ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SCIENTIFIC ADVICE

Programmatic management of latent tuberculosis infection in the European Union

www.ecdc.europa.eu

ECDC SCIENTIFIC ADVICE

Programmatic management of latent tuberculosis infection in the European Union

This guidance was commissioned by ECDC and coordinated by Senia Rosales Klintz, Netta Beer and Marieke J. van der Werf with the support of Helena de Carvalho Gomes (ECDC).

The inventory of expert opinions; the evidence collection, appraisal and synthesis; the expert consultation and the first draft of this guidance were produced by Marije Vonk Noordegraaf-Schouten, Femke van Kessel and Anouk Oordt, members of a consortium of Pallas Health Research and Consultancy (Rotterdam) and Erasmus University Medical Center (framework contracts no ECDC/2013/005 and ECDC/2014/032).

Invaluable input was received from ad hoc scientific panel chairs Gerard de Vries (the Netherlands) and Dominik Zenner (United Kingdom), and its members: Judith Bruchfeld (Sweden); Josie Garrett (United Kingdom); Walter Haas (Germany); Einar Heldal (Norway); Rein Houben (United Kingdom); Philip LoBue (USA); Mike Mandelbaum (United Kingdom); Alberto Matteelli (Italy); Giovanni Battista Migliori (Italy); Ivan Solovic (Slovakia); and Martina Vašáková (Czech Republic).

Erratum: 5 October 2020: The note under Tables 2, 4, 6 and 8 re. Intermediate TB burden in countries were corrected to > 40/100 000 from < 40/100 000.

Suggested citation: European Centre for Disease Prevention and Control. Programmatic management of latent tuberculosis infection in the European Union. Stockholm: ECDC; 2018.

Stockholm, October 2018

PDF	Print
ISBN 978-92-9498-266-7	978-92-9498-272-8
DOI 10.2900/971917	10.2900/451255
Catalogue number TQ-03-18-287-EN-N	TQ-03-18-287-EN-C

Contents

Tables

Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ART	Antiretroviral treatment
BCG	Bacille Calmette-Guérin
CI	Confidence interval
CXR	Chest X-ray
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
IGRA	Interferon gamma release assay
INH	Isoniazid
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
OR	Odds ratio
PLHIV	People living with human immunodeficiency virus
PPD	Purified protein derivative
PZA	Pyrazinamide
QFT-Plus	QuantiFERON-TB Gold Plus
RCT	Randomised controlled trial
RIF	Rifampicin
RPT	Rifapentine
RR	Relative risk/risk ratio
TB	Tuberculosis
TNF-alpha	Tumour necrosis factor alpha
TST	Tuberculin skin test
WHO	World Health Organization
XDR TB	Extensively drug-resistant tuberculosis

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, LTBI treatment. 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 WHO, in the development process of WHO's document *Guidelines on the management of latent tuberculosis infection* [4] and the present ECDC guideline. The results of the systematic reviews were extracted and used in the review of reviews report [5].
Contact	Someone who has been exposed to *M. 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 eight 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 euro/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 improve the knowledge, skills, attitudes, or behaviour of the target group. Education of patients is defined as counselling (see above) while 'training' is used for education of healthcare workers (see below).
Enablers	Things or measures that assist patients in adhering 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.
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]. The term 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 presumed 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 guidance document on programmatic management of LTBI, 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 of reviews in the development process of the present ECDC guidance. Relevant results from the systematic reviews were extracted and used in the review of systematic reviews and guidelines report [5] (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 [11]. 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.
Programmatic management of LTBI	Management of latent tuberculosis infection requires input from different components or units responsible for tuberculosis prevention and control. These components include detection of individuals with latent tuberculosis infection, treatment, surveillance, and monitoring and evaluation of the programme's performance (adapted from [12]).
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].
Source case	Person with infectious TB, having exposed other persons and is herewith the source of an outbreak [6,7]. This is not necessarily the first case found (index case).
Training	Education of healthcare workers designed to increase the knowledge of TB/LTBI and raise awareness of the disease, which will help in informing and effectively treating TB patients, thereby contributing to the control of LTBI [14,15].
Tuberculosis	Clinically, bacteriologically, histologically and/or radiologically active disease [3].

Executive summary

Programmatic management of latent tuberculosis infection (LTBI) is a key component of the global tuberculosis (TB) elimination strategy. This document provides evidence-based guidance for the implementation of programmatic management of LTBI in the European Union and European Economic Area (EU/EEA).

Scope

This guidance covers four key areas in relation to programmatic management of LTBI: target risk groups; diagnosis; treatment and programmatic issues of LTBI management.

Evidence-based public health guidance

A comprehensive assessment of the public health options for implementing programmatic management of LTBI was conducted. The key topic areas and corresponding research questions were identified through consultation with experts. Scientific evidence was collected using systematic literature reviews, mathematical modelling and cost-effectiveness analyses. An ad hoc scientific panel reviewed and appraised this evidence and provided expert advice by formulating scientific conclusions on the options for programmatic management of LTBI. On the basis of these inputs ECDC formulated the key conclusions summarised below.

Key conclusions

Programmatic management of LTBI implies the implementation of a package of public health measures which can be categorised under the following components:

- **Identification of groups at risk** of LTBI and/or having an increased risk of progressing to active TB. Among the prioritised target groups for LTBI screening and treatment are:
  - people living with HIV (regardless of their CD4 cell count and antiretroviral therapy status);
  - immunocompromised persons, such as patients on anti-TNF alpha treatment, patients preparing for transplantation, patients with end-stage renal diseases and/or preparing for dialysis;
  - patients with silicosis;
  - people with pulmonary fibrotic lesions;
  - contacts of infectious TB cases, based on a risk assessment of their exposure.

  Additional at-risk groups may be considered depending on the TB epidemiology in specific Member States.
- **Definition of diagnostic approach for LTBI detection**, including both the selection of diagnostic test(s) and the diagnostic algorithm most appropriate for each target group. LTBI screening should be conceptualised as a comprehensive strategy that includes availability of and accessibility to diagnostic tests; the intention to provide LTBI treatment (if appropriate) and the implementation of interventions promoting the uptake and completion of LTBI screening procedures. The tuberculin skin test and interferon gamma release assays or a combination of both tests can be used to diagnose LTBI.
- **Provision of LTBI treatment** using treatment regimens that are effective and promote adherence and enhance completion by different target groups. The selection of LTBI treatment regimen can be based on an individual risk assessment. The following regimens can be considered: isoniazid alone (for 6–9 months), rifampicin alone (for 3–4 months), isoniazid and rifapentine (for three months) and isoniazid and rifampicin (for 3–4 months).
- **Implementation of patient-centred strategies for service delivery**. Patient-centred case management including material incentives and enablers, counselling and education, peer-based support and culturally-sensible approaches can be considered as part of an integrated strategy for LTBI treatment provision.
- **Effective health education and communication with target groups and healthcare providers.** The purpose of this comprehensive educational approach is to increase awareness about the importance of detecting and treating LTBI.
- **Programme monitoring and evaluation.** To measure the effect and appropriateness of programmatic management of LTBI, reporting and monitoring procedures need to be in place. Reporting systems should have developed or revised adequate data collection processes, performance indicators should be defined and regular programme monitoring should be performed to enable an overall assessment of programme implementation. National procedures should preferably be aligned with global and regional monitoring and evaluation frameworks, to allow inter-country comparability.

1. Introduction

1.1 TB elimination in the European Union

Tuberculosis (TB) remains a major global health problem (see Chapter 2). In 2014, the World Health Assembly approved with full support the new post-2015 Global TB Strategy (commonly referred to as the 'End TB strategy') with ambitious targets. This strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB. It sets interim milestones for 2020, 2025, and 2030 [16]. Moreover, ending the TB epidemic by 2030, defined as <10 TB cases per 100 000 population, is among the health targets of the Sustainable Development Goals that were adopted by the United Nations General Assembly in September 2015 [17].

Although the European Union and European Economic Area (EU/EEA) has a heterogeneous TB epidemiological profile, most EU/EEA Member States are low-incidence countries (i.e. notification rate <10 TB cases per 100 000). In this context, TB mainly affects vulnerable populations, such as people living with human immunodeficiency virus (PLHIV), homeless people, prison inmates and migrants. The framework for TB elimination in low-incidence settings [18] provides an outline of key aspects to consider for accelerating progress towards TB elimination (<1 TB case per million population) in EU/EEA settings already approaching or at pre-elimination phase (<10 TB case per million population). This framework builds upon the End TB strategy. One of the eight priority areas for low-incidence countries striving for TB elimination is to 'undertake screening for active TB and latent TB infection in TB contacts and selected high-risk groups, and provide appropriate treatment'.

People with latent TB infection (LTBI) represent a large human reservoir for the disease [19]. The control of LTBI is an important step towards TB elimination. Currently, EU/EEA Member States are addressing LTBI in various ways. Some Member States have more developed and systematically implemented interventions targeting LTBI incorporated into a national programmatic approach, while others give less attention to management of LTBI. Incorporating programmatic management of LTBI into the national strategies to fight TB may be of value for all EU/EEA Member States. Therefore, the European Centre for Disease Prevention and Control (ECDC) identified as a priority the need to provide EU/EEA Member States with scientific advice and guidance on programmatic management of LTBI. Consequently, a comprehensive assessment of approaches, benefits and risks of LTBI programmatic management in the EU/EEA was conducted, with the aim of issuing this ECDC guidance document. The assessment included the collation of evidence through an inventory of expert opinions, systematic reviews, mathematical modelling, cost-effectiveness analysis and complementary synthesis of the evidence for interventions relating to LTBI management in programmatic TB prevention and control in the EU/EEA. The collected evidence served as input for the guidance development process.

1.2 Scope and objectives of the guidance

The aim of this guidance is to support EU/EEA Member States in the decision-making process underlying the implementation of LTBI programmatic management into their national TB programmes. Acknowledging the heterogonous spectrum of national determinants influencing this decision-making process, ECDC is providing evidence-based options for public health measures that can be included in national guidelines. This ECDC guidance complements the global World Health Organization (WHO) guideline [20], adapts it to the EU/EEA context and explores further benefits and risks of implementing a programmatic approach for LTBI control in the region.

This document summarises the evidence, provides an overview of interventions, and presents evidence-based consensus opinions on how to best perform programmatic management of LTBI. This guidance includes four key areas: target risk groups; diagnosis of LTBI; treatment of LTBI; and programmatic issues of LTBI management.

1.3 Target audience

Target audiences for this document are national policymakers, entities responsible for the planning of healthcare and social support systems, national TB programmes, and civil society organisations with an interest in TB and/or working with vulnerable populations.

2. Background

2.1 Tuberculosis and latent tuberculosis infection

TB is a serious infectious disease in humans caused by *Mycobacterium tuberculosis*. TB is transmitted by inhaling aerosol droplets containing the bacillus produced when people with pulmonary TB cough, sneeze, talk, or otherwise exhale. In 2016, it was estimated that 10.4 million people fell ill with TB and 1.3 million died from the disease worldwide [21]. TB is a leading cause of death from infectious diseases worldwide [22,23]. The risk of infection with *M. tuberculosis* increases with the number of infectious people in the community, the duration and frequency of exposure, and the characteristics of the place of exposure (i.e. sun exposure, ventilation etc.) [24].

Following exposure to *M. tuberculosis*, in some people the innate immune response is capable of preventing infection. Others develop latent infection with *M. tuberculosis* (i.e. LTBI), a state in which the host immune system controls the replication of the bacillus to the extent that the progression to TB is prevented [25,26]. The majority of those who have LTBI never develop TB disease. In these people, live TB bacilli remain inactive for a lifetime without causing disease. However, the TB bacilli can become active, multiply, and cause TB disease [27]. Risk of progressing from LTBI to active TB disease is related to the virulence of the *M. tuberculosis* strain [28] and to the susceptibility of the host (e.g. malnutrition, immunocompromised status) [25,29,30]. Without an exogenous re-infection, progression from LTBI to active TB is defined as endogenous reactivation.

2.2 TB/LTBI as a public health priority for EU/EEA

TB is prevalent in all EU/EEA Member States, both in high and middle-income countries and remains a public health priority irrespective of its local incidence rates. In 2016, nearly 59 000 cases of TB were reported in the EU/EEA [31]. Of all notified TB cases, 70% were newly diagnosed and 71% of new pulmonary TB cases were confirmed by culture, smear or nucleic acid amplification test [31]. In a majority of the EU/EEA countries, the notification rates have steadily declined during the period 2010–2016; the number of new TB cases is slowly decreasing by around 5% each year. However, these annual rates of decline are still too small to envisage TB elimination by 2050 in European countries with low incidence of TB [31].

According to a recent estimate, approximately 1.7 billion people have LTBI, representing a large human reservoir [19]. In low-incidence countries, a majority of TB cases occur due to progression of LTBI to active disease [18]. In these countries TB tends to be concentrated in vulnerable and hard-to-reach populations. As long as people with LTBI exist, elimination of TB will not be feasible [27]. Therefore, public health guidance on programmatic management of LTBI should answer the following key questions in relation to LTBI:

- **Which risk groups?** Two broad categories of risk groups can be defined: people with an increased risk of LTBI but without an increased risk of progression to active TB [32-34] and people with LTBI who have a higher risk of progression to active TB compared to others with LTBI [35-39]. Specific risk groups, such as contacts of TB cases, PLHIV, homeless people and migrants, can be included in one or both of these categories.
- **How to identify people with LTBI?** Proper diagnosis of LTBI is challenging due to the inherent limitations of currently available diagnostic tests. Both the tuberculin skin test (TST) and the interferon gamma release assays (IGRA) assess the adaptive immune response against *M. tuberculosis*. None of these tests can differentiate between recent and remote (> 2–5 years) LTBI, between cleared and persistent infection, or between LTBI and active disease [40].
- **What treatment to offer?** Different treatment regimens for LTBI are available. LTBI treatment aims to decrease the probability of progression to active TB but it may cause drug-related adverse events. Therefore, careful consideration must be given to the risks and benefits of providing treatment at the individual level [20].
- **How to implement LTBI interventions?** Programmatic implementation of LTBI management requires the identification of optimal approaches to operationalise the selection, identification and treatment of people with LTBI.

3. Guidance development

The main steps undertaken during the development of this guidance were (in chronological order):

- Inventory of expert opinions (Section 3.1)
- Evidence collection, appraisal and synthesis (Section 3.2)
  - Assessment of scientific evidence (Section 3.2.1)
  - Mathematical modelling and cost-effectiveness analysis (Section 3.2.2)
- Expert consultation (Section 3.3)
  - Delphi process (Section 3.3.1)
  - Ad hoc scientific panel meeting (Section 3.3.2)

The different steps are briefly described in the sections below, with references to annexes or supporting publications containing more detailed description.

3.1 Inventory of expert opinions

The guidance development process started in 2013 with an inventory of expert opinions on components of LTBI management. Representatives of the EU/EEA Member States and additional stakeholders in the field of TB were consulted by means of a modified Delphi approach, with three rounds. First, a questionnaire was sent out to collect opinions on LTBI management. The collected information served as input for the two subsequent interactive discussion rounds which were conducted during a workshop meeting. At the workshop, the experts discussed elements to be considered when introducing programmatic management of LTBI into the EU/EEA's TB prevention and control strategy. The relevant aspects of LTBI programmatic management were identified (See Box 1) [41].

Box 1

Aspects for programmatic management of LTBI in the EU/EEA requiring comprehensive assessment

- Identification of risk groups for programmatic management of LTBI
- Prevalence of LTBI in specific risk groups and the general population
- Factors influencing LTBI prevalence (e.g. changing migration patterns and increased incidence of multidrug-resistant TB)
- Risk of progression to active TB over time in infected persons, with or without LTBI treatment
- Cost of LTBI in the EU/EEA
- Identification of the most reliable tests for diagnosis of LTBI with the highest yield in different epidemiological settings (e.g. high and low TB burden) and populations (e.g. immunocompromised patients, children, migrants and close contacts of TB patients)
- The effect of tests being free of charge
- Assessment of strategies for improved screening and case finding for both LTBI and active TB (e.g. combination with other health programmes, assessment of the existing legislation and potential changes needed)
- Assessment of the effectiveness of different regimens for LTBI treatment, in specific target groups and specific situations
- Adherence to LTBI treatment in different risk groups
- Frequency and severity of adverse events of LTBI treatment regimens and the best monitoring approach
- Effectiveness of different interventions to improve uptake and adherence of LTBI treatment (e.g. directly observed treatment and incentives)
- Identification of strategies to improve access of target risk groups to LTBI screening and treatment
- Interventions providing information and education to increase awareness and knowledge on LTBI and TB among specific target groups (e.g. policymakers, healthcare workers, medical students, community workers, risk groups and general population.)

3.2 Evidence collection, appraisal and synthesis

3.2.1 Assessment of scientific evidence

A detailed description of the methods for identification, collection and appraisal of scientific evidence, and the corresponding results are provided in a separate report [5]. The following sections briefly summarise the methodology applied.

Questions addressed in the guidance

The contributions from the inventory of expert opinions were regrouped into four key areas and corresponding main research questions to be answered in the guidance for programmatic management of LTBI (Annex 1):

1. Target risk groups: in which populations will LTBI management measures provide the largest benefit?

2. Diagnosis of LTBI: what is the optimal and most reliable diagnostic test or combination of tests for LTBI?

3. Treatment of LTBI: what is the optimal approach for LTBI treatment? (What? Who? When?)

4. Programmatic issues of LTBI management: what is the optimal approach for programmatic management of LTBI?

- Case detection; screening*:* what is the optimal approach for screening for LTBI? (Who? When? Where? How?)
- Case detection; contact investigation: what is the optimal approach for contact investigation? (Who? When? Where? How?)
- Treatment-related interventions; improving treatment adherence: what treatment related interventions lead to an optimal result of treatment of LTBI?
- Treatment-related interventions; adverse events: can adverse events management improve the results of LTBI treatment?
- Education: what is the optimal approach for education relating to LTBI? (Who? When? How?)
- Implementation: can LTBI management be integrated into existing health programmes in EU/EEA countries?
- Programme monitoring and evaluation: how should monitoring and evaluation of programmatic management of LTBI be arranged?

Inventory of evidence

In order to collect evidence for the main research questions listed above, specific research questions were developed (also referred as 'review questions', Annex 1) and the following steps were taken:

- **Step 1. Inventory of systematic reviews jointly commissioned by ECDC and WHO**: relevant information from primary studies included in three systematic reviews [42-44] and from findings reported in other systematic reviews [44] are summarised in this guidance document.
- **Step 2**. **Review of non-commissioned systematic reviews/meta-analyses:** a PubMed search was conducted for systematic reviews addressing topics that were not covered by the systematic reviews commissioned by ECDC/WHO, or by the guidelines found during the guideline inventory (see below). Inclusion criteria and search strategies are described elsewhere [5].
- **Step 3. Inventory of national and international evidence-based guidelines:** an inventory of national and international evidence-based guidelines was conducted following a pre-defined protocol [5].
- **Step 4. Web search:** a general search engine (Google) was used to address the remaining gaps in evidence, using a pre-defined search strategy [5].
- **Step 5. Consultation with the ad hoc scientific panel:** after completion of steps 1 to 4, a list of the references included in the selected systematic reviews and evidence-based guidelines was prepared. The ad hoc scientific panel appointed by ECDC was asked to review the list and to indicate additional publications relevant for the guidance development process.

The quality of selected systematic reviews and evidence-based guidelines was assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool [45] and the AGREE (Appraisal of Guidelines for Research and Evaluation) instrument [46], respectively.

Grading of the evidence

Grading of the evidence from included systematic reviews

The evidence of each systematic review included was graded as 'weak evidence', 'moderate evidence', or 'strong evidence'. For the commissioned systematic reviews included in this report (see above), this was done based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [47,48], where possible. The evidence provided by the other systematic reviews included was graded using a method based on a combination of the following three aspects: the included study designs (as in GRADE), the quality assessment of

the evidence within the systematic 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 (randomised control trials) - 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

GRADE: Grading of Recommendations Assessment, Development and Evaluation [47,48]; NOS: Newcastle-Ottawa Scale [49]; RCT: randomised controlled trial; SIGN: Scottish Intercollegiate Guidelines Network [50] .

**Developed by Pallas Health Research and Consultancy for the review of systematic reviews and guidelines [5].*

Evidence statements and grading of body of evidence

The evidence base was summarised in short evidence statements for each of the specific research questions identified in the inventory of evidence. These evidence statements are based on the results of one or more relevant systematic reviews of comparative studies presenting quantitative estimates (e.g. Odds ratios (OR), Relative risks (RR)). Multiple evidence statements could be formulated for one research question, when more than one relevant outcome was identified [5].

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 above, assuming the highest assessed level of evidence to be in place when more than one systematic review was included as evidence base for a statement.

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

3.2.2 Mathematical modelling and cost-effectiveness analyses

Mathematical modelling was performed to estimate the potential of various LTBI screening strategies in reducing transmission, and to assess their contribution in moving towards elimination of TB in the EU/EEA. A comprehensive, deterministic TB transmission model for four European Union countries (the Netherlands, the Czech Republic, Portugal, and Spain) was developed. The model accounts for transmission within and between the general population and different target risk groups (i.e. migrants from TB high-endemic countries, homeless people, people who inject drugs, and prisoners.) The quantified model was used to predict the impact of different LTBI screening and treatment strategies in the four representative countries. Detailed descriptions of the methodology and outcomes can be found in the mathematical modelling report [51].

In addition, cohort versions of the same model were used to predict the impact of LTBI screening (i.e. screening and subsequent treatment, when positive) in cohorts of people with a temporary increased risk of infection, as well as an increased risk of disease following infection, and different cohorts of migrants. The cost-effectiveness of the selected strategies was expressed as incremental cost-effectiveness ratio. The costs of interventions were analysed from both the healthcare and societal perspective. Detailed descriptions of the methodology and outcomes can be found in the cost-effectiveness report [52].

3.3 Expert consultation

An ad hoc scientific panel was set-up to advise ECDC on the content of the guidance, to review and interpret the body of evidence resulting from systematic reviews and the results of the modelling and cost-effectiveness studies, to assess the draft guidance document, and to contribute to the further development of the guidance with their expert knowledge by formulating scientific conclusions. See Annex 2 for the list of panel members and the terms of reference for the ad hoc scientific panel.

The panel members were identified using the ECDC Expert Directory, suggestions from the ECDC Advisory Forum, by searching the scientific literature for experts that publish on related topics, and through professional contacts of ECDC TB Surveillance and other networks and working groups. The panel members were officially appointed by the ECDC Acting Director in April 2016. The panel members were asked to provide opinions based on their professional and scientific experience, and to do so on a personal basis, as an independent expert and not representing the interests of any commercial body, Member State or professional body. All panel members signed a declaration of interest, which was reviewed and approved by the ECDC compliance officer. None of the members of the panel declared any interests that could be considered a conflict with the topic or reason to prevent their participation in the panel. All members of the panel agreed that their names, affiliation and declarations of interests be published on ECDC's website, as recorded in the minutes of the expert panel meeting. The ad hoc scientific panel was independent of ECDC.

3.3.1 Ad hoc scientific panel meeting

A meeting of the ad hoc scientific panel was held on 7–8 November 2016 to discuss the body of evidence and formulate conclusions for the guidance. Before the meeting, the panel members received a report of the evidence base (see Section 3.2.1) and the preliminary results of the mathematical modelling and cost-effectiveness studies (see Section 3.2.2). Based on this, opinions on the evidence from the systematic reviews were collected by means of a Delphi process (see Section 3.3.2 below).

A meeting report with detailed minutes of discussions during the ad hoc scientific panel meeting, including the guidance conclusions developed, was shared with the panel members [53]. All ad hoc scientific panel members have read and approved the final version of the report, including the draft conclusions.

3.3.2 Delphi process

To guide the process from evidence to guidance, a modified Policy Delphi process was used. A Policy Delphi is a tool to present all options and supporting evidence/expertise to a group for their consideration, to examine acceptability or feasibility of any particular component or to build consensus for public policy [54]. In a classic Delphi approach, participants usually discuss in multiple, mostly anonymous, Delphi rounds. Results of each round are summarised and reported back to the participants, who may reconsider their first opinions based on the feedback. This particular modified Policy Delphi process included three steps:

- Before the ad hoc scientific panel meeting the panel members' opinions were collected on what evidence was considered relevant for the guidance document (Step 1). In a questionnaire, the evidence statements based on the collected data in the review of systematic reviews and guidelines (see Section 3.2.1.2), were rated on relevance, acceptability, feasibility, use of resources, and anticipated cost-effectiveness. The exercise aimed at familiarising the panel members with the evidence base as provided in the review of systematic reviews and guidelines report and for the panel members to provide a first input on the guidance conclusions.
- During the ad hoc scientific panel meeting, the results of Step 1 were presented to the panel members and formed a basis for the discussions. The discussions focussed on the risk groups to be targeted, LTBI diagnostics, LTBI treatment and intervention options for programmatic management of LTBI and on the guidance conclusions to be made. The panel members were asked to formulate draft conclusions on the pre-defined topics, based on the evidence base, the outcomes of the first Delphi round and their own expertise. Consensus was reached on draft conclusions and intervention options that the panel members considered relevant for the guidance.
- The third step took place after the ad hoc scientific panel meeting and consisted of two consensus rounds in writing for the further development and formulation of the conclusions for the guidance and the full guidance document, respectively.

4. Conclusions

This chapter summarises the main conclusions regarding the different components of LTBI programmatic management. The conclusions are presented following a similar outline to that of the key areas addressed in the guidance development process (Chapter 3):

- Target risk groups
- Diagnosis of LTBI
- Treatment of LTBI
  Programmatic issues of LTBI management.

The evidence base (i.e. peer-reviewed literature and main findings from the mathematical modelling and cost-effectiveness analyses) is summarised in text and tables to provide an overview of the evidence that informed the possible options for programmatic management of LTBI. Complementary, topic-relevant evidence based guidelines are considered in the narrative text.

In the tables with the evidence base, the following is presented:

- Specific research questions used in the evidence collection process as headings/sub-headings;
- Systematic reviews (commissioned and non-commissioned) and technical reports (i.e. mathematical modelling and cost-effectiveness analyses) on which conclusions have been based in the column 'source';
- Outcomes of relevant systematic reviews with an evidence statement in the column 'finding';
- The strength of the body of evidence from the underlying systematic reviews for each evidence statement in the column 'level of evidence'.

The tables with the evidence base are accompanied by a narrative summary of the evidence, main topics discussed at the ad hoc scientific panel meeting, and conclusions of the ad hoc scientific panel.

4.1 Target risk groups

To determine which populations benefit most from LTBI control measures, the assessment of scientific evidence aimed to identify populations at increased risk of having LTBI and progressing towards active TB.

4.1.1 Clinical risk groups

Summary of evidence

Overall, the quality of the scientific evidence was considered weak. Clinical risk groups mostly had no increased risk of LTBI (Table 2), but evidence of increased risk of progression to active TB in people with LTBI belonging to clinical risk groups (i.e. PLHIV and severely immunocompromised persons) was found in all systematic reviews (Table 3).

One evidence-based guideline for programmatic management of LTBI listed specific clinical risk groups (based on their risk of progression to active disease) for targeted screening and treatment, differentiated according the country's socioeconomic and epidemiological profile (e.g. high- and upper-middle income countries with TB incidence below 100 per 100 000 population versus low- and lower-middle-income countries with TB incidence above 100 per 100 000 population) [4].

Table 1. Evidence base of LTBI risk among clinical risk groups

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis?*			
Risk group	**Source**	**Finding**	**Level of evidence**
PLHIV	One commissioned systematic review with 34 cross-sectional and cohort studies[a] reporting on PLHIV [44]	**No increased risk of LTBI in PLHIV compared to the general population (as measured by TST and IGRA in low and high TB burden countries; and by TST in intermediate TB burden countries).** Pooled risk ratios (range) of LTBI compared to the general population in -low TB burden countries[b]; TST: 0.99 (0.43-3.09), IGRA: 0.89 (0.31-3.09) -intermediate TB burden countries[c]; TST: 0.86 (0.77-1.17), IGRA: 1.54[d] -high TB burden countries[e]; TST: 0.76 (0.24-2.08), IGRA: 0.94 (0.48-1.68).	Weak evidence
Immuno-compromised	One commissioned systematic review with: • 31 cross-sectional and cohort studies[a] reporting on patients with renal or liver conditions [44]	**No increased risk of LTBI in patients with renal or liver conditions compared to the general population (as measured by TST and IGRA in low and high TB burden countries; and by TST in intermediate TB burden countries).** Pooled risk ratios (range) of LTBI in patients with renal or liver conditions compared to general population in -low TB burden countries[b]; TST: 1.43 (0.40-3.68), IGRA: 2.21 (0.40-5.14) -intermediate TB burden countries[c]; TST: 1.02 (0.63-2.71), IGRA: 1.19[d] -high TB burden countries[e]; TST: 0.74 (0.24-3.32), IGRA: 1.23 (0.49-3.16).	Weak evidence
	• 20 cross-sectional and cohort studies[a] reporting on candidates for anti- TNF alpha therapy [44]	**Increased risk of LTBI in candidates for anti-TNF alpha therapy compared to the general population (as measured by IGRA in low TB burden countries).** Pooled risk ratios (range) of LTBI in candidates for anti-TNF alpha therapy compared to general population in -high TB burden countries[e]; IGRA: 2.11f -low TB burden countries[b]; TST: 1.84 (0.38-5.94), IGRA: 2.40 (1.56-3.30) -intermediate TB burden countries[c]; TST: 0.54[d].	Weak evidence
	• 20 cross-sectional and cohort studies[a] reporting on patients with autoimmune disorders or immune-mediated inflammatory disorders [44]	**No increased risk of LTBI in patients with autoimmune disorders or immune-mediated inflammatory disorders compared to the general population (as measured by TST and IGRA in low TB burden countries; and TST in high TB burden countries).** Pooled risk ratios (range) of LTBI in patients with autoimmune disorders or immune-mediated inflammatory disorders compared to general population in -low TB burden countries[b]; TST: 1.62 (0.07-4.42), IGRA: 0.95 (0.04-3.33) -intermediate TB burden countries[c]; TST: 0.84c, IGRA: 0.52[f] -high TB burden countries[e]; TST: 1.24 (0.90-2.15), IGRA: 0.78[d].	Weak evidence

[a]No further specification. [b]Low TB burden countries= incidence rate < 40 per 100 000 population. [c]Intermediate TB burden countries= incidence rate > 40 per 100 000 population. [d]Based on two studies, no range provided. [e]High TB burden countries = incidence rate >100 per 100 000 population. [f]Based on one study, no range provided.

IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; PLHIV: people living with human immunodeficiency virus; TB: tuberculosis; TNF alpha: tumour necrosis factor alpha; TST: tuberculosis skin test.

Table 3. Evidence base on progression to active TB among clinical risk groups with LTBI

Research question: Which populations are at increased risk of developing active TB?			
Risk group	**Source**	**Finding**	**Level of evidence**
PLHIV	Two commissioned systematic reviews with 10 cohort studies reporting on PLHIV[44].	**Increased risk of active TB in PLHIV compared to the general population.** Incidence rate ratio (95% CI) of active TB in TST+ PLHIV (with concomitant risk factor) compared to HIV-negatives: -PLHIV and people who inject drugs: 10.46 (1.34-471.2) -PLHIV and homeless people: 9.42 (2.90-27.11). Pooled relative risk (95% CI) of active TB in PLHIV with LTBI (determination of LTBI status not specified) compared to the general population (LTBI status general population unknown): 183.0 (41.7-803.4).	Weak evidence
Immuno-compromised	Three systematic reviews (two commissioned and one non-commissioned) with: • One cohort study reporting on end stage renal disease patients receiving dialysis [44]	**Increased risk of active TB in end-stage renal disease patients receiving dialysis compared to general population.** Adjusted relative risk/100 person years (95% CI) of progression from LTBI to TB disease in end stage renal disease patients receiving dialysis compared to the general population: TST (5-9mm): 8.4 (3.1-13.6); TST (>9mm): 41.4 (37.9-44.8).	Weak evidence
	• Three cohort studies reporting on patients with terminal renal failure/dialysis [44]	**Increased risk of active TB in LTBI-positive patients with terminal renal failure or on dialysis compared to the general population.** Pooled relative risk (95% CI) of active TB of LTBI positive patients with terminal renal failure/dialysis compared to the general population (LTBI status general population unknown): 703.2 (38.1-12984.5).	Weak evidence
	• Five observational studies[a] reporting on dialysis patients [55]	**Increased risk of active TB in dialysis patients compared to the general population.** Incidence rate ratio (95% CI) of active TB development: 2.59 (1.20–5.57).	Weak evidence
	• One cohort study reporting on patients with autoimmune diseases receiving TNF alpha inhibitors [44]	**Increased risk of active TB in LTBI-positive patients with autoimmune diseases receiving TNF alpha inhibitors.** Pooled relative risk (95% CI) of active TB for LTBI positive patients with autoimmune diseases receiving TNFα inhibitors compared to the general population (LTBI status general population unknown): 16.2 (14.6-18.0).	Weak evidence
	• One cohort study reporting on patients with silicosis [44]	**Increased risk of active TB in LTBI-positive patients with silicosis compared to the general population.** Pooled relative risk (95% CI) of active TB of LTBI positive patients with silicosis compared to the general population (LTBI status general population unknown): 170.3 (137.9-210.2).	Weak evidence
	• One cohort study reporting on patients with diabetes [44]	**Increased risk of active TB in LTBI-positive patients with diabetes mellitus compared to the general population.** Pooled relative risk (95% CI) of active TB for LTBI positive patients with diabetes mellitus compared to the general population (LTBI status general population unknown): 10.3 (5.9-17.6).	Weak evidence

[a]*No further specificatopm.*

CI: confidence interval; HIV: human immunodeficiency virus; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; PLHIV: people living with human immunodeficiency virus; TB: tuberculosis; TNF alpha*: tumour necrosis factor alpha; TST: tuberculosis skin test.*

Ad hoc scientific panel opinion

The ad hoc scientific panel concluded that programmatic management of LTBI is advisable for all PLHIV (regardless of cluster of differentiation 4 [CD4+] cell counts, viral load, or antiretroviral treatment (ART) status), considering the increased risk of active TB in PLHIV shown in two systematic reviews [44], and the recommendation for PLHIV in the WHO guidelines on LTBI [4]. The panel considered that PLHIV who are on ART also benefit from LTBI screening and treatment.

The ad hoc scientific panel concluded that programmatic management of LTBI is advisable for severely immunocompromised persons such as patients on immunosuppressive drugs (e.g. tumour necrosis factor alpha

(TNF alpha) inhibitors), patients preparing for transplantations, patients who have diseases that affect the immunological status (e.g. those preparing for dialysis or with end-stage renal diseases). More specifically, the ad hoc scientific panel noted that active TB in immunocompromised groups is likely to cause severe disease.

The ad hoc scientific panel, based on weak evidence and their expert opinion, considered that programmatic management of LTBI is advisable for patients with silicosis, although the disease is now rare in EU/EEA.

LTBI screening of patients receiving steroid treatment and patients with pulmonary fibrotic lesions was also discussed. Despite the scarce available evidence, the ad hoc scientific panel considered that programmatic management of LTBI is advisable for patients with fibrotic lesions. It was acknowledged that patients with fibrotic lesions have an increased risk for progression to active TB and it was suggested that persons with fibrotic lesions who have a positive LTBI test should be individually assessed.

4.1.2 Population risk groups

Summary of evidence

Only limited evidence of weak quality was available to assess the risk of LTBI or progressing to active TB among migrants and close contacts of TB patients, compared to other populations (Table 4 and 5). The evidence showed that migrants and close contacts of TB cases have an increased risk of being infected and progressing to active TB disease, depending on socioeconomic and epidemiological determinants. One evidence-based guideline for programmatic management of LTBI included these population risk groups (based on their risk of progressing to active disease) in its recommendations for systematic LTBI screening and treatment in countries with low TB incidence.

Table 4. Evidence base for LTBI risk among population risk groups

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*?			
Risk group	**Source**	**Finding**	**Level of evidence**
TB contacts	Two systematic reviews (one commissioned and one non-commissioned) with: • 71 cross-sectional and cohort studies[a] reporting on TB contacts [44].	**Increased risk of LTBI in TB contacts compared to the general population** (as measured by TST in intermediate TB burden countries[b]). Pooled estimate risk ratio (range) of LTBI compared to general population as measured by TST in intermediate TB burden countries[b]: 2.09 (1.29-2.44).	Weak evidence
		No increased risk of LTBI in TB contacts compared to the general population (as measured by IGRA in intermediate TB burden countries[b]; as measured by TST and IGRA in low[c] and high[d] TB burden countries). Pooled estimate risk ratios (range) of LTBI compared to general population in • low TB burden countries[c]; TST: 2.25 (0.15-11.7), IGRA: 1.58 (0.06-8.33) • intermediate TB burden countries[b]; IGRA: 0.97 (0.54-1.80) • high TB burden countries[d]; TST: 1.07 (0.43-2.2), IGRA: 1.06 (0.40-2.59).	Weak evidence
	• 168 studies reporting on LTBI in TB contacts[e] [56]	**Increased risk of LTBI in TB contacts in low-middle-income countries compared to TB contacts in high-income countries.** Annual incidence rate of TB in contacts per 100 000 by year of follow-up: statistically significant difference ($p<0.05$) between contacts from high compared to low–middle-income countries in the first 3 years follow-up after exposure to index patient.	Weak evidence
		Increased risk of LTBI in foreign-born TB contacts in high-income countries compared to locally born TB contacts. OR (95% CI) of LTBI in contacts born overseas compared to born locally: 3.39 (3.10–3.71).	Weak evidence
Migrants	Two systematic reviews (one commissioned and one non-commissioned) with: 23 cross-sectional and cohort studies[a] reporting on immigrants/refugees [44]	**Increased risk of LTBI in migrants compared to the general population** (as measured by TST in low TB burden countries[c]). Pooled risk ratio (range) of LTBI compared to general population: 3.27 (1.00-8.31).	Weak evidence
		No increased risk of LTBI in migrants compared to the general population (as measured by IGRA in low TB burden countries[c]). Pooled risk ratio (range) of LTBI compared to general population as measured by IGRA: 2.26 (0.79-8.08).	Weak evidence

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*?			
	• Eight studies (study designs not reported) reporting on immigrants [57]	**Increased risk of LTBI in BCG vaccinated migrants compared to unvaccinated migrants** (as measured by TST)[c]. Likelihood (OR) of a positive TST in BCG-vaccinated immigrants compared to BCG unvaccinated immigrants: 2.10 (95% CI 1.54-2.88).	Weak evidence
		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). Likelihood (OR) of a positive TST in immigrants from countries with ≥30 cases per 100 000 compared to immigrants from countries with <30 cases per 100 000: 2.38 (95% CI 1.14-4.98)	Weak evidence

[a]No further specification. [b]Intermediate TB burden countries= incidence rate < 40 per 100 000 population. [c]Low TB burden countries= incidence rate > 40 per 100 000 population. [d]High TB burden countries = incidence rate >100 per 100 000 population. [e]Study design specified for all included studies in the systematic review (n=203 on TB & LTBI; 15 cross-sectional studies, 185 cohort studies, 2 case control studies, 1 RCT (randomised control trial), not for the study on LTBI only (n=168 studies)[f]. The possibility of false positive TST due to BCG should be considered.
BCG: Bacillus Calmette-Guerin; CI: confidence interval; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; TB: tuberculosis; TST: tuberculosis skin test.

Table 5. Evidence base for progression to active TB among population risk groups with LTBI

Research question: Which populations are at increased risk of developing active TB?			
Risk group	**Source**	**Finding**	**Level of evidence**
TB contacts	One commissioned systematic review with three cohort studies reporting on TB contacts [44].	**Increased risk of active TB in LTBI-positive contacts (children and adults) compared to the general population.** Pooled relative risk (95% CI) of active TB for LTBI positive contacts compared to the general population (LTBI status general population unknown) in children: 425.4 (208.14-869.4) and adults: 8.0 (4.8-13.4).	Weak evidence
Migrants	One commissioned systematic review with four cohort studies reporting on migrants/refugees [44]	**Increased risk of active TB in LTBI-positive migrants compared to the general population** (from high to low TB burden countries). Pooled relative risk (95% CI) of active TB of LTBI positive migrants compared to the general population (LTBI status general population unknown): 90.7 (22.8-361.5).	Weak evidence

CI: confidence interval; LTBI: latent tuberculosis infection; OR: odds ratio; TB: tuberculosis.

Ad hoc scientific panel opinion

Recent TB contacts (i.e. persons with recent exposure to persons with infectious pulmonary TB) were considered to be at increased risk of progression to active TB. They would be eligible for programmatic management of LTBI since, if infected and if they develop disease, this would occur within five years in most cases. The ad hoc scientific panel concluded that LTBI screening and treatment during contact investigation is advisable for all close contacts of persons with infectious pulmonary TB, despite the weak evidence (mainly based on studies in low income countries). This conclusion is in line with the recommendation on systematic LTBI testing and treatment for contacts of pulmonary TB cases set out in the WHO guidelines [4].

Similarly, specific migrant populations can be considered for programmatic management of LTBI, depending on the epidemiological situation of TB in the receiving country and specific characteristics of the migrants, such as TB incidence in country of origin or migration route, type of migrant and time since migration. This is in line with the conditional recommendation to consider systematic LTBI testing and treatment for immigrants from high-TB burden countries set out in the WHO guidelines [4] and supported by the outcomes of the mathematical modelling and cost-effectiveness analyses.

4.1.3 Vulnerable and hard-to-reach populations

Summary of evidence

Weak evidence showed an increased risk of LTBI and increased risk of progression to active TB for prisoners. For homeless people, weak evidence showed they have an increased risk of infection (Table 6 and 7). One evidence-based guideline for programmatic management of LTBI recommended high- and upper-middle-income countries with low TB incidence to systematically test and treat prisoners, homeless people and people who use illicit drugs for LTBI [4].

Table 6. Evidence base for risk of LTBI among vulnerable and hard-to-reach populations

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*?			
Risk group	**Source**	**Finding**	**Level of evidence**
Prisoners	One commissioned systematic review with nine cross-sectional and cohort studies[a] reporting on prisoners [44]	**Increased risk of LTBI in prisoners compared to the general population** (as measured by TST in low[b] and intermediate[c] TB burden countries)**.** Pooled estimates of risk ratios (range) for LTBI in prisoners compared to general population, as measured by TST in low[b] and intermediate[c] TB burden countries: 2.33 (2.40-3.57) and 2.77 (2.58-2.92), respectively.	Weak evidence
Homeless people	One commissioned systematic review with six cross-sectional and cohort studies[a] reporting on homeless people [44]	**Increased risk of LTBI in homeless people compared to the general population** (as measured by TST and IGRA in low TB burden countries[b])**.** Pooled estimates of risk ratios (range) of LTBI in homeless people compared to general population as measured by TST and IGRA: 2.43 (1.15-3.81) and 2.40 (1.56-3.30), respectively.	Weak evidence
People with drug use disorders	One commissioned systematic review with nine cross-sectional and cohort studies[a] reporting on people with drug use disorders [44]	**No increased risk of LTBI in people with drug use disorders compared to the general population** (as measured by TST and IGRA in low TB burden countries[b])**.** Pooled estimates of risk ratios (range) of LTBI in people with drug use disorders compared to general population as measured by TST and IGRA: 0.91 (0.04-3.44) and 3.24 (0.02-5.00), respectively.	Weak evidence

[a]Not further specified. [b]Low TB burden countries= incidence rate < 40 per 100 000 population. [c]Intermediate TB burden countries= incidence rate > 40 per 100 000 population.

IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; TB: tuberculosis; TST: tuberculosis skin test.

Table 7. Evidence base on progression to active TB among vulnerable and hard-to-reach populations

Research question: Which populations are at increased risk of developing active TB?			
Risk group	**Source**	**Finding**	**Level of evidence**
Prisoners	One commissioned systematic review with one cohort study reporting on prisoners [44]	**Increased risk of active TB in prisoners compared to the general population.** Relative risk (95% CI) of active TB for LTBI-positive prisoners compared to the general population (LTBI status general population unknown): 15.3 (7.6-30.5).	Weak evidence
Homeless people	One commissioned systematic review with two cohort studies reporting on homeless people [44]	**No increased risk of active TB in persons residing in homeless shelters compared to the general population.** Pooled relative risk (95% CI) of active TB for LTBI positive persons residing in homeless shelters compared to the general population (LTBI status general population unknown): 7.3 (0.5-103.7).	Weak evidence
People with drug use disorders	No systematic review identified on this topic		

CI: confidence interval; LTBI: latent tuberculosis infection; TB: tuberculosis.

Ad hoc scientific panel opinion

The ad hoc scientific panel concluded that programmatic management of LTBI could be considered for prisoners, homeless people and people with drug use disorders depending on the epidemiological situation of TB in the country and in the specific risk group and the feasibility (based on weak evidence). They took into consideration the available evidence, the conclusions in the ECDC guidance on vulnerable and hard-to-reach populations [3], and the conditional recommendation of considering systematic LTBI testing and treatment for prisoners, homeless people, and illicit drug users in the WHO guidelines on LTBI management [4].

The ad hoc scientific panel considered that prisoners were a difficult population to target for programmatic management of LTBI because of the 'revolving door' situation (very short stays and moving from one prison to another) that may result in the loss to follow-up. However, LTBI screening of prisoners at time of incarceration appeared to be a cost-effective strategy, according to the mathematical modelling and cost-effectiveness analyses [51,52].

Although screening and treatment of homeless populations is difficult, the ad hoc scientific panel concluded that it can be considered in specific situations. Similarly, the ad hoc scientific panel suggested, based on their expert opinion (e.g. knowledge of high transmission and multidrug-resistant (MDR) TB rates in people with drug use disorders and outbreaks in drug houses), that people with drug-use disorders can be considered for programmatic management of LTBI, especially in countries that have a substantial drug user problem (e.g. eastern European countries) despite the limited evidence.

4.1.4 Occupational groups

Summary of evidence

Scientific evidence was available for healthcare workers, but not for other occupational groups, such as prison and homeless shelter staff. For healthcare workers, weak evidence showed no increased risk of LTBI, but an increased risk of active TB compared to the general population (Table 8). Modelling showed that LTBI screening of healthcare workers is not likely to be cost-effective, except when people have been exposed to high rates of transmission (i.e. with working with infectious patients or material, e.g. in the laboratory, or travelling in outbreak areas) [51].

Table 8. Evidence base for risk of LTBI and progression to active TB among occupational risk groups

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*?			
Risk group	**Source**	**Finding**	**Level of evidence**
Healthcare workers	One commissioned systematic review with 63 cross-sectional and cohort studies[a] reporting on healthcare workers and undergraduate health sciences students [44]	**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 low[b], intermediate[c] and high[d] TB burden countries). Pooled estimates of risk ratios (range) of LTBI in healthcare workers and undergraduate health sciences students compared to general population in • low TB burden countries[b]; TST: 1.88 (0.12-8.25), IGRA: 0.59 (0.03-8.83) • intermediate TB burden countries[c]; TST: 1.13 (0.28-2.06), IGRA: 0.79 (0.32-2.15) • high TB burden countries[d]; TST: 1.14 (0.42-1.68), IGRA: 0.75 (0.15-1.32).	Weak evidence
Research question: Which populations are at increased risk of developing active TB?			
Risk group	**Source**	**Finding**	**Level of evidence**
Healthcare workers	One commissioned systematic review with one systematic review reporting on healthcare workers [44]	**Increased risk of active TB in LTBI-positive healthcare workers compared to the general population** (high[d] to low[b] TB burden countries)**[e].** Pooled relative risk (95% CI) of active TB of LTBI positive healthcare workers compared to the general population (LTBI status general population unknown): 2.97 (2.43-3.51).	Weak evidence

[a]No further specification. [b]Low TB burden countries= incidence rate < 40 per 100 000 population. [c]Intermediate TB burden countries= incidence rate > 40 per 100 000 population. [d]High TB burden countries = incidence rate >100 per 100 000 population. [e]Outcome based on one systematic review [58] included in the qualitative synthesis of the commissioned systematic review [44] .
CI: confidence interval; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; TB: tuberculosis; TST: tuberculosis skin test.

Ad hoc scientific panel opinion

The ad hoc scientific panel felt that occupational groups could be considered when implementing programmatic management of LTBI.

The ad hoc scientific panel included several reasons for targeting healthcare workers, such as:

- Healthcare workers' increased risk of TB infection due to exposure in the healthcare setting (although occasional and depending on setting);
- Employers' legal responsibilities for providing maximum protection to healthcare workers at risk of infectious diseases, including LTBI screening and treatment;

- The risk of transmission to patients if a healthcare worker develops TB. The evidence for increased risk of transmission from healthcare workers to patients is limited;
- Information on LTBI conversion among healthcare workers may be used to monitor breaches in infection control in a healthcare system.

Views from the ad hoc scientific panel on a programmatic approach to LTBI management in healthcare workers varied considerably, from no screening to annual screening of healthcare workers or screening in specific healthcare worker groups and/or in specific situations only (e.g. for occupational health, in the event of repeated contact with TB patients or exposure to infectious TB patients in the healthcare facility).

It was concluded that programmatic management of LTBI could be considered for healthcare workers, but should be focused on healthcare workers at higher risk of TB (e.g. those who are working in settings with a high risk of TB transmission, and those identified in a contact investigation.)

4.1.5 Other risk groups

Summary of evidence

There was limited evidence available on increased risk of LTBI and increased risk of progression to active TB among other potential risk groups stratified by age, gender, weight or concurrent risk factor (e.g. exposure to second-hand smoking) (Table 9). The majority of these other risk groups were not assessed in the mathematical modelling and cost-effectiveness analyses. Only travellers were included separately in the cost-effectiveness analyses; LTBI screening for long-term travellers is not likely to be cost-effective, except when people have been exposed to extremely high rates of transmission for at least six months [51,52].

Table 9. Evidence base for risk of LTBI and progression to active TB among other risk groups

Research question: Which populations are at increased risk of becoming (latently) infected with *M. tuberculosis*?			
Risk group	**Source**	**Finding**	**Level of evidence**
Age	Two non-commissioned systematic reviews with eight studies[a] [57] and 39 studies[a] reporting on immigrants [59]	**Increased risk of LTBI in migrants in older age groups (i.e. ≥35 compared to <35 years; ≥18 compared to <18 years)** (as measured by TST or IGRA). • Likelihood (OR) of a positive TST in ≥35 years of age compared to <35 years of age: 1.59 (95% CI 1.32-1.92) • Positive TST or IGRA test results among those tested <18 years compared to ≥18 years: p<0.0001.	Weak evidence
Other	Two non-commissioned systematic reviews with • six cross-sectional studies reporting on people exposed to second hand smoking [60].	**Increased risk of LTBI in people exposed to second-hand smoking.** Relative risk (95% CI) of LTBI in children and adults exposed to second hand smoking: 1.64 (1.00–2.83) and 1.58 (1.03–2.43), respectively.	Weak evidence
	• eight included studies[a] reporting on immigrants [57].	**Increased risk of LTBI in males (as measured by TST and IGRA).** Likelihood (OR) of a positive TST and IGRA in males compared to females: 1.38 (95% CI 1.20-1.58) and 1.34 (1.08-1.66), respectively.	Weak evidence
Research question: Which populations are at increased risk of developing active TB?			
Risk group	**Source**	**Finding**	**Level of evidence**
Age	No systematic review identified presenting statistically analysed quantitative evidence		
Other	One commissioned systematic review with one systematic review reporting on alcohol abusers and one systematic review reporting on tobacco users.[44]	**Increased risk of active TB in alcohol misusers[b].** Pooled relative risk (95% CI) of active TB compared to the general population: 2.94 (1.89-4.59).	Weak evidence
		Increased risk of active TB in tobacco users[c]. OR (95% CI): 2.70 (1.37-5.29).	Weak evidence
	One commissioned systematic review with two cohort studies reporting on military recruits with low weight [44]	**Increased risk of active TB in LTBI-positive military recruits with low weight compared to LTBI-positive recruits with normal weight.** Relative risk of active TB compared to normal weight: 3.4 (95% CI could not be calculated).	Weak evidence

[a]No further specification, [b]Outcome based on one systematic review [61] included in the qualitative synthesis of the commissioned systematic review [44] , [c] Outcome based on one systematic review [62] included in the qualitative synthesis of the commissioned systematic review [44] .

CI: confidence interval; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; TB: tuberculosis; TST: tuberculosis skin test.

Ad hoc scientific panel opinion

The ad hoc scientific panel found insufficient evidence to recommend LTBI screening for other risk groups than those defined in the sections above.

4.2 Diagnosis of LTBI

In order to identify the optimal and most reliable diagnostic test or diagnostic algorithm for programmatic management of LTBI, the assessment of scientific evidence aimed at identifying tests or combinations of tests that are effective, cost-effective, feasible, accessible and/or acceptable for diagnosis of LTBI (in specific risk groups).

Summary of evidence

Both TST and IGRA were shown to be effective and cost-effective diagnostic tools for LTBI despite the weak evidence (Table 10 and 11). No quantitative evidence (i.e. including statistical comparisons) on diagnostic algorithms (i.e. order and combination of tests) was identified. The cost-effectiveness evaluation studies identified were heterogeneous in terms of outcome measures and definitions of cost-effective and willingness-to-pay thresholds (if reported). Relevant findings from the cost-effectiveness analyses are incorporated in Table 11. No systematic review was identified on the effect of tests being free-of-charge.

Six existing evidence-based guidelines on diagnostic tests for LTBI [4,63-67] provided recommendations on the use of TST and IGRA (alone or in combination) depending on the target risk group and country's socioeconomic and epidemiological profile. Some of these guidelines also outlined diagnostic algorithms for LTBI diagnosis and for ruling out active TB.

Table 10. Evidence base for effectiveness of diagnostic test for LTBI

Research question: Which tests are effective for diagnosis of LTBI? (in specific risk groups)?			
Diagnostic test	**Source**	**Finding**	**Level of evidence**
TST	One commissioned systematic review with • eight prospectively followed cohorts reporting on adults and children without active TB at baseline [44]	**TST is effective for diagnosis of LTBI** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 2.58 (1.72-3.88).	Weak evidence
	• three prospectively followed cohorts reporting on immunocompromised patients [44]	**TST appears not effective for diagnosis of LTBI in immunocompromised patients** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 2.96 (0.38-23.18).	Weak evidence
	• three prospectively followed cohorts reporting on TB contacts [44]	**TST is effective for diagnosis of LTBI in TB contacts** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 2.31 (1.43-3.71).	Weak evidence
IGRA	One commissioned systematic review with • eight prospectively followed cohorts reporting on adults and children without active TB at baseline [44]	**IGRA is effective for diagnosis of LTBI** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 4.94 (1.79-13.65).	Weak evidence
	• three prospectively followed cohorts reporting on immunocompromised patients [44]	**IGRA appears not effective for diagnosis of LTBI in immunocompromised patients** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 5.15 (0.26-100.43).	Weak evidence
	• three prospectively followed cohorts reporting on TB contacts [44]	**IGRA appears not effective for diagnosis of LTBI in TB contacts** (based on risk of progression to active TB, compared to no screening). Pooled RR (95% CI)[a]: 5.95 (0.57-62.05).	Weak evidence
TST & IGRA	No systematic review identified presenting statistically analysed quantitative evidence.		

[a]Pooled RR for development of incident tuberculosis of a positive test result compared to a negative test result in head-to-head studies.

CI: confidence interval; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; RR: relative risk; TB: tuberculosis; TST: tuberculosis skin test.

Table 11. Evidence base for cost-effectiveness of LTBI diagnostic tests

Research question: Which diagnostic tests are cost-effective for LTBI? (in specific risk groups)?			
Diagnostic test	**Source**	**Finding**	**Level of evidence**
TST	Two non-commissioned systematic reviews with: • one cost-effectiveness study reporting on PLHIV [68]	**TST followed by LTBI treatment if positive (≥5 mm) for PLHIV is highly cost-effective* for diagnosis of LTBI** (as compared to no screening and no treatment in PLHIV)**.**	Weak evidence
	• two cost-effectiveness studies reporting on recently arrived migrants from high TB burden countries [68]	**TST (≥10mm) and subsequent treatment for new adult migrants is highly cost-effective* for diagnosis of LTBI** (as compared to no screening).	Weak evidence
	• two cost-effectiveness studies reporting on recently arrived migrants [69]	**TST (≥5mm) for migrants is cost-effective** for diagnosis of LTBI (as compared with TST (≥5mm) positive followed by QFT-GIT or T-SPOT.TB of QFT-GIT alone).**	Weak evidence
IGRA	Three non-commissioned systematic reviews with • two cost-effectiveness studies reporting on children [69]	**Screening children with IGRA is the most cost-effective** strategy compared to TST (≥ 10 mm).**	Weak evidence
	• five cost-effectiveness studies reporting on recently arrived migrants from high TB burden countries [68]	**Screening adult migrants with IGRA is moderately cost-effective* for diagnosis of LTBI** (as compared to no screening).	Weak evidence
	• One cost-effectiveness study reporting on PLHIV [68]	**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)**.**	Weak evidence
	• Eight cost-effectiveness studies reporting on selected risk groups [70]	**Screening high-risk groups, such as healthcare workers, migrants from high-incidence countries, and close contacts with IGRA is moderately cost-effective*.**	Weak evidence
TST and IGRA	Two non-commissioned systematic reviews with: • two cost-effectiveness studies reporting on children [69]	**Negative TST (cut off value ≥ 5mm) followed by QFT-GIT is the most cost-effective** strategy for diagnosis of LTBI in children**	Weak evidence
	• six cost-effectiveness studies reporting on immunocompromised [69]	**Negative QFT-GIT followed by TST (cut off value ≥ 5 mm) for the immunocompromised population is cost-effective** for diagnosis.**	
	• eight cost-effectiveness studies [70]	**Screening high-risk groups, such as healthcare workers, migrants from high-incidence countries, and close contacts with IGRA in TST positives is cost-effective***.**	Weak evidence
	Cost-effectiveness analyses [52]	• Regardless of the population group at risk, LTBI screening is most cost-effective when done using TST, when positive followed by IGRA, from the healthcare perspective. • IGRA alone or TST alone are comparable in their cost effectiveness. • From the societal perspective, using only IGRA is often the most cost-effective option, because it requires one visit to do the testing.	NA

IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; NA: not applicable; PLHIV: people living with human immunodeficiency virus; QFT-GIT: QuantiFERON-TB Gold In-Tube; TB: tuberculosis; TST: tuberculosis skin test.

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

Ad hoc scientific panel opinion

Acknowledging the weakness of the available evidence, the ad hoc scientific panel concluded that both TST and IGRA can be used for diagnosing LTBI. The choice of test needs to take the circumstances and practicalities into consideration (further discussed in Chapter 5). Limitations of the currently available tests include low positive predictive value for TB developing in the near future; the lack of a gold standard for diagnosis of LTBI; cut-off value issues; relatively high percentage false-negatives; and their inability to differentiate between recent and remote infection.

The two tests can be combined in different ways to increase sensitivity and decrease the number needed to treat or increase specificity, depending on the situation. Based on the available evidence, three possibilities for diagnosis of LTBI using TST and/or IGRA were considered by the ad hoc scientific panel:

- One or the other test.
- Sequential testing (second test is performed only if the result of the first test is positive).
- Parallel testing (with any positive test counting as a positive result).

Practical considerations and public health implications of these approaches are discussed in Chapter 5.

Regardless of the selected approach for initial LTBI diagnosis, it is advisable to perform further investigations of people who test positive to rule out active TB. The subsequent investigation to exclude active TB in people who test LTBI positive can be done in accordance with the recommendation in the WHO guidelines (i.e. CXR) [4].

4.3 Treatment of LTBI

In order to identify the optimal approach for LTBI treatment, the assessment of scientific evidence aimed to identify LTBI treatment regimens that are effective, cost-effective, feasible and acceptable (based on initiation rates, completion rates and the risk of adverse events).

Summary of evidence

Several LTBI treatment regimens were found effective in preventing the development of active TB in randomised controlled trials that were placebo controlled or with a no treatment arm. Specifically, regimens providing isoniazid (INH) alone (for 6, 9 or ≥12 months), rifampicin (RIF) alone (for 3-4 months), INH and RIF (for 3-4 months), INH and ethambutol (for 12 months) and pyrazinamide (PZA)-containing regimens (RIF+INH+PZA and RIF+PZA) (Table 12). Although PZA containing regimens were found to be efficacious, they generally showed unacceptable toxicity.

In general treatment for LTBI was also found to be cost-effective (Table 13). Provision of short treatment regimens (i.e. duration less than six months) was associated with better adherence to and completion of treatment (Table 14). The strength of the evidence ranged from weak to moderate (Tables 12 to 14). Four existing evidence-based guidelines on LTBI treatment [4,63,71,72] mainly recommended INH-containing regimens (alone or in combination with RIF or rifapentine (RPT)), except for one that also recommended a RIF-only regimen (for 3-4 months) [4].

Table 12. Evidence base for the effectiveness of LTBI treatment regimens

Research question: What is the effectiveness of different LTBI treatment regimens for certain risk groups?		
Source	**Finding** (summarised by treatment)	**Level of evidence**
One commissioned systematic review with: • nine (placebo controlled) and three (no treatment) RCTs [44]	**INH for six months (compared to placebo or no treatment) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: - Placebo: 0.61 (0.48-0.77) - No treatment: 0.47 (0.30-0.73)	Weak evidence
• two RCTs [44]	**INH for 9 months (compared to no treatment) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: 0.37 (0.18-0.76)	Weak evidence
• seventeen (placebo controlled) and five (no treatment) RCTs [44]	**INH for ≥12 months (compared to placebo or no treatment) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: - Placebo: 0.53 (0.42-0.67) - No treatment:0.40 (0.19-0.84)	Weak evidence
• one RCT [44]	**RIF alone (compared to placebo) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: 0.48 (0.26-0.87)	Moderate evidence
• two (placebo controlled) and one (no treatment) RCTs [44]	**RIF+INH for 3 -4 months (compared to placebo and no treatment) is an effective treatment regimen for LTBI**. Pooled OR (95% CI) of progression to active TB: - Placebo: 0.52 (0.33-0.84) - No treatment: 0.20 (0.06-0.62)	Weak evidence
• two (placebo vs RIF-INH-PZA), one (no treatment vs RIF-INH-PZA) and one (placebo vs RIF-PZA) RCTs [44]	**PZA-containing regimens (RIF-INH-PZA and RIF-PZA) (compared to placebo or no treatment) are effective treatment regimens for LTBI.** Pooled OR (95% CI) of progression to active TB: RIF-INH-PZA - Placebo: 0.47 (0.22-0.98) (2 studies) - No treatment: 0.02 (0.00-0.41) (1 study) RIF-PZA - Placebo: 0.80 (0.49-1.31) (1 study)	Weak evidence
• one RCT [44]	**INH-EMB for 12 months (compared to no treatment) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: 0.06 (0.00-0.98)	Weak evidence
• three RCTs [44]	**INH for 12-72 months (compared to INH for 6 months) is an effective treatment regimen for LTBI.** Pooled OR (95% CI) of progression to active TB: 0.69 (0.51-0.93)	Moderate evidence

CI: confidence interval; EMB: ethambutol; INH: isoniazid; LTBI: latent tuberculosis infection; OR: odds ratio; PZA: pyrazinamide; RCT: randomised controlled trial; RIF: rifampin/rifampicin; TB: tuberculosis; vs: versus.

Table 13. Evidence base for cost-effectiveness of LTBI treatment regimens

Research question: What is the cost-effectiveness of different LTBI treatment regimens for specific risk groups?		
Source	**Finding**	**Level of evidence**
Two systematic reviews (one commissioned and one non-commissioned) with 47 cost-effectiveness studies [44,73]	**LTBI treatment is cost-effective* for preventing the development of active TB in high risk people with LTBI.**	Weak evidence
One non-commissioned systematic review with 24 cost-effectiveness studies [74]	**In PLHIV and healthcare workers, LTBI treatment after primary screening is cost-effective for preventing the development of active TB.**	Weak evidence
Cost-effectiveness analyses [52]	LTBI treatment with INH+RIF for three months is more cost-effective than treatment with RIF for four months or INH for six months since all are assumed to be equally effective and INH+RIF for three months is both cheaper and has a shorter duration, increasing treatment completion. All three treatment options are cost effective.	NA

INH: isoniazid; LTBI: latent tuberculosis infection; NA: not applicable; PLHIV: people living with human immunodeficiency virus; RIF: rifampin/rifampicin; TB: tuberculosis.

** 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 14. Evidence base for feasibility and acceptability of LTBI treatment regimens

Source	Finding	Level of evidence
Research question: How often is LTBI treatment initiated? (in specific risk groups)		
No systematic review identified presenting statistically analysed quantitative evidence		
Research question: How often is LTBI treatment completed? (in specific risk groups)		
One commissioned systematic review with • three RCTs reporting on contacts of TB cases [42]	**Contacts of TB cases had better LTBI treatment adherence and completion if they received short treatment regimens[a] rather than long treatment regimens[b].** Pooled OR (95% CI) of adherence and completion of short treatment[a] compared to long[b] LTBI treatment regimen: 1.5 (1.0-2.3) (adherence) and 2.1 (1.9-2.3) (completion)	Moderate evidence
• one RCT reporting on migrants [42]	**Migrants had better LTBI treatment completion if they received short treatment regimens[a] rather than long treatment regimens[b].** Pooled OR (95% CI) of completion to long[b] LTBI treatment regimen: 2.5 (1.7-3.6).	Moderate evidence
• three RCTs reporting on general population [42]	**The general population had better LTBI treatment completion if they received short treatment regimens[a] rather than long treatment regimens[b].** Pooled OR (95% CI) of completion to long[b] LTBI treatment regimen: 1.9 (1.1-3.5).	Moderate evidence
Research question: What is the risk of adverse events of LTBI treatment? (in specific risk groups)		
One commissioned systematic review with • one (INH 6 months) and three (INH 9 months) RCTs [44]	**RIF (compared to INH for six or nine months) gives a lower risk of hepatotoxicity.** Pooled OR (95% CI) of hepatotoxicity: - RIF vs INH 6 months: 0.03 (0.00-0.48) - RIF vs INH 9 months: 0.17 (0.06-0.47)	Weak evidence

[a]Short treatment regimens= duration less than six months. [b]Long treatment regimens= duration more than six months.
CI: confidence interval; INH: isoniazid; LTBI: latent tuberculosis infection; OR: odds ratio; RCT: randomised controlled trial; RIF: rifampin/rifampicin; TB: tuberculosis.

Ad hoc scientific panel opinion

The members of the ad hoc scientific panel expressed unanimously their preference for shorter treatment regimens. Short course RIF-containing regimens appear to be less toxic than longer INH (6-9 months) regimens (weak evidence). In addition, shorter LTBI treatment regimens and treatments with less frequent administration (e.g. three months of INH + RPT [75,76]) are preferred over longer LTBI treatment regimens by target risk groups based on moderate evidence. While the efficacy of longer treatment regimens may be high, there may be low levels of treatment acceptance and adherence to prolonged therapy. Shorter treatments (under directly observed therapy) and lower pill burden increase adherence, which is specifically important in populations at risk of non-adherence, such as homeless people and people who inject drugs, and has been shown to result in fewer adverse events.

The ad hoc scientific panel concluded that LTBI can be treated effectively with INH (6–9 months), INH + RPT (3 months), INH + RIF (3–4 months), or RIF (3–4 months). This was mainly based on weak evidence, except for the effectiveness of RIF for 3–4 months which was based on moderate evidence. Regimens with PZA should not be used due to increased risk of hepatotoxicity [77,78].

Moreover, careful clinical monitoring and follow-up of people who are prescribed LTBI treatment is advisable in order to detect drug-related adverse events. For contacts of MDR TB and extensively drug-resistant (XDR) TB patients identified as having LTBI, the evidence base is currently not robust enough to recommend LTBI treatment for all contacts. It is advisable to provide them with careful clinical observation, information and health education from a healthcare worker experienced in management of LTBI and TB disease. Moreover, in line with the ECDC guidance on the management of contacts of MDR TB and XDR TB patients [6], most of the ad hoc scientific panel members agreed that it is advisable to conduct an overall individual risk assessment before deciding whether to provide LTBI treatment. This risk assessment should take into consideration the contact person's risk for progression to TB disease; the drug susceptibility pattern of the likely source case of infection; and the contact person's risk of adverse drug events if initiating LTBI treatment.

4.4 Programmatic issues of LTBI management

The following areas were assessed in order to discuss the optimal approach for programmatic management of LTBI:

- Case detection
  - A. Screening: what is the optimal approach for screening for LTBI? (Who? When? Where? How?)
  - B. Contact investigation: what is the optimal approach for contact investigation? (Who? When? Where? How?)
- Treatment-related interventions: what treatment-related interventions lead to an optimal result in LTBI treatment?
- Education: what is the optimal approach for education on LTBI? (Who? When? How?)
- Implementation: can LTBI management be integrated into existing health programmes in EU/EEA countries?
- Programme monitoring & evaluation: How should monitoring and evaluation of programmatic management of LTBI take place?

4.4.1 Case detection

In order to identify the optimal approach for screening and contact investigation, scientific evidence on screening and contact investigation for LTBI was assessed with the purpose of determining:

- the effectiveness of LTBI screening programmes and contact investigation approaches for certain risk groups;
- the cost-effectiveness of LTBI screening programmes and contact investigation approaches for certain risk groups;
- how to identify and get access to target risk groups for LTBI screening services and contact investigation;
- the effectiveness of interventions to improve screening and contact investigation uptake;
- the effectiveness, cost-effectiveness, and/or feasibility of mandatory LTBI screening.

Summary of evidence

The level of evidence for the systematic reviews included was weak (Table 15). The studies identified assessing the effectiveness of LTBI screening were heterogeneous with regard to the outcome measure used (e.g. yield of LTBI cases, proportion of people who tested positive and were offered LTBI treatment) and the approach to the screening strategy (e.g. screening before migration, integration of LTBI screening into HIV healthcare services). Cost-effectiveness studies showed, despite the heterogeneity in the methodology used, that LTBI screening is cost-effective in populations at risk of infection and/or progression to active disease. The mathematical modelling and cost-effectiveness analyses showed that LTBI screening strategies (i.e. screening and subsequent treatment, when positive) in clinical risk groups are only cost-effective when applied to groups with assumed high prevalence of LTBI, for example migrants from high endemic countries (WHO estimated incidence >50/100 000)[51,52]. In addition, the mathematical model showed that a higher cut-off (of TB incidence in country of origin) for migrant screening results in a more cost-effective intervention, but with a smaller impact on population level. It also showed that the effect of migrant screening upon entry on population incidence is limited, due to large number of migrants already in Europe [51,52]. Three existing evidence-based guidelines for LTBI screening [65,66,72] highlighted the responsibility of healthcare providers to facilitate access to LTBI screening and provide LTBI treatment, particularly for vulnerable and hard-to-reach populations.

No evidence statement could be formulated based on the (limited number of) systematic reviews included for contact investigation. The studies identified lacked a clear description of the approach used for contact investigations and the definition of 'close contact' varied across studies. Five existing evidence-based guidelines for contact investigation of LTBI [63,65,72,79,80] included definitions and categorisation of contacts, established priorities and suggested the use of multidisciplinary teams in the implementation of the contact investigation.

Table 15. Evidence base on LTBI screening

Source	Finding	Level of evidence
Research question: What is the effectiveness of screening programmes for specific risk groups?		
One non-commissioned systematic review with 18 studies[a] reporting on immigrants [59]	**The proportion of migrants recommended LTBI treatment when testing positive is significantly higher when tested with TST than with IGRA.** % immigrants recommended LTBI treatment of those tested TST or IGRA positive: 53.9% and 43.1% respectively (p<0.0001).	Weak evidence
Research question: What is the cost-effectiveness of different screening programmes for specific risk groups?		
One commissioned systematic review with 39 cost-effectiveness studies [44]	**Screening and treatment for LTBI in high-risk populations is cost-effective*.**	Weak evidence
One non-commissioned systematic review with six cost-effectiveness studies [68]	**Screening PLHIV with TST is highly cost-effective**.**	Weak evidence
Two non-commissioned systematic reviews with eight cost-effectiveness studies [68,70]	**Screening high-risk populations with IGRA is cost-effective*.**	Weak evidence
Mathematical modelling and cost-effectiveness analyses [51,52]	**LTBI screening and treatment (INH+ RIF for 3 months) is cost effective for**: • contacts of TB patients, • immunocompromised patients (only if they are migrants) • migrants (entry screening), • prisoners (screening at the moment of incarceration), • people who inject drugs and homeless people (triennial screening) • healthcare workers and travellers (only if they have extremely high temporary exposure to infection)	NA
Research question: How to identify and get access to target groups for LTBI screening services?		
No systematic review identified presenting statistically analysed quantitative evidence.		
Research question: What is the effectiveness of interventions to improve screening uptake?		
One non-commissioned systematic review with 6 RCTs reporting on effectiveness of interventions to improve screening uptake [81]	**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.** Risk ratio (95% CI) of return for reading TST results: Incentives vs. routine care: 2.16 (1.41-3.29) Cash vs. non-cash incentives: 1.13 (1.07-1.19) Different values of cash incentive: 1.08 (1.01-1.16) Incentives vs. any other intervention: 2.16 (1.56-3.00)	Weak evidence
Research question: Is mandatory LTBI screening effective, cost-effective, and/or feasible (for specific risk groups)?		
No systematic review identified on this topic.		

[a] *Study design not reported.*

CI: confidence interval; IGRA: interferon gamma release assay; IPT: isoniazid preventive treatment; LTBI: latent tuberculosis infection; NA: not applicable; PLHIV: people living with human immunodeficiency virus; RCT: randomised controlled trial; TST: tuberculosis skin test; vs: versus.

* *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: and incremental cost-effectiveness ratio (ICER) < USD 20 000 = highly cost-effective; ICER between USD 20 000 and 100 000 = moderately cost-effective; ICER > USD 100 000 = not cost-effective.*

Ad hoc scientific panel

The members of the ad hoc scientific panel acknowledged the lack of evidence for both screening and contact investigation on how to identify and access specific risk groups. They considered two guidelines on the screening of active TB to be useful for LTBI screening (ECDC's guidance on 'TB control in vulnerable and hard-to-reach populations', 2016 [3] and the NICE guidance on 'clinical diagnosis and management of tuberculosis, and measures for its prevention and control', 2011 [65]. The latter was included in the review of systematic reviews and guidelines [5].

Despite the scarcity of evidence and its weak level of evidence, the ad hoc scientific panel concluded that the screening of vulnerable and hard-to-reach populations can be facilitated by having accessible health services that are committed to service provision for specific risk groups.

In addition, incentives and enablers could improve screening uptake and completion of the screening process (e.g. returning for follow-up visit, if needed). The usage and effectiveness of incentives and enablers is dependent on the specific target group and resources in different settings and countries, based on weak evidence. The included evidence showed that material incentives and enablers were effective at improving screening uptake in people with drug use disorders, leading to a significantly higher return for reading of the TST result than with routine care, non-cash incentives or any other intervention. In addition to the included evidence, the ad hoc scientific panel members discussed other interventions to improve screening uptake in prisoners and homeless people. They concluded that the experience of interventions to increase screening uptake was mostly based on screening for active TB.

The panel concluded that identification of contacts can be improved by appropriately trained healthcare workers establishing a good rapport with an index case during contact investigation and/or implementation of specific interventions (based on weak evidence). The ad hoc scientific panel stated that contact investigation should prioritise close contacts, and there should be a clear indication for transmission before contact investigation is expanded to non-close contacts. They also recommended contact investigation in aircraft according to the ECDC 'Risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA) – Tuberculosis' [80].

4.4.2 Treatment-related interventions

In order to identify interventions that support LTBI treatment, the assessment of scientific evidence aimed to identify determinants of LTBI treatment initiation, adherence and completion. In addition, evidence was assessed on interventions to improve initiation, adherence and completion of LTBI treatment and on approaches for monitoring and managing adverse events.

Summary of evidence

Table 16 summarises the findings and Annex 3 provides an elaborated description of the interventions. The level of evidence was considered weak for most interventions, except for four interventions to improve completion of LTBI treatment:

- Social intervention providing peer-based or counsellor support for treatment adherence, which acknowledged the clients' social needs, fears and motivations (strong evidence);
- Case management of LTBI in homeless people by community-based nurses promoting self-esteem and health-seeking behaviour, providing direct health education and linkage to medical and social services (strong evidence);
- Provision of monetary incentives to people who inject drugs returning for TST reading (moderate evidence);
- Educational programmes targeting inmates (moderate evidence).

The mathematical modelling and cost-effectiveness analyses performed for the guidance development did not provide information on treatment-related interventions. There were no guidelines identified of sufficient quality in accordance with AGREE II that had been published in the last 10 years providing information on treatment-related interventions that support treatment of LTBI or on adverse events management.

Table 16. Evidence base - treatment-related interventions for programmatic management of LTBI

Source	Finding	Level of evidence
Research question: What are the determinants of LTBI treatment initiation, adherence and completion?		
No systematic review identified presenting statistically analysed quantitative evidence.		
Research question: What interventions are effective at improving initiation, adherence and completion of LTBI treatment?		
One commissioned systematic review with • one observational study[a] reporting on immigrants [42]	**A social intervention using case management with attention to an individual's cultural background in migrants (compared to standard care) is effective at improving the initiation rate of LTBI treatment.** OR (95% CI) for initiation of LTBI treatment: 2.7 (1.9-3.8)	Weak evidence
• one observational study[a] reporting on healthcare workers [42]	**Use of IGRAs (compared to TST) is associated with increased initiation rates of LTBI treatment in healthcare workers.** OR (95% CI) for initiation of LTBI treatment: 8.8 (3.1-23)	Weak evidence
• three RCTs reporting on general population [42]	**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 at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 1.4 (1.1-1.9)	Strong evidence
• one observational study[a] reporting on immigrants [42]	**A social intervention using case management with attention to the cultural background of migrants (compared to standard care) is effective at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 7.8 (5.7-10.7)	Weak evidence
• one RCT reporting on homeless people [42]	**Nurse case management in homeless people (compared to standard care) is effective at improving completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 3.0 (2.2-4.2)	Strong evidence
• one RCT reporting on people who inject drugs [42]	**Methadone treatment + directly observed therapy (compared to no methadone treatment + self-administered therapy) in people who inject drugs is effective at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 14.5 (5.0-42)	Weak evidence
• one RCT reporting on people who inject drugs [42]	**Monetary incentive (compared to no incentive) in people who inject drugs is effective at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 32.0 (7.1-145)	Moderate evidence
• one RCT reporting on contacts of TB patients [42]	**Directly observed therapy + short treatment regimen (compared to self-administered therapy + long treatment regimen) in contacts of TB patients is effective at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI: 2.1 (1.9-2.3)	Weak evidence
• one RCT reporting on illegal immigrants [42]	**Clinic-based directly observed therapy (compared to daily self-administered therapy) in migrants decreases the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 0.1 (0.04-0.3)	Weak evidence
• one RCT reporting on prisoners [42]	**Education in inmates (compared to no education) is effective at improving the completion rate of LTBI treatment.** OR (95% CI) for completion of LTBI treatment: 2.2 (1.0-4.7)	Moderate evidence
Research question: What is an effective approach for monitoring and managing adverse effects?		
No systematic review identified presenting statistically analysed quantitative evidence		

[a]No further specification, [b]For interventions effective to improve initiation, adherence and completion of LTBI treatment, it was decided to include one commissioned systematic review.
CI: confidence interval; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; OR: odds ratio; RCT: randomised controlled trial; TB: tuberculosis; TST: tuberculosis skin test.

Ad hoc scientific panel

The paucity of evidence regarding patient-related, treatment-related or social-economic determinants of LTBI treatment initiation, adherence and completion was acknowledged by the ad hoc scientific panel. Various levels of evidence (weak-moderate-strong) were observed, depending on type of intervention.

The ad hoc scientific panel concluded that using culturally appropriate 'patient-centred' case management can improve treatment initiation and treatment adherence/completion, especially in vulnerable and hard-to-reach populations. However, it was also recognised that distilling the effective elements of social interventions (i.e. case management with attention to an individual's cultural background, adherence coaching, counselling, contingency contracting, education, nurse case management, peer-based interventions (see Annex 3 for an elaborated description of the interventions), is complicated. 'Social interventions' is often used as a broad term under which multiple interventions are implemented simultaneously. Therefore, key elements related to social interventions could not be distinguished by the ad hoc scientific panel.

In addition, the ad hoc scientific panel considered that using different interventions including support, incentives and enablers, can improve adherence to treatment and treatment completion, especially in homeless people and people who inject drugs. Furthermore, directly observed therapy can be used to improve adherence and treatment completion in people who are at risk of non-adherence.

Due to the lack of sufficient evidence on adverse events, no conclusion was formulated on this topic.

4.4.3 Education

In order to identify the optimal approach to education on LTBI, scientific evidence was assessed for the effectiveness and cost-effectiveness of education, who should be targeted and when, and what information should be provided.

Summary of evidence

A limited number of systematic reviews (n=2) were identified providing information on the optimal approach for education on LTBI. One-to-one education sessions were effective to improve adherence to and completion of LTBI treatment. No systematic review was identified on the cost-effectiveness of education. Table 17 summarises the findings of the review of systematic reviews and guidelines [5].

The mathematical modelling and cost-effectiveness analyses performed for the guidance development did not include an assessment of different education methods. In addition, no guidelines were identified of sufficient quality, according to AGREE II, that had been published in the last 10 years and provided information on the optimal approach for LTBI education.

Table 17. Evidence base for education on programmatic management of LTBI

Research questions: **Who should be targeted for education and when?** **What information should be provided?** **How effective are the different education methods?**		
Source	**Finding**	**Level of evidence**
One non-commissioned systematic review with two RCTs reporting on prisoners and mothers of LTBI positive children [82]	**Education based on CDC guidelines for prisoners (one-to-one sessions with research assistant) and for mothers of LTBI-positive children (discussions with specialised nurse or physician and information leaflet) compared to control group is effective for improving adherence of LTBI treatment** - Risk ratio (95% CI) of completing first TB clinic visit one month after release from jail: 1.56 (1.02-2.37) - Range of risk ratio for adherence in mothers of LTBI-positive children (mean age 6.5 years) measured by Eidus-Hamilton reaction (educational interventions: education by telephone, home visits and via physicians at the clinic): 1.33-1.61 (all significant).	Weak evidence
	Education based on CDC guidelines for prisoners (one-to-one sessions with research assistant) and for mothers of LTBI-positive children compared to control group is effective for improving completion rates of LTBI treatment - Risk ratio (95% CI) of completing LTBI treatment six months in prisoners: 1.94 (1.03-3.68) - Range of risk ratio in mothers of LTBI-positive children (mean age 6.5 years) measured by attendance at the last clinic visit (educational interventions: education by telephone, home visits and via physicians at the clinic): 1.20-1.46 (all but one significant).	Weak evidence
One non-commissioned systematic review with two RCTs reporting on people drug use disorders [81]	**Education (compared to material incentives) is less effective for improving return for TST reading in people with drug use disorders compared to material incentives.** Risk ratio (95% CI) for return to clinic for TST reading in people with drug use disorders, education compared to material incentives: 2.16 (1.56-3.00).	Weak evidence
Research question: Is education cost-effective?		
No systematic review identified on this topic.		

CDC: US Centers for Disease Prevention and Control; CI: confidence interval; LTBI: latent tuberculosis infection; RCT: randomised controlled trial; TB: tuberculosis; TST: tuberculosis skin test.

Ad hoc scientific panel opinion

The ad hoc scientific panel preferred the word 'training' for clinicians and 'counselling' for possible patients instead of the word 'education' in general. They considered healthcare workers, TB and LTBI patients and TB contacts target groups for education. Education can be used to emphasise the importance of the programmatic management of LTBI, to increase the understanding of the disease and to introduce or explain interventions or a diagnostic test.

The ad hoc scientific panel concluded that appropriate training of healthcare workers on LTBI identification and management could be effective in improving target populations' willingness to be diagnosed and treated for LTBI. In addition, patient counselling and education could be effective in improving adherence and completion rates in certain population groups.

4.4.4 Implementation

A search was made for scientific evidence with the purpose of ascertaining whether LTBI management can be integrated into existing health programmes. Specifically, efforts were made to identify country-specific circumstances that should be taken into account for successful implementation of programmatic management of LTBI. In addition, the evidence was assessed for effectiveness, cost-effectiveness, and/or feasibility of integrating LTBI case detection and treatment into existing health programmes.

Summary of evidence

Limited information on the topic was available. No quantitative evidence was identified; only two systematic reviews were retrieved, both of them presenting descriptive results on the integration of LTBI case detection and treatment into integrated TB/HIV service delivery. These studies assessed different models for integration of TB and HIV services; highlighted the implementation challenges (e.g. additional infrastructure and training of staff is required); touched upon the shortcoming of the monitoring and evaluation approaches (e.g. focus on outputs rather than impact) and identified the need to establish the effectiveness, efficiency and cost-effectiveness of integrated strategies [83,84]. The mathematical modelling and cost-effectiveness analyses performed for the guidance development did not assess integration in existing health programmes. One existing evidence-based guideline provided recommendations on integrating LTBI screening into existing health programmes for people with drug use disorders and prisoners [72].

Ad hoc scientific panel conclusion

The ad hoc scientific panel noted the scarcity of evidence on this topic. Nevertheless, the ad hoc scientific panel concluded that integration of programmatic management of LTBI into existing TB and other health and social care programmes and services is likely to be beneficial.

4.4.5 Programme monitoring and evaluation

Scientific evidence was searched to establish the best format for implementing monitoring and evaluation of programmatic management of LTBI.

Summary of evidence

No systematic reviews were found presenting evidence on how monitoring and evaluation of programmatic management or LTBI should take place. The mathematical modelling and cost-effectiveness analyses did not assess different options for programme monitoring and evaluation. One existing evidence-based guideline on programme monitoring and evaluation [4] provided relevant information. It recommends careful documentation of people treated for LTBI, combined with implementation of a system for monitoring and evaluation that is aligned with national TB policies [4].

Ad hoc scientific panel conclusion

Given the absence of evidence and after discussing the scope of the recommendation presented in the WHO guidelines [4], the ad hoc scientific panel concluded that the implementation of programmatic management of LTBI can be monitored and evaluated using the WHO monitoring and evaluation indicators.

The ad hoc scientific panel suggested staying in line with existing indicators (and their definitions) to monitor implementation of the End TB Strategy, as included in the WHO Global tuberculosis report 2016 [23]:

- Number eligible for screening (target groups);
- Number screened (coverage);
- Number tested positive (yield);
- Number started on treatment;
- Number completing treatment.

4.5 ECDC assessment

ECDC considers the key components in Box 2 to be suitable for inclusion in a package of public health measures for programmatic management of LTBI. ECDC's assessment is based on the scientific evidence available and the expert opinion of the ad hoc scientific panel.

For each component, ECDC has identified suitable public health measures that can be considered for implementation at national level, which are further explained in the text. These options can be used by EU/EEA Member States when formulating or updating their approaches to LTBI programmatic management.

Box 2

Key components for programmatic management of LTBI in the EU/EEA

- Identification of groups at-risk of having LTBI and/or an increased risk of progressing to active TB. These target groups should be prioritised for LTBI screening and treatment.
- Definition of diagnostic approach for LTBI detection, including both the selection of diagnostic test(s) and the diagnostic algorithm most appropriate for each target group.
- Provision of LTBI treatment using treatment regimens that are effective and promote adherence and completion by different target groups.
- Implementation of patient-centred strategies for service delivery.
- Effective health education and communication with target groups and healthcare providers.
- Programme monitoring and evaluation.

4.5.1 Identification of groups at risk

The following groups could be prioritised for LTBI management interventions – i.e. targeted screening and treatment for LTBI:

- PLHIV (regardless of their CD4 counts and ART status);
- immunocompromised persons, such as patients on anti-TNF alpha treatment, patients preparing for transplantation, patients with end-stage renal diseases and/or preparing for dialysis;
- patients with silicosis;
- people with fibrotic lesions;
- contacts of confirmed TB cases, based on a risk assessment of their exposure.

Depending on the specific epidemiological characteristics of TB in the EU/EAA country, Member States may consider additional at-risk groups. For example, selected vulnerable and hard-to-reach populations (e.g. migrants, prisoners, homeless people, and people with drug use disorders) or healthcare workers.

4.5.2 Definition of diagnostic approach for LTBI detection

Ideally, LTBI screening would entail a comprehensive strategy including:

- the availability of and accessibility to diagnostic tests;
- the intention to provide LTBI treatment (if appropriate); and,
- the implementation of interventions supporting the uptake and completion of LTBI diagnostic procedures.

First, it is important to establish a diagnostic algorithm that identifies LTBI and rules out active TB. LTBI diagnosis can be done either by using TST alone, IGRA alone or by integrating both tests in the LTBI screening strategy. Which test or combination of tests is most appropriate depends on the resources available and the target group. Member States should also decide on the periodicity for the implementation of LTBI diagnostic interventions.

Complementary strategies, such as integration of LTBI screening in already existing health services and the implementation of programmes providing material incentives and enablers, may also be considered.

4.5.3 Provision of LTBI treatment

Once the diagnosis of LTBI has been made, the most appropriate and effective treatment regimen should be chosen, keeping in mind the feasibility and acceptability of different LTBI treatment regimens for the targeted risk groups. The selection of LTBI treatment regimen can be based on an individual risk assessment.

LTBI treatment with INH (6–9 months) is a suitable LTBI treatment regimen for any risk group. In the EU/EEA context, RIF-containing regimens (i.e. RPT+INH (3 months)[85], INH+RIF (3–4 months) and RIF (3–4 months)) are recommended for LTBI treatment (where RIF/RPT is not contraindicated). These regimens have the advantage of a shorter treatment duration compared to INH (6–9 months). Even shorter courses are under investigation and results of a one-month course with once daily INH/RPT in HIV-infected persons have shown that INH/RPT was non-inferior to INH (nine months), had fewer adverse events, and was more likely to be completed [86].

4.5.4 Implementation of patient-centred strategies for service delivery

Interventions aiming to increase the uptake and completion of LTBI screening and treatment are just as relevant as the medical solutions for diagnosis and treatment of LTBI. Patient-centred case management including material incentives and enablers, counselling and education, peer-based support and culturally-sensible approaches can be considered as part of an integrated strategy for LTBI treatment provision.

4.5.5 Effective health education and communication with target groups and healthcare providers

A comprehensive educational programme targeting both the at-risk groups, particularly vulnerable and hard-to-reach populations, as well as healthcare providers could be embedded within the programmatic management of LTBI. The purpose of such an educational approach would be to increase general awareness of the importance of detecting and treating LTBI. For example, training healthcare providers on establishing a rapport with the target populations for LTBI screening. This would facilitate the implementation of the patient-centred strategies listed above. Similarly, targeted populations can benefit from health education tailored to their needs and delivered through different models of integrated healthcare services.

4.5.6 Programme monitoring and evaluation

To monitor and evaluate the implementation of LTBI programmatic management, reporting and monitoring procedures need to be established and put into effect. Acknowledging the limitations of dealing with a non-notifiable condition such as LTBI, initial attempts could focus on the case-based registration of TB contacts identified during routine contact investigations. For a reporting system adequate data collection processes should be developed or revised, performance indicators should be defined and regular programme monitoring should be performed in order to inform the overall assessment of programme implementation. National procedures should preferably be aligned with global [87] and regional [88] monitoring and evaluation frameworks, to allow inter-country comparability.

5. Implications for public health practice and research

5.1 Public health practice

The ad hoc scientific panel reflected on the possible implications for public health by means of the Delphi questionnaire and in discussions during the panel meeting. The ad hoc scientific panel also reflected on acceptability and feasibility of targeting specific populations and using certain interventions described in the evidence; the use of resources to implement the interventions; and the anticipated cost-effectiveness of the interventions.

The ad hoc scientific panel concluded that active TB control should always be prioritised over LTBI management, especially when resources and capacities are limited. Further public health-related aspects of LTBI programmatic management discussed by the ad hoc scientific panel are summarised in this chapter.

5.1.1 Target risk groups

Organisational aspects

The definition of priority risk groups should be informed by the best evidence available. For instance, migrant groups prioritised for LTBI screening are often defined based on the TB incidence in the country of origin. In addition, host countries may take into account epidemiology, organisation of health service provision, and resource availability in their country, together with cost-effectiveness considerations, when defining the TB incidence threshold in countries of origin to be used to prioritise targeting. The threshold currently used varies among Member States, ranging from 40 to 100 TB cases per 100 000 population. The thresholds use WHO estimates for the whole country of origin. Certain types of migrants or migrants coming from certain areas (specifically in large countries) might originate from a (sub-) population with a lower or higher TB incidence. Hence, it may be useful to consider recent screening data in the selected sub-populations, in addition to WHO data. Other relevant factors to take into consideration when formulating or updating screening policies are the routes that migrants have taken (i.e. the epidemiological situation in the transit countries and how long they have been in those countries), the vulnerability of the migrants (e.g. asylum seekers, undocumented migrants) and how long they have been residing in the host country.

The choice of target risk groups for programmatic management of LTBI in Member States will depend on the importance of the risk group in national TB epidemiology and the size of the at-risk population. The ad hoc scientific panel noted that certain risk groups may overlap – e.g. PLHIV who also inject drugs; healthcare workers who are close contacts of pulmonary TB patients or migrants who are prisoners or homeless people. This concurrence of risk factors may provide an entry point to approach vulnerable and hard-to-reach populations through already existing health services such as HIV clinics and needle exchange programmes.

Another aspect to consider when targeting groups for programmatic management of LTBI is the geographic distribution of selected risk groups (e.g. higher density in urban settings compared to rural areas) and how it facilitates or hinders access to and utilisation of health services [89]. Provision of LTBI screening, when provided as an outreach intervention, can become an entry point for TB control for populations who normally have limited access to health services.

Different modes of delivery of components for programmatic management of LTBI can be considered depending on the structure of the health system, feasibility and resources available. For example, LTBI screening can be conducted systematically (e.g. among PLHIV), as part of an active TB outbreak investigation (e.g. among homeless people and healthcare workers) or through outreach programmes (e.g. among people who inject drugs).

Similarly, when deciding on TB contacts to target (e.g. only close contacts, or also non-close contacts), the feasibility for implementation by the existing health system and the effects on the health system must be considered. Contact investigations normally focus on those at highest risk of TB infection. Close contacts and household contacts can be screened in the first instance, and contact investigation can be extended beyond close contacts depending on the findings of the initial investigation – i.e. when there is substantial evidence of transmission to the close contacts.

The organisation and structure of the national health services will determine the different roles and degree of coordination required to ensure the provision of high-quality programmatic management of LTBI. Identification of public and private health providers involved with the target populations, the latter including a wide spectrum of actors such as private hospitals/clinics (including single-handed practice), civil society organisations, charities and non-profit organisations, would be a necessary first step followed by definition of the roles of each actor in identifying those at risk, diagnosing LTBI, providing LTBI treatment and education, monitoring and evaluation.

Ideally, the roles and responsibilities of different stakeholders, as well as standard reporting and communication procedures for the national/federal, regional and local level should be described in a (sub-) strategy or plan for programmatic management of LTBI.

Cost-effectiveness and resources availability

The feasibility, possible effectiveness and cost-effectiveness of screening for LTBI should be assessed per type of risk population, with accessibility (i.e. how to reach them) as an important criterion.

For migrants from high TB-burden countries (i.e. TB incidence >50/100 000), LTBI screening (i.e. screening and subsequent treatment, when positive) at entry or during a defined period after entry to an EU/EEA or candidate country is cost-effective according to the mathematical modelling and cost-effectiveness analyses [51,52]. LTBI screening for immunocompromised and PLHIV is only cost-effective when applied for groups with high prevalence of LTBI, for example migrants from high TB- incidence countries, homeless people and people who inject drugs [51,52]. LTBI screening of contacts of TB patients, prisoners, homeless people and people who inject drugs is cost-effective according to the model [51,52]. In contrast, LTBI screening for healthcare workers or long-term travellers is not likely to be cost-effective, except when people have been highly exposed e.g. during healthcare work [51,52]. Cost effectiveness depends on the local epidemiology and costs and the willingness to pay and would need an assessment when considering implementation of LTBI screening.

Implementation of LTBI screening requires the procurement of supplies and equipment. To exclude active TB a CXR machine needs to be available and accessible. Particularly in prisons, the availability of a CXR machine needs to be taken into account when designing an LTBI screening programme.

In homeless populations, more efforts and costs could be expected in addition to the usual costs of screening and treatment, due to the need for special outreach programmes and provision of incentives, enablers (e.g. food vouchers) and other means of support (such as use of video observed therapy or directly observed therapy), to increase adherence and/or completion of testing and LTBI treatment.

Social aspects

Involvement of peers and community leaders could improve reaching members of specific target groups. Designated 'TB ambassadors' and 'national champions' can help to raise awareness and clarify misconceptions about LTBI [90,91]. Similarly, application of behavioural techniques, such as social marketing, can help to understand risk groups' health-seeking behaviour, and develop appropriate interventions through governmental or non-governmental stakeholders. Social marketing is a behavioural science approach which aims to encourage voluntary behaviour change. It applies marketing theories and techniques to the planning, implementation and evaluation of interventions with the aim of improving individual and societal wellbeing [92].

TB-related stigma, self-chosen social isolation, stress, depression, perceived discrimination and fear of deportation among migrants or fear of opiate withdrawal among people who inject drugs are important barriers for seeking healthcare [93,94]. Community-based and outreach health providers need to be aware of these barriers and also facilitate access to healthcare, not only for treatment of symptomatic diseases but also for prevention activities such as management of LTBI. Thus, the establishment of rapport and trust between healthcare providers and people with LTBI, in the context of socio-economic vulnerability, is a facilitator for risk groups to access diagnosis and treatment of LTBI [94].

Ethical aspects

Choices of target groups for programmatic management of LTBI should take into consideration possible cultural sensitivity for certain target groups. The ad hoc scientific panel highlighted that there should not be any perceived or actual coercion for LTBI screening or treatment in vulnerable populations.

Among migrant sub-populations, while it might be harder (i.e. less feasible and more costly) to approach and access undocumented migrants, the benefits of preventing active TB by LTBI treatment may be greater, since this group often has limited or no access to healthcare and, if progressing to TB they are likely to have a higher morbidity and potentially increased delays in being diagnosed as well as prolonged infectiousness. Asylum seekers and refugees may be more easily accessible for programmatic management of LTBI; however, special efforts should be made to ensure that testing results will not affect their legal status.

5.1.2 Diagnosis of LTBI

Organisational aspects

The choice of diagnostic test to apply may differ per country, based on setting, target group, availability of tests, and specific advantages and limitations of the diagnostic tests available. Accessibility to testing should be ensured. Depending on the structure of the national health system, it will be necessary to define the level of service at which LTBI testing will be provided.

The administration and interpretation of the LTBI diagnostic tests requires adequate training for healthcare workers to guarantee the reliability of the results. For TST, crucial technical aspects relate to the use of the correct injection

technique and reading and interpretation of induration. Although IGRA testing is not affected by healthcare worker perception or bias in relation to BCG and most environmental mycobacteria, it is pertinent to establish clear standard operating procedures and quality assurance programmes for the laboratory work in order to capture any significant variation in performance.

Cost-effectiveness and resources availability

From the healthcare system perspective, the selection of LTBI diagnostic test or combination of tests should depend on the purpose of testing, country-specific circumstances (e.g. varying prices/costs and availability of diagnostic tests for LTBI between the EU/EEA countries), practical/operational issues (e.g. number of visits needed) and patient-specific considerations of the targeted group (see Table 18).

Table 18. Considerations for selection of LTBI testing method, as discussed by the ad-hoc scientific panel

Target groups	Preferred test	Reason
Children under 5 years of age	TST	Children's immune system, difficulty of drawing blood, little data on performance of IGRAs in young children.
Vulnerable and hard-to-reach populations	IGRA	No need for a second visit to read the test result.
Immunocompromised patients (including PLHIV)	Combination of TST and IGRA (parallel testing)[a]	LTBI tests are less sensitive in immunocompromised people. In order not to miss *M. tuberculosis* infected people who may face significant adverse health effects due to TB, a more inclusive approach is advisable.
Migrant populations	IGRA or TST acceptable. (IGRA for large numbers)	No need for a second visit to read the IGRA result.
BCG-vaccinated people	IGRA	TST may be affected by prior vaccination with BCG.

[a]After the initiation of ART, which may restore the immune response, repeated testing for LTBI may be considered for PLHIV previously known to have negative TST or IGRA results [95].

BCG: Bacillus Calmette-Guerin; IGRA: interferon gamma release assay; LTBI: latent tuberculosis infection; PLHIV: people living with human immunodeficiency virus; TB: tuberculosis; TST: tuberculosis skin test.

Using IGRA alone might be considered more cost-effective since it only requires one visit to do the testing. Mathematical modelling and cost-effectiveness analyses showed however, that regardless of the population group at risk, LTBI screening is most cost-effective when done using TST followed by IGRA (if TST is positive), from the healthcare perspective. From the societal perspective, screening with TST followed by IGRA or IGRA alone were the most cost-effective strategies in the four countries studied [51,52].

In sequential testing TST is first applied and if positive followed by an IGRA, ensuring a higher specificity. This approach is useful in reducing unnecessary treatment (i.e. in situations where it is more important not to incorrectly treat those who have falsely tested positive with TST) and related costs. As it requires more visits, it could best be considered in situations where the operational circumstances support sequential testing.

Parallel testing, i.e. testing with TST and IGRA at the same time, is a more inclusive approach (higher sensitivity) and can be used in situations where it is important not to miss an LTBI case. This approach is especially relevant in immunocompromised people [96] because the affected immune response makes LTBI diagnosis more difficult, and missing LTBI might have severe consequences for the patient.

Both TST and IGRA are not able to differentiate between recent and remote infection, and consequently the risk of progression to active TB. According to the ad hoc scientific panel, further research should focus on developing better tests for LTBI that should be able to make this differentiation.

Depending on the country's health infrastructure, out-of-pocket payments may be necessary in order to access initial LTBI screening [97]. Out-of-pocket payments are known to discourage healthcare seeking. In addition, the perceived lack of severity of a condition that does not present with signs and symptoms, is not contagious and may not progress to the active disease, can discourage healthcare seeking. In fact, some people suspected of having LTBI may take the conscious decision to 'wait and see' whether they progress to active TB because, as 'confirmed TB cases', they would be entitled to free-of-charge medical care.

Ethical aspects

Testing for LTBI should be done with the intention of offering treatment when the screening is positive, although the feasibility, the individual's characteristics and the balance between benefits and harm should be taken into consideration.

5.1.3 Treatment of LTBI

Organisational aspects

To gain optimal benefits of LTBI treatment, treatment should be organised with the aim of achieving maximal adherence. Standard ECDC guidance principles for increasing adherence to treatment in vulnerable populations are available – for example, communicating with the people in their native language [3]. Various interventions have been suggested in the aforementioned guidance for improving treatment adherence in different target groups. Particular attention should be given to social interventions and catering for the psycho-social needs of target populations, for example nurse-led case management, counselling programmes delivered by non-medical staff and peer-support (Annex 3). Member States are encouraged to gather programmatic evidence on the implementation to assess the effectiveness and impact of this type of intervention.

Case-based monitoring of the treatment should be applied, including monitoring for the occurrence of hepatotoxicity or other serious side effects. At the population level the benefits of the screening and treatment should be monitored and evaluated.

Cost-effectiveness and resources availability

Mathematical modelling showed that LTBI treatment with a scenario of INH+RIF for three months is more cost-effective than treatment with RIF alone for four months or longer treatment with INH (six months). All (RPT/INH, INH, RIF, RIF/INH) are assumed to be equally effective, but INH+RIF for three months is both cheaper and has a shorter duration, increasing treatment completion. INH+RPT LTBI treatment once weekly with 12 doses has recently been evaluated and was found to be cost effective in a setting comparable to the EU [98,99]. In addition, taking into account the fact that LTBI treatment generally concerns otherwise healthy persons, a shorter treatment duration may be preferable in most cases.

It is important to promote access to, availability and affordability of RPT-containing treatment regimens [100]. At present, RPT is not registered with the European Medicines Agency and this remains an important health-system-related barrier. A multi-stakeholder effort would be necessary to encourage the completion of regulatory procedures by pharmaceutical companies that would warrant the availability of quality-assured drugs for LTBI treatment in the EU/EEA [101].

Social aspects

Numerous reasons for low treatment adherence have been reported, such as (fear of) side effects of the treatment, lack of symptomatic disease and thus lack of motivation for taking LTBI treatment, or low risk perception of progression to active TB [102-104]. These should be taken into account when deciding on implementing interventions to improve adherence.

From the patients' perspective, availability of psychological support may help them cope with long–term treatment and its related adverse effects, thus contributing to their adherence to treatment. Directly observed treatment can improve adherence, particularly if there is trust between the patient and the healthcare workers delivering this service. However, some patients may experience directly observed treatment as condescending and be averse to the idea that it exposes their health status to others. Directly observed treatment may be perceived as a contributing factor for TB-related stigma, especially in communities with poor knowledge of TB infection and disease [94].

Ethical aspects

Since LTBI management is a preventive, rather than a curative measure, benefits for otherwise healthy people need to outweigh risks, such as the daily burden of taking medications and potential adverse events due to treatment. However, in programmatic management of LTBI, both individual aspects and TB control through prevention of transmission should be considered. For example, in contact investigations, detection and LTBI treatment is crucial for prevention of disease and interruption of transmission chains. Alternatively, LTBI treatment can be offered only to people having higher risk of progression to active disease. In Norway and Sweden not all migrants with LTBI are treated for LTBI, but only the groups at higher risk of progression to TB, such as children, teenagers and persons with fibrotic lesions. In United Kingdom, research has shown that vulnerable populations in high TB incidence areas, such as migrants, tend to overlap with clinical groups with higher risk for progression to TB (e.g. chronic liver disease, diabetes). These pre-existing health conditions may influence uptake of LTBI screening and treatment because these people are aware of their risk of developing active disease and already have access to care through the monitoring of their co-morbidities [105].

The type of treatment should be adapted to the individual situation of the LTBI-positive person and the acceptability for them. For example, in clinical populations LTBI treatment should be adjusted to the treatment they

are already receiving. Furthermore, it may be confusing (difficult to understand) for a contact if the index case (a patient) receives six months of treatment while a contact (healthy person) receives nine months of treatment.

Programmatic issues

Programmatic management of LTBI requires the identification of individuals at risk; application of an appropriate diagnostic test, obtaining and reporting of the test result and, if positive, evaluation of whether preventive treatment should be initiated. This is followed by initiation of preventive treatment, and finally successful completion of preventive treatment. The LTBI cascade of care framework conceptualises where and why people with LTBI are lost in the process [107]. This framework describes a continuum of sequential steps (i.e. initial identification of at-risk populations, testing, initiation and completion of treatment) that need to be successfully completed and identifies barriers and facilitators for the management of LTBI. This section further explores the region-specific challenges and discusses strategies to improve programmatic implementation of LTBI management.

Organisational aspects

Contact investigation can be implemented by using well-known methodologies such as the 'stone in the pond principle' [106]. Attention should be paid to the identification of contacts. Approaches on identifying contacts are described in Erkens et al [7]. In addition, contact tracing can be improved by including it as a part of index case management, by performing source tracing for children diagnosed with TB, and by active follow up of contacts in contrast to the more passive approach through invitation of contacts by cases [100].

Programmatic LTBI screening should follow a systematic approach working towards population health, including the collection of information on the number of contacts tested in contact investigations, the number tested positive, the uptake and completion of LTBI treatment. This requires the availability of resources. The creation of a treatment register of TB contacts was suggested (as a first step in adopting a systematic approach) by the ad hoc scientific panel. The treatment-register can be developed according to available resources and expertise in the country and does not need to be standardised. Such a register would be a start but will not be sufficient to provide input to internationally agreed monitoring and evaluation frameworks [87,88].

Some EU/EEA Member States already have a case-based registry embedded in their TB surveillance system [97,105]. However, data collection is non-mandatory which potentially leads to underreporting and does not allow for estimation of coverage, since the number of people eligible for LTBI screening is unknown [97,105].

The paucity of evidence on implementation of programmatic management of LTBI highlights the need to conduct operational research. Documenting lessons learned and good practices in low incidence TB settings would facilitate the exchange of experiences between countries. A recent example is the assessment of an LTBI screening programme in a high-risk area for TB in London. This study showed that low uptake of LTBI screening treatment was associated with key demographics (i.e. country of birth), risk (i.e. current smokers) and provider-related factors. Low LTBI treatment uptake, on the other hand, was provider-dependent only (i.e. some general practitioners were more likely to prescribe LTBI treatment than others) [105]. These findings emphasise the importance of providing adequate training and incentives to healthcare providers.

In low TB incidence countries several barriers to providing LTBI treatment have been reported. In Australia physicians were more likely to prescribe LTBI treatment if they were familiar with evidence on the risk of progression to active TB disease. Conversely, practitioners' perceptions (i.e. that men are less likely to accept and adhere to LTBI treatment) or strong belief in limited scientific evidence (i.e. age-related risks for hepatotoxicity) were behind their decision not to offer LTBI treatment [107]. Among the main perceived barriers to prescribing LTBI treatment in primary care, as reported by British general practitioners, were insufficient experience with screening and treating LTBI, lack of timely support from specialist TB services and insufficient resources for sustainable delivery of the programme, including financial incentives for general practitioners [108]. Dutch physicians have reported low adherence to national recommendations for LTBI screening and treatment in PLHIV [109]. Instead of screening all PLHIV for LTBI, as was recommended, a TB risk-stratification patient-level approach was applied which implied that not all new patients with HIV were screened for LTBI [109]. Physicians considered the screening tests unreliable, were afraid of over-treating, were concerned about side-effects and drug interactions, and were uncertain about the actual risk of progression to active TB [109]. This variation in LTBI treatment provision based on the patient's individual risk-benefit balance has also been reported among Australian practitioners [110]. These findings emphasise the conflict faced by healthcare providers when trying to balance population-level public health measures and individual-level benefits that outweigh potential harms.

Communication barriers during medical encounters with migrants from diverse cultural and linguistic backgrounds have also been reported [93,110,111]. Explaining the abstract concept of LTBI and the associated risks and benefits of LTBI treatment to people with limited health literacy and/or who are interpreter-dependent is challenging for health providers [110]. Efforts should be made to ensure that services for programmatic management of LTBI are provided with a culturally appropriate 'patient-centred' approach which is acceptable and tailored to those being targeted. Integration with services or programmes for other diseases can be considered in order to reach specific risk groups. Continuity of care should be ensured, especially in mobile risk groups such as

prisoners [112] who may be moved from one facility to another or released, and in people with drug use disorders or the homeless [3], where follow-up might be challenging.

To improve return rates for reading of TST results or to improve the initiation and completion of LTBI treatment after positive testing, social interventions, education, incentives or enablers, or treatments with directly observed therapy could be considered. However, it is also necessary to tackle provider-related barriers to implementation. Variations in implementation of policies, guidelines and programmes may be caused by health providers' divergent opinions on the selected approach for LTBI management. Thus it is advisable to promote the involvement of end-users and beneficiaries, such as national professional associations, communities and patient associations, to overcome the perceived gaps between public health recommendations and day-to-day practice [109,110].

Cost-effectiveness analyses and resources availability

Mathematical modelling results showed that LTBI screening of high risk groups is a cost-effective policy option for Member States. The programmatic LTBI screening (and consecutive treatment) approach may be adapted to the selected risk group. For example, since there is a higher risk of progression to active TB in the first few years after infection, it would be more cost-effective to screen and treat LTBI in the first years after migration.

The decision on whether or not to implement incentives and the type of incentive would require careful consideration of the potential benefits and feasibility of the selected approach. Incentives may increase the cost-effectiveness of screening by increasing screening uptake and treatment initiation. Conditional incentives like vouchers (e.g. for food) or enablers (e.g. bus tickets) may increase screening uptake. Furthermore, providing travel fare to patients could help them overcome accessibility barriers to screening and treatment. Unconditional incentives (e.g. money) may give a better effect but at the same time there would be the danger that certain risk groups would spend this on alcohol and/or drugs.

Operational research is necessary for collection of data on costs of implemented interventions and to perform economic evaluations that assess the impact and effectiveness of programmatic LTBI management.

Ethical aspects

LTBI screening should not be mandatory and should be offered on a voluntary basis, with the consent of the people screened and/or treated. Special efforts should be made to ensure that vulnerable groups do not feel coerced into undergoing LTBI screening and treatment. This is especially relevant in prisoners who may feel obliged to undergo screening, or asylum seekers, refugees and undocumented migrants, who may be worried that their refusal to cooperate may affect their legal status. In addition, consideration should be given to who should pay the costs of LTBI treatment, since the persons to be treated are healthy. As stated in the guidance for TB control in vulnerable populations [3], to increase the uptake of LTBI screening and treatment in the framework of programmatic management of LTBI, healthcare and social support services should be accessible to all and screening and treatment free of charge, or at least without financial consequences for those targeted. Every effort should be made to make LTBI services affordable and accessible to those at risk (e.g. by instituting the necessary legal, social and economic policies.)

5.1 4 Programmatic issues

Programmatic management of LTBI requires the identification of individuals at risk, the application of an appropriate diagnostic test, obtaining and reporting of the test result and evaluation of whether preventive treatment should be initiated. This is then followed by initiation of preventive treatment, and finally successful completion of preventive treatment. The LTBI cascade of care framework conceptualises where and why people with LTBI are lost in the process [114]. This framework describes a continuum of sequential steps (i.e. initial identification of at-risk populations, testing, initiation and completion of treatment) that are needed to be successfully completed and identifies barriers and facilitators for the management of LTBI. This section further explores the region-specific challenges and discusses strategies to improve programmatic implementation of LTBI management.

Organisational aspects

Contact investigation can be implemented by using well-known methodologies such as the 'stone in the pond principle' [106]. Attention should be paid to the identification of contacts. Approaches to identifying contacts are described in Erkens et al [7]. In addition, contact tracing can be improved by including it as a part of index case management, by performing source tracing for children diagnosed with TB, and by active follow up of contacts in contrast to the more passive approach of inviting contacts by cases [100].

Programmatic LTBI screening should follow a systematic approach working towards population health, including the collection of information on e.g. the number of contacts tested in contact investigations, the number tested positive, the uptake and completion of LTBI treatment. This requires the availability of resources. The creation of a treatment register of TB contacts was suggested (as a first step in adopting a systematic approach) by the ad hoc scientific panel. The treatment-register can be developed according to available resources and expertise in the

country and does not need to be standardised. Such a register would be a start but would not be sufficient to provide input to internationally agreed monitoring and evaluation frameworks [87,88].

Some EU/EEA Member States already have a case-based registry embedded in their TB surveillance system [97,105]. However, data collection is non-mandatory which potentially leads to underreporting and does not allow for estimation of coverage, since the number of people eligible for LTBI screening is unknown [97,105].

The paucity of evidence on implementation of LTBI programmatic management highlights the need to conduct operational research. Documenting lessons learned and good practices in low incidence TB settings would facilitate the exchange of experiences between countries. A recent example is the assessment of an LTBI screening programme in a high-risk area for TB in London. This study showed that low uptake of LTBI screening treatment was associated with key demographics (i.e. country of birth), risk (i.e. current smokers) and provider-related factors. Low LTBI treatment uptake, on the other hand, was provider-dependent only (i.e. some general practitioners were more likely to prescribe LTBI treatment than others) [105]. These findings emphasise the importance of providing adequate training and incentives to healthcare providers.

In low TB incidence countries, several barriers have been reported to providing LTBI treatment. In Australia, physicians were more likely to prescribe LTBI treatment if they were familiar with evidence concerning the risk of progression to active TB disease. Conversely, practitioners' perceptions (i.e. that men are less likely to accept and adhere to LTBI treatment) or strong beliefs in limited scientific evidence (i.e. age-related risks for hepatotoxicity) were behind their decision not to offer LTBI treatment [107]. Among the main perceived barriers to prescribing LTBI treatment in primary care, as reported by British general practitioners, were insufficient experience with screening and treating LTBI, lack of timely support from specialist TB services and insufficient resources for sustainable delivery of the programme, including financial incentives for general practitioners [108]. Dutch physicians have reported low adherence to national recommendations for LTBI screening and treatment in PLHIV [109]. Instead of screening all PLHIV for LTBI, as was recommended, a TB risk-stratification patient-level approach was applied, which implied that not all new patients with HIV were screened for LTBI [109]. Physicians considered the screening tests unreliable, were afraid of over-treating, were concerned about side-effects and drug interactions, and were uncertain of the actual risk of progression to active TB [109]. This variation in LTBI treatment provision based on the patient's individual risk-benefit balance has also been reported among Australian practitioners [110]. These findings emphasise the conflict faced by healthcare providers when trying to balance population-level public health measures and individual-level benefits that outweigh potential harms.

Communication barriers during medical encounters with migrants from diverse cultural and linguistic backgrounds have also been reported [93,110,111]. Explaining the abstract concept of LTBI and the associated risks and benefits of LTBI treatment to people with limited health literacy and/or who are interpreter-dependent is challenging for health providers [110]. Efforts should be made to ensure that services for programmatic management of LTBI are provided with a culturally appropriate 'patient-centred' approach which is acceptable and tailored to the those targeted. Integration with services or programmes for other diseases can be considered in order to reach specific risk groups. Continuity of care should be ensured, especially in mobile risk groups such as prisoners [112] who may be moved from one facility to another or released, and in people with drug use disorders or the homeless [3], where follow-up might be challenging.

To improve return rates for TST results or the initiation and completion of LTBI treatment after positive testing, social interventions, education, incentives or enablers, or treatments with directly observed therapy could be considered. However, it is also necessary to tackle provider-related barriers to implementation. Variations in implementation of policies, guidelines and programmes may be caused by health providers' divergent opinions on the selected approach for LTBI management. Thus, it is advisable to promote the involvement of end-users and beneficiaries, such as national professional associations, communities and patient associations, to overcome the perceived gaps between public health recommendations and day-to-day practice [109,110].

Cost-effectiveness analyses and resources availability

Mathematical modelling results showed that LTBI screening of high risk groups is a cost-effective policy option for Member States. The programmatic LTBI screening (and consecutive treatment) approach may be adapted to the selected risk group. For example, since there is a higher risk of progression to active TB in the first few years after infection, it would be more cost-effective to screen and treat LTBI in the first years after migration.

The decision on whether or not to implement incentives, and if so, the type of incentive to be used would require careful consideration of the potential benefits and feasibility of the selected approach. Incentives may increase the cost-effectiveness of screening by increasing screening uptake and treatment initiation. Conditional incentives like vouchers (e.g. for food) or enablers (e.g. bus tickets) may increase screening uptake. Furthermore, providing travel fare to patients could help them overcome accessibility barriers to screening and treatment. Unconditional incentives (e.g. money) may give a better effect but there is the danger that certain risk groups will spend this on alcohol and/or drugs.

Operational research is necessary to collect data on costs of implemented interventions and to perform economic evaluations that assess the impact and effectiveness of programmatic LTBI management.

Ethical aspects

LTBI screening should not be mandatory but should be offered on a voluntary basis, with the consent of the people screened and/or treated. Special efforts should be made to ensure that vulnerable groups do not feel coerced to undergo LTBI screening and treatment. This is especially relevant in prisoners who may feel obliged to undergo screening, or asylum seekers, refugees and undocumented migrants, who may be worried that their refusal to cooperate may affect their legal status. In addition, consideration should be given to who will pay the costs of LTBI treatment, since the persons to be treated are healthy. As stated in the guidance for TB control in vulnerable populations [3], to increase the uptake of LTBI screening and treatment in the framework of programmatic management of LTBI, healthcare and social support services should be accessible to all and screening and treatment free of charge, or at least without financial consequences for those targeted. Every effort should be made to make LTBI services affordable and accessible to those at risk (if necessary by instituting the necessary legal, social and economic policies.)

5.2 Strengths and limitations

5.2.1 Strengths

The strengths of the approach for development of this guidance document include:

- The comprehensive approach to the inventory of relevant questions and accompanying review questions by consulting a large group of experts;
- The systematic approach of summarising existing evidence for the relevant review questions. For this, a broad search of scientific publications was conducted in the commissioned systematic reviews, which was supplemented by an additional review of reviews and searches for existing relevant guidelines. A rigorous methodology was applied to identify, critically appraise, analyse and summarise the relevant evidence in order to minimise selection and confirmation bias due to preconceived opinions. The high-quality methodology of this systematic review followed international methodology and reporting standards, such as Cochrane [113] and GRADE [47];
- The ad hoc scientific panel closely involved in the assessment of the review results and providing expert opinions on the main questions;
- The comprehensive mathematical modelling and cost-effective analyses, taking into account multiple population groups and their interactions simultaneously, incorporating all transmission effects of a screening strategy using information from pilot countries and incorporating the input of the ad hoc scientific panel.

5.2.2 Limitations of the evidence base

- There is significant heterogeneity among studies in the peer-reviewed literature, making comparisons difficult. Moreover, the lack of statistically significant results may sometimes due to low numbers.
- By performing a review of reviews, data available in primary articles but not summarised in the included systematic review publications (both commissioned and non-commissioned) were not taken into account. Data from primary articles were only assessed for three commissioned systematic reviews [42,43,44].
- Studies varied widely with regard to study populations and (healthcare) settings, and several studies failed to describe study population characteristics and settings in detail, although these may have influenced the outcomes.
- Not all studies retrieved were conducted in the EU/EEA region. Studies were also retrieved from outside the EU/EEA (e.g. USA, south-east Asia, Mexico, Uganda) which are different with regard to the healthcare system and population. These results cannot always simply be extrapolated to the EU/EEA setting.
- Outcome definitions varied among the studies included, which makes comparison of outcomes for specific review questions complicated.
- As no gold standard currently exists for the diagnosis of LTBI, no conclusions can be drawn on the exact diagnostic accuracy of LTBI diagnostic methods.
- In studies investigating treatment of LTBI it is not always possible to determine the factors responsible for the observed effects due to the fact that interventions were often part of a combination of measures and could therefore not be examined in isolation (i.e. regimens, use of DOT, adherence interventions).
- Many studies did not take confounding or modifying factors into account. Correction for such factors can have a large impact on the outcomes.

5.2.3 Limitations of mathematical modelling and cost-effectiveness analyses

- Data provided by four Member States (the Netherlands, the Czech Republic, Portugal and Spain) were used in the mathematical modelling and cost-effectiveness analyses. Thus, the conclusions reached in these studies are context-specific but can probably be generalised to apply to other EU countries with similar epidemiological profiles.

- Not all at-risk populations could be taken into account in the transmission model, such as immunocompromised patients, long-term travellers, and healthcare workers. The cost-effectiveness of LTBI screening in these specific risk groups has been determined through a cohort-based approach, without considering any potential indirect effects through averted secondary cases and reduced overall transmission.
- Finally, an important aspect that determines the cost-effectiveness of LTBI screening in the cost-effectiveness study is the chosen baseline strategy.

5.3 Knowledge gaps

Studies of higher quality with conclusive 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.
- New LTBI tests for distinguishing remote infection (i.e. previous infection that has remained latent for more than two years and may progress to active disease) and re-infection.
- The effect of interventions to improve treatment uptake and adherence, including cost-effectiveness analysis of such interventions.
- Programmatic aspects of LTBI management, specifically regarding the effectiveness and impact of programmatic management of LTBI

6. Next steps

Efforts will be made to update this guidance as new evidence becomes available or to reflect developments in the EU/EEA Member States.

ECDC uses the monitoring framework for follow up of the Tuberculosis action plan for the WHO European Region 2016–2020 [88]. This monitoring framework contains indicators on LTBI.

References

1. US Centers for Disease Control and Prevention. Tuberculosis. Definitions for Consideration Georgia, USA: CDC; 2012 [cited 2017 April 18th]. Available from: https://www.cdc.gov/tb/programs/laws/menu/definitions.htm.
2. World Health Organization. Systematic screening for active tuberculosis: principles and recommendations: World Health Organization; 2013.
3. European Centre for Disease Prevention and Control. Guidance on tuberculosis control in vulnerable and hard-to-reach populations. Stockholm: ECDC; 2016. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-vulnerable-groups.pdf.
4. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization, 2015.
5. European Centre for Disease Prevention and Control. Review of reviews and guidelines on target groups, diagnosis, treatment and programmatic issues of latent tuberculosis control. Stockholm: ECDC, 2018.
6. European Centre for Disease Prevention and Control. Management of contacts of MDR TB and XDR TB patients. Stockholm: ECDC; 2012. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/201203-Guidance-MDR-TB-contacts.pdf.
7. Erkens C, Kamphorst M, Abubakar I, Bothamley G, Chemtob D, Haas W, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. European Respiratory Journal. 2010;36(4):925-49.
8. Lutge EE, Wiysonge CS, Knight SE, Volmink J. Material incentives and enablers in the management of tuberculosis. Cochrane Database Syst Rev. 2012 Jan 18;1:CD007952.
9. United Nations Statistics Devision. Recommendations on statistics of international migration. Revision 1 1998. Available from: https://unstats.un.org/unsd/demographic/sconcerns/migration/migrmethods.htm.
10. International organisation for migration. The UN Migration Agency. Key migration terms . Available from: https://www.iom.int/key-migration-terms.
11. United Nations Office on Drugs and Crime, World Health Organisation. International Standards for the Treatment of Drug Use Disorders. Draft for field testing. Vienna, Austria: 2016.
12. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update. Geneva: WHO, 2011.
13. Convention relating to the Status of Refugees United Nations Conference of Plenipotentiaries on Status of Refugees and Stateless Persons; 1950. Available at: http://www.unhcr.org/protection/travaux/40a8a7394/final-act-united-nations-conference-plenipotentiaries-status-refugees-stateless.html
14. Brassard P, Anderson KK, Menzies D, Schwartzman K, Macdonald ME. Knowledge and perceptions of tuberculosis among a sample of urban Aboriginal people. J Community Health. 2008 Aug;33(4):192-8.
15. Hoa NP, Diwan VK, Thorson AE. Diagnosis and treatment of pulmonary tuberculosis at basic health care facilities in rural Vietnam: a survey of knowledge and reported practices among health staff. Health Policy. 2005 Apr;72(1):1-8.
16. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet. 2015 May 02;385(9979):1799-801.
17. United Nations General Assembly. The Sustainable Development Goals 2015. Available from: http://www.un.org/sustainabledevelopment/sustainable-development-goals/.
18. Lonnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J. 2015 Apr;45(4):928-52.
19. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct;13(10):e1002152.
20. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO, 2018.
21. World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organisation, 2017.
22. World Health Organization. Global Health Observatory (GHO) data. Top 10 causes of death - Situation and trends 2017 [07 April 2017]. Available from: http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/.
23. World Health Organization. Global tuberculosis report 2016. Geneva: World Health Organisation, 2016.
24. Bailey WC, Gerald LB, Kimerling ME, Redden D, Brook N, Bruce F, et al. Predictive model to identify positive tuberculosis skin test results during contact investigations. JAMA. 2002 Feb 27;287(8):996-1002.
25. Barry CE, 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009 Dec;7(12):845-55.
26. Lin PL, Flynn JL. Understanding latent tuberculosis: a moving target. J Immunol. 2010 Jul 01;185(1):15-22.
27. Centers for Disease Control and Prevention. Latent TB Infection and TB Disease 2016 [updated 11 March 2016; cited 2017 7th of February]. Available from: https://www.cdc.gov/tb/topic/basics/tbinfectiondisease.htm.

28. de Jong BC, Hill PC, Aiken A, Awine T, Antonio M, Adetifa IM, et al. Progression to active tuberculosis, but not transmission, varies by *Mycobacterium tuberculosis* lineage in The Gambia. J Infect Dis. 2008 Oct 01;198(7):1037-43.
29. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003 May 12;163(9):1009-21.
30. Lillebaek T, Dirksen A, Baess I, Strunge B, Thomsen VO, Andersen AB. Molecular evidence of endogenous reactivation of Mycobacterium tuberculosis after 33 years of latent infection. J Infect Dis. 2002 Feb 01;185(3):401-4.
31. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2018-2016 data. Stockholm: European Centre for Disease Prevention and Control; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/ecdc-tuberculosis-surveillance-monitoring-Europe-2018-19mar2018.pdf.
32. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. PLoS Med. 2006 Dec;3(12):e494.
33. Moss AR, Hahn JA, Tulsky JP, Daley CL, Small PM, Hopewell PC. Tuberculosis in the homeless. A prospective study. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):460-4.
34. O'Grady J, Maeurer M, Atun R, Abubakar I, Mwaba P, Bates M, et al. Tuberculosis in prisons: anatomy of global neglect. Eur Respir J. 2011 Oct;38(4):752-4.
35. US Centers for Disease Control and Prevention. Missed opportunities for prevention of tuberculosis among persons with HIV infection--selected locations, United States, 1996-1997. MMWR Morb Mortal Wkly Rep. 2000 Aug 04;49(30):685-7.
36. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003 Mar;3(3):148-55.
37. Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin Infect Dis. 2006 Jun 01;42(11):1592-5.
38. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013;2013:828939.
39. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 Mar 02;320(9):545-50.
40. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers. 2016 Oct 27;2:16076.
41. Sandgren A, Vonk Noordegraaf-Schouten JM, Oordt-Speets AM, van Kessel GB, de Vlas SJ, van der Werf MJ. Identifying components for programmatic latent tuberculosis infection control in the European Union. Euro Surveill. 2016 Aug 25;21(34).
42. Stuurman AL, Vonk Noordegraaf-Schouten M, van Kessel F, Oordt-Speets AM, Sandgren A, van der Werf MJ. Interventions for improving adherence to treatment for latent tuberculosis infection: a systematic review. BMC Infect Dis. 2016;16(1):257.
43. Stagg HR, Zenner D, Harris RJ, Munoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. Ann Intern Med. 2014 Sep 16;161(6):419-28.
44. World Health Organization. Evidence to decision framework. Appendix to the Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organisation, 2015 WHO/HTM/TB/2015.01.
45. 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;7:10.
46. AGREE Next Steps Consortium. Appraisal of guidelines for research & evaluation II. UPDATE: September 2013. AGREE II Instrument The Agree Research Trust. 2009.
47. The GRADE working group. Available from: http://www.gradeworkinggroup.org.
48. GRADE's software for Summary of Findings tables, Health Technology Assessment and Guidelines. Available from: https://gradepro.org.
49. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Hospital Research Institute Ottawa [Internet]. 2007. Available from: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf.
50. Scottish Intercollegiate Guidelines Network, Harbour RT, Forsyth L. SIGN 50: A guideline developer's handbook: Scottish Intercollegiate Guidelines Network; 2008.
51. European Centre for Disease Prevention and Control. Mathematical modelling of programmatic screening strategies for latent tuberculosis infection in countries with low tuberculosis incidence. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/Technical-Report_LTBI_math_modelling.pdf.
52. European Centre for Disease Prevention and Control. Cost-effectiveness analysis of programmatic screening for latent tuberculosis infection in the EU/EEA. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/LTBI%20cost-effectiveness%20report.pdf.

53. van Kessel F, Oordt-Speets A, Vonk Noordegraaf-Schouten M, Verver S. Meeting report ad hoc scientific panel meeting "Guidance on introducing programmatic latent tuberculosis infection control in the EU/EEA and candidate countries". Stockholm: Pallas Health research and consultancy, 2016.
54. Franklin K, Hart J. Idea Generation and Exploration: Benefits and Limitations of the Policy Delphi Research Method. Innov High Educ 2007;31:237.
55. Campbell JR, Krot J, Marra F. Latent tuberculosis diagnostic tests to predict longitudinal tuberculosis during dialysis: a meta-analysis. Int J Tuberc Lung Dis. 2016 Jun;20(6):764-70.
56. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013 Jan;41(1):140-56.
57. Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Molecular diagnosis & therapy. 2015 Apr;19(2):107-17.
58. Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. Emerg Infect Dis. 2011 Mar;17(3):488-94.
59. Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. Molecular diagnosis & therapy. 2015 Feb;19(1):9-24.
60. Patra J, Bhatia M, Suraweera W, Morris SK, Patra C, Gupta PC, et al. Exposure to second-hand smoke and the risk of tuberculosis in children and adults: a systematic review and meta-analysis of 18 observational studies. PLoS Med. 2015 Jun;12(6):e1001835; discussion e.
61. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lonnroth K, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health. 2009 Dec 05;9:450.
62. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med. 2007 Jan;4(1):e20.
63. Working Group of the Clinical Practice Guideline on the Diagnosis Treatment and Prevention. Clinical practice guideline on the diagnosis, treatment and prevention of tuberculosis. Madrid (Spain): Agency for Health Quality and Assessment of Catalonia (AQuAS), 2010.
64. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States. MMWR Recomm Rep. 2010;59(RR-5):1-25.
65. National Collaborating Centre for Chronic Conditions. Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London (UK): National Institute for Health and Clinical Excellence (NICE), 2011.
66. Audain G, Bookhardt-Murray LJ, Fogg CJ, Gregerson P, Haley CA, Luther P, et al. Adapting your practice: treatment and recommendations for unstably housed patients with HIV/AIDS. . Health Care for the Homeless Clinicians' Network, National Health Care for the Homeless Council, 2013.
67. Baughman RP, Meyer KC, Nathanson I, Angel L, Bhorade SM, Chan KM, et al. Monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;142(5):e1S-e111S.
68. Campbell JR, Sasitharan T, Marra F. A Systematic Review of Studies Evaluating the Cost Utility of Screening High-Risk Populations for Latent Tuberculosis Infection. Applied health economics and health policy. 2015 Aug;13(4):325-40.
69. Auguste P, Tsertsvadze A, Pink J, Court R, Seedat F, Gurung T, et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2016 May;20(38):1-678.
70. Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Services Research. 2011;11:247.
71. Milburn H, Ashman N, Davies P, Doffman S, Drobniewski F, Khoo S, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. British Thoracic Society Standards of Care Committee and Joint Tuberculosis Committee, 2010 Contract No.: 6.
72. National Institute for Health and Clinical Excellence. Identifying and managing tuberculosis among hard-to-reach groups. Manchester (UK): National Institute for Health and Clinical Excellence, 2012.
73. Chavan S, Newlands D, Smith C. A systematic review of economic evaluations of chemoprophylaxis for tuberculosis. Journal of Tropical Medicine. 2011;2011:130976.
74. Diel R, Lampenius N, Nienhaus A. Cost Effectiveness of Preventive Treatment for Tuberculosis in Special High-Risk Populations. Pharmacoeconomics. 2015 Aug;33(8):783-809.
75. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66.
76. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. 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 pediatrics. 2015 Mar;169(3):247-55.

77. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States, 2001. MMWR Morb Mortal Wkly Rep. 2001 Aug 31;50(34):733-5.
78. van Hest R, Baars H, Kik S, van Gerven P, Trompenaars MC, Kalisvaart N, et al. Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. Clin Infect Dis. 2004 Aug 15;39(4):488-96.
79. World Health Organization. Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries. WHO Guidelines Approved by the Guidelines Review Committee. Geneva: World Health Organization; 2012.
80. European Centre for Disease Prevention and Control. Risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA) – Tuberculosis. Stockholm: ECDC; 2014. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/tuberculosis-risk-assessment-guidelines-aircraft-May-2014.pdf.
81. Lutge EE, Wiysonge CS, Knight SE, Sinclair D, Volmink J. Incentives and enablers to improve adherence in tuberculosis. Cochrane Database Syst Rev. 2015 Sep 03(9):CD007952.
82. M'Imunya J M, Kredo T, Volmink J. Patient education and counselling for promoting adherence to treatment for tuberculosis. Cochrane Database Syst Rev. 2012 May 16(5):CD006591.
83. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2011 Nov;11(11):855-67.
84. Legido-Quigley H, Montgomery CM, Khan P, Atun R, Fakoya A, Getahun H, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. Trop Med Int Health. 2013 Feb;18(2):199-211.
85. Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Am J Prev Med. 2018 Aug;55(2):244-52.
86. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz JT, Omoz-Oarhe A, et al. One month of rifapentine/isoniazid to prevent TB in people with HIV: BRIEF-TB/A5279. Conference on retroviruses and opportunistic infections; Boston, Massachusetts: CROI Foundation; 2018.
87. World Health Organization. Implementing the End TB strategy: the essentials. Geneva: WHO, 2015.
88. WHO Regional Office for Europe. Roadmap to implement the tuberculosis action plan for the WHO European Region 2016-2020. Copenhagen: World Health Organisation, 2016.
89. World Health Organization. Towards tuberculosis elinination: An action framework for low-incidence countries. Geneva: WHO, 2014.
90. Mayors Office London. Mayor of London: TB ambassador Emma Thompson urges TB testing [Video]2016.
91. Stop TB Partnership. Champions against tuberculosis. Available from: http://www.stoptb.org/global/people/ambassadors/national.asp.
92. TB Alert, NHS England, Public Health England. Access, testing and treatment. A toolkit for new entrant latent tuberculosis programmes. London: TB Alert; 2016.
93. Abarca Tomas B, Pell C, Bueno Cavanillas A, Guillen Solvas J, Pool R, Roura M. Tuberculosis in migrant populations. A systematic review of the qualitative literature. PloS one. 2013;8(12):e82440.
94. de Vries SG, Cremers AL, Heuvelings CC, Greve PF, Visser BJ, Belard S, et al. Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. Lancet Infect Dis. 2017 May;17(5):e128-e43.
95. US Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Atlanta: CDC, 2013.
96. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm: ECDC; 2011. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1103_GUI_IGRA.pdf.
97. De Vries G, van Hest R, Bakker M, Erkens C, van den Hof S, Meijer W, et al. Policy and practice of programmatic management of latent tuberculosis infection in The Netherlands. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2017;7:40-8.
98. Belknap R, Holland D, Feng PJ, Millet JP, Cayla JA, Martinson NA, et al. Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial. Ann Intern Med. 2017 Nov 21;167(10):689-97.
99. Denholm JT, McBryde ES, Eisen D, Street A, Matchett E, Chen C, et al. SIRCLE: a randomised controlled cost comparison of self-administered short-course isoniazid and rifapentine for cost-effective latent tuberculosis eradication. Intern Med J. 2017 Dec;47(12):1433-6.
100. Global TB Programme, World Health Organization. Final report : first meeting of the re-organised Global Task Force on latent TB infection. Geneva: World Health Organisation, 2018.
101. KNVC Tuberculosis Foundation. KNCV Tuberculosis Foundation and European partners request Sanofi to take steps to register rifapentine (Priftin®) with the European Medicines Agency (EMA) 2016 Available from: https://www.kncvtbc.org/en/2016/06/28/kncv-and-european-partners-request-sanofi-to-take-steps-to-register-rifapentine-with-the-ema/.

102. Haley CA, Stephan S, Vossel LF, Sherfy EA, Laserson KF, Kainer MA. Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. Int J Tuberc Lung Dis. 2008 Feb;12(2):160-7.
103. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. Int J Tuberc Lung Dis. 2008 Nov;12(11):1235-54.
104. Shukla SJ, Warren DK, Woeltje KF, Gruber CA, Fraser VJ. Factors associated with the treatment of latent tuberculosis infection among health-care workers at a midwestern teaching hospital. Chest. 2002 Nov;122(5):1609-14.
105. Loutet MG, Burman M, Jayasekera N, Trathen D, Dart S, Kunst H, et al. National roll-out of latent tuberculosis testing and treatment for new migrants in England: a retrospective evaluation in a high-incidence area. Eur Respir J. 2018 Jan;51(1).
106. Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. Tuber Lung Dis. 1992 Apr;73(2):73-6.
107. Dobler CC, Luu Q, Marks GB. What patient factors predict physicians' decision not to treat latent tuberculosis infection in tuberculosis contacts? PloS one. 2013;8(9):e76552.
108. Atchison C, Zenner D, Barnett L, Pareek M. Treating latent TB in primary care: a survey of enablers and barriers among UK General Practitioners. BMC Infect Dis. 2015 Aug 13;15:331.
109. Evenblij K, Verbon A, van Leth F. Intention of physicians to implement guidelines for screening and treatment of latent tuberculosis infection in HIV-infected patients in The Netherlands: a mixed-method design. BMC Public Health. 2016 Sep 1;16(1):915.
110. Dobler CC, Bosnic-Anticevich S, Armour CL. Physicians' perspectives on communication and decision making in clinical encounters for treatment of latent tuberculosis infection. ERJ Open Research. 2018 Jan;4(1).
111. Kulane A, Ahlberg BM, Berggren I. "It is more than the issue of taking tablets": the interplay between migration policies and TB control in Sweden. Health Policy. 2010 Sep;97(1):26-31.
112. European Centre for Disease Prevention and Control. Systematic review on the diagnosis, treatment, care and prevention of tuberculosis in prison settings. Stockholm: ECDC; 2017. Available from: https://ecdc.europa.eu/sites/portal/files/documents/Systematic-review-tuberculosis-in-prisons-May2017.pdf.
113. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
114. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(11):1269-1278.

Annex 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 Risk of TB after exposure to an infectious index case with or without chemoprophylaxis or preventive therapy Risk of and time to developing TB, related to the country of origin, when migrating to a low incidence area Target risk groups Costs of LTBI in EU/EEA			Which populations are at increased risk of developing active TB?
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, focussing on:	**LTBI treatment (chemopro-phylaxis 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. What are currently the optimal preventive treatment regimens for LTBI for different situations and in different risk groups?? Adherence to LTBI treatment in different risk groups? Frequency and severity of major and minor adverse events of chemoprophylaxis and preventive therapy? Monitoring adverse events (regular liver function test etc.)	**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 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 of LTBI treatment? (in certain risk groups)
			Treatment of LTBI	**Treatment-related interventions (adverse events control and improving treatment adherence)**	What is an effective approach to monitor and manage adverse events?

Impact of and conditions for interventions (i.e. possible components of LTBI control) on LTBI incidence, focussing on:		Patient/doctor factors to increase acceptability	**Programmatic issues of LTBI management**		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			
	Contact investigation	Yield of contact investigation in different settings and population		**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 contact investigation?
					What is the effectiveness of interventions to improve contact investigation uptake?
	Screening of certain populations	Effect of screening programme (for specific risk groups)		**Case detection – screening:** What is the optimal approach for screening of 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 setting, risk groups, general population	**Programmatic issues of LTBI management**	**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?
		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 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	How should monitoring and evaluation of programmatic management of LTBI take place?

Annex 2. Terms of reference for ad hoc scientific panel

Background

Latent tuberculosis infection (LTBI) is the reservoir of infection in a population. As long as a tuberculosis (TB) reservoir exists, elimination will not be feasible. Thus, the control of LTBI has been acknowledged as an important aspect of TB elimination, and the EU/EEA Member States are addressing LTBI in their national TB control plans in various ways. Some Member States have more developed and systematically implemented interventions to target latent TB and incorporated these into a national programmatic approach. Examples of this programmatic approach are also seen in the United States of America, Canada, and Australia, who have implemented various preventive measures to reducing LTBI and TB disease in their countries. Incorporating programmatic latent TB control into the national and EU/EEA strategies to fight TB may be of value for all EU/EEA Member States.

Programmatic LTBI control can consist of several different components which all contribute towards preventing TB disease and onward infection transmission. What we refer to as 'components' may include, but not be limited to: preventive therapy of infected individuals; different screening programmes to detect latent TB infection among specific populations with increased incidence; screening of specific occupational groups; contact investigation, etc.

Scope and purpose of scientific advice

ECDC plans to issue scientific advice in the form of a guidance on programmatic latent TB control in the EU/EEA and candidate countries. The aim is to present the latest evidence base on the topic, provide an overview of interventions and evidence-based consensus opinions on options for how to best perform programmatic latent TB control.

Methods for developing the scientific advice

The scientific advice on interventions for programmatic latent TB prevention and control will take the format of a guidance document. For this, a comprehensive assessment was performed of the potential benefits and risks of introducing programmatic latent TB control in the TB prevention and control strategy, considering the specific components of LTBI prevention, and the situation, needs and opportunities of the EU/EEA and candidate countries. The assessment consisted of an extensive **workshop meeting with experts** (held in 2013); a review of the **scientific evidence base**; and **mathematical modelling and cost-effectiveness studies.** ECDC has outsourced the work of the assessment to a consortium consisting of Pallas health research and consultancy, and Erasmus University Medical Center Rotterdam, Netherlands ('the ECDC funded consortium').

Workshop meeting 2013

In 2013, ECDC hosted a workshop where the introduction of programmatic latent TB control in the TB prevention and control strategy of the EU/EEA and candidate countries was discussed. An inventory of expert opinions was collected from representatives of the EU/EEA Member States and candidate countries as well as additional stakeholders in the field of TB. The workshop resulted in the identification of key areas and research questions that needed further attention in the assessment of the potential benefits and risks of introducing programmatic LTBI control in TB prevention and control strategies.

Scientific evidence base

Since the workshop, ECDC and WHO have jointly worked towards building the evidence base to address the key areas/research questions identified in the inventory of expert opinions and through a separate WHO process which led to the publication of WHO guidelines on LTBI control for low incidence settings globally. A number of systematic literature reviews have been conducted to provide the information required both for the WHO guidelines and the ECDC comprehensive assessment.

Mathematical modelling and cost-effectiveness analyses

The ECDC funded consortium has performed mathematical modelling and cost-effectiveness studies to provide further insight into the benefits and costs of introducing various components of programmatic LTBI control. From the model, a user-friendly tool will be developed, which can be used by representatives of EU/EAA Member States to assess the effects of introducing LTBI interventions.

Objective of the ad hoc scientific panel

The panel, as established by ECDC, will advise ECDC on the content of the guidance, review and interpret the body of evidence resulting from systematic reviews, cost-effectiveness and modelling studies, assess the draft strategic/guidance document, and contribute to the further development of the guidance with their expert knowledge by formulating guidance statements.

Expected work of the panel

Before the panel meeting: the panel members will be provided with a report of the evidence base and the results of the cost-effectiveness and modelling studies to review the content of these. If ECDC, the panel and/or the chairs of the panel so wish, ECDC can arrange a telephone conference before the panel meeting to initiate the discussion on providing advice and to discuss the guidance document to be developed. Alternatively, panel members may be asked to perform a small exercise prior to the meeting.

At the panel meeting: The panel members will attend a two-day *ad hoc* scientific panel meeting on 7-8 November 2016. During this meeting the evidence base will be presented and panel members are expected to formulate advice on the topic, based on the evidence base and their own expertise. The aim is to reach consensus on key messages and options for interventions that the panel considers relevant to be included in the guidance.

After the panel meeting the chair will deliver the formulated guidance statements to ECDC, and ECDC will then incorporate these statements into the guidance document. If ECDC so decides, the panel will be asked to review the draft guidance document and provide additional input.

Terms and conditions of panel members

ECDC will provide the panel members with per-diem compensation as well as cover the costs of accommodation and travel related to attendance of the panel meetings, in accordance with EU Commission rules and regulations. This will all be arranged by Pallas, Health Research and Consultancy as lead partner of the ECDC funded consortium.

The members of the advisory group will not be remunerated for the work performed. ECDC will acknowledge all members for their work as having been a part of the LTBI advisory group. The final guidance document will be in the public domain.

Mandate of panel members

ECDC asks for experts to provide advice based on their professional and scientific merits. Opinions expressed and advice in the *ad hoc* scientific panel shall be considered the personal professional advice of the expert. Experts in the *ad hoc* scientific panel may not represent the interests of a commercial body, a Member State or a professional body. Membership of the latter does, however, not automatically disqualify a candidate from participation. Selected experts have submitted declarations of interests using an ECDC procedure before they were officially appointed by the ECDC Director to be members of the panel.

Members of the ad hoc scientific panel officially appointed by ECDC's director

Name	Organisation	Country
Gerard de Vries (chair)	KNCV Tuberculosis Foundation	The Netherlands
Dominik Zenner (chair)	Public Health England	UK
Judith Bruchfeld	Karolinska University Hospital	Sweden
Josie Garrett*	Patient representative	UK
Walter Haas*	Robert Koch Institute	Germany
Einar Heldal	Norwegian Institute of Public Health	Norway
Rein Houben	London School of Hygiene and Tropical Medicine	UK
Philip LoBue*	US Centers for disease control and prevention	USA
Mike Mandelbaum	NGO representative (TB Alert)	UK
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 joining the meeting of the ad hoc scientific panel

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

Annex 3. Interventions and their descriptions

Intervention	Description
Adherence coaching Hovell MF, Sipan CL, Blumberg EJ, et al. Increasing Latino adolescents' adherence to treatment for latent tuberculosis infection: a controlled trial. Am J Public Health. 2003;93:1871–7.	Coaches were bilingual college students. Coaches used interviewing, contingency contracting, and shaping procedures (i.e. 'small step' solutions to adherence problems). Coaching involved an overview of LTBI treatment, the setting of adherence goals, interviews regarding pills taken or missed, a review of conditions leading to adherence or non-adherence, and a discussion of changes that could be made to enhance adherence. Coaches praised successful adherence and suggested that participants use adherence cues. Coaches encouraged participants to obtain assistance from family and friends for pill taking and provided help in planning compensating adherence strategies to overcome potential barriers. They assisted with physician appointments and transportation. Five 30-minute in-person sessions and seven 15-minute telephone sessions were conducted over six months.
Cash incentives - Malotte CK, Rhodes F, Mais KE. Tuberculosis screening and compliance with return for skin test reading among active drug users. American Journal of Public Health 1998; 88(5):792–6. - Malotte CK, Hollingshead JR, Rhodes F. Monetary versus nonmonetary incentives for TB skin test reading among drug users. American Journal of Preventive Medicine 1999; 16(3):182–8.	USD 5–10 provided at return for skin test reading.
Contingency contracting Kominski GF, Varon SF, Morisky DE, et al. Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial. J Adolesc Health. 2007;40:61–8.	A reward was negotiated between the parent and the adolescent in exchange for the adolescent's compliant behaviour and completion of care. Gifts included tangible items, or outings with friends and other types of privileges that are valued by the adolescent. These incentives were paid for by the parents.
Cultural case management Goldberg SV, Wallace J, Jackson JC, Chaulk CP, Nolan CM. Cultural case management of latent tuberculosis infection. Int J Tuberc Lung Dis. 2004;8:76–82.	Case manager cultural mediators (CCM) who serve patient-defined needs in addition to performing TB control functions. A bilingual, bicultural case management approach for targeted testing and treatment of LTBI. 'Case management' included home readings of TSTs, culturally appropriate TB education, referrals for non-TB health and social service needs. The CCMs attempted to establish trusting relationships with the refugees and their communities. The CCM delivered refills to the clients' homes and at each visit reinforced TB education and made a renewed offer of other services. CCMs performed symptom checks during the monthly visits. Two simple flyers describing standard TB information were translated into Somali, Russian, and Bosnian by the CCMs and given to each patient.
Cultural intervention Ailinger RL, Martyn D, Lasus H, Lima Garcia N. The effect of a cultural intervention on adherence to latent tuberculosis infection therapy in Latino immigrants. Public Health Nurs. 2010;27:115–20.	It was based on Latino cultural values and had five components: 1. Clients saw the same interventionist nurse for each visit. The relationship with the client was based on the Latino value of personalismo (personal attention). 2. At each monthly clinic visit, the interventionist nurse inquired about the client's family members before starting care. During the first clinic visit, the names of several family members (e.g., children, spouse) were recorded in the medical record. This was based on the Latino value of family ties (familism). 3. A common Latino proverb was stated by the interventionist nurse at each clinic visit: 'es mejor prevenir que lamentar' ('It is better to prevent than to lament'). This proverb became the logo for the study and was used on stickers and small gifts (e.g., keyring flashlight) that were distributed to the subjects at random visits. 4. Latino-adapted educational materials written at the sixth-grade level, which included pictures of Latino families, were given to clients. The materials also included the study proverb. 5. The interventionist nurses were fluent in Spanish or bicultural/bilingual. In addition, culturally appropriate nonverbal communication was included at the end of the visit.
DOT: supervised isoniazid preventive treatment Matteelli A, Casalini C, Raviglione MC, et al. Supervised preventive therapy for latent tuberculosis infection in illegal immigrants in Italy. Am J Respir Crit Care Med. 2000;162:1653–5.	Supervised isoniazid preventive treatment at a dose of 900 mg twice weekly for six months.
DOT + short treatment regimen (3RPT+INH) Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155–66.	3 RPT once-weekly (at a dose of 900 mg, with incremental adjustment for subjects weighing ≤50 kg) plus INH (at a dose of 15 to 25 mg per kilogram of body weight, rounded up to the nearest 50 mg, with a maximum dose of 900 mg) given under direct observation (combination-therapy group).
Education White MC, Tulsky JP, Goldenson J, Portillo CJ, Kawamura M, Menendez E. Randomized controlled trial of interventions to improve follow-up for latent tuberculosis infection after release from jail. Arch Intern Med. 2002;162:1044–50.	Two-weekly visit for the duration of the jail stay, to reinforce the initial information and message of the first sessions.
IGRA (whole blood) Sahni R, Miranda C, Yen-Lieberman B, et al. Does the implementation of an interferon gamma release assay in lieu of a tuberculin skin test increase acceptance of preventive therapy for latent tuberculosis among healthcare workers? Infect Control Hosp Epidemiol. 2009;30:197–9.	A whole-blood IGRA was implemented to screen for LTBI among newly hired healthcare workers.

Intervention	Description
Location chosen by participants + monetary incentive Malotte CK, Hollingshead JR, Larro M. Incentives vs outreach workers for latent tuberculosis treatment in drug users. Am J Prev Med. 2001;20:103–7.	Twice weekly DOT supplied by the study outreach worker at a location chosen by the participant, and the provision of a $5 incentive at each visit.
Methadone treatment (minimal) Batki SL, Gruber VA, Bradley JM, Bradley M, Delucchi K. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. Drug Alcohol Depend. 2002;66:283–93.	DOPT of INH and pyridoxine as well as daily methadone doses in the 60–90 mg range, 7 days per week for 6 months, followed by a 6-week taper off methadone. No counselling or any other services, except on an emergency basis or to enforce programme rules. Counsellors and clients were not informed of urine or breathalyser test results. No take-home doses of methadone could be earned.
Methadone treatment (standard) Batki SL, Gruber VA, Bradley JM, Bradley M, Delucchi K. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. Drug Alcohol Depend. 2002;66:283–93.	DOPT of INH in addition to daily methadone doses in the 60–90 mg range, 7 days per week for 6 months, followed by a 6-week taper off methadone. They also received twice monthly counselling sessions, weekly random observed urine samples, medical services, psychiatric treatment as needed, and social work referrals. Participants could earn up to two take-home doses of methadone per week as a reward for negative urine drug and breath alcohol tests.
Nurse case-managed with incentives Nyamathi AM, Christiani A, Nahid P, Gregerson P, Leake B. A randomized controlled trial of two treatment programs for homeless adults with latent tuberculosis infection. Int J Tuberc Lung Dis. 2006;10:775–82.	The programme emphasizes effective coping and communication skills, feelings of self-worth and self-esteem, and promotion of health-seeking behaviour. Health-seeking behaviours such as completion of LTBI treatment were supported through direct health education, psychosocial support and linkage to medical and social services by community-based nurses trained in the care of homeless patients. Intervention participants received eight one-hour TB education sessions, which included visual coping scenarios, delivered in a culturally competent and tailored manner by their nurse and outreach worker over the 24 weeks of treatment. Intervention group participants were provided with community resources and were escorted to their medical and social service appointments. Participants were tracked when they missed a DOT dose. All participants received $5 US for each DOT dose.
Peer-based adherence support Hirsch-Moverman Y, Colson PW, Bethel J, Franks J, El-SadrWM. Can a peer-based intervention impact adherence to the treatment of latent tuberculous infection? Int J Tuberc Lung Dis. 2013;17:1178–85.	Experimental subjects were paired with peer workers who had completed LTBI or anti-TB treatment and had attended a 4-week training programme. Peers attempted to meet one-on-one with assigned subjects at least once a week. They provided health care and social service system navigation, liaised with patients and health workers to enhance patient-provider communication, educated and coached patients on adherence, and provided social and emotional support.
Peer counselling Kominski GF, Varon SF, Morisky DE, et al. Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial. J Adolesc Health. 2007;40:61–8.	An adolescent who had successfully completed care stressed the importance of medication-taking and clinic attendance to participants.
Self-esteem (attention control) counselling Hovell MF, Sipan CL, Blumberg EJ, et al. Increasing Latino adolescents' adherence to treatment for latent tuberculosis infection: a controlled trial. Am J Public Health. 2003;93:1871–7.	Bilingual Latino college students served as self-esteem counsellors. Adolescents were encouraged to discuss problems affecting their self-esteem. Topics included relationships and communication with family, friends, and cultural identity. Counsellors encouraged goal setting and changes in relationships or skills (e.g., assertiveness) to enhance self-esteem, and used shaping procedures similar to those employed in adherence coaching. No advice regarding TB was provided and questions about TB were referred to physicians.

European Centre for Disease Prevention and Control (ECDC)

Address:
Gustav III:s boulevard 40, SE-169 73 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.
www.ecdc.europa.eu/en/aboutus/transparency

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Publications Office