TECHNICAL REPORT

Review of reviews and guidelines on target groups, diagnosis, treatment and programmatic issues for implementation of latent tuberculosis management

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Abbreviations

3INH	Three months of isoniazid
AE	adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation
AHEHP	Applied Health Economics and Health Policy
aHR	adjusted hazard ratio
AIDS	acquired immune deficiency syndrome
AID	autoimmune disorder
Amstar	A Measurement Tool to Assess Systematic Reviews
ART	antiretroviral therapy
ATS	American Thoracic Society
BCG	Bacillus Calmette–Guérin
CD4	cluster of differentiation 4
CDC	Centers for Disease Prevention and Control
CEA	cost-effectiveness analysis
CI	confidence interval
CXR	chest X-ray
DOT	directly observed therapy
DST	drug susceptibility testing
ECDC	European Centre for Disease Prevention and Control
EMB	ethambutol
ESRD	end-stage renal disease
EU/EEA	European Union/European Economic Area
FP	false positive
GRADE	grading of recommendations assessment, development and evaluation [75]
HBC	high-burden countries (TB incidence rate: > 100 cases per 100 000)
HBeAG	hepatitis B antigen protein
HIV	human immunodeficiency virus
IBC	intermediate-burden countries (TB incidence rate: 40-100 cases per 100 000)
ICER	incremental cost-effectiveness ratio
IGRA	interferon gamma release assay
IJTLD	International Journal of Tuberculosis and Lung Disease
IMID	immune-mediated inflammatory disorder
INH	isoniazid
IPT	isoniazid preventive treatment
IQR	interquartile range
IRneg	incidence rate of incident TB (per 1 000 pyr) after a negative test result
IRpos	incidence rate of incident TB (per 1 000 pyr) after a positive test result
IRR	incidence rate ratio
LBC	low-burden countries (TB incidence rate: < 40 cases per 100 000)
LTBI	latent tuberculosis infection
MA	meta-analysis
MDR-TB	multidrug-resistant tuberculosis
Mg	milligram
mm	millimetre
mo	months
NA	not applicable/not available
NICE	National Institute for Health and Clinical Excellence
n/N	number of individuals with LTBI who initiated, or adhered to or completed treatment/total number of subjects
NOS	Newcastle-Ottawa Scale [77]
NPV	negative predictive value

OR	odds ratio
PLHIV	people living with HIV
PPD/PPD-S	purified protein derivative
PPV	positive predictive value
pyr	person-years
PZA	pyrazinamide
QALY	quality-adjusted life-year
QFT	QuantiFERON-TB
QFT-GIT	QuantiFERON-TB Gold In-Tube
QFT-IT	QuantiFERON-TB In-Tube
Quadas	quality assessment of diagnostic accuracy studies
RA	rheumatoid arthritis
RCT	randomised controlled trial
RFB	rifabutin
RIF	rifampin/rifampicin
RPT	rifapentine
RR	relative risk/rate ratio
SAT	self-administered therapy
SD	standard deviation
SEAR	south-east Asian region
SIGN	Scottish Intercollegiate Guidelines Network [78]
SR	systematic review
TB	tuberculosis
TNF	tumour necrosis factor
T-SPOT.TB	tuberculosis-specific Elispot assay
TST	tuberculosis skin test
UK	United Kingdom
USD	United States dollar
WHO	World Health Organisation
XDR-TB	extensively drug-resistant TB
yrs	years

Glossary

Acceptability	How acceptable the intervention is to the target population in relation to the effect.
Accessibility	How accessible the intervention is to the target population (availability of good health services within reasonable reach and when needed).
Active tuberculosis	A disease that is caused by *Mycobacterium tuberculosis* or other members of the Mycobacterium tuberculosis complex in any part of the body and that is in an active state, characterised by signs or symptoms of disease [1,2].
Case management	The comprehensive follow-up of a presumptive or confirmed tuberculosis case, including diagnosis, treatment and patient-centred support and the investigation of their contacts, and, if needed, treatment of LTBI. Case management will usually be provided by a specialist tuberculosis nurse or a nurse with responsibilities that include tuberculosis. Dependent upon the patient's particular circumstances and needs, case management can also be provided by appropriately trained and supported non-clinical members of a tuberculosis multidisciplinary team [3].
Commissioned systematic review	Systematic reviews commissioned by ECDC and the WHO, in the development process of the WHO document Guidelines on the management of latent tuberculosis infection [4] and the ECDC guideline

	Programmatic management of latent tuberculosis infection in the European Union [5]. The results of the systematic review were extracted and used in this report (not the outcomes of the primary articles).
Contact	Someone who has been exposed to *Mycobacterium tuberculosis* infection by sharing air space with a person with infectious tuberculosis, the so-called source case, with the probability of being infected increasing with the duration and closeness of contact, as well as the infectiousness of the source case and susceptibility of the contact [6].
Household contacts	Those who live in the same household as the tuberculosis case. Household contacts are considered, by definition, to share breathing space on a daily basis with the source case [7].
Close contacts	This group includes: those persons with short exposure times to direct face-to-face streams of air with a particularly high density of infectious droplet nuclei, such as may occur during bronchoscopy or otorhinolaryngeal examination of patients with sputum smear-positive tuberculosis; those with an arbitrarily defined cumulative exposure time of 8 hours, if the index case is sputum smear-positive, or 40 hours, if only culture-positive; contacts with regular, prolonged contact with the source case, who share breathing space but do not necessarily live in the same household or who have spent time with the source case in a confined space, such as a car, sweatshop or prison cell. These may also include contacts such as close friends and colleagues [7].
Contact investigation	The systematic case finding and assessment of contacts of patients with infectious tuberculosis disease [6].
Cost-effectiveness	The extent to which an intervention or prevention programme is effective in relation to its costs, for example euros/life-years gained.
Counselling	An interactive process where an individual risk assessment is undertaken and tailored information to the individual is delivered (patient-level). Patient counselling aims to ensure that people have sufficient knowledge and understanding to make informed choices [8].
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].
Education	Any programme that improves the knowledge, skills, attitudes or behaviours of the target group. Education to patients is defined as counselling (see above) while 'training' is used for education of healthcare workers (see below).
Enablers	Things or measures which assist patients to adhere to diagnosis and treatment by overcoming barriers to completing investigations and tuberculosis treatment. Economic constraints due to absences from work to attend appointments, or the direct and indirect costs of accessing treatment, are commonly cited by patients as important barriers to completing tuberculosis treatment. Other barriers that are likely to impact on outcomes include housing, nutrition, immigration status and transport. Possible enablers could be, for example, a mobile telephone or public transport tickets [3].
Feasibility	Ability to implement an intervention in terms of time, money or other circumstances.
Full commissioned systematic review	Systematic reviews commissioned by ECDC and the WHO in the development process of the WHO document Guidelines on the management of latent tuberculosis infection [4] and the ECDC guidance Programmatic management of latent tuberculosis infection in the European Union [5]. Relevant information from the primary articles of the systematic reviews were extracted and used in the data synthesis report.

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 [9]. 'Immigrant' is used only if the cited reference has used that term, otherwise 'migrant' is used.
Incentives	Financial or material rewards that patients and/or providers receive, conditional on their explicitly measured performance or behaviour. Rewards that encourage patients with both presumed and confirmed tuberculosis to attend tuberculosis screening, out-patient follow-up and directly observed therapy appointments must meet patients' interests and needs, and may include money, vouchers or other 'in kind' rewards [3].
Index case	A person with suspected or confirmed tuberculosis disease, who is found as the initial case of tuberculosis for a contact investigation; this is not necessarily identical with the source case [6,7].
Intervention	Any measure to improve the success of tuberculosis prevention, diagnosis and treatment [3].
Latent tuberculosis infection (LTBI)	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 [4].
LTBI treatment	Treatment of patients that are latently infected with *Mycobacterium tuberculosis* that aims to prevent progression to active TB. In this technical report, the terms 'LTBI treatment' or 'treatment of LTBI' are used instead of 'TB preventive treatment'.
Migrant	Any person who is moving or has moved across an international border or within a State away from his/her habitual place of residence, regardless of (1) the person's legal status; (2) whether the movement is voluntary or involuntary; (3) what the causes for the movement are; or (4) what the length of the stay is [10] .
Non-commissioned systematic review	Systematic reviews identified during the review. Relevant results from the systematic reviews were extracted and used in this report (not the outcomes of the primary articles).
People with drug use disorders	Persons who use narcotic drugs and psychotropic substances without medical supervision, for non-medical purposes [12]. This definition includes people who inject drugs. Other terms such as drug users, injecting drug users or problematic drug users are used only if the cited reference has used these terms.
Refugee	A person who, owing to a well-founded fear of persecution for reasons of race, religion, nationality, membership of a particular social group or political opinions, is outside the country of his or her nationality and is unable or, owing to such fear, is unwilling to avail himself of the protection of that country [13].
Self-administered	Related to a situation where the patient takes responsibility to collect, organise and administer their medication [11].
Source case	Person with infectious TB, having exposed other persons and who is herewith the source of an outbreak [6,7]. This is not necessarily the first case found (index case).
Training	Education of healthcare workers that is aimed at increasing the knowledge of TB/LTBI and raising awareness of the disease, which will help in informing and effectively treating of TB patients, and will therewith contribute to the controlling LTBI [14,15].
Tuberculosis	Clinically, bacteriologically, histologically and/or radiologically active disease [3].

Executive summary

The implementation of a comprehensive and systematic strategy for reducing the burden of latent tuberculosis infection (LTBI) is essential for achieving tuberculosis (TB) elimination. To support the development of public health guidance on programmatic management of LTBI in the European Union and the European Economic Area, this review summarises relevant evidence collected from systematic reviews and evidence-based guidelines on target groups, diagnosis, treatment and programmatic issues for implementation of programmatic management of LTBI.

The search and selection strategy included:

- an inventory and summary of systematic reviews commissioned by the European Centre for Disease Prevention and Control and the World Health Organisation (referred to as commissioned systematic reviews);
- a PubMed search (initial search 2015; updated June 2016) for additional or updated published systematic reviews (referred to as non-commissioned systematic reviews);
- an inventory of national and international evidence-based guidelines (initial search 2015; updated July 2016);
- a Google search for remaining gaps in evidence (initial search 2015; updated July 2016);
- a consultation of the ad hoc scientific panel for identification of additional publications (June 2016).

Forty-three systematic reviews were included in this report: 12 commissioned systematic reviews, 29 non-commissioned systematic reviews and two systematic reviews suggested by the ad hoc scientific panel. Ten evidence-based guidelines of sufficient quality were deemed pertinent and relevant recommendations were summarised. Where possible, summarising evidence statements were formulated for the various topics.

Scientific evidence was found for most of the topics included in the review, although the strength of the evidence was predominantly weak. The main findings are summarised below.

Target groups. People living with HIV, immunocompromised patients (e.g. candidates for anti-TNF-alpha therapy, end-stage renal disease (ESRD) patients), close contacts of TB patients, migrants, healthcare workers, prisoners and homeless people have an increased risk of being TB infected and/or of progressing to active TB disease.

Diagnosis. According to evidence derived mainly from low-TB-incidence, high-income settings, both the tuberculin skin test (TST) and the interferon gamma release assays (IGRA) are suitable and cost-effective diagnostic tools for LTBI. Cost-effectiveness evaluation methodologies were heterogeneous in terms of outcome measures and definitions of cost-effective and willingness-to-pay thresholds (if reported). No systematic reviews were identified presenting statistically analysed quantitative evidence on feasibility, accessibility, acceptability or the effectiveness of a LTBI diagnostic algorithm (e.g. combining TST, IGRA and tests for active TB). No systematic reviews were found on the effect of tests being offered free of charge.

Treatment. Various treatment regimens appeared efficacious and cost-effective for LTBI treatment. The reported definition for a cost-effective intervention varied across studies, if reported. No systematic reviews were identified presenting statistically analysed quantitative outcomes on treatment initiation. Evidence of moderate quality showed that short treatment regimens (i.e. 3- to 4-month duration) have better adherence. Rifampicin (compared to isoniazid for 6 months or for 9 months) is associated with a lower risk of hepatotoxicity.

Programmatic issues. Seven areas considered relevant for optimal implementation of programmatic management of LTBI were pre-identified, namely: screening; contact investigation; treatment-related interventions; adverse effect management; education; integration of LTBI management into existing health programmes; and monitoring and evaluation. Evidence on these areas, if available, was limited. The main findings were as follows.

Screening: cost-effective in populations at high risk of LTBI and/or progression to active TB disease. Cost-effectiveness definitions varied across studies. Material incentives and/or enablers can improve screening uptake, for example by increasing return for reading TST results.

Treatment-related interventions: various interventions are found to be effective to improve initiation, adherence and completion of LTBI treatment.

Education: certain types of education (e.g. one-to-one education sessions) were effective in improving adherence/completion of LTBI treatment.

For contact investigation, adverse event management, integration of LTBI management, and programme monitoring and evaluation, no systematic reviews were identified presenting statistically analysed quantitative evidence.

Relevant existing guidelines for the components of programmatic management of LTBI were identified and (mostly weak) scientific evidence was found for most of the relating review questions. Still, important gaps in evidence exist, such as limited information on populations at increased risk of LTBI and/or progression to active TB; limited information on the feasibility, accessibility and acceptability of LTBI diagnostic tests; and heterogeneous or non-existing information on the cost-effectiveness of various strategies for LTBI screening. Studies of higher quality, i.e. using study designs that result in less risk of bias, indirectness, inconsistencies and imprecisions, and with conclusive (comparative) evidence are needed.

1. Background

1.1. Introduction

Active tuberculosis (TB) is a bacterial infectious disease caused by *Mycobacterium tuberculosis*. The World Health Organisation (WHO) estimated that 10.4 million people fell ill with TB and 1.4 million died from TB in 2015 [16], making it a leading cause of death worldwide, causing more deaths than human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) [16,17]. Exposure to *M. tuberculosis* may result in latent tuberculosis infection (LTBI), a state in which the host immune system controls the replication of the bacillus to the extent that progression to TB disease is prevented. Persons with LTBI do not have any symptoms and cannot spread the infection to others [18]. LTBI may progress to TB disease, especially if the immune system is compromised [19,20].

In 2014, it was estimated that the global burden of LTBI was 23.0 %, amounting to approximately 1.7 billion people. Prevalence of recent infection (i.e. infection two years prior to diagnosis) was 0.8 % of the global population, amounting to 55.5 million individuals currently at high risk of TB disease. Current LTBI alone, assuming no additional infections from 2015 onwards, would be expected to generate TB incidences in the region of 16.5 per 100 000 per year in 2035 and 8.3 per 100 000 per year in 2050 [21].

As long as individuals with LTBI (i.e. a *M. tuberculosis* reservoir) exist, elimination of TB will not be feasible. Thus, the control of LTBI is an important step towards TB elimination. This was acknowledged in the 'End TB strategy' adopted by the 67th World Health Assembly in May 2014 [22,23]. In addition to TB case detection and treatment, TB is controlled by identifying individuals who are latently infected with *M. tuberculosis* and offering them LTBI treatment, especially in high-income countries [24-26]. However, diagnosis of LTBI poses a challenge. Individuals with LTBI are asymptomatic and no live mycobacteria can be extracted [27]. Therefore, LTBI diagnosis is based on the adaptive immune response against *M. tuberculosis*. Once LTBI has been diagnosed, prophylactic treatment will prevent the development of TB disease in most cases [28,29]. However, initiation, adherence and completion rates of LTBI treatment are often low and differ between treatment regimens and risk groups [30].

In 2013, the European Centre for Disease Prevention and Control (ECDC) initiated a comprehensive assessment of different components that could be integrated into national TB-control strategies with the purpose of reducing LTBI in the European Union/European Economic Area (EU/EEA) region. As part of this assessment, a workshop was held in September 2013 with representatives of the EU/EEA Member States and candidate countries, along with 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 [31]. The present report focuses on four key areas identified then, namely: (i) risk groups, (ii) diagnosis, (iii) treatment and (iv) programmatic management of LTBI.

1.2. Risk groups

Generally, two types of risk groups can be distinguished: persons who are at higher risk of LTBI, but without an increased risk of progression to active TB [32-34]; and persons with LTBI who are at higher risk of progression to active TB compared to others with LTBI [35-39]. Contacts of TB cases appear to have both a higher risk of TB infection and a higher risk of progression to active TB due to recent infection [32,35].

Persons with a higher risk of LTBI often belong to sociodemographic groups with an increased chance of interaction with a person with infectious TB or reside in environments in which exposure more often occurs. Crowded, poorly ventilated living and working places, prisons and homeless shelters are examples of environments where exposure to TB and risk of infection is more frequent [40,41]. The second type of risk group, persons with an increased risk of progression to active TB, may consist of individuals with recent infection or with an impaired host defence due to different causes, including medical conditions and therapeutic interventions that impair the immune system. Examples are people living with HIV (PLHIV) [42], silicosis, patients using immunosuppressive medication, those with undernutrition [43], diabetes [44], smoking [45] and problematic alcohol use [46]. Poverty and low socioeconomic status are important underlying determinants of many factors important in both types of risk groups, and there are often synergistic effects of several concurrent risk factors [41,47].

Risk groups can further be distinguished based on specific characteristics, for example:

- clinical risk groups (i.e. individuals who, when diagnosed with LTBI, have a higher risk of progression towards active TB, like PLHIV, immunocompromised persons and persons with silicosis);
- population risk groups (i.e. populations who are, due to a higher risk of exposure, at higher risk of having LTBI, and may be at higher risk of progression to active TB, like TB contacts and specific migrant populations);
- vulnerable and hard-to-reach groups (i.e. prisoners, homeless people and people with drug use disorders, whose socioeconomic conditions or lifestyle makes it difficult to recognise TB symptoms, access health services, self-administer therapy (SAT) and attend regular healthcare appointments [48]); and

- occupational groups: individuals who are at higher risk of LTBI by exposure related to their occupation, like healthcare workers.

1.3. Diagnosis of LTBI

Some high-income countries have opted for actively identifying individuals who are latently infected with *M. tuberculosis* (and subsequently offering them treatment that will prevent the development of TB disease; see Section 2.5) [25,26,49]. Making a proper diagnosis is a challenge. Individuals with LTBI are asymptomatic and all microbiological examinations are negative [27], therefore LTBI diagnosis is based on tests assessing the adaptive immune response against *M. tuberculosis*. For over a century, the tuberculin skin test (TST) was the only available test to measure this immune response. It identifies an in vivo cell-mediated immune response to tuberculin, a purified protein derivative (PPD) of *M. tuberculosis*. The test includes the intradermal injection of tuberculin PPD and the tested person has to return to the clinic 48-72 hours after the antigen injection, to measure the TST reaction. PPD is a mixture of antigens, many of which are shared by *M. tuberculosis*, M. bovis, and Bacille Calmette–Guérin (BCG), and other environmental mycobacteria. As a result, the specificity of the TST is low in populations with a high coverage of BCG vaccination and infection with environmental mycobacteria. This applies to many people from low- and middle-income countries [50].

In the early 2000s, blood tests were developed for the diagnosis of LTBI: interferon gamma release assays (IGRAs). These tests are based on the principle that T-cells of individuals infected with *M. tuberculosis* produce interferon gamma when these are exposed to *M. tuberculosis* specific antigens [51]. The interferon gamma production in response to these specific mycobacterial antigens is assumed to be indicative of infection with *M. tuberculosis*. Two IGRAs are currently commercially available, the QuantiFERON®-TB Gold Plus (QFT-Plus) (Qiagen, Hilden, Germany) and the T-SPOT®.TB test (Oxford Immunotec, United Kingdom). QFT-Plus measures the interferon gamma production in whole blood via the method of Enzyme Linked ImmunoSorbent Assay (ELISA). Additional clinical value compared to older QFT-GIT comes from the exclusive TB-specific antigens that elicit CD4+ and CD8+ T-cell responses. T-SPOT.TB is based on an enzyme-linked immunospot (Elispot) method enumerating the interferon gamma producing T-cells [52,53]. An advantage of these in vitro tests is the possibility of adding a positive control to discriminate true negative responses from anergy, a condition in which the body fails to react to an antigen. It should be kept in mind that both the TST and the IGRAs can differentiate neither between recent or old LTBI, or cleared and persistent infection, nor between LTBI and active TB. Chest radiography (CXR) can be used to discriminate between LTBI and pulmonary TB disease in individuals with positive tests for TB infection.

1.4. Treatment of LTBI

LTBI can be treated to decrease the probability of it progressing to active TB [54]. Once identified with LTBI, individuals can be treated with different regimens, for example 6- or 9-months of isoniazid (INH), or a 3-month regimen of weekly rifapentine (RPT) plus INH, or 3-4 months of INH plus rifampicin (RIF), or 3-4 months of RIF alone [4]. For contacts of MDR TB cases, LTBI treatment regimens may contain other drugs to which the strain of the anticipated source case is susceptible (e.g. fluoroquinolones). Individuals who receive treatment for LTBI are not sick, so the decision to treat individuals with LTBI and the type of treatment must carefully balance the risks (e.g. drug-related adverse events [20]) and benefits to the individual [4]. Several LTBI treatment regimens have shown effectiveness [29], however adherence to these treatment regimens is sometimes low and differs between treatment regimens and populations [55-63].

1.5. Programmatic management or LTBI in the EU/EEA

Programmatic management of LTBI consists of several components which all contribute towards preventing TB disease and, through reducing the prevalence of people with TB disease, also reduce the risk of onward transmission of the *M. tuberculosis*. The components included in this report are case detection, treatment-related interventions, education, implementation, and programme monitoring and evaluation.

For a programmatic approach of LTBI management each country should consider organisational aspects (who should be screened, when and where), cost-effectiveness of interventions and available resources, political commitment and social and ethical aspects.

Case detection

LTBI screening refers to offering tests (IGRA or TST) to people in a defined population who are considered to be at increased risk of infection compared with the general population and are also more likely to be helped rather than harmed by the test or the subsequent treatment of LTBI [64,65]. A systematic screening approach detects individuals latently infected with *M. tuberculosis* and offers treatment to those individuals infected with the most appropriate and effective treatment regimen to prevent progression to TB in the future and transmission of TB in the population. Populations that may be considered difficult to reach and that are less accessible for screening are

migrants and vulnerable and hard-to-reach populations. Incentives can be used to improve screening uptake or increase return rates to the clinic to read TST results in some risk groups.

Contact investigation involves the systematic identification and evaluation of the contacts of known TB patients to identify active disease or LTBI [66]. This is considered to be beneficial because contacts of patients with TB are at higher risk of exposure to the causative organism than members of the general population (and if found positive, at higher risk of disease progression due to recent infection) [67]. Whether limited or extensive case finding among contacts will be performed depends on factors including the available resources. Limited case finding within a contact investigation approach includes an assessment of individuals at high risk, such as household contacts, PLHIV and young children [6].

Treatment-related interventions

For effective programmatic management of LTBI, LTBI treatment should be initiated for those identified as an LTBI case and treatment should be completed. To increase the uptake of and adherence to LTBI treatment, treatment-related interventions may be effective, such as cultural case management, adherence coaching and peer counselling.

Patients on LTBI treatment should be monitored to minimise the risk of adverse events. Drug-specific adverse reactions can occur with isoniazid (peripheral neuropathy and hepatotoxicity), and rifampicin and rifapentine (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity) [4]. While most adverse drug reactions are minor and occur rarely, attention should be paid to prevention of drug-induced hepatotoxicity.

Education

Education can support programmatic management of LTBI. In general, education can be used to increase the knowledge and skills or improve the attitude or behaviour of individuals. Various groups can be targeted for education, for example by training for healthcare workers or counselling for the general population, in particular individuals at risk of *M. tuberculosis* infection.

Counselling has been defined as a deliberate process of influencing patient behaviour and producing the changes in knowledge, attitudes and practices necessary to maintain or improve health [68]. Providing patients with complete and current information about their health helps to create an atmosphere of trust, enhances the healthcare worker–patient relationship and empowers patients to take responsibility (care) for their own health [69].

Training for healthcare workers will increase the knowledge of TB/LTBI and raise awareness of the disease, which will help in informing and effectively treating TB patients, and will thereby contribute to controlling LTBI [14,15].

Implementation

Implementation is a specified set of activities designed to put an activity, programme or intervention into practice [70]. Offering an intervention or set of activities within an existing health programme can be a good option to reduce cost, and can increase acceptability and feasibility. Integration refers to coordinated provision of healthcare services and includes several models ranging from locating two services in one facility to a one-stop-shop model that provides a complete package of services delivered by one healthcare team [70].

Programme monitoring and evaluation

Programme evaluation is the collection of information about programme/intervention activities to determine the extent of implementation of the programme and the results achieved by the programme/intervention. Evaluation studies provide credible information for improving programmes/interventions, identifying lessons learned and informing decisions about future resource allocation. Monitoring is the routine tracking and reporting of priority information about a programme/project, its inputs and its intended outputs, outcomes and impacts. Monitoring and evaluation can be used to demonstrate how programmes are progressing towards their goals – and, if programmes are failing, to identify the reasons and solutions [71].

1.6. 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 of 90 % reduction of TB incidence and 95 % reduction of TB mortality by 2035 [23].

The objectives of this review were as follows:

- To collect and appraise relevant systematic reviews and meta-analyses regarding target risk groups, diagnosis, treatment and programmatic issues for LTBI management implementation.
- To identify, retrieve and appraise national and international evidence-based guidelines relevant to the topics mentioned above.
- To summarise the existing evidence base on the different options for programmatic management of LTBI.

1.7. Outline of this report

Section 2 presents the review questions derived from the key areas identified in the inventory conducted in 2013 [31]. It also describes the methods of data collection, data extraction and quality assessment of the evidence. Section 3 summarises the results of the review, including relevant statements of existing national and international evidence-based guidelines, structured according to the review questions. Summary tables describing the data extracted from the systematic reviews are presented in the appendices. Section 4 begins with a summary of the main findings, presented as evidence statements. It also presents the knowledge gaps identified during the review process and discusses the strengths and limitations of this report.

Finally, general conclusions and next steps are presented in Sections 5 and 6, respectively.

2. Methods

2.1. Review questions

Four key areas and preliminary research questions important for the assessment of the potential benefits and risks of introducing programmatic management of LTBI in TB prevention and control strategies were identified in the interactive expert panel workshop in 2013 [31] (see Appendix 1). These were restructured into the following final four key areas and corresponding main questions, for which review questions were formulated to be answered for the guidance for programmatic management of LTBI.

Who to diagnose and treat (target risk groups)

Main question: In which populations will LTBI management measures provide the largest benefit?

Review questions

- Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*? For example, what is the LTBI prevalence in different risk groups such as home- and shelterless persons, prisoners, immunocompromised persons, migrants and refugees, people living with HIV (PLHIV), drug users, healthcare workers, TB contacts, other risk groups?
- Which populations are at increased risk of developing active TB?

When and how to detect LTBI

Diagnostic tests (TST and IGRA)

Main question: What is the optimal and most reliable diagnostic test or combination of tests for LTBI?

Relevant outcomes: effectiveness (e.g. sensitivity/specificity, LTBI positivity rates, LTBI incidence/prevalence), cost-effectiveness, measures of feasibility, accessibility, acceptability.

Review questions

- Which tests are effective for diagnosis of LTBI? (In certain risk groups)
- Which diagnostic tests are cost-effective for LTBI? (In certain risk groups)
- Which diagnostic tests are feasible, accessible and/or acceptable for LTBI? (In certain risk groups)
- What is the effect of tests being free of charge?
- In what order should a combination of LTBI tests (and tests for active TB) be done?

When and how to apply LTBI treatment

Main question: What is the optimal approach for LTBI treatment? (Which treatment regimens? Who? When?)

Relevant outcomes: effectiveness (e.g. initiation, completion, cure, change in risk of developing TB, relative predictive value, incident TB over time), cost-effectiveness, measures of feasibility, accessibility, acceptability.

Review questions

- What is the effectiveness of different LTBI treatment regimens for certain risk groups? (Summarised by treatment)
- What is the cost-effectiveness of different LTBI treatment regimens for certain risk groups?
- What is the feasibility and acceptability of different LTBI treatment regimens for certain risk groups?
- How often is LTBI treatment initiated? (In certain risk groups)
- How often is LTBI treatment completed? (In certain risk groups)
- What is the risk of adverse events (AEs) of LTBI treatment? (In certain risk groups)

Programmatic issues of LTBI management

Main question: What is the optimal approach for programmatic management of LTBI?

Case detection (screening, contact investigation)

- Screening

Main question: What is the optimal approach for screening for LTBI? (Who (target groups)? When? Where? How?)

Relevant outcomes: effectiveness (e.g. uptake, change in number or % tested, LTBI positivity rate, LTBI incidence/prevalence, incident TB, change in risk of developing TB, relative predictive value), cost-effectiveness, measures of feasibility, acceptability.

Review questions

- What is the effectiveness of screening programmes for certain risk groups?
- What is the cost-effectiveness of different screening programmes for certain risk groups?
- How can target groups be identified and accessed for LTBI screening services?
- What is the effectiveness of interventions to improve screening uptake?
- Is mandatory LTBI screening effective, cost-effective and/or feasible (for specific target groups)?

Contact investigation

Main question: What is the optimal approach for contact investigation? (Who (target groups)? What (contacts)? When? Where? How?)

Relevant outcomes: effectiveness (uptake, secondary LTBI cases identified, incidence LTBI/TB, preventive treatment initiation), cost-effectiveness, measures of feasibility, accessibility, acceptability.

Review questions

- What is the effectiveness of (different) contact investigation approaches in certain risk groups?
- What is the cost-effectiveness of (different) contact investigation approaches in certain risk groups?
- How can target groups be identified and accessed for contact investigation?
- What is the effectiveness of interventions to improve contact investigation uptake?

Treatment-related interventions

Improving treatment adherence

Main question: What interventions lead to improved results of treatment of LTBI?

Relevant outcomes: effectiveness (positive/negative association with initiation and completion, odds ratio (OR), risk ratio).

Review questions:

- What are determinants of LTBI treatment initiation, adherence and completion?
- What interventions are effective to improve initiation, adherence and completion of LTBI treatment?

AE control

Main question: Can AE management improve the results of LTBI treatment?

Relevant outcomes: mortality and morbidity related to toxicity and tolerability of the preventive therapy.

Review question

- What is an effective approach to monitor and manage AEs?

Education

Main question: What is the optimal approach for education relating to LTBI? (Who? When? How?)

Relevant outcomes: effectiveness (relative risk, completion of treatment).

Review questions

- Who should be targeted for education and when?
- What information should be provided?
- What is the effectiveness of different education methods?
- Is education cost-effective?

Implementation

Main question: Can LTBI management be integrated into existing health programmes in EU/EAA countries?

Relevant outcomes: effectiveness (output of delivery, outcomes for patient, proportion screened for IPT eligibility, adherence), experiences of different models.

Review questions

- What country-specific circumstances should be taken into account for successful implementation of programmatic management of LTBI?
- Is integration of LTBI case detection and treatment into existing health programmes effective, cost-effective and/or feasible (for specific target groups)?

Programme monitoring and evaluation

Main question: How should monitoring and evaluation of programmatic management of LTBI take place?

Relevant outcomes: effectiveness, description of different approaches (e.g. by country, by population of interest), frequency of monitoring.

2.2. Search and selection strategy

In order to collect evidence for the main questions and the review questions, the following steps were performed:

- an inventory and summary of commissioned systematic reviews by ECDC and WHO (in the development process of the WHO document *Guidelines on the management of latent tuberculosis infection* [4] and the ECDC guidance *Programmatic management of latent tuberculosis infection in the European Union* [5]);
- a PubMed search for additional or updated published systematic reviews (non-commissioned systematic reviews);
- an inventory of national and international evidence-based guidelines;
- a Google search for remaining gaps in evidence;
- a consultation of the ad hoc scientific panel for identification of additional publications.

2.2.1. Step 1: Inventory of commissioned systematic reviews by ECDC/WHO

ECDC and WHO have jointly worked towards building the evidence base to address the review questions relevant for the ECDC guidance and for the separate process by the WHO towards the WHO guidelines on LTBI management for low-incidence settings globally [4]. The relevant documents on LTBI included:

- a systematic review on LTBI diagnostics (included as a full commissioned systematic review in this report);
- an updated systematic review on treatment effectiveness (included as a full commissioned systematic review in this report);
- a systematic review on treatment adherence (included as a full commissioned systematic review in this report)
- reports of the other systematic reviews commissioned by ECDC and WHO (referred to as commissioned systematic reviews) which formed the basis of the WHO document *Guidelines on the management of latent tuberculosis infection* [4] (summarised together with the results of the additional review of systematic reviews in this report (referred to as non-commissioned systematic reviews), see Section 2.2.2).

2.2.2. Step 2: Review of systematic reviews/meta-analyses (non-commissioned systematic review)

For all topics, except for LTBI diagnostics, LTBI treatment effectiveness and LTBI treatment adherence (see Section 2.2.1), a PubMed search was conducted to find systematic reviews. The initial search was performed on 4 March 2015 for research topics that were not covered by the systematic reviews performed for the WHO guidelines and the ECDC guidance (Section 2.2.1), and the guidelines found during the guideline search (Section 2.2.3); the search was updated on 1 June 2016 for all topics, except for LTBI diagnostics, LTBI treatment effectiveness and LTBI treatment adherence.

Search strategy

For each research topic, a search string was composed (Appendix 2). The initial search was restricted to systematic reviews and meta-analyses published in the last 10 years. During the update the search was restricted to articles published in the last 5 years.

Selection

The references resulting from the search were critically appraised by one researcher using a two-step selection procedure. First, the titles and abstracts were screened. Articles with titles and abstracts that suggested that they did not contain information relevant to the research questions and reviews that were not conducted systematically were not selected for full-text assessment. Secondly, the full texts of articles that were selected during the title and abstract screening were assessed. These articles were either included in the report and critically appraised on quality or excluded when it turned out that the article did not contain relevant information. In cases of doubt, the article was discussed with the senior researcher. When disagreements on relevance occurred, these were solved in consultation with the project leader.

Quality assessment of systematic reviews

For the quality assessment of the systematic reviews, the Amstar (A Measurement Tool to Assess Systematic Reviews) tool (Appendix 3) was used. The Amstar tool is an instrument for assessing the methodological quality of systematic reviews [72]. It is based on two instruments (the Overview of Quality Assessment Questionnaire

developed by Oxman and Guyat [73], and Sacks' instrument [74]), empirical evidence and expert consensus. The Amstar checklist consists of 11 questions related to methodological quality to be answered by 'yes',' no', 'can't answer' or 'not applicable'.

No articles were excluded based on quality.

Grading of the evidence from included systematic reviews

The evidence of each included systematic review was graded as 'weak evidence', 'moderate evidence' or 'strong evidence'. For the three full commissioned systematic reviews included in this report (see Section 2.2.1), this was done based on the grading of recommendations assessment, development and evaluation (GRADE) criteria [75,76].

Assessing the strength of evidence of the non-commissioned systematic reviews included was done by a method based on the same GRADE criteria. The level of evidence depended on a combination of the following three aspects: the included study designs, the quality assessment of the evidence within the review (i.e. this includes both the quality assessment method used in the review and the quality of the included studies) and the Amstar score (see Table 1 below).

Table 1. Grading of the evidence of included systematic reviews*

	Definition	Included study designs	Quality assessment of evidence within the review**	Amstar
No evidence	No evidence or clear conclusions from any studies	No studies included	Not applicable	Not applicable
Weak evidence	No clear or strong evidence/conclusions from high-quality studies and only tentative evidence/conclusions from moderate-quality studies or clear evidence/conclusions from low-quality studies	RCTs Cohort/case-control studies Cost-effectiveness studies Cross-sectional studies Outbreak studies No study design reported	Unknown or insufficient quality assessment method Very low/low-quality RCTs Moderate/low-quality cohort/case-control studies Moderate/low-quality cost-effectiveness studies Cross-sectional studies irrespective of quality No study design reported irrespective of quality	Low to high-quality review
Moderate evidence	Tentative evidence/conclusions from multiple high-quality studies, or clear evidence/conclusions from one high-quality study or multiple medium-quality studies, with minimal inconsistencies across all studies	Mostly RCTs; and/or Mostly cohort/case-control studies; and/or Mostly cost-effectiveness studies	Sufficient quality assessment method (e.g. GRADE, NOS, SIGN) Moderate/low-quality RCTs High-quality cohort/case-control studies High-quality cost-effectiveness studies	Moderate to high-quality review
Strong evidence	Clear conclusions from multiple high-quality studies	Mostly RCTs included	Sufficient quality assessment method (e.g. GRADE, NOS, SIGN) High-quality RCTs	High-quality review

** Developed by Pallas Health Research and Consultancy for this review of systematic reviews.*

*** The majority of the primary reports included in the systematic review should be RCTs, cohorts, case-control or cost-effectiveness studies and not cross-sectional studies, outbreaks reports or no study design reported. Meta-analyses were considered as an analysis method rather than a study design.*

2.2.3. Step 3: Guidelines inventory

The search for guidelines was started at the website of the United States National Guideline Clearinghouse (http://www.guideline.gov on 2 March 2015; updated on 25 July 2016). This website contains guidelines developed by organisations such as National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) [78]. In addition, the Centers for Disease Control and Prevention (CDC) website was searched for relevant guidelines (http://www.cdc.gov on 10 and 11 March 2015, updated on 25 July 2016). The search terms *tuberculosis*, *tuberculos** and *TB* were used to find potentially relevant guidelines.

During the update, the following websites were also searched:

- ECDC: http://ecdc.europa.eu/
- International Union against Tuberculosis and Lung diseases (the Union): http://www.theunion.org/
- WHO: http://www.who.int/
- Stop TB Partnership: http://www.stoptb.org/
- European Respiratory Society: www.ersnet.org
- Health Protection Surveillance Centre, Ireland: http://www.hpsc.ie/
- The National Institute for Public Health and the Environment, the Netherlands: http://www.rivm.nl/

- Department of Health, United Kingdom: https://www.gov.uk/government/organisations/department-of-health
- Geneva Foundation for Medical Education and Research. Tuberculosis. Guidelines, reviews, statements, recommendations, standards: http://www.gfmer.ch/Guidelines/Tuberculosis/Tuberculosis_mt.htm

In addition to the guideline search, ECDC provided several documents for screening, including the following.

Guidelines

- *Approach to managing the child exposed to tuberculosis*, 2012, from James Nuttall (Red Cross War Memorial Children's Hospital and University of Cape Town) [79]
- *Latent tuberculosis infection: A guide for primary healthcare providers*, 2013, from CDC, developed in partnership with the New Jersey Medical School Global Tuberculosis Institute [80]
- *Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control*, published by Royal College of Physicians (also found on the Clearinghouse website) [25]
- *WHO guidelines on the management of latent tuberculosis infection* [4]

Grey literature

- *Progressing towards TB elimination*, 2010, from ECDC [81]
- *Surveillance report: Tuberculosis surveillance and monitoring in Europe*, 2016 [82]
- *Framework action plan to fight tuberculosis in the European Union*, 2008, from ECDC [83]

Quality assessment and selection of guidelines

The Appraisal of Guidelines for Research and Evaluation (AGREE) tool [84] was used for the quality assessment of the guidelines (Appendix 4). Inclusion or exclusion was based on a stepwise approach. In a first step, guidelines were included or excluded primarily based on three main criteria from the AGREE tool, i.e.:

- the overall objective(s) of the guideline is (are) specifically described;
- systematic methods were used to search for evidence;
- the recommendations are specific and unambiguous.

In cases of doubt on the quality of a guideline, the guideline was assessed on all 23 criteria from the AGREE II tool and thereafter included or excluded.

Recommendations presented in the guidelines could be evidence based, practice based or a combination of both. Evidence-based recommendations are exclusively based on the scientific literature and not on good clinical practices or expert opinions. Practice-based recommendations are not based on scientific evidence and reflect expert opinion or information derived from good clinical practices. In this report, evidence-based guidelines and recommendations that were a combination of evidence-based and practice-based guidelines are included. Guidelines older than 10 years (i.e. published before 2006) were not included. If more than one version of a guideline was available, the most comprehensive version was included.

All potentially relevant guidelines of sufficient quality were extensively searched for recommendations relevant for the questions as formulated in Section 2.1.

2.2.4. Step 4: Google search

For the remaining gaps in evidence, a Google search was performed on 26 March 2015 (updated on 25 July 2016). Keywords used to define each research topic (see Section 2.1) were used for the search, for example contact* AND yield AND TB. From each search, the first four pages of Google results were screened. For all hits that appeared potentially relevant, the webpage was screened.

2.2.5. Step 5: Consultation with the ad hoc scientific panel on the evidence base

After steps 1-4, an overview was made of the references of the included systematic reviews and evidence-based guidelines. Also, the primary articles that are part of these included reviews/guidelines were listed.

An ad hoc scientific panel was appointed by ECDC (see Appendix 5) to review and interpret the evidence collected in this review. Hence, the ad hoc scientific panel was asked to review the list of included systematic reviews/guidelines and primary articles and to indicate whether specific studies were missing that, in their opinion, were highly relevant for consideration in the guidance development process.

The full-texts of suggested articles were downloaded and the results were, if relevant, compared to see if they were in line with the results of the already included systematic reviews. Agreement or disagreement with the existing evidence base is indicated in the last row of the summary table concerned.

2.3. Data extraction

2.3.1. Data extraction for commissioned reviews and the review of reviews

For each included systematic review, relevant information was extracted into an evidence table, ordered by topic. Each evidence table contained information on reference, study objective, inclusion and exclusion criteria, search method, included articles, outcome definition and outcome measurement, results and remarks.

For each review question, relevant results from included systematic reviews are presented in summary tables in this report (Appendices 6-9). A review could appear multiple times in the data synthesis report if it presents data for multiple review questions. In the summary tables, the results are sorted by 'commissioned systematic reviews' (commissioned by ECDC and WHO), which have also been included in the WHO document *Guidelines on the management of latent tuberculosis infection* [4], and reviews found in the additional review of systematic reviews/meta analyses ('non-commissioned systematic reviews').

Full commissioned systematic reviews

For three commissioned systematic reviews performed according to GRADE, an update was planned. In consultation with ECDC, it was decided to include the findings of these systematic reviews separately, i.e. not in the review of reviews summary. Thus, these selected reviews are referred to as full commissioned systematic reviews. For each of the three full commissioned systematic reviews (i.e. Stagg et al. [29], Kik et al. [85], Stuurman et al. [86]), relevant information from primary articles was extracted into evidence tables in either Word or Excel. Each evidence table contains information on, amongst other things, reference, study objective, population, test, LTBI treatment, intervention, outcome definition and outcome measurement, results and quality criteria of the study.

For each review question, relevant results based on included primary studies are presented in GRADE tables in this report.

2.3.2. Data extraction for guidelines

The recommendations from the guidelines were extracted into guideline tables. The table contains information on reference, society or organisation that produced the guidelines, recommendation and type (i.e. evidence-based guidelines or a combination of evidence-based and practice-based guidelines).

For each guideline, all recommendations were individually reviewed for their content and recommendations relevant for the topics identified for the guidance were used. For each main question, relevant statements from evidence-based guidelines (including source) are listed.

2.4. Quality control

During the process, the following quality control measures were implemented.

- Data extraction: the evidence and summary tables were compiled by a researcher and reviewed by a second researcher.
- Interpretation and presentation of the results: the review team discussed the results of the review early in the reporting phase. Results were summarised by two researchers and reviewed by a third researcher.

2.5. Evidence statements and grading of the body of evidence

For each of the review questions as listed in Appendix 1 the included evidence base was further summarised in short evidence statements, with a grading of the strength of the body of evidence for these statements. For each review question, the evidence statements are based on the results of one or more relevant systematic reviews of comparative studies that present statistically analysed quantitative estimates. Multiple evidence statements could be formulated for one review question, when more than one relevant outcome was identified.

For each evidence statement, the strength of the body of evidence from the underlying systematic reviews was graded as 'weak evidence', 'moderate evidence' or 'strong evidence'. This was based on the assessed strength of evidence of each included systematic review, as described in Section 2.2.2.

Results of studies that are non-comparative or did not perform statistical analyses (e.g. only presented descriptive analyses results) are not used as basis of the evidence statement, but are presented as additional information relevant for the topic.

The evidence statements served as input for the assessment of the body of evidence of each review question and, together with the additional information, for further discussion on the guidance for programmatic LTBI control by an ad hoc scientific panel.

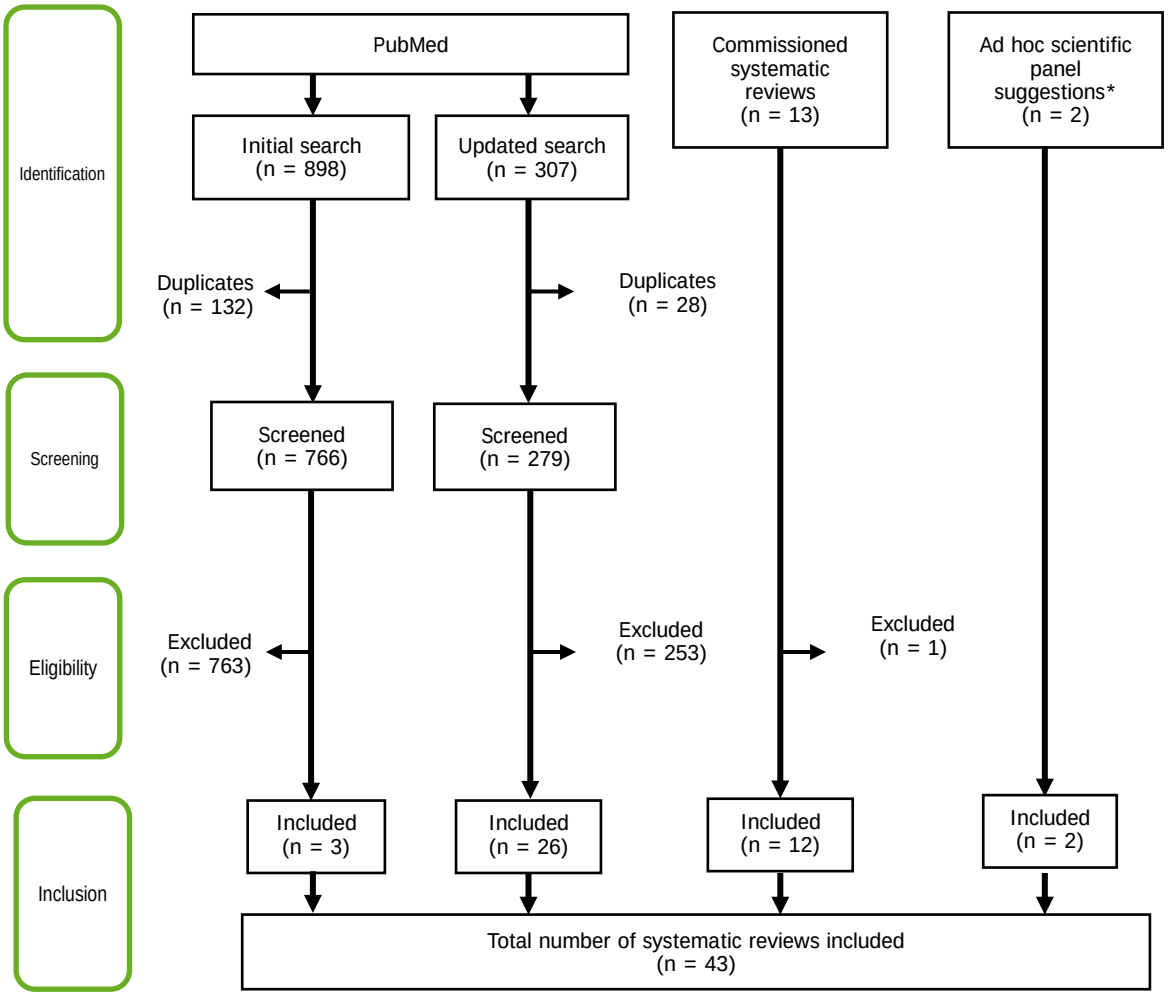
3. Results

3.1. Search results

The results of the inventory of systematic reviews and of existing relevant high-quality guidelines is summarised in the flow charts below.

3.1.1. Systematic reviews

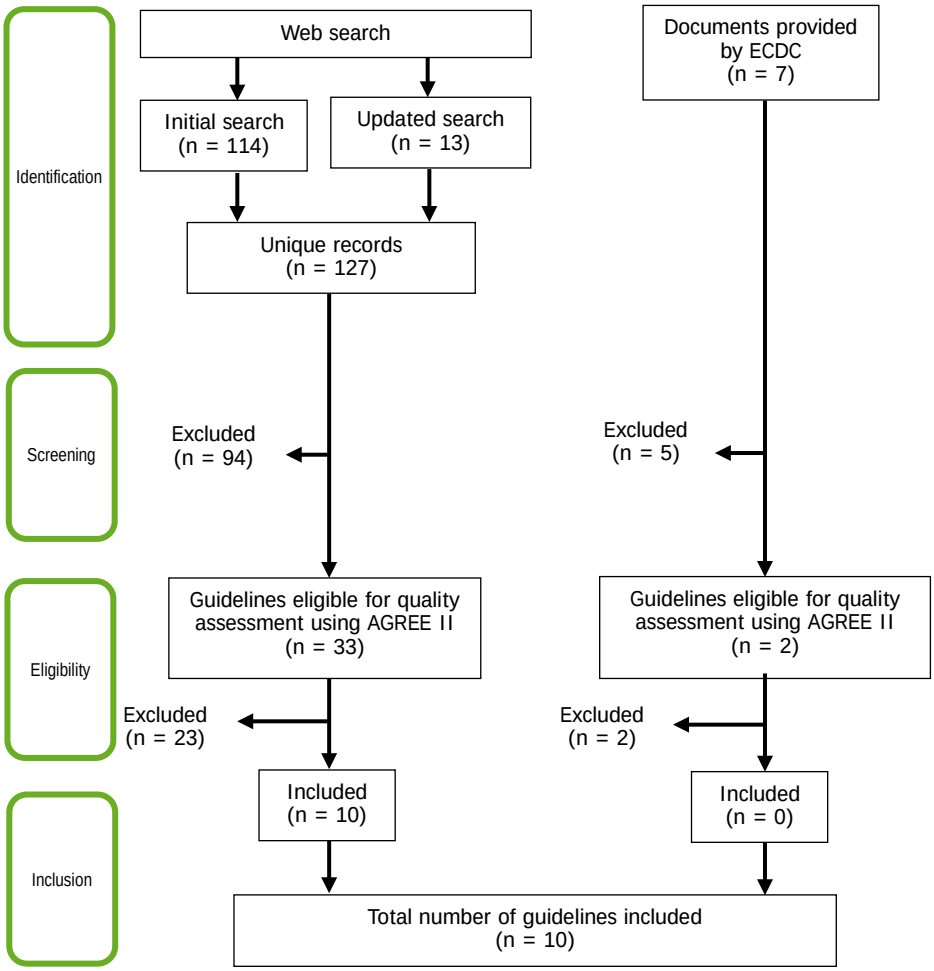
Figure 1. Flowchart of selection process, systematic reviews



Forty-three reviews were selected for data extraction, consisting of 12 commissioned systematic reviews, 29 systematic reviews resulting from the review of systematic reviews (three from the initial search and 26 from the update search) and two suggested by the ad hoc scientific panel during the meeting. Ten articles reporting on primary studies were suggested during the consultation round with the ad hoc scientific panel, of which outcomes of seven primary studies are mentioned as footnotes under the relevant summary tables in this report but not included in the total count of included systematic reviews.

3.1.2. Evidence-based guidelines

Figure 2. Flowchart of selection process, evidence-based guidelines



3.2. Who to diagnose and treat (target risk groups)

The results of the searches on target risk groups (systematic reviews and guidelines) are shown below. Appendix 6 (Tables A6.1-A6.4) provides a detailed summary of relevant data extracted from the systematic reviews. Target risk groups were initially selected in the expert panel workshop in 2013 [31] and subsequently refined after an initial assessment of the scientific literature.

3.2.1. Systematic reviews

To provide information useful for answering the main question, the following review questions were formulated:

- Which populations are at increased risk of becoming (latently) infected with TB?
- Which populations are at increased risk of developing active TB?

Which populations are at increased risk of becoming (latently) infected with TB?

Four systematic reviews calculated ratios for the risk of becoming (latently) infected with TB after exposure to TB cases for various risk groups [66,87-89] (see Table A6.1). Nine systematic studies presented TB infection rates or LTBI prevalence in risk groups [66,87,89-95]. Two of these studies performed statistical analyses to assess if significant differences existed between risk groups [66,91] (see Table A6.1).

PLHIV

Based on pooled risk ratios, no significant evidence for increased risk of LTBI was found in PLHIV (identified by TST and IGRA) in low- (TB incidence rate: < 40 cases per 100 000) and high-TB-burden countries (TB incidence rate: > 100 cases per 100 000); see Table A6.2. For intermediate-TB-burden countries (TB incidence rate: 40-100 cases per 100 000), the pooled estimate risk ratio could only be calculated for PLHIV identified by TST. For this group, no significant evidence for increased risk of LTBI was found either [96]. LTBI prevalence was present in PLHIV in

seven included studies, varying from 6.9 % to as high as 97.2 %; see Table A6.1 [92]. For the pooled prevalence of LTBI (established by TST and IGRA) in PLHIV in low, intermediate and high-TB-burden countries, see Table A6.3 [96].

Immunocompromised

Govindasamy et al. calculated pooled risk ratios for LTBI infection in various immunocompromised populations compared to the general population [96]. Based on this, no significant evidence for increased risk of LTBI was found in patients with renal or liver conditions (identified by TST and IGRA) in low and high-TB-burden countries; see Table A6.2. For intermediate-TB-burden countries, the pooled estimate risk ratio could only be calculated for patients with renal or liver conditions identified by TST. For this group, there was also no significant evidence for increased risk of LTBI found.

In low-TB-burden countries, candidates for anti-tumour necrosis factor (TNF) therapy (identified by IGRA) seemed to have a higher risk of LTBI compared to the general population, while no significant evidence for increased risk of LTBI was found in candidates for anti-TNF-alpha therapy identified by TST. No calculation could be performed for intermediate and high-TB-burden countries.

No significant evidence for increased risk of LTBI was found in patients with autoimmune disorders (AIDs) or immune-mediated inflammatory disorders (IMIDs) (identified by TST and IGRA) in low-TB-burden countries and in this population identified by TST (no calculation possible for IGRA) in high-TB-burden countries. For intermediate-TB-burden countries, no calculation could be performed [96].

See Table A6.3 for the pooled prevalence of LTBI [96] in:

- patients with renal or liver conditions in low-, intermediate- and high-TB-burden countries (established by TST and IGRA);
- candidates for anti-TNF-alpha therapy in low (established by TST and IGRA) and intermediate (established by TST) TB burden countries;
- patients with AIDs or IMIDs in low and high-TB-burden countries (established by TST and IGRA);
- transplant candidates or recipients in low and high-TB-burden countries (established by IGRA);
- patients with cancer in low-TB-burden countries (established by IGRA).

Migrants

Govindasamy et al. reported the risk ratio for LTBI infection in various risk populations compared to the general population. In low-TB-burden countries, immigrants and refugees (as measured by TST) seemed to have higher risk of LTBI compared to the general population. No significant evidence for increased risk of LTBI was found in immigrants and refugees (identified by IGRA) in low-TB-burden countries; see Table A6.2 [96].

Campbell et al. calculated ORs to assess predictors for a positive TST (n = 23 studies) or IGRA (n = 8). In this study, BCG-vaccinated immigrants had a higher likelihood of a positive TST. Immigrants from countries with ≥ 30 cases per 100 000 (compared to immigrants from countries with < 30 cases per 100 000) tested with TST or IGRA had a higher likelihood of a positive test: 2.38 (95 % CI 1.14-4.98) (TST) or 17.25 (95 % CI 1.03-289.34) (IGRA). With only one study comparing immigrants from low-incidence to high-incidence TB countries, a meta-analysis was not performed [87].

Campbell et al. performed a statistical analysis which showed that positive TST or IGRA results were found significantly more often in immigrants ≥ 18 years of age compared to those aged < 18 years. For immigrants tested with TST the positivity rate was 41.6 %, while for those tested with IGRA the positivity rate was 23.8 % (no statistical analyses performed) [91]. The other review of Campbell et al. on immigrants to low-incidence countries found TST and IGRA positivity rates of 40.7 % and 32.2 %, respectively [87].

LTBI prevalence in migrants was included in eight studies, varying from 0.3 % to as high as 50.0 %; see Table A6.1 [92]. For the pooled prevalence of LTBI (established by TST and IGRA) in immigrants and refugees in low-TB-burden countries, see Table A6.3 [96].

Healthcare workers

Govindasamy et al. reported the risk ratio for LTBI infection in healthcare workers and students (identified by TST and IGRA) compared to the general population. No significant evidence for increased risk of LTBI was found for this population in low-, intermediate- and high-TB-burden countries; see Table A6.2 [96].

One review on outbreak studies reported the proportion of cases who acquired TB infection after exposure to index healthcare workers. Among the included studies, the proportion was 2.62 % (95 % CI 1.05-4.88) in healthcare workers, which was lower than in adult contacts, but higher than in children and infant contacts (no statistical analyses performed) [90]. LTBI prevalence was present in healthcare workers in five included studies, varying from 10.0 % to 17.0 %; see Table A6.1 [92]. For the pooled prevalence of LTBI (TST and IGRA) in healthcare workers and medical and nursing students in low-, intermediate- and high-TB-burden countries, see Table A6.3 [96].

TB contacts

Govindasamy et al. reported the risk ratio for LTBI infection in various risk populations. In intermediate-TB-burden countries, TB contacts (identified by TST) were at higher risk of LTBI compared to the general population. No significant evidence for increased risk of LTBI was found in TB contacts (identified by IGRA) in intermediate-TB-burden countries. Also, no significant evidence for increased risk of LTBI was found in TB contacts (identified by TST and IGRA) in low and high-TB-burden countries, see Table A6.2 [96].

Fox et al. provided the proportion of LTBI in screened contacts in low/middle-income settings (51.5 %), high-income settings (28.1 %), for contacts born locally (17.0 %) and born overseas (39.2 %). Fox et al. also performed a statistical analysis on prevalence estimates and found that the prevalence of LTBI among contacts is significantly less in high-income countries than in low–middle-income countries, although this difference was not evident among household contacts. Foreign-born contacts are significantly more likely to have LTBI than locally born contacts in high-income countries [66].

In the article of Girardi et al., LTBI prevalence was present in contacts in six included studies, varying from 25.0 % to as high as 59.5 %; see Table A6.1 [92]. Shah et al. reported that household contact investigation around patients with drug-resistant TB appears to be a high-yield intervention for detection of drug-resistant TB and prevention of ongoing transmission; the overall proportion of household contacts with LTBI is 47.2 %, with the lowest yield in paediatric contacts and the highest yield in adult contacts [95].

For the pooled prevalence of LTBI (TST and IGRA) in TB contacts in low-, intermediate- and high-TB-burden countries, see Table A6.3 [96].

Schepisi et al. presented the percentage of cases who acquired TB infection after exposure to an index case (healthcare worker) for adults (4.32 %, 95 % CI 1.43-8.67), children (0.90 %, 95 % CI 0.40-1.60) and infants (0.57 %, 95 % CI 0.00-2.02) [90]. The prevalence range of TB infection after exposure to an index case in child contacts < 5 years of age, aged 5-15 years and < 15 years was 5.5 %-51.2 %, 35.7 %-76.9 % and 24.4 %-69.9 %, respectively [90].

Prisoners

Govindasamy et al. reported the risk ratio for LTBI infection in various risk populations. In low and intermediate-TB-burden countries, prisoners (as identified by TST) seemed to have a higher risk of LTBI compared to the general population (see Table A6.2) [96]. No calculation could be performed for high-TB-burden countries and for prisoners as identified by IGRA. In prisoners, the median LTBI prevalence in high-income countries in Europe was as high as 36.5 % (interquartile range: 10.1-55.9) [93]. For the pooled prevalence of LTBI (established by TST) in prisoners in low and intermediate-TB-burden countries, see Table A6.3 [96].

Homeless people

Govindasamy et al. reported the risk ratio for LTBI infection in various risk populations. In low-TB-burden countries, homeless people (identified by TST and IGRA) seemed to have a higher risk of LTBI compared to the general population (see Table A6.2). No calculation could be performed for intermediate and high-TB-burden countries [96]. For the pooled prevalence of LTBI (established by IGRA) in homeless people in low-TB-burden countries, see Table A6.3 [96].

People with drug use disorders

Govindasamy et al. reported the risk ratio for LTBI infection in various risk populations. No significant evidence for an increased risk of LTBI was found in people with drug use disorders (identified by TST and IGRA) in low-TB-burden countries; see Table A6.2 [96]. For intermediate and high-TB-burden countries, no calculation could be performed. For the pooled prevalence of LTBI (TST and IGRA) in people with drug use disorders in low-TB-burden countries, see Table A6.3 [96].

Age

Campbell et al. calculated ORs to assess predictors for a positive TST (n = 23 studies) or IGRA (n = 8). In this study, age is a predictor of TST positivity resulting in a higher likelihood of a positive TST in those ≥ 35 years of age [87].

Campbell et al. performed a statistical analysis which showed that risk of infection may be associated with age: a significantly higher proportion of positive TST or IGRA results were found in immigrants ≥ 18 years of age (26.1 % (IGRA) – 44.7 % (TST)) – compared to those aged < 18 years (13.9 % (IGRA) – 24.0 % (TST)) [91].

One review on outbreak studies reported the pooled proportion of cases who acquired TB infection after exposure to index healthcare workers. The proportion was the highest in adults, followed (besides healthcare worker contacts) by children and infants (no statistical analyses performed on differences between groups) [90].

Triasih et al. found that the proportion of TB infection was more common in older children than in younger children (within a group of children and adolescents aged 0-15) (no statistical analyses performed on differences between groups) [94]. LTBI prevalence was presented in children and the elderly in six included studies, varying from 14.8 % to 15.0 % in children and from 25.0 % to 36.0 % in the elderly (no statistical analyses performed on differences between groups); see Table A6.1 [92]. In the study of Govindasamy et al., the pooled estimate of LTBI in the elderly ranged from 16.3 % to 59.4 % (as measured by TST and IGRA) [96].

Other risk groups

Statistical analyses of the relative risk (RR) showed that second-hand smoking exposure has been associated with an increased risk of LTBI after controlling for age, biomass fuel use and contact with a TB patient. However, there was no significant association of second-hand smoking exposure with LTBI after adjustment for socioeconomic status and study quality (see Table A6.1) [88].

Campbell et al. calculated ORs to assess predictors for a positive TST (n = 23 studies) or IGRA (n = 8); see Table A6.1. In this study, male gender was found to be a predictor of TST positivity. Those from high-TB-incidence countries are at increased odds of a positive TST. Males were also found to have a higher likelihood of positive IGRAs [87].

Freeman et al. ([1]). presented the cumulative incidence of LTBI among long-term travellers (military and civilian) from low-prevalence countries for both groups combined (2.0 %, 99 % CI 1.6-2.4), the cumulative incidence risk estimates for studies on military travellers (2.0 %, 99 % CI 1.6-2.4) and for studies on civilian travellers (2.3 %, 99 % CI 2.1-2.5). The cumulative incidence ranged from 0.96 % to 3.59 % [97].

Which populations are at higher risk of developing active TB?

Reviews that were identified reporting on risk of TB disease in risk groups presented a wide variety of variables. All data relevant for the question 'Which individuals are at higher risk of developing active TB?' are presented. Eleven systematic reviews reported on the risk of developing active TB for specific risk factors or risk groups. These comprised:

- the relative risk of active TB in LTBI- or TST/IGRA-positive populations compared to the general population (measure for risk of progression);
- proportions of, or progression rates to, active TB in LTBI- or TST/IGRA-positive populations (measure for risk of progression);
- risk or proportions of active TB in TB contacts with known or unknown original LTBI/TST status (this can be a combination of higher risk of infection or progression).

Except for TB contacts, only studies on risk populations with known LTBI or TST baseline status were included. Three of the included reviews performed a statistical analysis to look for significant differences in active TB prevalence between risk groups [90,92,94].

Age

Age appears to be a risk factor for developing active TB. Within one review, children exposed to an infectious case were reported to show the highest pooled proportions of developing active TB, followed by infants, adults and healthcare workers [90]. This is in line with the results from the review of Triasih et al, where the prevalence range of active TB after exposure to an index case showed that TB disease was more commonly found among children aged less than 5 years in a group of children and adolescents aged 0-15 exposed to an infected case (no further analyses performed) [94]. In another review, for the elderly the minimal and maximal annual LTBI reactivation rates reported were 0.22 and 3.59, while for children it ranged from 0.08 to 5.00 [92].

PLHIV

Four systematic reviews reported data on active TB development in PLHIV infected with TB (see Table A6.4). The incidence rate ratio (IRR) of active TB in PLHIV with TST+ results (untreated; with concomitant risk factor) compared to HIV-negatives (LTBI status unknown) in two prospective cohort studies was 10.46 (95 % CI 1.34-471.2) and 9.42 (95 % CI 2.90-27.11), respectively [89]. Compared to the general population (LTBI status unknown), PLHIV with a positive LTBI test (test not defined) had a relative risk of developing active TB of 183.0 (95 % CI 41.7-803.4) [98]. In Diel et al., the pooled positive predictive value (PPV) of commercial IGRAs for studies monitoring only PLHIV was 6.0 % [99]. The annual LTBI reactivation rate in PLHIV presented by Girardi et al. ranged from 1.4 % to 7.0 % [92]

Immunocompromised individuals

Three systematic reviews reported data on active TB development in immunocompromised individuals infected with TB (see Table A6.4). The adjusted relative risk per 100 person-years (pyr) of active TB for ESRD patients undergoing dialysis vs the general population ranged over TST reaction categories (0-4 mm; 5-9 mm; > 9 mm) from 24.5/100 pyr, 8.4/100 pyr, and 41.1/100 pyr, respectively [89], and for LTBI-positive patients with terminal renal failure/dialysis the relative risk of TB compared to the general population (LTBI status unknown) was 703.2 (95 % CI 38.1-12 984.5) [98]. For LTBI-positive patients with autoimmune diseases receiving anti-TNF-alpha inhibitors, LTBI-positive patients with silicosis and LTBI-positive patients with diabetes mellitus, the relative risk of TB compared to the general population (LTBI status unknown) was 16.2 (95 % CI 14.6-18.0), 170.3 (95 % CI 137.9-210.2) and 10.3 (95 % CI 5.9-17.6), respectively [98]. In a study on dialysis patients, the crude estimate of likely TB reactivation (positive test with subsequent TB) was 35.15 cases/1 000 pyr, the IRR of TB development was found to be 2.59 and the PPV of TST was 11.93 % (range 4.60-29.39) [100].

([1]) Published after the search period of the current inventory of evidence. Included after a suggestion made at the ad hoc scientific panel meeting held in November 2016 at ECDC. This meeting was held to discuss the body of evidence and formulate conclusions for the guidance.

Migrants

Three systematic reviews reported data on active TB development in migrants infected with TB (see Table A6.4). Sotgiu et al. reported a relative risk of active TB in LTBI-positive migrants/refugees from high- to low-burden countries compared to the general population (LTBI status unknown) of 90.7 (95 % CI 22.8-361.5) [98]. The annual LTBI reactivation rate in migrants ranged from 0.08 to 13.35 % [92]. Campbell et al. reported the number of active TB cases in TST-positive migrants for three studies. For the two studies on TSTs, 13 of the 591 TST-positive immigrants developed active TB. The IGRA study followed up 238 QuantiFERON-TB Gold in-Tube (QFT-GIT)-positive immigrants not treated for LTBI for development of active TB and found eight cases [91].

Healthcare worker

Two systematic reviews reported data on active TB development in LTBI-infected healthcare workers (see Table A6.4). Sotgiu et al. reported a relative risk of active TB of 2.97 (95 % CI 2.43-3.51) in LTBI-positive healthcare workers compared to the general population (LTBI status unknown). When stratified on TB incidence, the pooled relative risk in low-, intermediate- and high-TB-incidence countries was 2.42, 2.45 and 3.68, respectively. The annual risk of TB disease in healthcare workers was 69-5 780/100 000 population [98]. The annual LTBI reactivation rate in HWC ranged from 0.40 % to 1.20 % [92].

Prisoners

One systematic review reported data on the risk of developing active TB in prisoners (see Table A6.4). The pooled relative risk of developing TB in prisoners vs the general population (LTBI status unknown) was 15.3 for LTBI-positive prisoners. The annual incidence rate ratio was 23 (interquartile range (IQR): 11.7-36.1) [98].

Persons residing in homeless shelters

One systematic review reported data on active TB development in persons residing in homeless shelters (see Table A6.4). The pooled relative risk of developing TB in persons residing in homeless shelters vs the general population (LTBI status unknown) was 7.3 for LTBI-positive persons residing in homeless shelters [98].

Alcohol abusers

One systematic review reported data on active TB development in alcohol abusers, defined as alcohol exposure of ≥ 40 g/day (see Table A6.4). The pooled relative risk of developing TB in alcohol abusers vs the general population (LTBI status unknown) was 2.94 for LTBI-positive alcohol abusers [98].

Other risk groups

Three systematic reviews reported data on active TB development in other risk groups (infected with TB) than described above (see Table A6.4). The OR of developing active TB for **tobacco smokers** (not further defined) was 2.40 (relative risk not available) [98]. Govindasamy et al. found an increased risk of progression in skin converters (negative on baseline, turned positive during follow-up) compared to individuals with a positive test at baseline (rate ratio of 1.7 and 3.0). The risk of progression in LTBI-infected military recruits with **low weight** compared to LTBI-infected recruits with normal weight showed that individuals with low weight had a three times increased risk of progression to active TB [89]. Diel et al. presented the pooled PPV of commercial IGRAs and TSTs for progression to active TB. For all populations combined (including individuals at high risk), the PPV was 2.7 % and 1.5 % for IGRA and TST, respectively. For TB high-risk populations combined (including the PLHIV and contacts, described above), the PPV was 6.8 % and 2.4 % for IGRA and TST, respectively [99].

TB contacts

Studies presenting data on active TB in TB contacts did not always provide information on LTBI or TST status before being exposed to a TB index case. Still, these data were included in the review to provide insight into the risk of active TB in TB contacts.

Nine systematic reviews reported data on the risk of active TB in TB contacts (see Table A6.4). The rate ratio of active TB of close contacts vs casual contacts varied over TST reaction categories from 5.2 to10.6, while the risk of progression in TST+ contacts with CXR lesions was found to be five times greater compared to TST+ contacts without CXR lesions abnormalities [89]. One review on outbreak studies reported the proportion of individuals with active TB after exposure to an index case. For children, the proportion was 0.38 % (95 % CI 0.01-1.60), for infants 0.11 % (95 % CI 0.04-0.21), for adults 0.09 % (95 % CI 0.02-0.2) and for healthcare workers 0.00 % (95 % CI 0.00-0.38) [90]. The annual LTBI reactivation rate in contacts ranged from 0.10 to 12.60 % [92]. For child contacts aged < 15 years, the prevalence of active TB after exposure to an index case ranged from 3 to 16.4 % [94]. For childhood contacts and adult contacts, the pooled relative risk of active TB compared to the general population (LTBI status unknown) was 425.4 (95 % CI 208.14-869.4) and 8.0 (95 % CI 4.8-13.4), respectively [98]. Pooled PPV of commercial IGRAs for progression to active TB in untreated healthy contact persons was 8.5 % (95 % CI 6.5-10.9) (reported time periods were 22 months (median), 24 months in two studies and 46 months (mean)) [99]. A review on contact investigation after TB exposure in an airplane found a rough estimate of TST positivity of 0.1-1.3 % of aircraft contacts in long-haul flights (> 8 hours), which might have contracted the infection from a sputum-smear-positive index case. The risk of infection seems to be the highest among passengers seated within two rows of the index case [101]. Contacts exposed to patients with TB, in a variety of settings, are at a substantial risk of active TB. The incidence of new cases is highest in the first year and remains above background incidence for at least 5 years after exposure to a patient with TB. The prevalence of TB among

contacts is significantly less in high-income countries than in low–middle-income countries, although this difference was not evident among household contacts [66]. Household contact investigation around drug-resistant TB patients is a high-yield intervention for detection of drug-resistant TB and prevention of ongoing transmission; the overall proportion among household contacts for active TB cases was 7.8 % (almost all studies with drug susceptibility testing (DST) reported that > 50 % of the secondary cases with DST results concerned drug-resistant TB or drug resistance categories that were concordant with the source case) [95].

3.2.2. Evidence-based guidelines

One supranational guideline was included on target risk groups. Table 2 summarises its relevant recommendations on who to diagnose and who to treat.

Table 2. Summary of guidelines on target risk groups

Guideline	Who to diagnose	Who to treat
WHO (2015) [4]	'In high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000 population: Systematic testing and treatment of LTBI should be performed in PLHIV, adult and child contacts of pulmonary TB cases, patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for organ or hematologic transplantation and patients with silicosis. Systematic testing and treatment of LTBI should be considered for prisoners, healthcare workers, immigrants from high-TB-burden countries, homeless people and drug users. Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers, and underweight people unless they are already included in the above recommendations.'	'For resource-limited countries and other middle-income countries that do not belong to the above category: PLHIV and children below 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB but have LTBI.'

3.3. When and how to detect LTBI

The search results on LTBI diagnosis are summarised below (systematic reviews and guidelines). See Appendix 7 (Tables A7.1-A7.8) for a more detailed summary of relevant data extracted from the systematic reviews.

3.3.1. Systematic reviews

To provide information relevant for answering the main question, the following review questions were formulated.

- Which tests are effective for diagnosis of LTBI? (In certain risk groups)
- Which diagnostic tests are cost-effective for LTBI? (In certain risk groups)
- Which diagnostic tests are feasible, accessible and/or acceptable for LTBI? (In certain risk groups)
- What is the effect of tests being free of charge?
- In what order should a combination of LTBI tests (and tests for active TB) be done?

Which tests are effective for diagnosis of LTBI? (In certain risk groups)

Full commissioned systematic review

TST and IGRA

One systematic review, using the GRADE methodology, was performed by Kik et al. [85] to comprehensively summarise data on the effectiveness of diagnostic tests for LTBI among persons at high risk of LTBI who are not on TB-preventive therapy. The results included in our analysis are extracted from the initial review performed for the WHO guidelines and correspond to the period 1999 up to 25 February 2014. An update of this systematic review is ongoing, however the results were not available by the time the current data synthesis was finalised. For a list of all articles included in the initial review, see Appendix 10.

Twenty-nine studies fulfilled the inclusion criteria and provided sufficient information for extraction or estimation of effect measures. Study populations were diverse: 13 studies assessed TB contacts (two studies in children and 11 studies in adolescents and adults), 11 studies assessed cohorts of individuals with medical conditions leading to impaired immune response (seven studies included PLHIV, four studies included other medical conditions), one study was performed among prisoners, one study was performed among asylum seekers, one study was performed among adolescents living in high-TB-prevalence countries and one study was performed among silicosis patients.

The overall quality of the evidence, as summarised in the GRADE table (Table A7.1), was low to very low for all review outcomes evaluated. This is largely due to a high risk of bias, inconsistency, imprecision and indirectness.

Results

Pooled analysis of all studies that did not provide preventive therapy resulted in an overall risk ratio for development of TB in those with a positive TST compared to a negative TST result of 2.64 (95 % CI 2.04-3.43, n = 22 studies) and 8.45 for IGRA (95 % CI 4.13-17.31, n = 16 studies). Of the latter, six studies evaluated T-SPOT.*TB* and 10 evaluated QFT-GIT. The pooled risk ratio for QFT-GIT was 10.28 (95 % CI 4.07-25.97) and 6.43 for T-SPOT.*TB* (95 % CI 1.85-22). The pooled risk ratios for QFT-GIT and T-SPOT.*TB* were similar and confidence intervals (CIs) greatly overlapped.

There was heterogeneity in the populations included in the 29 studies and only eight out of 29 studies had evaluated both IGRA and the TST (head-to-head comparison). Observed differences in the effect estimates may be due to differences in study population rather than reflecting true differences between the tests. The remaining analyses were thus restricted to studies that assessed both the TST and one or both commercial IGRAs in the same study population (see Table A7.1 for the GRADE summary table). The PPV for the TST and IGRA were similar and ranged between 1-7 % for the TST and 0-13 % for IGRA. The same was observed for the negative predictive value (NPV); this ranged between 92 % and 100 % for TST and between 88 % and 100 % for IGRA (see Table A7.2). Although the IRR is the preferred effect measure of predictive utility in longitudinal studies, only three out of eight head-to-head comparison studies provided sufficient information on person-time of follow-up. Thus, both the risk ratio and the IRR estimates are reported. The pooled risk ratio estimate for the TST was 2.58 (95 % CI 1.72-3.88, n = 8 studies) and for IGRA was 4.94 (95 % CI 1.79-13.65, n = 8 studies). The pooled IRR analysis of studies that evaluated both the TST and IGRA was 2.07 (95 % CI 1.38-3.11, n = 3 studies) for the TST and 2.40 (95 % CI 1.26-4.60, n = 3 studies) for IGRA (see Table A7.3). In all analyses the CIs around effect estimates for the TST and IGRA overlapped and were imprecise.

Conclusion

The authors concluded that there is little evidence that based on effectiveness either the TST or the IGRA test should be preferred above the other when assessing risk of progression to TB disease. There was insufficient data to provide evidence that the tests differed in predictive utility among specific high-risk subpopulations or groups. There was no data to inform whether the addition of other proxies for LTBI to either TST or IGRA results would improve predictive utility.

Which diagnostic tests are cost-effective for LTBI? (In certain risk groups)

Costs

August et al. presented the cost of diagnostic tests in children, immunocompromised patients and recently arrived populations (e.g. migrants) as being GBP 17.48 for TST, GBP 48.73 for QFT-GIT, GBP 59.57 for TB-specific Elispot assay (T-SPOT.*TB)*, GBP 35 for CXR and GBP 7 for sputum examination. For children, the costs of gastric lavage procedures were also presented: GBP 916. All costs were adjusted to 2012/2013 prices using the Hospital and Community Health Services pay and price index and discounted at a rate of 3.5 % per annum. It was assumed that TST was costed similarly for those that were read and those that were not read, that people being assessed for initial active TB undergo CXR and, if positive, receive a sputum examination and that children being assessed for initial active TB undergo CXR and, if positive, undergo a gastric lavage procedure [102]. In Campbell et al., the cost of the TST ranged from USD 15.55 to USD 42.33 (in 2013), the cost of the IGRA ranged from USD 53.58 to USD 90.31 (excluding two studies that were performed from a healthcare programme perspective) [103].

Nienhaus et al. provided an overview of TST and IGRA costs per country in different currencies extracted from multiple studies. In one study performed in Germany, the reported cost of TST was USD 145.99 and of IGRA USD 171.78 (in 2007, including CXR and consultation if test is positive), while in another study performed in Germany the TST and IGRA (including salary of staff) cost EUR 117.5 and EUR 145.98, respectively. In the United Kingdom, the prices of a test were GBP 15.43 for TST and GBP 45 (QFT-GIT) or GBP 55 (T-SPOT) for IGRA. In France, prices were EUR 10.86 and EUR 44.83, respectively [104].

In a review of cost-effectiveness analysis by Oxlade et al., the costs for a TST ranged from USD 15 to USD 121 (in 2011), while the IGRA test costs ranged from USD 21 to USD 219 (in 2011). Both included direct cost and time/salary-related cost. One study reported T-SPOT.*TB* costs of USD 100 and USD 82 for QFT [105].

Girardi et al. reported the average screening cost for LTBI with TST or with IGRA by country (2012 USD) and the cost of screening candidates for eligibility for preventive therapy (which typically included a CXR, clinical evaluation and liver function tests); see Table A7.4.

Cost-effectiveness

A summary of four systematic reviews of cost-effectiveness analysis (CEA) studies on diagnostic tools is presented in Table A7.5. The criteria for cost effectiveness used in the systematic reviews were applied to define whether a diagnostic strategy was cost-effective.

PLHIV

One systematic review concluded that screening PLHIV with a TST appears to be strongly cost-effective [103] ([2]).

([2]) This systematic review includes studies conducted mainly in high-income, low-TB-incidence countries. Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.

Immunocompromised individuals

One systematic review reported that diagnosing LTBI that progresses to active TB with QFT-GIT-negative followed by TST (≥ 5 mm) appears to be cost-effective ([3]) in the immunocompromised population [102].

Migrants

One systematic review reported that diagnosing LTBI that progresses to active TB with TST (≥ 5 mm) appears to be cost-effective in recent arrivals [102], while a second systematic review concluded that screening adult immigrants with an IGRA appears to be moderately cost-effective ([2]) [103].

Children

One systematic review reported that a diagnostic algorithm comprising TST (≥ 5 mm, negative result) followed by QFT-GIT appears to be cost-effective ([3]) for diagnosing progression to active TB in children with LTBI [102].

High-risk populations

One systematic review concluded that the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries and close contacts, appears to be cost-effective ([4]). If the increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds true, the IGRA-only screening strategy should prove to be the more cost-effective test [104].

Which diagnostic tests are feasible, accessible and/or acceptable for LTBI? (In certain risk groups)

One qualitative systematic review comprising 30 studies (design not reported; several studies combined qualitative methods or used them together with quantitative methods) published between 1997 and 2011 explored the perceptions, knowledge, attitudes and treatment-adherence behaviour relating to TB and their social implications in patients receiving treatment, healthy persons with LTBI, untreated TB patients, healthcare workers and other key informants (Amstar negative on items 1, 2, 4, 5, 7, 8, 9, 10, 11). Generally, respondents were migrants from rural to urban contexts or from high- to low-TB-incidence countries and were unaware of their LTBI status. Some studies showed that a positive result of a TST was perceived as a very serious clinical diagnosis. Multiple studies reported illiteracy or lack of familiarity with the local language and dissatisfaction or cultural differences with 'Western' medical services (not further specified), fear of a painful test or the social consequences of a positive result, having to miss work to attend a clinic appointment, transport difficulties, queues and waiting lists, not having health insurance, irregular residence status, feeling 'singled out' and the stigma associated with being seen entering a TB clinic, economic costs of medical consultations and the presence of 'clinics for immigrants' in dangerous neighbourhoods as barriers to accessing healthcare services and therefore TB diagnosis [106]. Nothing was reported on the quality of the included studies.

What is the effect of tests being free of charge?

No systematic reviews were identified that were published in the last 10 years and provided information on the effect of tests being free of charge.

In what order should a combination of LTBI tests (and tests for active TB) be done?

Van't Hoog et al. (see Tables A7.6-A7.8) tried to establish investigations and clinical parameters most predictive of the absence of active TB. The modelling screening exercise described by Van't Hoog provided information about the NPV and the PPV (according to prevalence) for ruling out active TB amongst those who are at risk of LTBI and might be eligible for preventive treatment. They found that the NPV after CXR screening is high, especially if 'any CXR abnormality' was used. Symptom screening has lower sensitivity, resulting in a lower NPV, and screening for 'any TB symptom' also has lower specificity, resulting in a greater proportion of persons with false-positive (FP) results that cannot be started on LTBI treatment after screening. Adding screening for any TB symptom to CXR screening in a parallel algorithm results in a slight increase in NPV and a decrease in the already low number of false negatives, but gives a further increase in the number of FPs after screening that cannot be started on LTBI immediately.

All three modelled algorithms with the highest NPV (1.00) used culture as a confirmatory test, but differed in screening method and assumptions: (1) CXR any abnormality (prevalence of TB: 0.1 %; pre-test probability of no TB: 0.9990); (2) any TB symptom and/or CXR any abnormality (parallel) (prevalence of TB: 0.1 %; pre-test probability of no TB: 0.9990); and (3) any TB symptom and/or CXR any abnormality (parallel) (prevalence of TB: 10 %; pre-test probability of no TB: 0.9000). Limitations of the study addressed were: (a) the sensitivity of CXR screening and of the combined symptom-CXR screening (100 %) may be a slight overestimate, if the target condition is defined as positive sputum mycobacteriology only; (b) several studies assume that persons without

(3) The review included primary studies conducted in low- and high-incidence settings. An ICER below GBP 20 000 was considered cost-effective.
(4) Primary studies were performed in low-to-medium TB incidence, high-income countries using different outcome measures (e.g. QALY, averted TB cases or life-years gained) and different willingness-to-pay thresholds (e.g. USD 30 000, USD 50 000, USD 100 000).

CXR abnormalities and without a minimum set of symptoms do not have active TB, and that a positive culture only may be transient, laboratory cross-contamination or due to subclinical TB; (c) the results focus on numbers of FN, FP and NPV, and do not take into account the risk of developing TB in the future (with or without treatment for LTBI); (d) the quality of the evidence on the accuracy of the screening methods is low to very low [107].

3.3.2. Evidence-based guidelines

Table 3 presents the recommendations of the three supranational guidelines and three national guidelines that were included on diagnosis of LTBI, reporting when and how to diagnose LTBI according to type of population, and who to screen.

Table 3. Summary of guidelines on latent tuberculosis infection diagnosis, according to type of population

Guideline	When and how to diagnose LTBI
General population	
WHO (2015) [4]	'Individuals should be asked about symptoms of TB before being tested for LTBI. CXR can be done if efforts are intended also for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions. Either TST or IGRA can be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000. • IGRA should not replace TST in low-income and other middle-income countries. • Remark: HIV testing should be incorporated into the medical evaluation of LTBI treatment candidates based on national or local policies.'
Population at low risk	
AQuAS (2010) [108]	• Tuberculin tests are not recommended for populations at low risk of infection to screen for LTBI.'
MMWR (2010) [109]	• 'In healthy persons who have a low likelihood both of *M. tuberculosis* infection and of progression to active TB if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection. In such situations, the likelihood of *M. tuberculosis* infection and of disease progression should be reassessed, and the initial test results should be confirmed. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis.'
Individuals that are BCG vaccinated	
AQuAS (2010) [108]	• 'An IGRA is recommended in addition to the tuberculin test if the tuberculin test is positive for someone who has previously received the BCG vaccine (particularly in the last 15 years).'
NICE (2011) [25]	• 'Consider IGRA for people whose Mantoux testing (TST) shows positive results, or in people for whom Mantoux testing (TST) may be less reliable, for example BCG-vaccinated people.'
MMWR (2010) [109]	• 'An IGRA is preferred for testing persons who have received BCG. Use of IGRAs in this population is expected to increase diagnostic specificity and improve acceptance of treatment for LTBI.'
Homeless people and people with drug use disorders	
MMWR (2010) [109]	• 'An IGRA is preferred for testing persons from groups that historically have low rates of returning to have TSTs read. For example, use of an IGRA might increase test completion rates for homeless persons and drug-users.'
Children	
AQuAS (2010) [108]	• 'An IGRA is recommended in addition to the TST if the TST is negative for someone who is less than 5 years old.'
MMWR (2010) [109]	• 'A TST is preferred for testing children aged < 5 years.'
Contacts of TB cases	
NICE (2011) [25]	• 'Offer Mantoux testing (TST) in line with the Green Book to diagnose LTBI in people who are household contacts (aged 5 years and older) of all people with active TB and non-household contacts (other close contacts for example, in workplaces and schools). • Household Contacts Aged 2-5 Years: Offer Mantoux testing (TST) as the initial diagnostic test for LTBI in child household contacts between the ages of 2 and 5 years. • Household Contacts Aged 2-5 Years: If the initial Mantoux test (TST) is negative but the child is a contact of a person with sputum-smear-positive disease, offer an IGRA test after 6 weeks and repeat the Mantoux test (TST) to increase the sensitivity • Contacts – Outbreak Situation: In an outbreak situation when large numbers of people may need to be screened, consider a single IGRA test for people aged 5 years and older.'
MMWR (2010) [109]	• 'An IGRA or a TST may be used without preference to test recent contacts of persons known or suspected to have active TB with special considerations for follow-up testing. IGRAs offer the possibility of detecting *M. tuberculosis* infection with greater specificity than with a TST. If IGRAs are to be used in contact investigations, negative results obtained prior to 8 weeks after the end of exposure typically should be confirmed by repeat testing 8-10 weeks after the end of exposure. This recommendation is similar to one used for TST. Use of the same test format for repeat testing will minimise the number of conversions that occur as a result of test differences.'
New entrants from high-incidence countries	
NICE (2011) [25]	• 'Offer a Mantoux test (TST) to children aged 5-15 years. If positive, follow with IGRA. • Offer either IGRA alone or a dual strategy in people aged 16-35 years. For people aged 35 years or older, consider the individual risks and benefits of likely subsequent treatment, before offering testing. • Offer Mantoux testing (TST) as the initial diagnostic test for LTBI in children younger than 5 years who have recently arrived from a high-incidence country.'
PLHIV	
NICE (2011) [25]	• 'For PLHIV and CD4 counts less than 200 cells/mm3, offer IGRA and a concurrent Mantoux test (TST). If either test is positive a clinical assessment should be performed to exclude active TB. • For PLHIV and CD4 counts of 200-500 cells/mm3, offer IGRA alone or an IGRA with a concurrent Mantoux test (TST). If either test is positive a clinical assessment should be performed to exclude active TB.'
Audain (2013) [110]	• 'Test unstably housed adults and adolescents HIV+ patient for LTBI using TST or blood assay test QuantiFERON-TB Gold.'
Other immunocompromised patients	

Guideline	When and how to diagnose LTBI
NICE (2011) [25]	• 'For other people who are immunocompromised, offer IGRA alone or an IGRA test with a concurrent Mantoux test (TST). If either test is positive a clinical assessment should be performed to exclude active TB.'
AQuAS (2010) [108]	• 'An IGRA is recommended in addition to the tuberculin test if the tuberculin test is negative for someone who is immunosuppressed.'
Baughman (2012) [111]	• 'Patients with diffuse interstitial or inflammatory lung disease or lung transplant recipients: For patients who will undergo anti-TNF-alpha therapy, a TST is recommended to screen for LTBI prior to treatment.'
Healthcare workers	
NICE (2011) [25]	• 'Offer a Mantoux test (TST) to new National Health Service (NHS) employees who will be in contact with patients or clinical materials if the employees are not new entrants from high-incidence countries and have not had BCG vaccination. • Offer IGRA to new NHS employees who have recently arrived from high-incidence countries or who have had contact with patients in settings where TB is highly prevalent. • If the Mantoux test (TST) is negative, refer to the Green Book for BCG immunisation guidance. If the Mantoux test (TST) is positive, offer an IGRA.'
Hard-to-reach populations	
NICE (2011) [25]	• 'Offer people from hard-to-reach groups a single IGRA.'

3.4. When and how to apply LTBI treatment

The summary below presents the main review results on LTBI treatment from systematic reviews and evidence-based guidelines. See Appendix 8 (Tables A8.1-A8.11) for a more detailed description of the evidence extracted from the systematic reviews.

3.4.1. Systematic reviews

To provide information useful for answering the main question, the following review questions were formulated.

- What is the effectiveness of different preventive treatment regimens for certain risk groups? (Summarised by treatment)
- What is the cost-effectiveness of different preventive treatment regimens for certain risk groups?
- What is the feasibility and acceptability of different preventive treatment regimens for certain risk groups?
  - How often is preventive treatment initiated? (In certain risk groups)
  - How often is preventive treatment completed? (In certain risk groups)
  - What is the risk of adverse events (AEs) of LTBI treatment? (In certain risk groups)

What is the effectiveness of different preventive treatment regimens for certain risk groups?

Full commissioned systematic review

The systematic review performed by Stagg et al. [29] was updated to comprehensively summarise data on the effectiveness of LTBI treatment and the safety of different LTBI treatment regimens. The update was done using the same methodology as in the original systematic review [29].

Only preliminary results (including GRADE tables) were available by the time the current data synthesis was discussed by the ad hoc scientific panel in November 2016. Consequently, the estimates included in this report differ from those in the published update of the systematic review [112]. For a list of all articles included in the initial review, see Appendix 11.

In total, 61 publications met the inclusion criteria. In some cases, extractable data from these publications were either merged (if two publications reported results from the same study) or analysed separately (if one publication reported on different target populations). Thus, the number of publications included does not correspond to the number of studies (i.e. data sets) analysed. Thirty-one studies included immunosuppressed individuals, and 22 included individuals with HIV. Many of the included studies were deemed to be of unclear or high risk of bias in the following domains: randomisation n = 33 (56 %); allocation concealment n = 39 (66 %); blinding n = 37 (63 %); blinding of outcome assessment n = 42 (71 %); incomplete outcome reporting n = 33 (56 %); and selective reporting n = 15 (25 %) [29].

Fifty-one randomised controlled trials (RCTs) reporting on progression to active TB were included in the meta-analysis. These 51 RCTs report data on 14 regimens that were included in the network analysis (see Table A8.1). Six of the regimens were efficacious versus placebo: INH for 6 months or 12 months or longer, RIF alone, RIF-INH for 3 to 4 months, pyrazinamide (PZA)-containing regimens (RIF-INH-PZA and RIF-PZA) and INH-ethambutol (EMB) for 12 months. GRADE tables presenting results of the standard direct meta-analyses are presented in Table A8.2. These conclusions are in agreement with the final results of the updated systematic review [112].

Non-commissioned systematic reviews

Six additional systematic reviews were found on the effectiveness of preventive treatment (see Table A8.3).

INH vs no treatment or placebo

Relative risk calculated for PLHIV indicated a protective effect of isoniazid preventive treatment (IPT) on development of TB, where TST-positive patients benefit to a greater extent than patients with a negative TST [113].

Continuous INH vs INH for 6 months

Den Boon et al. calculated relative risks and found that for PLHIV in settings with high TB and HIV prevalence and transmission, continuous INH (≥ 36 months or longer) is beneficial and probably outweighs the risk of increased AEs compared with an INH regimen for 6 months. Antiretroviral therapy (ART) and IPT had additional effect in reducing TB incidence in TST-positive but not in TST-negative individuals [114].

Short treatment regimens compared to INH 6–9 months

Sharma et al. compared shortened preventive regimens containing RIF or weekly RPT + INH with directly observed therapy (DOT) to INH monotherapy given for 6 to 9 months for preventing active TB in HIV-negative people at risk. For shortened preventive regimens with RIF or RPT + INH no higher rates of active TB were found than for longer regimens with INH [28].

Treatment regimen not specified

TB risk ratios calculated by Ai et al. showed that rheumatoid patients using TNF-alpha antagonists who received preventive treatment for LTBI were at lower risk of developing TB than patients who did not receive LTBI preventive treatment. There was no significant difference in risk of TB between rheumatoid patients with LTBI who received chemoprophylaxis and patients without LTBI [115].

The efficacy (% relative reduction in risk of TB) of preventive therapy varied among population groups; for almost all groups, the maximum % efficacy ranged between 90-100 %, while the minimum % efficacy ranged from 20 %-70 % between groups (no statistical analyses comparing groups) [92].

There was a trend towards a protective effect of preventive treatment in contacts of MDR TB patients, but except for the outcome of confirmed and probable TB in one study in children, none of the results were significant [116].

What is the cost-effectiveness of different preventive treatment regimens for certain risk groups?

Costs

The estimated costs per person of treatment of LTBI with 6 months of INH was GBP 677.07, including full blood count, liver function test, outpatient visits, nurse contact and drugs. The cost of adherence and non-adherence to LTBI treatment in children, immunocompromised patients and recently arrived (e.g. migrants) populations were also presented. For all groups, the costs were set at GBP 677.07 for adherence (based on NHS drug tariff) and GBP 112.85 for non-adherence (based on assumptions, not further specified). All costs were adjusted to 2012/2013 prices using the Hospital and Community Health Services pay and price index and discounted at a rate of 3.5 % per annum, and it was assumed that people who do not adhere to LTBI treatment take medication for one month [102].

The cost of LTBI treatment for nine months with INH ranged from USD 478.23 to USD 1 045 .94 (adjusted to 2013 USD) in Campbell et al. [103].

Oxlade et al. focused on the diagnosis of LTBI but also presented full LTBI treatment costs (including costs for complete regimen cited in the publication; 2011 USD). Six studies assumed INH 9 months, five studies assumed INH 6 months and one study assumed INH + RIF 3 months. The costs ranged from USD 224 to USD 953, excluding one outlying result of USD 1 577. One study presented the cost for drugs and incentives only (USD 264); administrative and delivery expenses associated with LTBI treatment were included in the fixed programme costs of USD 150 per year per study participant [105].

The average cost of preventive therapy (drugs and monitoring) by countries ranged from USD 22.7 to USD 472.1 (2012 USD); see Table A8.4.

Cost-effectiveness

A summary of three systematic reviews of CEA studies on preventive treatment is presented in Table A8.5.

PLHIV

One systematic review concluded that preventive treatment (not further specified) after primary screening with either TST or IGRA was likely to be cost-effective ([5]) in PLHIV [117].

([5]) Cost-effectiveness was defined differently across primary studies, using different outcome measures (e.g. QALY, averted TB cases or life-years gained) and different willingness-to-pay thresholds (e.g. USD 10 000, USD 50 000, USD 100 000 or GBP 20 000 to GBP 30 000), if reported. Primary studies were performed predominantly in low-TB-incidence, high-income countries.

Healthcare workers

One systematic review concluded that preventive treatment (not further specified) after primary screening with either TST or IGRA was likely to be cost-effective ([5]) in healthcare workers [117].

High-risk populations

One systematic review concluded that chemoprophylaxis for TB (INH versus no intervention; RIF versus no intervention; INH + RPT versus RIF) appears to be cost-effective ([6]) [118].

One systematic review concluded that screening and treatment for LTBI appears to be a cost-effective intervention ([7]) for some population groups characterised by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high-TB-incidence countries, contacts of active TB cases and PLHIV [92]

What is the feasibility and acceptability of different preventive treatment regimens for certain risk groups?

One study explored the perceptions, knowledge, attitudes and treatment-adherence behaviour relating to TB and their social implications in patients receiving treatment, healthy persons with LTBI, untreated TB patients, healthcare workers and other key informants (Amstar negative on items 1, 2, 4, 5, 7, 8, 9, 10, 11). Generally, respondents were migrants from rural to urban contexts or from high- to low-TB-incidence countries and were unaware of their LTBI status. A range of economic, legislative, cultural, social and health-system barriers could delay treatment seeking. Fears of deportation and having contacts traced could prevent individuals from seeking medical assistance. Problems of accessibility can constitute a barrier to health seeking and early diagnosis, and can also present obstacles to prophylaxis and the periodic visits that adequate TB treatment necessitates. At times, the need to travel, difficulties in understanding complex information in a strange language or in a way considered too mechanical and impersonal, lack of awareness of free treatment or the form in which and the rigid opening hours when medication is provided do not correspond with patients' working hours and lifestyles. The use of interpreters as part of healthcare for TB patients and during their periodic visits was also problematic due to the sensitivity of the information and the fear of loss of privacy and stigmatisation. Factors facilitating adherence to treatment included family support, receiving personal advice from health staff and social contacts and receiving care provided by staff specially trained in TB or with sensitivity and the ability to establish a personal relationship on the same cultural terms. Having positive relationships with healthcare workers was perceived to be a crucial element, especially when close contact was established through home visits and phone discussions [106]. Nothing was reported on the quality of the included studies.

How often is preventive treatment initiated? (In certain risk groups)

One systematic review reported data on how often preventive treatment is initiated (see Table A8.6). Initiation rates of LTBI treatment in the general population, contacts of TB cases, healthcare workers, homeless people, people with drug use disorders, PLHIV, inmates, immigrants and patients with comorbidities ranged from 26 % to 99 %, 40 % to 95 %,47 % to 98 %, 34 % to 90 %, 52 % to 91 %, 67 % to 92 %, 7 % to 90 %, 23 % to 97 % and 82 % to 93 %, respectively, varying with type of treatment (short, long, or short/long combined). Initiation rates for LTBI treatment regimens were frequently suboptimal and varied greatly within and across different populations [30].

How often is preventive treatment completed? (In certain risk groups)

Full commissioned systematic review

Stuurman et al. included 20 prospective studies on interventions to improve LTBI treatment initiation, adherence, and/or completion and provided evidence for five groups of interventions (see Section 3.5.3 under research questions 'What interventions are effective to improve initiation, adherence and completion of LTBI treatment?) [86]. In their review, they also compared the adherence and completion of short versus long LTBI treatment.

Contacts of TB cases had better adherence if they received short treatment compared to those on long treatment regimens. Also, completion rates of LTBI treatment were better overall among groups receiving shorter regimens than those with longer treatment regimens (see Table A8.7).

Non-commissioned systematic reviews

Three systematic reviews reported data on how often preventive treatment is completed (see Table A8.8). In a review of Sharma et al., treatment completion is probably higher with shorter RIF regimens compared to longer regimens, and a weekly regimen of RPT + INH had higher completion rates compared to daily INH SAT for 9 months [28]. Sandgren et al. found that completion rates for LTBI treatment regimens were frequently

([6]) Willingness-to-pay thresholds were not reported. The evidence was derived almost totally from low-TB-incidence, high-income countries.
([7]) A cost-effective intervention (dominant intervention) had lower costs and higher effectiveness when compared to no intervention or another screening strategy. A favourable ICER indicated an intervention with higher costs and higher effectiveness than the comparator.

suboptimal and varied greatly within and across different populations. Completion rates of LTBI treatment in the general population, case contact, healthcare workers, homeless people, people who inject drugs, PLHIV, inmates, immigrants and patients with comorbidities ranged from 26 % to 99 %, 40 % to 95 %,47 % to 98 %, 34 % to 90 %, 52 % to 91 %, 67 % to 92 %, 7 % to 90 %, 23 % to 97 % and 82 % to 93 %, respectively, varying with type of treatment (short, long, or short/long combined, see full commissioned systematic review Stuurman et al. above) [30]. In another review, the minimum completion rate ranged from 21 % (contacts) to 60 % (children) while the maximum completion rate ranged from 62.6 % (contacts) to 100 % (healthcare workers, migrants, PLHIV) [92].

What is the risk of AEs of LTBI treatment? (In certain risk groups)

Full commissioned systematic review

In the preliminary results of Zenner et al. [112] (see description under review question 1 of this chapter), 27 RCTs reporting on hepatotoxicity were included in the meta-analysis (see Table A8.9). These studies reported on eight regimens that were included in the network analysis (see Table A8.10). RIF + PZA was significantly associated with hepatotoxicity compared with no treatment.

Non-commissioned systematic reviews

Four additional systematic reviews were found on AEs of LTBI treatment (see Table A8.11).

RIF regimens vs INH

The study of Sharma et al. compared the effects of RIF monotherapy or rifamycin-combination therapy versus INH monotherapy and reported the AEs. Relative risks show that AEs may be fewer with shorter RIF regimens while RIF + PZA is associated with more AEs. A weekly regimen of RPT + INH has less liver toxicity, though treatment discontinuation due to AEs is probably more likely than with INH [28].

Continuous INH

Two studies within the review of Den Boon et al. found no evidence of an increase in AEs in PLHIV receiving continuous INH, whereas a third study that used a different definition for AEs (i.e. grade 3 or grade 4 elevation in the aspartate or alanine aminotransferase level) provided strong evidence for increased risk of AEs in the continuous INH group compared to the group receiving six months of INH with or without EMB) [114].

PZA-containing treatments

One review summarised the occurrence of AE in contacts of MDR TB receiving preventive treatment with PZA, scheduled for 6 months. Treatment was discontinued in 58-100 % of the subjects due to adverse events, which ranged from mild AEs such as nausea and dizziness to serious events requiring treatment [119].

Ethionamide

In another review of Den Boon et al., one study reported rates of AEs. Of the 61 MDR TB child contacts receiving ethionamide, 30 (49 %) experienced gastrointestinal side effects and the drug was stopped in four cases [116].

3.4.2. Evidence-based guidelines

Table 4 presents the recommendations of two supranational guidelines and two national guidelines on LTBI treatment, reporting on when and how to apply LTBI treatment according to type of population.

Table 4. Summary of guidelines on latent tuberculosis infection treatment, according to type of population

Guideline	When and how to apply LTBI treatment
General population	
WHO (2015) [4]	• 'Treatment options recommended for LTBI include: 6-month INH, or 9-month INH, or 3-month regimen of weekly RPT plus INH, or 3-4 months INH + RIF, or 3-4 months RIF alone.'
Children	
AQuAS (2010) [108]	• 'Primary prophylaxis with INH (300 mg/day or 5 mg/kg/day) is recommended for 8-12 weeks in children less than 5 years old, if they have come into contact with infectious patients. • To prevent TB in children and adolescents with positive tuberculin tests, treatment with any treatment regimen routinely used in adults, at appropriate doses, is recommended.'
Immunosuppressed patients – adults with chronic kidney disease	
Milburn (2010) [120]	• 'There is no evidence to support chemoprophylaxis regimens of longer than 6 months for INH alone, 3 months for INH + RIF, or 4-6 months for RIF alone. • For chemoprophylaxis use 6 months of INH 300 mg daily plus pyridoxine 10-25 mg daily, or INH plus RIF (as Rifinah) plus pyridoxine for 3 months or RIF alone for 4-6 months. Any of these regimens is adequate for chemoprophylaxis. Long-term use of INH is not recommended.'
Prisoners	
NICE (2012) [121]	• 'In high incidence areas prisons (and in prisons which receive prisoners from high incidence areas): If the under-35s IGRA test is positive, preventive DOT should be arranged alongside the existing support. • Where practical, multi-disciplinary tuberculosis teams should start preventive DOT for prisoners with LTBI who, on release, will also receive support from other services.'

3.5. Programmatic issues of LTBI management

Results of the review searches on various programmatic issues (systematic reviews and guidelines) are summarised below, presented by topic. Appendix 9 (Tables A9.1-A9.14) presents a detailed summary of the relevant evidence extracted from systematic reviews.

3.5.1. Case detection; screening

3.5.1.1. Systematic reviews

To provide information useful for answering the review question, the following review questions were formulated.

- What is the effectiveness of LTBI screening programmes for certain risk groups?
- What is the cost-effectiveness of different screening programmes for certain risk groups?
- How can target groups be identified and accessed for LTBI screening services?
- What is the effectiveness of interventions to improve screening uptake?
- Is mandatory LTBI screening effective, cost-effective and/or feasible (for specific target groups)?

What is the effectiveness of LTBI screening programmes for certain risk groups?

Four systematic reviews reported data on of screening programmes for certain risk groups (see Table A9.1).

One study by Campbell et al. on screening in immigrants migrating from TB-endemic countries to low-TB-burden countries found that compared to TST, significantly fewer immigrants tested positive with the IGRA and were considered for preventative treatment [91]. In another review by Campbell et al., it was reported that in screened immigrants migrating from high-incidence TB countries to low-incidence TB countries, 27.5 % (95 % CI 4.2-76.6 %) of those that tested positive with IGRA were recommended LTBI treatment while 59.0 % (95 % CI 47.7-69.5 %) of those that tested positive with TST were recommended LTBI treatment [87].

In a systematic review of Aldridge et al. on any screening before migrating to low-incidence countries, three studies reported data on LTBI. Using varying TST cut-off, a total of 1 884 latent infections were identified in 20 587 individuals screened (9.1 %; ranging from 1.0 % to 28.8 % in the primary studies).

The authors only concluded that targeting high-prevalence countries for screening could result in the highest yield for active disease; nothing was concluded for LTBI [122].

One systematic review examined the overall effect of service integration of HIV and TB/LTBI on output of delivery and on the outcomes for patients. IPT was given at standalone voluntary counselling and testing centres in two studies, at hospitals in three and at both a clinic and a hospital in one. The proportion of PLHIV screened for IPT eligibility in the different study sites ranged from 81-93 % (weighted mean: 87.7 %). Of those eligible, 67-100 % started IPT. Studies reported high levels of adherence: 75-92 % of the study participants took IPT appropriately as prescribed. 47-88 % of patients completed treatment for the prescribed duration – i.e. 6 months of treatment within the study's follow-up period [123].

What is the cost-effectiveness of different screening programmes for certain risk groups?

A summary of three systematic reviews of CEA studies on screening regimens is presented in Table A9.2.

PLHIV

One systematic review concluded that screening PLHIV with a TST appears to be strongly cost-effective ([8]) [103].

Migrants

One systematic review concluded that screening adult immigrants with an IGRA appears to be moderately cost-effective ([8]) [103].

High-risk populations

One systematic review concluded that screening and treatment for LTBI appears to be a cost-effective intervention ([9]) for some population groups characterised by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high-TB-incidence countries, contacts of active TB cases and PLHIV [92].

Similarly, another systematic review concluded that the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries and close contacts, appears to be cost-effective ([10]). This systematic review also concluded that if the increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds true, the IGRA-only screening strategy should prove to be the more cost-effective test [104].

How can target groups be identified and accessed for LTBI screening services?

For identification of target groups for LTBI screening, see Section 3.2 'Who to diagnose and treat (target risk groups)'.

One systematic review by Vinkeles-Melchers et al. [93] on prisoners listed limitations of current TB-control programmes (including LTBI) in prison facilities as being:

- limited accuracy of diagnostic algorithms and lack of adequate laboratory facilities, as well as fragile TB screening tools;
- inadequate financing and logistic accomplishments, due to lack of political priority of prison environments and prisoner health;
- lack of well-organised health services, including poorly coordinated and supervised prison health services and lack of motivated prison medical staff;
- high-risk prison environment with little attention to institutional vulnerabilities (e.g. overcrowding, ventilation) and fragile populations (e.g. female inmates, foreign-born inmates).

Steps to enhance TB control in prison facilities for both high- and middle/low-income countries were listed for the areas of screening, case management, prevention of transmission, screening algorithms and logistic and policy improvement. Steps that are relevant for LTBI management included:

- more regular and rapid screening of prisoners for active TB and LTBI for early diagnosis, e.g.
  - entry and exit screening for all inmates,
  - TB screening for all (prospective) prison employees);
- TST implementation and IPT provision for high-risk groups, including HIV-infected prisoners, staff and guards; logistic and policy improvement (i.e. increase national political commitment), including:
  - funding,
  - good governance,
  - adherence of established (international) infection control policies,
  - stimulate greater monetary and technical support from international donors to increase TB prison screening leverage, sustainability and consistency with international standards,
  - establishing a prison TB diagnostic and management unit for coordination,
  - implementation of an efficient information system involving all prison facilities and non-governmental organisations).

([8]) This systematic review includes studies conducted mainly in high-income, low-TB-incidence countries. Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective;
ICER > USD 100 000 = not cost-effective.
([9]) A cost-effective intervention (dominant intervention) had lower costs and higher effectiveness when compared to no intervention or another screening strategy. A favourable ICER indicated an intervention with higher costs and higher effectiveness than the comparator.
([10]) Primary studies were performed in low-to-medium TB incidence, high-income countries using different outcome measures (e.g. QALY, averted TB cases or life-years gained) and different willingness-to-pay thresholds (e.g. USD 30 000, USD 50 000, USD 100 000).

What is the effectiveness of interventions to improve screening uptake?

One systematic review reported on the effectiveness of interventions to improve screening uptake (see Table A9.3). The effects of material incentives and enablers in patients undergoing diagnostic testing were evaluated. The risk ratio of return for TST results was calculated. Material incentives increased the proportion of people who returned for reading of the TST compared to routine care, with quantitatively important large effects. The cash incentive was significantly more effective at increasing return for reading of TST than any of the non-cash incentives. The USD 10 incentive significantly increased the proportion of patients returning to the clinic to have their TST read compared to the USD 5 incentive. The material incentives (USD 5 to USD 10) significantly increased the rate of return for TST reading compared to motivational education alone [124].

Is mandatory LTBI screening effective, cost-effective and/or feasible (for specific target groups)?

No systematic reviews were identified that were published in the last 10 years and provided information on the effectiveness, cost-effectiveness and/or feasibility of mandatory LTBI screening.

3.5.1.2. Evidence-based guidelines

Two supranational guidelines and one national guideline were included on LTBI screening. Table 5 summarises their recommendations on who, when and how to screen according to type of population.

Table 5. Summary of guidelines on latent tuberculosis infection screening, according to type of population

Guideline	When and how to screen for LTBI
Vulnerable migrant populations	
NICE (2012) [121]	• 'Screen all vulnerable migrants who have not previously been checked, in line with NICE guidance on TB for new entrants. This is regardless of when they arrived in England. People born in countries with an incidence of more than 150 per 100 000 per year should be made a priority for LTBI screening when they arrive here. • In high incidence areas (and at prisons which receive prisoners from high incidence areas), prison health services should offer IGRA testing for TB to inmates aged under 35 who are in regular contact with substance misuse or other support services.'
Healthcare workers	
NICE (2011) [25]	• 'Healthcare professionals, including primary care staff, responsible for screening new entrants should maintain a coordinated programme to: – detect active TB and start treatment – detect latent TB and start treatment'
Unstably housed adults and adolescents with HIV/AIDS	
Audain, 2013 [110]	• 'Re-check unstably housed patients with negative test result every 6 months; for those testing positive, do baseline CXR followed by symptom screen every 6 months regardless of CD4 count.'

3.5.2. Case detection; contact investigation

3.5.2.1. Systematic reviews

To provide information useful for answering the review question, the following review questions were formulated.

- What is the effectiveness of (different) contact investigation approaches in certain risk groups?
- What is the cost-effectiveness of (different) contact investigation approaches in certain risk groups?
- How can target groups be identified and accessed for contact investigation?
- What is the effectiveness of interventions to improve contact investigation uptake?

What is the effectiveness of (different) contact investigation approaches in certain risk groups?

Five systematic reviews reported data on contact investigation approaches (see Table A9.4).

Schepisi et al. systematically reviewed healthcare-associated TB incidents to quantify the magnitude of the risk of transmission of *M. tuberculosis* from **healthcare workers with pulmonary TB to patients and co-workers**. In the majority of studies, all individuals who were in the healthcare setting during the period of infectivity of the index case were considered as candidates for screening and no criteria for prioritisation were reported. In seven incidents, priority for screening was defined based on the risk of progression to active TB of exposed individuals, while the classic concentric circle approach for contact screening was followed in two incidents. In two incidents, the exposed patients were not screened for LTBI, as only surveillance of active TB was performed. Among individuals identified as candidates for screening (all individuals, patients and healthcare workers in the healthcare setting during the period of infectivity of the index case), the proportion of those who were actually screened for LTBI (except for two studies where only surveillance of active TB was performed) ranged between studies from 12.8 % to 100.0 % for patients and from 67.3 % to 100.0 % for healthcare workers [90].

One review on contact investigation after **aircraft exposure** pooled data or outbreak studies where the contact investigation strategy included all passengers and crew (n = 7 studies). Among a total of 1 287 aircraft contacts for whom a test result (TST or IGRA) was available, 10 (0.8 %) passengers were possibly infected during the flight (positives with no other risk factors for test positivity). Of those, seven (0.5 %) had a TST conversion. For incidents where only five rows surrounding the index case were traced (n = 4 studies), among a total of 905 aircraft contacts with test results, 12 (1.3 %) passengers were possibly infected during the flight (positives with no other risk factors for test positivity), one (0.1 %) of whom had a TST conversion. The main reasons for the unavailability of testing results were insufficient contact information, loss-to-follow-up, residence in a foreign country and previous TB infection positivity. In addition, the infectiousness of the index patients varied across the records. Passengers seated within two rows of the index case seemed to have the highest risk of infection [101].

In a review on the prevalence of TB infection and disease among **child household contacts** in south-east Asia, the authors reported that TB infection is common among children who are household contacts of TB cases in south-east Asia. Contact investigation approaches were not defined and there was no uniform definition of a household contact across the studies, but the most common definition was a child living in the same house as the index case. They concluded that contact investigation studies indicate the potential of screening and IPT to reduce the risk of TB disease in child contacts, yet it is rarely implemented [94].

In the review of Fox et al. the contact investigation approach was not defined. When looking at the definitions of '**household contact**' there was a considerable variety between studies. Some authors described household based on location, such as a common eating or sleeping area, while some studies stipulated a minimum duration of exposure or degree of proximity. Definitions of close contact also varied considerably in the requisite intensity of exposure to patients. Some studies had a broad definition, with close contacts including those with any known

exposure; others used expressions such as intimate, sharing the air for a prolonged period or specifying a minimum duration of exposure in other closed spaces such as the workplace. Some studies did not provide precise definitions of close contacts. The authors found that contacts exposed to patients with TB are at substantial risk of LTBI and active TB. The prevalence of LTBI and TB among contacts is significantly less in high-income countries than in low–middle-income countries, although this difference was not evident among household contacts. In high-income countries, contact investigation in foreign-born contacts results in a significantly higher LTBI prevalence than contact investigation in locally born contacts [66].

Household contact investigation around drug-resistant TB patients appears to be a high-yield intervention for detection of drug-resistant TB and prevention of ongoing transmission. Among the household contacts, the overall yield for active TB cases was 7.8 % and 47.2 % for LTBI. The contact investigation approach was not further specified. The yield varied between high- or low-burden settings of the contacts and between target groups [95].

What is the cost-effectiveness of (different) contact investigation approaches in certain risk groups?

No systematic reviews were identified that were published in the last 10 years and provided information on the cost-effectiveness of (different) contact investigation approaches in certain risk groups.

How can target groups be identified and accessed for LTBI screening services?

For identification of target groups for contact investigation, see Section 3.2 'Who to diagnose and treat (target risk groups)'.

No systematic reviews were identified that were published in the last 10 years and provided information on how to get access to target groups for contact investigation.

What is the effectiveness of interventions to improve contact investigation uptake?

No systematic reviews were identified that were published in the last 10 years and provided information on the effectiveness of interventions to improve contact investigation uptake.

Evidence-based guidelines

Four supranational guidelines and one national guideline were included that had recommendations on contact investigation, Table 6 presents their recommendations on when and how to conduct contact investigations and on whom.

Table 6. Summary of guidelines on contract investigation

Guideline	When and how to conduct contact investigation
AQuAS (2010) [108]	• 'Contact studies should begin promptly when pulmonary, pleural or laryngeal TB is diagnosed.'
WHO (2012) [125]	• 'Contact investigation should be conducted for household and close contacts when the index case: – has sputum smear-positive pulmonary TB, – has MDR-TB or XDR-TB (proven or suspected), – is a PLHIV or – is a child < 5 years of age • It is suggested that contact investigation be conducted for household and close contacts of all other index cases with pulmonary TB. • Clinical evaluation of household and close contacts for active TB is recommended as a priority on the basis of their risk of having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to: – people of all ages with symptoms suggestive of TB – children < 5 years of age – people with known or suspected immunocompromising conditions (especially PLHIV) and contacts of index cases with MDR-TB or XDR-TB (proven or suspected) • In settings of high HIV prevalence, it is recommended that all household and close contacts be counselled and tested for HIV.'
NICE (2011) [25]	• 'Casual contacts of people with TB, who will include the great majority of workplace contacts, should not normally be assessed. • If a school pupil is diagnosed with sputum smear-positive TB, the rest of his or her class (if there is a single class group), or the rest of the year group who share classes, should be assessed as part of contact investigation. • If a teacher has sputum smear-positive TB, the pupils in his or her classes during the preceding 3 months should be assessed as part of contact investigation.'
NICE (2012) [121]	• 'Multi-disciplinary TB teams (MDTB teams) should coordinate contact investigations at places where the person with TB spends significant amounts of time. Examples of the latter may include a pub, crack house or parks and community centres. The aim is to help identify people who have been living with them and people they frequently socialise with. • MDTB teams dealing with someone from a hard-to-reach group should work alongside health and social care professionals known to them to help trace relevant contacts. They should also work in partnership with voluntary, community and statutory organisations to conduct outreach contact investigations. • MDTB teams should, where available and appropriate, encourage peer educators to help with contact investigations when it involves hard-to-reach people who have complex social networks.'

Guideline	When and how to conduct contact investigation
ECDC (2010) [64]	• 'Contact investigation of passengers exposed to TB during air travel should only be undertaken following a risk assessment based on the infectiousness of the index patient, the amount of effective contact/exposure and, where possible, an assessment of the susceptibility of exposed individuals, as it is done during any routine contact investigation • Contact investigation should be considered: – if the index case is confirmed as having infectious pulmonary TB (positive smear microscopy in a sample of spontaneously produced or induced sputum, or a sample from bronchoalveolar lavage); AND – there is evidence of transmission to other contacts (refers to cases with evidence of transmission in household or other close contacts); AND – the duration of the flight is longer than eight hours; AND – the time elapsed between flight and diagnosis of the case is no longer than three months. • If all conditions presented in this algorithm are met, exposed passengers in the relevant rows should be contacted – using the procedures outlined in the WHO guidelines – and investigated and managed for LTBI according to national guidelines. It is recognised that often only limited contact information is available. Therefore, it is accepted that, after reasonable attempts to retrieve the data, the proper public health decision might be to cease the investigation • It is recommended to limit contact investigation to passengers sitting in the same row, two rows ahead and two rows behind the index case in accordance with the WHO guidelines. The exposure of the cabin crew is generally less intensive and should be assessed by the airline's medical service • If contact investigation is decided after the risk assessment and there is evidence that passengers with higher susceptibility to TB, such as infants or children, travelled in the same row or two rows ahead or behind the index case, special efforts should be initiated to trace them.'

3.5.3. Treatment-related interventions

3.5.3.1. Systematic reviews

To provide information useful for answering the main question, the following review questions were formulated

- What are determinants of LTBI treatment initiation, adherence and completion?
- What interventions are effective to improve initiation, adherence and completion of LTBI treatment?
- What is an effective approach to monitor and manage AEs?

What are determinants of LTBI treatment initiation, adherence and completion?

One full commissioned systematic review, using the GRADE methodology, was performed that comprehensively summarised data on any determinant of LTBI treatment initiation, adherence and completion in all types of populations [86]. For a list of all articles included in the review, see Appendix 12.

Full commissioned systematic review

Sixty-two articles (27 prospective studies and 35 retrospective studies) reporting on determinants of treatment initiation and completion were included. Most determinants were from studies in the general population, i.e. primarily unselected patients with LTBI at clinics, and most determinants related to LTBI treatment completion (see Table A9.5).

Initiation

The most frequently reported determinant associated with LTBI treatment uptake in the general population was age, although the direction of the effect was inconsistent.

Completion

The most frequently found determinants of LTBI treatment completion were patient related (i.e. type of population with LTBI, demographic factors, drug/alcohol abuse), therapy related (e.g. short therapy regimens, DOT, occurrence of AEs) and socioeconomic status (e.g. unemployment, lack of social support). Unfavourable socioeconomic factors were consistently associated with poor completion of LTBI therapy. These results should be interpreted with care, since different measures of associations were used in the studies, the reference groups varied between studies, and data on non-significant factors were not always quantified in the studies and were therefore not listed in the review.

Non-commissioned systematic review

Alsdurf et al. (2016) [126] ([11]) performed a systematic review and meta-analysis of aspects influencing the cascade of care in diagnosis and treatment of LTBI. Steps in the cascade associated with the most important losses included completion of testing (71.9 % (95 % CI 71.8-72.0) of people intended for screening), completion of medical evaluation if test was positive (43.7 % (42.5-44.9)), recommendation for treatment (35.0 % (33.8-36.4)). Steps with fewer losses included receiving test results, referral for evaluation if test positive and agreeing to start therapy if recommended. Factors associated with fewer losses were immune-compromising medical indications, being part of contact investigations and use of rifamycin-based regimens.

([11]) Published after the search period of the current inventory of evidence. Included after a suggestion made at the ad hoc scientific panel meeting held in November 2016 at ECDC. This meeting was organised to discuss the body of evidence and formulate conclusions for the guidance.

What are interventions to improve LTBI treatment initiation, adherence and completion?

Full commissioned systematic review of primary articles

One full commissioned systematic review, using the GRADE methodology, was performed that comprehensively summarised data on interventions to improve LTBI treatment initiation, adherence and completion in all types of populations [86]. For a list of all articles included in the review of Stuurman et al., see Appendix 12.

Twenty prospective studies on interventions to improve LTBI treatment initiation, adherence, and/or completion provided evidence for four groups of interventions: DOT versus SAT (see Table A9.6), (monetary) incentives versus treatment not supported by incentives (see Table A9.7), social interventions versus standard care (see Table A9.8) and other interventions versus standard care (see Table A9.9).

Initiation

Some evidence was found that the use of IGRAs rather than TSTs, or a social intervention using **case management** with attention to an individual's cultural background, might positively influence the initiation rate of LTBI treatment.

Adherence

Social interventions in the form of **adherence coaching** of adolescents with LTBI and cultural interventions among immigrants with LTBI resulted in improved adherence.

Completion

Mixed results were found on the effect of **DOT** on completion rates of LTBI treatment. Of the studies reporting on the effect of **incentives**, two studies conducted in people with drug use disorders with LTBI found a positive result (one of which was confounded), and the other study in released inmates found no effect. The success of incentives is likely to be population, incentive and setting dependent. **Social interventions** to improve LTBI treatment uptake included case management with attention on an individual's cultural background, adherence coaching, counselling, contingency contracting, education, nurse case management and peer-based interventions. Most studies on this topic showed better completion rates in the intervention group than in the standard-care group, regardless of the type of social intervention.

Non-commissioned systematic reviews

Additionally, three systematic reviews reported data on interventions to improve initiation, adherence and completion of LTBI treatment (see Table A9.10).

The effects of **material incentives and enablers** in patients receiving prophylactic therapy for TB were evaluated in the review by Lutge et al. Incentives compared to routine care improved clinic attendance for initiation or continuation of treatment for LTBI. For completion of TB prophylaxis, three studies were included and their results were presented separately. One study showed large effects with incentives, with over 50 % completing treatment with an incentive, contrasted with very low completion in the control group (3.6 %). In the second study, completion of treatment in the control group was similar to that of the incentive group (76.4 %), while in the last study completion remained low in both groups despite the intervention (13.8 % control versus 14.1 % intervention). The participants who received the immediate incentives completed treatment more often than those whose incentives were deferred (83 % versus 75 %), but the difference was not statistically significant. The cash incentive was more effective than the non-cash incentives at increasing the completion rates of TB prophylaxis. There was no significant difference between material incentives and education or peer counselling in the number of clinic visits to start or continue TB prophylaxis, nor in TB prophylactic treatment completion rates [124].

The review of M'Imunya et al. evaluated the effects of **patient education or counselling**, or both, on treatment completion in people requiring treatment for LTBI. There is very low-quality evidence that in children at risk of TB, treatment adherence is improved by mothers receiving an educational intervention delivered by nurses by telephone or by a home visit. Another study found that prison inmates receiving an educational intervention were more likely to complete treatment for LTBI than those who do not. There is no evidence that peer counselling improves completion of treatment in adolescents with LTBI [69].

One qualitative systematic review comprising 30 studies (design not reported; several studies combined qualitative methods or used them together with quantitative methods) published between 1997 and 2011 explored the perceptions, knowledge, attitudes and treatment-adherence behaviour relating to TB and their social implications in patients receiving treatment, healthy persons infected with LTBI, untreated TB patients, health professionals and other key informants (Amstar negative on items 1, 2, 4, 5, 7, 8, 9, 10, 11). Since this review provided limited quantitative data, it was not described in summary Table A9.10. Generally, respondents were migrants from rural to urban contexts or from high- to low-TB-incidence countries and were unaware of their LTBI status. Several factors facilitating adherence to treatment were reported in single studies: Family support, receiving personal **advice from healthcare workers** and social contacts and receiving **care provided by staff specially trained in TB**, receiving personal advice with sensitivity and the ability to establish a personal relationship on the same cultural terms. **Having positive relationships with healthcare workers** was perceived to be a crucial element, especially when close contact was established through home visits and phone discussions [106]. Nothing was reported on the quality of the included studies.

What is an effective approach to monitor and manage AEs?

One systematic review was performed to identify the best clinical approach to monitor toxicity in individuals treated for LTBI. The outcome measurements were: mortality and morbidity related to toxicity and tolerability of the preventive therapy. However, the search failed to identify any study providing direct evidence on best practices for clinical monitoring of LTBI treatment. The authors reviewed purposefully selected national LTBI guidelines from low-incidence countries, which were issued after 2003. No quality assessment (i.e. with AGREE) of the included guidelines was performed. A summary of the recommendations from the guidelines is reported in Table A9.11. All seven guidelines consistently recommend baseline evaluation with information on potential undesired drug events, and monthly interaction between healthcare providers and the individual on treatment, either through physical visit or telephone contact. Additionally, individuals on treatment should inform healthcare providers in the event of signs or symptoms such as jaundice, abdominal pain, nausea or fever, which should result in physical examination and investigation of liver transaminases and bilirubin. Routine baseline laboratory testing prior to starting treatment is only recommended for selected subgroups of treatment candidates. Laboratory evaluation during treatment is usually recommended in cases where signs or symptoms described above were found and for individuals with abnormal baseline liver function test results [127].

3.5.3.2. Evidence-based guidelines

No guidelines of sufficient quality according to AGREE II were identified that were published in the last 10 years and provided information on treatment-related interventions that lead to a more optimal result of preventive treatment.

Similarly, no guidelines of sufficient quality according to AGREE II were identified that were published in the last 10 years and provided information on AE management to improve the result of preventive treatment.

3.5.4. Education

3.5.4.1. Systematic reviews

To provide information useful for answering the main question, the following review questions were formulated.

- Who should be targeted for education and when?
- What information should be provided?
- What is the effectiveness of education methods?
- Is education cost-effective?

Who should be targeted for education and when?

Two systematic reviews were identified that were published in the last 10 years and provided information on the effect of targeted education in specific risk groups [69,124]. For the results, see the description under ‘What is the effectiveness of education methods?’ above, and Table A9.12.

What information should be provided?

One systematic review was identified that was published in the last 10 years and provided information on the effect of targeted education comprising specified information [69]. For the results, see the description under ‘What is the effectiveness of education methods?’ above, and Table A9.12.

What is the effectiveness of education methods?

Two systematic reviews reported data on the effectiveness of education methods (see Table A9.12).

M’Imunya et al. evaluated the effects of patient education or counselling, or both, on treatment completion in people requiring treatment for LTBI by describing three RCT’s. Primary studies were conducted in the United States (n = 2) and Spain (n = 1). In one study, calculated relative risks showed that in children at risk of TB, treatment adherence is improved by **mothers** receiving an educational intervention consisting of discussions on the importance and need for chemoprophylaxis and re-issuing informative leaflets compared to a control group. The education can be delivered by nurses, by telephone or by a home visit. Another study found that **prison inmates** receiving an educational intervention, delivered by research assistants and consisting of a one-to-one session in English or Spanish, were more likely to complete treatment for LTBI than those who did not. For **adolescents**, no significant difference was found for the group receiving education and the control group. As would be expected, the magnitude of the benefit is likely to depend on the nature of the intervention, and the reasons for low completion rates in the specific setting [69].

The review by Lutge et al. (n = 8 studies, all from United States) reported relative risks for completion of preventive treatment and clinic visits to start or continue preventive treatment. No significant difference in relative risks was found between material incentives and education or counselling for **jail inmates, homeless adults and adolescents**. However, material incentives (USD 5 to USD 10) significantly increased the rate of return for TST reading compared to motivational education alone in **people with drug use disorders** [124].

Is education cost-effective?

No systematic reviews were identified that were published in the last 10 years and provided information on cost-effectiveness of an education approach on LTBI

3.5.4.2. Evidence-based guidelines

No guidelines of sufficient quality according to AGREE II were identified that were published in the last 10 years and provided information on the most optimal approach for education on LTBI.

3.5.5. Implementation

3.5.5.1. Systematic reviews

To provide information on implementation, the following review questions were formulated.

- What country-specific circumstances should be taken into account for successful implementation of programmatic management of LTBI?
- Is integration of LTBI case detection and treatment into existing health programmes effective, cost-effective and/or feasible (for specific target groups)?

What country-specific circumstances should be taken into account for successful implementation of programmatic management of LTBI?

No systematic reviews were identified that were published in the last 10 years and provided information on country specific circumstances that should be taken into account for successful implementation of programmatic management of LTBI.

Is integration of LTBI case detection and treatment into existing health programmes effective, cost-effective and/or feasible (for specific target groups)?

Two systematic reviews reported data on the integration of LTBI case detection and treatment into existing health programmes.

One systematic review examined the overall effect of service integration of HIV and TB on output of delivery and on the outcomes for patients (see Table A9.13). IPT was given at standalone voluntary counselling and testing centres in two studies, at hospitals in three and at both a clinic and a hospital in one. The proportion of PLHIV screened for IPT eligibility at each site ranged from 81 % to 93 % (weighted mean: 87.7 %). Of those eligible, 67-100 % started IPT. Studies reported high levels of adherence: 75-92 % of the study participants took IPT appropriately as prescribed. 47-88 % of patients completed treatment for the prescribed duration – i.e. 6 months of treatment within the study's follow-up period [123].

Legido-Quigley et al. reviewed the experiences with different models of integration of TB and HIV services. The focus was mainly on active TB instead of LTBI. Information related to LTBI was provided only for the model 'HIV: screens and refers' (HIV service entry, screening, then referral for TB treatment) (not included in table). An advantage of the current model was increased TB case detection and facilitated IPT provision. The infrastructure needed for integration of services varied considerably, depending on whether IPT was offered by the HIV clinic, which was reported to require healthcare workers trained to provide IPT. Moreover, a system for procuring and storing tuberculin for TST is needed, as well as medical officers to exclude active TB among sputum-negative clients. In clinics that do not provide IPT, requirements for HIV centres to manage TB included tools for screening prevention, treatment and quality control. In programmes providing IPT in HIV care facilities, authors recommend ensuring adequate INH supplies, effective referrals between TB and HIV services, accurate recording and reporting of TB/HIV data and human resources to supervise and monitor the programme [128]. Although not performed in the EU, a summary of a review of CEA studies on LTBI control integrated into existing health programmes is presented in Table A9.14.

3.5.5.2. Evidence-based guidelines

One supranational guideline was included on implementation, reporting on incorporation of programmatic management of LTBI into existing health programmes (Table 7).

Table 7. Summary of guidelines on implementation of programmatic latent tuberculosis infection control

Guideline	How to implement LTBI management into existing health programmes
NICE (2012) [121]	• 'Substance misuse services and prison health services should incorporate IGRA testing with screening for hepatitis B and C and HIV testing and refer prisoners and substance misusers with positive IGRA tests to local multi-disciplinary TB teams for further clinical investigations. For prisoners, these investigations should be undertaken within the prison wherever practically possible.'

3.5.6. Programme monitoring and evaluation

3.5.6.1. Systematic reviews

No systematic reviews were identified that were published in the last 10 years and provided information on how monitoring and evaluation of programmatic management of LTBI should take place.

3.5.6.2. Evidence-based guidelines

One supranational guideline was included on monitoring and evaluation, and reporting on critical public health considerations for routine monitoring and evaluation (Table 8).

Table 8. Summary of guidelines on monitoring and evaluation of programmatic management of latent tuberculosis infection

Guideline	How to conduct monitoring and evaluation of programmatic LTBI management
WHO (2015) [4]	• 'Critical public health considerations for routine monitoring and evaluation include: initiation and completion of treatment, active surveillance of AEs and the development of active TB during and after the completion of treatment for LTBI. Additionally, programme monitoring is needed to evaluate quality, programme effectiveness and impact. Nationally standardised indicators and data capturing mechanisms are also required.'

4. Evidence statements

The evidence base was, when sufficient, further summarised into evidence statements (see Section 2.5). The evidence statements are listed below (Tables 9-29), structured for the review questions as defined for target risk groups, diagnostics tests, LTBI treatment and programmatic issues of LTBI management. Multiple evidence statements could be formulated for one review question.

4.1. Evidence statements on target risk groups

To answer the question in which populations LTBI screening measures will lead to the largest benefit, evidence statements (Tables 9-18) have been formulated for the following review questions.

- Which populations are at increased risk of becoming (latently) infected with TB?
- Which populations are at increased risk of developing active TB?

Table 9. Evidence statements formulated for people living with HIV

Review question	Evidence statement	Evidence	Additional information
1	No increased risk of LTBI in PLHIV compared to the general population (as measured by TST and IGRA in LBC and HBC; TST in IBC)	One commissioned review, weak evidence [96]	Two commissioned reviews presented prevalence of LTBI for PLHIV* [92,96]
2	Increased risk of active TB in PLHIV compared to the general population	Two commissioned reviews, weak evidence [89,98]	One commissioned review presented the prevalence of annual LTBI reactivation rates [92] One non-commissioned systematic review presented pooled positive predictive values of TST [99]

** Without statistical comparisons*

Table 10. Evidence statements formulated for immunocompromised populations

Review question	Evidence statement	Evidence	Additional information
1	No increased risk of LTBI in patients with renal or liver conditions compared to the general population (as measured by TST and IGRA in LBC and HBC; TST in IBC)	One commissioned systematic review, weak evidence [96]	One commissioned systematic review presented prevalence of LTBI for immunocompromised persons*
	Increased risk of LTBI in candidates for anti-TNF-alpha therapy compared to the general population (as measured by IGRA in LBC)	One commissioned systematic review, weak evidence [96]	
	No increased risk of LTBI in patients with AIDs or IMIDs compared to the general population (as measured by TST and IGRA in LBC; TST in HBC)	One commissioned systematic review, weak evidence [96]	
2	Increased risk of active TB in end-stage renal disease patients receiving dialysis compared to general population	One commissioned systematic review, weak evidence [89]	One non-commissioned systematic review presented the crude estimate of likely TB reactivation rates and PPV in dialysis patients*
	Increased risk of active TB in LTBI-positive patients with terminal renal failure or on dialysis compared to the general population	One commissioned systematic review, weak evidence [98]	
	Increased risk of active TB in LTBI-positive patients with autoimmune diseases receiving TNF-alpha inhibitors	One commissioned systematic review, weak evidence [98]	
	Increased risk of active TB in dialysis patients compared to the general population	One non-commissioned systematic review, weak evidence [100]	
	Increased risk of active TB in LTBI-positive patients with silicosis compared to the general population	One non-commissioned systematic review, weak evidence [98]	
	Increased risk of active TB in LTBI-positive patients with diabetes mellitus compared to the general population [98]	One non-commissioned systematic review, weak evidence [98]	

** Without statistical comparisons*

Table 11. Evidence statements formulated for migrants

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in migrants compared to the general population (as measured by TST in LBC)	One commissioned systematic review, weak evidence [96]	Two commissioned reviews and two non-commissioned systematic reviews presented prevalence of LTBI for migrants* [87,91,92,96]
	No increased risk of LTBI in migrants compared to the general population (as measured by IGRA in LBC)	One commissioned systematic review, weak evidence [96]	

Review question	Evidence statement	Evidence	Additional information
	Increased risk of LTBI in BCG vaccinated migrants compared to unvaccinated migrants (as measured by TST)	One non-commissioned systematic review, weak evidence [87]	
	Increased risk of LTBI in migrants from countries with ≥ 30 cases per 100 000 compared to migrants from countries with < 30 cases per 100 000 (as measured by TST)	One non-commissioned systematic review, weak evidence [87]	
2	Increased risk of active TB in LTBI-positive migrants/refugees compared to the general population (from HBC to LBC)	One commissioned systematic review, weak evidence [98]	One commissioned review and one non-commissioned systematic review presented reactivation rates in migrants* [91,92]

** Without statistical comparisons*

Table 12. Evidence statements formulated for tuberculosis contacts

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in TB contacts compared to the general population (as measured by TST in IBC)	One commissioned systematic review, weak evidence [96]	Two commissioned systematic reviews and four non-commissioned systematic reviews presented prevalence of LTBI for TB contacts* [66,90,92,94-96]
	No increased risk of LTBI in TB contacts compared to the general population (as measured by IGRA in IBC; as measured by TST and IGRA in LBC and HBC)	One commissioned systematic review, weak evidence [96]	
	Increased risk of LTBI in TB contacts in low-middle-income countries compared to contacts in high-income countries	One non-commissioned systematic review, weak evidence [66]	
	Increased risk of LTBI in foreign-born TB contacts in high-income countries compared to locally born contacts	One non-commissioned systematic review, weak evidence [66]	
2	Increased risk of active TB in LTBI-positive contacts (children and adults) compared to the general population	One commissioned systematic review, weak evidence [98]	Two commissioned systematic reviews and six non-commissioned systematic reviews presented risk of active TB in TB contacts being exposed to a TB index case* [66,90,92,94-96,101,117]

** Without statistical comparisons*

Table 13. Evidence statements formulated for healthcare workers

Review question	Evidence statement	Evidence	Additional information
1	No increased risk of LTBI in healthcare workers and undergraduate health sciences students compared to the general population (as measured by TST and IGRA in LBC, IBC, HBC)	One commissioned systematic review, weak evidence [96]	Two commissioned systematic reviews and one non-commissioned systematic review presented prevalence of LTBI for healthcare workers* [90,92,96]
2	Increased risk of active TB in LTBI-positive healthcare workers compared to the general population (HBC to LBC)	One commissioned systematic review, weak evidence [98]	Two commissioned systematic reviews presented reactivation rates and annual risk of TB in healthcare workers* [92,98]

** Without statistical comparisons*

Table 14. Evidence statements formulated for prisoners

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in prisoners compared to the general population (as measured by TST in LBC and IBC)	One commissioned systematic review, weak evidence [96]	One commissioned systematic review and one non-commissioned systematic review presented prevalence of LTBI for prisoners* [93,96]
2	Increased risk of active TB in prisoners compared to the general population	One commissioned systematic review, weak evidence [98]	One commissioned systematic review presented incidence rate ratios of active TB in prisoners* [98]

** Without statistical comparisons*

Table 15. Evidence statements formulated for homeless people

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in homeless people compared to the general population (as measured by TST and IGRA in LBC)	One commissioned systematic review, weak evidence [96]	One commissioned systematic review presented prevalence of LTBI for homeless people * [96]
2	No increased risk of active TB in persons residing in homeless shelters compared to the general population	One commissioned systematic review, weak evidence [98]	Not available

** Without statistical comparisons*

Table 16. Evidence statements formulated for people with drug use disorders

Review question	Evidence statement	Evidence	Additional information
1	No increased risk of LTBI in people with drug use disorders compared to the general population (as measured by TST and IGRA in LBC)	One commissioned systematic review, weak evidence [96]	One commissioned systematic review presented prevalence of LTBI for people with drug use disorders* [96]
2	No systematic review identified on this topic		Not available

** Without statistical comparisons*

Table 17. Evidence statements formulated for age

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in migrants in older age groups (i.e. ≥ 35 compared to < 35; ≥ 18 compared to < 18 years) (as measured by TST or IGRA)	Two non-commissioned systematic reviews, weak evidence [87,91]	Two commissioned systematic reviews and three non-commissioned systematic reviews presented prevalence of LTBI in different age groups* [90-92,94,96]
2	No systematic review identified presenting statistically analysed quantitative evidence		One commissioned systematic review and two non-commissioned systematic reviews presented the proportion active TB, the prevalence of TB and the annual LTBI reactivation rate in different age groups* [90,92,94]

** Without statistical comparisons*

Table 18. Evidence statements formulated for other risk groups

Review question	Evidence statement	Evidence	Additional information
1	Increased risk of LTBI in individuals exposed to second-hand smoking	One non-commissioned systematic review, weak evidence [88]	One non-commissioned systematic review presented the cumulative incidence of LTBI, as measured by TST conversion in long-term travellers from low-prevalence countries (military and civilian)* [97]
	Increased risk of LTBI in males (as measured by TST and IGRA)	One non-commissioned systematic review, weak evidence [87]	
2	Increased risk of active TB in alcohol misusers	One commissioned systematic review, weak evidence [98]	
	Increased risk of active TB in tobacco users	One commissioned systematic review, weak evidence [98]	Not available
	Increased risk of active TB in LTBI-positive military recruits with low weight compared to LTBI-positive recruits with normal weight	One commissioned systematic review, weak evidence [89]	

** Without statistical comparisons*

4.2. Evidence statements on diagnostics of LTBI

To answer the question of what the most optimal and reliable diagnostic test or combination of tests is for LTBI, evidence statements (Tables 19-21) have been formulated for the following Review questions.

- Which tests are effective for diagnosis of LTBI? (In certain risk groups)
- Which diagnostic tests are cost-effective for LTBI? (In certain risk groups)
- Which diagnostic tests are feasible, accessible and/or acceptable for LTBI? (In certain risk groups).

The remaining review questions – (i) What is the effect of tests being free of charge? (ii) In what order should a combination of LTBI tests (and tests for active TB) be done? – could not be answered due to the lack of scientific evidence. Consequently, no evidence statements were formulated.

Table 19. Evidence statements formulated for tuberculin skin test

Review question	Evidence statement	Evidence	Additional information
1	TST is effective for diagnosis of LTBI (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	One non-commissioned systematic review of qualitative studies on migrants' perceptions, knowledge, attitudes and treatment-adherence behaviour relating to LTBI/TB and their social implications* indicated that positive TST results were perceived as very serious clinical diagnosis [106]
	TST appears not effective for diagnosis of LTBI in immunocompromised patients (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	
	TST is effective for diagnosis of LTBI in TB contacts (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	
2	TST followed by LTBI treatment if positive (≥ 5 mm) for PLHIV is strongly cost-effective** for diagnosis of LTBI (as compared to no screening and no treatment in PLHIV)	One non-commissioned systematic review, weak evidence [103]	
	TST (≥ 10 mm) and subsequent treatment for new adult migrants is strongly cost-effective ** for diagnosis of LTBI (as compared to no screening)	One non-commissioned systematic review, weak evidence [103]	
	TST (≥ 5 mm) for migrants is cost-effective *** for diagnosis of LTBI (as compared with TST (≥ 5 mm) positive followed by QFT-GIT or T-SPOT.*TB* of QFT-GIT alone)	One non-commissioned systematic review, weak evidence [102]	
3	No systematic review identified presenting quantitative evidence		

** Without statistical comparisons*
*** Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.*
**** An ICER below GBP 20 000 was considered cost-effective.*

Table 20. Evidence statements formulated for interferon gamma release assays

Review question	Evidence statement	Evidence	Additional information
1	IGRA is effective for diagnosis of LTBI (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	Not available
	IGRA appears not effective for diagnosis of LTBI in immunocompromised patients (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	
	IGRA appears not effective for diagnosis of LTBI in TB contacts (based on risk of progression to active TB, compared to no screening)	One full commissioned systematic review, weak evidence [85]	
2	Screening children with IGRA is the most cost-effective * strategy compared to TST (≥ 10 mm)	One non-commissioned systematic review, weak evidence [102]	
	Screening adult migrants with IGRA is moderately cost-effective** for diagnosis of LTBI (as compared to no screening)	One non-commissioned systematic review, weak evidence [103]	
	Screening high-risk groups, such as healthcare workers, migrants from high-incidence countries and close contacts with IGRA is moderately cost-effective**	One non-commissioned systematic review, weak evidence [103]	
	IGRA for PLHIV followed by INH 6 months if positive is highly cost-effective*** for diagnosis of LTBI (as compared to no screening programme in PLHIV)	One non-commissioned systematic review, weak evidence [104]	
3	No systematic review identified presenting statistically analysed quantitative evidence		

** An ICER below GBP 20 000 was considered cost-effective. The review included primary studies conducted in low- and high-incidence settings.*
*** Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.*
**** Primary studies used different willingness-to-pay thresholds to identify cost-effective interventions.*

Table 21. Evidence statements formulated for tuberculin skin test and interferon gamma release assays combined

Review question	Evidence statement	Evidence	Additional information
1	No systematic review identified presenting statistically analysed quantitative evidence		One non-commissioned systematic review of qualitative studies on migrants' perceptions, knowledge, attitudes and treatment-adherence behaviour relating to LTBI/TB and their social implications*, identifying the following. The screening process was perceived as a socially responsible act in terms of helping to prevent further cases. Several perceived barriers for accessing health services: • illiteracy or lack of familiarity with the local language • having to miss work to attend a clinic appointment, transport difficulties, queues and waiting lists • not having health insurance • irregular residence status • Misconceptions about TB transmission • Fear of stigma [106]
2	Negative TST (cut off value ≥ 5 mm) followed by QFT-GIT is the most cost-effective** strategy for diagnosis of LTBI in children	One non-commissioned systematic review, weak evidence [102]	
	Negative QFT-GIT followed by TST (cut off value ≥ 5 mm) for the immunocompromised population is cost-effective** for diagnosis	One non-commissioned systematic review, weak evidence [102]	
	Screening high-risk groups, such as healthcare workers, migrants from high-incidence countries, and close contacts with IGRA in TST-positives is cost-effective***	One non-commissioned systematic review, weak evidence [104]	
3	No systematic review identified presenting statistically analysed quantitative evidence		

** Without statistical comparisons*
*** An ICER below GBP 20 000 was considered cost-effective.*
**** Primary studies used different willingness-to-pay thresholds to identify cost-effective interventions.*

4.3. Evidence statements on LTBI treatment

To answer the question of what the most optimal approach for LTBI treatment is (what, who, when), evidence statements (Tables 22–26) have been formulated for the following review questions (except for question number 3).

- What is the effectiveness of different preventive treatment regimens for certain risk groups? (Summarised by treatment)
- What is the cost-effectiveness of different preventive treatment regimens for certain risk groups?
- What is the feasibility and acceptability of different preventive treatment regimens for certain risk groups?
  - How often is preventive treatment initiated? (In certain risk groups)
  - How often is preventive treatment completed? (In certain risk groups)
  - What is the risk of AEs of LTBI treatment? (In certain risk groups)

Table 22. Evidence statements formulated on latent tuberculosis infection treatment

Review question	Evidence statement	Evidence	Additional information
1	INH for 6 months (compared to placebo or no treatment) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, weak evidence [112]	• One full commissioned systematic review presented the outcomes of a network meta-analyses that confirmed that INH for 6 or 12 months, RIF alone, RIF-INH for 3 months, PZA-containing regimens (RIF-INH-PZA and RIF-PZA) and INH-EMB for 12 months were efficacious versus placebo. • INH for 6, 9 or 12 months, RFB-INH, RPT-INH, RIF alone, RIF-INH for 3-4 months, PZA containing regimens (RIF-INH-PZA and RIF-PZA) and INH-EMB for 12 months were efficacious versus no treatment [29] • Three commissioned reviews and three non-commissioned systematic reviews presented measures for effectiveness of various treatment regimens, also for PLHIV and immunocompromised persons [28,92,113-116]
	INH for 9 months (compared to no treatment) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, weak evidence	
	INH for ≥ 12 months (compared to placebo or no treatment) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, weak evidence [29,112]	
	RIF alone (compared to placebo) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, moderate evidence [29,112]	
	RIF + INH for 3-4 months (compared to placebo) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, weak evidence	
	PZA-containing regimens (RIF-INH-PZA and RIF-PZA) (compared to placebo or no treatment) are an effective treatment regimen for LTBI	One full commissioned systematic review, weak evidence [112]	
	INH-EMB for 12 months (compared to placebo) is an effective preventive treatment regimen for LTBI	One full commissioned systematic review, weak evidence [112]	
	INH for 12-72 months (compared to INH for 6 months) is an effective treatment regimen for LTBI.	One full commissioned systematic review, weak evidence [112]	

Table 23. Evidence statements formulated on the cost-effectiveness of latent tuberculosis infection treatment

Review question	Evidence statement	Evidence	Additional information
2	LTBI treatment is cost-effective* for preventing the development of active TB in high risk individuals with LTBI	One commissioned systematic review and one non-commissioned systematic review, weak evidence [92,118]	Not available
	In PLHIV and healthcare workers, preventive treatment after primary screening is cost-effective for treatment of LTBI	One non-commissioned systematic review, weak evidence [117]	

** Cost-effectiveness was defined either as (i) an intervention that had lower cost and higher effectiveness when compared to no intervention or another screening or (ii) using different willingness-to-pay thresholds (if reported) across primary studies.*

Table 24. Evidence statements formulated on the completion of latent tuberculosis infection treatment

Review question	Evidence statement	Evidence	Additional information
4	Contacts of TB cases had better LTBI treatment adherence and completion if they received short treatment regimens compared to long treatment regimens	One full commissioned systematic review, moderate evidence [86]	Two commissioned systematic reviews provided treatment completion rates for various risk groups* [30,92] One non-commissioned systematic review confirmed with moderate evidence that shorter versus longer treatment regimens are more often completed [28]
	Migrants had better LTBI treatment completion if they received short treatment regimens compared to long treatment regimens	One full commissioned systematic review, moderate evidence [86]	
	The general population had better LTBI treatment completion if they received short treatment regimens compared to long treatment regimens	One full commissioned systematic review, moderate evidence [86]	

** Without statistical comparisons*

Table 25. Evidence statements formulated on adverse events of latent tuberculosis infection treatment

Review question	Evidence statement	Evidence	Additional information
5	RIF (compared to INH for 6 or 9 months) gives a lower risk of hepatotoxicity	One full commissioned systematic review, weak evidence	One full commissioned systematic review presented the outcomes of a network meta-analysis that confirmed that INH for 6 months, RPT-INH, RIF alone and RIF-INH gives higher hepatoxicity risk compared to placebo. RIF alone gives higher hepatoxicity risk compared to no treatment [29] Two commissioned systematic reviews and two non-commissioned systematic reviews presented measures for safety of various treatment regimens, also for PLHIV, child contacts and contacts of MDR TB [28,114,116,119]

4.4. Evidence statements of programmatic issues of LTBI management

For assessing the optimal approach for programmatic management of LTBI, review questions have been addressed for seven areas, i.e. case detection (screening and contact investigation); treatment-related interventions (improving treatment adherence and AE control); education; implementation; monitoring and evaluation.

4.4.1. Case detection; screening

To answer the question what the optimal approach for screening for LTBI is (who, when, where, how), evidence statements (Table 27) have been formulated for the following review questions (except for questions 3 and 5).

- What is the effectiveness of screening programmes for certain risk groups?
- What is the cost-effectiveness of different screening programmes for certain risk groups?
- How can target groups be identified and accessed for LTBI screening services?
- What is the effectiveness of interventions to improve screening uptake?
- Is mandatory LTBI screening effective, cost-effective and/or feasible (for specific target groups)?

Table 26. Evidence statements formulated for screening

Review question	Evidence statement	Evidence	Additional information
1	The proportion of migrants recommended LTBI treatment when tested positive is significantly higher when tested with TST than with IGRA	One non-commissioned systematic review, weak evidence [91]	Three non-commissioned systematic reviews provided information on yield of screening in migrants, the general population and PLHIV* [87,122,123]
2	Screening and treatment for LTBI in high-risk populations is cost-effective**	One commissioned systematic review, weak evidence [92]	Not available
	Screening PLHIV with TST is strongly cost-effective***	One non-commissioned systematic review, weak evidence [103]	
	Screening high-risk populations with IGRA is cost-effective*	Two non-commissioned systematic reviews, weak evidence [103,104]	
3	No systematic review identified presenting statistically analysed quantitative evidence		One non-commissioned systematic review described limitations of current TB-control programmes in prison facilities, including access to target groups* [93]
4	Material incentives and enablers lead to a significantly higher return for reading TST results in people with drug use disorders, compared to routine care, non-cash incentives or any other intervention	One non-commissioned systematic review, weak evidence [124]	Not available
5	No systematic review identified on this topic		Not available

** Without statistical comparisons*
*** Cost-effectiveness was defined either as (i) an intervention that had lower cost and higher effectiveness when compared to no intervention or another screening or (ii) using different willingness-to-pay thresholds (if reported) across primary studies.*
**** Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.*

4.4.2. Case detection; contact investigation

The limited number of systematic reviews on contact investigation did not allow to answer the question of what the optimal approach for contact investigation for LTBI is (who, when, where, how). Consequently, no evidence statements have been formulated for the following review questions.

- What is the effectiveness of (different) contact investigation approaches in certain risk groups?
- What is the cost-effectiveness of (different) contact investigation approaches in certain risk groups?
- How can target groups be identified and accessed for contact investigation?
- What is the effectiveness of interventions to improve contact investigation uptake?

4.4.3. Treatment-related interventions

To answer the question of what treatment-related interventions lead to an optimal result of preventive treatment, evidence statements (Table 28) have been formulated for the following review question (question number 2 only).

- What are determinants of LTBI treatment initiation, adherence and completion?
- What interventions are effective to improve initiation, adherence and completion of LTBI treatment?

Table 27. Evidence statements formulated for treatment-related interventions

Review question	Evidence statement	Evidence	Additional information
1	No systematic review identified presenting statistically analysed quantitative evidence		One full commissioned systematic review presented determinants of LTBI treatment initiation, adherence and completion* [86] One non-commissioned systematic review presented influencing aspects on the cascade of care in diagnosis and treatment of LTBI* [126]
2	A social intervention using case management with attention to an individual's cultural background in migrants (compared to standard care) is effective to improve initiation rate of LTBI treatment	One full commissioned systematic review, weak evidence [86]	Three non-commissioned systematic reviews presented results on interventions to improve initiation, adherence and completion of LTBI treatment, which were in line with the evidence statements [69,106,124]
	Use of IGRAs (compared to TST) is associated with increased initiation rates of LTBI treatment in healthcare worker	One full commissioned systematic review, weak evidence [86]	
	A social intervention (treatment counsellor/contingency contracting and adherence coaching/self-esteem counselling and peer based) in the general population (compared to standard care) is effective to improve completion rates of LTBI treatment	One full commissioned systematic review, strong evidence [86]	
	A social intervention using case management with attention to the cultural background of migrants (compared to standard care) is effective to improve completion rate of LTBI treatment	One full commissioned systematic review, weak evidence [86]	
	Nurse case management in homeless people (compared to standard care) is effective to improve completion rates of LTBI treatment	One full commissioned systematic review, strong evidence [86]	
	Methadone treatment + DOT compared to no incentive + SAT in people who inject drugs is effective to improve completion rates of LTBI treatment	One full commissioned systematic review, weak evidence [86]	
	Monetary incentive (compared to no incentive) in people who inject drugs is effective to improve completion rates of LTBI treatment	One full commissioned systematic review, moderate evidence [86]	
	DOT + short treatment regimen (compared to SAT + long treatment regimen) in contacts of TB cases is effective to improve completion rates of LTBI treatment	One full commissioned systematic review, weak evidence [86]	
	Clinic-based directly observed therapy (compared to daily self-administered therapy) in migrants decreases completion rates of LTBI treatment	One full commissioned systematic review, weak evidence [86]	
	Education in inmates (compared to no education) is effective to improve completion rate of LTBI treatment	One full commissioned systematic review, moderate evidence [86]	

** Without statistical comparisons*

4.4.4. Adverse effect management

No systematic review identified presented statistically analysed quantitative evidence on adverse effect (AE) management to improve the results of preventive treatment.

- What is an effective approach to monitor and manage AEs?

Additional information: one commissioned review presented information on approaches to monitor toxicity in individuals treated for LTBI without statistical comparisons [127].

4.4.5. Education

To answer the question of what the optimal approach is for education on LTBI (who, when, how), evidence statements (Table 29) have been formulated for the following review questions.

- Who should be targeted for education and when?
- What information should be provided?
- What is the effectiveness of different education methods?
- Is education cost-effective?

Table 28. Evidence statements formulated for education

Review question	Evidence statement	Evidence	Additional information
1/2/3	Education based on CDC guidelines for prisoners (one-to-one sessions with research assistant) and mothers of LTBI-positive children (discussions with specialised nurse or physician and information leaflet) compared to control group is effective to improve adherence of LTBI treatment	One non-commissioned systematic review, weak evidence [69]	Not available
	Education based on CDC guidelines for prisoners (one-to-one sessions with research assistant) and mothers of LTBI-positive children compared to control group is effective to improve completion rates of LTBI treatment	One non-commissioned systematic review, weak evidence [69]	

Review question	Evidence statement	Evidence	Additional information
	Education (compared to material incentives) is less effective to improve return for reading of TST induration in people with drug use disorders compared to material incentives	One non-commissioned systematic review, weak evidence [124]	
4	No systematic review identified on this topic		Not available

4.4.6. Integration of LTBI management into existing health programmes in EU/EAA countries

No systematic review was identified on country specific circumstances and no systematic review was identified presenting statistically analysed quantitative evidence on the effectiveness, cost-effectiveness and feasibility of integration of LTBI case detection and treatment into existing health programmes.

- What country-specific circumstances should be taken into account for successful implementation of programmatic LTBI management?
- Is integration of LTBI case detection and treatment into existing health programmes effective, cost-effective and/or feasible (for specific target groups)?

Additional information: two non-commissioned systematic reviews provided descriptive information on TB and HIV service integration [123,128]. One review of cost-effectiveness analyses (in African high-incidence countries) provided some information on cost-effectiveness of TB and HIV service integration [123].

4.4.7. Monitoring and evaluation

No systematic reviews were identified on monitoring and evaluation of programmatic LTBI management.

4.5. Knowledge gaps

No or limited information was found for one or more research question for each of the main topics: risk groups, diagnosis, treatment and programmatic issues. Table 30 summarises the knowledge gaps that were identified that were relevant for programmatic management of LTBI in the EU/EEA.

Table 29. Knowledge gaps

	Knowledge gaps
Risk groups	• Limited information from scientific literature on populations at increased risk of becoming infected with TB • Limited information from scientific literature on populations at increased risk of developing active TB after infection • Only part of the data found based on EU/EEA countries
Diagnosis	• Limited information on which tests are effective for diagnosis in certain risk groups • Limited information on the feasibility, accessibility and acceptability of diagnostic LTBI tests • No information on the effect of tests being free of charge • Limited information on the order of combination of LTBI tests (and tests for excluding active TB) • Few data directly applicable to the EU/EEA setting
Treatment	• Limited information on how often preventive treatment is initiated
Programmatic issues	*Screening* • Although relevant background information is provided, the research question on how to get access to target groups for LTBI screening services could not be answered • Limited information on the effectiveness of interventions to improve screening uptake • Limited information on the effect of mandatory LTBI screening, the cost-effectiveness and/or feasibility (for specific target groups) *Contact investigation* • No information was found on the cost-effectiveness of (different) contact investigation approaches in certain risk groups • No information was found on how to get access to target groups for contact investigation • No information was found on the effectiveness of interventions to improve contact investigation uptake *Treatment-related interventions* • Limited scientific evidence on the effectiveness of interventions aiming at AE control *Education* • Limited scientific evidence on the effectiveness of educational interventions • Limited scientific evidence on target groups and type of information for educational interventions • No information was found on the cost-effectiveness of educational interventions *Implementation* • No information was found on country-specific circumstances that should be taken into account for successful implementation of programmatic LTBI management • Limited scientific evidence on effectiveness, cost-effectiveness and/or feasibility of the integration of LTBI case detection and treatment into existing health programmes. *Monitoring and evaluation* • No information was found on how monitoring and evaluation of programmatic LTBI management should take place

4.6. Strengths and limitations

This report builds upon a comprehensive inventory which outlined the main areas and formulated the research questions in relation to programmatic LTBI management [31]. Using a systematic approach, relevant evidence was synthesised allowing the identification of feasible options for programmatic management of LTBI in the EU/EEA, as well as current knowledge gaps. This evidence base was critically appraised, analysed and summarised using a rigorous methodology (Cochrane [129] and GRADE [75]) in order to minimise selection and confirmation bias due to preconceived opinions.

A limitation of this review is that only one literature database was searched (i.e. Medline). Therefore, measures were taken to maximise the identification of potentially relevant articles, for example hand search, web search and consultation of experts. However, publication bias may have occurred. Also, unpublished articles were not considered in this review.

As part of the overarching review process used, backtracking of primary studies was not conducted. Thus, data reported in the primary studies but not summarised in the selected systematic reviews were not taken into account. In addition, it is possible that individual primary studies were included in more than one systematic review.

A large amount of heterogeneity was observed between included reviews, for example regarding study populations, (healthcare) settings, treatment components (not always clear what factors are responsible for observed effect), outcome definitions, comparisons made, or part of these aspects were not well described. Many studies did not take confounding or modifying factors into account. Furthermore, several included systematic reviews only presented descriptive results without statistical analyses, which cannot be used to assess effectiveness or causality because of the lack of control groups. Therefore, these results could not be used as the basis for evidence statements, but were included into the evidence base as 'additional information'. In reviews that did present comparative statistical analyses, the lack of statistically significant results within the included systematic reviews may sometimes be an effect of the low number of primary studies (and therewith estimates) included.

Finally, not all studies retrieved were on the EU/EEA region. These results cannot always simply be extrapolated to the EU/EEA setting, since healthcare systems and populations may be not comparable.

5. Conclusions

The implementation of a comprehensive and systematic strategy for reducing the burden of LTBI is essential for achieving TB elimination. Relevant components of programmatic LTBI management include identification of target groups; diagnosis, treatment and programmatic issues including screening; contact investigation; treatment-related interventions; adverse-event management; education; integration of LTBI management into existing health programmes; and monitoring and evaluation.

Relevant existing guidelines for these components were identified and scientific evidence was found for most of the relating review questions, although the strength of the latter was predominantly weak. Still, important gaps in evidence exist. In general, there is a large amount of heterogeneity between studies in the peer-reviewed literature, making comparisons difficult. Studies of higher quality and with conclusive (comparative) evidence are needed, particularly in the following areas.

- Data on population sizes of risk groups, data on overlap and transmission between these groups and precise data on risk of TB in risk groups.
- Understanding of LTBI tests, including distinguishing remote infection and re-infection.
- Interventions to improve treatment uptake and adherence.
- Programmatic aspects of LTBI management, specifically regarding the effectiveness and impact of programmatic LTBI management.
- Cost and cost-effectiveness data, including interventions with proven cost-effectiveness for the control of other diseases that might be used for LTBI management.

6. Next steps

This document provides a body of evidence that may support the decision-making process for the identification and implementation of adequate measures for prevention and control of LTBI at country level.

The findings of this review contributed to the development of an ECDC public health guidance document on programmatic management of LTBI in the EU/EEA.

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Appendix 1. Overview review questions

Expert panel workshop 2013			Data synthesis report and *ad hoc scientific panel* meeting 2016		
Key areas		Preliminary research questions	Key areas: Main questions		Review questions
General information on (latent) TB	Prevalence of LTBI in Europe	Prevalence of LTBI in different risk groups and the general population	Target groups: In which populations will LTBI management measures lead to the largest benefit?		Which populations are at increased risk of becoming (latently) infected with TB?
		Factors influencing the prevalence of LTBI, e.g. increased MDR-TB incidence and changing migration patterns			
	Risk of developing TB	Risk of active TB over time after infection			Which populations are at increased risk of developing active TB?
		Risk of TB after exposure to an infectious index case with or without chemoprophylaxis or preventive therapy			
		Risk of developing and time to develop TB, related to the country of origin, when migrating to a low-incidence area			
		Target risk groups			
		Costs of LTBI in EU/EEA			
Diagnosis of LTBI		Efficacy	Diagnosis of LTBI: What is the optimal and most reliable diagnostic test or combination of tests for LTBI?		Which tests are effective for diagnosis of LTBI? (In certain risk groups)
		Optimal and most reliable diagnostic test or combination of diagnostic tests			In what order should a combination of LTBI tests (and tests for active TB) be done?
		Current or new diagnostic test			Which diagnostic tests are feasible, accessible and/or acceptable for LTBI? (In certain risk groups)
					Which diagnostic tests are cost-effective for LTBI? (In certain risk groups)
		The effect of tests being free of charge			What is the effect of tests being free of charge?
Impact of and conditions for interventions (i.e. possible components of LTBI control) on LTBI incidence, focusing on:	LTBI treatment (chemoprophylaxis and preventive therapy) in certain populations, e.g. HIV patients, migrants, close contacts	Effectiveness of LTBI treatment in specific target groups and specific situations/Effectiveness of different possible LTBI treatment regimens, e.g. shorter regimens	Treatment of LTBI	Treatment of LTBI: What is the optimal approach for LTBI treatment?	What is the effectiveness of different preventive treatment regimens for certain risk groups? (Summarised by treatment)
		What are currently the optimal preventive treatment regimens for LTBI for different situations and in different risk groups?			What is the cost-effectiveness of different preventive treatment regimens for certain risk groups?
		Adherence to LTBI treatment in different risk groups			What is the feasibility and acceptability of different preventive treatment regimens for certain risk groups? • How often is preventive treatment initiated? (In certain risk groups) • How often is preventive treatment completed? (In certain risk groups) • What is the risk of AEs of LTBI treatment? (In certain risk groups)
		Frequency and severity of major and minor AEs of chemoprophylaxis and preventive therapy			
		Monitoring adverse events (regular liver function test etc.)		Treatment-related interventions (AE control and improving treatment adherence)	What is an effective approach to monitor and manage AEs?
		Patient/doctor factors to increase acceptability			What are determinants of LTBI treatment initiation, adherence and completion?
		Effectiveness of different interventions to improve LTBI treatment uptake and adherence, such as DOT and different incentives			What interventions are effective to improve initiation, adherence and completion of LTBI treatment?
		The effect of drugs being free of charge			
Impact of and conditions for interventions (i.e. possible components of LTBI control) on LTBI incidence, focusing on:	Contact investigation	Yield of contact investigation in different settings and population	Programmatic issues of LTBI management	Case detection; contact investigation: What is the optimal approach for contact investigation?	What is the effectiveness of (different) contact investigation approaches in certain risk groups?
					What is the cost-effectiveness of (different) contact investigation approaches in certain risk groups?
		Access to TB contacts			How can target groups be identified and accessed for LTBI screening services?
					What is the effectiveness of interventions to improve contact investigation uptake?
	Screening of certain populations	Effect of screening programmes (for specific risk groups)		Case detection; screening: What is the optimal approach for screening for LTBI?	What is the effectiveness of screening programmes for certain risk groups?
		Diagnostic tools to be used			What is the cost-effectiveness of different screening programmes for certain risk groups?
		Access to risk groups (identification of target groups, improving access)			How can target groups be identified and accessed for LTBI screening services?
		Developing a robust system for LTBI and TB case finding			What is the effectiveness of interventions to improve screening uptake?
		Laws mandating screening programmes			Is mandatory LTBI screening effective, cost-effective and/or feasible (for specific target groups)?
LTBI education to reduce LTBI		Target groups: on policy level, healthcare workers, medical students, personnel in community settings, risk groups, general population		Education: What is the optimal approach for education on LTBI?	Who should be targeted for education and when?
		Effective methods to distribute information; use of social networks			What is the effectiveness of different education methods? Is education cost-effective?
		Content of education and information strategy			What information should be provided?

Expert panel workshop 2013		Data synthesis report and *ad hoc scientific panel* meeting 2016		
Key areas	Preliminary research questions	Key areas: Main questions		Review questions
	Potential for combining LTBI screening with other health programmes	Programmatic issues of LTBI management	Implementation: Can LTBI management be integrated into existing health programmes in EU/EEA countries?	What country-specific circumstances should be taken into account for successful implementation of programmatic LTBI management ?
				Is integration of LTBI case detection and treatment into existing health programmes effective, cost-effective and/or feasible (for specific target groups)?
			Programme monitoring and evaluation	How should monitoring and evaluation of programmatic LTBI management take place?

Appendix 2. Search string of review of systematic reviews/meta-analyses

General information on aspects of (latent) TB

I LTBI prevalence in EU/EEA

I.a LTBI prevalence in the general population in Europe

(Prevalence[tiab] AND ("latent tuberculosis"[MeSH] OR "latent tuberculosis"[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND (European Union[tiab] OR EU[tiab] OR Scandinavia* [78] or Scandinavia*[ad] OR Mediterranean[78] OR Mediterranean[ad] OR Baltic[78] OR Baltic[ad] OR (Austria*[78] OR Austria*[ad]) OR (Cyprus[78] OR Cyprus[ad] OR Cypriot*[ad] OR Cypriot*[78]) OR (Czech[78] OR Czech[ad]) OR (Belgi*[78] OR Belgi*[ad]) OR (Bulgaria*[78] OR Bulgaria*[ad]) OR (Denmark[78] OR Denmark[ad] OR Danish[78] OR Danish[ad]) OR (Estonia*[78] OR Estonia*[ad]) OR (Finland[78] OR Finland[ad] OR Finnish[78] OR Finnish[ad]) OR (France*[78] OR French*[78] OR France*[ad] OR French*[ad]) OR (German*[78] OR German*[ad]) OR (Greece[78] OR Greece[ad] OR Greek[78] OR Greek[ad]) OR (Hungar*[78] OR Hungar*[ad]) OR (Ital*[78] OR Sicil*[78] OR Sardinia*[78] OR Ital*[ad] OR Sicil*[ad] OR Sardinia*[ad]) OR (Latvi*[78] OR Latvi*[ad]) OR (Lithuania*[78] OR Lithuania*[ad]) OR (Luxembourg*[78] OR Luxembourg*[ad]) OR (Malta[78] OR Malta[ad] OR Maltese[78] OR Maltese[ad]) OR (Netherlands[78] OR Netherlands[ad] OR Dutch[78] OR Dutch[ad]) OR (Poland*[78] OR Polish*[78] OR Poland*[ad] OR Polish*[ad]) OR (Portugal[78] OR Portugal[ad] OR Portuguese[ad] OR Portuguese[78]) OR (Romania*[78] OR Romania*[ad] OR Roumania*[78] OR Roumania*[ad] OR Rumania*[78] OR Rumania*[ad]) OR (Slovak*[78] OR Slovak*[ad]) OR (Slovenia*[78] OR Slovenia*[ad]) OR (Spain*[78] OR Spanish*[78] OR Spain*[ad] OR Spanish*[ad]) OR (Sweden[78] OR Sweden[ad] OR Swedish[78] OR Swedish[ad]) OR (Great Britain*[78] OR Brittish*[78] OR British*[78] OR Channel Islands*[78] OR Guerns*[78] OR England*[78] OR English*[78] OR Hebrid*[78] OR Ireland*[78] OR Irish*[78] OR Scotland*[78] OR Scotch*[78] OR Scottish*[78] OR Wales*[78] OR Welsh*[78] OR United Kingdom*[78] OR UK[78] OR Great Britain*[ad] OR Brittish*[ad] OR British*[ad] OR Channel Islands*[ad] OR Guerns*[ad] OR England*[ad] OR English*[ad] OR Hebrid*[ad] OR Ireland*[ad] OR Irish*[ad] OR Scotland*[ad] OR Scottish*[ad] OR Scotch*[ad] OR Wales*[ad] OR Welsh*[ad] OR United Kingdom*[78] OR UK[78] OR Gibraltar[78] OR Gibraltar[ad]) OR Iceland*[78] OR Iceland*[ad] OR Norway[ad] OR Norway[78] OR Norwegian*[ad] OR Norwegian*[78] or Svalbard*[78] OR Svalbard*[ad] OR Liechtenstein*[78] OR Liechtenstein*[ad] OR EEA[78] OR European Economic Area[78]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat])) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

I.b/I.c LTBI prevalence in different risk groups and factors influencing LTBI prevalence

(Prevalence[tiab] AND ("latent tuberculosis"[MeSH] OR "latent tuberculosis"[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II Risk of developing TB in different situations

II.a/II.b Risk of active TB over time after infection, after exposure to an infectious index case with/without preventive treatment

(((develop*[tiab] OR reactivat*[tiab] OR activ*[tiab]) AND (TB[tiab] OR tuberc*[tiab])) AND (infect*[tiab] OR expos*[tiab] OR contact[tiab] OR latent[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis[tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II.c Risk of developing and time to develop TB, related to the country of origin, when migrating to a low-incidence area

(((develop*[tiab] OR reactivat*[tiab] OR active*[tiab]) AND (TB[tiab] OR tuberc*[tiab])) AND
(migrat*[tiab] OR migran*[tiab] OR moving[tiab] OR move*[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis[tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

III Costs of LTBI in EU/EEA

(("latent tuberculosis"[MeSH] OR "latent tuberculosis"[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab])) AND (cost-effectiv*[tiab] OR costeffectiv*[tiab] OR "Costs and Cost Analysis"[Mesh] OR Cost-Benefit Analysis[mesh] OR cost-benefit*[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR economic evaluation*[tiab]) AND (European Union[tiab] OR EU[tiab] OR Scandinavia* [78] or Scandinavia*[ad] OR Mediterranean[78] OR Mediterranean[ad] OR Baltic[78] OR Baltic[ad] OR (Austria*[78] OR Austria*[ad]) OR (Cyprus[78] OR Cyprus[ad] OR Cypriot*[ad] OR Cypriot*[78]) OR (Czech[78] OR Czech[ad]) OR (Belgi*[78] OR Belgi*[ad]) OR (Bulgaria*[78] OR Bulgaria*[ad]) OR (Denmark[78] OR Denmark[ad] OR Danish[78] OR Danish[ad]) OR (Estonia*[78] OR Estonia*[ad]) OR (Finland[78] OR Finland[ad] OR Finnish[78] OR Finnish[ad]) OR (France*[78] OR French*[78] OR France*[ad] OR French*[ad]) OR (German*[78] OR German*[ad]) OR (Greece[78] OR Greece[ad] OR Greek[78] OR Greek[ad]) OR (Hungar*[78] OR Hungar*[ad]) OR (Ital*[78] OR Sicil*[78] OR Sardinia*[78] OR Ital*[ad] OR Sicil*[ad] OR Sardinia*[ad]) OR (Latvi*[78] OR Latvi*[ad]) OR (Lithuania*[78] OR Lithuania*[ad]) OR (Luxembourg*[78] OR Luxembourg*[ad]) OR (Malta[78] OR Malta[ad] OR Maltese[78] OR Maltese[ad]) OR (Netherlands[78] OR Netherlands[ad] OR Dutch[78] OR Dutch[ad]) OR (Poland*[78] OR Polish*[78] OR Poland*[ad] OR Polish*[ad]) OR (Portugal[78] OR Portugal[ad] OR Portuguese[ad] OR Portuguese[78]) OR (Romania*[78] OR Romania*[ad] OR Roumania*[78] OR Roumania*[ad] OR Rumania*[78] OR Rumania*[ad]) OR (Slovak*[78] OR Slovak*[ad]) OR (Slovenia*[78] OR Slovenia*[ad]) OR (Spain*[78] OR Spanish*[78] OR Spain*[ad] OR Spanish*[ad]) OR (Sweden[78] OR Sweden[ad] OR Swedish[78] OR Swedish[ad]) OR (Great Britain*[78] OR Brittish*[78] OR British*[78] OR Channel Islands*[78] OR Guerns*[78] OR England*[78] OR English*[78] OR Hebrid*[78] OR Ireland*[78] OR Irish*[78] OR Scotland*[78] OR Scotch*[78] OR Scottish*[78] OR Wales*[78] OR Welsh*[78] OR United Kingdom*[78] OR UK[78] OR Great Britain*[ad] OR Brittish*[ad] OR British*[ad] OR Channel Islands*[ad] OR Guerns*[ad] OR England*[ad] OR English*[ad] OR Hebrid*[ad] OR Ireland*[ad] OR Irish*[ad] OR Scotland*[ad] OR Scottish*[ad] OR Scotch*[ad] OR Wales*[ad] OR Welsh*[ad] OR United Kingdom*[78] OR UK[78] OR Gibraltar[78] OR Gibraltar[ad]) OR Iceland*[78] OR Iceland*[ad] OR Norway[ad] OR Norway[78] OR Norwegian*[ad] OR Norwegian*[78] or Svalbard*[78] OR Svalbard*[ad] OR Liechtenstein*[78] OR Liechtenstein*[ad] OR EEA[78] OR European Economic Area[78]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

Target risk groups

((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND ((risk*[tiab] OR target[tiab] OR vulnerab*[tiab]) AND (group*[tiab] OR people*[tiab] OR population*[tiab])) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

Diagnostic tests for LTBI

No search performed, outcomes of the full systematic review commissioned by ECDC/WHO were used

III LTBI (preventive) treatment

No search performed, outcomes of the full systematic review commissioned by ECDC/WHO were used

Programmatic issues of LTBI control

I Contact investigation

I.a/I.b Contact investigation: Yield in different settings and populations and access to TB contacts
((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR TB[tiab] OR tuberc*[tiab]) AND contact*[tiab] AND (trace*[tiab] OR tracing[tiab] OR follow-up*[tiab] OR investigat*[tiab] OR access*[tiab] OR approach*[tiab] OR reach*[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II Screening

II.a/II.c Screening: Effectiveness of screening programmes for specific risk groups and access to risk groups
((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND (screen*[tiab] OR find*[tiab]) AND ((risk*[tiab] OR target[tiab] OR vulnerab*[tiab]) AND (group*[tiab] OR people*[tiab] OR population*[tiab])) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II.d Developing a robust system for LTBI and TB case finding
((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR TB[tiab] OR tuberc*[tiab]) AND (case*[tiab] OR patient[tiab] OR patients[tiab]) AND (screen*[tiab] OR find*[tiab] OR trace*[tiab] OR tracing[tiab] OR investing*[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II.e Potential for combining LTBI screening with other health programmes
((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND ((screen*[tiab] OR find*[tiab] OR trace*[tiab] OR tracing[tiab] OR investing*[tiab])) AND (combin*[tiab] OR duel[tiab] OR together[tiab] OR simultaneous*[tiab] OR joint[tiab] OR incorporat*[tiab] OR Within[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

II.f Laws mandating screening programmes
((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR TB[tiab] OR tuberc*[tiab]) AND (screen*[tiab] OR find*[tiab] OR trace*[tiab] OR tracing[tiab] OR investing*[tiab]) AND (law[tiab] OR rule[tiab] OR mandatory[tiab] OR compuls*[tiab] OR obligator*[tiab] OR forc*[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

III Adherence to LTBI treatment

(“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND ("therapeutics"[Mesh] OR "therapy"[Subheading] OR "treatment outcome"[Mesh] OR "primary prevention"[Mesh] OR "secondary prevention"[Mesh] OR “prevention and control”[Subheading] OR treatment*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutics[tiab] OR prevent*[tiab] OR management[tiab] OR “antibiotic prophylaxis”[Mesh] OR “chemoprevention“[Mesh] OR prophyla*[tiab] OR chemoprophylaxis[tiab] OR DOT[tiab] OR DOTS[tiab] OR "isoniazid"[Mesh] OR isoniazid[tiab] OR INH[tiab] OR IPT[tiab] OR "rifapentine"[Supplementary Concept] OR rifapentine[tiab] OR RPT[tiab] OR "rifampin"[Mesh] OR rifampin[tiab] OR RIF[tiab] OR rifampicin[tiab] OR Ethambutol[tiab] OR EMB[tiab] OR Ethionamide[tiab] OR ETH[tiab] OR Pyrazinamide[tiab] OR PZA[tiab] OR Fluroquinolones[tiab] OR FLQ[tiab] OR moxifloxacin[tiab] OR levofloxacin[tiab] OR gatifloxacin[tiab]) AND ("Attitude"[Mesh] OR adher*[tiab] OR “medication adherence”[Mesh] OR “guideline adherence”[mesh] OR “patient compliance”[mesh] OR complian*[tiab] OR comply*[tiab] OR accordance[tiab] OR according[tiab] OR agreement[tiab] OR “withholding treatment”[mesh] OR Initiat*[tiab] OR Start[tiab] OR Commenc*[tiab] OR Begin*[tiab] OR Introduc*[tiab] OR enroll*[tiab] OR Complet*[tiab] OR Finaliz*[tiab] OR finalis*[tiab] OR Fulfill*[tiab] OR Ending[tiab] OR finish*[tiab] OR Terminat*[tiab] OR accomplish*[tiab] OR realiz*[tiab] OR realis*[tiab] OR attain*[tiab] OR Implement*[tiab] OR apply*[tiab] OR application*[tiab] OR “Medication therapy management”[mesh]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

IV Adverse events of LTBI treatment

No search performed, outcomes of the full systematic review commissioned by ECDC/WHO were used

V Education to reduce LTBI

((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND (educat*[tiab] OR train*[tiab]) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

VI Patient/doctor factors to increase acceptability

((“latent tuberculosis”[MeSH] OR “latent tuberculosis”[tiab] OR LTB[tiab] OR LTBI[tiab] OR ((laten*[tiab] OR dorman*[tiab]) AND (TB[tiab] OR tuberc*[tiab]))) AND ("Physician-Patient Relations"[Mesh] OR ((case*[tiab] OR patient[tiab] OR patients[tiab]) AND (doctor*[tiab] OR physician*[tiab]))) AND (comprehensive review[tiab] OR meta-analysis[pt] OR meta-analysis[tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) AND "last 5 years"[PDat]) NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))

Appendix 3. Amstar checklist

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of Amstar: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15; 7:10. PMID: 17302989.

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. NB: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a 'yes.'	☐Yes ☐No ☐Can't answer ☐Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. NB: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.	☐Yes ☐No ☐Can't answer ☐Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Keywords and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references in the studies found. NB: If at least 2 sources + one supplementary strategy used, select 'yes' (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).	☐Yes ☐No ☐Can't answer ☐Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. NB: If review indicates that there was a search for 'grey literature' or 'unpublished literature,' indicate 'yes.' SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.	☐Yes ☐No ☐Can't answer ☐Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. NB: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select 'no.'	☐Yes ☐No ☐Can't answer ☐Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. NB: Acceptable if not in table format as long as they are described as above.	☐Yes ☐No ☐Can't answer ☐Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. NB: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ('low' or 'high' is fine, as long as it is clear which studies scored 'low' and which scored 'high'; a summary score/range for all studies is not acceptable).	☐Yes ☐No ☐Can't answer ☐Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. NB: Might say something such as 'the results should be interpreted with caution due to poor quality of included studies.' Cannot score 'yes' for this question if scored 'no' for question 7.	☐Yes ☐No ☐Can't answer ☐Not applicable

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). NB: Indicate 'yes' if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.	☐Yes ☐No ☐Can't answer ☐Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). NB: If no test values or funnel plot included, score 'no'. Score 'yes' if mentions that publication bias could not be assessed because there were fewer than 10 included studies.	☐Yes ☐No ☐Can't answer ☐Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. NB: To get a 'yes,' must indicate source of funding or support for the systematic review AND for each of the included studies.	☐Yes ☐No ☐Can't answer ☐Not applicable

Additional notes made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.
http://amstar.ca/Amstar_Checklist.php

Appendix 4. AGREE tool

Instructions for using AGREE II

I. Preparing to use AGREE II

i) Accompanying guideline documents

Before applying the AGREE II, users should first carefully read the guideline document in full. In addition to the guideline document, users should attempt to identify all information about the guideline development process prior to the appraisal. This information may be contained in the same document as the guideline recommendations or it may be summarised in a separate technical report, methodological manual or guideline developer policy statement. These supporting documents may be published or may be available publicly on websites. While it is the responsibility of the guideline authors to advise readers on the existence and location of relevant additional technical and supporting documents, every effort should be made by the AGREE II users to locate and include them as part of the materials appropriate for assessment.

ii) Number of Appraisers

We recommend that each guideline is assessed by at least 2 appraisers and preferably 4 as this will increase the reliability of the assessment. Reliability tests of the instrument are on-going.

II. Structure and content of AGREE II

The AGREE II consists of 23 key items organised within 6 domains followed by 2 global rating items ('Overall Assessment'). Each domain captures a unique dimension of guideline quality.

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3).

Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6).

Domain 3. Rigour of Development relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations, and to update them (items 7-14).

Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline (items 15-17).

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18-21).

Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).

Overall assessment includes the rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice.

III. Rating Scale and User's Manual Sections

Each of the AGREE II items and the two global rating items are rated on a 7-point scale (1 – strongly disagree to 7 – strongly agree). The User's Manual provides guidance on how to rate each item using the rating scale and also includes 3 additional sections to further facilitate the user's assessment. The sections include User's Manual Description, Where to Look, and How to Rate.

i) Rating scale

All AGREE II items are rated on the following 7-point scale:

1 Strongly disagree	2	3	4	5	6	7 Strongly agree

Score of 1 (*Strongly disagree*). A score of 1 should be given when there is no information that is relevant to the AGREE II item or if the concept is very poorly reported.

Score of 7 (*Strongly agree*). A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User's Manual have been met.

Scores between 2 and 6. A score between 2 and 6 is assigned when the reporting of the AGREE II item does not meet the full criteria or considerations. A score is assigned depending on the completeness and quality of reporting. Scores increase as more criteria are met and considerations addressed. The 'How to Rate' section for each item includes details about assessment criteria and considerations specific to the item.

ii) User's manual description

This section defines the concept underlying the item in broad terms and provides examples.

iii) Where to look

This section directs the appraiser to where the information in the guideline can usually be found. Included in this section are common terms used to label guideline sections or chapters. These are suggestions only. It is the responsibility of the appraiser to review the entire guideline and accompanying material(s) to ensure a fair evaluation.

iv) How to rate

This section includes details about assessment criteria and considerations specific to each item.

- The *criteria* identify explicit elements that reflect the operational definition of the item. The more criteria that are met, the higher the score the guideline should receive on that item.
- The *considerations* are aimed to help inform the assessment. As in any evaluation, judgments by the appraisers are required. The more the considerations have been taken into account in the guideline, the higher the score the guideline should receive on that item.

It is important to note that guideline ratings require a level of judgment. The criteria and considerations are there to guide, not to replace, these judgments. Thus, none of the AGREE II items provide explicit expectations for each of the 7 points on the scale.

v) Other considerations when applying AGREE II

On occasion, some AGREE II items may not be applicable to the particular guideline under review. For example, guidelines narrow in scope may not provide the full range of options for the management of the condition (see item 16). AGREE II does not include a '*Not Applicable*' response item in its scale. There are different strategies to manage this situation including having appraisers skip that item in the assessment process or rating the item as 1 (absence of information) and providing context about the score. *Regardless of strategy chosen, decisions should be made in advance, described in an explicit manner, and if items are skipped, appropriate modifications to calculating the domain scores should be implemented. As a principle, excluding items in the appraisal process is discouraged.*

Upon completing the 23 items, AGREE II users will provide 2 overall assessments of the guideline. The overall assessment requires the user to make a judgment as to the quality of the guideline, taking into account the criteria considered in the assessment process. The user is also asked whether he/she would recommend use of the guideline

23 items of the AGREE II

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Appendix 5. Members of the ad hoc scientific panel

Name	Organisation	Country
Gerard de Vries (chair)	KNCV Tuberculosis Foundation	Netherlands
Dominik Zenner (chair)	Public Health England	United Kingdom
Judith Bruchfeld	Karolinska University Hospital	Sweden
Josie Garrett*	Patient representative	United Kingdom
Walter Haas*	Robert Koch Institute	Germany
Einar Heldal	Norwegian Institute of Public Health	Norway
Rein Houben	London School of Hygiene and Tropical Medicine	United Kingdom
Philip LoBue*	US Centers for Disease Control and Prevention	United States
Mike Mandelbaum	NGO representative (TB Alert)	United Kingdom
Alberto Matteelli	University of Brescia	Italy
Giovanni Battista Migliori	Istituti Clinici Scientifici Maugeri, IRCCS	Italy
Ivan Solovic	National Institute for TB, Lung Disease and Thoracic Surgery	Slovakia
Martina Vašáková	Chief of physicians at Thomayer Hospital	Czech Republic

** Participants not able to attend the meeting. Their contribution to the guidance was limited to input beforehand and reviewing the guidance.*

Observers of the ad hoc scientific panel to join the meeting

Name	Organisation	Country
Andrei Dadu	WHO	Denmark
Senia Rosales-Klintz	Karolinska Institutet	Sweden

Appendix 6. Summary tables – risk groups

Table A6.1. Summary of groups at possible increased risk of acquiring (latent) tuberculosis infection after exposure to tuberculosis cases – (risk of) tuberculosis infection (based on systematic reviews)

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic reviews											
Govindasamy, 2014 [96] Low & high (a)	2003-2014	n = 71	Low-, intermediate- and high-TB-burden countries	TB contacts	Not reported	Pooled estimate risk ratio in low-, intermediate-, high-TB-burden countries per type of test Pooled prevalence of LTBI in low-, intermediate-, high-TB-burden countries per type of test	Risk ratio (pooled) Prevalence of LTBI (pooled)	See Tables A6.2a-c below See Tables A6.3a-c	*Bias of the studies (no more information provided)* Low to high	Negative on 1, 3, 4, 5, 10, 11	Weak evidence
		n = 63		healthcare workers and students							
		n = 34		PLHIV							
		n = 31		Patients with renal or liver conditions							
		n = 23		Immigrants and refugees							
		n = 20		Candidates for anti-TNF-alpha therapy							
		n = 20		Patients with AIDs or IMIDs							
		n = 9		Drug users							
		n = 9		Prisoners							
		n = 6		Homeless people							
		n = 5		Transplant candidates or recipients							
		n = 3		Elderly							
		n = 2		Miners							
		n = 2		Patients with cancer							
		n = 1 (designs not reported (k))		Patients with diabetes							
Girardi, 2014 [92] Low & high (b)	1981-2013	n = 7 on PLHIV n = 6 on contacts n = 8 on migrants n = 3 on elderly n = 5 on healthcare workers n = 3 on children (Mathematical modelling studies reported to be based on published literature (n = 19), based on observational studies (n = 6), based on clinical trial (n = 1). One economic evaluation based on observational studies) (l)	Not reported	PLHIV	Not reported	LTBI prevalence	Min-max %	6.9 %-97.2 %	*Drummond checklist* [130] Low to medium	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence
				Contacts				25.0 %-59.5 %			
				Migrants				0.3 %-50.0 %			
				Elderly				25.0 %-36.0 %			
				Healthcare worker				10.0 %-17.0 %			
				Children				14.8 %-15.0 %			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews											
Patra, 2015 [88] Low & high (c)	2005-2014	n = 6 (all cross-sectional studies)	Various settings (hospital, population-based, community-based, nationally representative sample)	Children exposed to second-hand smoking	5 534	Relative risk of LTBI	RR (95 % CI)	1.64 (1.00-2.83)	*NOS* Good quality: n = 3 — Poor to moderate quality: n = 3	Negative on 1, 2, 4, 5, 11	Weak evidence
				Adults exposed to second-hand smoking	3 857			1.58 (1.03-2.43)			
Campbell, 2015a [87] Country not reported	1999-2013	n = 8 (design not reported)	Not reported	Immigrants to low-incidence countries, tested with TST (exposure not established)	3 028	Positive test result	% (n)	40.7 % (1 232)	SIGN — High quality	Negative on 2, 5, 6, 10, 11	Weak evidence
						Likelihood of a positive TST in ≥ 35 years of age vs < 35 years of age	OR (95 % CI)	1.59 (1.32-1.92)			
						Likelihood of a positive TST in males vs females		1.38 (1.20-1.58)			
						Likelihood of a positive TST in immigrants from countries with ≥ 30 cases per 100 000 vs from countries with < 30 cases per 100 000		2.38 (1.14-4.98)			
						Likelihood of a positive TST in BCG vaccinated immigrants vs BCG unvaccinated immigrants		2.10 (1.54-2.88)			
				Immigrants to low-incidence countries, tested with IGRA (exposure not established)	3 028	Positive test result	% (n)	32.2 % (974)			
						Likelihood of a positive IGRA in males vs females	OR (95 % CI)	1.34 (1.08-1.66)			
						Likelihood of a positive IGRA in immigrants from countries with ≥ 30 cases per 100 000 vs from countries with < 30 cases per 100 000		17.25 (1.03-289.34) (m)			
Schepisi, 2015 [90] Low (d) Main objectives of this review were not similar to our review question	1974-2013	n = 28 articles in quantitative analysis (all observational outbreak studies)	Healthcare settings	Adults	Not reported	Percentage of cases who acquired TB infection after exposure to index healthcare worker	% (95 % CI)	4.32 % (1.43-8.67)	*NOS checklist* Median score 4 (max score 9)	Negative on 1, 2, 5, 6, 7, 8, 10, 11	Weak evidence
				Healthcare workers	Not reported			2.62 % (1.05-4.88)			
				Children	Not reported			0.90 % (0.40-1.60)			
				Infants	Not reported			0.57 % (0.00-2.02)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Campbell, 2015b [91] Low & high (e)	1986-2014	Total included: n = 51 n = 34 on TST n = 9 on IGRA n = 8 on both IGRA and TST) (designs not reported)	Not reported	Immigrants tested with TST (exposure not established) — All ages — Aged < 18 yrs — Aged ≥ 18 yrs	— 29 818 — 6 784 — 3 307	Positive TST test results among those tested (n)	% (12) p-value < 18 years vs ≥ 18 years	— 41.6 % — 24.0 % — 44.7 %; p < 0.0001	*SIGN* — High quality: n = 25 — Acceptable quality: n = 14	Negative on 2, 4, 5, 8, 10, 11	Weak evidence
				Immigrants tested with IGRA (exposure not established) — All ages — Aged < 18 yrs — Aged ≥ 18 yrs	— 6 602 — 331 — 4 914	Positive IGRA test results among those tested		— 23.8 % — 13.9 % — 26.1 % p < 0.0001				
Vinkeles Melchers, 2013 [93] Low & high (f) Main objectives of this review were not similar to our review question	1993-2011	n = 52 (75 % cross-sectional design, 23.1 % cohort design, 5 conference abstracts)	Prison facilities	Prisoners in: American region	437 prison facilities and 437 430 prisoners	LTBI (%) by WHO region and income area according to the World Bank classification	Median (IQR) High Middle/low income	12.8 (1.6-26.9) 56.6 (53.6-59.7)	*Downs & Black checklist* — Quality average: 50·0 % — Quality high: 35·4 % *External validity:* — Average & high: 87·5 % *Internal validity:* — Average & high: 86·5 %	Negative on 1, 2, 4, 5, 7, 8, 10, 11	Weak evidence
				European region				36.5 (10.1-55.9) —			
				Eastern Mediterranean region				.2 (o) 24.1 (3.1-45.2)			
				Western Pacific region				9.5 (1.2-22.1)			
				African region				.5 (o)			
				South-east Asian region							
				Overall				17.9 (3.0-33.6)			
Fox, 2013 [66] Country not reported (g)	1935-2012	n = 203 studies included 168 studies reporting LTBI status (n = 15 cross-sectional studies, 2 case control studies, 185 cohort studies, 1 RCT (designs not specified on outcome))	Low-middle-income and high-income setting	TB contacts in low/middle-income setting	60 557	Proportion LTBI in screened contacts	% (95 % CI)	51.5 % (47.1-55.8 %)	Not reported	Negative on 1, 5, 7, 8, 11	Weak evidence
				in high-income setting	284 505			28.1 % (24.2-32.4 %) (p)			
				born locally	7 576			17.0 % (11.8-24.0)			
				born overseas	4 298			39.2 % (30.0-49.3)			
						LTBI in contacts born overseas vs born locally	OR (95 % CI); p-value	3.39 (3.10-3.71); p < 0.0001			
Triasih, 2012 [94] High (h)	1961-2009	n = 11 (all observational outbreak studies)	Household settings	Child contacts 5-15 yrs	3 321	Prevalence of TB infection after exposure to index case	Range	35.7 %-76.9 %	Not reported	Negative on 1, 2, 3, 5, 7, 8, 9, 10, 11	Weak evidence
				Child contacts < 15 yrs				24.4 %-69.9 %			
				Child contacts < 5 yrs				5.5 %-51.2 %			
Shah, 2014 [95] Low & high (i)	1970-2010	n = 25 n = 9 studies with only MDR-TB source cases n = 3 studies with mono- or poly-resistant TB source cases n = 5 studies in high-burden settings	Low and high-burden TB settings	Individuals living with drug-susceptible TB patients	Median of 111 household contacts (active and LTBI)	Overall pooled yield of LTBI	% (95 % CI)	47.2 % (30.0-61.4)	Not reported	Negative on 1, 2, 3, 4, 5, 6, 7, 8, 10, 11	Weak evidence
						Yield of LTBI in contacts of MDR-TB source cases		50.7 % (41.5-59.9)			
						Yield of LTBI in contacts of mono- or poly-resistant TB source cases		41.5 % (8.19-74.8)			

(12) Calculated by researchers performing this review of systematic reviews.

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
		n = 9 studies in low-burden settings n = 5 studies on both children and adults (design not reported)				Yield of LTBI among contacts in high and low-burden TB settings		High: 52.5 % (33.8-71.2) Low: 44.1 % (24.9-63.4)			
						Yield of LTBI in paediatric contacts and adults contacts		Peadiatric:7.3 % (3.9-50.6) Adult: 51.9 % (25.6-78.2)			
Freeman, 2010 [97] Low & high (*i*)	1995-2007	n = 9 (7 studies on military travellers; 2 studies among civilian travellers) (1 prospective study, 8 retrospective surveillance studies)	Travellers	Long-term travellers from low-prevalence countries	2 259 527 military travellers 44 726 civilian travellers	Overall cumulative incidence of LTBI, as measured by TST conversion	% (99 % CI)	2.0 % (1.6-2.4)	Quality scoring was based on criteria adapted from Seidler [131]. As only 1 study had sufficient information to calculate a quality score, analysis of study quality was done by comparing this study with the others based on surveillance data	Negative on 1, 5, 6, 7, 8, 10, 11	Weak evidence
						Overall cumulative incidence risk estimate for military studies		2.0 % (1.6-2.4)			
						Overall cumulative incidence risk estimate for civilian studies		2.3 % (2.1-2.5)			
						Estimates of overall cumulative incidence	Range	0.96 % to 3.59 %.			

(a) Low TB burden: n = 207 (majority from Italy (n = 34) and Spain (n = 29)). Intermediate TB burden: n = 35 (majority from Brazil (n = 13) and China (n = 7). High TB burden: n = 57 (majority from South Korea (n = 12) followed by India (n = 10).
(b) United States: n = 9. Canada: n = 5. United Kingdom: n = 3. India: n = 2. Australia, France, Italy, Kenya, South Africa, Uganda, Zambia: n = 1. For three articles, the countries could not be identified (all on the elderly).
(c) South Africa: n = 2. India, Mexico, Turkey, United States: n = 1.
(d) United States: n = 66 incidents. France: n = 34 incidents. Netherlands: n = 6 incidents. United Kingdom: n = 5 incidents. Canada: n = 2 incidents. Australia, Ireland, Italy, Japan: n = 1 incident. NB: Two articles did not present data on LTBI, but these cannot be removed from this list.
(e) Campbell et al. included participants originating from a wide variety of countries across Africa, Asia, the Americas and Europe (n = 49). Not reported: n = 2.
(f) American region: 34.6 %. European region: 17.3 %. African region: 15.4 %. Eastern Mediterranean region: 13.5 %. Western Pacific region: 11.5 %. South-east Asian region: 7.7 %.
(g) Fox et al. reported the outcomes per low–middle-income countries (n = 95) and high-income countries (n = 108).
(h) India: n = 4 studies. Thailand: n = 2. Cambodia, Indonesia, Laos, Pakistan, Philippines: n = 1.
(i) United States: n = 4. South Africa: n = 2. Brazil, Micronesia, Philippines, Spain, Switzerland, Taiwan, United Kingdom, US Virgin Islands: n = 1.
(j) Travel region: Worldwide: n = 3. Bosnia and Herzegovina/SW Asia, South West Asia: n = 2. Bosnia and Herzegovina, Haiti: n = 1.
(k) Only cross-sectional study designs or cohort designs were included.
(l) Some articles comprised multiple population groups.
(m) A meta-analysis could not be performed. Results are from a stand-alone study.
(n) Only two articles excluded those with active TB from their study.
(o) Data available from one study.
(p) The prevalence of LTBI among contacts is significantly less in high-income countries than in low–middle-income countries, $p < 0.05$.

Table A6.2a. Pooled estimates of risk ratios of latent tuberculosis infection in risk groups compared to general population, low-tuberculosis-burden countries (TB incidence rate: < 40 cases per 100 000) (Govindasamy, 2014)

Risk group	TST			IGRA		
	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1
TB contacts (n = 71)	37	2.25 (0.15-11.7)	6	31	1.58 (0.06-8.33)	8
Healthcare workers and students (n = 63)	33	1.88 (0.12-8.25)	8	24	0.59 (0.03-8.83)	15
PLHIV (n = 34)	15	0.99 (0.43-3.09)	8	20	0.89 (0.31-3.09)	11
Patients with renal or liver conditions (n = 31)	21	1.43 (0.40-3.68)	6	12	2.21 (0.40-5.14)	1
Immigrants and refugees (n = 23)	17	3.27 (1.00-8.31)	1	13	2.26 (0.79-8.08)	1
Candidates for anti-TNF therapy (n = 20)	16	1.84 (0.38-5.94)	3	14	2.40 (1.56-3.30)	0
Patients with AIDs or IMIDs (n = 20)	13	1.62 (0.07-4.42)	3	14	0.95 (0.04-3.33)	7
Drug users (n = 9)	3	0.91 (0.04-3.44)	1	5	3.24 (0.02-5.00)	1
Prisoners (n = 9)	5	2.33 (2.40-3.57)	0	1	5.83	NA
Homeless people (n = 6)	3	2.43 (1.15-3.81)	0	3	2.40 (1.56-3.30)	0
Transplant candidates or recipients (n = 5)	2	0.58	2	2	1.37	0
Elderly (n = 3)	2	3.54	0	1	1.17	NA
Miners (n = 2)	-	-	-	1	4.2	NA
Patients with cancer (n = 2)	1	0.91	NA	2	1.59	0

** = Number of studies pooled. ~ = Number of studies with RR < 1.*

Table A6.2b. Pooled estimates of risk ratios of latent tuberculosis infection in risk groups compared to general population, intermediate-tuberculosis-burden countries (TB incidence rate: 40-100 cases per 100 000) (Govindasamy, 2014)

Risk group	TST			IGRA		
	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1
TB contacts (n = 71)	4	2.09 (1.29-2.44)	0	3	0.97 (0.54-1.80)	2
Healthcare workers and students (n = 63)	10	1.13 (0.28-2.06)	3	4	0.79 (0.32-2.15)	3
PLHIV (n = 34)	3	0.86 (0.77-1.17)	2	2	1.54	0
Patients with renal or liver conditions (n = 31)	4	1.02 (0.63-2.71)	2	2	1.19	1
Immigrants and refugees (n = 23)	-	-	-	13	1.6	NA
Candidates for anti-TNF therapy (n = 20)	2	0.54	2	-	-	-
Patients with AIDs or IMIDs (n = 20)	1	0.84	NA	1	0.52	NA
Drug users (n = 9)	2	2.47	0	1	1.60	
Prisoners (n = 9)	3	2.77 (2.58-2.92)	0	-	-	-
Homeless people (n = 6)	-	-	-	-	-	-
Transplant candidates or recipients (n = 5)	1	0.23	NA	-	-	-
Elderly (n = 3)	1	1.25	NA	-	-	-

** = Number of studies pooled. ~ = Number of studies with RR < 1.*

Table A6.2c. Pooled estimates of risk ratios of latent tuberculosis infection in risk groups compared to general population, high-tuberculosis-burden countries (TB incidence rate: > 100 cases per 100 000) (Govindasamy, 2014)

Risk group	TST			IGRA		
	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1	n*	Pooled estimate risk ratio (range)	n~ with RR ≤ 1
TB contacts (n = 71)	20	1.07 (0.43-2.2)	8	11	1.06 (0.40-2.59)	4
Healthcare workers and students (n = 63)	11	1.14 (0.42-1.68)	11	7	0.75 (0.15-1.32)	3
PLHIV (n = 34)	8	0.76 (0.24-2.08)	4	3	0.94 (0.48-1.68)	1
Patients with renal or liver conditions (n = 31)	5	0.74 (0.24-3.32)	4	3	1.23 (0.49-3.16)	1
Immigrants and refugees (n = 23)	1	2.27	NA	-	-	-
Candidates for anti-TNF therapy (n = 20)	-	-	-	1	2.11	NA
Patients with AIDs or IMIDs (n = 20)	3	1.24 (0.90-2.15)	2	2	0.78	1
Drug users (n = 9)	-	-	-	-	-	-
Prisoners (n = 9)	1	0.29	NA	-	-	-
Homeless people (n = 6)	1	2.34	NA	1	2.11	NA
Transplant candidates or recipients (n = 5)	2	0.14	2	2	0.71	1
Elderly (n = 3)	-	-	-	-	-	-
Miners (n = 2)	1	1.75	NA	-	-	-
Patients with cancer (n = 2)	-	-	-	-	-	-
Patients with diabetes	1	0.79	NA	-	-	-

** = Number of studies pooled. ~ = Number of studies with RR < 1*

Table A6.3a. Pooled prevalence of latent tuberculosis infection across risk groups, low-tuberculosis-burden countries (TB incidence rate: < 40 cases per 100 000) (Govindasamy, 2014)

Risk group	TST (≥ 5 mm)		TST (≥ 10 mm)		IGRA	
	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)
TB contacts	25	39 (29-50)	8	32 (16-48)	30	27 (22-31)
Healthcare workers and students	3	46 (7-85)	25	39 (29-48)	24	13 (10-16)
PLHIV	14	16 (11-21)	0	-	20	12 (10-15)
Patients with renal or liver conditions	4	22 (5-39)	17	21 (15-27)	12	33 (24-43)
Immigrants and refugees	3	34 (13-55)	12	36 (30-43)	13	27 (20-34)
Candidates for anti-TNF-alpha therapy	12	28 (15-42)	1	22	14	13 (9-18)
Patients with AIDs or IMIDs	9	34 (20-48)	1	2.2	13	15 (11-20)
Drug users	2	18 (11-26)	0	-	4	49 (34-64)
Prisoners	2	24 (8-40)	3	39 (23-56)	1	53.8
Homeless people	0	-	1	45.6	3	40 (19-62)
Transplant candidates or recipients	1	4.5	1	15.9	2	21 (17-25)
Elderly	1	31.7	1	59.4	1	16.3
Miners	0	-	0	-	1	16.3
Patients with cancer	0	-	1	10.5	2	20 (14-27)
Patients with diabetes	0	-	0	-	0	-

** Number of studies pooled*
The following article was suggested by the members of the ad hoc scientific panel as highly relevant for consideration in the guidance development process:
Choudhury IW, West CR, Ormerod LP. The outcome of a cohort of tuberculin-positive predominantly South Asian new entrants aged 16-34 to the UK: Blackburn 1989-2001. J Public Health (Oxf). 2014 Sep;36(3):390-5.
Results. After 10 and 15 years of follow-up 13.5 % and 16.3 % of individuals, respectively, had progressed on to active disease. The results presented in the article of Choudhury et al. are higher than the percentages of progression to active disease presented in included reviews on migrants (Campbell et al., 2015 and Girardi et al.).

Table A6.3b. Pooled prevalence of latent tuberculosis infection across risk groups, intermediate-tuberculosis-burden countries (TB incidence rate: 40-100 cases per 100 000) (Govindasamy, 2014)

Risk group	TST (≥ 5 mm)		TST (≥ 10 mm)		IGRA	
	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)
TB contacts	0	-	2	52 (43-62)	3	32 (19-46)
Healthcare workers and students	2	63 (44-82)	8	33 (16-51)	4	35 (0.1-70)
PLHIV	3	25 (16-35)	0	-	2	55 (30-80)
Patients with renal or liver conditions	0	-	3	28 (21-35)	2	42 (28-57)
Immigrants and refugees	0	-	0	-	0	-
Candidates for anti-TNF-alpha therapy	2	13 (10-17)	0	-	0	-
Patients with AIDs or IMIDs	1	30.2	0	-	1	18.6
Drug users	0	-	0	-	1	57.5
Prisoners	2	69 (61-77)	0	-	0	-
Homeless people	0	-	0	-	0	-
Transplant candidates or recipients	0	-	1	8.1	0	-
Elderly	0	-	1	46.3	0	-
Miners	0	-	0	-	0	-
Patients with cancer	0	-	0	-	0	-
Patients with diabetes	0	-	0	-	0	-

** Number of studies pooled*

Table A6.3c. Pooled prevalence of LTBI across risk groups, high-tuberculosis-burden countries (TB incidence rate: > 100 cases per 100 000) (Govindasamy, 2014)

Risk group	TST (≥ 5 mm)		TST (≥ 10 mm)		IGRA	
	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)
TB contacts	4	62 (45-79)	15	41 (36-46)	11	21 (15-26)
Healthcare workers and students	0	-	9	43 (35-51)	7	34 (15-52)
PLHIV	8	33 (22-44)	0	-	3	40 (20-60)
Patients with renal or liver conditions	0	-	5	30 (12-48)	3	38 (15-61)
Immigrants and refugees	0	-	1	81.5	0	-
Candidates for anti-TNF-alpha therapy	0	-	0	-	0	-
Patients with AIDs or IMIDs	2	63 (3-100)	1	34.6	2	28 (21-36)
Drug users	0	-	0	-	0	-

Risk group	TST (≥ 5 mm)		TST (≥ 10 mm)		IGRA	
	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)	n*	Pooled estimate % (95 % CI)
Prisoners	0	-	0	-	0	-
Homeless people	0	-	1	79.8	1	75.9
Transplant candidates or recipients	1	16	1	1.5	2	27 (6-49)
Elderly	0	-	0	-	0	-
Miners	0	-	0	-	0	-
Patients with cancer	0	-	0	-	0	-
Patients with diabetes	0	-	1	29.8	0	-

** Number of studies pooled*

Table A6.4. Individuals at risk of developing active tuberculosis after exposure or infection in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic reviews											
Sotgiu, 2014 [98] Low & high [a]	2004-2013	n = 2 on childhood contacts n = 1 on adult contact n = 8 on PLHIV n = 1 on anti-TNF-alpha treatment n = 3 on chronic renal failure/dialysis patients n = 1 on silicosis n = 1 on diabetes n = 4 on migrants/refugees n = 2 on homeless people n = 2 on prisoners (including 1 SR) n = 2 on healthcare workers[l] n = 1 on alcohol abusers [k] n = 1 on tobacco smokers [k] (mostly observational studies and 3 SRs)	School, supermarket, municipal health services, hospitals, national shelters, other	Childhood contacts	548	Pooled relative risk of active TB of LTBI-positive population vs the general population (LTBI status unknown)	RR (95 % CI)	425.4 (208.14-869.4)	*GRADE* — Very low: child and adult contact, anti-TNF-alpha, renal failure, silicosis, prisoners, homeless people — Low: diabetes, migrants, PLHIV — Not reported for healthcare worker	Negative on 2, 3, 4, 5, 9, 10, 11	Weak evidence
				Adult contacts	21 326			8.0 (4.8-13.4)			
				PLHIV	53 780			183.0 (41.7-803.4)			
				Autoimmune diseases patients receiving TNF-alpha inhibitors	346 000			16.2 (14.6-18.0)			
				Patients with terminal renal failure/dialysis	3 436			703.2 (38.1-12 984.5)			
				Patients with silicosis	435			170.3 (137.9-210.2)			
				Patients with diabetes	1 158			10.3 (5.9-17.6)			
				Migrants/refugees from high to low-burden countries	3 656 413			90.7 (22.8-361.5)			
				Persons residing in homeless shelters	154 861			7.3 (0.5-103.7)			
				Prisoners	1 508			15.3 (7.6-30.5)			
					Not reported	Annual incidence rate ratio	IRR (IQR)	23 (11.7-36.1)			
				Healthcare workers	Not reported	Annual risk of TB disease (based on SR)		69-5 780/100 000 population			
						Pooled relative risk of TB vs the general population	RR (95 % CI)	2.97 (2.43-3.51)			
				Alcohol abusers	Not reported	Pooled relative risk of active TB vs the general population	RR (95 % CI)	2.94 (1.89-4.59)			
				Tobacco smoker	Not reported	Odds ratio	OR (95 % CI)	2.70 (1.37-5.29)			
Govindasamy, 2014 [89] Low [b]	1970-2009	PLHIV: n = 2 studies ([l]) Immunocompromised: n = 1 Infected contacts: n = 2 Underweight: n = 2 Recent skin converters: n = 1 (n = 2 longitudinal study design; 1 observational study design, 3 observational study and 1 SR (results of the placebo-arm of 1 RCT used ([m])))	Not reported	PLHIV with PPD+	Not reported	Incidence rate ratio of active TB vs HIV-negatives	IRR (95 % CI)	10.46 (1.34-471.2)	*GRADE* — Low: TST+ contacts, skin converters — Very low: PLHIV, immunocompromised, close contacts, underweight	Negative on 1, 3, 4, 5, 6, 10, 11	Weak evidence
				PLHIV with TST+				9.42 (2.90-27.11)			
				ESRD patients under dialysis with TST reactions of 0-4 mm	Not reported	Relative risk of progression to TB disease in ESRD patients under dialysis vs matched controls from the general population	Adjusted RR/100 pyr (95 % CI)	24.5/100 pyr (22.5-26.5)			
				ESRD under dialysis TST reactions of 5-9 mm	27			8.4/100 pyr (3.1-13.6)			
				ESRD under dialysis TST reactions of > 9 mm	62			41.4/100 pyr (37.9-44.8)			
				Adult close contacts of contagious TB cases with: TST reactions of 5-9 mm	185	Rate ratio of active TB vs casual contacts	RR (95 % CI)	10.6 (1.18-94.8)			
				TST reactions of 10-14 mm	335			5.2 (2.2-12.3)			
				TST reactions of > 15 mm	405			9.7 (5.1-18.3)			
				TST+ contacts with CXR abnormalities	Not reported	Relative risk of active TB vs TST+ contacts without CXR abnormalities		5.2 (2.3-11.8)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
				TST converters	837	Rate ratio of active TB vs TST+ at baseline		1.7 (1.07-2.64)			
				Skin converters in the first 3 yrs	1 472	Rate ratio of active TB vs same groups in the following 4-10 yrs		3.0 (1.4-6.4)			
				Underweight TST+ recruits	Not reported	Relative risk of active TB vs normal weight		3.4 (95 % CI could not be calculated)			
Girardi, 2014 [92] Low (c)	1981-2013	n = 8 on migrants n = 6 on contacts n = 7 on PLHIV n = 5 on healthcare workers n = 3 on children n = 3 on elderly (Mathematical modelling studies reported to be based on published literature (n = 19), based on observational studies (n = 6), or based on clinical trial (n = 1). One economic evaluation based on observational studies) (n)	Multiple settings	Children	Not reported	Annual LTBI reactivation rate	Min-max %	0.08 %-5.00 %	*Drummond checklist [130]* Low-medium	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence
				Contacts				0.10 %-12.60 %			
				Elderly				0.22 %-3.59 %			
				Healthcare workers				0.40 %-1.20 %			
				Migrants				0.08 %-13.35 %			
				PLHIV				1.4 %-7.0 %			
Non-commissioned systematic reviews											
Campbell, 2016 [100] Countries not reported	2002-2014	n = 5, of which n = 4 were also just to calculate PPV (all prospective studies)	Not reported	Dialysis patients with TST ≥ 10 mm	540.6 pyr	Crude estimate of likely TB reactivation rate	Cases/1 000 pyr	35.15/1 000 pyr	*SIGN* High quality: n = 6 Acceptable quality: n = 1	Negative on 5, 8, 11	Weak evidence
						Positive predictive value	% (range)	11.93 % (4.60 %-29.39 %)			
						Incidence rate ratio of active TB development	IRR (95 % CI)	2.59 (1.20-5.57)			
Campbell, 2015b [91] Low & high (d)	1997-2010	n = 3 studies (follow-up studies)	Not reported	Immigrants with positive TST (two studies)	591	Number of cases who developed active TB	Active TB cases in follow-up	13 (reactivation rate: 2.20 ([13]))	*SIGN* — High quality: n = 1 — Acceptable quality: n = 2	Negative on 2, 4, 5, 8, 10, 11	Weak evidence
				Immigrants with positive IGRA (one study)	238			8 (reactivation rate: 3.36 ([13]))			
Schepisi, 2015 [90] Low (e) Main objectives of this review were not similar to our review question	1974-2013	n = 28 articles in quantitative analysis (all observational outbreak studies)	Healthcare settings	Children	3 167	Percentage active TB after exposure to index healthcare worker (meta-analysis)	% (95 % CI)	0.38 (0.01-1.60)	*NOS checklist* Median score 4, over a maximum score of 9	Negative on 1, 2, 5, 6, 7, 8, 10, 11	Weak evidence
				Infants	6 080			0.11 (0.04-0.21)			
				Adults	3 660			0.09 (0.02-0.2)			
				Healthcare workers	2 411			0.00 (0.00-0.38)			
Diel, 2012 [99] Low & intermediate & high (f) Main objectives of this review were not similar to our review question	2002-2011	*IGRA* All studies/populations: n = 17 TB high-risk populations: n = 13 PLHIV: n = 4 Contacts: n = 4 *TST* All studies/populations: n = 16 TB high risk population: n = 13 (design not reported)	Various settings	All studies on IGRA	Not reported	Pooled PPV of commercial IGRAs for progression to active TB	% (95 % CI); n progression; [111]	2.7 % (2.3-3.2); (0 %-17.2 %)	*Quadas* — All studies met 12 of the 14 indicators. 46 % scored 100 %	Negative on 1, 4, 5, 8, 10, 11	Weak evidence
				IGRA: All TB high-risk populations	Not reported			6.8 % (5.6-8.3)			
				IGRA: PLHIV	182			6.0 % (3.1-10.6); 11			
				IGRA: Untreated healthy contact persons	648			8.5 % (6.5-10.9); 55			
				All studies/populations on TST	Not reported	Pooled PPV of TSTs for progression to active TB		1.5 % (1.2-1.7)			
				TST: TB high-risk populations	Not reported			2.4 % (1.9-2.9); (0 %-6.6 %)			
Kotila, 2016 [101] Country not reported Main objectives of this review were not similar to our review question	1993-2012	n = 21 (design not reported)	Aircraft	Aircraft contacts (crew and travellers)	279 flights n = 1 287 all passengers and crew in contact investigation strategy for whom a test result was available	% possibly infected during the flight (positives with no other risk factors for test positivity)	% (n)	0.8 % (10)	The quality of all the evidence varied from low to very low (not further specified)	Negative on 1, 2, 4, 5, 7, 8, 9, 10, 11	Weak evidence
						% TST conversion		0.5 % (7)			
					n = 905 aircraft contacts with test results for incidents where only five rows	% possibly infected during the flight (positives with no other risk factors for test positivity)		1.3 % (12)			

([13]) Calculated by researchers performing this review of systematic reviews.

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
					surrounding the index case were traced	% TST conversion		0.1 % (1)			
Triasih, 2012 [94] High (g)	1961-2009	n = 11 (all observational outbreak studies)	Household settings	Child contacts < 15 yrs	3 321	Prevalence of active TB after exposure to index case	%, range	3.3-5.5	Not reported	Negative on 1, 2, 3, 5, 7, 8, 9, 10, 11	Weak evidence
				Child contacts 5-15 yrs				3			
				Child contacts < 5 yrs				3.2-16.4			
Shah, 2014 [95] Low & high (h)	1970-2011	n = 25 n = 16 studies with only MDR-TB source cases, n = 7 studies with only mono- or poly-resistant TB source cases n = 12 studies from high-burden TB settings n = 13 studies from low-burden settings n = 11 studies on both children and adults n = 17 reported DST results of secondary cases (design not reported)	Low and high-burden TB settings	Individuals living with drug-susceptible TB patients	Median of 111 household contacts (active and LTBI combined)	Pooled yield of TB	% (95 % CI)	7.8 % (5.6-10.0)	Not reported	Negative on 1, 2, 3, 4, 5, 6, 7, 8, 10, 11	Weak evidence
						Overall		6.5 % (4.6-8.4)			
						Contacts of MDR-TB source cases		11.6 % (2.7-20.4)			
						Contacts of mono- or poly-resistant TB source cases		High: 8.7 % (6.08-11.2) Low: 6.3 % (2.4-10.1)			
						Contacts in high and low-burden TB settings		Paed: 4.0 % (1.5-6.5) Adult: 4.9 % (2.7-7.0)			
						Paediatric contacts and adults contacts					
Fox, 2013 [66] Country not reported (i)	1935-2012	n = 203 studies included 158 studies reporting data on TB disease status (n = 15 cross-sectional studies, 2 case control studies, 185 cohort studies, 1 RCT (designs not specified on outcome))	Low–middle-income and high-income setting	Contacts of patients with TB	Contacts screened — Low/middle-income setting: n = 878 724 — In high-income setting: n = 284 505	Proportion active TB — In low/middle-income setting — In high-income setting	% (95 % CI)	— 3.1 % (2.2-4.4) — 1.4 % (1.1-1.8)	Not reported	Negative on 1, 5, 7, 8, 11	Weak evidence

(a) United States: n = 4. Brazil, Netherlands, Turkey, United Kingdom: n = 2. China, Canada, Columbia, Ethiopia, France, Israel, Malta, Mozambique, Saudi Arabia, South Korea, Spain, Taiwan: n = 1.

(b) United States: n = 3. Canada, Greece: n = 1. Countries of articles included in SR not reported.

(c) United States: n = 9. Canada: n = 5. United Kingdom: n = 3. India: n = 2. Australia, France, Italy, Kenya, South Africa, Uganda, Zambia: n = 1. For three articles, the countries could not be identified (all on the elderly).

(d) Study 1: South-east Asia. Study 2: 45 % India, 43 % Tibet, 12 % other. Study 3: 45 % Asia, 42 % Africa, 13 % Europe.

(e) United States: n = 66 incidents. France: n = 34 incidents. Netherlands: n = 6 incidents. United Kingdom: n = 5 incidents. Canada: n = 2 incidents. Australia, Ireland, Italy, Japan: n = 1 incident.

(f) Japan, South-Korea: n = 3. England, Germany: n = 2. Austria, Bangladesh, Canada, China, Colombia, Ethiopia, Hong Kong, Kenya, Netherlands, Northern Ireland, Norway, Portugal, Senegal, South Africa, Spain, Taiwan, The Gambia, Turkey: n = 1.

(g) India: n = 4 studies. Thailand: n = 2. Cambodia, Indonesia, Laos, Pakistan, Philippines: n = 1.

(h) United States: n = 7. Peru, South Africa: n = 3. Brazil, India: n = 2. Kuwait, Micronesia, Philippines, Spain, Switzerland, Taiwan, United Kingdom, US Virgin Islands: n = 1.

(i) Fox et al. reported the outcomes per low–middle-income countries (n = 95) and high-income countries (n = 108).

(j) No studies met the selection criteria. After an experts' consultation two systematic reviews were included by the authors: Joshi R, Reingold AL, Menzies D, Pai M (2006) Tuberculosis among healthcare workers in low and middle-income countries: A systematic review. PLoSMed 3(12): e494; Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F (2011) Tuberculosis among healthcare workers. Emerg Infect Dis 17(3):488-94.

(k) Previously published systematic reviews.

(l) A third study on PLHIV presented only reactivation rates (rate of reactivation in HIV+: 1.82/100 pyr (CI1.74-1.89), rate of reactivation in HIV-infected: 0.07/100 pyr (0.070-0.075)). IRR not reported.

(m) One trial among contacts of persons with active TB and another trial among patients in mental hospitals. Analysis comparing a cohort of skin converters during the 12 months of placebo treatment with TST-positive at entry controls.

(n) Some articles comprised multiple population groups.

(o) In one study, only secondary cases with drug resistance patterns and genotypes concordant with their source cases were reported. Of the remaining 16 studies, 15 reported that > 50 % of secondary cases with DST results were drug-resistant tuberculosis (Table 1), and 14 reported that > 50 % of secondary cases with DST results had drug resistance categories that were concordant with that of the source case.

Appendix 7. Summary tables – LTBI diagnosis

Review question. Among persons at high risk of LTBI who are not on TB-preventive therapy, which test(s) (e.g. TST or IGRA), alone or in combination with other proxies for LTBI, when positive, can best identify individuals most at risk of progression?

SR outcome 1. The predictive utility of the TST vs the commercial IGRA for progression to active TB.

SR outcome 2. The predictive utility of the TST vs the commercial IGRA for progression to active TB when combined with proxies for LTBI.

Patients/population. Longitudinal studies of adults and children without active TB at baseline.

Setting. Community-based cohorts, individuals attending outpatient clinics, individuals participating in randomised clinical trials.

Index test. TST (PPD-S) and/or commercial IGRA assays.

Importance. Longitudinal studies on the predictive value of a positive IGRA are still emerging, in particular studying high risk groups.

Reference standard. All diagnoses of incident active TB.

Studies. Any longitudinal study design (e.g. prospective or retrospective cohort), in any setting (low-, middle- or high-income country), regardless of immunological status (HIV-infected or not). Follow-up length should be minimum 1 year on average, but can be either active or passive follow-up.

Table A7.1. GRADE summary table: studies that conducted head-to-head evaluations of the tuberculin skin test and interferon gamma release assays (n = 8)

		Quality				Effect		Quality	Importance
No of studies (No of individuals)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Relative (pooled) (95 % CI) I2 (a)	Absolute		
A. SR outcome 1. The predictive utility of the TST vs the commercial IGRA for progression to active TB									
8 (N = 9 488)	Prospectively followed cohorts	Likely (A1)	Serious inconsistency I2 = 72.3 %, IGRA (A2) (-1)	Serious Indirectness (A3) (-1)	No serious imprecision	TST RR = 2.58 (CI: 1.72-3.88) I2 = 14 % IGRA RR = 4.94 (CI:1.79-13.65) I2 = 72.3 %	TST Category A country (n = 6) PPV = 0.03 (CI: 0.03-0.03), I2 = 0 % Category B country (n = 2) PPV = 0.02 (CI: 0.01-0.02), I2 = 92.1 % IGRA Category A country (n = 6) PPV = 0.03 (CI: 0.03-0.03), I2 = 68.1 % Category B country (n = 2) PPV = 0.02 (CI: 0.01-0.02), I2 = 92.8 %	Low	Critical (7-9)
3 (n = 6 592)	Prospectively followed cohorts	Likely (A4)	Some inconsistency for IGRA (I2 = 41 %)	Some indirectness (A5) (-1)	No serious imprecision	TST Pooled IRR = 2.07 (CI: 1.38-3.11) I2 = 0 % IGRA Pooled IRR = 2.40 (CI: 1.26-4.60) I2 = 41 %		Low	Critical (7-9)
B. SR outcome 2. The predictive utility of the TST vs the commercial IGRA for progression to active TB when combined with other proxies for LTBI (WHO defines LTBI proxies to include fibrotic lesions, anaemia, weight loss)									
No studies									
C. SR outcome 3. The predictive utility of the TST vs the commercial IGRA for progression to active TB amongst those immunocompromised (includes HIV and other immunosuppressive conditions)									

		Quality				Effect		Quality	Importance
3 (N = 1 095)	Prospectively followed cohorts	Likely (C1)	Serious inconsistency (I2 = 74.2 %, IGRA I2 = 62.1 %, TST) (C2) (-1)	Very serious indirectness (C3) (-2)	Very serious Imprecision (C4) (-2)	TST RR = 2.96 (CI: 0.38-23.18) I2 = 62.1 % IGRA RR = 5.15 (CI:0.26-100.43) I2 = 74.2 %	TST Category A countries (n = 3) PPV = 0.04 (0.02-0.07), I2 = 0 % Category B countries No studies IGRA Category A countries (n = 3) PPV = 0.06 (CI: 0.03-0.09), I2 = 3.7 % Category B countries No studies	Low	Important (4-6)
1 (n = 241)	Prospectively followed cohort (silicosis patients)	Likely (C1)	Unclear, since only 1 study	Very serious indirectness (C5) (-2)	Very serious imprecision (C6) (-2)	TST IRR, single study = 1.69 (CI: 0.52-5.50) IGRA IRR, single study = 8.50 (CI:1.11-65.41)		Low	Important (4-6)
D. SR outcome 4. The predictive utility of the TST vs the commercial IGRA for progression to active TB amongst TB case contacts (regardless of definition)									
3 (N = 2 309)	Prospectively followed cohorts	Likely (D1)	Serious inconsistency (I2 = 85.8 %, IGRA) (D2) (-1)	Very serious Indirectness D3 (-2)	Very Serious imprecision D4 (-2)	TST RR = 2.31 (CI: 1.76-3.70) I2 = 0 % IGRA RR = 5.95 (CI: 0.57-62.05) I2 = 85.8 %	TST Category A countries (n = 2) PPV = 0.03 (0.03-0.03), I2 = 9.4 % Category B countries (n = 1) PPV = 0.06 (0.03-0.08) IGRA Category A countries (n = 2) PPV = 0.03 (CI: 0.03-0.03), I2 = 90.7 % Category B countries (n = 1) PPV = 0.05 (CI: 0.03-0.06)	Low	Important (4-6)
1 (n = 1 107)	Prospectively followed cohort	Likely (D5)	Unclear, since only 1 study	Very serious indirectness (D6) (-2)	Serious imprecision (D7) (-1)	TST IRR, single study = 1.76 (CI: 0.98-3.17) IGRA IRR, single study = 1.55 (CI: 0.80-3.01)		Low	Important (4-6)

Category A countries = high-income countries and upper-middle-income countries with a TB prevalence < 100/100 000; Category B countries = low-income countries, lower-middle-income countries and upper-middle-income countries with a TB prevalence of ≥ 100/100 000.

(a) Heterogeneity was explored using the I2-statistic. If the I2 is 50 % or above, possible reasons for heterogeneity are assessed through subgroup analysis.

Overall quality. All studies start with one point docked because none were randomised controlled trials. The lowest quality score achievable is 1 out of 4; no minus scores are given.

Quality assessment. Based on the relative effect measure (RR or IRR) for both TST and IGRA. Studies not marked down if estimates for both tests score high on a specific GRADE quality item.

Other study quality considerations. There were none.

A1. Risk of bias is likely. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and results of these were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.

A2: Serious inconsistency of IGRA RR estimate.

A3. Most studies were from high/intermediate-prevalence countries. Difficult to generalise to other settings with confidence. Moreover, data from three out of eight head-to-head studies was based on a non-random selection of the study population that did not receive preventive therapy.

A4. Risk of bias is likely. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and results of these were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review. TB ascertainment differed across the three studies and relied on passive follow-up with database linkage (Leung 2008), active follow-up but self-reporting by the participant (Shanaube 2013, unpublished) or active follow-up but incorporation of the TST and IGRA result in the case definition (Mahommed 2011).

A5. Study populations included in the analysis were diverse and included a silicosis cohort living in China, adolescents living in South Africa and TB close contacts living in Zambia or South Africa. Cut-offs for a positive TST result differed across studies (two used 10 mm and one used 5 mm). Two out of the three studies used QFT-GIT as the commercial IGRA, while one use the T-SPOT.TB assay. Although the IRR did not differ much between studies, and heterogeneity of the pooled IRR estimate was low, one should be cautious with generalising these results to other study populations or settings.

B. No studies

C1. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and results of these were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.

C2. Heterogeneity was high both for pooled RR for TST and for pooled RR estimate for the commercial IGRA.

C3. All three studies were from high/intermediate-TB-prevalence countries. Pooled estimate is based on only three studies. Immunocompromised individuals who did not receive preventive therapy might not be representative for all immunocompromised individuals.

C4. Very serious imprecision of both TST and IGRA RR estimates. RR estimates for IGRA span the null.

C5. One study included; representativeness to other populations is limited (poor external validity).

C6. One study included with limited number of events; CIs around the IRR estimate are very wide.

D1. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and results of these were not included in this analysis. However, addition of results is not expected to change the overall conclusions of this review.

D2. Heterogeneity was very high (86 %) for the pooled RR estimate for the commercial IGRA.

D3. Based on small number of studies with different definition of case contact. Two studies from low-prevalence countries and one study from a high-prevalence country. Concern, despite lack of heterogeneity. Contacts of TB cases in three studies might not be representative of all TB contact individuals.

D4. Very serious imprecision of IGRA RR estimates; RR estimates for IGRA span the null.

D5. Publication bias not formally assessed, but expected to be likely. Several large prospective studies are ongoing and results of these were not included in this analysis.

D6. One study included; representativeness to other populations is limited (poor external validity).

D7. One study included with limited number of events; CIs around the IRR estimate are wide.

Table A7.2. Stratified results for meta-analyses of positive predictive value, negative predictive value and relative risk in head-to-head comparison studies, n = 8 (Kik, 2014)

		Category A countries [a]			Category B countries [a]			Overall	
		N studies	PPV (95 % CI); I2 [c]	NPV (95 % CI); I2 [c]	N studies	PPV (95 % CI); I2 [c]	NPV (95 % CI); I2 [c]	N Studies	RR (95 % CI); I2 [c]
TST	Overall	6	0.03 (0.03-0.03) I2 = 0 %	1.00 (1.00-1.00) I2 = 56.8 %	2	0.02 (0.01-0.02) I2 = 92.1 %	0.99 (0.99-1.00) I2 = 92.1 %	8	2.58 (1.72-3.88) I2 = 14 %
	Immunocompromised	3	0.04 (0.02-0.07) I2 = 0 %	1.00 (1.00-1.00) I2 = 48.2 %	0	-	-	3	2.96 (0.38-23.18) I2 = 62.1 %
	Non immunocompromised	3	0.03 (0.03-0.03) I2 = 0 %	0.99 (0.99-1.00) I2 = 20.0 %	2	0.02 (0.01-0.02) I2 = 92.1 %	0.99 (0.99-1.00) I2 = 92.1 %	5	2.56 (1.76-3.70) I2 = 0 %
	TB contacts	2	0.03 (0.03-0.03) I2 = 9.4 %	0.99 (0.98-1.00) I2 = 0 %	1 [d]	0.06 (0.03-0.08)	0.97 (0.96-0.98)	3	2.31 (1.43-3.71) I2 = 0 %
	No TB contacts	4	0.04 (0.01-0.06) I2 = 0 %	1.00 (1.00-1.00) I2 = 45.1 %	1 [e]	0.01 (0.01-0.02)	0.99 (0.99-1.00)	5	2.93 (1.34-6.39) I2 = 34.7 %
	Country A [a]							6	3.30 (1.59-6.88) I2 = 20.6 %
	Country B [a]							2	2.19 (1.43-3.36) I2 = 0 %
	High-income country [b]							3	4.08 (1.93-8.60) I2 = 0 %
	Low/middle-income country [b]							5	2.24 (1.28-3.92) I2 = 32.4 %
IGRA	Overall	6	0.03 (0.03-0.03) I2 = 68.1 %	1.00 (1.00-1.00) I2 = 0 %	2	0.02 (0.01-0.02) I2 = 92.8 %	0.99 (0.99-1.00) I2 = 85.8 %	8	4.94 (1.79-13.65) I2 = 72.3 %
	Immunocompromised	3	0.06 (0.03-0.09) I2 = 3.7 %	1.00 (1.00-1.00) I2 = 11.4 %	0	-	-	3	5.15 (0.26-100.43) I2 = 74.2 %
	Non-immunocompromised	3	0.03 (0.03-0.03) I2 = 0 %	1.00 (1.00-1.00) I2 = 0 %	2	0.02 (0.01-0.02) I2 = 92.8 %	0.99 (0.99-1.00) I2 = 85.8 %	5	4.52 (1.48-13.76) I2 = 76.1 %

		Category A countries (a)			Category B countries (a)			Overall	
		N studies	PPV (95 % CI); I2 (c)	NPV (95 % CI); I2 (c)	N studies	PPV (95 % CI); I2 (c)	NPV (95 % CI); I2 (c)	N Studies	RR (95 % CI); I2 (c)
	TB contacts	2	0.03 (0.03-0.03) I2 = 90.7 %	1.00 (1.00-1.00) I2 = 23.7 %	1*	0.05 (0.03-0.06)	0.97 (0.95-0.99)	3	5.95 (0.57-62.05) I2 = 85.8 %
	No TB contacts	4	0.04 (0.02-0.05) I2 = 37.5 %	1.00 (1.00-1.00) I2 = 0 %	1**	0.01 (0.01-0.02)	0.99 (0.99-1.00)	5	5.72 (1.27-25.78) I2 = 62.9 %
	Country A (a)							6	9.85 (1.56-62.21) I2 = 71.1
	Country B (a)							2	2.16 (1.20-3.88) I2 = 40.8 %
	High-income country (b)							3	19.64 (0.88-438.69) I2 = 80.3 %
	Low/middle-income country (b)							5	2.87 (1.11-7.43) I2 = 63.5 %

(a) Category A countries: high-income countries and upper-middle-income countries with a TB prevalence < 100/100 000. Category B countries: low-income countries, lower-middle-income countries and upper-middle-income countries with a TB prevalence of ≥ 100/100 000. Low versus high/intermediate country TB prevalence as defined by WHO.

(b) World Bank income classification.

(c) Heterogeneity was explored using the I2-statistic. If the I2 is 50 % or above, possible reasons for heterogeneity are assessed through subgroup analysis.

NB: (d) Shanaube et al. and (e) Mahomed et al: Not enough studies to conduct meta-analysis. Estimates given are as derived from original data provided in those studies. Careful interpretation of estimates warranted given high I2

Table A7.3. Stratified results for meta-analyses of incidence rate after positive or negative test result and incidence rate ratio in head-to-head comparison studies, n = 3 (Kik, 2014)

		N studies	IRpos (95 % CI); I2 (c)	IRneg (95 % CI); I2 (c)	IRR (95 % CI); I2 (c)
TST	Overall	3	15.62 (5.31-45.91); I2 = 94.7 %	7.80 (2.06-29.49); I2 = 92.9 %	2.07 (1.38-3.11); I2 = 0 %
	Immunocompromised	1	26.72 (13.90-51.36)	15.79 (5.92-42.06)	1.69 (0.52-5.50)
	Non immunocompromised	2	12.21 (3.01-49.48); I2 = 96.7 %	5.71 (0.94-34.82); I2 = 96.2 %	2.13 (1.38-3.28); I2 = 0 %
	TB contacts	1	25.08 (16.81-37.42)	14.23 (9.28-21.82)	1.76 (0.98-3.17)
	No TB contacts	2	12.32 (2.86-53.06); I2 = 93.9 %	5.71 (0.85-38.47); I2 = 91.2 %	2.41 (1.37-4.24); I2 = 0 %
	Country A (a)	1	26.72 (13.90-51.36)	15.79 (5.92-42.06)	1.69 (0.52-5.50)
	Country B (a)	2	12.21 (3.01-49.48); I2 = 96.7 %	5.71 (0.94-34.82); I2 = 96.2 %	2.13 (1.38-3.28); I2 = 0 %
	Low/middle-income country (b)	3	15.62 (5.31-45.91); I2 = 94.7 %	7.80 (2.06-29.49); I2 = 92.9 %	2.07 (1.38-3.11); I2 = 0 %
IGRA	Overall	3	16.43 (6.06-44.58); I2 = 94.9 %	5.13 (1.21-21.81); I2 = 90.3 %	2.40 (1.26-4.60); I2 = 41.2 %
	Immunocompromised	1	34. 74 (19.73-61.18)	4.08 (0.58-29.00)	8.50 (1.11-65.41)
	Non immunocompromised	2	11.59 (3.56-37.79); I2 = 96.2 %	5.50 (0.93-32.64); I2 = 95.1 %	2.13 (1.17-3.87); I2 = 42.1 %
	TB contacts	1	21.22 (15.09-29.85)	13.67 (7.76-24.07)	1.55 (0.80-3.01)
	No TB contacts	2	14.61 (2.77-77.17); I2 = 96.2 %	2.32 (1.37-3.92); I2 = 0 %	3.14 (1.72-5.74); I2 = 0.1 %
	Country A (a)	1	34. 74 (19.73-61.18)	4.08 (0.58-29.00)	8.50 (1.11-65.41)
	Country B (a)	2	11.59 (3.56-37.79); I2 = 96.2 %	5.50 (0.93-32.64); I2 = 95.1 %	2.13 (1.17-3.87); I2 = 42.1 %
	Low/ middle-income country (b)	3	16.43 (6.06-44.58); I2 = 94.9 %	5.13 (1.21-21.81); I2 = 90.3 %	2.40 (1.26-4.60); I2 = 41.2 %

(a) Category A countries: high-income countries and upper-middle-income countries with a TB prevalence < 100/100 000. Category B countries: low-income countries, lower-middle-income countries and upper-middle-income countries with a TB prevalence of ≥ 100/100 000. Low versus high/intermediate country TB prevalence as defined by WHO.
(b) World Bank income classification.
(c) Heterogeneity was explored using the I2-statistic. If the I2 is 50 % or above, possible reasons for heterogeneity are assessed through subgroup analysis.

Table A7.4 Average screening cost (2012 USD) for latent tuberculosis infection with tuberculosis skin test or with interferon gamma release assays by country (Girardi, 2014)

Country	TST	IGRA	Screening costs for eligible candidates to preventive therapy
Uganda	1.3	-	-
India	1.6	-	37.1
South Africa	3.0	-	-
Italy	10.9	-	381.9
Canada	14.2	42.5	481.2
Australia	15.8	-	-
France	17.6	72.6	507.6
United States	27.6	95.2	432.6
United Kingdom	31.5	97.1	1 129.9
Mexico	-	22.5	-
Kenya	-	-	44.7
Zambia	-	-	17.2
Japan	-	60.2	629.8
Overall	20.3	77.7	435.3

Table A7.5. Summary of results of systematic reviews on cost-effectiveness analyses of diagnostic tests

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews							
Auguste, 2016 [102] Low & high [a]	10 CEA studies (children n = 2; immunocompromised n = 6; recently arrived from high-incidence countries n = 2) Review authors developed a de novo CEA model	National health payer perspective n = 5; Societal perspective n = 5	Range 1 year-lifetime	*In children:* — TST (≥ 5 mm)-negative followed by QFT-GIT was the most cost-effective strategy [b], with an incremental cost-effectiveness ratio (ICER) of £18 900 per QALY gained. — T-SPOT.*TB* was the most cost-effective strategy [b] with an ICER of approximately £2 700 per diagnostic error avoided compared with TST (≥ 10 mm). *In immunocompromised people:* — QFT-GIT-negative followed by TST (≥ 5 mm) was the most cost-effective strategy [b] with an ICER of approximately £18 700 per QALY gained. — QFT-GIT-positive followed by TST (≥ 5 mm) was the most cost-effective strategy [b] with an ICER of approximately £300 per diagnostic error avoided compared with TST (≥ 10 mm). *In the recently arrived population from high-TB-incidence countries:* — TST (≥ 5 mm) alone was the most cost-effective strategy [b] with an ICER of approximately £1 500 per QALY gained compared with QFT-GIT. — TST (≥ 5 mm)-positive followed by QFT-GIT was the most cost-effective strategy [b] with an ICER of approximately £700 per diagnostic error avoided compared with QFT-GIT alone. — TST (≥ 5 mm) alone was less costly and more effective than TST (≥ 5 mm)-positive followed by QFT-GIT or T-SPOT.*TB* or QFT-GIT alone.	Given the current (limited) evidence, TST (≥ 5 mm)-negative followed by QFT-GIT for children, QFT-GIT-negative followed by TST (≥ 5 mm) for the immunocompromised population and TST (≥ 5 mm) for recent arrivals were the most cost-effective strategies for diagnosing LTBI that progresses to active TB.	Negative on 1, 3, 4, 10	Weak evidence

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Campbell, 2015 [103] Low & high ([c])	n = 8 CEA studies (children n = 2; immunocompromised n = 6; recently arrived n = 2)	Societal perspective n = 4; Healthcare system perspective n = 2; Healthcare programme perspective n = 2	Range 20 years-lifetime	— Three studies evaluated the cost-effectiveness of screening tests on the basis of the options of no screening and screening with a TST. Screening new adult immigrants and PLHIV was strongly cost-effective ([d]) with a TST. — The remaining five studies evaluated screening more comprehensively through evaluating TST, IGRA, no screening, and other options. The IGRA was found moderately cost-effective ([d]) in new adult immigrants and 6- to 44-year-old immigrants that landed more than 5 years prior, while the TST was dominated by no screening in both cases. One study reported HIV screening was strongly cost-effective ([d]) with a TST and moderately cost-effective ([d]) with an IGRA, while the other reported either dual TST/QFT or T-SPOT.*TB* alone would be the most cost-effective, depending on the situation. No test was cost-effective ([d]) for renal diseases; however, the IGRA was found to be the most cost-effective ([d]) test more often than the TST, if screening had to be performed. While screening for diabetics was not cost-effective ([d]), the TST was found to be most cost-effective if screening was done. All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test ([d]) if screening had to occur.	Screening PLHIV with a TST is strongly cost-effective, while screening adult immigrants with an IGRA is moderately cost-effective.	Negative on 5, 10, 11	Weak evidence
Nienhaus, 2011 [104] Low & high ([e]) Main objectives of this review were not similar to our review question	n = 5 cost analyses and n = 8 cost-effectiveness analyses	Not reported	Range 1 year-lifetime	— One study analysed the alternative use of TST or IGRA and seven studies compared the (1) TST-only, (2) positive TST followed by IGRA and (3) IGRA-only strategies. — Two studies favoured the IGRA-only strategy, and four studies found the IGRA in TST-positives to be the most cost-effective ([f]).	The available studies on cost-effectiveness provide strong evidence in support of the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries and close contacts. In general, the higher unit cost of the IGRAs compared to that of the TST is compensated for by cost savings through the more targeted performance of CXRs and offering of chemoprevention. If the increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds true, the IGRA-only screening strategy should prove to be the more cost-effective test.	Negative on 1, 2, 3, 5, 7, 8, 10, 11	Weak evidence
Oxlade, 2013 [105] Low & high ([g])	13 cost-effectiveness analyses ([h])	Patient perspective n = 6; not reported n = 7	Range 2 years-lifetime	— Of all studies that compared effectiveness with use of IGRA versus TST, only one study predicted a gain of more than 1 day with use of the IGRA over an analytic horizon of 20 years of more ([h]).	No conclusion was given for these cost data, only on the methodological issues that contribute to inconsistent results and reduced study quality.	Negative on 1, 4, 5, 7, 8, 10, 11	Weak evidence

(a) Japan, United Kingdom, South Africa, United States: n = 1.

(b) An ICER below GBP 20 000 was considered cost-effective.

(c) Japan, Mexico, United States, multiple low-TB-incidence countries, Uganda: n = 1.

(d) Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > 100 000 US = not cost-effective.

(e) Canada, France, Germany, Israel, Japan, Switzerland, United Kingdom, United States: n = 1.

(f) Different willingness-to-pay thresholds (e.g. USD 30 000, 50 000, 100 000) were used to define cost-effectiveness in the primary studies.

(g) Japan: n = 3. Canada, United Kingdom, United States: n = 2. France, Germany, Mexico, Switzerland: n = 1.

(h) Primary studies used either a willingness-to-pay threshold of USD 50 000 or did not report clear parameters for identifying cost-effective interventions.

Table A7.6. Summary of the order in which a combination of latent tuberculosis infection tests (and tests for active tuberculosis) should be done in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic review											
Van't Hoog, 2014 [107] Low & high (a)	1998-2012	n = 17 (all cross-sectional design)	Various settings	Mostly general population	Not reported	NPV calculated based on the sensitivity and specificity of symptom screening or CXR to identify individuals to be treated for LTBI	Algorithm with NPV = 1-	(1) Screen: CXR any abnormality & Confirmatory test: culture (prevalence of TB: 0.1 %; pre-test probability of no TB: 0.9990) (2) Screen: any TB symptom and/or CXR any abnormality (parallel) and confirmatory test: culture (prevalence of TB:0.1 %; pre-test probability of no TB: 0.9990) (3) Screen: any TB symptom and/or CXR any abnormality (parallel) and confirmatory test: culture (prevalence of TB: 10 %; pre-test probability of no TB: 0.9000) See Table A7.7 and Table A7.8 below	*GRADE* — Low: articles on CXR — Very low: articles on symptom screening	Negative on 1, 4, 5, 11	Weak evidence

(a) South Africa: n = 3. Cambodia, India: n = 2. Ethiopia, Eritrea, Haiti, Kenya, Malawi, Myanmar/Burma, United States, Vietnam, Zambia, Zimbabwe: n = 1.

Table A7.7. Results for algorithms of screening methods and confirmatory tests when screening 100 000 persons, showing for 0.5 % tuberculosis prevalence

Screening tool	Sensitivity	Specificity	False negative at screening	NPV after negative screening	False positive at screening
Any TB symptom	0.770	0.677	115	99.83	32 139
CXR: any abnormality	0.978	0.754	11	99.99	24 447
CXR: any abnormality plus any TB symptom	1.00	0.612	0	100	38 588
CXR: TB abnormality	0.868	0.894	66	99.93	10 547
Cough > 2-3 weeks	0.351	0.947	325	99.66	5 274
If cough > 2-3 weeks then CXR	0.351/0.90	0.947/0.56	342	99.65	2 320
If any TB symptoms then CXR	0.770/0.90	0.677/0.56	154	99.82	14 141

Source: Van't Hoog, 2014

Table A7.8. Results for algorithms of screening methods and confirmatory tests when screening 100 000 persons, showing for 10 % tuberculosis prevalence

Screening tool	Sensitivity	Specificity	False negative at screening	NPV after negative screening	False positive at screening
Any TB symptom	0.770	0.677	2 300	96.36	20 070
CXR: any abnormality	0.978	0.754	220	99.68	22 140
CXR: any abnormality plus any TB symptom	1.00	0.612	0	100	34 903
CXR: TB abnormality	0.868	0.894	1 320	98.39	9 540
Cough > 2-3 weeks	0.351	0.947	6 490	92.92	4 770
If cough > 2-3 weeks then CXR	0.351/0.90	0.947/0.56	6 841	92.78	2 099
If any TB symptoms then CXR	0.770/0.90	0.677/0.56	3 070	96.18	12 791

Source: Van't Hoog, 2014

Appendix 8. Summary tables – LTBI treatment

Table A8.1. Odds ratios for active tuberculosis, derived from the Network Meta-analysis

Regimen	OR (95 % CI)*
No treatment	2.22 (1.04-4.76)
INH 4 mo	0.89 (0.51-1.50)
INH 6 mo	0.62 (0.48-0.80)
INH 9 mo	0.66 (0.30-1.44)
INH 12 mo	0.51 (0.40-0.64)
RFB-INH	0.29 (0.05-1.47)
RFB-INH (high)	0.30 (0.05-1.53)
RPT-INH	0.54 (0.27-1.09)
RIF	0.39 (0.17-0.85)
RIF-INH 1 mo	0.98 (0.33-2.70)
RIF-INH 3 mo	0.49 (0.32-0.75)
RIF-INH-PZA	0.33 (0.17-0.60)
RIF-PZA	0.53 (0.31-0.87)
INH-EMB	0.87 (0.31-2.50)
INH-EMB 12 mo	0.23 (0.04-0.98)

** All comparisons vs. placebo*

Table A8.2. Grading of the body of evidence for the effectiveness of different latent tuberculosis infection treatments (outcome = risk of active TB)

Number and references of studies*	Design	Limitations	Direct							
			Inconsistency	Indirectness	Imprecision	Publication bias	Treatment-cases/ participants	Baseline-cases/ participants	OR (95% CI)	Quality
No treatment vs INH 3-4 mo										
1 (Gupta, 1993)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	10/82 (12.2 %)	17/85 (20.0 %)	0.56 (0.24-1.30)	Low
Placebo vs INH 3-4 mo										
2 (Temprano ANRS 12136 Study Group, 1982; Veening, 1968)	Randomised trials	Not serious	Very serious	Serious	Not serious	Not available	77/7 089 (1.1 %)	109/7 118 (1.5 %)	0.30 (0.03-3.03)	Very low
No treatment vs INH 6 mo										
2 (Temprano ANRS 12136 Study Group, 2015)	Randomised trials	Serious	Not serious	Serious	Not serious	Not available	27/1 030 (2.6 %)	58/1 026 (5.7 %)	0.46 (0.27-0.77)	Low
Placebo vs INH 6 mo										
9 (Gordin, 1997; Hawken, 1997; Horwitz, 1966; Johnson, 2001; Mwinga, 1998; Xie, 2009; International Union Against Tuberculosis Committee on Prophylaxis, 1982; Centre, 1992)	Randomised trials	Serious	Not serious	Serious	Not serious	Undetected	406/13 280 (3.1 %)	598/12 918 (4.6 %)	0.61 (0.48-0.77)	Low
No treatment vs INH 9 mo										
2 (Debre, 1973; Kim, 2015)	Randomised trials	Very serious	Not serious	Serious	Not serious	Not available	10/1 650 (0.6 %)	27/1 583 (1.7 %)	0.37 (0.18-0.76)	Very low
No treatment vs INH 12-72 mo										
6 (Agarwal, 2004; Fitzgerald, 2010; Naqvi, 2010; Pape, 1993; Vikrant, 2005; Ma, 2014)	Randomised trials	Serious	Not serious	Serious	Not serious	Undetected	23/519 (4.4 %)	72/569 (12.7 %)	0.35 (0.16-0.75)	Low
Placebo vs INH 12-72 mo										
16 (John, 1994; Madhi, 2011; Mohammed, 2007; Zar, 2007;	Randomised trials	Serious	Serious	Not serious	Not serious	Undetected	331/42 280 (0.8 %)	670/41 931 (1.6 %)	0.54 (0.42-	Low

Number and references of studies*	Design	Limitations	Direct							
			Inconsistency	Indirectness	Imprecision	Publication bias	Treatment-cases/ participants	Baseline-cases/ participants	OR (95% CI)	Quality
International Union Against Tuberculosis Committee on Prophylaxis, 1982; Ferebee, 1962; Ferebee, 1963; MOUNT, 1962; del Castillo, 1965; Bush, 1965; Comstock, 1967; Egsmose, 1965; Falk, 1978; Gray, 2014; Rangaka, 2014)									0.68)	
Placebo vs RIF										
1 (Hong Kong Chest Service/TB Research Centre, Madras/British Medical Research Council, 1992)	Randomised trials	Not serious	Not available	Serious	Not serious	Not available	20/172 (11.6 %)	36/167 (21.6 %)	0.48 (0.26-0.87)	Moderate
No treatment vs RIF-INH 1 mo										
1 (Gupta, 1993)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	9/83 (10.8 %)	17/85 (20.0 %)	0.49 (0.20-1.16)	Low
No treatment vs RIF-INH 3-4 mo										
1 (Gupta, 1993)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	4/85 (4.7 %)	17/85 (20.0 %)	0.20 (0.06-0.62)	Low
Placebo vs RIF-INH 3-4 mo										
2 (Johnson, 2001; Centre, 1992)	Randomised trials	Serious	Not serious	Serious	Not serious	Not available	48/723 (6.6 %)	78/631 (12.4 %)	0.52 (0.33-0.84)	Low
Placebo vs RIF-PZA										
1 (Mwinga, 1998)	Randomised trials	Serious	Not available	Serious	Not serious	Not available	33/351 (9.4 %)	40/350 (11.4 %)	0.80 (0.49-1.31)	Low
No treatment vs RIF-INH-PZA										
1 (Gupta, 1993)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	0/80 (0 %)	17/85 (20.0 %)	0.02 (0.00-0.41)	Low
Placebo vs RIF-INH-PZA										
2 (Johnson, 2001; Cowie, 1996)	Randomised trials	Serious	Serious	Serious	Serious	Not available	26/653 (4.0 %)	57/655 (8.7 %)	0.47 (0.22-0.98)	Very low
No treatment vs INH + EMB 12 mo										
1 (Ma, 2014)	Randomised trials	Very serious	Not available	Serious	Not serious	Not available	0/66 (0 %)	8/70 (11.4 %)	0.06 (0.00-0.98)	Very low
INH 6 mo vs INH 12-72 mo										
3 (Martinson, 2011; International Union Against Tuberculosis Committee on Prophylaxis, 1982; Samandari, 2015)	Randomised trials	Not serious	Not serious	Serious	Not serious	Not available	72/8 089 (0.9 %)	114/8 281 (1.4 %)	0.69 (0.51-0.93)	Moderate
INH 6 mo vs RIF										
1 (Hong Kong Chest Service/TB Research Centre, Madras/British Medical Research Council, 1992)	Randomised trials	Not serious	Not available	Serious	Not serious	Not available	20/172 (11.6 %)	25/173 (14.5 %)	0.78 (0.41-1.46)	Moderate
INH 6 mo vs RIF-INH 3-4 mo										
6 (Geijo, 2007; Johnson, 2001; Martinson, 2011; Rivero, 2007; Centre, 1992; Jimenez-Fuentes, 2013)	Randomised trials	Serious	Not serious	Serious	Not serious	Undetected	78/1 499 (5.2 %)	87/1 482 (5.9 %)	0.89 (0.65-1.23)	Low
INH 6 mo vs RPT-INH										
1 (Martinson, 2011)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	24/328 (7.3 %)	22/327 (6.7 %)	1.09 (0.60-1.99)	Low

Number and references of studies*	Design	Limitations	Direct							
			Inconsistency	Indirectness	Imprecision	Publication bias	Treatment-cases/ participants	Baseline-cases/ participants	OR (95% CI)	Quality
INH 9 mo vs RIF-INH 3-4 mo										
1 (Martínez Alfaro, 1998)	Randomised trials	Serious	Not available	Serious	Serious	Not available	1/98 (1 %)	0/98 (0 %)	3.03 (0.12-75.31)	Very low
INH 9 mo vs RPT-INH										
1 (Sterling, 2011)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	7/3 986 (0.2 %)	15/3 745 (0.4 %)	0.44 (0.18-1.07)	Low
INH 12-72 mo vs RIF-INH 3-4 mo										
2 (Martinez Alfaro, 2000; Martinson, 2011)	Randomised trials	Serious	Not serious	Serious	Serious	Not available	26/398 (6.5 %)	12/228 (5.3 %)	1.06 (0.35-3.21)	Very low
INH 12-72 mo vs RPT-INH										
1 (Martinson, 2011)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	24/328 (7.3 %)	8/164 (4.9 %)	1.54 (0.68-3.51)	Low
RIF vs RIF-INH 3-4 mo										
1 (Hong Kong Chest Service/TB Research Centre, Madras/British Medical Research Council, 1992)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	26/167 (15.1 %)	20/172 (11.6 %)	1.40 (0.75-2.62)	Low

** References: see Appendix 11*

Table A8.3. Summary of the effectiveness of different preventive treatment regimens for certain risk groups in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic reviews											
36 mo 300 mg INH											
Den Boon, 2016 [114] High [a]	2011-2012	n = 3 (all RCTs)	High-TB-burden countries	PLHIV (adults) Overall	3 168	Pooled relative risk of incident active TB vs 6 mo 300 mg INH + 800 mg EMB (1 study) or 6 mo 300 mg INH (2 studies)	RR (95 % CI)	0.62 (0.42-0.89)	*Study quality* High	Negative on 2, 5, 8, 11	Moderate evidence
				Positive TST	1 232			0.51 (0.30-0.86)			
				Negative TST	1 861			0.73 (0.43-1.26)			
				Negative TST, continuous INH + ART [g]	Not reported	Adjusted hazard ratio vs 6 mo 300 mg INH	aHR (95 % CI)	0.45 (0.16-1.30)			
				Positive TST, continuous INH + ART [g]	Not reported			0.04 (0.005-0.35)			
				PLHIV (adults) — Overall — TST-positives — TST-negatives	Not reported	Number needed to treat to prevent 1 case of active TB	n	— 50 — 28 — 125			
				PLHIV (adults) — Overall — TST-positives	Not reported	Pooled relative risk of mortality vs 6 mo INH	RR (95 % CI)	— 0.87 (0.63-1.19) — 0.50 (0.27-0.91)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
				PLHIV (adults) — Overall	Not reported	Pooled relative risk of mortality due to TB vs 6 mo INH		0.52 (0.17-1.64)			
Preventive treatment, not specified											
Den Boon, 2014 [116] Low & high (b) Main objectives of this review were not similar to our review question	1996-2012	n = 4 (all cohort studies)	Not reported	Child and adult, — MDR contacts	476	Incidence of (MDR-) TB. Protective effect of prophylaxis (mainly INH; ciprofloxacin + PZA; not specified) vs no prophylaxis (outcomes of individual studies)	Risk difference (95 % CI)	0.00 (– 0.02-0.02) 0 cases	*NOS* Ranged from 6-7 points (l)	Negative on 5, 11	Weak evidence
				— MDR contacts	49		OR (95 % CI)	0.32 (0.01-7.02)			
				— Contacts — Infected contacts	218 (h) 188 (h)			0.49 (0.11-2.23) 0.46 (0.07-2.32)			
				— Confirmed TB — Confirmed and probable TB	105 (i) 105 (i)			0.21 (0.01-4.21) 0.20 (0.04-0.94)			
Girardi. 2014 [92] Low & high (c) Main objectives of this review were not similar to our review question	1981-2013	n = 3 on children n = 6 on contacts n = 3 on elderly n = 5 on healthcare workers n = 8 on migrants n = 7 on PLHIV (Mathematical modelling studies reported to be based on published literature (n = 19), based on observational studies (n = 6), or based on clinical trial (n = 1). One economic evaluation based on observational studies) (k)	Multiple settings	Children	Not reported	Efficacy of preventive therapy (% relative reduction in risk of TB) in different population groups	%, min-max	70.0-90.0	*Drummond checklist [130]* Low-medium	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence
				Contacts				65.0-90.0			
				Elderly				65.0-70.0			
				Healthcare worker				20.0-100.0			
				Migrants				60.0-90.0			
				PLHIV				60.0-100.0			
Non-commissioned systematic reviews											
RIF, RIF + INH, RIF + PZA, RPT + INH (DOT)											
Sharma, 2013 [28] Low & high (d)	1992-2011	n = 1 on RIF (l) n = 1 on RIF + INH n = 2 on RIF + PZA (m) n = 1 on RPT + INH (all trials)	Academic and public institutions, pneumoconiosis clinic	HIV-negative adults and children on: RIF 3-4 mo	332	Relative risk of TB infection vs INH 6-9 mo	RR (95 % CI)	0.81 (0.47 to 1.4)	*Grade* — Moderate: RIF + INH (DOT) — Very low: RIF, RIF + INH, RIF + PZA	Negative on 1, 11	Moderate evidence
				RIF + INH 3 mo	328	vs INH 6-9 mo		1.08 (0.65 to 1.79)			
				RIF + PZA 2 mo	176	vs INH 6 mo		1.32 (0.42 to 4.13)			
				RPT + INH (DOT) 3 mo weekly	7 731	vs INH (SAT) 9 mo daily		0.44 (0.18 to 1.07)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Preventive treatment, not specified											
Ai, 2015 [115] Low (e) Main objectives of this review were not similar to our review question	2006-2010	n = 4 (all registry and longitudinal cohort studies)	Hospital setting	Patients with RA, who were screened and treated for LTBI before the TNF-alpha antagonist treatment (regimen of the prophylaxis differs among the studies)	1 349	TB risk ratio of patients with RA/LTBI who received prophylaxis versus patients with RA/LTBI who did not	RR (95 % CI)	0.35 (0.15-0.82)	*NOS* Satisfying quality (at least 5 stars)	Negative on 1, 2, 3, 4, 5, 8, 10, 11	Weak evidence
Isoniazid preventive treatment (IPT)											
Ayele, 2015 [113] Low & high (f)	1993-2015	n = 5 (all RCTs)	Not reported	Adult PLHIV with positive TST	1 703	Pooled estimates of IPT effect on all types of TB (probable to confirmed) vs untreated or treated with placebo	RR 95 % CI	0.48 (0.29-0.82)	*Risk of bias assessment* No major methodological flaws	Negative on 2, 5, 7, 10, 11	Moderate evidence
				Adult PLHIV with positive TST	112	Pooled estimates of IPT effect on confirmed TB vs untreated or treated with placebo		0.13 (0.01-2.32)			

One article was suggested by the members of the ad hoc scientific panel as highly relevant for consideration in the guidance development process.

- Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, Goldberg SV, Sterling TR; International Maternal Pediatric and Adolescents AIDS Clinical Trials Group; Tuberculosis Trials Consortium. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar;169(3):247-55. doi: 10.1001/jamapediatrics.2014.3158 (http://archpedi.jamanetwork.com/article.aspx?articleid=2089639) [133]. Erratum in: JAMA Pediatr. 2015 Sep;169(9):878. PMID: 25580725

Results. None of the 471 in the combination-therapy (3 mo RIF + INH) group developed TB vs 3 of 434 (cumulative rate, 0.74 %) in the INH-only group (9 mo INH), for a difference of − 0.74 % and an upper bound of the 95 % CI of the difference of + 0.32 %, which met the non-inferiority criterion.

The results are in line with the updated review of Stagg et al.

(a) Botswana, India, South Africa: n = 1.
(b) Australia, Brazil, Israel, South Africa: n = 1.
(c) United States: n = 9. Canada: n = 5. United Kingdom: n = 3. India: n = 2. Australia, France, Italy, Kenya, South Africa, Uganda, Zambia: n = 1. For three articles on the elderly, the countries could not be identified.
(d) Greece, Hong Kong, South Korea, Spain: n = 1.
(e) Hong Kong: n = 2. Brazil, Canada, Germany, Spain, United States: n = 1.
(f) Australia, Brazil, Israel, South Africa: n = 1.
(g) Based on one study.
(h) Same study. Comprised contacts and infected contacts, respectively.
(i) Same study. Outcomes are confirmed TB and confirmed and suspected TB, respectively.
(j) The quality of evidence was determined for only one article and was graded very low.
(k) Some articles comprised multiple population groups.
(l) No active TB cases detected in any treatment regimen in two other trials.
(m) No active TB cases detected in any treatment regimen in one other trial.

Table A8.4. Average cost (2012 USD) of preventive therapy by country (Girardi, 2014)

Country	Cost (2012 USD) of preventive therapy (drugs plus monitoring)
Zambia	22.7
India	30.9
Mexico	36.0
Japan	44.3
Italy	115.5
Canada	147.0
United States	193.4
Australia	354.4
United Kingdom	472.1
Overall	159.8

Table A8.5. Summary of the cost-effectiveness of different preventive treatment regimens for certain risk groups in systematic reviews

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic review							
Girardi, 2014 [92] Low & high (a)	39 cost-effectiveness analyses. n = 32 articles reported on analyses conducted in upper-middle-income countries with TB incidence less than 100/100 000	Healthcare system n = 24; societal n = 7; local TB-control programme n = 1; not reported n = 7	Time horizon: range < 10 years-lifetime	Migrants: — Eight studies analysing screening and treatment of LTBI in persons migrating to high or upper-middle-income countries with TB incidence less than 100/100 000 show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b), when screened persons originate from countries with high TB incidence (above 120-150/100 000). TB contacts: — Six studies (all conducted in upper-middle-income countries with TB incidence less than 100/100 000) on contacts of patients with active TB also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b). PLHIV: — Six studies on PLHIV both in upper-middle-income countries with TB incidence less than 100/100 000 and in low-income or high-TB-incidence countries also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b). The effect of antiretrovirals in lowering TB risk in PLHIV was not taken into account in all but one of these studies. Healthcare workers: — For healthcare workers there is an indication of possibly favourable incremental cost-effectiveness ratio (b) in some of the analyses on these persons.	The available evidence suggests that screening and treatment for LTBI may be a cost-effective intervention for some population groups characterised by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high-TB-incidence countries, contacts of active TB cases and PLHIV. However, a marked variability across studies in economic inputs, in epidemiologic and TB natural history parameters, as well as in assumptions on effectiveness of preventive treatment, made the extrapolation measures of cost-effectiveness from one setting to another problematic.	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
				Other populations: — Limited evidence is available for other population groups.			
Non-commissioned systematic reviews							
Chavan, 2011 [118] Low & high (c)	8 economic evaluations (study design not reported)	Not reported	Not reported	— INH dominates (i.e. it costs less and provides greater health benefits) vs no intervention for all groups or high risk groups. — Two studies found that RIF dominates INH. — Only three studies presented incremental cost-effectiveness ratio (ICER) results but none were comparable, one being the ICER of INH over no intervention, for low risk groups, the second RIF over no intervention and the third INH + RPT over RIF. The ICER values reported were all reasonable, implying that each first named (more expensive) treatment is cost-effective (d).	The included studies provide clear evidence of the health benefits and cost-effectiveness of chemoprophylaxis (INH vs no intervention; RIF vs no intervention; INH + RPT vs RIF) for TB, but this evidence is derived almost totally from three high-income countries: the United States, Canada, and Germany.	Negative on 1, 2, 5, 7, 8, 10, 11	Weak evidence
Diel, 2015 [117] Low (e)	24 cost-effectiveness analyses	Societal costs n = 9; public healthcare provider n = 7; direct costs n = 7; national health service n = 1	Range 1 year-lifetime	— With the exception of one study focusing on active TB case-finding rather than LTBI screening, a general statement in favour of preventive treatment was given for PLHIV and healthcare workers. One single study on the cost-effectiveness (f) of preventive treatment in Japanese prisoners was available; however, further study of that risk group (incarcerated individuals) is needed before a generalising statement can be made. — No clear recommendation can be given on the basis of currently available cost-effectiveness analyses on preventive treatment as intervention prior to starting immunosuppressive medication, in patients with end-stage renal disease or in immigrants. — Only one cost-effectiveness analysis (f) in patients with diabetes mellitus suggested that, from an economic point of view, the old principle 'intention to test is intention to treat' is clearly not applicable to random diabetic patients due to a general low LTBI prevalence and a very low annual probability of progression to TB in the United States. — When the concept of a fixed willingness-to-pay threshold as a prerequisite for final categorisation was used, the sums ranged between 'no specification' and USD 100 000 per quality-adjusted life-year.	— The only two groups, apart from close contacts (a group outside the scope of this review), for which preventive treatment after primary screening with either TST or IGRA was likely to be cost-effective across all plausible estimates were PLHIV and healthcare workers; however, the epidemiological assumptions provided in the respective studies have to be reassessed. — Due to either an assumed low LTBI prevalence, low annual reactivation rates or extraordinarily poor adherence to INH treatment, no consistent support could be found for preventive treatment in any of the other currently recommended TB risk groups. — The historical definition of the willingness-to-pay threshold as USD 50 000 per life-year gained for assigning cost-effectiveness is outdated (due to currency depreciation since the threshold emergence in 1992 when, according to the US consumer price index, USD 1 was worth 49 % more than it is in 2015) and must be revised.	Negative on 1, 2, 5, 7, 8, 10, 11	Weak evidence

One article was suggested by the members of ad hoc scientific panel as highly relevant for consideration in the guidance development process.

– Shepardson D, MacKenzie WR. Update on cost-effectiveness of a 12-dose regimen for latent tuberculosis infection at new rifapentine prices. Int J Tuberc Lung Dis. 2014 Jun;18(6):751. doi: 10.5588/ijtld.14.0052 [134].

(Update of the article Shepardson D, Marks SM, Chesson H, Kerrigan A, Holland DP, Scott N, Tian X, Borisov AS, Shang N, Heilig CM, Sterling TR, Villarino ME, Mac Kenzie WR Cost-effectiveness of a 12-dose regimen for treating latent tuberculous infection in the United States. Int J Tuberc Lung Dis. 2013 Dec;17(12):1531-7.

Results. Over a 20-year period, the cost to the health system per TB case prevented by 3 mo INH + RIF compared to 9 mo INH is USD 8 861, while the cost to the health system per QALY gained by 3 mo INH + RIF compared to 9 mo INH is USD 1 879. From the societal perspective, 3 mo INH + RIF is cost-saving compared to 9 mo INH. The cost-effectiveness analysis assumed that 3 mo INH + RIF was administered by DOT, adding substantially to the cost of the 12-dose regimen as compared to SAT 9 mo INH. If adherence to SAT 3 mo INH + RIF is maintained at levels achieved by DOT, then 3 mo INH + RIF would be a cost-saving compared to 9 mo INH from both a health system and a societal perspective. Under these conditions, over a 20-year period, United States TB programmes would save USD 141 per individual treated by switching from 9 mo INH to 3 mo INH + RIF (including the cost of treatment and prevention of future cases of TB for each regimen). From the societal perspective, these savings would rise to USD 231 per individual treated.

Outcomes are in line with the included reviews.

(a) United States: n = 8. Canada: n = 5. United Kingdom: n = 3. India: n = 2. Australia, France, Kenya, South Africa, Uganda, Zambia: n = 1.
(b) A cost-effective intervention (dominant intervention) had lower costs and higher effectiveness when compared to no intervention or another screening strategy. A favourable ICER indicated an intervention with higher costs and higher effectiveness than the comparator.
(c) British Colombia/Canada, Canada, Germany, Saudi Arabia/Brazil, United States: n = 1.
(d) Willingness-to-pay thresholds were not reported. Reported 'reasonable ICER' implied an intervention with higher costs and higher effectiveness than the comparator.
(e) Canada, France, Japan, Netherlands, Spain, United Kingdom, United States: n = 1.
(f) Different willingness-to-pay thresholds were used in primary studies (if reported).

Table A8.6. Summary of initiation rates of preventive treatment for certain risk groups in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome			Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
								Short	Long	Combined			
Commissioned systematic review													
Sandgren, 2016 [30] Countries not reported	1997-2014	n = 13 on general population n = 10 on contacts of TB cases n = 6 on healthcare worker n = 3 on homeless people n = 4 on drug users n = 4 on PLHIV n = 3 on inmates n = 9 on immigrants n = 5 on patients with comorbidities (designs not reported (a))	Various settings	General population	Not reported	Initiation rates of short, long, short/long combined treatment regimen	%, min-max	86	44-99	26-83	*Bias assessment* Quality assessed per study, no general conclusion provided	Negative on 1, 5, 10	Weak evidence
				Contacts of TB cases				-	40-85	53-95			
				Healthcare workers				98	92	47-89			
				Homeless people				-	76-90	34			
				Drug users				-	52-91	-			
				PLHIV				-	67-92	91			
				inmates				-	65	7-90			
				Immigrants				-	77-97	23-82			
				Patients with comorbidities				93	82	-			

(a) Included were primary articles describing RCTs, non-randomised prospective comparative studies of interventions, prospective longitudinal observational studies and retrospective studies.

Table A8.7. Grading of the body of evidence for effectiveness of short versus long latent tuberculosis infection treatment

			Quality assessment					n/N = %*	Effect		Quality	Importance
No of studies (No of participants)	Design	Population Intervention	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short LTBI treatment / Long LTBI treatment	OR (95 % CI)**	Absolute (per 1 000 (95 % CI)) ***		
Initiation												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Adherence												
2 (822) Spyridis, 2007 Tortajada, 2005	RCT	Contacts of TB cases 3 mo INH + RIF or 2 mo RIF + PZA vs 6 mo INH or 9 mo INH	Serious	Not serious	Not serious	Not serious	None	344/391 = 88 % (range: 82-92 %) 353/431 = 82 % (range:7-86 %)	1.5 (1.0-2.3)	55 (4-92)	⊕⊕⊕O Moderate	Critical
Completion												
1 (352) Tortajada, 2005	RCT	Contacts of TB cases 2 mo RIF + PZA vs 6 mo INH	Serious	Not serious	Not serious	Not serious	None	106/153 = 69 % 145/199 = 73 %	0.8 (0.5-1.3)	– 46 (– 156-49)	⊕⊕⊕O Moderate	Critical
1 (7 731) Sterling, 2011	RCT	Contacts of TB cases 3 mo INH + RPT + DOT vs 9 mo INH + SAT	Very serious	Not serious	Not serious	Not serious	None	3 273/3 986 = 82 % 2 585/3 745 = 69 %	2.1 (1.9-2.3)	134 (119-146)	⊕⊕OO Low	Critical
1 (590) Jimenez-Fuentes, 2013	RCT	Immigrants 3 mo INH + RIF vs 6 mo INH	Serious	Not serious	Not serious	Not serious	None	213/296 = 72 % 154/294 = 52 %	2.5 (1.7-3.6)	206 (125-273)	⊕⊕⊕O Moderate	Critical
3 (1 552) Jasmer, 2002 Menzies, 2004 Menzies, 2008	RCT	General population 2 mo RIF + PZA or 4 mo RIF vs 6 mo INH or 9 mo INH	Serious	Not serious	Not serious	Not serious	None	568/785 = 72 % (range: 61-91 %) 459/767 = 60 % (range: 57 %-76 %)	1.9 (1.1-3.5)	141 (23-241)	⊕⊕⊕O Moderate	Critical

** If > 1 article, weighed pooled point estimates and 95 % CI were calculated.*
*** If > 1 article, weighed pooled estimates and 95 % CI were calculated using a random effects model (without quality index).*
**** Calculated via GradePro [76].*

Table A8.8. Summary of completion rates of preventive treatment for certain risk groups in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome			Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
								Short	Long	Combined			
Commissioned systematic reviews													
Sandgren, 2016 [30] Countries not reported	1997-2014	n = 40 on general population n = 16 on contacts of TB cases n = 6 healthcare worker n = 6 on homeless people n = 5 on drug users n = 10 on PLHIV n = 6 on inmates n = 27 on immigrants n = 3 on patients with comorbidities (designs not reported (c))	Various settings		Not reported	Completion rates of short, long, short/long combined treatment regimen	%, min-max				*Bias assessment* No summary of quality provided	Negative on 1, 5, 10, 11	Weak evidence
				General population				61-95	39-96	54			
				Contacts of TB cases				63-82	53-78	48-81			
				Healthcare workers				-	17-75	40-79			
				Homeless people				44-71	23-33	44			
				Drug users				-	38-89	-			
				PLHIV				62-95	55-89	-			
				Inmates				48-100	4-68	-			
				Immigrants				60-85	7-86	53-79			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
				Patients with comorbidities				87-92 75 -			
Girardi, 2014 [92] Low & high ([a])	1981-2013	n = 3 on children n = 6 on contacts n = 3 on elderly n = 5 on healthcare workers n = 8 on migrants n = 7 on PLHIV (Mathematical modelling studies based on published literature (n = 19), on observational studies (n = 6), or on clinical trial (n = 1). One economic evaluation based on observational studies) ([d])	Multiple settings	Children	Not reported	Completion rate of preventive therapy	%, min-max	60.0 %-74.0 %	*Drummond checklist [130]* Low to medium	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence
				Contacts				21.0 %-62.6 %			
				Elderly				50.0 %-80.0 %			
				Healthcare workers				44.0 %-100.0 %			
				Migrants				21.0 %-100.0 %			
				PLHIV				52.0 %-100.0 %			
Non-commissioned systematic review											
Sharma, 2013 [28] Low & high ([b]) Main objectives of this review were not similar to our review question	1992-2012	n = 5 on RIF n = 2 on RIF + INH n = 4 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	Prison, pneumoconiosis clinic, (university-affiliated respiratory) hospitals, government-run and charitable shelters, public healthcare centres, academic and public institutions	HIV-negative adults and children on: RIF 3-4 mo	1 768	Relative risk of adherence vs INH 6-9 mo	RR (95 % CI)	1.13 (1.01-1.28)	*Grade* — High: RIF + INH — Moderate: RIF, RIF + INH (DOT) — Very low: RIF + PZA	Negative on 1, 11	Moderate evidence
				RIF + INH 3 mo	524	vs INH 6-9 mo		1.07 (0.98-1.17)			
				RIF + PZA 2 mo	700	vs INH 6 mo		1.06 (0.86-1.29)			
				RPT + INH (DOT) 3 mo weekly	7 731	vs INH (SAT) 9 mo daily		1.19 (1.16-1.22)			

One article was suggested by the members of the ad hoc scientific panel as highly relevant for consideration in the guidance development process.

- Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, Goldberg SV, Sterling TR; International Maternal Pediatric and Adolescents AIDS Clinical Trials Group; Tuberculosis Trials Consortium. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar;169(3):247-55. doi: 10.1001/jamapediatrics.2014.3158 (http://archpedi.jamanetwork.com/article.aspx?articleid=2089639) [133]. Erratum in: JAMA Pediatr. 2015 Sep;169(9):878. PMID: 25580725

Results. Of 471 in the combination-therapy group (12 once-weekly doses of the RIF + INH, given with supervision by a healthcare professional, for 3 mo), 415 (88.1 %) completed treatment vs 351 of 434 (80.9 %) in the INH-only group (270 daily doses of INH, without supervision by a healthcare professional, for 9 mo) (p = 0 .003).

The completion rate in the short and the long treatment groups were in the higher range of the completion rates of the included systematic reviews.

(a) United States: n = 9. Canada: n = 5. United Kingdom: n = 3. India: n = 2. Australia, France, Italy, Kenya, South Africa, Uganda, Zambia: n = 1. For three articles on the elderly, the countries could not be identified.

(b) Spain: n = 4. Canada: n = 3. Brazil, Hong Kong: n = 2. Germany, Saudi Arabia, Taiwan, United States: n = 1.

(c) Included were primary articles describing RCTs, non-randomised prospective comparative studies of interventions, prospective longitudinal observational studies and retrospective studies.

(d) Some articles comprised multiple population groups.

Table A8.9. Grading of the body of evidence for the safety of different latent tuberculosis infection treatments (outcome = hepatotoxicity)

Number of studies*	Design	Limitations	Direct							
			Inconsistency	Indirectness	Imprecision	ication bias	Treatment cases/ participants	seline cases/ participants	OR (95 % CI)	Quality
Placebo vs INH 6 mo										
1 (Gordin, 1997)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	11/260 (4.2 %)	11/257 (4.3 %)	0.99 (0.42-2.32)	Low
No treatment vs INH 6 mo										
2 (Temprano ANRS 12136 Study Group, 2015)	Randomised trials	Serious	Not serious	Serious	Very Serious	Not available	12/1 030 (1.2 %)	13/1 026 (1.3 %)	0.92 (0.42-2.02)	Low
No treatment vs INH 12-72 mo										
2 (Bailey, 1974; Vikrant, 2005)	Randomised trials	Serious	Serious	Serious	Serious	Not available	19/139 (13.7 %)	6/148 (4.1 %)	4.96 (0.27-90.37)	Very low
Placebo vs INH 12-72 mo										
4 (John, 1994; Madhi, 2011; Rangaka, 2014)	Randomised trials	Serious	Serious	Serious	Very Serious	Not available	56/1 430 (3.9 %)	55/1 434 (3.8 %)	0.87 (0.40-1.92)	Very low
Placebo vs RIF-INH-PZA										
1 (Johnson, 2001)	Randomised trials	Serious	Not available	Serious	Serious	Not available	1/462 (0.2 %)	0/464 (0 %)	3.02 (0.12-74.31)	Very low
INH 6 mo vs INH 12-72 mo										
2 (Martinson, 2011; Samandari, 2011)	Randomised trials	Not serious	Serious	Serious	Serious	Not available	44/1 170 (3.8 %)	23/1 316 (1.7 %)	2.92 (0.90-9.44)	Very low
INH 6 mo vs RIF										
1 (Chan, 2012)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	0/190 (0 %)	15/183 (8.2 %)	0.03 (0.00-0.48)	Low
INH 6 mo vs RIF-INH 3-4 mo										
4 (Geijo, 2007; Martinson, 2011; Rivero, 2007; Jimenez-Fuentes, 2013)	Randomised trials	Serious	Not serious	Serious	Serious	Not available	25/776 (3.2 %)	28/773 (3.6 %)	0.89 (0.52-1.55)	Very low
INH 6 mo vs RPT-INH										
1 (Martinson, 2011)	Randomised trials	Not serious	Not available	Serious	Serious	Not available	17/328 (5.2 %)	17/327 (5.2 %)	1.00 (0.50-1.99)	Low
INH 9 mo vs RIF										

Number of studies*	Design	Limitations	Direct							
			Inconsistency	Indirectness	Imprecision	lication bias	Treatment cases/ participants	seline cases/ participants	OR (95 % CI)	Quality
3 (Menzies, 2004; Menzies, 2008; White, 2012)	Randomised trials	Serious	Not serious	Serious	Not serious	Not available	4/656 (0.6 %)	25/664 (3.8 %)	0.17 (0.06-0.47)	Low
INH 9 mo vs RIF-INH 3-4 mo										
1 (Martínez Alfaro, 1998)	Randomised trials	Serious	Not available	Serious	Serious	Not available	6/98 (6.1 %)	8/98 (8.2 %)	0.73 (0.24-2.20)	Very low
INH 12-72 mo vs RPT-INH										
1 (Martinson, 2011)	Randomised trials	Not serious	Not available	Serious	Not serious	Not available	17/328 (5.2 %)	35/164 (21.3 %)	0.20 (0.11-0.37)	Moderate

** Reference list in Appendix 11.*

Table A8.10. Odds ratios for hepatotoxicity, derived from the Network Meta-analysis

Comparison	OR (compared to no treatment)	OR (compared to placebo)
Placebo	4.36 (1.20, 20.57)	
INH 6 mo	1.48 (0.41, 6.06)	0.34 (0.14, 0.72)
INH 9 mo	2.15 (0.37, 12.07)	0.49 (0.10, 1.95)
INH 12 mo	2.69 (0.93, 8.07)	0.62 (0.23, 1.34)
RPT-INH	0.65 (0.14, 3.39)	0.15 (0.04, 0.51)
RIF	0.17 (0.02, 1.22)	0.04 (< 0.01, 0.19)
RIF-INH 3 mo	0.92 (0.23, 3.85)	0.21 (0.06, 0.57)
RIF-INH-PZA	2.56 (0.26, 23.68)	0.58 (0.07, 3.93)
RIF-PZA	4.58 (1.12, 20.63)	1.05 (0.33, 2.86)

Table A8.11. Summary of the risk of adverse events of latent tuberculosis infection treatment in certain risk groups in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic reviews											
Treatment-limiting AEs											
Den Boon, 2016 [114] High (a)	2011-2012	n = 3 (all RCTs)	High-TB-burden countries	PLHIV (adults) on continuous preventive therapy (300 mg INH for 36 mo)	3 168	Risk of temporarily or permanent discontinuation due to AEs vs 6 mo 300 mg INH + 800 mg EMB (1 study) or 6 mo 300 mg INH (2 studies)	Relative Risk (95 % CI)	5.96 (4.12-8.62)	*Study quality* High	Negative on 2, 5, 8, 11	Moderate evidence
Den Boon, 2014 [116] High (b)	2002	n = 1 (cohort study)	Not reported	MDR-TB child contacts on ethionamide + ofloxacin	61	Gastrointestinal side effects causing treatment to stop	%	4/61 = 6.6 %	*NOS* At least 5 stars	Negative on 5, 11	Weak evidence
Gastrointestinal intolerance											
Den Boon, 2014 [116] High (b)	2002	n = 1 (cohort study)	Not reported	MDR-TB child contacts on ethionamide + ofloxacin	61	Gastrointestinal side effects	%	30/61 = 49 %	*NOS* At least 5 stars	Negative on 5, 11	Weak evidence
Any AEs											
Den Boon, 2016 [114] High (a)	2011-2012	n = 3 (all RCTs)	High-TB-burden countries	PLHIV (adults) on continuous preventive therapy (300 mg INH for 36 months)	3 168	Relative risk of AEs vs 6 mo 300 mg INH + 800 mg EMB (1 study) or 6 mo 300 mg INH (2 studies)	Relative Risk (95 % CI)	2.03 (0.83-2.30) 1.26 (0.72-2.22)	*Study quality* High	Negative on 2, 5, 8, 11	Moderate evidence

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
						Grade 3 or grade 4 elevation in the aspartate or alanine aminotransferase level and more AEs vs 6 mo 300 mg INH + 800 mg EMB (1 study) or 6 mo 300 mg INH (2 studies)		3.41 (2.28-5.09)			
Non-commissioned systematic reviews											
Serious AEs											
Sharma, 2013 [28] Low & high ([c])	1998-2011	n = 2 on RIF n = 1 on RIF + INH n = 0 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	University-affiliated respiratory hospital, general hospital, academic and public institution	HIV-negative adults and children on: RIF 3-4 mo	956	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	0.36 (0.17-0.77)	*No risk of bias provided for this outcome*	Negative on 1, 11	Weak evidence
				RIF + INH 3 mo	196	vs INH 6-9 mo		0.78 (0.30-2.01)			
				RPT + INH (DOT) 3 mo weekly	7 799	vs INH (SAT) 9 mo daily		0.55 (0.40-0.74)			
Langendam, 2013 [119] Country not reported	1994-2005	n = 1 on PZA + EMB	Divers	Contacts of MDR-TB patients receiving preventive MDR-TB treatment (apparently healthy subjects	12	Number of serious AEs as reported by authors	% ([14]) (n)	0 % (0)	*NOS* High methodological quality *GRADE* Very low quality of evidence	Negative on 5, 6, 7, 8, 11	Weak evidence
		n = 1 on PZA + levofloxacin			12			0 % (0)			
		n = 1 on PZA + ofloxacin (all observational studies)			22			13.6 % (3)			
Treatment-limiting AEs											
Sharma, 2013 [28] Low & high ([d])	1992-2012	n = 4 on RIF n = 2 on RIF + INH n = 2 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	University-affiliated respiratory hospital, pneumoconiosis clinics, male prison, general hospital, healthcare centres, academic and public institution	HIV-negative adults and children on: RIF 3-4 mo	1 674	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	0.48 (0.23-1.00)	*Grade* —High: RIF + PZA —Moderate: RIF + INH (DOT) —Low: RIF + INH —Very low: RIF	Negative on 1, 11	Moderate evidence
				RIF + INH 3 mo	536	vs INH 6-9 mo		1.16 (0.74-1.82)			
				RIF + PZA 2 mo	368	vs INH 6 mo		3.61 (1.82-7.19)			
				RPT + INH (DOT) 3 mo weekly	7 731	vs INH (SAT) 9 mo daily		1.32 (1.07-1.64)			
Langendam, 2013 [119] Country not reported	1994-2005	n = 1 on PZA + EMB	Divers	Contacts of MDR-TB patients receiving preventive MDR-TB treatment (apparently healthy subjects	12	Number of AE that were reason for dropout	% (n)	58 % (7)	*NOS* High methodological quality *GRADE* Very low quality of evidence	Negative on 5, 6, 7, 8, 11	Weak evidence
		n = 1 on PZA + levofloxacin			17			100 % (17)			
		n = 2 on PZA + ofloxacin (all observational studies)			-16 —22			-88 % (14) —59 % (12)			
Hepatotoxicity											
Sharma, 2013 [28] Low & high ([e])	1992-2012	n = 5 on RIF n = 2 on RIF + INH n = 4 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	University-affiliated respiratory hospital, pneumoconiosis clinics, male prison, general hospital, healthcare centres, unclear, academic and public institution	HIV-negative adults and children on: RIF 3-4 mo	1 774	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	0.15 (0.07-0.35)	*Grade* —High: RIF + INH (DOT) —Moderate: RIF, RIF + PZA —Low: RIF + INH	Negative on 1, 11	Moderate evidence
				RIF + INH 3 mo	536	vs INH 6-9 mo		0.88 (0.43-1.81)			
				RIF + PZA 2 mo	640	vs INH 6 mo		4.59 (2.14-9.85)			
				RPT + INH (DOT) 3 mo weekly	7 799	vs INH (SAT) 9 mo daily		0.16 (0.10-0.27)			
Gastrointestinal intolerance											
Sharma, 2013 [28] Low & high ([f])	1992-2012	n = 3 on RIF n = 2 on RIF + INH	University-affiliated respiratory hospital,	HIV-negative adults and children on: RIF 3-4 mo	1 535	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	1.46 (0.73-2.92)	*No general risk of bias provided*	Negative on 1, 11	Weak evidence
				RIF + INH 3 mo	510	vs INH 6-9 mo		1.34 (0.80-2.27)			

([14]) Calculated by researchers performing this review of systematic reviews.

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
		n = 2 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	pneumoconiosis clinics, male prison, general hospital, healthcare centres	RPT + PZA 2 mo	368	vs INH 6 mo		2.19 (1.37-3.49)			
Rash											
Sharma, 2013 [28] Low & high (g)	2003-2012	n = 2 on RIF n = 0 on RIF + INH n = 1 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	University-affiliated respiratory hospital, male prison, pneumoconiosis clinic, academic and public institution	HIV-negative adults and children on: RIF 3-4 mo	1 213	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	0.53 (0.21-1.32)	*No general risk of bias provided*	Negative on 1, 11	Weak evidence
				RIF + PZA 2 mo	76	vs INH 6 mo		1.8 (0.35-9.25)			
				RPT + INH (DOT) 3 mo weekly	7 799	vs INH (SAT) 9 mo daily		1.37 (0.79-2.39)			
Any AEs											
Sharma, 2013 [28] Low & high (h)	1992-2011	n = 2 on RIF n = 1 on RIF + INH n = 2 on RIF + PZA n = 1 on RIF + INH (DOT) (all trials)	Pneumoconiosis clinics, healthcare centres, academic and public institution, university-affiliated respiratory hospital	HIV-negative adults and children on: RIF 3-4 mo	1 162	Relative risk of an AE vs INH 6-9 mo	RR (95 % CI)	0.99 (0.68-1.43) Haematological AEs: 0.50 (0.05-5.44)	*No general risk of bias provided*	Negative on 1, 11	Weak evidence
				RIF + INH 3 mo	314	vs INH 6-9 mo		1.16 (0.82-1.65)			
				RIF + PZA 2 mo	292	vs INH 6 mo		1.71 (1.24-2.35) Pruritus: 1.95 (0.83-4.59)			
				RPT + INH (DOT) 3 mo weekly	7 799	vs INH (SAT) 9 mo daily		0.84 (0.76-0.93) Hypersensitivity: 8.32 (5.05-13.71)			
Langendam, 2013 [119] Country not reported	1997	n = 1 on PZA + ofloxacin (observational study	Not reported	healthcare workers contacts of MDR-TB patients receiving preventive MDR-TB treatment (apparently healthy subjects	17	Number of subjects with one or more AE	% ([15]) (n)	76.5 % (13)	*NOS* High methodological quality *GRADE* Very low quality of evidence	Negative on 5, 6, 7, 8, 11	Weak evidence

Three articles were suggested by the members of the ad hoc scientific panel as highly relevant for consideration in the guidance development process.

Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999 Mar 17;281(11):1014-8 [136].

Results. Eleven patients (0.10 % of those starting and 0.15 % of those completing treatment) had hepatotoxic reactions to INH during preventive treatment.

Compared to the results of Stagg et al., the presented percentages of hepatotoxic cases in INH-treated group were in the lower range. No comparison could be made with the other included reviews because they presented the relative risk of hepatotoxicity and no absolute number of hepatotoxic cases

Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, Drobeniuc J, Bock N, Villarino ME; TB Trials Consortium. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. Int J Tuberc Lung Dis. 2015 Sep;19(9):1039-44, i-v. doi: 10.5588/ijtld.14.0829 [137].

Results. Of 6 862 participants: 77 (1.1 %) developed hepatotoxicity; 52 (0.8 %) were symptomatic; 1.8 % (61/3 317) were on 9 mo INH and 0.4 % (15/3 545) were on 3 mo RIF + INH (P < 0.0001). The risk of hepatotoxicity during LTBI treatment with 3 mo RIF + INH was lower than the risk with 9 mo INH.

Although no significant difference was found in hepatotoxicity between 3 mo RIF + INH and 6-9 mo INH in the included systematic reviews Sharma et al. and Stagg et al., the outcomes are in line with the results of Bliven-Sizemore et al.

Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, Goldberg SV, Sterling TR; International Maternal Pediatric and Adolescents AIDS Clinical Trials Group; Tuberculosis Trials Consortium. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar;169(3):247-55. doi: 10.1001/jamapediatrics.2014.3158 (http://archpedi.jamanetwork.com/article.aspx?articleid=2089639) [133]. Erratum in: JAMA Pediatr. 2015 Sep;169(9):878. PMID: 25580725

Results. The 95 % CI for the difference in rates of discontinuation attributed to an AE was – 2.6 to 0.1, which was within the equivalence range. In the safety population, three of 539 participants (0.6 %) who took the combination drugs (3 mo RIF + INH)

([15]) Calculated by researchers performing this review of systematic reviews.

had a grade 3 AE vs one of 493 (0.2 %) who received INH (9 mo INH) only. Neither arm had any hepatotoxicity, grade 4 AEs or treatment-attributed death.

The results for discontinuation of LTBI treatment attributed to an AE are in line with the included review Sharma et al.

The findings that neither arm (INH 9 mo vs RIF + INH 3 mo) had any hepatotoxicity cases are in contrast with the finding of Stagg et al. (8.2 % (n = 8 cases) vs 6.1 % (n = 6 cases)).

For the other outcomes, no comparison could be made with the outcomes of the included systematic reviews.

(a) Botswana, India, South Africa: n = 1
(b) South Africa: n = 1
(c) Canada: n = 3. Brazil, Spain: n = 2. Saudi Arabia, United States: n = 1
(d) Canada, Spain: n = 3. Brazil, Hong Kong: n = 2. Saudi Arabia, Taiwan, United States: n = 1
(e) Canada: n = 3. Brazil, Germany, Hong Kong, Spain: n = 2. Saudi Arabia, Taiwan, United States: n = 1
(f) Hong Kong, Spain: n = 2. Brazil, Canada, Saudi Arabia, Taiwan: n = 1
(g) Brazil, Canada: n = 2. Hong Kong, Saudi Arabia, Spain, Taiwan, United States: n = 1
(h) Brazil, Canada, Hong Kong, Spain: n = 2. Saudi Arabia, United States: n = 1.

Appendix 9. Summary tables – programmatic issues

Table A9.1. Summary of the effectiveness of screening programmes for latent tuberculosis infection in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews											
Aldridge, 2014 [122] Low & high (a) Main objectives of this review were not similar to our review question	1989-2013	n = 3 studies on LTBI as assessed by TST n = 15 studies on TB (all observational studies)	Not reported	Migrants, adoptees, refugees migrating to low-incidence countries, screened before entry	20 587	Number of LTBI cases identified during screening; range	n; min-max %	1 884; 1.0 %-2.7 %	*GRADE* Very low	Negative on 1, 4, 5, 7, 8, 10, 11	Weak evidence
					452 971	Culture-positive TB cases		755			
					569 210	Smear-positive TB cases		987			
					Not reported	Culture-positive cases of TB by WHO prevalence of TB in country of origin: 50−149 cases per 100 000 population	Yield per 100 000 (95 % CI)	19.7 (10.3-31.5)			
						150−249 cases per 100 000 population		166.2 (140.1-194.4)			
						250−349 cases per 100 000 population		133.5 (110.7-158.4)			
						≥ 350 cases per 100 000 population		335.9 (283.0-393.2)			
Campbell, 2015b [91] Low & high (b)	1999-2014	Total included: n = 51 n = 18. n = 15 studies on TST; n = 2 studies on QFT-GIT; n = 1 study on T-SPOT.*TB* (design not reported)	Not reported	Immigrants with positive TST	9 349	Immigrants recommended LTBI treatment of those tested positive	% (n); p-value TST+ vs IGRA+	53.9 % (5 041)	*SIGN* — High quality: n = 9 — Acceptable quality: n = 9	Negative on 2, 4, 5, 8, 10, 11	Weak evidence
				Immigrants with positive IGRA	1 186			43.1 % (511); p < 0.0001			
Campbell, 2015a [87] Country not reported	1997-2014	n = 3 on IGRA n = 15 on TST (design not reported)	Not reported	Tested positive with IGRA or TST	Not reported	— Pooled estimates of IGRA positives — Of those, recommendations of LTBI treatment	% (95 % CI)	— 23.7 % (17.7-30.8) — 27.5 % (4.2-76.6)	SIGN — High quality: 2 on IGRA, 7 on TST — Acceptable quality: 1 on IGRA, 8 on TST	Negative on 2, 5, 6, 10, 11	Weak evidence
						— Pooled estimates of TST-positives — Of those, recommendations of LTBI treatment		— 44.7 % (36.4-53.3) — 59.0 % (47.7-69.5)			
Uyei, 2011 [123] High (c)	1995-2010	n = 16 (design not reported)	HIV-healthcare settings	PLHIV	13 829	Proportion of PLHIV screened for TB	% weighted mean (SD); range	88.7 % (12.1); 48-100 %	Not reported	Negative on 1, 2, 3, 4, 5, 6, 7, 8, 10, 11	Weak evidence
					13 468	Proportion of PLHIV screened for IPT eligibility		87.7 % (4.5); 81-93 %			
					4 547	Proportion IPT eligible started treatment		72.6 % (12.5); 67-100 %			
					27 204	Proportion of PLHIV started on IPT		13.5 % (16.6); 5-95 %			
					Not reported	IPT taken appropriately as prescribed		Not reported; 75-92 %			
					Not reported	6 month of treatment within the study's follow-up period		Not reported; 47-88 %			

(a) Country of origin: Vietnam: n = 5. Multiple countries: n = 4. Bhutan, Ethiopia, Haiti, Iraq, South Korea: n = 1. Country where screening took place: Vietnam: n = 5. Multiple countries: n = 4. Ethiopia, Jordan, Nepal, South Korea, Thailand, United States naval base in Guantanamo Bay Cuba: n = 1

(b) Campbell et al. included participants originating from a wide variety of countries across Africa, Asia, the Americas and Europe (n = 49). Country not reported: n = 2.

(c) Uganda: n = 6. South Africa: n = 5. Ethiopia: n = 2. Botswana, Rwanda, Tanzania: n = 1.

Table A9.2. Summary of the cost-effectiveness of screening regimens for certain risk groups in systematic reviews

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Commissioned systematic review							
Girardi, 2014 [92] Low & high (a)	39 cost-effectiveness analyses. n = 32 articles reported on analyses conducted in upper-middle-income countries with TB incidence less than 100/100 000	Healthcare system n = 24; societal n = 7; local TB-control programme n = 1; not reported n = 7	Time horizon: range < 10 years-lifetime	Migrants: — Eight studies analysing screening and treatment of LTBI in persons migrating to high or upper-middle-income countries with TB incidence less than 100/100 000, show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b), when screened persons originate from countries with high TB incidence (above 120-150/100 000). TB contacts: — Six studies (all conducted in upper-middle-income countries with TB incidence less than 100/100 000) on contacts of patients with active TB also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b). PLHIV: — Six studies on PLHIV both in upper-middle-income countries with TB incidence less than 100/100 000 and in low-income or high-TB-incidence countries also show that this intervention may determine savings for the healthcare system or have a favourable incremental cost-effectiveness ratio (b). The effect of antiretrovirals in lowering TB risk in PLHIV was not taken into account in all but one of these studies. Healthcare workers: — For healthcare workers there is an indication of possibly favourable incremental cost-effectiveness ratio (b) in some of the analyses on these persons. Other populations: — Limited evidence is available for other population groups.	The available evidence suggests that screening and treatment for LTBI may be a cost-effective intervention for some population groups characterised by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high-TB-incidence countries, contacts of active TB cases and PLHIV. However, a marked variability across studies in economic inputs, in epidemiologic and TB natural history parameters, as well as in assumptions on effectiveness of preventive treatment made problematic the extrapolation measures of cost-effectiveness from one setting to another.	Negative on 1, 2, 5, 6, 9, 10, 11	Weak evidence
Non-commissioned systematic reviews							
Campbell, 2015 (AHEHP) [103] Low & high (c)	n = 8 CEA studies (children n = 2; immunocompromised n = 6; recently arrived n = 2)	Societal perspective n = 4; Healthcare system perspective n = 2; Healthcare programme perspective n = 2	Range 20 years-lifetime	— Three studies evaluated the cost-effectiveness of screening tests on the basis of the options of no screening and screening with a TST. Screening new adult immigrants and PLHIV was strongly cost-effective (d) with a TST. — The remaining five studies evaluated screening more comprehensively through evaluating TST, IGRA, no screening, and other options. The IGRA was found moderately cost-effective (d) in new adult immigrants and 6- to 44-year-old immigrants that landed more than 5 years prior, while the TST was dominated by no screening in both cases. One study reported screening PLHIV was strongly cost-effective (d) with a TST and moderately cost-effective with an IGRA, while the other reported either dual TST/QFT or T-SPOT.*TB* alone would be the most cost-effective, depending on the situation. No test was cost-effective (d) for renal diseases; however, the IGRA was found to be the most cost-effective test more often than the TST, if screening had to be performed. While screening for diabetics was not cost-effective (d), the TST was found to be most cost-effective if screening was done. All ICERs for other immunocompromising conditions were cost prohibitive, although the TST was found to be the most cost-effective test if screening had to occur.	Screening PLHIV with a TST is strongly cost-effective, while screening adult immigrants with an IGRA is moderately cost-effective.	Negative on 5, 10, 11	Weak evidence

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Nienhaus, 2011 [104] Low & high ([e])	5 cost analyses and n = 8 cost-effectiveness analyses	Not reported	Range 1 year-lifetime	— One study analysed the alternative use of TST or IGRA and seven studies compared the (1) TST-only, (2) positive TST followed by IGRA and (3) IGRA-only strategies. — Two studies favoured the IGRA-only strategy, and four studies found the IGRA in TST-positives to be the most cost-effective ([f]).	The available studies on cost-effectiveness provide strong evidence in support of the use of IGRAs in screening high-risk groups, such as healthcare workers, immigrants from high-incidence countries and close contacts. In general, the higher unit cost of the IGRAs compared to that of the TST is compensated for by cost savings through the more targeted performance of CXRs and offering of chemoprevention. If the increasing evidence that IGRA-positive subjects have a higher probability of progression to active TB holds true, the IGRA-only screening strategy should prove to be the more cost-effective test.	Negative on 1, 2, 3, 5, 7, 8, 10, 11	Weak evidence

(a) United States: n = 8; Canada: n = 5; United Kingdom: n = 3; India: n = 2; Australia, France, Kenya, South Africa, Uganda, Zambia: n = 1.
(b) A favourable ICER indicated an intervention with higher costs and higher effectiveness than the comparator.
(c) Japan, Mexico, Uganda, United States, multiple low-TB-incidence countries: n = 1.
(d) Cost-effectiveness was defined as follows: ICER < USD 20 000 = strongly cost-effective; ICER between USD 20 000 and USD 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.
(e) Canada, France, Germany, Israel, Japan, Switzerland, United Kingdom, United States: n = 1.
(f) Different willingness-to-pay thresholds were used in primary studies.

Table A9.3. Summary of the effectiveness of interventions to improve screening in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic review											
Lutge, 2015 [124] Low ([a])	1998-2001	n = 2 on incentives vs routine care n = 1 on cash versus non-cash incentives n = 1 on different values of cash incentives n = 2 on incentives versus any other intervention (all were trials) ([b])	Community-based TB clinic, urban research clinic	Drug users	1 371	Risk ratio of return for TST results; incentives vs routine care	RR (95 % CI)	2.16 (1.41-3.29)	*GRADE* All studies were graded low	Negative on 1, 5, 111	Weak evidence
				Injection drug and crack cocaine users	652	Cash vs non-cash incentives		1.13 (1.07-1.19)			
				Population not specified	404	Different values of cash incentive		1.08 (1.01-1.16)			
				Drug users	1 366	Incentives vs any other intervention		2.16 (1.56-3.00)			

Two articles were suggested by the members of the ad hoc scientific panel as highly relevant for consideration in the guidance development process.

– Chaisson, R. E., Keruly, J. C., McAvinue, S., Gallant, J. E., & Moore, R. D. (1996). Effects of an incentive and education program on return rates for PPD test reading in patients with HIV infection. JAIDS Journal of Acquired Immune Deficiency Syndromes, 11(5), 455-459 [138].

Results. For PLHIV, return rates for PPD reading were 96 (35 %) of 272 for the control group, 111 (48 %, p = 0.004) of 229 for the food voucher group and 96 (61 %, p < 0.0001) of 158 for the food voucher and patient education group.

No direct comparison could be made with the outcomes of the included articles, but the results of Chaisson et al. were not in conflict with the included systematic reviews.

FitzGerald, J. M., Patrick, D. M., Strathdee, S., Rekart, M., Elwood, R. K., Schecter, M. T., Montaner, J. et al., Vancouver Injection Drug Use Study Grp (1999). Use of incentives to increase compliance for TB screening in a population of intravenous drug users. International Journal of Tuberculosis and Lung Disease, 3(2), 153-155 [139].

Results. During the initial period 558 subjects were evaluated and no incentive was offered. During the second phase of the study 549 drug users were assessed but were also offered USD 5 if they returned to have their TST read. Use of incentives increased compliance from 43 % to 78 % (p = 0.001).

Excluded by Lutge et al. because there was no RCT design: essentially two cross-sectional studies in which the first group was not given an incentive and the second group was.

The results of FitzGerald et al. are in line with the outcomes of the included systematic review of Lutge et al.

(a) United States: n = 3

(b) Some studies addressed multiple interventions.

Table A9.4. Summary of contact investigation approaches in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Target population and approach	Test	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews												
Schepisi, 2015 [90] Low [a]	1974-2013	n = 43 articles in quantitative analysis; 117 healthcare associated TB incidents (all observational outbreak studies)	Healthcare settings	*Target population* All individuals (patients and healthcare workers) in the healthcare setting during the period of infectivity of the index case *Approach* — All individuals who were in the healthcare setting during the period of infectivity of the index case were considered as candidates for screening — Priority for screening was defined based on the risk of progression to active TB of exposed individuals — Classic concentric circle approach	IGRA not otherwise specified, QFT, T-SPOT.*TB*, QFT-IT, or TST	Not reported	% candidates for screening	%	In the majority of the studies: 100 %	*NOS checklist* Median score 4, over a maximum score of 9	Negative on 1, 2, 5, 6, 7, 8, 10, 11	Weak evidence
							Percentage actually screened — Patients — Healthcare workers	Median (% range)	— 78.0 % (12.8-100.0 %) — 97.3 % (67.3-100.0 %)			
Kotila, 2016 [101] Country not reported	1993-2012	n = 21 (design not reported)	Aircraft	*Target population* Aircraft contacts (crew and travellers) *Approach* — All passengers and crew — Only five rows surrounding the index case	TST or IGRA	279 flights n = 1 287 all passengers and crew in contact investigation strategy for whom a test result was available	% possibly infected during the flight (positives with no other risk factors for test positivity)	% (n)	0.8 % (10)	The quality of all the evidence varied from low to very low (not further specified)	Negative on 1, 2, 4, 5, 7, 8, 9, 10, 11	Weak evidence
							% TST conversion		0.5 % (7)			
						n = 905 aircraft contacts with test results for incidents where only five rows surrounding the index case were traced	% possibly infected during the flight (positives with no other risk factors for test positivity)		1.3 % (12)			
							% TST conversion		0.1 % (1)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Target population and approach	Test	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Triasih, 2012 [94] High (b)	1961-2009	n = 11 (all observational outbreak studies)	Household settings	*Target population* Child contacts < 15 yrs *Approach* — Approach was not defined — There was no uniform definition of a household contact across the studies, but the most common definition was a child living in the same house as the index case	TST	1 612 source cases; 3 321 child contacts	TB infection (not active) among child contacts	Range	24.4-69.2 %	Not reported	Negative on 1, 2, 3, 5, 7, 8, 9, 10, 11	Weak evidence
Fox, 2013 [66] Country not reported (c)	1935-2012	n = 203 studies included 158 studies reporting data on TB disease status and 168 studies reporting LTBI status (n = 15 cross-sectional studies, 2 case control studies, 185 cohort studies, 1 RCT)	Low–middle-income and high-income setting	*Target population* Contacts of patients with TB *Approach* — Approach not defined — Definitions of household contact: based on location, such as a common eating or sleeping area; minimum duration of exposure or degree of proximity — Definitions of close contact: any known exposure; intimate; sharing the air for a prolonged period; minimum duration of exposure in other closed spaces such as the workplace	TST	Contacts screened — Low/middle-income setting: n = 878 724 — In high-income setting: n = 284 505	Proportion active TB — In low/middle-income setting — In high-income setting	% (95 % CI)	— 3.1 % (2.2-4.4) — 1.4 % (1.1-1.8)	Not reported	Negative on 1, 5, 7, 8, 11	Weak evidence
						Contacts screened — In low/middle-income setting: n = 60 557 — In high-income setting: n = 284 505	Proportion LTBI — In low/middle-income setting — In high-income setting		— 51.5 % (47.1-55.8 %) — 28.1 % (24.2-32.4 %)			
						Contacts screened — Contacts born locally: n = 7 576 — Contacts born overseas: n = 4 298	Proportion LTBI — Contacts born locally — Contacts born overseas		— 17.0 % (11.8-24.0) — 39.2 % (30.0-49.3)			
							Prevalence LTBI contacts born overseas vs contacts born locally	OR (95 % CI); p-value	3.39 (3.10-3.71); p < 0.0001			
Shah, 2014 [95] Low & high (d)	1970-2011	LTBI n = 9 studies with only MDR-TB source cases n = 3 studies with mono- or poly-resistant TB source cases n = 5 studies in high-burden settings n = 9 studies in low-burden settings n = 5 studies on both children and adults (design not reported) Active TB n = 16 studies with only MDR TB source	Low and high-burden TB settings	*Target population* Individuals living with drug-susceptible TB patients *Approach* — Approach and contact definitions not reported	TST	Median of 111 household contacts	Overall pooled yield of LTBI	% (95 % CI)	47.2 % (30.0-61.4)	Not reported	Negative on 1, 2, 3, 4, 5, 6, 7, 8, 10, 11	Weak evidence
							Yield of LTBI in contacts of MDR-TB source cases		50.7 % (41.5-59.9)			
							Yield of LTBI in contacts of mono- or poly-resistant TB source cases		41.5 % (8.19-74.8)			
							Yield of LTBI among contacts in high and low-burden TB settings		High: 52.5 % (33.8-71.2) Low: 44.1 % (24.9-63.4)			
							Yield of LTBI in paediatric contacts and adults contacts		Paediatric: 7.3 % (3.9-50.6) Adult: 51.9 % (25.6-78.2)			

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Target population and approach	Test	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
		cases, n = 7 studies with only mono- or poly-resistant TB source cases n = 12 studies from high-burden TB settings n = 13 studies from low-burden settings n = 11 studies on both children and adults (design not reported)					Overall pooled yield of TB		7.8 % (5.6-10.0)			
							Yield of active TB in contacts of MDR-TB source cases		6.5 % (4.6-8.4)			
							Yield of active TB in contacts of mono- or poly-resistant TB source cases		11.6 % (2.7-20.4)			
							Yield of TB among contacts in high and low-burden TB settings		High: 8.7 % (6.08-11.2) Low: 6.3 % (2.4-10.1)			
							Yield of LTBI in paediatric contacts and adults contacts		Paediatric: 4.0 % (1.5-6.5) Adult: 4.9 % (2.7-7.0)			

(a) Incidences: United States: n = 66. France: n = 34. United Kingdom: n = 5. Netherlands: n = 6. Canada: n = 2. Australia, Ireland, Italy, Japan: n = 1.
(b) India: n = 4. Thailand: n = 2. Cambodia, Indonesia, Laos, Pakistan, Philippines: n = 1.
(c) Fox et al. reported the outcomes per low–middle-income countries (n = 95) and high-income countries (n = 108).
(d) United States: n = 7. Peru, South Africa: n = 3. Brazil, India: n = 2. Kuwait, Micronesia, Philippines, Spain, Switzerland, Taiwan, United Kingdom, US Virgin Islands: n = 1.

Table A9.5. Overview of determinants of latent tuberculosis infection treatment initiation, adherence and completion in the general population diagnosed with latent tuberculosis infection (Stuurman et al., 2016)

Determinant	Specification determinant (vs reference group)	Number of articles			
		Positive association		*Inverse association*	
		Prospective studies	Retrospective studies	Prospective studies	Retrospective studies
Determinants of LTBI treatment initiation					
Age	Older age (vs younger age)	-	1	-	2
Gender	Men (vs women)	-	1	-	1
Sub-population within general population with LTBI	Refugee/immigrants (vs born in country of study)	1	1	-	-
	Immigrants born in WHO category 3 or 5 country (vs category 1 country) (a)	1	-	-	-
	Healthcare workers (vs no healthcare worker)	-	-	-	2
	Case contact (vs no case contact)	1	2	-	-
Education	Lower education level (vs not reported)	1	-	-	-
Behaviour	Alcohol use reported at baseline (vs no alcohol use reported)	-	-	-	1
Other	Continuity of primary care by consulting a regular physician (vs not reported)	1	-	-	-
	Pregnant (vs not pregnant)	-	-	-	1
	Prior incarceration (vs not reported)	1	-	-	-
	Fear of becoming sick with TB without medicine (vs no fear of becoming sick)	1	-	-	-
	Previous BCG vaccination (vs not reported)	-	-	-	1
	Abnormal CXR findings consistent with previous TB (vs not reported)	-	1	-	-
	A non-employment reason for screening (vs not reported)	1	-	-	-
Determinants of LTBI treatment adherence					
Age	Older age (vs younger age)	-	-	1	-
Ethnicity	Bicultural (d) (vs Hispanic or non-Hispanic)	1	-		-
Education	Higher grades in school (vs lower grades)	1	-	-	-
Behaviour	Risk behaviours (vs not reported) (e)	-	-	2	-

Determinant	Specification determinant (vs reference group)	Number of articles			
		Positive association		*Inverse association*	
		Prospective studies	Retrospective studies	Prospective studies	Retrospective studies
AEs	Some somatic complaints (vs not reported)	-	-	1	-
Determinants of LTBI treatment completion					
Age	Older (vs younger)	3 (b) (c)	4 (g)	3	6
Gender	Male (vs female)	-	-	-	2
Ethnicity	Hispanic/Latino ethnicity (vs Asian ethnicity)	-	-	1	
	White Hispanic (vs black, non-Hispanic)	-	1	-	-
	Country of birth (i.e. Haiti, Dominican Republic, China with Hong Kong, or Vietnam) (vs other countries)			Varying results found between countries (n = 1)	
	Asian/Pacific islander (vs white)	-	2	-	-
	Region of origin (i.e. Latin America and Caribbean or Asia and other) (vs United States, Canada, Europe)	-	1	-	-
	Black race (vs not reported)	-	-	-	1 (g)
	Ethnicity (i.e. Asian, non-Hispanic black or Hispanic (vs non-Hispanic white)		1		
Sub-population within source population	Healthcare worker (vs no healthcare worker)	-	-	-	1
	Case contact (vs no case contact)	-	1	-	1 (f)
	Currently homeless (vs not currently homeless)	-	-	-	2
	Drug users (vs people who do not use drugs)	-	-	-	2
	Refugees/immigrants (vs born in country of study)	1	4 (g)		2
	Indication for LTBI treatment immunosuppression (vs case contact)	1 (c)	-	-	-
Health	History of hepatitis A, B or C (vs no history of liver disease)	1	-	-	-
	Other medications reported at baseline (vs none reported)	-	-	-	1 (f)
	Use of concomitant medications by women (vs no use of concomitant medication)	-	-	-	1
Behaviour	(Excess) alcohol use (vs no alcohol use)	-	-	-	4 (f)
	Smoking (vs non-smoking)	1 (c)	-	-	-
Treatment	Treatment without INH (vs treatment with INH)	1 (c)	5	-	-
	9 months' INH (vs other regimens)	-	-	-	1
	Regimen choice offered (vs no regimen choice offered)	-	1	-	-
	Twice weekly RIF + PZA (vs daily RIF + PZA)	-	1	-	-
	DOT (vs SAT)	-	3	-	-
AEs	AEs (vs no AEs)	-	-	-	7
	AEs (i.e. grade 1 or 2 hepatotoxicity, grade 3 or 4 hepatotoxicity or AEs other than hepatotoxicity) (vs not reported)		Conflicting results found between AEs (n = 1)		
Other	Not having been incarcerated within 6 months of diagnosis (vs not reported)	1	-	-	-
	Referral reason (i.e. correctional/rehabilitation or postpartum women) (vs TST-positive from screening)	-	-	-	1
	Risk group (i.e. contact, medical risk (h), population risk (i)) (vs low risk (i))	-	1	-	-
	Cause of screening/referral (i.e. asylum seekers or contacts) (vs anti-TNF-alpha candidates)	-	-	-	1
	Fear for venepuncture (vs not reported)	-	-	1	-
	Low TB risk perception (vs not reported)	-	-	1	-
	Plan to tell friends or family about LTBI diagnosis (vs not reported)	1	-	-	-
	Home situation (i.e. child living with no natural parents or one natural parent) (vs living with both natural parents)	-	-	1	-
	Spanish language (vs non-Spanish language)	-	1	-	-
	Resident in a congregate setting (vs never or unknown)	-	-	-	1
	Missed appointment call or letter (vs no missed appointment call)	-	-	-	1
	No medical insurance (vs medical insurance)	-	-	-	1
	Clinic attendance before treatment (vs clinic non-attendance before treatment)	-	1	-	-
	Presumed non-recent TB infection (vs presumed recent TB infection)	-	-	-	1
	Public health nurse referral (vs no public health nurse referral)	-	-	-	1

(a) WHO defined five categories of TB prevalence based on 1st (least prevalent) to 5th (most prevalent).
(b) Data analysed in individuals who underwent three QFT-GIT.
(c) Data analysed in individuals who underwent at least one serial QFT-GIT.

(d) Bicultural is defined by questions separated into the domains Hispanic and non-Hispanic, considering language use, linguistic proficiency and electronic media use. Individuals scoring high in both domains are considered bicultural.
(e) Risk behaviours: ever used alcohol, cigarettes, marijuana, been expelled or suspended from school or been in a physical fight.
(f) Data analysed in Hispanic subjects for one study.
(g) Data analysed in non-Hispanic subjects for one study.
(h) Persons with medical risk factors such as having a TST conversion within two years of a negative TST, HIV infection, untreated or partially treated prior TB, suspected TB with an abnormal CXR, being younger than 5 years of age with a positive TST or having a clinical condition associated with an increased risk of TB disease.
(i) Persons with population risk factors such as: recent immigrants to the United States (5 years) from countries with high TB prevalence, homeless persons, residents and employees of congregate settings such as prisons and jails, and healthcare facilities.
(j) Persons with low risk of developing TB disease (no case contact, no medical risk, no population risk factors).

Table A9.6. Grading of the body of evidence for effectiveness of directly observed treatment versus self-administered treatment

			Quality assessment					n/N = %	Effect			
No of studies (no. of participants)	Design	Population Treatment Intervention	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOT / SAT	OR (95 % CI)	Absolute [a] (per 1 000 (95 % CI))	Quality	Importance
Initiation												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Adherence												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Completion												
1 (199) Chaisson, 2001	RCT	Drug users [b] long INH Outreach DOT vs SAT	Serious [e]	Not serious	Not serious	Not serious	None	79/99 = 80 % 79/100 = 79 %	1.1 (0.5-2.1)	15 (– 137-98)	Moderate	Critical
1 (111) Batki, 2002	RCT	Drug users [b] long INH DOT + Methadone treatment vs SAT + no incentive [c]	Very serious [f]	Not serious	Not serious	Serious [i]	None	49/72 = 68 % 5/39 = 13 %	14.5 (5.0-42)	552 (296-732)	Very low	Critical
1 (7 731) Sterling, 2011	RCT	Contacts of TB cases DOT + 3INH + RPT vs SAT + long INH	Very serious [g]	Not serious	Not serious	Not serious	None	3 273/3 986 = 82 % 2 585/3 745 = 69 %	2.1 (1.9-2.3)	134 (119-146)	Low	Critical
1 (135) Matteelli, 2000	RCT	Immigrants long INH Clinic-based DOT [d] vs SAT daily [e]	Serious [h]	Not serious	Not serious	Serious [i]	None	6/82 = 7.3 % 22/53 = 41 %	0.1 (0.04-0.3)	– 342 (– 239-387)	Low	Critical

(a) Calculated via GradePro [76].
(b) Both studies with drug users population are presented separately, since one of the studies applies DOT + an incentive as intervention.
(c) Approximately half of the intervention group (37/72) also received substance abuse counselling.
(d) Most likely DOT, however terminology not very clear in the methods and results sections of the article.
(e) Chaisson et al. 2001: unclear allocation concealment; no blinding; use of unvalidated patient-reported outcomes in SAT arm (self-report; urine tests and medication event monitoring system in a subset of patients in this study show that self-reported adherence was greatly overestimated, thereby possibly underestimating the effect of DOT).
(f) Batki et al. 2002: no blinding; use of unvalidated patient-reported outcomes in SAT arm (monthly medication pick-up); dissimilarities between treatment arms (age, Addiction Severity Index Psychiatric and Beck depression inventory); exposure bias (incentive in DOT arm).
(g) Sterling et al. 2011: unclear allocation concealment; no blinding; use of unvalidated patient-reported outcomes in SAT arm (pill count and self-report); dissimilarities between treatment arms (with respect to North American Indians, subjects enrolled in a cluster, homelessness); exposure bias (short treatment in DOT arm).
(h) Matteelli et al. 2000: unclear allocation concealment; no blinding; very large loss to follow-up; unclear treatment adherence assessment in SAT arm; unequal numbers in treatment arms; early termination (due to low completion rates in DOT arm). Early termination partially accounts for the low numbers in this study, and the study was already downgraded for this (serious imprecision); it was decided not to downgrade for it again in the risk of bias.
(i) Total number of events < 125.

Table A9.7. Grading of the body of evidence for the effectiveness of (monetary) incentives

			Quality assessment					n/N = %	Effect			
No of studies (No of participants)	Design	Population – treatment intervention	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Incentives / No incentives	OR (95 % CI)	Absolute [a] (per 1 000 (95 % CI))	Quality	Importance
Initiation												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Adherence												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Completion												
1 (111) Batki, 2002	RCT	Drug users – long INH [b] Methadone treatment + DOT vs no incentive + SAT [c]	Very serious [g]	Not serious	Not serious	Serious [k]	None	49/72 = 68 % 5/39 = 13 %	14.5 (5.0-42)	552 (296-732)	Very low	Critical
1 (108) Malotte, 2001	RCT	Drug users – long INH [b] Monetary incentive vs no incentive	Not serious [h]	Not serious	Not serious	Serious [k]	None	29/53 = 53 % 2/55 = 3.6 %	32.0 (7.1-145) [l]	511 (174-809)	Moderate	Critical
1 (216) White, 2002	RCT	Inmates [d] - long INH Non-cash [e] incentive vs no incentive	Not serious [i]	Not serious	Not serious	Serious [k]	None	14/113 = 12 % 12/103 = 12 %	1.1 (0.5-2.4) [m]	7 (-58-124)	Moderate	Critical
1 (119) Tulsky, 2004	RCT	Homeless people – long INH or short INH + RIF Cash vs non-cash incentive [f]	Serious [j]	Not serious	Not serious	Serious [k]	None	58/68 = 85 % 44/57 = 77 %	1.7 (0.7-4.3)	80 (-69 -164)	Low	Critical

(a) Calculated via GradePro.[76].
(b) Both studies with drug users population are presented separately, since one of the studies applies incentive + DOT as intervention.
(c) Approximately half of the intervention group (37/72) also received substance abuse counselling.
(d) Inmates who started treatment in jail and were released before treatment completion.
(e) USD 25 equivalent in food or transportation vouchers.
(f) Patients with normal CXR were prescribed H, while those with evidence of old TB on CXR were prescribed HR. Participants randomly assigned to the cash or non-cash incentive. Non-cash incentives consisted of a choice of USD 5 equivalent in fast-food or grocery store coupons, phone cards or bus tokens.
(g) Batki et al. 2002: no blinding; use of unvalidated patient-reported outcomes in SAT arm (monthly medication pick-up); dissimilarities between treatment arms (age, Addiction Severity Index psychiatric and Beck depression inventory); exposure bias (DOT in incentive arm).
(h) Malotte et al. 2001: unclear sequence generation; partly blinded.
(i) White et al. 2002: partly blinded.
(j) Tulsky et al. 2004: partly blinded; dissimilarities between treatment arms (primary housing in last year shelter/street; not found to be an independent predictor of completion in this study); this study presents data for incentive vs another incentive (rather than vs no incentive).
(k) Total number of events < 125.
(l) Adjusted OR, adjusted for: treatment condition, recruitment status, binge drinking.
(m) Adjusted OR, not reported which factors this OR was adjusted for.

Table A9.8. Grading of body of evidence for the effectiveness of social interventions

			Quality assessment					n/N = % [b]	Effect			
No of studies (No of participants)	Design	Population Intervention [a]	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Social intervention / No social intervention	OR (95 % CI) [c]	Absolute [d] (per 1 000 (95 % CI))	Quality	Importance
Initiation												
1 (946) Goldberg, 2004	Observational study	Immigrants Cultural case management	Not serious [f]	Not serious	Not serious	Not serious	None	389/442 = 88 % 557/762 = 73 %	2.7 (1.9-3.8)	149 (107-181)	Low	Critical
Adherence												
								N	*Cumulative mean number of pills taken over 9 months* [o]			
1 (286) Hovell, 2003	RCT	General population Adherence coaching	Not serious [g]	Not serious	Not serious	Serious [m]	None	92 98	*180* *151*	-	Low	Critical
1 (184) Ailinger, 2010	Observational study	Immigrants Cultural intervention	Not serious [h]	Not serious	Not serious	Serious [m]	None	53 131	*157* *129*	-	Very low	Critical
Completion												
3 (928) Hirsch-Moverman, 2013 Hovell, 2003 Kominski, 2007	RCT	General population Counsellor/contingency contracting & adherence coaching/self-esteem counselling & peer based	Not serious [i]	Not serious	Not serious	Not serious	None	331/515 = 64 % (range: 46 %-84 %) 253/413 = 61 % (range: 38 %-76 %)	1.4 (1.1-1.9)	78 (53-80)	High	Critical
1 (946) Goldberg, 2004	Observational study	Immigrants Case management taking into account cultural background	Not serious [f]	Not serious	Not serious	Not serious	None	319/389 = 82 % 205/557 = 37 %	7.8 (5.7-10.7)	452 (400-494)	Low	Critical
1 (216) White, 2002	RCT	Inmates [e] Education	Not serious [j]	Not serious	Not serious	Serious [n]	None	24/106 = 23 % 12/103 = 12 %	2.2 (1.0-4.7) [p]	108 (4-267)	Moderate	Critical
1 (520) Nyamathi, 2006	RCT	Homeless people Nurse case management	Not serious [k]	Not serious	Not serious	Not serious	None	173/279 = 62 % 94/241 = 39 %	3.0 (2.2-4.2) [q]	268 (189-339)	High	Critical
1 (199) Chaisson, 2001	RCT	Drug users Peer support vs no peer support	Not serious [l]	Not serious	Not serious	Not serious	None	79/101 = 78 % 79/100 = 79 %	1.0 (0.7-1.5)	2 (-75-62)	High	Critical

(a) All groups INH > 4 months.
(b) If > 1 article, weighed pooled point estimates and 95 % CI were calculated.
(c) If > 1 article, pooled estimates and 95 % CI were calculated using a random effects model (without quality index).
(d) Calculated via GradePro [76].
(e) Inmates who started treatment in jail and were released before treatment completion.
(f) Goldberg et al. 2004: use of unvalidated patient-reported outcomes (self-report); proportion of children aged 5-14 years was higher during one period than the other (19 % vs 13 %, p = 0.003).
(g) Hovell et al. 2003: unclear allocation concealment; unclear sequence generation; partly blinded. Not downgraded for these risk-of-bias aspects because already downgraded for imprecision.
(h) Ailinger et al. 2010: use of unvalidated patient-reported outcomes (self-report) convenience sample.
(i) Hovell et al. 2003: unclear allocation concealment; unclear sequence generation; partly blinded. Kominski et al. 2007: unclear allocation concealment; no blinding; unclear if intention-to-treat analysis was performed; use of unvalidated patient-reported outcomes (self-report). Hirsch-Moverman et al. 2013: unclear allocation concealment; unclear sequence generation; partly blinded; use of unvalidated patient-reported outcomes (self-report).
(j) White et al. 2002: partly blinded.
(k) Nyamathi et al. 2006: unclear allocation concealment; unclear sequence generation; partly blinded; dissimilarities between treatment arms (daily alcohol or drug use (significantly associated with non-completion in this study); male, recruitment site (both not significantly associated with completion in this study), lifetime intravenous drug use, recent self-help programme).
(l) Chaisson et al. 2001: unclear allocation concealment; no blinding; use of unvalidated patient-reported outcomes (self-report; urine tests and medication event monitoring system in a subset of patients in this study show that self-report is subject to serious under-reporting).
(m) Total sample size < 230.
(n) Total number of events < 125.
(o) No adherence rates were provided as outcome; instead, the cumulative mean number of pills taken per group was presented.
(p) Adjusted OR, not reported which factors this OR was adjusted for.
(q) Adjusted OR, adjusted for: age, sex, high-school graduate, never married, medical insurance, recruited from homeless shelter, years homeless, treatment completion important, intended to adhere, daily alcohol/drug use, recent self-help programme, emotional well-being, social support, recent hospitalisation, recent victimisation.

Table A9.9. Grading of body of evidence for effectiveness of other interventions

			Quality assessment					n/N = %	Effect			
No of studies (No of participants)	Design	Population Treatment Intervention*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other intervention / Usual care	OR (95 % CI)	Absolute (a) (per 1 000 (95 % CI))	Quality	Importance
Initiation												
1 (107) Sahni, 2009	Observational study	Healthcare workers INH Use of IGRAs	Not serious (b)	Not serious	Not serious	Serious (c)		32/62 = 52 % 5/45 = 11 %	8.8 (3.1-23)	413 (168-631)	Very low	Critical
Adherence												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical
Completion												
0 (0)	No evidence available	-	-	-	-	-	-	-	-	-	-	Critical

(a) Calculated via GradePro [76].
(b) Use of unvalidated patient-reported outcomes (telephone interview).
(c) Total number of events < 125.

Table A9.10. Summary of interventions to improve initiation, adherence and completion of latent tuberculosis infection treatment in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews											
Lutge, 2015 [124] Low (a)	1996-2002	n = 5 on incentives vs routine care n = 1 on immediate versus deferred incentive n = 1 on cash versus non-cash incentives n = 4 on incentives versus any other intervention (all RCTs) (c)	Community-based TB clinic, urban research clinic, urban community based clinics, urban community based TB clinic, community-based TB clinic, prison	— Homeless people, recently released prisoners — Drug users, adolescents with their parents, recently released prisoners	— 595 — Not reported	— Risk ratio of clinic visit to start or continue TB prophylaxis — Risk ratio of completion TB prophylaxis	RR (95 % CI)	Incentives vs routine care — 1.58 (1.27-1.96) — No calculation performed	*GRADE* All were graded low except the study on return to clinic to start or continue treatment incentives vs routine care	Negative on 1, 5, 11	Weak evidence
				— Not available — Drug users	— Not available — 300			Immediate versus deferred incentive — Not available — 1.11 (0.98-1.24)			
				— Not available — Homeless and marginally housed adults	— Not available — 141			Cash versus non-cash incentives — Not available — 1.26 (1.02-1.56)			
				— Homeless adults, jail inmates — Jail inmates, homeless adults, adolescents	— 535 — 837			Incentives versus any other intervention — 1.10 (0.92-1.31) — 1.04 (0.59-1.83)			
M'Imunya, 2012 [69] Low (b)	1993-2002	n = 1 on adolescents n = 1 on prisoners n = 1 on mothers of children (all RCTs)	Prison, public and private sector primary schools, public clinics	Prisoners receiving education delivered by research assistants and consisted of a one-to-one session in English or Spanish based on CDC guidelines	558	Education vs control group Risk ratio of: — Completing LTBI treatment 6 mo — Completing first TB clinic visit 1 mo after release from jail	RR (95 % CI)	— 1.94 (1.03-3.68) — 1.56 (1.02-2.37)	*GRADE* All studies were graded of low quality	Negative on 1, 11	Weak evidence

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
				Mothers of children receiving education consisted of discussions on the importance and need for chemoprophylaxis and reissuing informative leaflets. Delivered by a specialised nurse through telephone calls or home visits, or by a physician at the TB clinic	264	Risk ratio of adherence: — Attendance at the last clinic visit — By Eidus-Hamilton reaction *Education by telephone*		—1.44 (1.21-1.72) —1.52 (1.22-1.89)			
						Education through home visits		— 1.46 (1.23-1.74) — 1.61 (1.30-1.99)			
						Education by physicians at the clinic		— 1.20 (0.98-1.47) — 1.33 (1.05-1.69)			
				Adolescents receiving education and counselling interventions	767	Education by specially trained peer counsellors		No statistically significant difference			

(a) United States: n = 8.
(b) United States: n = 2. Spain: n = 1.
(c) Some studies addressed multiple interventions.

Table A9.11. Summary recommendations of national bodies, all based on expert opinion (Sotgiu, 2015)

Intervention	Recommendation	Country (ref)
Clinical monitoring	At baseline and at monthly intervals during treatment.	Canada [a], United States [b] [c], France [d], Portugal [e], Sweden [f], Ireland [g]
Laboratory assessment at baseline [h]	Only recommended for individuals who are candidates for treatment aged > 35 years.	Canada [a]
	Only recommended for individuals who are candidates for treatment with risk factors [i].	United States (CDC) [b]
	Only recommended for individuals who are candidates for treatment with risk factors [j].	United States (ATS) [c]
	Only recommended for individuals who are candidates for treatment aged > 35 years and those with risk factors [k].	Portugal [e]
	Suggested for individuals who are candidates for treatment aged > 14 years.	Ireland [f]
	Recommended for all individuals who are candidates for treatment > 35 years and for those with risk factors [l].	
Laboratory assessment during treatment [n]	In case of symptoms: if aged 35-50 years, systematic testing should occur once at completion at 1 month. Monthly testing for all those aged > 50 years who have risk factors [m].	Canada [a]
	In case of symptoms and for those with baseline abnormal values, otherwise monthly for those with risk factors [i].	United States (CDC) [b]
	In case of symptoms, or monthly for all those aged > 35 years, those with abnormal baselines values for a liver function test or those with risk factors [j].	United States (ATS) [c]
	Every 2-4 weeks for those with HBeAG positivity.	United States (ATS) [c]
	Only recommended at 2 and 4 weeks after the start of therapy and monthly thereafter for those aged > 65 years and those with risk factors [m].	France [d]
	Monthly for those aged > 35 years or with risk factors [k].	Portugal [e]
	Systematic testing of all those receiving treatment twice during the first month, monthly thereafter in adults and every second month in children.	Sweden [f]
	Some experts recommend testing every 2-4 weeks for the first 2-3 months of treatment.	Ireland [g]

(a) Public Health Agency of Canada. Canadian Tuberculosis Standards 7th edition 2013. 2014. Ottawa, ON, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, 2014. Available from: www.respiratoryguidelines.ca/tb-standards-2013
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(d) Haut Conseil de la Santé Publique. Enquête Autour d'un Cas de Tuberculose: Recommandations Pratiques [Survey Around a Case of Tuberculosis Practical Recommendations]. Paris, Haut Conseil de la santé publique, 2013. Available from: www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20131025_enquetecastuberculoserecoprat.pdf
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(f) Socialstyrelson. Rekommendationer för preventiva insatser mot tuberkulos – hälsokontroll, smittspårning och vaccination [Recommendations for preventive measures against tuberculosis – health surveillance, contact tracing and vaccination]. www.socialstyrelsen.se/smittskydd/sjukdomar/smittsammasjukdomarochsmittamnen/tuberkulos Date last accessed: November 11, 2014. Date last updated: 1 March 2012.
(g) Health Protection Surveillance Centre. Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010. Dublin, Health Protection Surveillance Centre, 2010. Available from: www.hpsc.ie/AboutHPSC/ScientificCommittees/Publications/File,4349,en.pdf
(h) Includes measurements of transaminases and bilirubin in all guidelines. In addition, two referencesf,g include complete blood counts in case of RIF treatment, and another referencec includes: screening for viral hepatitis in intravenous drug users, born in endemic areas, HIV-infected, sexual or household contact with chronically infected, occupational exposure, chronic haemodialysis, recipients of clotting factors before 1987, have undiagnosed liver disease, are recipients of blood or solid organ transplants before 1992 and are infants born to infected mothers.
(i) Risk factors in referenceb include: liver disorders, history of liver disease (e.g. hepatitis B or C, alcoholic hepatitis, or cirrhosis), regular use of alcohol, risks for chronic liver disease, HIV infection, pregnancy, immediate post-partum period and exposure to drugs for chronic medical conditions.
(j) Risk factors in referencec include: possible liver disorders, history of chronic liver disease, regular use of alcohol, HIV infection treated with highly active ART, pregnancy, immediate post-partum period and exposure to drugs for chronic diseases.
(k) Risk factors in referencee include: HIV infection, regular use of alcohol, pregnancy, immediate post-partum period, liver disorders and exposure to drugs for chronic diseases.
(l) Risk factors in referenceg include: HIV infection, regular use of alcohol, pregnancy, immediate post-partum period, history of hepatitis, liver disease or heavy alcohol ingestion, intravenous drug use and treatment with other potential hepatotoxic agents.
(m) Risk factors in referencea include: pregnancy or first 3 months post-partum, history of previous drug-induced hepatitis, current cirrhosis or chronic active hepatitis of any cause, hepatitis C, hepatitis B with abnormal transaminases, daily alcohol consumption or concomitant treatment with other hepatotoxic drugs (e.g. methotrexate).
(n) Risk factors in referenced include: regular use of alcohol, other liver disorders, poor nutritional status, and history of chronic liver disease (including viral hepatitis infection).

Table A9.12. Summary of effectiveness of education methods in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic reviews											
M'Imunya, 2012 [69] Low (a)	1993-2002	n = 1 on adolescents n = 1 on prisoners n = 1 on mothers of children (all RCTs)	Prison, public and private sector primary schools, public clinics	Prisoners receiving education delivered by research assistants and education consisted of a one-to-one session in English or Spanish based on CDC guidelines	558	Education vs control group Risk ratio of: — Completing LTBI treatment 6 mo — Completing first TB clinic visit 1 mo after release from jail	RR (95 % CI)	— 1.94 (1.03-3.68) — 1.56 (1.02-2.37)	*GRADE* — All studies were graded of low quality	Negative on 1, 11	Weak evidence
				Mothers of children receiving education which consisted of discussions on the importance and need for chemoprophylaxis and re-issuing informative leaflets. Delivered by a specialised nurse through telephone calls or home visits, or by a physician at the TB clinic	264	Education vs control group Risk ratio of adherence: — Attendance at the last clinic visit — By Eidus-Hamilton reaction *Education by telephone*		— 1.44 (1.21-1.72) — 1.52 (1.22-1.89)			
						Education through home visits		— 1.46 (1.23-1.74) — 1.61 (1.30-1.99)			
						Education by physicians at the clinic		— 1.20 (0.98-1.47) — 1.33 (1.05-1.69)			
				Adolescents receiving education and counselling interventions	767	Education vs control group Education by specially trained peer counsellors		No statistically significant difference			
Lutge, 2015 [124] Low (b)	1996-2002	n = 3 studies on completion of TB prophylaxis n = 2 studies on return to clinic for	Prison, community-based TB clinic, urban community based clinics, urban	Jail inmates, homeless adults, adolescents	837	Risk ratio of — Completion preventive treatment. Material incentives vs education	RR (95 % CI)	1.04 (0.59-1.83)	*GRADE* All were graded low	Negative on 1, 5, 111	Weak evidence

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
		initiation or continuation of TB prophylaxis n = 2 studies on return to clinic for TST reading (all RCTs)	community based TB clinic, urban research clinic	Homeless men and women, inmates	535	— Return to clinic for initiation or continuation of preventive treatment. Material incentives vs education		1.10 (0.92-1.31)			
				Drug users	1 366	— Return to clinic for TST reading. Material incentives vs education		2.16 (1.56-3.00)			

(a) United States: n = 2, Spain: n = 1
(b) United States: n = 7

Table A9.13. Summary of latent tuberculosis infection control integrated into existing health programmes in systematic reviews

Reference, incidence category of country	Publication years of included articles	N included studies (study design)	Setting	Population	N population	Main outcome measure	Type of outcome measure	Outcome	Quality appraisal	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic review											
Uyei, 2011 [123] High*	1995-2010	n = 16 (design not reported)	HIV healthcare settings	PLHIV	13 829	Proportion of PLHIV screened for TB	% weighted mean (SD); range	88.7 % (12.1); 48-100 %	Not reported	Negative on 1, 2, 3, 4, 5, 6, 7, 8, 10, 11	Weak evidence
					13 468	Proportion of PLHIV screened for IPT eligibility		87.7 % (4.5); 81-93 %			
					4 547	Proportion IPT eligible started treatment		72.6 % (12.5); 67-100 %			
					27 204	Proportion of PLHIV started on IPT		13.5 % (16.6); 5-95 %			
					Not reported	IPT taken appropriately as prescribed		Not reported; 75-92 %			
					Not reported	6 mo of treatment within the study's follow-up period		Not reported; 47-88 %			

** Uganda: n = 6. South Africa: n = 5. Ethiopia: n = 2. Botswana, Rwanda, Tanzania: n = 1.*

Table A9.14. Summary of the cost-effectiveness of latent tuberculosis infection control integrated into existing health programmes in EU/EEA in systematic reviews

Reference, incidence category of country	Number of included studies; populations	Perspective	Time horizon	Cost-effectiveness results	Authors conclusion	Amstar	Overall grading of the evidence based on systematic reviews
Non-commissioned systematic review							
Uyei, 2011 [123] High*	8 cost-effectiveness analyses	The perspective of the health system and patients were of main interest	Not reported	8 articles from 7 studies reported cost-effectiveness** of TB and HIV service integration.	Integration of TB and HIV services does not harm either and the strategy is often a more beneficial method for delivery of services	Negative on 1, 2, 3, 4, 5, 7, 8, 10, 11	Weak evidence

** Uganda: n = 3. Zambia: n = 2. Malawi, South Africa: n = 1*
*** Cost-effectiveness definitions varied across interventions and primary studies (if reported).*

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