

Guidance for programmatic management of latent tuberculosis infection in the European Union/European Economic Area

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Worldwide efforts are being made to end tuberculosis (TB) by 2035, following the ambitions outlined in the World Health Organization's End TB strategy [1] and the United Nations Sustainable Development Goals [2]. Countries with a low incidence of TB, i.e. less than 10 incident cases per 100 000 population per year, should strive for TB elimination [3]. To this end, timely detection and treatment of latent tuberculosis infection (LTBI) is an important intervention [3]. Currently, the existence and implementation of national strategies including public health interventions targeting LTBI is heterogeneous across the European Union/European Economic Area (EU/EEA) [4]. To support the EU/EEA countries with developing national policies, as well as the planning and implementation of programmatic management of LTBI into national strategies for TB control, the European Centre for Disease Prevention and Control (ECDC) conducted a comprehensive assessment of the available evidence and developed an evidence-based guidance [5]. The guidance, published in October 2018, elaborates on population-level measures for LTBI management tailored to the EU/EEA context and it is complementary to the World Health Organization (WHO) guidelines [6]. Here we summarize the process that was followed to develop the guidance and we outline the key components proposed for programmatic management of LTBI, to inform European healthcare professionals.

The ECDC guidance includes four key areas: target risk groups for programmatic management of LTBI; diagnosis of LTBI; treatment of LTBI; and programmatic issues of LTBI management. The key areas and corresponding research questions were identified through consultation with experts [7]. Scientific evidence was collected through systematic literature reviews, with additional evidence derived from mathematical modelling and cost-effectiveness analyses [8-10], and the evidence was reviewed and appraised by an ad hoc scientific panel.

The systematic literature reviews collected available scientific evidence on target groups, diagnosis and treatment of LTBI, and programmatic issues and were performed in collaboration with WHO [11,12]. Additional steps for identification, collection and appraisal of relevant peer-reviewed and grey literature were conducted, as described in a detailed technical report [8]. The evidence showed an increased risk of becoming latently infected and/or progressing to active TB disease for people living with HIV, immunocompromised patients, close contacts of TB patients (risk of progression especially high in children), migrants, healthcare workers, prisoners and homeless people [11,12]. Both the tuberculin skin test (TST) and the interferon gamma release assays (IGRA) were regarded as suitable and cost-effective diagnostic tools [8,11,12]. Similarly, various treatment regimens showed good efficacy and cost-effectiveness. Short treatment regimens (i.e. less than 6-month treatment duration) had better adherence and completion rates [8,13]. Several interventions were shown to improve initiation, adherence and completion of LTBI treatment, including provision of monetary incentives to people who inject drugs; nurse-led community-based case management in homeless people, educational sessions with prison inmates and counsellor or peer-based social support [8,14,15].

The deterministic mathematical model for TB transmission estimated the contribution of LTBI screening and treatment strategies on reducing TB transmission. Various at-risk populations were considered in the model, i.e. people who inject drugs, homeless people, prisoners and migrants from high TB incidence countries. The model was applied to data from four EU countries: the Netherlands, the Czech Republic, Portugal, and Spain. Modelling results suggested that screening for and treatment of LTBI in prisoners or migrants from high-endemic countries at entry in the country, people who inject

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3 drugs and homeless people all result in a decrease in pulmonary TB incidence. The order of importance
4 of each of these groups depends on the country. The mathematical model informed the assessment of
5 cost-effectiveness of selected LTBI screening and treatment strategies. Across all at-risk populations
6 considered, model results found that performing a TST and if positive an IGRA was the most cost-
7 effective strategy for diagnosing LTBI. The cost-effectiveness analysis further suggested that LTBI
8 screening for migrants at entry, LTBI screening for prisoners and LTBI screening for people who inject
9 drugs/homeless people would all be cost-effective. The cost-effectiveness of screening and treatment
10 of four other groups was also assessed using cohort model variants: travellers, healthcare workers,
11 immunocompromised patients, and TB contacts. LTBI screening and treatment of travellers and
12 healthcare workers would only be cost-effective under unrealistically high levels of increased risk for
13 transmission in these populations. For immunocompromised patients LTBI screening and treatment
14 would be cost-effective if they are part of a migrant population or native populations in European
15 countries with a relatively high TB burden (i.e. more than 50 incident cases per 100 000 population).
16 For close contacts of active pulmonary TB patients the modelling found LTBI screening to be cost-
17 effective [9,10], which is in line with existing field studies [16,17].
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24 Based on the assessment of the scientific evidence and the expert opinion of the ad hoc scientific panel,
25 ECDC identified key components for implementation of programmatic management of LTBI (Table
26 1). Target groups proposed to be prioritised for LTBI screening and treatment are: people living with
27 HIV; immunocompromised persons (patients on anti-TNF alpha treatment, patients preparing for
28 transplantation, patients with end-stage renal diseases and/or preparing for dialysis); patients with
29 silicosis; people with pulmonary fibrotic lesions; and contacts of infectious TB cases. Additional at-risk
30 groups may be considered depending on the TB epidemiology. For diagnosing LTBI, both TST and
31 IGRA or a combination can be used. Table 2 summarises practical considerations for the selection of
32 testing methods, based on the expert opinion of the ad hoc scientific panel. For successful
33 implementation, LTBI screening should be conceptualised as a comprehensive strategy that requires
34 availability of and accessibility to diagnostic tests, and also the intention to provide LTBI treatment (if
35 appropriate) and the implementation of interventions promoting the uptake and completion of LTBI
36 screening procedures. For treatment of LTBI the following regimens can be considered: isoniazid alone
37 (for 6–9 months), rifampicin alone (for 3–4 months), isoniazid and rifapentine (once weekly for 12
38 weeks) and isoniazid and rifampicin (for 3–4 months) [13]. The selection of the most appropriate LTBI
39 treatment regimen should be based on an individual risk assessment [18,19]. Patient-centred case
40 management including provision of material incentives and enablers, counselling and education, peer-
41 based support and culturally-sensible approaches can be considered as part of an integrated
42 programmatic strategy for LTBI management.
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49 Country-level implementation of the suggested public health measures will need to take into account
50 the TB epidemiology in various risk groups, health system structure, resource allocation and political
51 commitment. In-depth knowledge of the local epidemiological profile will facilitate the identification
52 of at-risk groups to be prioritised for LTBI screening and treatment. Also, provision of high-quality
53 programmatic management of LTBI will benefit from a well-coordinated collaboration between
54 different levels of the health system (i.e. local, regional and national) and linkages with other health
55 programmes (e.g. HIV clinics). The healthcare work force will need to be made aware with appropriate
56 training as necessary, on new/updated national guidelines, procedures and specific technical (i.e.
57 administration and interpretation of diagnostic tests) and social (i.e. establishing rapport and providing
58 psycho-social support) skills.
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5 We acknowledge that physicians will be confronted with the challenge of assessing the patient-level
6 risk and benefits while implementing these population-level public health activities [20,21].
7 Educational interventions and incentives for frontline health care workers may support them in making
8 these assessments and help overcome provider-related barriers to access LTBI diagnosis and treatment
9 [22]. We also acknowledge the necessity to understand health practitioners' perceptions of and attitudes
10 towards LTBI management to tailor information and advice that aims to increase their adherence to
11 national guidelines.
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14 Similarly, patient-related barriers such as poor health literacy and barriers related to cultural background
15 and/or language, should be minimised [23,24]. Efforts can include implementation of patient-centred
16 approaches that take into consideration the social context and provision of psychological, social and
17 financial support to at-risk populations [25].
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20 Monitoring and evaluation of the programmatic approach to LTBI management can pose a major
21 challenge for a national TB control programme, but is important to tackle. We encourage EU/EEA
22 Member States to create or continue improving their LTBI surveillance systems, striving for data
23 completeness and more accurate reporting of those eligible, tested and treated for LTBI. These efforts
24 will contribute to quantify the country-specific cascade of care for LTBI and help identify areas for
25 adaptation and improvement of LTBI programmatic management [26].
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28 Finally, implementation and scale up of programmatic management of LTBI would benefit from the
29 exchange of lessons learned and experiences gained. There are already some published examples from
30 European settings that show the importance of documenting local or national experiences [27-29].
31 Operational research on the effectiveness and cost-effectiveness of implemented LTBI interventions
32 could help us further our understanding of the actual impact of programmatic LTBI management.
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Table 1. Summary of the European Centre for Disease Prevention and Control guidance on programmatic management of Latent Tuberculosis Infection in the European Union and European Economic Area [5]

Key components	Public health measures
<p><u>Target groups</u></p> <p>Identification of groups at-risk of having LTBI and/or an increased risk of progressing to active TB</p>	<p>Prioritization of target groups for LTBI screening:</p> <ul style="list-style-type: none"> – people living with HIV; – immunocompromised persons, (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.
<p><u>Diagnosis of LTBI</u></p> <p>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</p>	<p>Implementation of comprehensive strategy including :</p> <ul style="list-style-type: none"> – use of tuberculin skin test and interferon gamma release assays (alone or a combination) to diagnose LTBI; – availability of and accessibility to diagnostic tests; – intention to provide LTBI treatment (if appropriate); – implementation of interventions promoting the uptake and completion of LTBI screening procedures.
<p><u>Treatment of LTBI</u></p> <p>Provision of LTBI treatment using treatment regimens that are effective and promote adherence and completion by different target groups</p>	<p>Selection of LTBI treatment regimen from the following treatment regimens based on an individual risk assessment:</p> <ul style="list-style-type: none"> – isoniazid alone (for 6–9 months), – rifampicin alone (for 3–4 months), – isoniazid and rifapentine (for three months) – isoniazid and rifampicin (for 3–4 months)
<p><u>Programmatic issues</u></p> <p>Implementation of patient-centred strategies for service delivery.</p> <p>Effective health education and communication with target groups and healthcare providers.</p> <p>Programme monitoring and evaluation.</p>	<p>Implementation of an integrated strategy including:</p> <ul style="list-style-type: none"> – material incentives and enablers; – counselling and education; – peer-based support; – culturally-sensible approaches. <p>Implementation of a comprehensive educational programme aiming at increasing awareness of the importance of detecting and treating LTBI.</p> <p>Implementation of programme monitoring and evaluation including:</p> <ul style="list-style-type: none"> – Establishment of a case-based registry of TB contacts identified during routine contact investigations. – Revision/development of data collection processes. – Definition of performance indicators. – Implementation of regular programme monitoring, aligned with global [1] and regional [30] monitoring and evaluation frameworks

HIV= human immunodeficiency virus; LTBI= latent tuberculosis infection; TB=tuberculosis; TNF= tumour necrosis factor.

Table 2. Considerations for selection of latent tuberculosis infection testing method [5].

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 ¹	IGRA	No need for a second visit to read the test result.
Immunocompromised patients (including PLHIV)	Combination of TST and IGRA (parallel testing) ²	LTBI tests are less sensitive in immunocompromised people. In order not to miss <i>Mycobacterium tuberculosis</i> 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.

¹ Adults, young people and children whose social circumstances or lifestyle, or those of their parents or carers, make it difficult to recognise TB symptoms, access health services, self-administer treatment and attend regular healthcare appointments [25].

²After the initiation of antiretroviral treatment, repeated testing for LTBI may be considered for PLHIV previously known to have negative TST or IGRA results [31].

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.

References

1. World Health Organization. Implementing the End TB strategy: the essentials. Geneva: WHO, 2015.
2. United Nations General Assembly. The Sustainable Development Goals 2015 [cited 07 April 2017]. Available from: <http://www.un.org/sustainabledevelopment/sustainable-development-goals/>.
3. 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.
4. Kunst H, Burman M, Arnesen TM, Fiebig L, Hergens MP, Kalkouni O, et al. Tuberculosis and latent tuberculosis infection screening of migrants in Europe: comparative analysis of policies, surveillance systems and results. *Int J Tuberc Lung Dis*. 2017 Aug 1;21(8):840-51.
5. European Centre for Disease Prevention and Control. Programmatic management of latent tuberculosis infection in the European Union. Stockholm: ECDC; 2018.
6. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO, 2018.
7. 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).
8. 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.
9. 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.
10. 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>.
11. 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.
12. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015 Dec;46(6):1563-76.
13. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. *Ann Intern Med*. 2017 Aug 15;167(4):248-55.
14. Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. *BMC Infect Dis*. 2016 May 17;16:204.
15. 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.
16. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis*. 2011 Jun;11(6):435-44.
17. Zenner D, Hafezi H, Potter J, Capone S, Matteelli A. Effectiveness and cost-effectiveness of screening migrants for active tuberculosis and latent tuberculosis infection. *Int J Tuberc Lung Dis*. 2017 Sep 1;21(9):965-76.
18. Sotgiu G, Matteelli A, Getahun H, Girardi E, Sane Schepisi M, Centis R, et al. Monitoring toxicity in individuals receiving treatment for latent tuberculosis infection: a systematic review versus expert opinion. *Eur Respir J*. 2015 Apr;45(4):1170-3.
19. Migliori GB, Sotgiu G, Rosales-Klitz S, Centis R, D'Ambrosio L, Abubakar I, et al. ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update. *Eur Respir J*. 2018 May;51(5).
20. 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.

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- 2
- 3 21. Evenblij K, Verbon A, van Leth F. Intention of physicians to implement guidelines for screening
- 4 and treatment of latent tuberculosis infection in HIV-infected patients in The Netherlands: a mixed-
- 5 method design. *BMC Public Health*. 2016 Sep 1;16(1):915.
- 6 22. Atchison C, Zenner D, Barnett L, Pareek M. Treating latent TB in primary care: a survey of
- 7 enablers and barriers among UK General Practitioners. *BMC Infect Dis*. 2015 Aug 13;15:331.
- 8 23. Dobler CC, Bosnic-Anticevich S, Armour CL. Physicians' perspectives on communication and
- 9 decision making in clinical encounters for treatment of latent tuberculosis infection. *ERJ open research*.
- 10 2018 Jan;4(1).
- 11 24. Abarca Tomas B, Pell C, Bueno Cavanillas A, Guillen Solvas J, Pool R, Roura M. Tuberculosis
- 12 in migrant populations. A systematic review of the qualitative literature. *PloS one*. 2013;8(12):e82440.
- 13 25. European Centre for Disease Prevention and Control. Guidance on tuberculosis control in
- 14 vulnerable and hard-to-reach populations. Stockholm: ECDC; 2016. Available from:
- 15 [https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-](https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-vulnerable-groups.pdf)
- 16 [vulnerable-groups.pdf](https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-vulnerable-groups.pdf).
- 17 26. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and
- 18 treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2016
- 19 Nov;16(11):1269-78.
- 20 27. Loutet MG, Burman M, Jayasekera N, Trathen D, Dart S, Kunst H, et al. National roll-out of
- 21 latent tuberculosis testing and treatment for new migrants in England: a retrospective evaluation in a high-
- 22 incidence area. *Eur Respir J*. 2018 Jan;51(1).
- 23 28. De Vries G, van Hest R, Bakker M, Erkens C, van den Hof S, Meijer W, et al. Policy and
- 24 practice of programmatic management of latent tuberculosis infection in The Netherlands. *Journal of*
- 25 *Clinical Tuberculosis and Other Mycobacterial Diseases*. 2017;7:40-8.
- 26 29. Collin SM, de Vries G, Lonnroth K, Migliori GB, Abubakar I, Anderson SR, et al. Tuberculosis
- 27 in the European Union and European Economic Area: a survey of national tuberculosis programmes. *Eur*
- 28 *Respir J*. 2018 Oct 11.
- 29 30. WHO Regional Office for Europe. Roadmap to implement the tuberculosis action plan for the
- 30 WHO European Region 2016-2020. Copenhagen: World Health Organisation, 2016.
- 31 31. Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health
- 32 Care Providers. Atlanta: CDC, 2013.
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