ECDC/ERS TASK FORCE REPORT

European Union Standards for Tuberculosis Care

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ABSTRACT: **The European Centre for Disease Prevention and Control (ECDC) and the European Respiratory Society (ERS) jointly developed European Union Standards for Tuberculosis Care (ESTC) aimed at providing European Union (EU)-tailored standards for the diagnosis, treatment and prevention of tuberculosis (TB).**

The International Standards for TB Care (ISTC) were developed in the global context and are not always adapted to the EU setting and practices. The majority of EU countries have the resources and capacity to implement higher standards to further secure quality TB diagnosis, treatment and prevention. On this basis, the ESTC were developed as standards specifically tailored to the EU setting.

A panel of 30 international experts, led by a writing group and the ERS and ECDC, identified and developed the 21 ESTC in the areas of diagnosis, treatment, HIV and comorbid conditions, and public health and prevention. The ISTCs formed the basis for the 21 standards, upon which additional EU adaptations and supplements were developed.

These patient-centred standards are targeted to clinicians and public health workers, providing an easy-to-use resource, guiding through all required activities to ensure optimal diagnosis, treatment and prevention of TB. These will support EU health programmes to identify and develop optimal procedures for TB care, control and elimination.

KEYWORDS: European Respiratory Society, European Union Standards, guidelines, MDR-TB, TB

With more than 80,000 tuberculosis (TB) cases notified in the European Union and European Economic Area (EU/EEA) Member States in 2009 (EU/EEA countries comprise Austria, Belgium, Bulgaria, 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, UK; while Switzerland is not in the EEA, Swiss nationals have the same rights as EEA nationals), 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, the contrasts in TB disease burden remain great within the sub-region [1]. Drug-resistant TB and multidrug-resistant TB (MDR-TB) pose a specific public health threat in some countries. Furthermore, assessing the prevalence of HIV co-infection among TB cases is still compromised by suboptimal reporting in several countries [1–3].

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 [1], a uniform set of guidelines summarising the minimum standards clinicians and healthcare workers should look at to guide their practice, was still lacking. The recent finalisation of the International Standards for

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Tuberculosis Care (ISTC) [1–4], developed in 2009 by 50 experts from 15 countries to include the perspectives of several organisations and international societies (which endorsed them for universal use), offered the opportunity to tackle this gap in the EU.

The ISTC [1–4] prescribe a widely accepted level of TB care which guides all healthcare providers and clinicians, both public and private, in achieving optimal standards in managing patients who have, or are suspected of having, active TB. The 21 ISTCs [4] are organised into 4 sections: 1) standards for diagnosis, 2) standards for treatment, 3) standards for addressing HIV co-infection and other comorbid conditions and 4) standards for public health.

The standards, seen as ''a living document that will be revised as technology, resources and circumstances change'', are designed to complement existing national or international guidelines, and are consistent with World Health Organization (WHO) definitions and recommendations.

The specific characteristics of the EU/EEA Member States which justify the need to develop standards specifically tailored to the European context are [1, 2]:

1) The majority of EU/EEA countries have a low incidence of TB; however, a heterogeneous setting exists with a number of Member States having high and intermediate TB levels, with varying levels of MDR-TB and TB-HIV co-infection. Also a number of countries border non-EU countries with a higher TB and MDR-TB burden.

2) TB services are fully integrated and merged within the health system in the majority of EU/EEA countries. This presents peculiarities in allocating responsibilities for the optimal delivery of TB care.

3) The EU/EEA countries have a long-established tradition of TB control that has evolved over past decades. New tools and high standards of diagnosis and care are often implemented in EU/EEA countries.

4) The EU/EEA countries are committed to pursue elimination of TB, sharing a common platform based on the Wolfheze documents; the Framework action plan to fight TB in the EU; Progressing towards TB elimination, and the European Centre of Disease Prevention and Control (ECDC)-driven surveillance system [5–14].

In spite of efforts to introduce ISTCs among EU/EEA healthcare providers (including clinicians), their implementation has been suboptimal. A tailored set of standards present the potential to improve acceptability among clinical networks.

METHODS
A collaborative process, jointly led by the ECDC and the European Respiratory Society (ERS), was initiated to adapt the ISTCs to the EU/EEA setting and to develop the EU Standards for Tuberculosis Care (ESTC). While ERS has taken the lead in developing the clinically-related standards, ECDC has done the same for the public health standards.

A panel of more than 30 experts was convened representing the ERS and other international societies (American Thoracic Society (ATS), ECDC, national TB programmes and civil society (affected communities)) and organisations (WHO,

International Union against Tuberculosis and Lung Diseases (the Union, Europe Region) and KNCV Tuberculosis Foundation). Within this group, a writing committee consisting of eight experts was identified to lead the consensus and writing process of the document.

A non-systematic review of the evidence relevant for the development of the ESTC was performed (including the peer-reviewed manuscripts and systematic reviews/meta-analyses included in the ISTC document and those published after the second edition of the ISTC) to support the development of the document.

A Delphi process was performed to define the list of standards based on prior evidence [1, 2].

The panel of experts was asked to assign priorities to the first draft of 45 proposed standards and to complete the literature synopsis of the standards-supporting evidence with a score ranging from 5 (high relevance) to 1 (low relevance). Based on the results of the Delphi process, the draft concept of the standards and the literature synopsis were completed and circulated within the panel of experts for two rounds of review, comments and additions. Consensus was at this stage reached to formulate the standards around the existing four sections of the ISTCs (diagnosis, treatment, clinical management of TB/HIV and comorbidities, and public health and prevention). The Delphi exercise was completed by 85% of the panel of experts, with the main score per area being high, ranging between 4.04 and 4.74. The literature synopsis was also scored and 21 references were added to the 97 initially proposed.

The ESTC have been specifically developed to complement the ISTCs and other existing guidelines, being based mainly, but not exclusively, on the existing gaps in case management that were identified in a recent European MDR-TB case management survey as well as the survey of TB surveillance systems in low-incidence countries, including countries of the EU/EEA [2].

In the process of developing the standards and reaching a consensus, the panel of experts further identified the need and added value of complementing the standards with supporting enablers. These are aimed as a resource for policy makers, clinicians, public health workers and stakeholders as a support to identify resources and suggestions on how best to adopt, adapt, introduce and implement the ESTC in their setting.

The concept of ESTC was first presented and discussed in a symposium at the 2010 ERS Congress in Barcelona. Three working meetings between ERS and ECDC experts and a vis-à-vis meeting of the expert writing committee were organised in 2011, preceding circulation of the draft document to the entire expert panel. The draft ESTC document was presented and discussed further during a symposium at the September 2011 ERS conference in Amsterdam and finalised in October 2011 before going through an official clearance process of the ERS and the ECDC.

HOW TO READ THE DOCUMENT
Under four sections (diagnosis, treatment, HIV and comorbidities, and public health), 21 standards are defined, which correspond to those of the ISTC. Using the ISTC as a basis, the EU Standards for TB care were developed and are listed as either:

1) ''Valid'': the corresponding ISTC has been maintained and is considered the EU standard. When an ISTC was maintained as ''valid'', none-to-minimal wording will have been adapted to update to the EU-definition; *i.e.* smear-positive cases are now defined as culture-positive in diagnosis standards. Otherwise the original wording from the ISTC has been maintained in order to ensure consistency and comparability between the two documents.

2) ''Valid with an EU-adapted supplement'': the corresponding ISTC has been maintained but with an additional EU component that covers the minimal requirement for standards in the EU; as defined by the expert groups and EU definitions.

3) ''Replaces standard x'': the corresponding ISTC has been modified extensively in order to fit in with EU definitions and requirements.

When necessary, notes are listed after each standard to further define and explain specific components that the expert group deemed important to clarify. Where a standard replaces an ISTC, the original wording of the ISTC is listed under the heading Replaced ISTC at the end of the document.

STANDARDS FOR TB DIAGNOSIS
Standard 1 (replaces ISTC 1[*])

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

Notes
1) The most common symptoms of pulmonary TB are persistent cough with or without sputum production for more than 2–3 weeks [4], while haemoptysis (blood in mucus) is more rare. Respiratory symptoms can be accompanied by fever, night sweats and weight loss. These signs and symptoms are common in a wide range of respiratory conditions including acute respiratory infections and acute exacerbation of chronic obstructive pulmonary disease. It is also possible for patients to present with no signs and symptoms of disease [15]. For extrapulmonary TB, TB organ-specific signs and symptoms may occur.

2) It is important to investigate the history of the patient with regard to TB. For example, history of TB in the family context, history of previous contact with TB and previous TB diagnosis and/or treatment, and any condition attenuating the host immune system [4] are common risk factors for TB that should be considered as relevant to guide the correct diagnosis.

3) In the EU setting, TB is not the leading cause of persistent cough and, thus, cough is not the leading sign or symptom of TB disease. Based on its expert knowledge and experience of the EU setting and the current evidence [16] the expert group therefore adapted this first standard to better describe a patient who should be evaluated for TB disease in the EU-setting.

Standard 2 (replaces ISTC 2[#])

All patients (adults, adolescents and children who are capable of producing sputum) suspected of having pulmonary TB should have at least two sputum specimens submitted for microscopic examination, culture and drug susceptibility

testing (DST) in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained. In countries, settings or populations in which MDR-TB is suspected in a patient, rapid testing for the identification of rifampicin- and isoniazid-resistance, using validated tools in a quality-assured laboratory, should be performed.

Notes
1) Based on the EU/EEA practice and definitions [13, 14, 17], quality-assured DST should be performed on all diagnosed TB patients to rule out drug resistance [5–14]. This should follow international standards and guidelines with regard to methods used and drug concentrations, for testing of first- and second-line drugs [8–10]. Samples sent for bacteriological examinations (sputum smear, culture, DST and 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 [8–10, 18–21].

2) There are two categories of risk factors for MDR-TB: patient risk factors and setting risk factors [22, 23], which need to be considered when assessing the risk for MDR-TB [24]. Previous contact with MDR-TB patients and previous history of TB treatment are two key patient risk factors for MDR-TB. Originating from settings with a high prevalence of MDR-TB (*e.g.* Eastern European countries) are further relevant risk factors for MDR-TB [18, 25–28].

3) Countries should transform the process of risk assessment into guidelines and adapt them to their national needs [4, 7].

4) Quality bacteriological diagnosis includes the WHO recommended rapid molecular assays, which should be performed as early as possible (ideally on the same day as diagnosis) within evidence-based diagnostic algorithms and guidelines. Currently available methods are the automated real-time nucleic acid amplification technology for rapid and simultaneous detection of *Mycobacterium tuberculosis* and rifampicin resistance, and the line probe assays for rapid *M. tuberculosis* detection and rifampicin resistance or rifampicin and/or isoniazid resistance testing [19, 29, 30]. 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) [19–21, 29, 30, 31]. All molecular diagnostic results must be confirmed further by culture-based DST. All identified MDR-TB cases should be managed by specialised centres directly upon diagnosis and a second independent molecular test with a different technology should be performed to confirm the rapid diagnosis [32–37].

5) The choice of molecular methods for the rapid identification of rifampicin resistance and isoniazid resistance should be that of WHO-endorsed rapid diagnostic assays [29].

6) Optimal, clear and direct communication between the laboratory experts and clinicians is essential to obtain the optimal link of diagnosis and choice of treatment. The clinician needs to be informed whether the laboratory performs DST for second-line drugs and on which drugs. Furthermore, they need to be informed on whether proficiency testing (external quality assurance) for all provided DST methods is implemented according to evidence-based guidelines. The clinician

needs to ensure that the bacteriological sample undergoes first- and second-line DST according to evidence-based guidelines [8–10, 18, 38].

7) Based on feasibility and cost-effectiveness analyses, the WHO and the ISTC recommend the collection of at least two sputum samples for diagnosis. Given that the collection of a third 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) [4, 39, 40].

8) It is essential to obtain quality sputum samples in order to ensure quality and reliable bacteriological testing of the sample [4, 39]. This includes ensuring appropriate collection, storage, transportation and processing of sputum samples, as well as obtaining at least one early morning sample from the patient.

9) All the procedures aimed at obtaining samples for culture and DST should be used whenever possible according to evidence-based guidelines (sputum induction, bronchoscopy and gastric lavage in children).

Standard 3 (replaces ISTC 3¶)

For all patients (adults, adolescents and children) suspected of having extrapulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, DST and histopathological examination in a quality-assured laboratory. In countries, settings or populations in which MDR-TB is suspected in a patient, rapid testing for the identification of rifampicin and isoniazid resistance in a quality-assured laboratory could be performed.

Notes
1) This third standard has been accordingly updated to be in line with standards 1 and 2 with regard to essential, standard diagnosis.

2) It is essential to obtain bacteriological confirmation from extrapulmonary sites in order to confirm diagnosis and consequently provide optimal and effective treatment; this may include the more sensitive molecular test [4].

Standard 4 (replaces ISTC 4+)

All persons with chest radiographic findings suggestive of pulmonary TB should have sputum specimens submitted for microscopic examination, culture and DST in a quality-assured laboratory. In countries, settings or populations in which MDR-TB is suspected in a patient, rapid testing for the identification of rifampicin resistance and when possible isoniazid resistance in a quality-assured laboratory should be performed.

Notes
1) This standard has been updated to be consistent with the standards 1 and 2 with regard to essential, standard diagnosis [4].

Standard 5 (ISTC 5 valid with an EU-adapted supplement)

The diagnosis of culture-negative pulmonary TB 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 are compatible with TB; and there is a lack of response to a trial of broad spectrum antimicrobial agents (because the fluoro-quinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with TB, they should be avoided). In persons who are seriously ill or have known or suspected HIV infection or have any immune-compromising conditions, the diagnostic evaluation should be expedited and, if clinical evidence strongly suggests TB, a course of anti-TB treatment should be initiated.

EU-adapted supplement
As the EU has adopted the culture-based case definition, the main distinction of TB cases should be between culture-positive and -negative cases, and not sputum smear status [5, 8, 11, 41].

In order to ensure quality diagnosis of both pulmonary and extrapulmonary TB, adequate samples for bacteriological examination should be obtained and processed using available diagnostic tools (*e.g.* induced sputum, bronchoscopy and bronchoalveolar lavage, and gastric washing) [4, 42–44], and complemented by imaging (radiology, computed tomography and magnetic resonance imaging) and other necessary examinations performed according to evidence-based guidelines [4, 32, 35, 45, 46].

Culture, DST and rapid molecular testing should be performed on each sample from both pulmonary and extrapulmonary TB, including samples obtained through surgery or other invasive procedures which usually undergo histological examinations [5, 8, 11, 41].

Surgeons should be advised to save a biological specimen in normal saline for microbiological and molecular biological examinations and in formalin for histopathological examinations.

Notes
1) Other existing new diagnostic tools, *e.g.* additional nucleic acid amplification techniques and other new techniques in the development pipeline, after necessary validation has been achieved, should be used within evidence-based diagnostic algorithms and guidelines [19, 29, 46–54]. Before introducing any new tool or approach, the evidence has to be validated and have shown efficacy and patient value.

Standard 6 (ISTC 6 valid until specific EU paediatric standards are available, with an EU-adapted supplement)

In all children suspected of having intrathoracic (*i.e.* pulmonary, pleural, and mediastinal or hilar lymph node) TB, bacteriological confirmation should be sought through examination of appropriate biological samples (by expectoration or induced sputum, bronchial secretions, pleural fluid or gastric washings) for smear microscopy, culture and DST in a quality-assured laboratory. In the event of negative bacteriological results, a diagnosis of TB should be based on the presence of abnormalities consistent with TB on chest radiography or other imaging, a history of exposure to an infectious case, evidence of TB infection (positive tuberculin skin test (TST) and/or interferon-γ release assay (IGRA)) and clinical findings

suggestive of TB. For children suspected of having extra-pulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.

EU-adapted supplement
Once TB is confirmed in a child, as defined previously, standards 2–5 should be followed for complete diagnosis of the case [4, 55].

Notes
1) With the exception of two clarifications (use of the term ''appropriate biological samples''; and for smear microscopy, culture and DST in a quality-assured laboratory), this ESTC is the same as the ISTC 6 for paediatric diagnosis [4].

2) ISTC 6 is valid until specific EU paediatric standards are available.

3) Rapid DST testing could/should be considered in order to obtain a rapid, preliminary diagnosis. However, research is still ongoing to validate new molecular methods in this group.

STANDARDS FOR TB TREATMENT
Standard 7 (ISTC 7 valid)

Any practitioner treating a patient for TB 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 must not only prescribe an appropriate regimen, but also utilise local public and/or community health services, agencies and resources when necessary, to perform contact investigation, to assess the adherence of the patient and to address poor adherence when it occurs.

Notes
1) The ISTC was maintained with the inclusion of naming the need to involve community health services so as to highlight the important role of civil society in patient treatment and adherence [4, 56, 57].

Standard 8 (ISTC 8 valid with an EU-adapted supplement)

All patients (including those with HIV-infection) who have not been previously treated and without any risk factors for drug resistance should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase should consist of isoniazid and rifampicin given for four months (2HRZE/4HR). The doses of anti-TB 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 are highly recommended.

EU-adapted supplement
The selection of standardised regimens for WHO category I and III patients (*i.e.* new pulmonary sputum smear-positive and new sputum smear-negative/extrapulmonary cases) should be performed according to international recommendations in centres having the necessary expertise, as defined at the national

level and based on the number of cases managed every year and other relevant parameters [4, 32, 35, 40, 58, 59]. The clinician should ensure the correct drug regimen (including four active drugs for the intensive phase of treatment) at the correct dose for a sufficient duration. The daily dosage is recommended at least during the intensive phase of treatment.

Based on confirmed DST results, treatment must be adapted according to the drug-susceptibility pattern [4, 32, 34–37, 40, 58, 59].

Ideally, MDR-TB should be excluded in all TB cases. Retreatment cases should be managed according to the individual risk of MDR-TB until multi-drug resistance is excluded [24, 33, 34, 36, 37, 60].

This standard has implications for the standards of diagnosis, treatment and infection control.

Standard 9 (ISTC 9 valid)

To assess and foster adherence, a patient-centred approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients.

Supervision and support should be individualised and should draw on the full range of recommended interventions and available support services, including patient counselling and education. 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 when it occurs. These measures should be tailored to the individual patient's circumstances, based on a detailed anamnesis of the patient's clinical and social history, and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed treatment) and identification and training of a treatment supporter (for TB 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 psychosocial supports, may also serve to enhance treatment adherence [4, 61, 62].

Standard 10 (ISTC 10 valid with an EU-adapted supplement)

Response to therapy in patients with pulmonary TB should be monitored by follow-up smear microscopy and culture at the time of completion of the initial phase of treatment (two months for drug-susceptible TB). If the sputum smear and culture are positive at completion of the initial phase, sputum smears should be examined again at three months and, if positive, drug susceptibility testing should be performed. In patients with extrapulmonary TB and in children unable to produce sputum, the response to treatment is assessed clinically.

EU-adapted supplement
Treatment monitoring of MDR-TB cases should be performed based on sputum smear and culture on a monthly basis [34]. The practices for treatment monitoring should be performed according to international guidelines [40].

Standard 11 (replaces ISTC 11[§], see also ESTC 1, 2 and 3)

An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms and the community prevalence of drug resistance, should be obtained for all patients. Rapid testing, including rapid rifampicin and isoniazid resistance testing should be performed for all patients suspected of resistance as defined in standards 2 and 8. Furthermore, patient counselling and education should begin immediately for all TB 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.

Notes

1) This standard emphasises the need to use the WHO-recommended rapid molecular assays to rapidly rule out or confirm suspicions of MDR-TB, as described in standards 2 and 8.

2) As expressed in standard 2, rapid molecular testing for rifampicin and isoniazid resistance does not rule out the requirement to perform standard DST to confirm results from the molecular test as well as perform the comprehensive standard DST.

Standard 12 (replaces ISTC 12[ƒ])

Patients with, or highly likely to have, TB caused by drug-resistant (especially MDR/extensively drug-resistant (XDR)-TB) organisms should be treated with specialised regimens containing second-line anti-TB drugs. The regimen chosen may be standardised or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known, or presumed, to be susceptible to, including an injectable agent and pyrazinamide, should be used. Treatment should be given for at least 20 months, the recommended intensive phase of treatment being 8 months (instead of 6 months as in previous recommendations; see below the EU adaptations for further detail).

EU-adapted supplement

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 psychosocial support are required to ensure adherence. This is particularly important given that these patients often belong to socially and economically disadvantaged groups.

For the treatment of MDR-TB, the addition of pyrazinamide to a minimum of four second-line anti-TB drugs likely to be "effective" is recommended, including the use of second-line injectable drugs, as well as the use of fluoroquinolones (earlier generations of fluoroquinolones, ciprofloxacin and ofloxacin, are no longer recommended when later generation fluoroquinolones, levofloxacin or moxifloxacin, are available) and ethionamide (or prothionamide) and either cycloserine or p-aminosalicylic acid if cycloserine cannot be used [34].

Second-line DST should be performed to confirm the drug resistance pattern and to guide the correct choice of treatment.

Adverse events following prescription of second-line drugs should be managed according to international recommendations with the aim to limit the probability of losing an effective drug due to such adverse events [1–32].

Adverse events and the decision to start, modify or interrupt a second-line regimen should ideally be managed by a team of experts (*e.g.* ''Consilium'' or similar body) and not by individual physicians, in order to minimise mistakes and share responsibilities as well as share experience and expertise. All efforts should be made to avoid development of additional drug resistance [4, 36, 37, 63].

In addition to chemotherapy, surgery has proven to be effective in selected cases [37].

Notes

1) In order to prevent the selection of resistant *M. tuberculosis* mutants it is essential to treat with more than one effective drug and a minimum of four effective drugs. It is therefore essential not to add only one or two effective drugs to a failing regimen [36, 64–75].

Standard 13 (ISTC 13 valid with an EU-adapted supplement)

A written record of all medications given, bacteriological response and adverse reactions should be maintained for all patients.

EU-adapted supplement

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 and changes in the regimen, *etc.*) and compliance, 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 is moved to another health unit [76, 77].

Notes

1) Reporting forms for the described documentation can be obtained from several sources, some of which are listed here [2, 12, 41, 78].

STANDARDS FOR ADDRESSING HIV INFECTION AND COMORBID CONDITIONS

Standard 14 (replaces ISTC 14[**])

HIV testing and counselling should be recommended to all patients with, or suspected of having, TB. 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 and in patients with symptoms and/or signs of HIV-related conditions. Because of the close relationship between TB and HIV infection, integrated approaches to prevention and treatment of both infections are recommended.

Notes

1) The aspect related to the setting and choice of offering HIV testing was removed from the ESTC as it was deemed not

relevant to the EU setting. Rather, in the EU it is considered highly feasible to offer HIV testing to all TB patients. Furthermore, it is considered important that integrated TB-HIV management approaches be formed in the EU setting, regardless of the prevalence [79–86].

Standard 15 (replaces ISTC 15##)

All patients with TB and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for TB, according to the severity of their immunodeficiency. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for TB should not be delayed and the antiretroviral treatment prescribed as soon as possible based on evidence.

Notes
1) The consideration of treatment with cotrimoxazole 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 decisions to provide prophylactic treatment against infections other than TB.

Standard 16 (ISTC 16 valid with an EU-adapted supplement)

Persons with HIV 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 TB should be treated with isoniazid for 6–9 months or any new regimen for which evidence becomes available.

EU-adapted supplement
In persons with known HIV infection in whom LTBI is confirmed or highly probable, and in whom active TB is excluded, LTBI preventive treatment with isoniazid should be provided [84, 87–90].

As HIV infection is known to increase the probability of developing TB disease upon infection, HIV-seropositive persons who have been in contact of an index case harbouring an MDR-TB strain, should undergo strict regular clinical follow-up, allowing rapid initiation of specialised treatment in case of disease development. While waiting for, or in the absence of isolation of the responsible strain, the treatment should be based on the index case's drug-susceptibility pattern (see also ESTC standards for diagnosis and treatment).

Strict clinical monitoring and no treatment of latent infection should be provided if the index case is affected by an MDR-TB strain [4].

The ESTC above should also be applicable for persons with comorbidities or on treatments that increase the risk for TB reactivation.

Notes
1) Comorbidities for reactivation of TB, other than HIV infection, encompass conditions that decrease the host immune response, some of which are: diabetes mellitus, treatment with tumour necrosis factor (TNF)-antagonists, cancer chemotherapy and treatment with high-dose corticosteroids, *etc.* [90, 91].

Standard 17 (ISTC 17 valid with an EU-adapted supplement)

All providers should conduct a thorough assessment of conditions that could affect TB 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, of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programmes, tobacco smoking cessation programmes and other psychosocial support services, or to such services as antenatal or well-baby care.

EU-adapted supplement
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 in the remaining WHO package [79, 80, 82–84].

STANDARDS FOR PUBLIC HEALTH AND TB PREVENTION

Standard 18 (ISTC 18 valid with an EU-adapted supplement)

All providers of care for patients with TB should ensure that persons who are in close contact with patients who have infectious TB (*e.g.* in families, congregate settings like migrants shelters, schools and prisons), are evaluated and managed in line with international recommendations. The risk of TB transmission depends on the concentration of the mycobacteria in the air, the duration of the contact and the susceptibility of the contact to infection and disease. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed TB; 2) is at high risk of having been infected by the index case; 3) is at high risk of developing TB if infected; and 4) is at risk of having severe TB if the disease develops.

EU-adapted supplement
Individuals undergoing treatment with TNF-antagonists should be considered as high-risk contacts. According to ESTC number 16, in individuals who are HIV infected or affected by comorbidities, treatment of latent infection should be promptly initiated if TB infection is identified by TST and/or IGRAs and active TB disease is excluded [92–96]. In case of contact with an MDR-TB index case, strict clinical monitoring should be provided, as there is no evidence that treatment of latent infection with available drugs is presently effective.

Notes
1) The bullets listing the levels of priority for initiating contact investigation as described in the ISTC have been removed from the ESTC, as they were considered not to be relevant for the EU setting. Rather, an introductory sentence was added stating the determinants of TB transmission that should be considered when assessing whether transmission has occurred and the need for initiating contact tracing [46, 60, 94, 95, 97].

Standard 19 (ISTC 19 valid with an EU-adapted supplement)

Children under 5 yrs of age and persons of any age with HIV infection who are close contacts of an infectious index patient

and who, after careful evaluation, do not have active TB, should be treated for presumed latent TB infection with isoniazid.

EU-adapted supplement
As per previous ESTC, strict clinical monitoring and no treatment of latent infection should be provided if the index case is affected by an MDR-TB strain [4].

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 [94, 98–100].

Notes
1) Preventive treatment for presumed latent TB infection should be according to national and international recommendations [87, 89].

Standard 20 (ISTC 20 valid with an EU-adapted supplement)
Each healthcare facility caring for patients who have, or are suspected of having infectious TB, should develop and implement an appropriate TB infection control plan.

EU-adapted supplement
Clinicians should ensure that all newly admitted patients who are suspected of having infectious TB are subject to respiratory isolation until their diagnosis is confirmed and excluded [4].

In order to prevent transmission of mycobacteria to other patients, staff and/or visitors and smear-positive TB patients should ideally be isolated in appropriate rooms until they achieve bacteriological conversion (negative-sputum microscopy). Patients suspected of having TB (if feasible) and MDR-TB patients (strongly recommended) should be isolated in negative-pressure ventilation rooms.

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 [97]. Adequate administrative measures for TB 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 also be included in the infection control plan. Infection control committees, which cover airborne diseases, and includes infection control experts, should also be implemented [60, 97].

Notes
1) The implementation of an infection control plan is essential for the treating clinician, health facility and the overall health system. Clinicians should maintain dialogue within their health facility; develop a sound infection control plan, and their technical expertise. The health facility should engage with all healthcare workers, non-medical staff, patients and visitors and ensure optimal implementation, practice and monitoring of these infection control measures; all healthcare workers

should be (re)trained in the infection control plan [4, 38, 97, 101].

2) With regard to the need of isolating infectious TB patients, it is important to consider several options for isolation, and not only that of hospitalisation. For example, a patient with drug-susceptible TB that can be treated at home (*i.e.* no need for hospitalisation due to severe health status), does not need to be hospitalised, as long as appropriate measures for treatment and infection control are ensured at the residence [97, 102, 103].

3) Patients with a clinical indication for hospital admission, such as comorbidities, should not be hospitalised in a general medical ward. Ideally such patients should be placed in rooms that allow appropriate respiratory isolation. It is therefore important to have a designated infection control focal person with the required authority to ensure implementation of the infection control plan.

Standard 21 (ISTC 21 valid with an EU-adapted supplement)
All providers must report both new and retreatment TB cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

EU-adapted supplement
Clinicians should perform treatment outcome evaluations in their clinical unit at regular time intervals (*e.g.* quarterly) [6, 104, 105]. 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 own cases. This principle is also applicable to TB patients moving across the EU borders [5, 13, 25, 106, 107].

SUPPORTING ENABLERS TO THE ESTC
In the process of developing the standards and reaching a 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 policy makers, clinicians, public health workers and other stakeholders to identify how best to adopt, adapt, introduce and implement the ESTC in their setting with the ultimate goal of securing optimal TB care, prevention and control [2, 4, 12, 38, 60]. They are as follows:

1) Formal adoption of the European Standards for Tuberculosis Care, for the care, prevention and control, ideally translated into the country-specific language(s) after their endorsement by national medical associations. Ideally the ESTC should be incorporated into training curricula of health staff [108].

2) Development of consistent TB control and elimination strategies and policies according to the principles described in

the new European Framework [7] and the Framework action plan to fight TB in the EU and its follow-up [109–112].

3) Adoption of specific, updated, evidence-based TB and MDR-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-based) [63, 113, 114].

4) Planning and organisation of an adequate national laboratory network to ensure that a minimum and 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.*).

5) Development of policies ensuring a continuous availability of all first- and second-line TB drugs (*e.g.* through coordinated procurement with partner countries for the drugs not registered in the country or which are necessary in small quantities) [19, 110, 115].

6) 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 psychosocial 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 [57, 107, 116–118].

REPLACED ISTC
*ISTC 1: all persons with otherwise unexplained productive cough lasting 2–3 weeks or more should be evaluated for TB.

#ISTC 2: all patients (adults, adolescents and children who are capable of producing sputum) suspected of having pulmonary TB should have at least two sputum specimens submitted for microscopic examination in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained.

¶ISTC 3: for all patients (adults, adolescents and children) suspected of having extrapulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture and histopathological examination.

+ISTC 4: all persons with chest radiographic findings suggestive of TB should have sputum specimens submitted for microbiological examination.

§ISTC 11: an assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms and the community prevalence of drug resistance, should be obtained for all patients. DST should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear-positive at completion of three months of treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is

considered to be likely, culture and testing for susceptibility/resistance to at least isoniazid and rifampicin should be performed promptly. Patient counselling and education should begin immediately to minimise the potential for transmission. Infection control measures appropriate to the setting should be applied.

ƒISTC 12: patients with, or highly likely to have, TB caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialised regimens containing second-line anti-TB drugs. The regimen chosen may be standardised or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used and treatment should be given for at least 18–24 months beyond culture conversion. Patient-centred measures, including observation of treatment, are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR-TB should be obtained.

**ISTC 14: HIV testing and counselling should be recommended to all patients with, or suspected of having, TB. Testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of a high risk of HIV exposure. Because of the close relationship between TB and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

##ISTC 15: all patients with TB and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for TB. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for TB should not be delayed. Patients with TB and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

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