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European Union Standards for Tuberculosis Care

2017 update

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European Union Standards for Tuberculosis Care

2017 update

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Introduction

The European Centre for Disease Prevention and Control (ECDC) and the European Respiratory Society (ERS) have developed 21 patient-centred standards to guide clinicians and public health workers in their work to ensure optimal diagnosis, treatment and prevention of tuberculosis (TB) in Europe. In 2017, the European Union Standards for Tuberculosis Care (ESTC) were updated to incorporate the most recent technological developments and international recommendations for TB diagnosis, treatment and prevention.

Higher standards needed to progress towards TB elimination in the European Union

Why EU-adapted standards?

The International Standards for Tuberculosis Care (ISTC) were first published in 2006 and subsequently updated in 2009 and 2014. The ISTC describe a widely accepted level of TB care, however, they focus on high-burden, low-income settings.

In the EU/EEA the epidemiological context and availability of financial resources are different:

- Burden is low/intermediate but heterogeneous
- Long tradition of TB prevention and control
- Resources are available
- Need to ensure optimal use of these resources
- TB services are integrated into the health system
- Every patient has the right to access the best possible care

The ESTC are patient-centred standards designed for clinicians and public health workers

How were the ESTC developed and updated?

In this collaborative effort, the ERS has taken the lead in developing and updating the clinically-related standards and ECDC has developed and updated the public health-related standards. The development and update was guided by a task force of international experts representing different areas of expertise, organisations and TB patients' representatives. The evidence was reviewed against the background of published, international guidelines. A writing committee prepared a draft document

which was then reviewed and approved by the task force. The ESTC have been developed and updated to complement the ISTC and other existing guidelines.

An easy-to-use resource to ensure optimal diagnosis, treatment and prevention of TB

Rationale for ESTC

The ESTC seek to bridge current gaps in the case management of TB in the European Union/European Economic Area (EU/EEA).

The aim of the ESTC is to provide public health experts, clinicians and healthcare programmes with a structured set of evidence-based standards that describe the minimal requirements for assuring optimal TB care, prevention and control.

For more information:

ECDC is an EU agency whose mandate is to identify, assess and communicate threats to human health posed by infectious diseases. It supports the work of public health authorities in the EU/EEA Member States.
www.ecdc.europa.eu/en/tuberculosis

ERS is the leading professional organisation in its field in Europe. It has over 30 000 members in over 160 countries. ERS seeks to alleviate suffering from respiratory diseases and promote lung health through research, knowledge sharing and medical and public education.
www.ersnet.org

The complete ESTC update was published in the European Respiratory Journal (ERJ), in May 2018 (DOI: 10.1183/13993003.02678-2017)

Standards for tuberculosis diagnosis

Standard 1

All persons presenting with signs, symptoms, history or risk factors compatible with tuberculosis should be evaluated for pulmonary and / or extrapulmonary tuberculosis.

Standard 2

All patients (adults, adolescents and children who are capable of producing sputum) thought to have pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination and one for rapid testing for the identification of tuberculosis and drug resistance using an internationally recommended (rapid) molecular test. The sample should be sent for liquid culture and, if positive, for culture-based drug susceptibility testing (DST) in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained. Chest radiography can also be used.

Standard 3

For all patients (adults, adolescents and children) presumed to have extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microbiological testing (microscopy, rapid molecular tests, culture, species identification, DST with rapid molecular tests and culture-based techniques) and histopathological examination in quality-assured laboratories.

Standard 4

All persons with chest radiographic findings suggestive of pulmonary tuberculosis should have sputum specimens submitted for microscopic examination, rapid molecular tests, culture, species identification and DST with rapid molecular tests and culture-based techniques in a quality-assured laboratory.

Standard 5

The diagnosis of culture-negative pulmonary tuberculosis should be based on the following criteria: all bacteriological tests are negative (including direct sputum smear examinations, cultures and rapid molecular testing); chest radiographic findings compatible with tuberculosis; and lack of response to a trial of broad spectrum antimicrobial agents (note: because the fluoroquinolones are active against *M. tuberculosis* complex, and may cause transient improvement in persons

with tuberculosis, their use should be avoided). In persons who are seriously ill or have known or presumed human immunodeficiency virus (HIV)-infection or have any immune-compromising conditions, the diagnostic evaluation should be expedited and, if clinical evidence strongly suggests tuberculosis, a course of anti-tuberculosis treatment should be initiated.

EU specific requirements

In order to ensure quality diagnosis of both pulmonary and extrapulmonary tuberculosis, adequate samples for bacteriologic examination should be obtained. Sputum induction, bronchoscopy and bronchoalveolar lavage, gastric washing, biopsy or fine needle aspiration should be used where appropriate [1]. Samples should be processed using available diagnostic tools [2], and complemented by imaging (radiology, ultrasound, computerised tomography, magnetic resonance imaging, positron emission tomography-computed tomography) and other necessary examinations performed according to evidence-based guidelines [2-4].

WHO-recommended rapid molecular testing [5], culture and DST should be performed on each sample from patients with presumed pulmonary and extrapulmonary tuberculosis, including samples obtained during surgery or other invasive procedures which usually undergo histological examinations. Surgeons should thus be advised to save a biological specimen in normal saline for microbiological and molecular biological examinations and in formalin for histopathological examinations.

Standard 6

In all children presumed to have intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of appropriate biological samples (by expectorated or induced sputum, bronchial secretions, pleural fluid, gastric washings, or endoscopic ultrasound-guided biopsy) by smear microscopy, rapid molecular tests, species identification and DST with culture-based techniques in a quality-assured laboratory [3, 5-9]. In the event of negative bacteriological results, a diagnosis of tuberculosis should be based on the presence of abnormalities consistent with tuberculosis on chest radiography or other imaging, a history of exposure to an infectious case, evidence of tuberculosis infection (positive tuberculin skin test (TST) and/or a positive interferon-gamma release assay (IGRA)) [5, 10-13], and/or clinical findings suggestive of tuberculosis [3]. For children presumed to have extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, recommended rapid molecular tests, species identification and DST with culture-based techniques; and histopathological examination [5, 14, 15].

Standards for tuberculosis treatment

Standard 7

Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance. To fulfil this responsibility, the practitioner, in collaboration with public health authorities, must: 1) prescribe an appropriate regimen (guided by the genotypic and/or phenotypic DST results); 2) perform contact investigations; 3) assess and promote patient's adherence to treatment using a patient-centred approach in collaboration with family members, local public and/or community health services, and civil society organisations and 4) monitor treatment outcomes [2, 16, 17].

Standard 8

All patients (including those with HIV co-infection), who have not been previously treated and are without drug resistance (assessed by appropriate tests), should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). The continuation phase should consist of isoniazid and rifampicin given for 4 months (2HRZE/4HR). The doses of anti-tuberculosis drugs used should conform to international recommendations. Fixed dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs may provide a more convenient form of drug administration.

Standard 9

A patient-centred approach to treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients.

Standard 10

Response to therapy in patients with pulmonary tuberculosis should be monitored by follow-up smear microscopy and culture, at least, at the time of completion of the initial phase of treatment (two months for drug-susceptible tuberculosis). If the sputum smear and/or culture are positive at completion of the initial phase, molecular tests of drug resistance and further DST should be performed promptly. In patients with extrapulmonary tuberculosis and in children unable to produce sputum, the clinical response to treatment (weight, inflammatory markers and repeat imaging) is objectively assessed.

EU specific requirements

Treatment monitoring should be done according to international guidelines [2, 3, 6-8, 18-20]. In the EU, countries have resources to perform treatment monitoring on a monthly basis. For multidrug-resistant tuberculosis (MDR-TB) cases, this monthly monitoring should be done based on sputum smear and culture [21, 22].

Standard 11

An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case with drug-resistant tuberculosis, and the community prevalence of drug resistance, should be made, especially for patients who are not bacteriologically confirmed or for whom drug susceptibility testing cannot be performed. Rapid testing (genotypic rifampicin and isoniazid resistance testing and genotypic/phenotypic second-line drug resistance testing for patients with rifampicin resistance or MDR-TB) should be performed for all patients as defined in standards 2-4 and 8. Furthermore, patient counselling and education should begin immediately for all tuberculosis patients, in order to minimise the potential for transmission. Infection control measures appropriate to the setting should be applied as recommended in ESTC public health standard 20.

Standard 12

Patients with, or highly likely to have, tuberculosis caused by drug-resistant (especially rifampicin-resistant/MDR/ extensively drug-resistant (XDR)) organisms should be treated with individualised regimens containing second-line and add-on anti-tuberculosis drugs. The regimen chosen should be based on confirmed drug susceptibility patterns. Empirical regimens may cause further resistance and are not recommended, except for culture-negative tuberculosis.

Depending on the drug susceptibility pattern, treatment with a minimum of five effective anti- tuberculosis drugs should be provided for at least 20 months [5]. If the patient fulfils the eligibility criteria for the standard shorter MDR-TB regimen (9-11 months) this can be used.

EU specific requirements

As the treatment of MDR/XDR-TB often represents a last chance to ensure patient cure and survival, a full range of patient-centred measures, including counselling, observation and support of treatment, as well as psycho-social support are required to ensure adherence [5, 23-25]. This is particularly important given that these patients often belong to socially and economically disadvantaged groups.

For the treatment of MDR-TB, no drug should be administered to a patient with documented resistance (either by molecular or phenotypic DST). Thus, second-line DST

should be performed to confirm the drug resistance pattern as well as to guide the correct choice of treatment.

In the EU/EEA, DST to ethambutol is considered reliable when conducted in quality-assured laboratories [26]. Pyrazinamide testing could be performed by genotypic (detection of pncA mutations) or phenotypic test (i.e. growth-based (liquid) automated methods).

The individualised regimen should include at least five effective tuberculosis medicines during the intensive phase, including pyrazinamide and four core second-line tuberculosis medicines. Drugs should be chosen as follows: one chosen from group A, one from group B, and at least two from group C (Table). If the minimum number of five effective tuberculosis medicines cannot be composed from drugs included in Group A to C, an agent from group D2 and other agents from group D3 may be added to bring the total to five. If pyrazinamide cannot be used (e.g. due to resistance or toxicity) an additional agent from group C or D can be added to strengthen the regimen. Total treatment duration ranges from 20 to 24 months, with the recommended intensive phase being 8 months [5].

In patients with rifampicin-resistant tuberculosis or MDR-TB, who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB of 9–11 months recommended by WHO may be used instead of the conventional individualised regimen [5, 25, 27].

Treatment with new medicines including bedaquiline and delamanid along with repurposed medicines like linezolid and clofazamine and second-line medicines to which the M. tuberculosis strain is likely to be sensitive is required for patients suffering from XDR-TB or those patients suffering from strains resistant to fluoroquinolones or second-line injectables [28, 29]. For patients with serious adverse events to fluoroquinolones or second-line injectables new and repurposed medicines can also be considered.

Adverse events following prescription of second-line drugs should be managed according to international recommendations with the aim of limiting the probability of losing an effective drug due to such adverse events [2].

Adverse events, as well as the decision to start, modify or interrupt a second-line regimen should be managed by a team of experts (e.g. “TB Consilium” or similar body,) and not by individual physicians, in order to minimise mistakes and share responsibilities as well as share experience and expertise [28, 30, 31]. All efforts should be done to avoid development of additional drug resistance.

WHO suggested that, in addition to chemotherapy, surgery may be used in selected cases with pulmonary tuberculosis, e.g. those with large cavities confined to one lobe [23]. Further research in this direction is necessary.

Table. World Health Organization classification of anti-tuberculosis drugs [23]

Group	Drugs		Abbreviation
A. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin		Lfx Mfx Gfx
B. Second-line injectables	Amikacin Capreomycin Kanamycin (Streptomycin[1])		Am Cm Km (S)
C. Other core second-line agents	Ethionamide/ Prothionamide Cycloserine/Terizidone Linezolid Clofazimine		Eto/Pto Cs/Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regime)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H (high-dose)
	D2	Bedaquiline Delamamid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone[2])	PAS Ipm Mpm Amx-Clv (T)

1 Streptomycin can substitute other injectable drugs if none of these agents can be used and if the strain is shown not to be resistant.

2 Thioacetazone should not be used if the patient is HIV seropositive.

Standard 13

A written or electronic record of all medications administered, treatment monitoring (including bacteriologic response), adverse reactions and treatment outcomes, should be maintained for all patients.

EU specific requirements

At the first contact with each patient, the complete clinical and social history on tuberculosis should be collected and included in the medical records. It should include the available information on previous diagnosis, treatment (regimen, doses, duration, changes in the regimen, etc.) and adherence, as well as complete information on bacteriology at diagnosis and during follow-up (sputum smear, culture and species identification, drug susceptibility testing for first and second-line drugs). This information should be reported in the documentation released to the patient (discharge letter, transfer-out form or equivalent document) to facilitate continuum of care if the patient moves / is moved to another health unit [32, 33].

Standards for addressing HIV infection and comorbidities

Standard 14

HIV counselling should be done and HIV testing should be recommended to all patients with, or presumed to have, tuberculosis. Testing is of special importance as part of the routine management of all patients in areas with a high prevalence of HIV infection in the general population, or if the patient is from a high-risk population or has symptoms and/or signs of HIV-related conditions. Because of the close interaction between tuberculosis and HIV infection, integrated approaches to prevention and treatment of both infections are recommended [34].

Standard 15

All patients with tuberculosis and HIV infection should be carefully evaluated: antiretroviral therapy is recommended in all HIV-positive tuberculosis patients. Tuberculosis treatment should be started immediately and the antiretroviral treatment prescribed as soon as possible.

Standard 16

Persons with HIV co-infection who, after careful evaluation, have a positive test (TST and/or IGRAs) for presumed latent infection with *M. tuberculosis* but do not have active tuberculosis should be offered preventive treatment.

EU specific requirements

As HIV co-infection is known to increase the probability of developing active tuberculosis disease upon infection, HIV-seropositive persons who have been in contact with an index case harbouring an MDR-TB strain, should initially undergo an individual risk assessment. Regular clinical monitoring and follow-up should be provided for those with evidence of latent infection. [35].

Preventive treatment should take into account the drug resistance pattern of the source case, the CD4 count and the use of antiretroviral treatment. Preventive treatment should be provided with 6-month isoniazid, or 9-month isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3-4 month isoniazid plus rifampicin, or 3-4 month rifampicin alone [36, 37]. Rifampicin- and rifapentine-containing regimens should be prescribed with caution to people living with HIV who are on antiretroviral treatment due to potential drug-to-drug interactions [36, 38].

Standard 17

All providers should conduct a thorough assessment of conditions that could affect tuberculosis treatment response or outcome. At the time the case management plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualised plan of care. This plan should include assessment of and referrals for treatment for other illnesses with particular attention to those known to affect treatment outcome, for instance HIV, diabetes mellitus, drug and alcohol addiction, tobacco smoking, and other psycho-social problems [39]. Services such as antenatal or well-baby care should also be provided when needed.

EU specific requirements

Implementation of the entire package described in the WHO Interim Policy on Collaborative TB/HIV activities should be performed for all the activities, both those covered here and others included in the WHO package [34].

Standards for public health and tuberculosis prevention

Standard 18

All care providers for patients with tuberculosis should ensure that persons who have been in close contact with active and infectious tuberculosis patients are evaluated and managed in line with international recommendations. Close contacts include household and family members, and individuals with intensive or prolonged contact in congregate settings like prisons, homeless or migrant shelters, and indoor spaces like schools or offices.

The risk of tuberculosis transmission depends on the concentration of the tubercle bacilli in the air, the airflow, the duration of the contact and the susceptibility of the contact to infection. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed and hence untreated tuberculosis; 2) is at high risk of having been infected by the index case; 3) is at high risk of developing tuberculosis if infected; 4) is at risk of having severe tuberculosis if the disease develops.

EU specific requirements

The determinants of tuberculosis transmission and susceptibility should be carefully considered when assessing whether transmission has likely occurred and the need for initiating contact tracing [40].

Close contacts of MDR- and XDR-TB patients should be tested for latent tuberculosis infection (LTBI) and tuberculosis according to national guidelines. Contacts in which tuberculosis disease has been excluded and who are diagnosed with LTBI should undergo an individual risk assessment to determine: 1) the contact's risk for progression to tuberculosis disease; 2) the drug susceptibility pattern of the source case; and 3) the contact's risk for adverse events if initiating LTBI treatment [36, 38]. Irrespective of the clinical advice regarding LTBI treatment, these contacts should be provided with careful clinical observation, information and health education by healthcare workers experienced in management of LTBI and tuberculosis disease [35, 41].

Involvement of local, community-based organisations (including community healthcare workers, non-clinical professionals and peers), is advisable when conducting contact tracing among vulnerable and hard-to-reach populations. This approach can contribute to the successful identification of potential contacts [42, 43].

Clinicians and national programme managers are to interact with the relevant health authorities of host and/or home countries of tuberculosis patients belonging to migrant groups or mobile populations, to ensure continuum of care and contact investigation as appropriate [44].

Standard 19

Contacts of an infectious tuberculosis patient, persons with HIV infection, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematological transplantation, and patients with silicosis should be tested for latent tuberculosis infection. If latent tuberculosis infection is identified they should be carefully evaluated for active tuberculosis. When active tuberculosis is excluded, preventive treatment using a WHO-recommended regimen should be offered.

EU specific requirements

Clinicians should collaborate with public health authorities in implementing adequate contact tracing procedures, performed according to national and international recommendations on progressive circles, when an infectious index case is diagnosed and notified [40, 41, 45, 46]. Similarly, both source finding and contact investigation should be initiated if a child with tuberculosis (any site of infection) has been identified and where no source has been identified [41, 47].

Individuals undergoing treatment with anti-TNF-α should be considered as high-risk contacts. According to the ESTC number16, in individuals who are HIV-infected or affected by co-morbidities, treatment of latent infection should be promptly initiated if tuberculosis infection is identified by TST and/or IGRAs and active tuberculosis disease is excluded [10, 36, 38, 40, 48, 49].

Standard 20

Each healthcare facility caring for patients who have, or are presumed to have infectious tuberculosis, should develop and implement an appropriate tuberculosis infection control plan.

EU specific requirements

Community-based treatment, supported by infection control measures at home, should be available for patients preferring to undergo treatment at home [5, 24].

If hospitalisation is required, clinicians should ensure that all newly admitted patients who are presumed to have infectious tuberculosis are subject to respiratory isolation until their diagnosis is confirmed or excluded [2].

In order to prevent transmission of tubercle bacilli to other patients, staff and/or visitors, smear-positive tuberculosis patients should ideally be isolated in appropriate rooms until they achieve bacteriological conversion (negative sputum microscopy). Isolation should be in rooms with negative-pressure ventilation.

An appropriate infection control plan, managed by a designated person, should include the following four components; managerial activities; administrative controls; environmental controls; and personal protection interventions [5, 50]. Adequate administrative measures for tuberculosis infection control should be in place in all healthcare facilities, as well as adequate respiratory protection measures (including the use of respirators following respirator fit testing for staff and the use of surgical mask for infectious patients). Appropriate training on infection control to staff, and standardised health education of patients on cough etiquette, based on validated tools, should be also included in the infection control plan. Infection control committees, which cover airborne diseases, and includes infection control experts, should also be implemented [5, 50-52].

Standard 21

All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

EU specific requirements

Clinicians should perform treatment outcome evaluations in their clinical unit at regular time intervals (e.g. quarterly) [18, 53]. Treatment outcomes should be reported to local public health authorities, in conformance with applicable requirements and policies and, at the same time, be used as a monitoring and evaluation tool to improve the quality of patient management. Information on treatment outcome should also regularly be channelled back from the public health department to the healthcare providers, to allow a coordinated evaluation of the outcomes. Information on the final outcome of patients should be available at the clinical unit which initiated treatment, even when the patient is transferred out. Adequate training must be provided to health staff in charge of reporting treatment outcomes to public health authorities and performing the quarterly evaluation of the clinic's own cases. This principle is also applicable to tuberculosis patients moving across EU borders [54-57].

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