



## Early View

Task force report

### **ERS/ECDC Statement: European Union Standards for Tuberculosis Care - 2017 update**

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# ERS/ECDC Statement: European Union Standards for Tuberculosis Care - 2017 update

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## Summary

The International Standards for Tuberculosis (TB) Care define the essential level of care for managing patients who have or are presumed to have TB, or are at increased risk of developing the disease. The resources and capacity in the European Union and the European Economic Area (EU/EEA) permit higher standards of care to secure quality and timely TB diagnosis, prevention and treatment. On this basis, the European Union Standards for Tuberculosis Care (ESTC) were published in 2012 as standards specifically tailored to the EU-setting. Since the publication of the ESTC new scientific evidence has become available and, therefore, the standards were reviewed and updated.

A panel of international experts, led by a writing group from the European Respiratory Society (ERS) and the European Centre for Disease Prevention and Control (ECDC), updated the ESTC on the basis of new published evidence. The underlying principles of these patient-centred standards remain unchanged. The second edition of the ESTC includes 21 standards in the areas of diagnosis, treatment, HIV and co-morbidities, and public health and prevention.

The ESTC target clinicians and public health workers, provide an easy-to-use resource and act as a guide through all the required activities to ensure optimal diagnosis, treatment and prevention of TB.

## Introduction

With 60,195 tuberculosis (TB) cases notified in the European Union and European Economic Area (EU/EEA)<sup>1</sup> Member States in 2015 [1], TB continues to be a priority public health challenge in this setting. Although several EU/EEA countries are progressing towards sustained low levels of TB incidence and some towards the pre-elimination phase (defined as less than 10 cases per million population [1-3]), great diversity in TB disease burden remains within the sub-region [1]. Drug resistant TB, multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) pose a specific public health threat in many countries [4]. Furthermore, documenting the prevalence of HIV co-infection among TB cases is still compromised by sub-optimal reporting in several countries [5, 6].

While EU/EEA countries adopted the key principles of TB control and elimination through the European-specific, consensus-based documents born within the Wolfheze initiative [7] and subsequent documents [2], a uniform set of guidelines summarising the essential standards to guide European clinicians and health care workers was developed only in 2012 [8]. These European Union Standards for Tuberculosis Care (ESTC) were based on the second version of the International Standards for Tuberculosis Care (ISTC) issued in 2009 [9]. The documents were developed by experts selected to include the perspectives of several countries, organizations, national TB programmes, scientific and civil societies, as well as representatives of the affected communities, which endorsed them for universal (ISTC) or EU/EEA countries use (ESTC).

Both ISTC and ESTC [8-11] prescribe a widely-accepted level of TB care, to guide all health care providers and clinicians, both public and private, in achieving optimal standards in managing individuals who have active TB, latent TB infection (LTBI) or signs and symptoms compatible with the disease. The Standards are designed to complement existing national or international guidelines and are consistent with World Health Organization (WHO) definitions and recommendations [12].

The original ESTC include 21 standards organised into 4 sections: i) Standards for diagnosis, ii) Standards for treatment, iii) Standards for addressing HIV co-infection and other co-morbidities and iv) Standards for public health [8]. The Standards are a living document, and will thus be revised as technology, and circumstances change. In 2014, the 3rd edition of the ISTC was published [10]. An assessment and a survey among European Respiratory Society (ERS) members and European Centre for Disease Prevention and Control (ECDC) contacts concluded that a revision of the ESTC would be appropriate [13, 14].

The specific mix of characteristics among the EU/EEA Member States which justified the development of standards specifically tailored to the European Union context are still valid, and are summarised below [8, 11, 15]:

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<sup>1</sup> EU/EEA Countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Republic of Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

- Although the majority of EU/EEA countries have a low incidence of TB, a number of Member States have intermediate TB levels, with varying incidence of MDR-TB and TB-HIV co-infection. Furthermore, several countries located at the eastern border of the EU are neighbouring non-EU countries with a high TB and MDR-TB burden.
- TB services are fully integrated and merged within the health system in a majority of EU/EEA countries. This leads to individual country peculiarities in allocating responsibilities for the optimal delivery of TB care.
- The EU/EEA countries have a long-established tradition of TB control that has evolved over the past decades. New tools and high standards of diagnosis and care are often implemented in EU/EEA countries.
- The EU/EEA is committed to pursue elimination of TB, sharing a common platform based on the Wolfheze documents and subsequent documents; the global End TB strategy and its related action plan specific to the European region; as well as the surveillance system driven by ECDC and WHO Regional Office for Europe [2, 16-22].

The purpose of this document is to incorporate the new scientific evidence that has become available after the publication of the European Union Standards for Tuberculosis Care (ESTC) in 2012.

## Methods

A collaborative process, jointly led by the ERS and the ECDC was initiated in 2016 to revise the ESTC. The process received input from an ERS Task Force. The Task Force included a panel of experts representing the ERS, other international societies and organizations (World Health Organization, the UNION, KNCV Tuberculosis Foundation), national TB programmes, civil society, and affected communities. All Task Force members provided a conflict of interest declaration, in line with ERS regulations.

This update builds upon the main areas outlined in the previous ESTC edition, i.e. diagnosis, treatment, HIV and co-morbidities, and public health and prevention. The ERS has taken the lead in developing the clinically related Standards and ECDC has done the same for the public health Standards. After conducting an initial scoping search, it was determined that sufficient relevant evidence was already available for an update of ESTC. Hence, no systematic reviews were conducted as part of the ESTC updating process.

New evidence was identified through a targeted, non-systematic literature search. The search focused on evidence-based guidelines, systematic reviews/meta-analyses, peer-reviewed scientific articles, institutional reports and policy recommendations produced after the publication of the first edition of the ESTC (i.e. 2012). Relevant evidence was retrieved after consulting the expert panel, institutional websites and selected electronic databases, i.e., Medline (<https://www.ncbi.nlm.nih.gov/pubmed/>), PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>) and the Cochrane Database of Systematic Reviews (<http://www.cochranelibrary.com/>).

Task Force members assessed the synopsis of the evidence and provided their written input for the revision of the 21 standards and their supporting enablers for implementation. A writing committee consisting of six experts (four from ERS and two from ECDC) led the writing process of the document (mentioned as ‘equally contributed’ in the authors’ list). After three discussion rounds, consensus was reached and the final document was approved. All co-authors participated in the entire process and contributed to the final document.

This document provides up-to-date standards for tuberculosis care tailored to the European Union and the European Economic Area (EU/EEA) on the basis of recently published policy statements and international guidelines, in particular those listed in Table 1.

According to the ERS Task Force rules, the process to develop the ESTC was monitored by ERS, and underwent peer-review and approval before submission to the European Respiratory Journal. In parallel, the document gained clearance by ECDC.



## **How to read the document**

Divided into four sections (Diagnosis, Treatment, HIV and co-morbidities and Public Health), 21 standards are defined, following the structure of the first version of the ESTC. For each standard it is indicated if, in comparison with the previous version of the ESTC, a given standard remained unchanged or underwent modifications. Table 2 summarises all the changes. Under the heading “EU specific requirements” further considerations are provided. When necessary, notes are listed after each standard, to further define and explain specific components that the expert group deemed important to clarify.

## Standards for Tuberculosis Diagnosis

### Standard 1 (*Unchanged*)

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

Notes:

- The most common symptom of pulmonary TB is persistent cough with or without sputum production for more than 2-3 weeks [10], while haemoptysis (coughing up blood) is more unusual. These signs and symptoms are common in a wide range of respiratory conditions including acute respiratory infections (ARI) and acute exacerbation of chronic obstructive pulmonary disease (COPD). Respiratory symptoms can be accompanied by fever, night sweats and weight loss. For extrapulmonary TB, organ-specific signs and symptoms may occur. Individuals may also have TB, without specific signs and symptoms of disease, especially those who are immunosuppressed [33].
- It is important to question the patient with regard to TB. For example, a history of TB in the family, history of previous contact with TB as well as previous TB diagnosis and/or treatment, and any condition attenuating the host immune system [10] are common risk factors for TB that should be considered as relevant to the diagnosis. TB in a child is always a “sentinel event” for recent transmission (e.g. a source case is likely to exist in the family or in their class [34]).
- In the EU-setting, TB is not the leading cause of persistent cough. Also, cough is not necessarily the most common symptom of TB disease [35].

### Standard 2 (*Changed*)

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.

Notes:

- The order of execution of the microbiological tests mentioned in this and in the following standards will depend on the laboratory work-flow.
- The term ‘internationally recommended rapid (molecular) tests’ refers to diagnostic tests validated by internationally recognized organizations, including WHO. From this point onwards these tests will be referred to as ‘rapid molecular tests’.

- Based on the EU/EEA practice and definitions [36, 37], quality-assured DST should be performed on all diagnosed TB patients to rule out drug-resistance [16, 37-40]. This should follow international standards and guidelines with regard to methods used and drug-concentrations, for testing of first and second line drugs [16, 18]. Samples sent for bacteriological examinations (sputum smear, culture, drug susceptibility testing, new molecular methods) should be addressed to a mycobacteriology laboratory which implements optimal laboratory practices and quality assured procedures according to European and International recommendations [16, 18, 25].
- Quality bacteriological diagnosis includes the WHO-recommended rapid (molecular) assays [12, 41-46]; it should be done as early as possible (ideally initiated on the day the presumed patient is identified) within evidence-based diagnostic algorithms and guidelines. Currently available genotypic methods are the automated real-time nucleic acid amplification technology for rapid and simultaneous detection of *Mycobacterium tuberculosis* and rifampicin resistance (e.g. the GeneXpert platform) and the line probe assays for rapid *M. tuberculosis* detection and rifampicin resistance or rifampicin- and/or isoniazid-resistance testing [12, 46-48]. These approaches allow immediate identification of *M. tuberculosis* and rifampicin-resistance and/or MDR-TB (rifampicin-resistance can be considered a proxy of MDR-TB) [12, 41-46, 49, 50]. Whole Genome Sequencing (WGS) and WGS-based tools are available for diagnosis and identification of TB and of drug resistant variants; they are used in some EU countries [51-53]. Molecular diagnostic results must be confirmed by phenotypic testing, i.e. culture-based DST [38, 49, 50]; in case of discrepant results sequencing could be performed from the isolate to identify the mutation and, in case of high confidence mutations, the isolate should be regarded as resistant. The culture-based DST confirmation should be done by quality-assured laboratories [54, 55].
- At present the choice of molecular methods for the rapid identification of rifampicin-resistance and isoniazid-resistance should be that of WHO-recommended rapid diagnostic assays [12, 29]. We expect that in the near future the role of sequencing as a reference for molecular tests will be recognised and additional molecular tests will become available in Europe.
- Timely, clear and direct communication between the laboratory experts and clinicians is essential to obtain the optimal link between diagnosis and treatment regimen. The clinician needs to be informed whether the laboratory performs DST for second-line drugs and on which drugs [16].
- Given that the collection of a third sputum sample has been shown to increase the diagnostic yield by 2-3%, EU/EEA-countries may decide to maintain the previous recommendation of collecting three sputum-samples on the same day (not necessarily on consecutive days) [10, 56].
- It is essential to obtain good quality sputum samples in order to ensure reliable bacteriological testing of the sample [10, 56]. This includes providing clear instructions to the patient, ensuring appropriate collection, storage, transportation and processing of sputum samples [57].
- To ensure rapid diagnosis a sputum sample should be collected as soon as possible. In addition, it is recommended to obtain at least one early-morning sample from the patient.
- Every effort should be made to obtain samples for culture and DST, using the different procedures available according to evidence-based guidelines (sputum induction, bronchoscopy /bronchoalveolar lavage and gastric lavage in children [58, 59]).

- All MDR-TB strains should be collected and stored at the national level for monitoring drug-resistance trends and map national and cross-border clusters.

### **Standard 3** (*Changed*)

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.

#### Notes:

- This third standard has been accordingly updated to be in line with Standard 1 and 2 with regard to essential, standard diagnosis. So, rapid (molecular) testing is recommended for all cases[12].
- It is essential to use all efforts to obtain bacteriological confirmation from extrapulmonary sites in order to confirm diagnosis, allow DST and consequently provide optimal and effective treatment; this may include the more sensitive molecular test [10].

### **Standard 4** (*Changed*)

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

#### Note:

- This standard has been updated to be consistent with the standards 1 and 2 with regard to essential, standard diagnosis, including rapid molecular testing [10, 12].

### **Standard 5** (*Unchanged*)

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 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 [60]. Samples should be processed using available diagnostic tools [10], 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 [10, 25, 61].

WHO-recommended rapid (molecular) testing [12], culture and DST should be performed on each sample from patients with presumed pulmonary and extrapulmonary TB, 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.

Note:

- Other existing new diagnostic tools, e.g. additional molecular tests and other new techniques in the development pipeline, should be used within evidence-based diagnostic algorithms and guidelines. Before introducing any new tool or approach, the evidence has to be validated and have shown efficacy and patient-value.

## Standard 6 (*Changed*)

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 [12, 16-18, 25, 62]. 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)) [12, 63-66], and/or clinical findings suggestive of tuberculosis [25]. 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 [12, 59, 67].

## Standards for Tuberculosis Treatment

### Standard 7 (Changed)

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: a) prescribe an appropriate regimen (guided by the genotypic and/or phenotypic DST results); b) perform contact investigations; c) 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 d) monitor treatment outcomes [10, 68, 69].

### Standard 8 (Changed)

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 two months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). The continuation phase should consist of isoniazid and rifampicin given for four 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.

#### Notes:

- The clinician should ensure the correct drug regimen (including 4 drugs for the intensive phase of treatment) at the correct dose for a sufficient duration. Daily dosage is strongly recommended [10, 12, 26, 28, 55]. The continuation phase of treatment can be initiated if susceptibility to isoniazid and rifampicin is confirmed.
- It is suggested to treat cases with rifampicin mono-resistance and MDR-TB in centres with experience, to allow close patient monitoring and adaptation of the treatment regimen on the basis of latest scientific evidence and forthcoming updated recommendations.
- Rifampicin blood levels may be monitored if poor response to treatment due to under-dosing or malabsorption is suspected [26, 27].
- In the 2017 WHO TB treatment guidelines advocated the use of adjuvant corticosteroid therapy with dexamethasone or prednisone during the first 6-8 weeks for TB meningitis [30], TB pericarditis to prevent constrictive pericarditis and avoid surgery, in renal TB to prevent ureteric stenosis and in spinal TB (if evidence of spinal cord compression)[30].

## **Standard 9** (*Changed*)

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.

Notes:

- A central element of the patient-centred strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence. These measures should be tailored to the individual patient's circumstances, based on a detailed clinical and social history, and be mutually acceptable to the patient and the provider.
- Supervision and support should be individualized and should draw on the full range of recommended interventions and available support services. The aim is to prevent poor adherence before it occurs. Such measures may include direct observation of medication ingestion (directly observed treatment (DOT) or video-observed treatment (VOT)) and/or identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV-infection) who is acceptable and accountable to the patient and to the health system. Appropriate incentives and enablers, including financial, social and psycho-social support, may also serve to enhance treatment adherence [10, 12, 26, 27, 30, 70, 71].
- Additional services included in the package of interventions recommended in the 2017 WHO TB treatment guidelines to support the patient (with drug-susceptible or drug resistant TB) and promote adherence [12, 26, 27, 30, 70, 71] are:
  - o Health education and counselling
  - o Tracers or digital medication monitoring methods
  - o Material support to the patients
  - o Staff education
  - o Community or home-based observed treatment
- A decentralised model of service delivery for MDR-TB care is recommended. This approach is more convenient for patients and might ensure economic savings in some settings.

## **Standard 10** (*Changed*)

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 [10, 16-18, 23, 25-27]. In the EU, countries have resources to perform treatment monitoring on a monthly basis. For

MDR-TB cases, this monthly monitoring should be done based on sputum smear and culture [54, 72].

### **Standard 11** (*Changed*)

An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case with drug-resistant TB, 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 minimize the potential for transmission. Infection control measures appropriate to the setting should be applied as recommended in ESTC public health standard 20.

#### Notes:

- This standard emphasizes the need to use rapid molecular tests to rule-out or confirm presumed MDR-TB as described in standards 2-4 and 8 [12]. In the near future, other genotypic techniques such as WGS could be considered.
- As expressed in standards 2-4, rapid molecular testing for rifampicin- and isoniazid-resistance does not yet rule out the requirement to perform standard DST to confirm results from the molecular test as well as perform the comprehensive standard DST for other drugs.
- Resistance to other second line drugs in Europe is common [73-78].
- Phenotypic DST should only be performed and interpreted for drugs with critical concentration and clinical breakpoints established and fully validated [12, 53].
- Genotypic DST should be interpreted based on an agreed list of mutations and interpretations [12, 53]

### **Standard 12** (*Changed*)

Patients with, or highly likely to have, tuberculosis caused by drug-resistant (especially rifampicin-resistant/MDR/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-TB drugs should be provided for at least 20 months [12]. 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 [12, 28-30]. 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 [76]. 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 TB medicines during the intensive phase, including pyrazinamide and four core second-line TB medicines. Drugs should be chosen as follows: one chosen from Group A, one from Group B, and at least two from Group C (Table 3). If the minimum number of five effective TB 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 [12].

In patients with rifampicin-resistant TB 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 [12, 29, 79].

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 [77, 80]. 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 [10]

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 [77, 81, 82]. 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 TB, e.g. those with large cavities confined to one lobe [28]. Further research in this direction is necessary.

Note:

- In order to prevent the selection of resistant *M. tuberculosis* mutants it is essential to never add only one effective drugs to a failing regimen [28].
  
- The ‘shorter regimen’ recommended by WHO is as follows: 4-6 Km- Mfx-Pto-Cfz-Z-H <sup>high-dose</sup>-E / 5 Mfx-Cfz-Z- E. To note that in the original Bangladesh study gatifloxacin and not moxifloxacin was used [28].
  
- The WHO criteria preventing the use of the ‘shorter regimen’ include [12, 28, 29, 62, 76, 83-93]:
  - Confirmed resistance or presumed ineffectiveness to a medicine in the shorter MDR-TB regimen
  - Exposure to  $\geq 1$  second-line medicines in the shorter MDR-TB regimen for  $>1$  month
  - Intolerance to  $\geq 1$  medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
  - Pregnancy
  - Extrapulmonary disease
  - At least one medicine in the shorter MDR-TB regimen not available
  
- In Europe the growth-based liquid DST (e.g. the mycobacteria growth indicator tube [MGIT] system) for ethambutol is considered reliable. Therefore, it might be considered an element of judgement for eligibility to the ‘shorter regimen’ [75]. Line probe assays can be used as well, but there are mutations in additional genes conferring resistance to ethambutol that are not included in these assays. Ethionamide resistance can be predicted by molecular tests if mutations in *inhA* or *EthA* genes are detected by WGS. The association of *inhA* mutations with *katG* mutations makes the strains resistant to any dose of isoniazid [29, 79].
  
- The ATS/IDSA/CDC TB treatment guidelines support the use of TDM (treatment drug monitoring) in different situations, including difficult-to-treat MDR-TB cases [26, 27].
  
- Given the difficulties in managing patients with rifampicin-resistance/MDR-TB, and deciding correctly on the eligibility to the shorter regimen, referral of these patients to specialised centres is suggested.

### **Standard 13 (Changed)**

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 TB 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 [94, 95].

Note:

- Reporting forms for the described documentation can be obtained from several sources [23].
- WHO has recommended countries to activate aDSM (active tuberculosis drug-safety monitoring and management) [12, 96, 97].
- Depending on resources availability, healthcare providers should consider to follow up MDR-TB cases after treatment completion to detect early relapse [98].

## **Standards for Addressing HIV-Infection and Co-morbidities**

### **Standard 14** *(Changed)*

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 [99].

### **Standard 15** *(Changed)*

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.

Note:

- The consideration of treatment with co-trimoxazole was retracted from the ESTC as they refer to HIV-management and prevention of other infections. General prophylactic treatment against other infections is not relevant in the EU-setting. Rather, the risk of HIV-related infections must be considered individually for each patient based on risk factors and setting, and form the basis for decision to provide prophylactic treatment against infections other than tuberculosis.
- The 2017 WHO treatment guidelines suggest a delay between the initiation of TB therapy and the start of antiretroviral treatment of at least 14 days to reduce the risk of paradoxical reactions due to immune reconstitution syndrome [12, 30].

### **Standard 16** (Changed)

Persons with HIV co-infection who, after careful evaluation, have a positive test for presumed latent infection with *M. tuberculosis* (LTBI) (TST and/or IGRAs) 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 TB 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 [100]. 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 [31, 101]. 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 [31, 32].

### **Standard 17** (Changed)

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 individualized 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 psychosocial problems [102]. 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 [99].

## **Standards for Public Health and Tuberculosis Prevention**

### **Standard 18** (Changed)

All care providers for patients with tuberculosis should ensure that persons who have been in close contact with active and infectious TB 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 migrants' 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 TB transmission and susceptibility should be carefully considered when assessing whether transmission has likely occurred and the need for initiating contact tracing [34].

Close contacts of MDR- and XDR-TB patients should be tested for LTBI and TB according to national guidelines. Contacts in which TB disease has been excluded and who are diagnosed with LTBI should undergo an individual risk assessment to determine: i) the contact's risk for progression to TB disease; ii) the drug susceptibility pattern of the source case; and iii) the contact's risk for adverse events if initiating LTBI treatment [31, 32]. 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 TB disease [100, 103].

Involvement of local, community-based organisations (including community health care 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 [55, 104].

Clinicians and national programme managers are to interact with the relevant health authorities of host and/or home countries of TB patients belonging to migrant groups or mobile populations, to ensure continuum of care and contact investigation as appropriate [105].

### **Standard 19 (Changed)**

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 haematologic 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 [34, 103, 106, 107]. Similarly, both source finding and contact investigation should be initiated if a child with TB (any site of infection) has been identified and where no source has been identified [103, 108].

Individuals undergoing treatment with anti-TNF-alpha should be considered as high-risk contacts. According to the ESTC N°16, in individuals who are HIV-infected or affected by co-morbidities, treatment of latent infection should be promptly initiated if TB infection is identified by TST and/or IGRAs and active tuberculosis disease is excluded [31, 32, 34, 63, 109, 110].

Notes:

- As indicated in ESTC N°18, a comprehensive individual risk assessment and close clinical monitoring should be provided to close contacts of an MDR-TB or XDR-TB source case irrespective of the clinical advice regarding LTBI treatment [31, 100].
- Treatment for LTBI should be according to national and international recommendations, as outlined in ESTC N°16 [31, 107]

### **Standard 20** (*Changed*)

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 [12, 30].

If hospitalisation is required, clinicians should ensure that all newly admitted patients who are presumed to have infectious TB are subject to respiratory isolation until their diagnosis is confirmed or excluded [10].

In order to prevent transmission of tubercle bacilli to other patients, staff and/or visitors, smear-positive TB 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 [12, 111]. 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 [12, 111-113].

Notes:

- The implementation of an infection control plan is essential for the treating clinician and health facility as well as for the overall health system. Clinicians should maintain a dialogue within their health facility, develop a sound infection control plan, contributing with their technical expertise. The health facility should engage with all health care workers, non-medical staff, patients and

visitors and ensure optimal implementation, practice and monitoring of these infection control measures; all health care workers should be (re)trained in the infection control plan [10, 111, 114-116].

- It is important to have a designated infection control focal person with the required authority to ensure the implementation of the infection control plan.
- With regard to the need of isolating infectious tuberculosis patients, it is important to consider several options for isolation, and not only that of hospitalisation. For example, a patient with drug-susceptible TB who can be treated at home (i.e. no need for hospitalization due to severe health status), does not need to be hospitalized, as long as appropriate measures for treatment and infection control are ensured at the residence [111, 117, 118].
- Patients with a clinical indication for hospital admission, such as co-morbidities, should not be hospitalised in a general medical ward. Such patients should be placed in rooms that allow appropriate respiratory isolation.

#### **Standard 21** (*Unchanged*)

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) [23, 119]. 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 TB patients moving across the EU borders [1, 120-122].

#### **Supporting enablers to the ESTC**

In the process of developing the Standards and reaching consensus, the panel of experts identified the need and added-value of identifying and listing *supporting enablers* to the Standards. These are a resource for policymakers, clinicians, public health workers and other stakeholders to identify how best to adopt, adapt, introduce and implement the ESTCs in their setting with the ultimate goal of securing optimal TB care, prevention and control

- A. Formal adoption of the European Union Standards for Tuberculosis Care, for the care, prevention and control at national level. This current version of the ESTC is translated

into all EU languages. Thus, facilitating the endorsement by National Medical Associations and incorporation of the ESTC into training curricula of health staff [123].

- B. Development of consistent tuberculosis control and elimination strategies and policies according to the principles described in the End TB Strategy [2, 20, 22] and Tuberculosis Action Plan for WHO European Region 2016-2020 [21], taking into account best practices in and outside Europe [124, 125].
- C. Adoption of specific, updated, evidence-based tuberculosis and multidrug-resistant TB guidelines, together with mechanisms to update them on a regular basis and to monitor their implementation (audit- and or knowledge, attitudes and practices study (KAP study)-based) [22, 126-128].
- D. Planning and organisation of an adequate national laboratory network to ensure that a minimum, sufficient number, of mycobacteriology laboratories are in place, allowing implementation of the standards described in this document (adequate coverage of the country, adequate internal and external quality assurance procedures in place, sufficient numbers of samples per laboratory to ensure proficiency, availability of national laboratories with reference functions to support regional and local laboratories, etc.) [17, 18, 24].
- E. Development of policies ensuring the registration and continuous availability of all first- and second-line TB drugs and add-on agents (e.g. through coordinated procurement with partner countries for the drugs not registered in the country or which are necessary in small quantities) [22].
- F. Securing consistent and adequate funding for TB and MDR/XDR-TB care, prevention and control that is sufficient to run the activities mentioned in this document. This should include psycho-social support and coordination of care for all patients, as highlighted in the International Patients' Charter for rights to diagnosis and treatment. This applies particularly to patients belonging to vulnerable populations [22, 69, 129].



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**Table 1.** Core documents consulted for this update

	<b>Document</b>	<b>Type of publication</b>	<b>Year</b>	<b>Were systematic reviews conducted?</b>	<b>Was the GRADE approach applied?</b>	<b>Other relevant information</b>
<b>1</b>	WHO definitions and reporting framework for TB [23]	Policy document	2013	No	No	Developed through a consultation process
<b>2</b>	ISTC (3 <sup>rd</sup> edition) [10]	Standards of care	2014	No	No	Builds upon existing WHO guidelines and policy statements
<b>3</b>	WHO TB elimination framework for low-incidence countries [20]	Policy document	2014	No	No	Developed through revision of existing WHO policy documents and guidelines, and expert opinion consultation
<b>4</b>	WHO policy framework for implementation of TB diagnostics [24]	Policy document	2015	No	Yes	
<b>5</b>	ATS/CDC/IDSA guidelines for TB diagnosis [25]	Clinical guideline	2017	No	Yes	A comprehensive but non-systematic literature review was conducted to synthesize the evidence
<b>6</b>	ATS/IDSA/CDC guidelines for treatment of drug-susceptible TB [26, 27]	Clinical guideline	2016	Yes	Yes	
<b>7</b>	WHO treatment guidelines for drug-resistant TB [28, 29]	Clinical guideline	2016	Yes	Yes	
<b>8</b>	WHO treatment guidelines for drug-susceptible TB [30]	Clinical guideline	2017	Yes	Yes	
<b>9</b>	WHO guidelines on the management of latent TB infection [31, 32]	Clinical guideline	2015	Yes	Yes	
<b>10</b>	WHO compendium of guidelines and associated standards [12]	Policy document	2017	No	Yes	The document consolidates WHO policy recommendations and outlines WHO's standards for patient centre-care

ATS= American Thoracic Society; CDC= Centers for Disease Control and Prevention; GRADE= Grading of Recommendations Assessment, Development and Evaluation; IDSA=Infectious Diseases Society of America; ISTC= International Standards for Tuberculosis Care; TB= tuberculosis; WHO = World Health Organization

**Table 2.** Summary of changes in the second edition compared to the first edition of the European Union Standards for Tuberculosis Care.

Standard	Comparison with ESTC (1 <sup>st</sup> edition)	Description of the update
<b>Tuberculosis diagnosis</b>		
1	Unchanged	
2	Changed	Internationally recommended rapid (molecular) tests* added to the laboratory methods.
3	Changed	Internationally recommended rapid (molecular) tests* added to the laboratory methods.
4	Changed	Internationally recommended rapid (molecular) tests* added to the laboratory methods.
5	Unchanged	
6	Changed	Internationally recommended rapid (molecular) tests* added to the laboratory methods.
<b>Tuberculosis treatment</b>		
7	Changed	The importance of drug susceptibility testing for the selection of the treatment regimen is highlighted. In addition, patient-centred approaches are mentioned in the standard.
8	Changed	Highlighted that the assessment of drug resistance should be done using appropriate tests.
9	Changed	Simplified.
10	Changed	The need for conducting drug susceptibility testing is highlighted and monitoring of the response to treatment in patients with extrapulmonary tuberculosis and children is addressed.
11	Changed	The standard is harmonised with standards 2-4, 8 and 9.
12	Changed	The latest WHO-recommendations on treatment regimens are referenced.
13	Changed	The option of electronic records and the need for recording of treatment monitoring are included.
<b>Addressing HIV co-infection and co-morbidities</b>		
14	Changed	The importance of HIV testing for risk populations is highlighted.
15	Changed	The recommendation that all HIV-positive tuberculosis patients should be provided with antiretroviral therapy has been included.
16	Changed	Simplified to allow for alternative preventive treatment regimens.
17	Changed	Reworded.
<b>Public Health and tuberculosis prevention</b>		
18	Changed	Close contacts are specified.
19	Changed	The list of groups eligible for testing for latent tuberculosis infection has been extended. Reference is made to the WHO-recommended regimens for preventive treatment.
20	Changed	Reworded.
21	Unchanged	

WHO = World Health Organization. \* The term “internationally recommended rapid (molecular) tests” includes WHO-recommended tests.

- **Table 3.** WHO classification of anti-TB drugs [28]

<b>Group</b>	<b>Drugs</b>		<b>Abbreviation</b>
A. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin		Lfx Mfx Gfx
B. Second-line injectables	Amikacin Capreomycin Kanamycin (Streptomycin)		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 regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H <small>high-dose</small>
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate (Thioacetazone)	PAS Ipm Mpm Amx-Clv (T)