



SCIENTIFIC ADVICE

Expert Opinion on the introduction of new drugs for tuberculosis control in the EU/EEA

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EU/EEA**



This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Andreas Sandgren and produced by an ECDC editorial team consisting of Andreas Sandgren, Marieke J. van der Werf, the working groups and the ad hoc expert panel with the chair Tuula Vasankari. For a list of the experts involved in the work, see Appendix 1.

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Declarations of interest were received from the working groups and the ad hoc expert panel members in accordance with ECDC's Independence Policy (see Appendix 1 for interests declared by two of the ad hoc expert panel members) and no conflict was identified.

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Abbreviations

EU/EEA	European Union/European Economic Area
TB	Tuberculosis
MDR TB	Multidrug-resistant tuberculosis
XDR TB	Extensively-resistant tuberculosis
WHO	World Health Organization
CSO	Civil Society Organisation

Executive summary

Introduce new tuberculosis drugs and regimens responsibly

New drugs are becoming available for the treatment of multidrug-resistant tuberculosis (TB). There is also progress in developing new regimens of existing drugs to shorten the treatment duration of drug-susceptible and resistant tuberculosis. Facilitating rapid access to these drugs and regimens is important for the patients in need of them, but the adoption of the new drugs and regimens must be done responsibly to avoid inappropriate use.

The challenges and opportunities in the European Union and European Economic Area

The European Union and European Economic Area (EU/EEA) is a relatively low tuberculosis incidence setting, but there is a wide heterogeneity across Member States, with some struggling with a large number of multidrug-resistant tuberculosis cases. Treatment success rates of multidrug-resistant tuberculosis also vary widely between Member States with some having only very low success rates. Most patients with an unsuccessful treatment outcome can potentially benefit from the introduction of the new drugs. The introduction of new drugs offers an opportunity to EU/EEA Member States of advancing towards the elimination of TB. We need to use this opportunity, and this requires carefully addressing the steps Member States need to take to introduce not only new drugs but also repurposed drugs and regimens responsibly.

Need for public health guidance

The introduction of new tuberculosis drugs is a complex process that needs careful planning at various levels within Member States. There is a need to provide guidance on how to safely adopt these drugs at a programmatic level and for clinical guidelines for their use in the treatment of tuberculosis patients. This document addresses the first need, and is based on expert opinions which outline options for developing an optimal strategy for introduction of new TB drugs at the national level, building on global plans for introducing new drugs and taking into consideration the specificities of the EU/EEA.

Pre-conditions that need to be met before the introduction

The document reflects on 'pre-conditions' that are essential to be in place at the national level before even starting to consider the introduction and use of the new and repurposed drugs and regimens. Member States should ensure that there is appropriate diagnostic capacity and good clinical and operational case management of all TB cases, including those with drug-resistant TB. Adequate laboratory facilities for drug susceptibility testing of all relevant drugs should be in place. If proper patient management is not in place, the risk for development of resistance to the new drugs outweighs the benefit expected from them. Appropriate surveillance systems need to be in place to be able to rationalise the priority target groups and assess effects of introduction.

Expert opinions on what to specifically consider when introducing new drugs

To accomplish a responsible introduction, countries are encouraged to develop policies and guidelines on certain 'specific considerations' in order to successfully implement new TB drugs and regimens. The specific considerations are divided into programmatic, ethical, and monitoring and evaluation considerations. In the planning of the introduction, it is necessary to consider the individual country's legal requirements for the registration of a new drug. The possibility of compassionate use before registration should be considered. Continuous availability of the new drug should be ensured and clear clinical guidelines for use should be adopted. Patients must be informed and educated, and civil society and patient organisations involved. The development and use of additional indicators to monitor and evaluate the effect of new drugs and regimens should be considered.

Conclusions

It is essential that the new drugs, but also new regimens of existing and repurposed drugs, are optimally adopted in TB control programmes, and implemented in a rational, cost-effective and safe way to have maximum public health impact and to avoid inappropriate use and development of resistance to these drugs. This document is aimed at providing information on the steps countries need to consider towards implementing the use of new drugs and regimens, in order to build responsible national strategies and plans.

Background

Introduction

The rational use of antibiotics is crucial in order to ensure their continuing effectiveness, and remains an important global priority now and in the future. Due to drug resistance, not all tuberculosis (TB) patients can be treated effectively with available drugs, as some patients are resistant to most drugs available making it very difficult to design an adequate treatment regimen [3]. In recent years, progress has been made in the clinical development pipeline for drugs to be used in the treatment of TB. These new drugs could have the potential to become part of future regimens that could positively affect TB control. It is essential that the new drugs, but also new regimens of existing drugs, are optimally adopted in TB control programmes, and implemented in a rational way in order to have maximum public health impact, and to avoid inappropriate use and development of resistance to them.

TB treatment in the European Union and European Economic Area

Due to the nature of the disease, TB is always treated with a regimen consisting of at least four different drugs. Currently, EU/EEA Member States follow the European Standards for TB Care, or similar guidelines for the treatment and management of TB cases [4]. Due to the long duration of treatment and the large number of drugs needed, treatment of multidrug-resistant (MDR) TB is even more challenging than treatment of drug sensitive (DS) TB, and treatment outcomes are often suboptimal [2]. The treatment success rate of all TB cases for the treatment cohort 2012 was 73.5% [2]. The MDR TB treatment success rate was much lower with 37.8% of the MDR TB cases having a successful treatment outcome for the 2011 treatment cohort (range between countries 0–75%) [2]. The extensively drug-resistant (XDR) TB treatment success rate for the 2010 treatment cohort was only 25.9% (range between countries 0–100%) [2].

New drugs that could be included to strengthen current regimens are desperately needed to improve TB treatment. Also shorter, more efficacious and less toxic oral regimens for treatment of both drug sensitive (DS) TB and MDR TB need to be made available at a lower cost.

Two new drugs, Bedaquiline (in the medicinal product Sirturo produced by Janssen) and Delamanid (in the medicinal product Delyba produced by Otsuka) have been authorised EU-wide for treatment of TB [5]. In addition to these, other drug candidates are being evaluated and will become available in the near future. There are several on-going trials that aim to find a better regimen for treating active TB than the current standard regimen. These studies include new drug candidates in early phases of development, with some of them already in phase III trials [6]. In addition to the new drugs, there are a number of repurposed drugs (drugs that originally were developed for other infections) that are now tested and used for the treatment of TB.

Specific contribution of this expert opinion for EU/EEA Member States

Large differences in TB epidemiology exist between EU/EEA Member States (see Box 1).

Box 1. Tuberculosis (TB) epidemiology in 2013 in the EU/EEA at a glance. Data from the tuberculosis surveillance and monitoring report 2015 [2].

In 2013 across the EU/EEA:

- 64 844 TB cases
- 12.7 TB cases per 100 000 population (range 3.4 to 83.5).
- 86.9% drug susceptibility test results for isoniazid and rifampicin among laboratory-confirmed TB cases
- 4.1% MDR TB among laboratory-confirmed TB cases (range 0 to 22.7%)
- 2.4% MDR TB among new laboratory-confirmed TB cases (range 0 to 16.6%)
- 16.6% MDR TB among previously treated laboratory-confirmed TB cases (range 0 to 100%)
- 169 XDR TB cases were reported in the EU/EEA
- 17.5% XDR TB among tested MDR TB cases

Overall, the EU/EEA is a relatively low-incidence setting, and notification rates are continuing to decline. Notification rates were below 20 per 100 000 population in 24 Member States, and below 10 per 100 000 in 18 Member States in 2013 [2]. Thus more and more EU/EEA Member States are entering the TB elimination phase. To reach elimination goals and targets set by the Global End TB strategy and the TB Elimination Framework for low-incidence countries [7, 8], there is a need to push forward the development and rapid uptake of new tools, including new TB drugs that can effectively treat all people with TB which include drug-resistant forms.

There is also heterogeneity between healthcare systems across Member States, with various types of funding models, and different ways of organising TB prevention and control. In TB low-incidence Member States especially, many or all TB activities are integrated in the general healthcare system. Furthermore, Member States employ different strategies in drug management and procurement, which are both important areas that need to be taken into account when introducing new TB drugs.

As EU/EEA Member States generally have good financial and structural resources, more efforts can be made to implement prevention and control activities for TB in the EU/EEA than is possible in many other parts of the world. The clinicians treating and caring for TB patients in EU/EEA Member States have a history of early uptake of new tools for TB control, and this has also been the case for the new drugs, by taking part in clinical trials and getting access to the drugs for compassionate use. However, the introduction of new drugs at the programmatic level is a complex process that needs careful planning at various levels in the country, and guidelines on their safe introduction. In 2013, only seven EU/EEA Member States had a plan for how to introduce new tools for TB control, including new drugs [9].

This document aims to outline the options for developing an optimal strategy for introduction of new TB drugs at the national level, building on the global plan for the introduction of new drugs [10], and taking into consideration the specificities of the EU/EEA. It is expected that this ECDC expert opinion will facilitate rapid uptake of new TB drugs and regimens, and accelerate Member State efforts to develop their own plans for introduction of new drugs.

Scope of the expert opinion document

The aim of this document is to provide expert opinions on the introduction of new TB drugs in Member States of the EU/EEA. Similar principles can be applied to the introduction of repurposed drugs that are already in use for treating other diseases but show potential in curing TB, or introduction of new regimens with existing drugs. The main focus of the expert opinion document is on MDR TB treatment but the same principles are also applicable to drug-susceptible TB and latent TB infection.

This expert opinion outlines some pre-conditions that are considered to be essential at the national level before starting to use new drugs, as well as specific aspects that are needed in order to successfully implement new TB drugs/regimens.

Target audiences for the document are national policymakers, regulatory authorities, parties responsible for drug management and procurement, civil society organisations (CSOs) with an interest in TB, as well as those involved in national TB programmes.

This expert opinion does not substitute any international or national guidelines or clinical/risk management protocols for the treatment and management of TB. It should be read in the context of wider guidance documents for all forms of TB, including MDR and XDR TB [11-13]. In this context, the World Health Organization (WHO) has developed a global roadmap which reviews evidence, has developed recommendations for the rational introduction of new and repurposed drugs for TB [14], and published a policy implementation package for new TB drug introduction [10]. WHO has also published specific interim guidance with very specific considerations for the use of Bedaquiline and Delamanide [15, 16].

Methods

First consultation meeting and creation of working groups

A first consultation meeting was held on 8-9 April 2014. The 16 experts participating in this meeting were a selection of representatives from Member States, representatives from WHO, European Reference Laboratory for Tuberculosis Network, a civil society organisation, a patient organisation, and a representative from a public-private partnership supporting the TB drug pipeline (Appendix 1). To ensure ECDC output's independence, Declarations of Interests were collected from all the participants.

In the first consultation meeting, the topics to be included in the expert opinion were identified and agreed upon by the meeting participants. The objectives for all topics/chapters of the expert opinion document were defined and people were assigned to working groups which were responsible for drafting the individual chapters. After creating the working groups, ECDC made a request to the National Focal Points for Tuberculosis to suggest additional experts to contribute to the work of the working groups. Declarations of Interests were also collected from all additional experts who joined the working groups.

Ad hoc expert panel and document development

An ad hoc expert panel was convened and tasked to review, and where deemed necessary, revise the draft document produced by the working groups, and to agree on expert opinions independently from ECDC and the working groups. The eleven panel members were identified by ECDC's Chief Scientist and the TB programme by use of the ECDC Expert Directory, the ECDC Advisory Forum and by professional contacts through the ECDC TB networks and working groups. The ad hoc expert panel was officially appointed by the ECDC director. The experts were selected based on their expertise in the different areas of TB prevention and control, drug management, drug policy, community and regulatory aspects. Declarations of Interests were collected from all the panel members.

During a meeting on 25-26 September 2014, the ad hoc expert panel revised the draft document produced by the working groups and provided additional input. After the panel meeting, the panel members reviewed the revised expert opinion document based on the discussions at the meeting. The pre-final document was circulated to the ECDC Advisory Forum and the European Commission, Directorate-General for Health and Consumers, Unit D5 - Medicinal Products and authorisations for their input, and the final document was given clearance by the ECDC Chief Scientist in March, 2015.

See Appendix 1 for further details on the participants at the first consultation meeting, the members of the ad hoc expert panel and declared interests.

Results and discussion

Pre-conditions for introducing new drugs for TB control in the EU/EEA

This chapter outlines the most important and general aspects of comprehensive TB control programmes, which need to be considered at the national level before starting to consider introduction and use of the new and repurposed drugs and regimens.

TB guidelines

TB guidelines must be available in the country at national level and refer to the latest existing international guidelines. This includes following the international standards for diagnosis, laboratory, treatment, infection control, and contact investigation.

TB diagnosis and patient management

A robust system for the diagnosis of TB (including drug-resistant TB) and follow up of patients must be in place. The system for diagnosis must be free of charge and accessible to all, particular attention should be given to vulnerable groups. Early diagnosis, including diagnosis of drug resistance, enrolment in treatment, and infection control should be ensured.

Laboratory requirements

Quality-assured diagnostic procedures for the culture of *M. tuberculosis* and drug susceptibility testing for first and second line TB drugs should be in place. There is a need to have regularly updated diagnostic algorithms preferably combining rapid molecular testing and phenotypic drug susceptibility testing for resistance to isoniazid and rifampicin, and subsequent extended drug susceptibility testing for all detected cases of drug-resistant TB. The algorithm should be based on available high quality diagnostic tools and include all relevant anti-TB drugs.

Patient-centred care and support, including treatment of co-morbidities and ancillary drugs

The management of TB should have a patient-centred focus, i.e. patient-centred care. This includes involvement of communities and patients in the development of the programme in addition to a programme culture and structure that respond to the social and psychological needs of the individual patient.

The patient's charter for tuberculosis care [17] outlines the rights and responsibilities of people with TB. The European Charter of Patients' Rights [18], sets out patients' rights that together aim to guarantee a 'high level of human health protection' and to assure the high quality of services provided by the various National Health Services in Europe.

Patient-centred support to ensure completion of TB treatment should be available. This support should take into consideration the treatment of co-morbidities (diabetes, HIV, Hepatitis C, Hepatitis B etc.), adverse events and the use of ancillary drugs, nutritional support and vitamins. All of which should be accessible to patients for the full duration of their TB treatment. Psychological, social, and financial support systems and the engagement of (CSOs) should be in place to enhance adherence during in- and out-patient care. Incentives and enablers could be used to ensure that patients are able to complete treatment. Psychiatric and/or psychological support including support for those with addictions should be offered to improve the quality of life and the chances of treatment completion. Directly observed therapy is advisable for all patients with M/XDR TB.

Health inequalities in the access to new drugs should be avoided. In some countries, quality TB treatment, and even more so MDR and XDR TB treatment, may require long periods of hospitalisation in special centres requiring the patient to relocate at their own cost leaving their families, friends and support networks behind. This creates a major burden for patients, and may be difficult or impossible for the most vulnerable ones to undertake. Requirements like these may result in rejection of treatment and thus would make new drugs and new regimens unavailable to this population, resulting in health inequalities. These challenges should be taken into consideration when planning TB services. The possibility to shorten in-patient treatment or start treatment as an out-patient could be considered.

National concilium and advisory groups

It is recommended that a multidisciplinary concilium or advisory group be in place that can provide guidance on management and treatment of MDR and XDR TB patients. This group should function as a support to the treating physicians in developing treatment regimens and should guide all the amendments to or changes of treatment (e.g. when there are problems with side effects or treatment compliance).

There are different options for providing guidance by a concilium or advisory group. A number of EU/EEA Member States have experience in (online) concilium services [19], or provide access to national expert advice over the telephone. WHO, together with the European Respiratory Society also provides an online concilium, where TB specialists can obtain quick expert advice on difficult to treat patients (www.tbconsilium.org). This concilium can be used in the absence of a national concilium or when there is a need for further consultation. A concilium or advisory groups can provide an ideal forum to discuss cases with a range of different clinical specialties, as well as non-clinical or patient support services. Countries may consider using similar mechanisms for discussing TB patients, who are on a new drug regimen. This may help to share information and experiences within countries, and - as appropriate - could support sharing such information within the EU/EEA.

Education and information

Basic training and continuous education, including training on medical ethics, should be available for doctors, nurses and other staff involved in TB care and control. Information programmes should be in place for educating the community at large about TB. There should also be information initiatives for patients and families. Patient organisations can play an important role in training of healthcare staff and supporting and training patients, families and communities.

Surveillance and monitoring

Monitoring and evaluation is a prerequisite to making informed decisions for TB programme management and improvement, to understanding effectiveness, and to assessing the public health impact of new and repurposed drugs and regimens. Therefore, Member States that consider the introduction of new drugs should have a TB surveillance and monitoring system in place according to international standards for TB surveillance systems (ECDC, WHO etc.). Countries should aim to collect standardised and comparable data. The data should include drug susceptibility testing results and treatment outcome data. It is important to actively share relevant data and information with all stakeholders within and across countries, including with ECDC and WHO Europe. Data-information systems and networks need to be put in place or strengthened when the current system is not able to provide quality information for decision making. Regular aggregation of data, annual reporting of results at the national level, and reporting to ECDC are important to maintain an overview of developments at national and EU/EEA level.

Reliable data are essential for monitoring proper use of new and repurposed drugs and regimens. Accurate patient data help to quickly identify the development of drug-resistance and treatment failure, and ensure that patients receive optimal care.

Standardised surveillance of drug susceptibility testing results should be in place. Drug susceptibility test results should be available in the system for all drugs, and the system should have the possibility of adding data collection on new and repurposed TB drugs. There also needs to be in place a standardised monitoring of treatment outcomes, ideally allowing stratification for MDR and XDR TB. Also when patients move during treatment, it is important that the system allows for follow-up of final treatment outcomes.

Molecular epidemiological data, as far as is available, could be used to address the issue of transmission of MDR and XDR TB inside a country and across borders. Furthermore, molecular epidemiological data can support understanding of the dynamic of further drug resistance development.

Pharmacovigilance

A functioning pharmacovigilance system to monitor adverse events is a requirement [20], and an important source of data for the evaluation of safety of the new and repurposed drugs and regimens.

General drug procurement process

The country should have an appropriate mechanism for timely and sustainable procurement to ensure continuous availability of TB drugs. This requires close collaboration with suppliers and others, so as to establish well-defined roles and responsibilities for all parties. Drug distribution and management systems need timely planning. A strong system of supply and demand forecasting is the best means to avoid under- or over-supply of drugs. A centralised drug supply management will facilitate continuous availability, adequate quality and the best price for drugs.

Financing and accessibility of TB care

Budgets should be available to cover all costs necessary for ensuring access for all to TB prevention, diagnosis, treatment and care.

Palliative and End-of-Life Care

For the treatment of TB cases with no other treatment options left, it is essential to have a palliative care programme. Palliative care is defined by the WHO (<http://www.who.int/cancer/palliative/definition/en/>) as an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Thus, palliative care is much more than simply end of life or hospice care. All TB patients are entitled to palliative care throughout the course of their illness, beginning with treatment to ease their symptoms.

Specific considerations for introducing new drugs for TB control in the EU/EEA

This chapter outlines specific considerations to be taken into account when introducing a new or repurposed drug or regimen. These include programmatic considerations such as planning and adapting national policies, market authorisation, stakeholder engagement, procurement and distribution, necessary amendments and changes to national guidelines, laboratory considerations, and teaching and training considerations. The chapter also covers ethical, and monitoring and evaluation considerations.

Programmatic considerations

Planning and adapting national policies and guidelines

It is essential to plan the introduction of new drugs adequately, systematically and in a timely way. This requires a series of activities that include addressing licensing and registration requirements, ensuring country preparedness and adaptation of national policies, careful planning of drug procurement and delivery, as well as teaching and training for medical staff and allied professionals. All this requires engagement with relevant stakeholders, including civil society and patient organisations, both at national and international levels.

It is useful for EU/EEA Member States to carefully assess existing TB treatment regimens and treatment success rates, as well as patient acceptability and the incidence of adverse effects in order to find out possible weak points in the national TB programme. This is even more important for MDR TB regimens. New and repurposed TB drugs should not be introduced until there is clarity about how they should be used inside the country, and those recommendations will need to be built into national guidelines. Updating these guidelines usually requires close collaboration with key stakeholders, including pharmacists and clinicians [14]. Guidance should outline the TB regimens including the new TB drugs, the modalities of prescription (by whom and for which indications), as well as the precautions and contraindications of use, and detailing potential adverse reactions, their management and notification. The revised guidelines need to be disseminated to all who are likely to use the new drugs.

Market authorisation

A drug can be placed on the European Union market only after a marketing authorisation has been granted to the producer in accordance with the pharmaceutical legislation¹, either by the competent authority of a Member State for its own territory (national authorisation), or by the European Commission for the entire EU (EU authorisation). In both cases a marketing authorisation is granted to a drug only after its quality, safety and efficacy have been evaluated and a positive benefit-risk balance related to its use has been concluded. This assessment is carried out by Member States in the case of national authorisation, or the European Medicines Agency for EU authorisations². Before the introduction of new and repurposed drugs it is necessary to consider the individual country's legal requirements: for instance, there may be additional national registration conditions (e.g. with pharmaceutical or professional bodies) requiring approval or clearance, in addition to the EU-wide marketing authorisation. This affects the timelines for new and repurposed TB drugs to be available for treatment of TB patients in countries where this is applicable.

¹ Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, as amended, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, as amended.

² The requirements for marketing authorisation of medicinal products as regards the quality, safety and efficacy are set by the pharmaceutical legislation (Directive 2001/83/EC) and therefore are the same across the EU. In case of the EU wide

Stakeholder engagement

Countries should consider involving a wide range of stakeholders and organisations at an early stage of the process to facilitate the introduction of new and repurposed drugs, so as to avoid unnecessary delays and to build the ground for ownership by all key stakeholders, and facilitate country acceptance. Important stakeholders may include politicians, government officials, national regulatory authorities for medicinal products, professional organisations, clinicians, pharmacists, and representatives from civil society and patients' organisations.

Compassionate use

Until a new TB drug is available to patients, manufacturers make it available for compassionate use, respecting adequate patient selection, treatment and side effects monitoring capacity, which also have to be in line with ethical and human considerations. National TB programmes are encouraged to support patients to get access to drugs through compassionate use.

Compassionate use of new drugs is an important mechanism for early access to drugs for patients most in need. Early access to new drugs is crucial for patients who cannot successfully be cured by the current available treatment. Compassionate use is generally defined as the use of unlicensed medicines that are made available for patients with conditions for which there are no other satisfactory authorised therapies. This may be applicable to forms of resistant TB where there are no licensed treatment alternatives. Compassionate use programmes are usually subject to individual Member State's legislation, and drugs can then be made available on a named patient basis [22].

Drug procurement and affordability

It is important to establish and maintain a centralised procurement system, especially with respect to new drugs, to ensure proper control and response to any problems that might occur.

Procurement of new and repurposed TB drugs must be linked with the assurance of continuous supply of the standard TB medications, so as to ensure the continuation of effective combination therapy. Irregular supply and stockouts of all relevant TB drugs that are part of combination therapy is bound to increase the risk of treatment failure and the development of drug resistance.

Affordability of many of the most active drugs for resistant TB, including the new drugs is crucial, and determines access to them. Even within the EU/EEA the high cost of new drugs is an issue. These are matters for national and international negotiations bearing in mind the urgent need to be met for patients.

The list of ancillary drugs used in combating side effects, especially those of second-line drugs, should be revisited and be updated in order to include any new side effects that the introduction of new TB drugs or repurposed TB drugs can bring to patients. Adequate supply of ancillary drugs should also be secured.

Laboratory considerations

Quality-assured and timely drug susceptibility tests should be developed and implemented for the new and repurposed TB drugs, as well as for all relevant drugs used in the drug combinations.

Additional laboratory examinations and other examinations are needed for an appropriate selection of patients and for proper management during treatment (e.g. electrocardiogram, liver function and renal function tests).

Principles of using the new drugs to avoid resistance

When a new drug is introduced in the treatment of a patient, it should always be used in combination with drugs of proven efficacy to avoid resistance development in line with the general principles of TB treatment. It is very important that a single new drug is not added to a failing regimen. To make this possible, it is important to have second line drug DST results available.

Countries should consider limiting authorisation for prescription of new drugs to registered physicians who are experienced in the treatment of (drug-resistant) TB cases eligible for the new or repurposed drug, so as to prevent misuse and avoid development of drug resistance.

Conciliation for the use of new drugs

Professional network concilia for supporting clinicians have a role for guiding regimen use. Clinicians who are taking care of patients in need of the new drugs or treatment regimens should have access to timely expert advice to answer specific queries such as potential side effects, drug-drug interactions, etc. These advisory services could potentially also collect important clinical experience and information on experiences of early use of the new drug in the field.

centralised marketing authorisation, the approved product information for both healthcare professionals (The Summary of Product Characteristics) and patients (The package leaflet) is the same across the all EU Member States.

Education and training

Education and training of health professionals (e.g. clinicians, nurses, laboratory staff, staff from health authorities, and operational CSOs) should cover the clinical use and role of the new and repurposed drugs within combination therapy, use of the renewed guidelines and pathways, and ethical considerations related to treatment. Training should also include recording and reporting requirements as well as pharmacovigilance on all TB drugs, including new ones. Training opportunities should be accessible to all relevant implementers.

Involving affected communities and civil society

Affected communities and CSOs have a key role in planning and introducing new and repurposed TB drugs and regimens. They can be involved in educating the public, patients and their families about new treatments. In many countries, CSOs play a crucial role in TB treatment support and access to vulnerable groups such as the homeless, drug users, people living with HIV and AIDS patients, migrants and others. National TB programmes should consult with and involve CSOs in order to ensure that the benefits of new and repurposed drugs and regimens are enjoyed by the widest number of TB patients.

Ethical considerations

There are a number of ethical issues associated with TB treatment and control, relating to issues around access to diagnosis and treatment; obligations and rights of healthcare workers and patients; public health measures; and research.

Box 2. International Standards of Tuberculosis Care (ISTC), 3rd edition, 2014 [1].

'Tuberculosis care (including prevention) is a public good. The disease not only threatens the health of individuals, the health of the community is also at risk. It is generally agreed that universal access to health care is a human right and governments have the ethical responsibility to ensure access, a responsibility that includes access to quality-assured tuberculosis services. In particular, tuberculosis disproportionately affects poor and marginalized people, groups that governments and health care systems have an ethical obligation to protect ...Substandard care, be it on the part of program or non-program providers, is unethical.'

Ensuring broad and equitable access

All TB patients should have equitable access to high quality tuberculosis treatment within the EU/EEA (see Box 2). Informal rationing for access, where decisions based on reasons beyond the strict clinical eligibility criteria for which patients the new drugs are provided, should be avoided.

Patients suffering from TB in the EU/EEA should be provided the highest standard of care available, which includes treatment using new and repurposed TB drugs and regimens as necessary. This is motivated by concerns for the public health of the region and the human rights of individual patients.

Before concluding that no further treatment options are available and focusing on the provision of palliative care, patients should be carefully evaluated by adequately trained health workers. Given ongoing research, new and repurposed drugs may have become available that will still provide an option for cure. It is ethically imperative that all patients have access to potentially curative treatment, including those who have previously failed or defaulted from treatment.

Patient education and informed consent

All TB patients have the right to information about their health status and their therapeutic options, also with regard to new and repurposed TB drugs. They must be informed and educated as to the availability of TB treatment options. If patients are refusing to consent to potentially lifesaving treatments, it is possible that they have not been provided with adequate information and guidance. In order to get good information out to patients, medical staff could use the help of civil society organizations (CSOs) to counsel such patients when needed.

The patient should receive enough information about the new drugs with regard to evidence on effectiveness and their side effects, especially where there is conditional licensing of the drugs. It is important for TB patients who have very limited or no additional treatment options left, like some XDR TB patients, to understand the curative potential of a novel regimen, and the importance of adherence to the prescribed treatment.

Reassessment of patients in the light of new treatment

Novel therapies may prove beneficial to patients previously without any effective therapeutic options. Because of this, national programmes are urged to reassess all patients who might be eligible for new therapies. Patients' entitlement to these new drugs and regimens should be determined by clear clinical guidelines, taking into account the drug resistance pattern. It is recommended that a full risk assessment and evaluation of the needs of the patient and their family unit be completed in order to provide all necessary support.

When planning for the introduction of new drugs or regimens, special attention should be given to patients' needs, in terms of preserving human dignity, ensuring informed consent and confidentiality, and abiding by the 'do no harm' concept, including in vulnerable populations.

Supporting adherence to treatment

When patients' adherence to treatment is not achieved, a different approach to treatment should be adopted. It can, for example, include scheduling treatments at a different time, relying more heavily on directly observed therapy, or addressing any possible complicating factors such as drug or alcohol use. Civil society organisations can often arrange for volunteers to act as supporters to individual patients, helping them keep to treatment.

Programmes that frequently experience problems with adherence should reconsider their overall approach to treatment and patient management. While isolated cases of non-adherence may reflect patient-specific factors, on a larger scale it suggests that the system has failed to adequately implement a person-centred approach to care.

It is good practice for programmes to work with patients to facilitate their family and social networks in supporting them during and after hospitalisation to arrive at good treatment adherence.

Monitoring and evaluation considerations

In order to ensure best use of new and repurposed drugs and regimens, as well as optimal patient support, information on uptake, costs, treatment access and adherence, side effects, drug resistance to both new and existing drugs, and (long-term) treatment outcomes will be needed. For this purpose, existing information and data collection systems should be used. Adaptions to these systems and the use of additional indicators to strengthen monitoring and evaluation can be considered if necessary. Additional or new information sources could be identified and utilised. Appropriate operational research should be encouraged under monitoring and evaluation that can provide additional information on the efficacy and patient compliance with the new TB treatments.

Adjust national surveillance systems

EU/EEA Member States should assess whether their national notification and surveillance systems allow for comprehensive collection of information required for the evaluation of drug resistance, adverse events, treatment outcome and transmission of (MDR and XDR) TB. If the basic surveillance system is not ready for collection of this type of information, the Member State should consider adapting their existing national notification and surveillance system. There might be a need to identify additional standardised variables relevant to the introduction of new and repurposed drugs and regimens and to enable their incorporation in surveillance systems. To support the collection of data on patients moving across EU/EEA borders, mechanisms should be explored to evaluate the extent of cross-border migration of (MDR and XDR) TB patients seeking treatment with new drugs and regimens.

It is important to collect and share data on development of resistance against new drugs. In the medium term, the number of patients treated with new and repurposed drugs and regimens is expected to be small, particularly in low (MDR and XDR) TB incidence countries. It will therefore be crucial to share and make best use of country experiences. This could be accomplished through centralised collection, analysis, reporting and dissemination of data related to implementation of the drugs.

The data included in national surveillance systems should be from laboratories using quality assured methodologies for drug susceptibility testing. Inclusion on new variables could be considered, for instance inclusion of resistance to any new drug in the notification forms and surveillance databases for drug-susceptibility test result data collection.

Monitor the use of new and repurposed drugs and regimens

To monitor extent, trend of uptake and costs of new and repurposed TB drugs and regimens, Member States and national TB programmes should make use of all available data, such as sales data and consumption figures of new and repurposed drugs at the national programmatic level.

Pharmacovigilance for new and repurposed drugs and regimens

Currently most countries only use passive pharmacovigilance [20]. Active pharmacovigilance should be established and maintained at least during the first years of new drug introduction to assess adverse drug reactions caused by the new drug when used in routine settings [15]. Member States and national TB programmes should have access to the data of the national pharmacovigilance system and other potential pharmacovigilance information sources (See Box 3). Reports on pharmacovigilance should be made available to frontline clinicians and healthcare workers in a timely manner.

Box 3. EU-wide pharmacovigilance system.

The EudraVigilance system is a web-based information system designed to manage information on safety reports related to medicinal products in the EU. This allows information on serious adverse reactions to be shared between the national competent authorities and monitored.

An overview of EudraVigilance is available at the European Medicines Agency website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000239.jsp.

Identification of barriers and challenges faced with the introduction of new and repurposed drugs and regimens

Member States should explore mechanisms to identify and address barriers and challenges faced with the introduction and implementation of new and repurposed drugs and regimens at country level. This can, for example, be done by getting feedback from and using the experience of all main stakeholders, such as clinicians, centres of expertise, national concilium/advisory boards, relevant professional bodies, regulatory authorities, relevant research centres, public health bodies, CSOs, and patient organisations.

Countries could also consider and support the establishment of other data sources which can be used for retrieving additional information needed to assess the implementation of new and repurposed TB drugs and regimens. For example, observational studies can inform clinical guidance in a complementary manner to randomised controlled clinical trials. Therefore, it would be of value to facilitate the set-up of (MDR and XDR) TB patient cohorts to obtain observational data on treatment with new TB drugs and regimens, allowing for adequate observation time after treatment completion to assess long term outcomes.

Conclusions and potential implications

- Patients suffering from TB in the EU/EEA should be provided the highest standard of care available, which includes treatment using new and repurposed TB drugs and regimens as necessary.
- EU/EEA Member States have a responsibility to ensure that all patients have access to the best treatment available and build strategies and policies that facilitate in a responsible way, the rational introduction and use of new and repurposed TB drugs and regimens.
- There is a set of pre-conditions that countries need to have in place before even starting to consider introduction and use of the new and repurposed drugs and regimens. If these are not in place, there is a risk that the introduction and use of the new drugs and regimens will be more harmful than beneficial for the TB control programme efforts and for individual TB patients.
- Appropriate surveillance and monitoring systems, diagnostic capacity and good clinical and operational case management of all TB cases including those with drug-resistant TB should be in place before the introduction of new drugs.
- Adequate laboratory facilities for drug susceptibility testing of all relevant drugs, including the new and repurposed drugs should also be in place before considering the introduction of new drugs. Laboratory experts should be consulted and involved in the planning and implementation of this aspect of the introduction phase.
- In addition to these pre-conditions, countries need to take into account and develop strategies and policies on a number of specific considerations to secure the responsible and rational introduction.
- There is a need to consider the individual country's legal requirements for registration of a new drug and the possibility of compassionate use before registration.
- Continuous availability of new drugs should be ensured, clear guidelines adopted for their use, and it is recommended to utilise a concilium, that can provide support in the clinical management of patients for whom the new drugs are used.
- Patient education and support should be available, as it is a crucial part of the responsible provision of new and repurposed TB drugs and regimens.
- Civil society and patient organisations should be involved already in planning introduction of new drugs in this respect.
- The development and use of additional indicators for monitoring and evaluation at country level should be adopted.
- The introduction of new drugs and regimens in TB control requires careful monitoring to identify bottlenecks and to make adjustments to the introduction plan. This may need the development and use of additional indicators for monitoring and evaluation at country level.

These expert opinions should be considered as options and important aspects for the Member States to take into account, with the aim of facilitating the process of building strategies and policies. The result of this process will have consequences and potential implications for the national TB programmes, laboratories and clinicians way of working.

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Appendix 1

Working groups

The working group members that set the scope, defined the specific objectives and drafted the first version of the document during and after the first consultation meeting were: Ibrahim Abubakar, Public Health England, UK; Andra Cirule, Centre for TB and Lung Diseases, Latvia; Francis Drobniewski, Public Health England, UK; Edita Davidavičienė, Infectious Diseases Tuberculosis Hospital, Lithuania; Brian Farrugia, Geriatric Medicine and Chest Clinic (TB), Malta; Barbara Hauer, Robert Koch Institute, Germany; Dominica Iona Chiotan, Marius Nasta Institute, Romania; Mathilde Jachym, Centre Hospitalier de Bligny, France; Christian Lienhardt, World Health Organization, Switzerland; Theodore Lytras, Hellenic Centre for Disease Control and Prevention, Greece; Katerina Manika, Aristotle University of Thessaloniki, Greece; Laia Ruiz Mingote, Planeta Salud, Spain; Ikenna Obianwa, TB Alert, UK; Fabrizio Palmieri, L.Spallanzani National Institute for Infectious Diseases, Italy; Andreas Reis, World Health Organization, Switzerland; Laura Sanchez-Cambronero, Ministry of Health, Spain; Jonathan Stillo, TB Europe Coalition, Belgium/Romania; Stamatoula Tsikrika, Sotiria hospital, Greece; Martin van den Boom, World Health Organization, Denmark; Tonka Varleva, Ministry of Health, Bulgaria; Piret Viiklepp, National Institute for Health Development, Estonia; Gladys Xavier, Public health London Borough of Redbridge, UK; and Dominik Zenner, Public Health England, UK.

Ad hoc expert panel

The ad hoc expert panel consisted of the following experts:

Name	Organisation, country	Area of competence
Marina Carzol (<i>did not attend meeting</i>)	Patient representative, Romania, UK	Patient representative
Sarah Emami	Self-employed consultant, UK	Legal and ethics
Sven Hoffner	The Public Health Agency of Sweden, Sweden	Laboratory
Adriana Moisoiu	Institute of Pneumology "Marius Nasta", Romania	TB, clinical, microbiology, pharma,
Pierre-Yves Norval (<i>did not attend meeting</i>)	Technical Assistance for Management (TeAM), France	Drug management
Elisabetta Parretta (<i>did not attend meeting</i>)	Second University of Naples, Italy	Pharmacovigilance
Tom Schaberg (<i>did not attend meeting</i>)	Department of Respiratory Medicine, Rotenburg, Germany	TB expert
Paul Sommerfeld	TB Europe Coalition; and TB Alert, UK	Civil society
Susan van den Hof	KNCV Tuberculosis Foundation, The Netherlands	Monitoring and evaluation
Tuula Vasankari (CHAIR)	Finnish Lung Health Association (FILHA), Finland	TB expert
Michalakis Voniatis	Cyprus Foundation of Immunology and Allergology, Cyprus	TB programme and strategy

The opinions expressed by the ad hoc expert panel in this document are to be considered independent from ECDC, and provided as personal professional advice from the experts not representing the interests of a commercial body, a Member State or a professional body. The experts that did not attend the meeting contributed to the development of the document by commenting on the draft before the meeting and by being part of revising the document after the meeting.

Declared interests by ad hoc panel members

Declarations of interests for the ad hoc panel candidates were reviewed by the ECDC compliance officer before being officially appointed by the ECDC Director. The compliance officer noted that 7 out of 11 candidates appear to have no private sector or commercial interests, but are rather related to public services, hospitals or NGO's. One candidate acts as a patient representative and three candidates are self-employed. The nature of their self-employment was further investigated and appears not to be in conflict with their independent judgement. Two candidates, Sven Hoffner and Tom Schaberg, declared private sector interests related to the pharmaceutical companies that have developed the recently approved new TB drugs. Sven Hoffner provided technical support to Johnson&Johnson and Otsuka for developing and validating in vitro susceptibility test assays for bedaquiline and delamanid. Tom Schaberg had a consultant assignment for Otsuka and served as a member of a scientific advisory board during the approval of delamanid by the European Medicines Agency. The conclusion for both Dr Hoffner and Schaberg was that their declared interests will not be a problem and it would not disqualify their membership of the ad hoc expert panel, but if the discussion would be of a nature where specific drugs were discussed that the chair may ask them to leave the room. Thus, all candidates could participate in this panel with the restriction that the chair could decide that some panel members would have to leave the room for a particular part of the discussions.