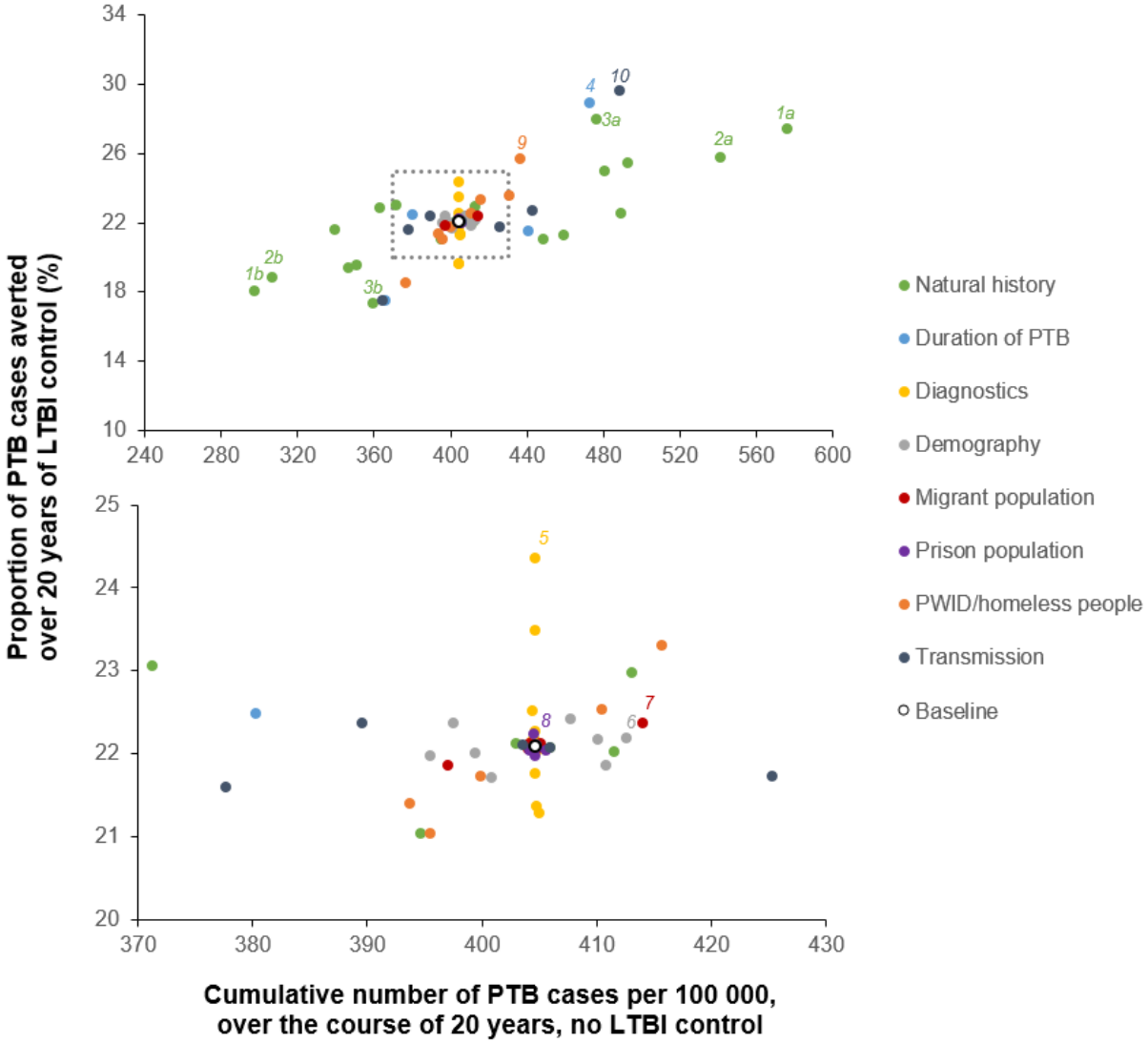
Figure 15. Impact of increasing/decreasing values of all parameters on model predictions regarding the impact of latent tuberculosis infection screening in the Netherlands



LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis, TB = tuberculosis.
Parameter values for all parameters were multiplied by 4/5th and 5/4th to decrease/increase values. Dots represent the corresponding predictions in terms of the cumulative total number of PTB cases per 100 000 people in a period of 20 years without LTBI screening (x-axis) and in terms of the proportion of PTB cases averted over the same period in the presence of LTBI screening (y-axis). The bottom graph provides an enlarged view of the dotted square in the top graph.
The LTBI screening scenario considered in these analyses was TST/IGRA for all risk groups.

The colours represent different parameter subsets. For each parameter subset, the most sensitive parameters are highlighted with numbers:
1a. Rate of progression from asymptomatic TB to PTB (multiplied with 5/4th)
1b. Rate of progression from asymptomatic TB to PTB (multiplied with 4/5th)
2a. Rate of progression from asymptomatic TB to remote LTBI (multiplied with 4/5th)
2b. Rate of progression from asymptomatic TB to remote LTBI (multiplied with 5/4th)
3a. Relative activation rate in PWID/homeless people (multiplied with 5/4th)
3b. Relative activation rate in PWID/homeless people (multiplied with 4/5th)
4. Duration of PTB for PWID/homeless people (multiplied with 5/4th)
5. Proportion positive for IGRA in stages R1, R2, L1, L2, A1, A2 (multiplied with 5/4th)
6. Duration of age group 15–44 (multiplied with 5/4th)
7. Size of the migrant population (multiplied with 5/4th)
8. Average time until incarceration for PWID/homeless people (multiplied with 5/4th)
9. Average duration of PWID/homeless people (multiplied with 5/4th)
10. Beta people (multiplied with 5/4th)

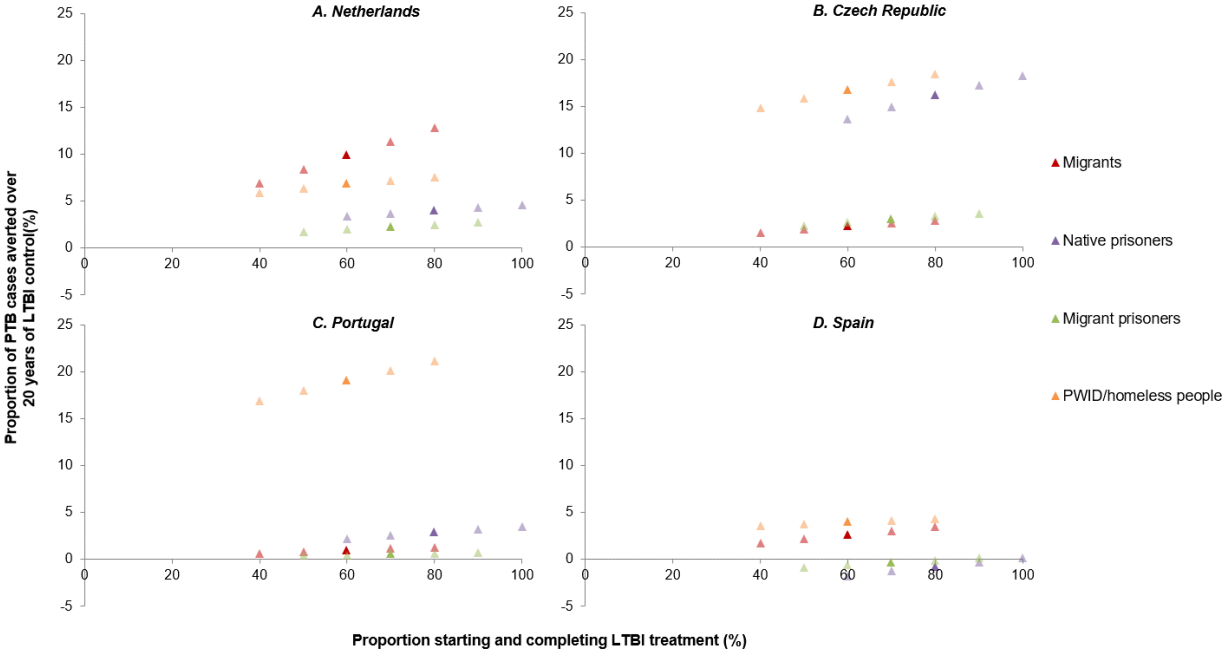
Figure 16. Impact of increasing and decreasing values of single parameters on model predictions regarding the impact of latent tuberculosis infection screening in Portugal



LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis, TB = tuberculosis.
Parameter values for all parameters were multiplied by 4/5th and 5/4th to decrease/increase values. Dots represent the corresponding predictions in terms of the cumulative total number of PTB cases per 100 000 people in a period of 20 years without LTBI screening (x-axis) and in terms of the proportion of PTB cases averted over the same period in the presence of LTBI screening (y-axis). The bottom graph provides an enlarged view of the dotted square in the top graph.
The LTBI screening scenario considered in these analyses was TST/IGRA for all risk groups.
The colours represent different parameter subsets. For each parameter subset, the most sensitive parameters are highlighted with numbers:
1a. Rate of progression from asymptomatic TB to PTB (multiplied with 5/4th)

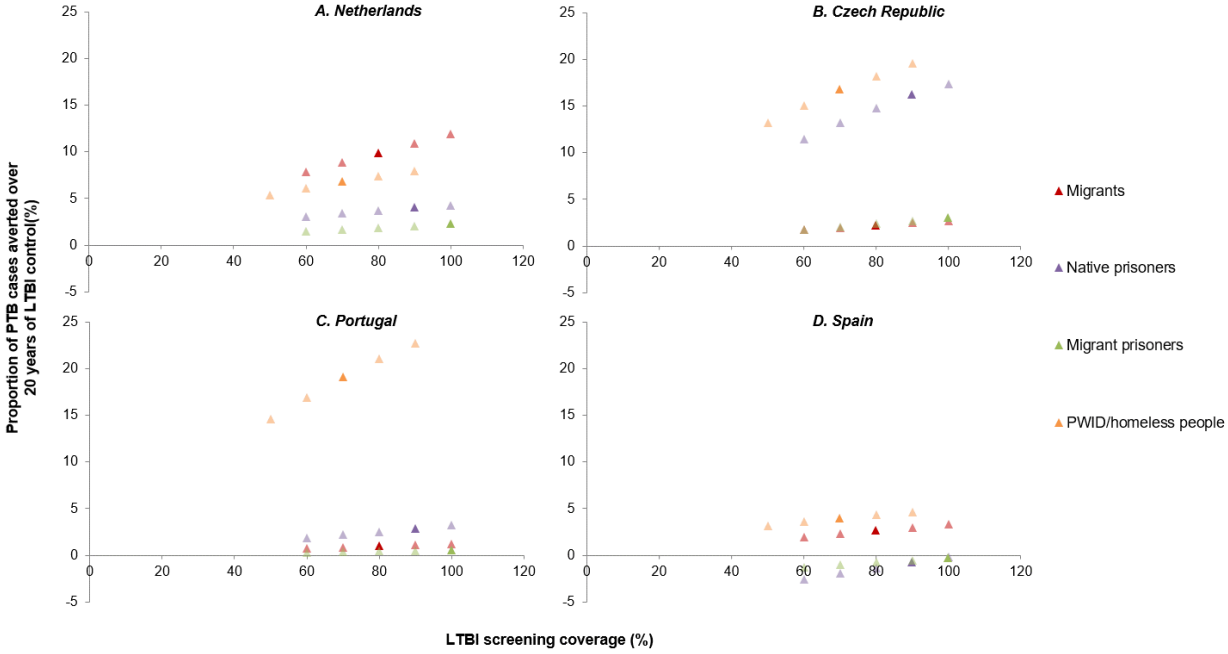
1b. Rate of progression from asymptomatic TB to PTB (multiplied with 4/5th)
2a. Rate of progression from asymptomatic TB to remote LTBI (multiplied with 4/5th)
2b. Rate of progression from asymptomatic TB to remote LTBI (multiplied with 5/4th)
3a. Relative activation rate in PWID/homeless people (multiplied with 5/4th)
3b. Relative activation rate in PWID/homeless people (multiplied with 4/5th)
4. Duration of PTB for PWID/homeless people (multiplied with 5/4th)
5. Proportion positive for IGRA in stages R1, R2, L1, L2, A1, A2 (multiplied with 5/4th)
6. Duration of age group 15–44 (multiplied with 5/4th)
7. Size of the migrant population (multiplied with 5/4th)
8. Average time until incarceration for the general population (multiplied with 4/5th)
9. Average duration of PWID/homeless people (multiplied with 5/4th)
10. Beta PWID/homeless people (multiplied with 5/4th)

Figure 17. Impact of alternative scenarios for the proportion of people identified infected with latent tuberculosis that successfully complete latent tuberculosis infection treatment on the proportion of pulmonary tuberculosis cases averted over 20 years of latent tuberculosis infection screening in the Netherlands, Czech Republic, Portugal, and Spain



LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis, TST = tuberculin skin test.
Tested strategies: triennial screening of PWID/homeless group (orange); entry screening of migrants (red); screening of native prisoners at incarceration (green); and screening of migrant prisoners at incarceration (green). Screening was done with TST. Alternative scenarios are displayed in lighter shades of the main colour, while the baseline is displayed in the main colour.

Figure 18. Impact of alternative scenarios for the coverage of latent tuberculosis infection screening on the proportion of pulmonary tuberculosis cases averted over 20 years of latent tuberculosis infection screening in the Netherlands, the Czech Republic, Portugal, and Spain



LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis.
Tested strategies: triennial screening of PWID/homeless group (orange); entry screening of migrants (red); screening of native prisoners at incarceration (green); and screening of migrant prisoners at incarceration (green). Screening was done with TST. Alternative scenarios are displayed in lighter shades of the main colour, while the baseline is displayed in the main colour.

4 Discussion

A novel deterministic transmission model of TB in low-endemic countries was developed which combines the most important risk groups contributing to transmission. The model also contains a detailed natural history component that was able to reproduce the results of several studies on different steps in the development from LTBI to active pulmonary disease, followed by severe pathology and death. It was used to estimate the effectiveness of LTBI screening for different risk groups in European settings in reducing transmission and reaching elimination of TB. The main outcomes were expressed as incidence trends for active PTB and prevalence of LTBI, both in different risk groups and in the population as a whole. The model was tested for the Netherlands, the Czech Republic, Portugal, and Spain. The most effective LTBI screening strategy in all countries was targeting PWID and homeless people, while LTBI entry screening of migrants showed the least impact on overall TB incidence. The WHO elimination threshold (TB incidence of less than one case per million) was not even remotely reached for any of the countries after a 50-year LTBI screening programme for all risk groups, even with maximum coverage and treatment uptake.

Chosen modelling approach

Initially, an individual-based modelling approach was chosen as main modelling approach. Individual-based modelling is particularly useful for simulating individual heterogeneities, such as different risks of TB transmission for people in different risk groups. In addition, individual-based modelling makes it possible to study contact investigations, but this would have required modelling the complex dynamics of contact networks (households, workplaces, etc.), which would have been very time-consuming. Instead, the implementation of an individual-based model (TBSIM) was initiated, using a flexible generic modelling environment developed in Java (Appendix 10).

The deterministic model (in Excel) was initially intended to be used as a verification of the calculations with TBSIM, which is an essential component of good modelling practice when using complex individual-based modelling. After gaining a better understanding of the epidemiological data, however, it became clear that individual-based modelling would be an unfeasible approach for modelling TB transmission in different population groups in European countries. The prisoner and PWID/homeless populations simply contain too few TB cases to provide accurate predictions within a reasonable time frame. To reduce stochastic variation for fitting and prediction in individual-based models, hundreds to thousands of repeated runs are required. Such models for infectious diseases therefore typically have a population size of around 100 000 people in order to keep calculation time at a reasonable level. Reproducing the 23 PTB cases that occur each year in Dutch prisons would have required a model with a total population of nearly 17 million people. Running a model at this population scale was not possible with the available ICT infrastructure.

Therefore, a deterministic population model was used for the population-based calculations, both for the effectiveness/elimination outcomes of this report and the population-based cost-effectiveness outcomes of the cost-effectiveness report. The cohort-based cost-effectiveness outcomes could still be based on a cohort version of TBSIM, with the population model providing the initial distribution across LTBI and TB stages, as well as the predicted transmission (i.e. FOI) over time with and without LTBI screening. In a cohort model, the number of people would be less of an issue, as people do not have to be simulated as a complete population (to allow for interactions through transmission). Although it was possible to simulate a migrant cohort with this approach, covering all information on initial LTBI/TB distribution and FOI for all modelled cohorts (including the verification of TBSIM with the deterministic model), the approach was considered too time-consuming. Therefore, the same modelling environment (Excel) was used for the cohort calculations as well. Incidentally, TBSIM provided similar results for the migrant cohort, which could be considered a verification of the predictions with the deterministic model.

As this report demonstrates, using deterministic modelling is sufficiently useful for the objectives at hand. The calculations are scientifically sound and have acceptable accuracy, given the limitations of the available data. Advanced individual-based modelling technologies may make it possible to further improve the calculations. Filling the gaps in knowledge about TB, its transmission and control, is likely a more important prerequisite for a significant step forward.

Combined high-risk group (PWID and homeless people)

The quantifications of the model differed substantially for each country. Most importantly, PWID/homeless groups in the Netherlands and the Czech Republic were relatively small, but had a relatively high TB incidence and a high rate of incarceration. By contrast, the PWID/homeless group in Portugal was relatively large, but had a much lower rate of incarceration. The data from Spain on the size of the PWID/homeless group seemed unrealistically low compared with other countries. Regardless of these differences, screening and treatment for LTBI in the

PWID/homeless group resulted in a rather steep decrease in PTB incidence in the total population overall. Three different aspects of the PWID/homeless group are particularly important for driving TB transmission. Firstly, people in the PWID/homeless group have a higher transmission rate (β_{high}) so that active PTB cases result in relatively more new infections than in the general population. Secondly, the TB activation rate in PWID/homeless people is twice as high as in the general population, due to generally poor health. And thirdly, the access of PWID/homeless people to treatment is worse (PTB lasts three months longer). The parameters governing the high relative rate of activation and duration of PTB were assumed, and only the value of β_{high} was fitted to the available epidemiological data, leading to a value crudely twice that of β_{low} for all countries. All aspects are important for the predictions, as demonstrated in the sensitivity analysis (Figures 15 and 16), but parameters are also largely interchangeable, as can be concluded from the sensitivity analysis where two parameters were replaced with opposite parameters (Figure A8-1)

While the PWID/homeless groups seems to be the most important group for determining transmission and measuring the impact of LTBI screening in European countries, it was also the group with the least amount of data available. Even more importantly, the received data may not be reliable, because monitoring hard-to-reach populations such as homeless people and PWID in order to determine their TB burden is notoriously difficult. Therefore, given both the relative importance of, and uncertainty in, the data pertaining to the PWID/homeless group, it is essential that screening tests for risk groups are conducted before expanding to a larger scale.

Findings on TB elimination

Even with maximum coverage, treatment completion in all risk groups, and the elimination of infections imported through travel, reaching the TB elimination threshold (< 1 case per million) within the next 50 years is almost impossible. European countries are considered to be in the TB pre-elimination phase if their TB case notification rate is below 10 cases per 100 000 population [34]. According to the ECDC 2016 surveillance report, 22 out of 30 reporting countries have reached this level [38]. Although two of the pilot countries are in the pre-elimination phase, our model predicts that it is not likely that any country will get even close to the WHO elimination target of < 1 case per million in Europe within the next 50 years, even if we assume maximum LTBI control efforts and an additional declining trend of 4%.

Two shortcomings of the model should be taken into account. Firstly, similar to many other TB transmission models, the quantifications of the TB epidemics were developed in equilibrium because the model is not very suitable for incorporating trends and getting fitted to historical trends. Secondly, there is no consensus on the reasons for the observed decline in TB incidence. Thirdly, data about long-term trends are lacking for many countries. Still, it is well known that TB incidence in most European countries has been declining substantially over the past decades (Figure A7-1). Therefore, if the current decline continues, the expected long-term contribution of LTBI screening to elimination might be more substantial than predicted in this report. However, when exploring a rather simple scenario with a superimposed annual decline of 4% in incidence on top of the most optimistic (and rather unrealistic) scenario (i.e. perfect coverage, 100% treatment uptake), elimination will be achieved after 50 years. It is, however, unlikely that the current decline persists; instead, the decline will probably decrease as TB incidence decreases further.

The second shortcoming of the model is its deterministic nature, in particular the stratification into only three age groups. As a result, the model is not able to accurately capture the effects of disappearing (remote) LTBI due to the mortality of cohorts. It will continue to simulate low levels of LTBI, which in turn can activate and cause transmission. In order to study elimination more accurately, an age-structured or individual-based model would be needed. Developing and applying an individual-based model that captures the same amount of detail as the current model would be a major challenge (see above under 'Chosen modelling approach'). An individual-based model would, however, be somewhat more optimistic about the prospects for TB elimination.

Findings on diagnostic tests

In all countries and for all risk groups, the impact of LTBI screening is slightly higher if TST is used instead of IGRA; IGRA after TST has the smallest effect. This is due to the assumed sensitivity of IGRA, which is slightly lower than for TST, based on actual data (Table 1). Studies comparing TST versus IGRA show contradicting results [54,58,101-104].

The decision which diagnostic to use should not be based on effectiveness alone, costs should also be considered. IGRA is more expensive than TST, but when used in combination with TST, the risk of false-positive LTBI detection will be reduced, leading to less LTBI overtreatment. In addition, due to its waning effect, IGRA will less often lead to the treatment of people with past infections that will not activate (see compartments N_1 and N_2 of the complete model, Figures A1-1 and A4-3). These issues are further discussed in the cost-effectiveness report, which uses the same transmission model as presented here.

Findings on LTBI screening of risk groups

The model confirms that screening and treating LTBI in foreign-born persons from high-TB-incidence countries may reduce incidence in low prevalence countries, although the effect is modest [25-27]. This can be explained by the progression to active disease of existing LTBI among migrants already in the country (and who therefore were not screened).

It should be noted that migrants from high-TB-endemic countries are not necessarily the ones that cause most TB cases in their country of destination. In the Netherlands, for example, migrants from Turkey rank high in the top 10 of countries that contribute TB cases, despite the fact that Turkey is not a high-TB-endemic country (migrants from Turkey are not eligible for TB screening). In the model, Turkish migrants are therefore included in the 'native' group. The external FOI assumed for natives is to some extent responsible for the introduction of LTBI from abroad by Turkish migrants. Similarly, migrants from Spain to Portugal also contribute TB cases, and Spain appears in the list of the 10 of countries that contribute the most TB cases. It should be noted in this context that migrants from EU countries, some of which are high-TB-endemic countries (e.g. Romania), have the legal right to refuse TB screening.

In 2010, among European countries, only Norway and Sweden were systematically offering LTBI screening to migrants (TST) entering the host country [105]. Since then, several more countries have begun offering screening [10,70]. In the Netherlands, a pilot project used IGRA for LTBI screening [70] and reported a 23.4% prevalence of LTBI among migrants from high-endemic countries. In Spain, migrants that report with symptoms or come for a general health check-up were screened for LTBI [99,100,106]. It was found that between 21% and 61% of migrants had a TST ≥ 10 mm. For Portugal and the Czech Republic, such information is not available. The yield of LTBI screening is usually larger than that of CXR screening [107,108]. A recent review of economic evaluations reported that 7 out of 9 studies showed that screening migrants from high-incidence countries for LTBI is cost-effective [109]. In the cost-effectiveness report that accompanies this report, LTBI screening of migrants from high-endemic countries was found cost-effective, in particular when migrants came from countries with very high TB burdens. LTBI screening of other groups, however, may provide a promising alternative.

Surprisingly, the model showed that LTBI screening for all prisoners can substantially reduce the incidence of PTB in the total population. This can be explained by the relatively high contribution of the PWID/homeless group among prisoners to TB transmission. As this PWID/homeless population is key in driving overall transmission, regular LTBI screenings for this group are an effective method to reduce TB incidence in prison, in the PWID/homeless group, and indirectly (as prisoners eventually get released) in the general population. A review of TB in prisons found that only 8 out of 34 high-income countries screened with TST [30].

In general, screening and caring for TB in prisons is hampered by insufficient laboratory capacities, insufficient diagnostic tools, interrupted supplies of medicines, unsatisfactory integration between civilian and prison TB services, inadequate infection control measures, and low policy priority for prison healthcare [29].

Strengths and limitations

The incorporation of multiple key populations and the assessment of transmission within and between these groups into a comprehensive model constitute the main strengths of this project. Different stages of LTBI plus asymptomatic TB disease were used, to enable modelling different diagnostic tests. In addition, a detailed reproduction of the cascade of diagnostic tests was included on the probability to be identified as a LTBI or TB case. The model approach includes (averted) transmission to secondary cases. This population approach has advantages over traditional cohort approaches in models, in that cohort approaches may overestimate the effects since there is no interaction between subgroups. For example, in the Netherlands, an estimated 24% of prisoners originate from the PWID/homeless group so effects of screening these groups may overlap and should not be double counted as a cohort approach may do. On the other hand, a cohort modelling approach cannot properly deal with (averted) secondary cases through transmission, leading to an underestimation of the overall effects for the population as a whole. This population model was developed for the European Union, but can also be adapted for other low and intermediate TB burden countries.

An important limitation of this report concerns the lack of representative data for LTBI prevalences in population (risk) groups. While the model was able to reproduce several aspects about TB transmission and development to disease, including a form of validation against independent data on PTB among migrants over time (Figure 9), it remains unclear whether the corresponding underlying levels of LTBI in the different population groups are close to the actual situation. The fact that the actual level of LTBI prevalence is higher (or lower) but results in the same predictions because of different levels of disease activation.

Data of sufficient quality to look at LTBI prevalences were only available for migrants to the Netherlands. In order to assess LTBI prevalences in other population groups (including the general population), new studies and additional data are needed. Such new data could be used to validate and improve our work.

Our estimate of LTBI prevalence seems reasonable for the following reason: a study on a supermarket outbreak in 2004/2005 in the Netherlands estimated the age-adjusted background prevalence of remote LTBI at 1.48% (extrapolated from military recruits) and observed LTBI at 1.69% in supermarket visitors (lowest exposure category) [110]. If we assume that this value decreased to 0.8% over the last ten years, it would be very similar to the total population value used in our study.

Another limitation is that some of the used data sources may no longer be representative, especially given the currently observed declining trends. The model has been fitted to migrant data from earlier studies [64,65,70] in the Netherlands (1998–2005 data and 2005–2011 data), but migrant flows have changed since then, as has the yield of screening [111,112]. In general, a reduction of TB incidence among migrants in the Netherlands was observed [113]. Data on TB prevalence among PWID and homeless people may have also been affected by previous screening strategies [114]. More recent data on LTBI prevalence among migrants would also be useful to improve the model.

The current model ignores aspects that could be potentially relevant for a TB modelling study. For example, MDR TB was not considered, although these patients may be infectious over a longer period because it takes more time to get diagnosed and receive treatment. The proportion of patients with MDR TB is relatively small in Western Europe but certainly not negligible in Eastern European countries [38]. The currently available cartridge-based automated real-time nucleic acid amplification system can diagnose TB and MDR TB early. A more widespread use of this automated molecular test may shorten the time before the start of appropriate treatment [115]. The model also ignores HIV and does not include key populations such as health workers and travellers that may have different risks of transmission and/or activation to disease. Due to their relatively small numbers, they were considered an inherent part of one of the modelled population groups. Still, LTBI screening for these groups could be beneficial and therefore is a subject of the cost-effectiveness analysis, using a cohort-version of the model.

For the Netherlands, underestimation of TB was estimated to be 7.3% in 1998; the model, however, does not correct for possible undernotification [116]. Experts estimate that the proportion of undernotification has been much lower in recent years because cases are notified electronically rather than by paper and mail at the time of the initial study. Also, laboratory notification has been obligatory since 2008 (personal communication, Gerard de Vries and Rob van Hest).

Some key epidemiological parameters could not be directly based on data. Data used on TB incidence in risk groups often have a different definition of numerator (used in TB records) and denominator (used in risk groups counting from e.g. Central Bureau of Statistics), and are therefore not always easy to interpret. Therefore, data from the Netherlands were often used for the other countries, in particular to relate rates for different risk or age groups to each other.

5 Conclusion

A deterministic TB transmission model has been developed using data from four European Union countries (Netherlands, Czech Republic, Portugal and Spain). The model accounts for transmission within and between the general population and different at-risk population groups. It was used to evaluate the contribution of selected LTBI screening strategies towards the achievement of WHO's TB elimination target (less than one TB case per million population).

According to the model, none of the modelled LTBI screening strategies will result in reaching the elimination target in any of the pilot countries, even under extremely optimistic assumptions on coverage and treatment uptake. This is largely due to the remaining presence of LTBI in the population, including the general population and the established migrant population (as opposed to newly arriving immigrants and refugees) in the country of interest. Both groups (established migrants and general population) are not targeted by any of the LTBI control strategies explored in this study.

LTBI screening shows potential for PWID/homeless people, prisoners, and new migrants from high-endemic countries. High screening coverage and treatment completion are important factors to further increase effectiveness of LTBI control. Better diagnostic tests and shorter preventive treatment would be welcomed as well. Dedicated screening measures, and, above all, a generous amount of time, are needed to ensure that all LTBI eventually disappears from the population.

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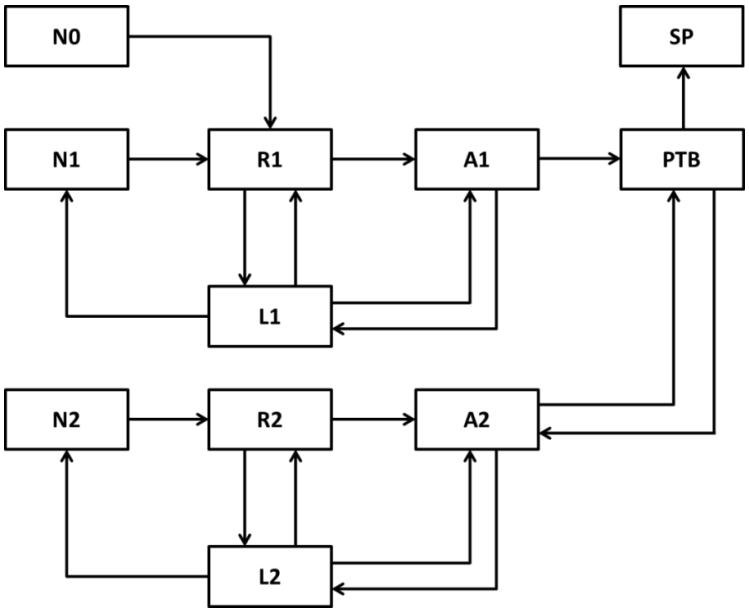
Appendix 1. Modelling the natural history of TB infection and disease

Figure A1-1 presents the same model as Figure 1, but includes an additional history component. This detail is necessary to correctly model the characteristics of the diagnostic tests considered in this report. The diagnostic parameters refer to the proportion of people who tested positive for TB (see also Appendix 4). Depending on the results of the diagnostic tests, people can be eligible for TB or LTBI treatment. Self-reported PTB cases and PTB cases detected through screening receive TB treatment; LTBI detected through screening will result in LTBI treatment at a certain uptake level.

Figure A1-1. Structure of the complete model regarding all health stages of the natural history



A = asymptomatic TB; CXR = chest X-ray; L = late (remote) latent tuberculosis infection; PTB = active pulmonary TB; N = not infected; R = recent latent tuberculosis infection; SP = severe pathology.
Number codes refer to TB infection/disease: 0 = never infected; 1 = infected or previously infected; 2 = previous (P)TB disease; may have lung lesions.

Number codes are used so that the model can memorise the infection and clinical history of a person, which is relevant for the diagnostic test outcomes (Appendix 4). People can either out-migrate compartments (if first-generation migrants) or die (if in age group 45+ years) from other causes than TB (not shown by arrows). People successfully treated for PTB move to compartment N_2 (arrow not shown). People successfully treated for LTBI move to N_1 or N_2, depending on their health state: R_1, L_1 and (half of) A_1 move to N_1; R_2, L_2 and (half of) A_2 move to N_2. The other half of A_1 and A_2, and all PTB cases are assumed not to be affected by LTBI treatment.

Transitions between different compartments of the TB natural history model can be represented by a set of ordinary differential equations. Table A1-1 lists the parameters used in the equations. Note that the force of infection (FOI) is presented as a fixed parameter (γ), which is reasonable choice for modelling the situation of migrants in the country of origin, which is assumed to be close to equilibrium. FOI in Europe, however, is a function of the number of infectious people (i.e. people with PTB) over time (Section 2.1.7) and may change due to LTBI control.

Table A1-1. Mathematical description of key model parameters of latent tuberculosis infection and tuberculosis natural history

Symbol	Description
Setting dependent parameters	
α	Rate of emigration
μ	Rate of natural mortality
γ	Force of infection (FOI); this can only be considered a fixed parameter in equilibrium situations or for cohorts, otherwise it is a function of time
Setting independent parameters	
p	Proportion of remote (late) LTBI (L) protected against reinfection due to acquired immunity
δ	Rate of remote LTBI clearance to not infected (N)
ε	Rate of activation from recent LTBI (R) to asymptomatic TB (A)

Symbol	Description
ζ	Rate of reactivation from remote LTBI (L) to asymptomatic TB (A)
ϵ	Rate of conversion from recent LTBI (R) to remote LTBI (L)
η	Rate of regression from asymptomatic TB (A) to remote LTBI (L)
θ	Rate of progression from asymptomatic TB (A) to PTB
ϑ	Rate of regression from PTB to asymptomatic TB (A)
ι	Rate of progression from PTB to severe pathology (SP)

Changes in the population distribution across the different TB health stages are described by a set of ordinary differential equations as follows:

$$\frac{dN_0}{dt} = -(\alpha + \mu + \gamma) \cdot N_0 + birth$$
$$\frac{dN_1}{dt} = -(\alpha + \mu + \gamma) \cdot N_1 + \delta \cdot L_1$$
$$\frac{dN_2}{dt} = -(\alpha + \mu + \gamma) \cdot N_2 + \delta \cdot L_2$$
$$\frac{dR_1}{dt} = -(\alpha + \mu + \varepsilon + \epsilon) \cdot R_1 + \gamma \cdot (N_0 + N_1) + \gamma \cdot (1 - p) \cdot L_1$$
$$\frac{dR_2}{dt} = -(\alpha + \mu + \varepsilon + \epsilon) \cdot R_2 + \gamma \cdot N_2 + \gamma \cdot (1 - p) \cdot L_2$$
$$\frac{dL_1}{dt} = -(\alpha + \mu + \gamma \cdot (1 - p) + \delta + \zeta) \cdot L_1 + \epsilon \cdot R_1 + \eta \cdot A_1$$
$$\frac{dL_2}{dt} = -(\alpha + \mu + \gamma \cdot (1 - p) + \delta + \zeta) \cdot L_2 + \epsilon \cdot R_2 + \eta \cdot A_2$$
$$\frac{dA_1}{dt} = -(\alpha + \mu + \eta + \theta) \cdot A_1 + \varepsilon \cdot R_1 + \zeta \cdot L_1$$
$$\frac{dA_2}{dt} = -(\alpha + \mu + \eta + \theta) \cdot A_2 + \varepsilon \cdot R_2 + \zeta \cdot L_2 + \vartheta \cdot PTB$$
$$\frac{dPTB}{dt} = -(\alpha + \mu + \vartheta + \iota) \cdot PTB + \theta \cdot (A_1 + A_2)$$
$$\frac{dSP}{dt} = \iota \cdot PTB$$

When using the model as a cohort (i.e. *birth* = 0), severe pathology (*SP*) was assumed to be an absorbing health state from which people cannot return to the previous stages. In the full transmission model, people with severe pathology are moved immediately to N_2, making *SP* basically a flow. Also, in the full transmission model all deaths return as *birth* in N_0 to keep the population at a stable size.

Appendix 2. Fitting transition rates of progression and regression of tuberculosis disease

Studies on the survival of smear-positive TB patients (as reviewed by Tiemersma et al. [43] and summarised by Berg et al. [44]) were used to estimate the period of time from PTB to severe pathology in the absence of treatment. Table A2-1 is based on all studies. The best-fitting trend can be found in Figure 2.

Table A2-1. Reported survival of pulmonary tuberculosis cases following diagnosis

Study	Years of survival of pulmonary tuberculosis cases (%)										
	1	2	3	4	5	6	7	8	9	10	15
Berg (1939) [44]			43.5		33.3					22.4	
Lindhardt (1939) [117]	56.5	43.7	37.5	34.0	30.4						
Tattersall (1947) [118]										23.6	
Rutledge & Crouch (1917) [119]					39.0						
Griep (1939) [120]					50.5					33.2	22.4
Baart de la Faille (1939) [121]		51.9		40.1		36.5		32.2		28.8	
Buhl & Nyboe (1967) [122]	77.8	68.8	63.4	58.2	54.8	51.7	50.0	47.4	45.8	43.5	
Münchbach (1933) [123]			59.0		48.0					34.0	
Braeuning & Neisen (1936) [124]			39.0		28.0					16.0	
Bentley (1936) [125]			34.0		24.0						
Lissant-Cox (1936) [126]			23.0*					12.0*			
Furth (1930) [127]			44.0		30.0					18.0	
Jacobson (1930) [128]			60.0		50.0						
Isager (1934) [129]			49.0		40.0					26.0	
Backer (1937) [130]			47.0		35.0					21.0	
Magnusson (1938) [131]				38.0						27.0	
Trail & Stockman (1931) [132]			64.0		50.0					34.0	

** Survival at year 3.5 (instead of 3) and 8.5 (instead of 8)*

A background mortality of 2% was estimated, i.e. an average survival of 50 years (in the absence of TB). This is supposed to reflect the average historical life span. Table A2-2 shows that the best-fitting probabilities of progressing from PTB to severe pathology. Progressing from asymptomatic TB to PTB does not depend too strongly on the chosen annual mortality rate, as long as it is not too high. For example, a higher death rate of 2.5% per year causes 28.2% of all cases with asymptomatic TB to progress to PTB (instead of 34.8%), whereas the best-fitting probability of PTB cases that deteriorates remains nearly the same. However, when assuming an unrealistically high natural mortality of 4% (i.e. an average remaining life expectancy of 25 years), nearly all deaths can be explained by mortality due to other causes, which results in only 6.5% of all PTB cases progressing to severe pathology and death.

The same split of 52% deteriorating to severe pathology and 48% regression to asymptomatic TB was maintained for those who do not receive treatment. Evidently, when including self-reporting and successful treatment, most people with PTB will never make these transitions, and people with PTB will remain in this compartment for a much shorter period than 18 months. Table A2-3 provides a complete overview of all durations of PTB considered in this report, together with the corresponding rates (per month) and proportions for those who move to successful treatment, severe pathology, or asymptomatic TB.

Table A2-2. Parameter estimates of progression from asymptomatic tuberculosis and deterioration from pulmonary tuberculosis when annual mortality rate is varied

Annual natural mortality rate	Progression from asymptomatic tuberculosis	Deterioration from pulmonary tuberculosis
1.0%	45.6%	51.8%
1.25%	43.2%	51.9%
1.5%	40.6%	51.9%
2.0%	34.8%	52.1%
2.5%	28.2%	52.4%
3.0%	20.6%	52.8%
4.0%	6.5%	52.9%

Estimates with grey overlay were used for further predictions.

Table A2-3. Overview of all average durations of active pulmonary tuberculosis used in this report

	Rates (per month)			Proportions (%)			When used
Duration of PTB (months)	Self-reporting and successful treatment	Deterioration to severe pathology	Regression to asymptomatic TB	To successful treatment	To severe pathology	To asymptomatic TB	
18	0.0000	0.0289	0.0266	0.0%	52.1%	47.9%	Pre-treatment era
7	0.0873	0.0289	0.0266	61.1%	20.3%	18.6%	PWID/homeless people (CZ, PT, ES)
6	0.1111	0.0289	0.0266	66.7%	17.4%	16.0%	PWID/homeless people (NL)
4	0.1944	0.0289	0.0266	77.8%	11.6%	10.6%	Other (CZ, PT, ES)*. **
3	0.2778	0.0289	0.0266	83.3%	8.7%	8.0%	Other (NL)
2	0.4444	0.0289	0.0266	88.9%	5.8%	5.3%	Prisoners (CZ, PT, ES)
1	0.9444	0.0289	0.0266	94.4%	2.9%	2.7%	Prisoners (NL)

CZ = Czech Republic; NL = Netherlands; other = general population and first-generation migrants; PT = Portugal; ES = Spain
** Also used for migrants during the stay in their country of origin (Section 2.1.5)*
*** Also used when fitting (re-)activation rates (Section 2.1.3 and Appendix 3).*
Values with grey overlay are those in Figures 1 and 2.

Appendix 3. Fitting transition rates of activation of recent and remote latent tuberculosis infection

The probabilities of progressing from recent LTBI to asymptomatic TB and progressing from remote LTBI to asymptomatic TB were fitted to best reproduce the outcomes of the study by Borgdorff et al. (2011) (dark grey) and verified by studies, as well as statements by experts in the field (light grey). The data points and statements and their references are given in Table A3-1, and the resulting fit in Figure 3.

Table A3-1. Statements and data on activation of latent tuberculosis infection, measured from time of infection

Reference	Data description/statement	Used in fitting
Borgdorff et al (2011) [45]	'Of those developing disease within 15 years, the Kaplan–Meier probability to fall ill within 1 year was 45%, within 2 years 62% and within 5 years 83%.'	After 2 years: 4.96%: After 5 years: 6.64% After 15 years: 8%
Fox et al (2013) [133] the web appendix 4 of this review	'The annual incidence rate for TB in high income countries was in year 1 to year 5 after exposure 524, 152, 233, 202 and 171 per 100 000 (based on respectively 28, 18, 5, 5 and 5 studies). Since on average 28.1% of contacts were infected we divide these numbers by 0.281 and add up the incidences by year to get cumulative proportions with disease'.	After 1 year: 1.86% After 2 years: 2.41% After 3 years: 2.69% After 4 years: 2.94% After 5 years: 3.11%
Kik et al. (2010) [134]	'The PPV for progression to TB during this period was 9/288 = 3.1% (95% CI 1.3–5.0%) for TST ≥10 mm'	After 2 years: 3.13%
Trauer et al. (2016) [135]	'Of 613 infected close contacts, 67 (10.9%) developed active TB during the study period. Assuming complete follow-up, the 1,650-day cumulative hazard was 11.5% (95% CI, 8.9-14.1).'	After 4.5 years: 11.5%
Horsburgh et al. (2010) [136]	'The rate of reactivation TB among persons with LTBI without HIV infection was 0.040 cases per 100 person-years (95% confidence interval CI, 0.024–0.067) using the n method and 0.058 cases per 100 person-years (95% CI, 0.038–0.089) using the n-1 method.'	After 5 years: 4-5.8%
Sloot et al. (2014) [137]	'The 5-year risk of coprevalent and incident TB among 739 contacts with evidence of infection was 9.5% (95% CI, 7.5–11.9).'	After 5 years: 9.5% After 10 years: 9.9% (Kaplan-Meier)
Choudhury et al. (2014) [138]	'This retrospective cohort study of immigrants with presumed LTBI aged 16–34 has shown a cumulative incidence rate for progression to active clinical TB of 13.5% after 10 years of observation without preventive therapy. The 15-year cumulative incidence rate for the cohort was 16.3%.'	After 10 years: 13.5%* After 15 years: 16.3%*
Styblo selected papers (1991) [139], referring to British MRC vaccine trial Bull WHO 1972 [140]and Sutherland TSRU 1968 [141]	[British MRC BCG trials] '8.1% had developed clinical TB in the 10 years following primary infection'. (enrolment of children aged 14-15)	After 10 years: 8.1%
Styblo selected papers (1991) [139]referring to Sutherland Adv Tuberc Res 1976[142]	[TSRU studies] The estimated annual risk of development of bacillary TB following primary infection 1.2%, implying that 6% will develop bacillary disease within 5 years	After 5 years: 6%
Styblo selected papers 1991 [139] referring to Barnett 1971 [143]	'[during 1960-1969] The risk of developing pulmonary TB [in Saskatchewan] in those with recent primary infection seems to be about 2.6%. For all forms of TB the rate is 6.4%'	After an average of 5 years: 6.4%
Rieder (1999) [144]	'A commonly used rule of thumb is that the lifetime risk of TB for a newly infected young child (1 to 3 years) might be 10 per cent, and that half of this risk falls within the first five years following infection.'	After 5 years: 5%
Comstock et al. (1974) [145]	'The lifetime risk for a young child who is a strongly positive reactor may run as high as 10%'	After 30 years: 10%
Vynnycky & Fine (2000) [40]	'The average lifetime risk of developing pulmonary tuberculosis (all forms), weighted according to the predicted number of persons initially infected at each age, is estimated to have declined during the early years of the 20th century, plateauing at about 12 percent by 1930 for all forms of pulmonary disease and at about 6 percent for infectious pulmonary forms.'	After 30 years: 12%

Statements and other modelling studies are shaded green.
** Value may be underestimated because the actual time passed since infection may be longer; value may be overestimated because risk of reinfection. This study was included because it is one of the few long-term studies.*

Table A3-2 shows that assuming a duration of six months in PTB (instead of four months) increases the best-fitting proportion for activating from recent LTBI from 19% to 26%, whereas it remains the same at 12% for reactivation of those with remote LTBI. These subtle changes result from our choice to consider only PTB cases after self-reporting or developing severe pathology, which takes two months longer in this example. Other changes result from the changes in asymptomatic TB, to which a higher proportion will return (i.e. 16% instead of 11%, Table A2-3), followed by a possible return in the PTB compartment after progression.

Table A3-2. Proportions activating and reactivating when leaving the compartments of recent and remote latent tuberculosis infection used to assume different durations of pulmonary tuberculosis

Average duration PTB (months)	Activation from recent LTBI	Activation from remote LTBI
2.0	16.5%	13.3%
3.0	17.5%	12.6%
4.0	18.9%	12.1%
5.0	21.3%	11.7%
6.0	25.5%	12.0%

LTBI = latent tuberculosis infection, PTB = pulmonary tuberculosis.
Values shaded grey are shown in Figure 1; alternative values used in this report are given in Table A3-3.

Table A3-3 shows the various alternative rates of activation and reactivation used to account for differences between age groups and the general health condition of cases with LTBI.

Table A3-3. Overview of all rates of activation of recent latent tuberculosis infection (upper part) and reactivation of remote latent tuberculosis infection (lower part) used in this report

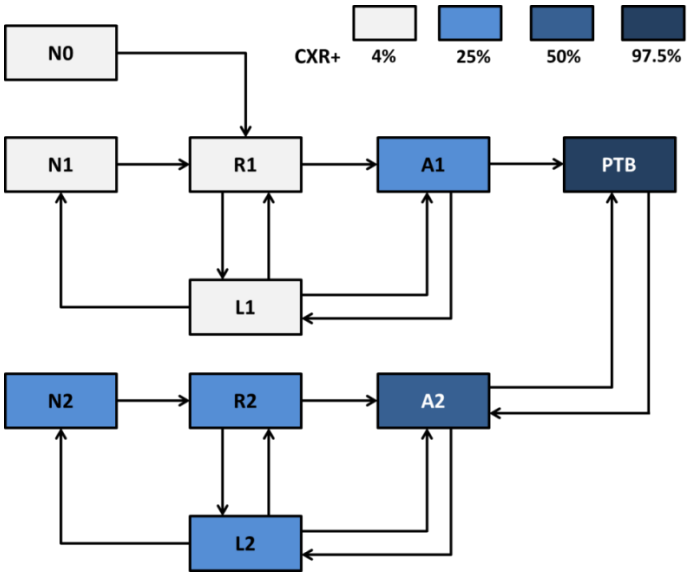
	Rates (per month)		Duration (months)	Proportions (%)		When used
Relative rate of activation	Dormancy from recent LTBI to remote LTBI	Activation from recent LTBI to asymptomatic TB	Average duration of recent LTBI	To remote LTBI	To asymptomatic TB	
200%	0.135	0.063	5.05	68.2%	31.8%	PWID/homeless people
100%	0.135	0.032	6.00	81.1%	18.9%	Age 15–44
75%	0.135	0.024	6.30	85.1%	14.9%	Age 45+
25%	0.135	0.008	6.99	94.5%	5.5%	Age 0–14
Relative rate of reactivation	Clearance from remote LTBI to not infected	Reactivation from remote LTBI to asymptomatic TB	Average duration of remote LTBI	To not infected	To asymptomatic TB	
200%	0.00366	0.00100	214	78.5%	21.5%	PWID/homeless people
100%	0.00366	0.00050	240	87.9%	12.1%	Age 15–44
75%	0.00366	0.00038	247	90.7%	9.3%	Age 45+
25%	0.00366	0.00013	264	96.7%	3.3%	Age 0–14

LTBI = latent tuberculosis infection.
Values shaded grey are those initially estimated in Figure 3 and given in Figure 1.

Appendix 4. Assumptions about diagnostic testing

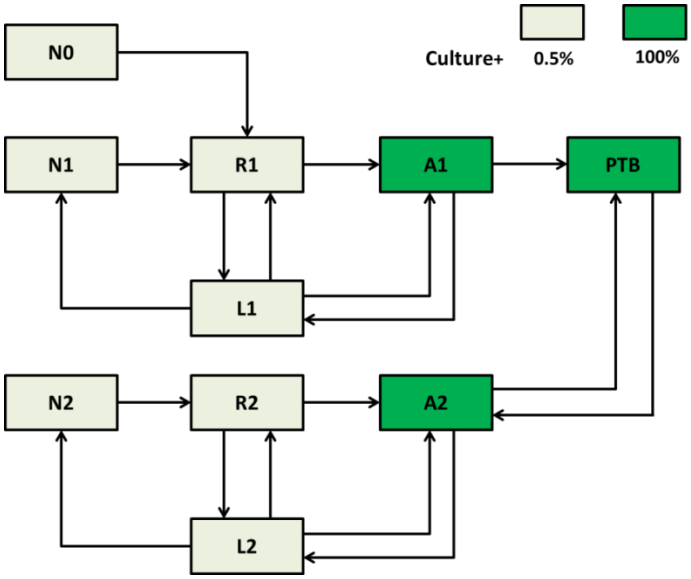
Figures A4-1, A4-2, A4-3 and A4-4 illustrate the probabilities of receiving a positive test result (different diagnostic tests administered to people in various TB health stages). Depending on the results of the diagnostic tests, people can be eligible for TB or LTBI treatment. The structure of the model is equal to Figure 1, but does not include the severe pathology state. For references, see Table 1.

Figure A4-1. Schematic representation of the probability to have a positive chest X-ray, based on history of tuberculosis infection or disease



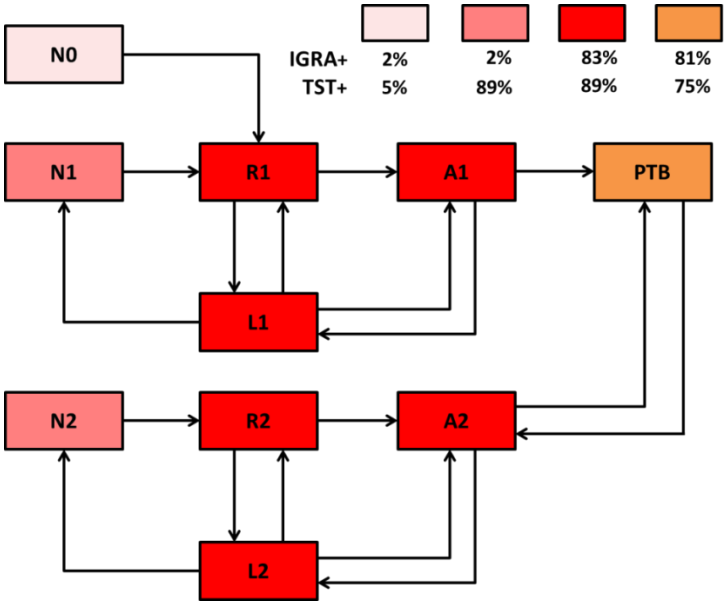
A = asymptomatic TB; CXR = chest X-ray; L = late (remote) latent tuberculosis infection; N = not infected; PTB = active pulmonary TB; R = recent latent tuberculosis infection.
Numbers reflect the the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease.

Figure A4-2. Schematic representation of the probability that repeated *M. tuberculosis* cultures are positive, based on history of tuberculosis infection or disease



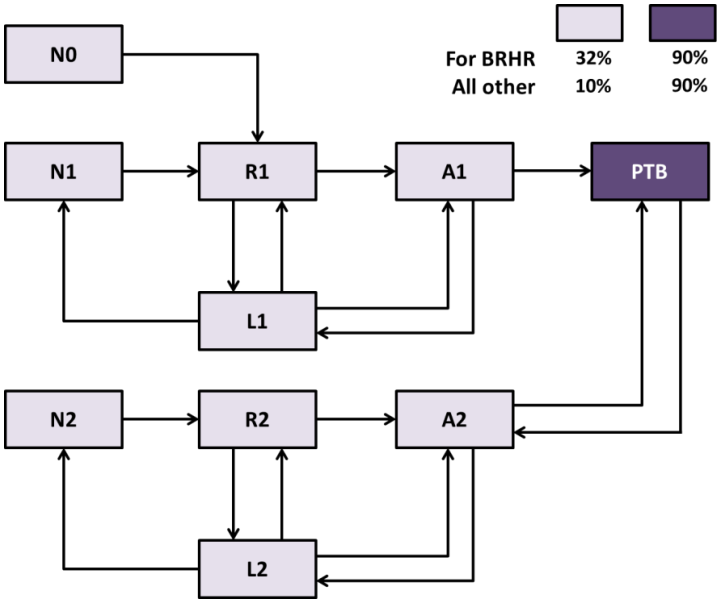
A = asymptomatic TB; L = late (remote) latent tuberculosis infection; N = not infected; PTB = active pulmonary TB; R = recent latent tuberculosis infection.
Numbers reflect the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease.

Figure A4-3. Schematic representation of the probability to have a positive tuberculin skin test or interferon gamma release assay based on history of tuberculosis infection/disease and bacillus Calmette–Guérin vaccination



A = asymptomatic TB; BCG = bacillus Calmette-Guérin; IGRA = interferon gamma release assay; L = late (remote) latent tuberculosis infection; N = not infected; PTB = active pulmonary TB; R = recent latent tuberculosis infection; TST = tuberculin skin test.
Numbers reflect the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease.
For IGRA, the proportion of N_1 and N_2 testing positive was set at 20% [59] to reflect its waning sensitivity over time.

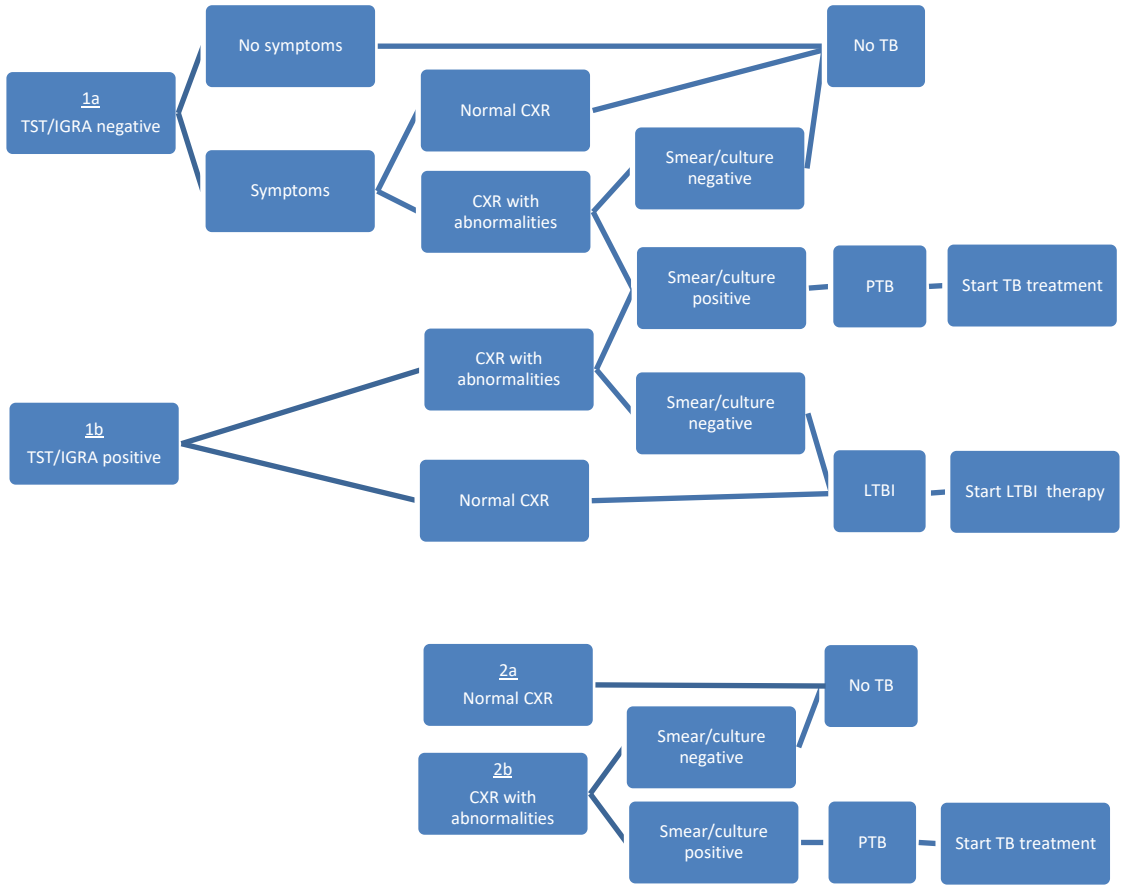
Figure A4-4. Schematic representation of the probability to report symptoms (suspicious for tuberculosis) based on history of tuberculosis infection or disease



A = asymptomatic TB; L = late (remote) latent tuberculosis infection; N = not infected; PTB = active pulmonary TB; R = recent latent tuberculosis infection.
Numbers reflect the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease.

This is a standard component of any LTBI-control strategy: to increase the probability of detecting PTB cases which are not always identified by IGRA and/or TST. PWID/homeless groups often experience several symptoms which may be indicative of TB.

Figure A4-6. Flow diagram of the cascade of possible test outcomes and testing sequences, predicting the impact of screening strategies for latent tuberculosis infection



CXR = chest X-ray; LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis; IGRA = interferon gamma release assay; TB = tuberculosis; TST = tuberculin skin test.
Smear/culture is indicated as a combined test because both are usually administered together; the sensitivity and specificity of culture was taken account of in the model.

Appendix 5. Fitting the model to data on the entry screening of migrants

Table A5-1. Overview of the distribution across stages of the natural history model for migrants from high-incidence countries to the Netherlands, the Czech Republic, Portugal and Spain, and the underlying force of infection and its relation to the average TB incidence in the country of origin

Country	Average TB incidence in top 10 countries of origin (per 100 000) *	CXR/culture positive (per 10 000) **	Annual FOI (×100)	Age group	N0	N1	N2	R1	R2	L1	L2	A1	A2	PTB
Netherlands	177.6	11.05	2.038	15–44	0.60781	0.13968	0.01566	0.00899	0.00018	0.22192	0.00321	0.00213	0.00012	0.00030
				45+	0.36424	0.30427	0.03888	0.00837	0.00047	0.27069	0.01073	0.00188	0.00017	0.00028
Czech Republic	106.7	6.64	0.939	15–44	0.79126	0.07865	0.00858	0.00465	0.00004	0.11445	0.00105	0.00111	0.00005	0.00015
				45+	0.62795	0.19256	0.02269	0.00453	0.00012	0.14761	0.00330	0.00102	0.00007	0.00015
Portugal	178.2	11.08	2.047	15–44	0.60649	0.14008	0.01571	0.00903	0.00018	0.22273	0.00323	0.00214	0.00012	0.00030
				45+	0.36257	0.30487	0.03899	0.00840	0.00047	0.27156	0.01080	0.00189	0.00017	0.00028
Spain	93.5	5.82	0.759	15–44	0.82714	0.06573	0.00714	0.00384	0.00003	0.09427	0.00078	0.00091	0.00004	0.00013
				45+	0.68665	0.16419	0.01909	0.00377	0.00008	0.12282	0.00239	0.00085	0.00005	0.00012

A = asymptomatic tuberculosis; CXR = chest X-ray; FOI = force of infection; L = late (remote) latent tuberculosis infection; N = not infected; PTB = active pulmonary TB; R = recent latent tuberculosis infection. TB = tuberculosis. Numbers reflect the history of TB infection and disease as follows: 0 = never infected; 1 = previously infected; 2 = previous PTB disease.

** The 10 TB-endemic countries with the most resident migrants (population data for the migrant countries with the highest absolute number of PTB cases between 2005–2014 in the reporting country) were as follows (in order of importance): Netherlands (Morocco, Indonesia, China, Iraq, Russian Federation, Afghanistan, Somalia, India, Ghana, Thailand), Czech Republic (Ukraine, Vietnam, Russian Federation, Mongolia, China, Kazakhstan, Moldova, Belarus, India, Korea), Portugal (Cape Verde, Ukraine, China, Angola, Guinea-Bissau, Sao Tomé and Principe, India, Russian Federation, Mozambique, Pakistan), and Spain (Morocco, Ecuador, Peru, Dominican Republic, China, Bolivia, Ukraine, Russian Federation, Algeria, Pakistan). See Appendix 9 for sources and references.*

*** For the Netherlands, the proportion of positive CXR to positive culture is close to the observed value of 11.05 per 10 000 [64,65]; the values for the Czech Republic, Portugal and Spain are assumed to be proportional to the observed value for the Netherlands, using the average TB incidence in country of origin.*

For the names assigned to model stages, please refer to Figure A1-1. The FOI for the Netherlands was tuned so that entry screening of migrants results in the observed proportion of 23.4% of tested migrants that have a positive IGRA [70]; 42.9% have a positive TST, and 0.1105% have a positive CXR and culture [64,65]. The FOI for the Czech Republic and Spain was tuned so that it resulted in a distribution across stages (positive CXR/culture) that corresponded to average TB incidence in the 10 TB-endemic countries with the most migrants. As these incidences hardly differed between the Netherlands and Portugal, the same distribution was used for Portugal and the Netherlands. For all countries, 10% of new migrants were assumed to be in the age group 45+ (here calculated for the age group 45–54); the remaining 90% who entered the country were assumed to be in the age group 15–44 years. Furthermore, the duration of PTB in the migrant's country of origin was assumed to be six months, as it provided to best fit to the data from the Netherlands (Figure 4).

Appendix 6. Size and composition of key populations groups in Europe

Table A6-1. Data about total population sizes in the four pilot countries, used in the model to calculate pulmonary tuberculosis cases and incidences

Values are as much as possible representative of the past 10 years. The general population (not shown here) is the total population minus the first-generation migrants from high-endemic countries.

	Netherlands (in thousands)	Czech Republic (in thousands)	Portugal (in thousands)	Spain (in thousands)
Total population	16 545.9 [5]	10 430.3 [6]	10 505.9 [7]	45 721.1 [8]
Natives	15 859.1	10 180.4	10 296.1	43 450.8
0–14	2 895.4	1 497.4	1 544.9	6 786.7
15–44	6 156.9	4 324.0	3 988.8	17 974.9
45+	6 806.8	4 359.0	4 762.3	18 689.2
First-generation migrants from high-endemic countries *	686.7 [1]	249.9 [9]	209.8 [3]	2 270.3 [4]
15–44	405.3	155.9	159.6	1 842.9
45+	281.5	94.0	50.2	427.3
New immigrants from high-endemic countries (per year)	33.7 [1]	*Unknown/missing*	15.9 [3]	132.8 [10]
People who inject drugs (PWID) [a]	19.0 [11]	36.6 [12]	30.4 [13]	14.2 [14]
Homeless people [b]	24.1 [15]	11.3 [8]	92.1 [16]	22.4 [10]
Overlap PWID and homeless people [c]	12% [17]	Assumed: 0	19.7% [18]	Assumed: 0

[5] Centraal Bureau voor de Statistiek (CBS), Netherlands, Statline population tables 2005–2014; The Hague: CBS; 2016. [cited 9 March 2018]. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37325/table?ts=1520599479043

[6] Český statistický úřad (ČSÚ) (Czech Statistical Office). Population 2005-2014. Czech Republic: ČSÚ; 2016; [cited 9 March 2018]. Available from: https://www.czso.cz/csu/czso/population

[7] Instituto Nacional de Estatística (INE)(Statistics Portugal). Population and migration tables, 2008–2014; [cited 9 March 2018]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0006055&contexto=bd&selTab=tab2

[8] Instituto Nacional de Estadística (INE), Spain, 2005–2014; Spain: INE; 2016. [cited 9 March 2018]. Available from: http://www.ine.es/dyngs/INEbase/en/operacion.htm?c=Estadistica_C&cid=1254736176951&menu=ultiDatos&idp=1254735572981.

[9]Český statistický úřad (ČSÚ)(Czech Statistical Office). Foreigners: number of foreigners 2008–2014. Czech Republic; CSU: 2016. [Cited 9 March 2018]. Available from https://www.czso.cz/csu/cizinci/1-ciz_pocet_cizincu

[10] Instituto Nacional de Estadística (INE), Spain, 2008–2014. Spain: INE; 2016. [cited 9 March 2018]. Available from: http://www.ine.es/dyngs/INEbase/en/operacion.htm?c=Estadistica_C&cid=1254736177000&menu=ultiDatos&idp=1254735573002.

[11] For the Netherlands, opiate/heroin users were used because no information about PWID was available (only PTB cases for all PWID were available). A few of the opiate/heroin users may actually be cocaine users. An average of 24 000 opiate users are usually assumed.
Source: Novadic Kentron. Hoeveel Nederlanders zijn verslaafd en wat kost dit de maatschappij [How many persons from the Netherlands are addicted and what is the cost for society?]. Vught, Netherlands: Novadic Kentron; 2015 [cited 9 March 2019] (data from 2012). Available from: https://www.novadic-kentron.nl/hoeveel-nederlanders-zijn-verslaafd-en-wat-kost-dit-de-maatschappij.
The assumed number of heroin users was 14 000. Source: National Drug Monitor 2014/2015, Trimbos Instituut.

[12] Supplied by the department of Respiratory Medicine of the First Medical School of Charles University, Prague, Czech Republic (PWID and prisoners: 2005–2014; homeless: 2007, 2010–2014).

[13] Provided by Raquel Duarte and Maria Gomez, 1 March 2017, means for years 2008–2014, from SICAD – Utentes em tratamento.

[14] Supplied by the Spanish Ministry of Health, Social Services and Equality (PWID: 2009–2013; homeless people: 2005 and 2012; prisoners: 2005–2014). Among prisoners, 27% were migrants, 15% of whom were from high-endemic countries. Age distribution was assumed to be the same as in the Netherlands.

[15] Centraal Bureau voor de Statistiek (CBS). Homeless by demographic characteristics. The Hague: CBS; 2009–2014 [cited 9 March 2018]. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/80799ned/table?ts=1520614769801

[16] Number of homeless people (92 053) was only available for 2011 [146]. Homeless people includes people who move from shelter to shelter.

[17] In the Netherlands, a 12% overlap between hard drug users and homeless people was used (2% for PWID, but since other data relate to opiate users and PWID, 12% was used) [81].

[18] [146]

	Netherlands (in thousands)	Czech Republic (in thousands)	Portugal (in thousands)	Spain (in thousands)
Total PWID/homeless people (i.e. sum of [a] + [b], minus [c])	37.9			
Native 15–44	19.4			
Native 45+	12.8	47.9	98.3	36.6
Migrant 15–44	3.4			
Migrant 45+	2.3			
Prisoners	10.9 [19]			50.1 [10]
Native 15–44	7.6			33.1
Native 45+	2.2	20.2 [8]	12.3 [20]	9.5
Migrant 15–44	0.8			5.8
Migrant 45+	0.2			1.7

** See Table A5-1 for a listing of the ten countries with the highest TB incidence. Values are based on all available data. Migrants under the age of 15 years are included in the age group 15–44 years.*

Table A6-2. Complete overview of parameters (durations and proportions) determining the size and composition of key population groups used in the tuberculosis transmission model

Parameter	Netherlands	Czech Republic	Portugal	Spain
Average time spent in age group (years) [A]				
0–14 years	14.1	10.4	11.6	11.3
15–44 years	30.0	30.0	30.0	30.0
45+ years (not- PWID/homeless people)	33.2	30.3	36.0	31.2
45+ years (PWID/homeless people) [B]	23.2	20.3	26.0	21.2
Total life span (not PWID/homeless people)	77.3	70.7	77.6	77.3
Proportion of the general population that is seen as vulnerable [C]	30%	30%	30%	30%
Parameters for first-generation migrants				
Proportion of immigrants in 45+ age group [D]	5%	5%	5%	5%
Proportion immigrants in leaving group (only for age group 15–44 years) [E]	70%	70%	80%	70%
Average time until (re)emigration for migrants in the leaving group (years) [E]	6.0	6.0	5.0	8.0
Average time until (re)emigration for 45+ migrants (years) [F]	42.5	34.8	10.3	7.8
Parameters for the PWID/homeless group (years)				
Average duration before becoming PWID/homeless people for vulnerable population and migrants in the age group 15–44 years [G]	421.2	208.1	96.8	1 329.9
Average duration to become PWID/homeless for vulnerable population and migrants in the age group 45+ years [G]	814.2	401.7	186.8	2 566.7
Average duration in PWID/homeless group [H]	5.0	5.0	5.0	5.0
Parameters for prisoners (years)				
Average time before incarceration for age group 15–44 years (not PWID/homeless people) [J]	308	133	149	173
Average time before incarceration for age group 45+ years (not PWID/homeless people) [J]	1 092	472	531	613
Average time before incarceration for age group 15–44 years (PWID/homeless people) [J]	3.1	1.3	14.9	1.7
Average time before incarceration for age group 45+ years (PWID/homeless people) [J]	10.9	4.7	53.1	6.1
Average length of prison stay [K]	0.25	0.25	0.25	0.25

See also Table 2 for age groups, key populations, and interactions between risk groups.

[A] *A duration of 30 years in the age group 15–44 years was preset for every country. Other durations were tuned so that the observed distribution across age groups (source: footnotes 1-8, Table A6-1) was reproduced at equilibrium. This caused slight differences with real-life life spans, as European populations are not in equilibrium, e.g. due to sinking birth rates and changing trends in migration. The resulting ranking for the total life span in the four countries is still largely in agreement with actual data.*

[B] *Assumed to be 10 years shorter for people in the PWID/homeless group, crudely based on data from the Netherlands [79,80].*

[C] *Chosen value that also lead to a slightly better fit of the observed overall distribution of age and risk groups (i.e. PWID/homeless vs. not PWID/homeless) in the Netherlands, as opposed to some alternative options (e.g. 25%, 33.3%).*

[D] *Somewhat arbitrarily chosen value, assumed to be similar for all countries, based on data for the Netherlands (http://www.cbs.nl/).*

[E] *Tuned to reproduce the Dutch data on emigration of first-generation migrants and country-specific data (Netherlands, Portugal, Spain) on immigration from high-endemic countries (see Figure 7 for data about emigration and Table A6-1 for data on immigration). For the Czech Republic, the same values were used as for the Netherlands.*

[19] Dienst Justitiële Inrichtingen (Dutch Custodial Institutions Agency) 2010, 2012, 2014 [84]. Proportion of migrants from high-TB-endemic countries: 7%; migrants in the age group 45 years and above: 22.4%.

[20] Supplied by Instituto de Saúde Pública (Public Health Institute), Porto University, Portugal, 2008–2014

[F] *Fitted so that the observed distribution of migrants across the age groups 15–44 years and 45+ years was achieved, using the above parameter values for the proportion migrants 45 years of age or older at entry screening (point D) and emigration (point E). Note that actual emigration is a result of the competing processes of emigration and natural death.*

[G] *Time spent in the age groups 15–44 years and 45+ years could be estimated only for the Netherlands by fitting the model to published data [81]. For the Czech Republic, Portugal and Spain, the same relative durations of moving to the high-risk group as was derived for the Netherlands was used: i.e. the time spent in the 45+ age group is 1.93 times longer than the time spent in the age group 15–44 years.*

[H] *Based on limited data from the Netherlands [81,82] and assumed to be the same for the other three countries.*

[J] *The same relative values for 'time before incarceration' were chosen for the Netherlands, the Czech Republic and Spain, i.e. the durations for the PWID/homeless group are 100 times shorter than for the general population, both for natives and migrants, based on data from the Netherlands. This results in about 24% of prisoners who originate from the PWID/homeless group. For Portugal, this factor was set to 10 in order to be able to reproduce PTB incidence among prisoners, which is relatively low compared with PTB incidence among the PWID/homeless group (see also Chapter 3.1). Time before incarceration for the age group 45+ years was assumed to be 3.55 times longer than the age group 15–44 years, based on the relative time resulting from the fit to the Dutch data [83,84,87].*

[K] *On average, 93 days (median 20 days) were spent in prison in the Netherlands [84]; for the other countries, the same value was assumed.*

Appendix 7. Modelling tuberculosis transmission in European countries

In order to adequately reproduce TB transmission in European countries, it was necessary to fit the model to observations of the number of PTB cases in each risk group considered. Table 4 gives an overview of the available data, reported as averages over the past 10 years (for Spain: past five years), and Table A7-1 gives details for the PWID/homeless group. These numbers depend on the screening interventions that were in place during these years. Table A7-2 gives an overview over the screening policies in each country for the same period. These policies were also used as the baseline scenarios for our predictions. To keep the modelling feasible equilibrium situations were assumed, but the countries actually experienced a substantial reduction in PTB incidence. See Figure A7.1 for the declining trends in each country.

Table A7-1. Composition of PWID/homeless groups among pulmonary tuberculosis patients in pilot countries, average 2005–2014

Annual number of PTB cases among:	Netherlands	Czech Rep.	Portugal	Spain
People who inject drugs [a]	12	11	217	unknown
Homeless people [b]	12	33	78	unknown
Total PWID/homeless people (sum of [a+b] minus overlap where available)	24	44	268	unknown

Sources and some justifications are given under the table. Only totals are given; the distribution across age groups (0–14, 15–44, 45+) is usually unknown except for the Netherlands and Portugal.
Sources:
Netherlands: RIVM/KNCV, average 20062015 used for overlap between groups. In the Dutch TB database only the variable 'problematic drug user' is included. These are not all PWID, but no better data are available. For the Netherlands prisoners who belong to PWID/homeless group could be excluded, but not for other countries.
Czech Republic: Supplied by Zsuzsanna Gyorfy, ECDC contact person from Czech Republic dd 080117. Of the total number of TB patients, 12 were PWID and 38 homeless. To adjust these numbers for PTB only the cost-effectiveness report was used: for natives EPTB/PTB ratio = 0.14. Calculate PTB = total/(1+ratio). For PWID PTB = 12/1.14 = 10.5. For homeless PTB = 38/1.14 = 33.3.
Portugal: Data for PWID (NOT any hard drugs) and total PWID/homeless provided by Raquel Duarte, Instituto de Saúde Pública (Public Health Institute), Porto University, Portugal. Homeless PTB patients (definition includes those who move from shelter to shelter) were 112 in 2011, of whom 70% had PTB [146]. Eight per cent of the migrant TB patients use drugs and 6% are homeless (Portugal 2008–2012) [147].

Table A7-2. Baseline screening policies for adults over 15 years of age in pilot countries

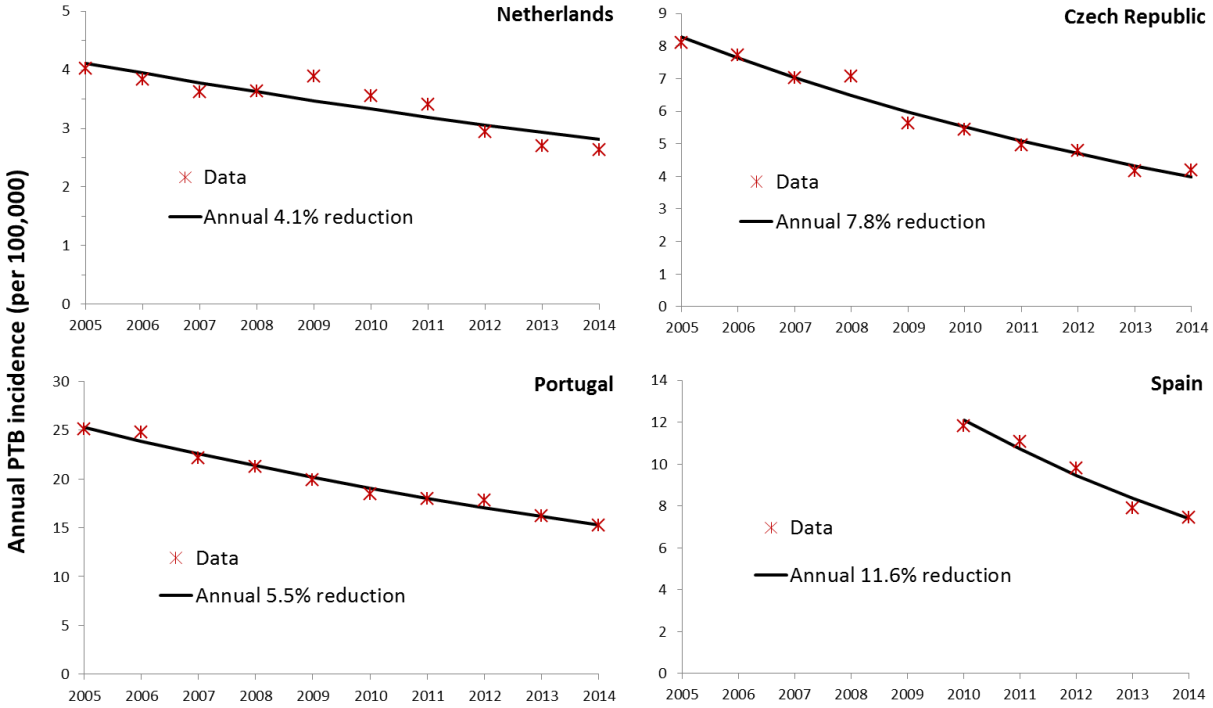
	Netherlands	Czech Republic	Portugal	Spain
Migrants	Migrants from countries with incidence > 50/100 000: entry screening CXR followed by culture for presumptive TB patients	Migrants from high-endemic countries: CXR	None	Migrants from high-endemic countries: TST screening; if positive, followed by CXR and sputum
Prisoners	Triage on risk factors* at entry, followed by one CXR if H PWID/homeless group; if positive, followed by culture (migrants and PWID/homeless groups)	CXR at entry	CXR at entry, followed by culture for presumptive TB patients	TST at entry, followed by CRX for those with a positive TST, followed by culture for those with presumptive TB. If no active TB, preventive therapy offered.
PWID/homeless group	None	None	None	None

CXR = chest X-ray; TB = tuberculosis; TST = tuberculin skin test.
** Since 2011, only offered for migrants and PWID/homeless people; Dutch prisoners from PWID/homeless group no longer screened*
See Chapter 2.2 for an overview of baseline coverage
Sources for screening policies: migrants [105,108,148]; prisoners [28,30]; homeless [32]; PWID [149]

Additional sources
Netherlands:
Policies on migrants/refugees and general risk groups: https://www.kncvtbc.org/uploaded/2016/02/6.1_risicogroepenbeleid.pdf and [64,65,108,150]. The Netherlands also conducts follow-up screening for migrants from countries with more than 200 cases per 100 000 population (every 6 months for 2.5 years with a coverage < 50%), but this was not included in the baseline.
A pilot project for IGRA screening of migrants was started in 2016; ignored in calculations.

Prisoners: previously CXR screening of all. Since 2010 this new policy. Source: https://www.kncvtbc.org/uploaded/2015/10/6.5_risicogroepenbeleid.pdf.
Homeless people: more than 10 years ago: regular screening with CXR bus. Currently, incidental LTBI screening for those starting special programmes (e.g. methadone) and CXR screening for those from high-risk countries in special situations. All ignored since not systematic.
PWID: no systematic screening. Source: https://www.kncvtbc.org/uploaded/2015/09/6.12_risicogroepenbeleid.pdf
ECDC contact persons: Gerard de Vries and Connie Erkens
Czech Republic
ECDC contact person: Zsuzsika Gyorfy
Portugal
Homeless people: only symptom-based screening [151]. Therefore ignored.
All groups except prisoners: it was assumed that no screening was carried out (no information available)
Spain
Not systematically carried out in the country and therefore ignored, despite some pilot projects that focus on specific screening strategies and risk groups [152].
ECDC contact person Laura Sánchez-Cambronero Cejudo provided information on screening policies.

Figure A7.1. Trends in overall pulmonary tuberculosis incidence in the Netherlands, the Czech Republic, Portugal and Spain; 2005–2014

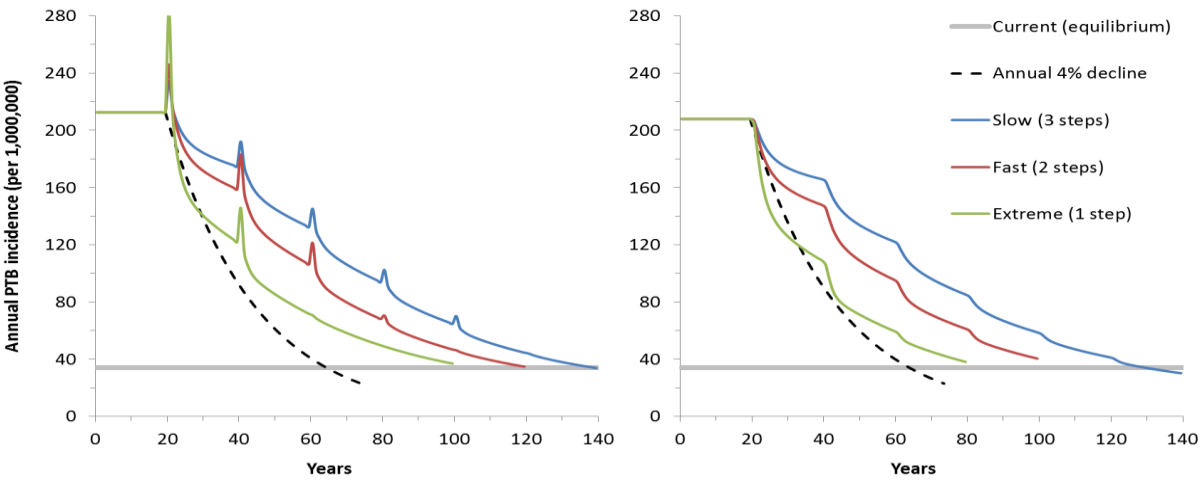


PTB = pulmonary tuberculosis

In this report, declining trends are ignored and equilibrium situations are assumed for fitting the model and to make predictions. This could be improved in future updates of this analysis if the model was expanded to include better age-based differentiation. More importantly, PTB incidence data over a much longer period (ideally another 50 years back in time) would be needed, as well as information and consensus about the different processes or interventions (and their timing) that are responsible for the declining trends. (Source: ECDC, TESSy database).

Appendix 8. Additional results

Figure A8-1. Attempt to reproduce declining trends in annual pulmonary tuberculosis incidence with a previous version of the model

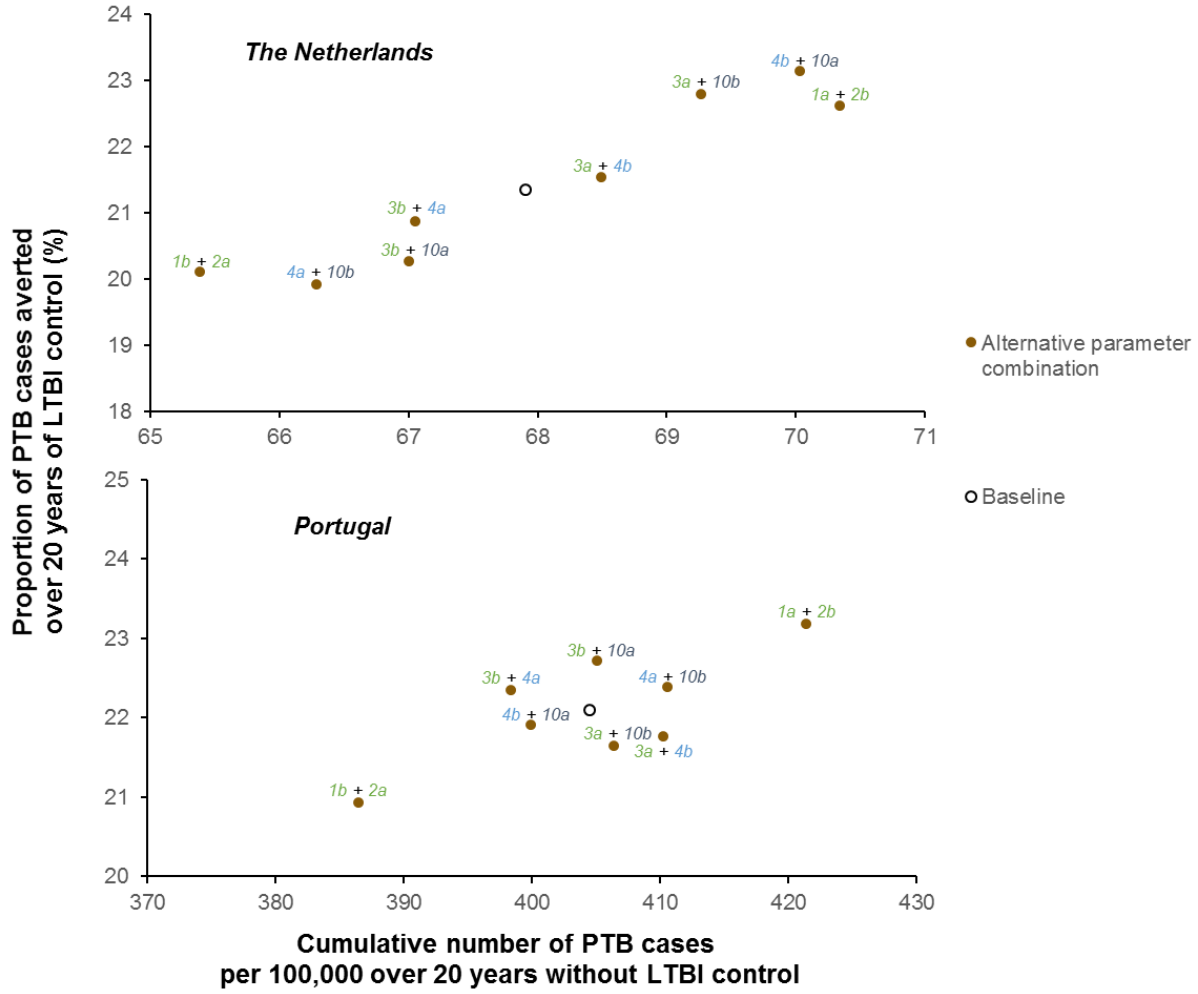


PTB = pulmonary tuberculosis; TB = tuberculosis.

The horizontal grey line indicates the average annual PTB incidence (2005–2014) in the Netherlands, as applied in this report (about 34 PTB cases per million). The dashed black line indicates a declining trend of 4% annually, which is representative for the Netherlands. In the left panel, the assumed durations of PTB for native/migrant, PWID/homeless people and prisoners were increased from three, six and one months to six, nine and four months, respectively. This resulted in a new equilibrium incidence of 213 PTB cases per million, which could be representative for a situation in the recent past. Starting from this situation, the PTB durations were changed over the course of 20 years so that the baseline values were reached in three steps (slow), two steps (fast) and one step (extreme). PTB durations were reduced in the same fashion, until the initial PTB incidence was reached. The spikes that appear in twenty- year intervals are due to the stepwise reduction in PTB duration; the associated faster rate of self-reporting, followed by TB treatment, results in a temporary increase of the number of reported cases.

The panel to the right shows a similar historical PTB incidence (208 cases per million). Transmission parameters beta were then proportionally increased by a factor of 60%. The original values were reached in three, two and one steps of 20 years, after which the beta values were decreased further. Regardless of the modelled speed of PTB incidence reduction, the proportion of PTB cases among natives in the age group 45+ starts with 42% during the first 20 years (as the model currently does), and increases to about 55% (result not shown). This proportion is close to the actual data (53% of all Dutch PTB cases among natives are in the 45+ age group (Table 4)). Clearly, the model cannot fully reproduce the strong decline in PTB incidence, but it has the potential to reflect the history of infection in older people.

Figure A8-2. Impact of simultaneously increasing and decreasing values of two parameters on model predictions regarding the impact of latent tuberculosis infection control in the Netherlands and Portugal



LTBI = latent tuberculosis infection; PTB = pulmonary tuberculosis infection; TB = tuberculosis.

The scale of the graph is identical to the zoomed-in sections (bottom panel) of Figures 16 (Netherlands) and 17 (Portugal). Only the parameters that resulted in the largest deviations of the baseline are included. The numbers above the dots show which two parameters were simultaneously quantified (identical numbering system as in Figures 16 and 17).

1a. Rate of progression from asymptomatic TB to PTB (multiplied with 5/4th)

1b. Rate of progression from asymptomatic TB to PTB (multiplied with 4/5th)

2a. Rate of regression from asymptomatic TB to remote LTBI (multiplied with 4/5th)

2b. Rate of regression from asymptomatic TB to remote LTBI (multiplied with 5/4th)

3a. Relative activation rate in PWID/homeless people (multiplied with 5/4th)

3b. Relative activation rate in PWID/homeless people (multiplied with 4/5th)

4a. Duration of PTB for PWID/homeless people (multiplied with 5/4th)

4b. Duration of PTB for PWID/homeless people (multiplied with 4/5th)

10a. Beta PWID/homeless people (multiplied with 5/4th)

10b. Beta PWID/homeless people (multiplied with 4/5th)

Appendix 9. Description of data sources

Sources from European countries

Data on natives and migrants were obtained from ECDC's TESSy database (case-based data). Data are averages over the period 2005–2014 for the Netherlands, the Czech Republic and Portugal; for Spain, data from 2010–2014 were used because data for 2007–2009 were incomplete (missing values for country of birth of PTB cases). No data were available for 2005–2006. Average data from multiple years was used to avoid modelling based on 'noise' (small annual variations). For Portugal, 11% of TB cases had an unknown country of origin. When PTB cases from Portugal were had an 'unknown' country of birth or were tagged 'not Portugal', they were counted as migrants. Native or migrant status was then imputed by the relative share of migrants from high-endemic countries within the total number of immigrants (per year; average 2005–2014: 49%). For each calendar year, the number of missing values for country of birth was distributed accordingly among natives and migrants (from high-endemic countries). For the Netherlands (0.4% unknown) and Spain (19.1% unknown in 2010–2014), migrants with unknown country of birth were tagged as coming from a 'high-endemic country', based on the mean proportion of migrants versus natives in the available data. For the Czech Republic, data for country of birth were complete.

Country-specific sources

Netherlands: The TBC-online[21] (RIVM/KNCV) database was used. Where possible, ECDC data were used in order to have comparable data for all four countries. Where more specific information was needed (e.g. mortality and proportion of cases detected through screening), TBC-online was used. Details on PWID/homeless people, prisoners and overlap between groups are means for 2006–2015 (data obtained from RIVM); PTB case data for 2005–2014 show only small differences to the total PTB cases for 2005–2014. Among prisoners, only 0.4 cases per year were also recorded as PWID/homeless people in the database; these cases were all considered cases in prisoners.

Czech Republic: No additional resources

Portugal: Data provided by Raquel Duarte from the national TB database. Migrants among PWID/homeless people and prisoners are only those from high-TB-incidence countries. Among migrant TB patients in Portugal 2008–2012, 2% were incarcerated [147]; 2% of 166 = 3; this largely agrees with the four cases reported by Portugal.

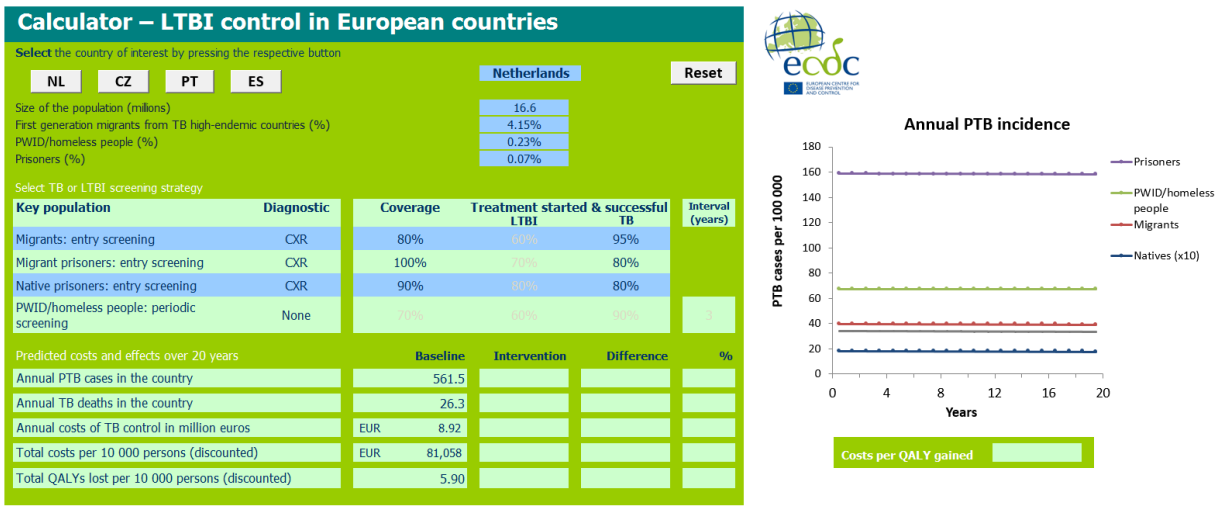
Spain: Supplied by Laura Sanchez, Spanish Ministry of Health, Social Services and Equality (8 Feb 2017): In Spain, 34% of TB cases in prison were in migrant prisoners (means for 2005–2014, all migrants, not only high-endemic countries). It was assumed that 2/3 of these (21%) are from high-TB countries. (21% of 67.0 = 14.1).

[21] URL: www.tbc-online.nl

Appendix 10. Calculator – LTBI control in European countries

An accompanying Excel tool was developed, the *Calculator – LTBI control in European countries*. It is based on the transmission model and was inspired by the 2008 *Calculator for TB among migrants* (Erasmus University Medical Center for ECDC, 2008). Users can adjust key characteristics of the TB epidemiology and select options for LTBI screening and treatment, e.g. by limiting measures to certain populations in European countries. The Calculator takes into account prevented secondary cases and interaction between population groups; most other tools are based on simple relative risks and cannot include interactions and prevented secondary cases.

Figure A10.1. Screenshot of the calculator tool



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

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