ECDC **GUIDANCE**

Management of contacts of MDR TB and XDR TB patients

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The content of this guidance was developed by the European Centre for Disease Prevention and Control (ECDC) Tuberculosis Programme, with the support of an external expert panel composed of experts in the different areas of tuberculosis control and clinical medicine (including paediatric medicine and experience in multidrug-resistant and extensively drug-resistant tuberculosis).

This guidance was written by Andreas Sandgren, with the support of Isabelle Magalhaes (as a consultant). We also acknowledge the comments received by the members of the ECDC Advisory Forum.

This guidance document is based on evidence collected in three systematic reviews on the effectiveness of preventive therapy for contacts of MDR TB patients and the adverse events of anti-tuberculosis drugs in MDR TB contacts and healthy individuals. These reviews were carried out under contracts ECDC/2010/2354 by Marieke J. van der Werf (KNCV Tuberculosis Foundation) and Miranda Langendam (Dutch Cochrane Centre) and ECDC/2011/2909 by Marieke J. van der Werf, Edine Tiemersma (both KNCV Tuberculosis Foundation) and Miranda Langendam (Dutch Cochrane Centre, University of Amsterdam).

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Contents

Abbreviations

ATS	American Thoracic Society
ART	Antiretroviral treatment
CDC	Centers for Disease Control and Prevention, USA
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ESTC	European Union Standards for Tuberculosis Care
EU	European Union
HIV	Human immunodeficiency virus
IGRAs	Interferon gamma release assays
ISTC	International Standards for Tuberculosis Care
KNCV	Koninklijke Nederlandse Centrale Vereniging ter bestrijding van de tuberculose
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
M. tuberculosis	*Mycobacterium tuberculosis*
NICE	National Institute for Health and Clinical Excellence
RCT	Randomised controlled trial
TB	Tuberculosis
TNF	Tumour necrosis factor
TST	Tuberculin skin test
WHO	World Health Organization
XDR TB	Extensively drug-resistant tuberculosis

Executive summary

The challenge

Multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant tuberculosis (XDR TB) are posing a major public health threat as well as a big challenge for TB prevention and control in the European Union and European Economic Area (EU/EEA). As the number of people afflicted with MDR TB or XDR TB increases, so does the number of their contacts – and it is precisely these contacts that need to be identified and properly managed. The management of contacts of MDR TB and XDR TB patients is particularly challenging as the evidence base for best practises is very limited.

Public health guidance

By presenting the most recent scientific evidence and expert opinions on the topic, this document provides guidance on issues relevant to the management of contacts of MDR TB and XDR TB patients. The target audience are public health experts and policy makers in EU/EEA Member States who are developing national guidelines or recommendations on the management of MDR TB and XDR TB contacts.

Two options

In drug-susceptible TB, the provision of preventive therapy to individuals with latent TB infection (LTBI) has been shown to be effective at reducing the risk of developing TB disease among infected contacts. The concept is also valid for MDR TB and XDR TB, but limited by the current lack of availability of drugs shown to be effective against MDR TB and XDR TB infection that show an acceptable adverse-event profile in an otherwise healthy individual.

The alternative to preventive therapy is to provide information and follow-up with careful clinical observation of the identified contact considered to have LTBI. This ensures the early detection of symptoms of TB disease so that TB treatment can be initiated at the earliest possible moment if the disease should develop.

Lack of solid evidence

The evidence for preventive therapy in MDR TB and XDR TB is very scarce. Studies conducted on the benefits and adverse events of preventive therapy are not conclusive. The lack of solid evidence is a limitation when providing guidance on the topic, and the recommendations made are largely based on expert opinions. It should be stressed that, as the current evidence base does neither reject nor support provision of preventive therapy with the currently available drugs, both aforementioned options remain valid for MDR TB and XDR TB infection.

Expert opinions

The expert panel expresses support for the two different options: preventive therapy and/or careful clinical observation. The central principle that the expert panel follows in their opinions is that a comprehensive risk assessment should be part of the evaluation of the MDR TB or XDR TB contact. The individual risk assessment should take into consideration the following: the MDR TB contact's risk for progression to TB disease; the drug susceptibility pattern of the source case of infection; and the contact's risk for adverse drug events if initiating preventive therapy. In case of XDR TB, the available possible drug regimens are very limited and without proven efficacy, thus close observation is likely the only option.

Conclusion

The management of contacts of MDR TB and XDR TB patients needs to be guided by a comprehensive individual risk assessment that takes into consideration the individual risks and benefits when weighing the pros and cons of preventive therapy.

There is an urgent need for further research, specifically in two areas: studies evaluating the benefits of preventive therapy in MDR TB and XDR TB contacts, and cost-benefit analyses on implementing preventive therapy in EU/EEA Member States. We acknowledge that there are ongoing studies which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings. Further, additional drugs may become available for the treatment of MDR TB, which will necessitate an update of this guidance document.

1 Introduction

1.1 Current situation

The spread of tuberculosis (TB) occurs mainly in settings where prolonged contact between people promotes the transmission from an infectious 'source case' with TB disease to one or several 'contacts'. A main component in stopping the spread of TB is to rapidly diagnose infectious TB disease cases and treat these so the patient can be cured and the chain of transmission will be stopped. As part of the prevention and control efforts for TB it is also important to trace people who have been in contact with the source case and are likely to have been exposed to infection. Screening of identified contacts for their infection status will allow detection of latent TB infection (LTBI) or TB disease. Diagnosing LTBI aims at identifying individuals who would benefit from preventive therapy or follow-up with careful clinical observation, thus reducing future development of TB disease or promoting early detection.

Multidrug-resistant TB (MDR TB) is defined as *Mycobacterium tuberculosis* (*M. tuberculosis*) that is resistant at least to isoniazid and rifampicin. Extensively drug-resistant TB (XDR TB) is defined as *M. tuberculosis* resistant to isoniazid, rifampicin, any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

As MDR TB and XDR TB have become more prevalent, our clinical and public health practices towards the prevention and control of TB are challenged. In order to deal with these resistant forms of TB and avoid further MDR TB and XDR TB cases, a comprehensive approach, as with drug-susceptible TB, needs to be taken to ensure rapid detection, proper treatment and public health measures to cure the patients and prevent further transmission of the infection. Intensive case finding and contact tracing are key components of the public health action required to promptly detect infected individuals. However, the management of contacts of MDR TB and XDR TB patients is particularly challenging as the evidence base for best practises is very limited and there are few therapies available.

1.2 Lack of evidence and conflicting existing guidelines

The management of contacts of MDR TB and XDR TB patients is controversial with little scientific evidence to support guideline development. A recent review of the management of MDR TB contacts in European Union/European Economic Area (EU/EEA) revealed a lack of national guidelines in several Member States and emphasised the discrepancies between national guidelines among other Member States [1]. For this survey, commissioned by the European Centre for Disease Prevention and Control (ECDC), KNCV Tuberculosis Foundation contacted thirty EU/EEA Member States and asked them to answer a questionnaire on the national guidelines of TB programmes or recommendations for the management of MDR TB contacts. Twenty-six Member States replied; 16 Member States had a guideline with recommendations for the management of MDR TB contacts, 10 Member States did not have such recommendations [1]. The recommendations varied in the different guidelines, and included – either as separate actions or in combination – the following measures: the follow-up of contacts for at least two years, specialist consultation, and/or preventive therapy. The International Standards for TB Care (ISTC) [2] and European Union Standards for TB Care (ESTC) [3, 4] indicate that strict clinical monitoring and no preventive therapy for LTBI should be provided if the source case is affected by an MDR TB strain. Preventive therapy of MDR TB contacts has been warranted by a panel of TB experts through a Delphi process, but without reaching a consensus on the treatment modalities [5]. Outside the EU/EEA, guidelines of the American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) recommend the prescription of preventive therapy [6] for MDR TB contacts, whilst the World Health Organization (WHO) opposes the prescription of preventive therapy and instead recommends careful clinical follow-up for a period of at least two years [7, 8].

Altogether, the lack of trials comparing different anti TB drug regimens (and of those evaluating a 'no intervention' approach) for MDR TB and XDR TB contacts, and the resulting conflicting treatment recommendations highlight the need for guidance on the management of MDR TB and XDR TB contacts. Such a guidance document would be particularly useful for the 10 EU/EEA Member States without a policy or guideline on management of MDR TB and XDR TB contacts.

1.3 Scope and purpose of this guidance

The overarching goal of this guidance is to contribute towards preventing as many MDR TB and XDR TB cases as possible in the EU/EEA. Given that MDR TB and XDR TB is becoming more prevalent, the issue of how to manage contacts of MDR TB patients is becoming increasingly relevant. The management of XDR TB is further complicated by very few treatment options currently available for this infection. The specific aim of this document is to provide

guidance on issues relevant to the management of contacts of MDR TB and XDR TB patients. The purpose of this guidance is not to give a comprehensive view on contact tracing or the use of preventive therapy in general, but rather focus on how to manage the individuals who have been identified as contacts of MDR TB and XDR TB patients.

This guidance document presents the most up-to-date evidence and expert opinion regarding the management of contacts of MDR TB and XDR TB patients, in order to provide the Member States with support when considering the topic in national TB programmes and/or TB control strategies. It describes the different options in the management of contacts and presents the corresponding evidence in support of these options.

1.4 Document development

Collecting evidence

ECDC aims to follow evidence-based methods in the production of its guidance documents. The scientific evidence on the benefits and adverse events of preventive therapy for LTBI among contacts of MDR TB patients formed the basis for the development of this guidance document. Three systematic reviews were conducted by KNCV Tuberculosis Foundation and the Dutch Cochrane Centre (DCC) under a service contract from ECDC with the objective to collect the necessary evidence for development of this guidance document. The overall aims of these KNCV/DCC/ECDC systematic reviews were:

- to evaluate the effectiveness of anti TB drugs for preventing TB disease in persons at risk of developing MDR TB and XDR TB disease [9];
- to evaluate the effectiveness of anti TB drugs, other than isoniazid and rifampicin, for preventing TB disease in persons at risk of developing susceptible, mono- or poly-resistant TB [9];
- to assess the adverse events of preventive therapy (anti TB drugs other than isoniazid or rifampicin) in healthy individuals (healthy volunteers or close contacts of MDR TB and XDR TB patients with or without proven TB infection)[10].

During the process of collecting the opinions by the expert panel, a new piece of evidence appeared through communications with the US CDC. An ongoing study evaluated two outbreaks of MDR TB in Chuuk, Federated States of Micronesia, and assessed the provision of second-line preventive therapy for MDR TB. It was judged by the expert panel that this piece of unpublished (as of February 2012) evidence was of value to inform the discussion, and a brief summary of the study has been included in this guidance with the approval of the US CDC and involved parties from the Federated States of Micronesia.

Expert panel

An expert panel was set up in order to assess the most up-to-date scientific evidence on the management of contacts of MDR TB patients, and subsequently express a consensus opinion on the topic. The panel members were identified by ECDC's chief scientist and the TB programme experts. The experts were selected based on their expertise in the different areas of TB control and clinical medicine – including paediatric medicine and experience in MDR TB and XDR TB. The experts were asked to provide opinions based on their professional and scientific merits. The expert opinions expressed are to be considered the personal professional advice of the expert, and the experts are not representing the interests of a commercial body, a Member State, or a professional body. Also, the opinions expressed should not be regarded as the ECDC point of view. All members signed a declaration of interest, which was reviewed by the ECDC chief scientist. One member of the panel, Lee Reichman, had a conflict of interest in relation to a company producing one of the interferon-gamma release assays (IGRAs) discussed and was excluded from any discussion that involved the use of IGRAs. None of the other members of the panel declared any conflicting interests in regard to the discussion topics. The panel was independent from ECDC, which organised, hosted and observed the panel meeting and the teleconference.

Assessment of evidence

Based on the presented evidence, the expert panel was asked to share expert opinions on the management of contacts of MDR TB and XDR TB patients. The expert panel judged it necessary to also give guidance on individual components for the management of contacts of MDR TB and XDR TB patients that were not directly related to the topic of the systematic reviews which focused only on the benefits and adverse events of preventive therapy in contacts of MDR TB and XDR TB patients. For these opinions we have collected and presented evidence, where available, from existing systematic reviews or key observational studies.

Table 1: Members of the expert panel

Name	Affiliation	Country
Jean-Pierre Zellweger	Swiss Lung Association	Switzerland
Luigi Codecasa	TB Ref Centre, Villa Marelli Inst, Niguarda Hospital	Italy
Manfred Danilovits	Tartu University Hospital, Lung Clinic	Estonia
Rob van Hest	Department of Public Health TB Control Metropolitan Public Health Service Rotterdam-Rijnmond	Netherlands
Elmira Ibraim	Marius Nasta Institute of Pulmonology - National Tuberculosis Programme	Romania
Marc Lipman	University College London Royal Free Hospital	United Kingdom
Robert Loddenkemper	German Central Committee against Tuberculosis	Germany
Lee Reichman	Global Tuberculosis Institute	USA
Hendrik Simon Schaaf	Stellenbosch University	South Africa

Work process for the expert panel and guidance development

A Delphi process was arranged to collect the opinions of the expert panel. Thereafter, an expert panel meeting was arranged in Stockholm, November 2011. Subsequent to the expert panel meeting, a draft of the guidance document was prepared by ECDC. A consultant (Isabelle Magalhaes) attended the expert panel meeting as a rapporteur and was involved in drafting the guidance document. A teleconference was held in January 2012 to complete the expert panel opinions and sort out remaining considerations of the draft of the guidance document. Comments were received by the ECDC Advisory Forum in February 2012. The final document was approved by the ECDC chief scientist in February 2012. The guidance provided here is based on the evidence available at the time of the expert panel meeting in November 2011. In the event of emergence of new evidence strongly affecting the opinions expressed, this guidance document will be updated in line with the new evidence.

Document format

The main part of the document is the summary of evidence and expert opinions. As the management of contacts of MDR TB and XDR TB patients covers several related sub-topics, these have been divided into five sections: contact tracing and initial investigations; responsibilities and involved caregivers; clinical consultation and information to the contact; preventive therapy of contacts; and, follow-up of contacts. Each section follows the format of giving general considerations, the expert opinions as formulated by the expert panel, and finally presenting the existing evidence base and background documents related to the specific sub-topic. The general considerations have been identified by the expert panel as important background concepts for the opinions expressed. As described above, the bulk of the evidence is based on the three KNCV/DCC/ECDC systematic reviews. Where needed, the evidence has been complemented with other published meta-analyses or systematic reviews. When such studies were not available, key studies are presented. As the evidence base is very weak for several of the opinions expressed, we have also included a chapter on future research needs, as identified by the expert panel and by ECDC.

2 Background

2.1 MDR TB and XDR TB in the EU

The World Health Organisation (WHO) European Region is faced with some of the highest proportions of drug-resistant TB and MDR TB in the world [11]. In 2010, an estimated 650 000 prevalent cases of MDR TB existed worldwide according to the WHO [11]. In terms of proportions of notified MDR TB cases in the EU, in 2009 MDR TB was most frequent in the Baltic States (combined MDR TB: 17.4%–28.0%) and Romania (combined MDR TB: 11.2%) [12]. Other countries reported lower levels of MDR TB (0%–8%), where it was generally more common in cases of foreign origin. In 2008 an estimated 440 000 (390 000–510 000) incident cases of MDR TB occurred worldwide according to the WHO, of which 81 000 (73 000–90 000) occurred in the WHO European Region [13]. There were 18 365 MDR TB cases reported in the WHO European Region, which accounted for only 23% of the estimated number [14].

In the EU, treatment outcome data show that among all laboratory-confirmed MDR TB cases of the 2007 cohort, only 32.0% had a successful outcome at 24 months, while 53.2% of all previously treated and 78.1% of all previously untreated culture-confirmed pulmonary TB cases had a successful outcome. In the WHO European Region, failure of treatment and default occurred for 11% and 12.7%, respectively, among the reported treated patients with MDR TB [12]. Treatment of MDR TB using second-line anti TB drugs has more adverse events, needs to be provided for an extended period of time (generally 18 to 24 months; the WHO recommendation is at least 20 months), and is expensive. Access to quality-assured second-line drugs and follow-up of patients to circumvent treatment failure is essential as inadequate treatment of patients with MDR TB poses a threat to patient survival, and can induce the emergence of XDR TB.

Previous treatment has been identified to be the strongest risk factor for MDR TB in Europe [15]. This was particularly true in Western Europe as compared to Eastern Europe, and can possibly be explained by the higher transmission rates of MDR TB to contacts in Eastern Europe. MDR TB was also associated, although to a lesser degree than previous treatment, with being foreign-born. Another contributing risk factor for developing MDR TB, linked to the aforementioned, is deficient treatment adherence; it is of utmost importance to promote full adherence to the prescribed drugs.

An action plan to contain the spread of drug-resistant TB in the European Region (2011–2015) was launched by the WHO Regional Office for Europe [16]. The goals set for the end of 2015 are: to decrease by 20% the proportion of MDR TB cases among previously treated patients, to diagnose at least 85% of estimated MDR TB cases, and to treat successfully at least 75% of notified MDR TB patients.

In light of the increasing number of MDR TB cases in Europe, rapid drug susceptibility testing and adequate monitoring of patients with MDR TB is essential, using both sputum smear microscopy and culture in order to identify treatment failures early [17]. Rapid testing should be supported by political commitment, the implementation of an uninterrupted supply of quality-assured second-line drugs, the monitoring of performance, and the evaluation of treatment outcomes [7].

It is equally essential that existing MDR TB cases are promptly detected, diagnosed and treated, and transmission from infectious sources is interrupted. Although these are standard practice in TB control, several deviations from international standards are evident even in settings with sufficient resources. A survey investigating clinical, public health, and infection control practices in the care of MDR TB and XDR TB patients in EU countries showed that TB infection control (e.g. the lack of a comprehensive infection control strategy or plan) [18] was not properly carried out and failed to meet international recommendations. Similar deficiencies were reported with regard to surveillance, clinical management, laboratory support, and diagnostic and treatment algorithms [19].

2.2 Latent tuberculosis infection (LTBI)

Upon exposure and inhalation of airborne droplets containing *M. tuberculosis*, a proportion of individuals will be infected and the majority of these develop an immune response that contains the infection. These individuals are asymptomatic but infected (LTBI). It is estimated that 5 to 10% of individuals with LTBI will develop TB disease during their lifetime. The infection reservoir represented by LTBI hinders efforts to eliminate TB globally. LTBI is often defined as a clinical condition in an individual considered to be infected with *M. tuberculosis*, but having no manifestations of disease, and from whom *M. tuberculosis* bacilli cannot be identified. However, LTBI is considered to include a wide spectrum of clinical states, from sterilising immunity to sub-clinical presence of replicating bacilli [20, 21]. In LTBI diagnosis, the direct detection of *M. tuberculosis* bacilli is usually not possible to demonstrate directly (except in some cases of recent infection, mainly for children, where cultures for *M. tuberculosis* may be temporarily positive in the absence of symptoms [22, 23]); instead LTBI is assessed indirectly by confirming the

presence of a cellular immune response directed against *M. tuberculosis* antigens, using the tuberculin skin test (TST) or IGRAs. Incidentally, Expert opinions and a summary of evidence on the use of IGRAs for the diagnosis of TB including LTBI is provided in another ECDC guidance document [24].

Individuals with LTBI are not a source of infection, however in the event of immunosuppression either induced (e.g. during transplantation; anti-tumour necrosis factor (TNF)-medication [25]) or acquired (e.g. infection with human immunodeficiency virus (HIV)), the risk of reactivating TB from LTBI is increased [25]. Other groups at high-risk of progression to TB disease once infected include recently infected subjects [26], diabetics [27], injecting drug users [28], infants and children under five years of age [29].

2.3 Contacts and contact tracing

For the purpose of this guidance document, we define a contact as someone who has been exposed to *M. tuberculosis* infection by sharing air space with a person with infectious TB, the so-called 'source case', with the probability of being infected increasing with the duration and closeness of contact, as well as the infectiousness of the source case. Close contacts are defined as people from the same household sharing common habitation rooms. This can also include individuals with evidence of prolonged and frequent exposure at, for example, the workplace, school, prison, hospital ward, or social settings. The 'index case', a person with suspected or confirmed TB disease, who is defined as the initial case of TB for a contact investigation, is not necessarily identical with the source case. For the purpose of this guidance we are focusing on the source case and not the index case, as it is the source case who will have exposed the contacts, not necessarily the index case. Contact tracing is defined as the systematic case finding of contacts of patients with infectious TB disease. Whether limited or extensive case finding among contacts will be performed depends, for instance, on the available resources [30]. Limited case finding includes an assessment of individuals at high risk such as household contacts, individuals with HIV infection, and young children.

No common EU/EEA guidelines currently exist on how to perform contact tracing, however, several EU/EEA Member States have national guidelines on TB contact tracing, and there has been a consensus statement developed on the topic which can help to guide national practices [31, 32]. A review of the national guidelines and recommendations for contact screening in Europe showed that some countries do not have national guidelines, and that among existing national guidelines, the criteria for the selection of contacts, the screening process, and the prescription of preventive treatment for LTBI differ [31].

Screening for TB infection is carried out with the same procedures regardless of the mycobacterium strain or pattern of resistance, assuming that MDR TB and XDR TB strains are equally transmissible as drug-susceptible strains. The observation that mutations resulting in antibiotic resistance in bacteria may come at a 'fitness cost' [33] (i.e. decreased growth and/or transmission) may not be true for MDR TB [34] as it depends on the specific mutation and strain genetic background of *M. tuberculosis* [2, 35]. Therefore, general contact tracing and infection screening guidelines can be used in the case of MDR TB and XDR TB.

2.4 Preventive therapy in drug-susceptible LTBI

Preventive therapy of patients with drug-susceptible LTBI is proven to be effective and is included in guidelines for TB control [6]. This section summarises the evidence for using isoniazid preventive therapy for LTBI after contact with drug-susceptible TB to give a background to the concept of preventive therapy. This chapter should therefore not be taken as direct evidence that preventive therapy is also effective for MDR TB and XDR TB. Other drug regimens for preventive therapy are also being tested and some examples are discussed here. A complete review of these, however, is not given.

Three recently published systematic reviews of randomised trials have assessed the effect of preventive anti TB therapy in people with LTBI (non-HIV-infected persons, no children) [36], in children with HIV infection [37], and in adults with HIV infection [38] in preventing development of TB disease.

Randomised trials have shown that isoniazid preventive therapy was effective in diverse (non-HIV-infected) populations, in preventing TB in approximately 60% [36] and as much as 90% [39] of the individuals. However, clinically significant isoniazid-induced hepatitis occurred in one of every 200 patients [36], with severe hepatotoxicity in up to 1% in older patients [39], while Nolan et al. reported hepatotoxicity in 0.1% of patients starting and 0.15% of patients completing treatment [40].

Individuals at high risk to reactivate TB from LTBI, such as individuals with HIV infection, also benefit from preventive TB therapy, as shown by a study including 11 026 patients with HIV infection in Brazil, where isoniazid preventive therapy, particularly in combination with antiretroviral treatment (ART), was associated with a lower risk of TB [41]. A review of studies assessing the effect of preventive therapy on patients with HIV infection showed that preventive therapy reduced the risk of TB by 32%. Interestingly, preventive therapy reduced the risk of TB by 62% among those who were TST-positive, whereas no effect among those who were TST-negative was evident. No reduction with preventive therapy in all-cause mortality was demonstrated [38].

Recent studies showed the benefit of preventive treatment for subjects with HIV infection. Samandari *et al*. reported that 36 months' isoniazid prophylactic treatment was more effective than six months prophylactic treatment in subjects with HIV infection (and particularly in those who were TST positive) [42]. Martinson *et al*. reported that short-course (12 weeks) rifampicin in combination with isoniazid, and rifapentine in combination with isoniazid were effective in adults with HIV infection (TST positive and no ART) [43].

Preventive therapy has been shown to provide long-term protection in children [44]. A significant decrease in TB incidence (-72%) and death (-54%) in children infected with HIV who received isoniazid preventive therapy (but no ART) in areas of high TB prevalence was observed. Whether isoniazid preventive therapy will achieve the same efficacy for children with HIV infection receiving ART in areas of high TB prevalence, or in areas of low prevalence (with or without ART) remains to be assessed [37].

Screening and preventive therapy of LTBI in patients undergoing renal transplantation seems to be efficient and well tolerated [45].

The WHO recommends isoniazid preventive therapy for HIV-infected adults (including pregnant women) and adolescents, irrespective of the degree of immunosuppression, as part of the TB prevention package, along with provision of ART, infection control and intensified case-finding of TB. Furthermore, preventive TB therapy within HIV prevention is likely to be a cost-effective measure, but more studies on cost-effectiveness are needed on this topic [46].

A recent report demonstrated that a combination of once-weekly isoniazid and rifapentine administered over three months was as effective in preventing TB as the administration of daily isoniazid for nine months [47]. Based on this and two other [43, 48] randomised control trials, the US CDC recommends for otherwise healthy LTBI patients over 12 years of age a new combination regimen of isoniazid and rifapentine administrated weekly for 12 weeks as directly observed therapy, as an equal alternative to the standard regimen of nine months of daily isoniazid [49].

As listed in Table 2, in non-HIV-infected people, treatment (with varying duration in the different studies) with isoniazid reduced the risk of developing active TB by 60% as compared to non-treated, non-HIV-infected people [36].

Table 2: The risk ratio of developing active TB in non-HIV infected people after treatment with isoniazid [36]

No. of studies	Follow-up	Total sample size Prophylaxis[1] + no prophylaxis (n)	Relative risk (95% CI)
11	At least two years	73 375	**Active TB:** 0.40 (0.31-0.52)

[1] *Isoniazid. Isoniazid treatment was administered for up to two years.*

As listed in Table 3, only one study (by Zar et. al [50]) was identified in the systematic review of randomised studies of children with HIV infection who received TB-preventive therapy or a placebo [37]. Preventive therapy in children with HIV infection with isoniazid resulted in a risk ratio of developing definite or probable TB of 0.28, or a risk ratio reduction of 72% as compared to non-treated children with HIV infection.

Table 3: Effect of treatment with isoniazid on the risk ratio of developing definite or probable TB in children with HIV infection [37]

Study	Sample size (n)	Median age (months)	Follow up (months) median (IQR)	Incidence of TB[1]		
				Prophylaxis[2]	No prophylaxis	Hazard ratio (95% CI)
Zar 2007	263 children with HIV infection	24.7	5.7 (2-9.7)	5/132	13/131	0.28 (0.10-0.77)

[1] *Confirmed or probable TB and drug-resistant TB*

[2] *Co-trimoxazole and isoniazid*

As listed in Table 4, in adults with HIV infection, preventive anti TB therapy resulted in a risk ratio of developing active TB of 0.68, or a risk ratio reduction of 32% as compared to non-treated adults with HIV infection [38]. The following risk of bias assessment in the studies included in the above review [38] was identified: Allocation concealment was adequate in five studies and unclear in seven studies. In seven trials, providers and participants were blinded.

Table 4: Effect of preventive anti TB treatment on the risk ratio of developing active TB in adults with HIV infection [38]

No. of trials	Sample size (n)		Incidence of active TB
	Prophylaxis[1]	**No prophylaxis**	**Relative risk (95% CI)**
9	3 728 adults with HIV infection	2 034 adults with HIV infection	0.68 (0.54-0.85)

[1] *Any anti TB drug. The prophylaxis regimen included: isoniazid, isoniazid in combination with rifampicin, rifampicin in combination with pyrazinamide, isoniazid in combination with rifampicin and pyrazinamide.*

3 Summary of evidence and panel opinions

3.1 Contact-tracing and initial investigations

General considerations

- Contact investigation should be a priority for public health as it is an important component of prompt case detection of individuals with TB or LTBI and increases the chance of reducing TB transmission in the community.
- Contact investigation should be performed in line with existing national guidelines.
- If no national guidelines on contact investigations of drug-susceptible TB patients/MDR TB patients are available, guidelines should be developed. In the meantime, it is suggested that use is made of this guidance document or the European Standards for Tuberculosis Care (ESTC) [4] or other international guidelines and recommendations which can guide the adoption and creation of national guidelines.
- Contact investigation relies on the cooperation of the source case or the index case; national legislation and policies must be followed.
- LTBI is diagnosed by performing an overall risk assessment that should consider the individual's history of *M. tuberculosis* exposure, clinical history and risk factors, and presence of an immunological response by TST or IGRA (if applicable). TB disease should be excluded by, for example, chest radiography in the overall clinical examination and investigation.
- TB disease is diagnosed by evaluating a patient's medical history, conducting a physical examination, making a chest x-ray, and identifying *M. tuberculosis* bacilli using microbiologic and rapid molecular diagnostic methods (sputum-smear microscopy, *M. tuberculosis* culture and nucleic acid amplification), and/or histopathology [4, 51].

Evidence and background documents

The importance of contact investigation to identify individuals with TB or LTBI was highlighted in a recent publication summarising evidence-based and best-practice recommendations for contact investigation in Europe [32].

For guidance on the use of IGRAs in the diagnosis of LTBI, ECDC has issued a guidance document on IGRA [24]. There are also other international guideline documents, e.g. the guide on latent tuberculosis infection published by the US CDC [52].

'International standards for tuberculosis care (ISTC)' [2] and the ESTC [4] include the evaluation and management of children under five years of age and persons with HIV infection as a standard for public health responsibilities. Children represent a high-risk group for progressing to TB, therefore the ISTC and ESTC recommend the screening of all children in close contact with an infectious source case of TB and exclusion of TB disease (prior to initiation of preventive anti TB therapy) [2, 4], particularly for children with HIV infection [53].

The WHO provides guidelines on intensified TB case-finding for people living with HIV in resource-constrained settings. In the WHO guidelines, contact tracing is recommended for all, and priority should be given to contacts with HIV infection or other immunocompromised individuals [46].

The WHO is currently developing comprehensive guidelines for contact tracing; these guidelines will serve as an important document for adopting national recommendations on contacting tracing.

Expert opinions

These opinions are valid for both MDR TB and XDR TB contacts.

Who should be assessed by contact tracing?

At the least, all household and close contacts of MDR TB and XDR TB cases should be offered screening according to national guidelines.

How should MDR TB and XDR TB contact tracing be conducted?

Contact tracing around MDR TB and XDR TB cases should be performed according to national guidelines. If no guidelines exist, public health authorities should refer to existing international guidelines and standards-of-care guidelines. The national guidelines should include a definition of the source case. As in all contact tracing, the definition of source case will be relevant for the level of infectiousness, e.g. sputum-smear positive pulmonary TB might be given a higher priority than sputum-smear negative pulmonary TB or extrapulmonary TB.

How should identified MDR TB and XDR TB contacts be screened for LTBI and TB?

MDR TB and XDR TB contacts should be tested for LTBI and TB according to national guidelines. If no national guidelines are available, recommendations for LTBI and TB testing can be adapted to the national conditions based on existing international guidelines and guidance documents.

If a contact older than five years of age is found to be TST and/or IGRA positive or shows symptoms suggestive of TB, TB disease should be excluded through clinical examination and investigation. In children under five years of age and in immunocompromised persons, TB disease should be excluded, irrespective of the TST/IGRA response.

3.2 Responsibilities and involved health providers

General considerations

As TB services are integrated within the health system in several EU Member States, this presents challenges in allocating responsibilities for optimal delivery of TB services. Therefore the expert panel identified the need to give its opinions on involved caregivers and their responsibilities.

Each Member State's own expertise in assessing which structure or system of TB prevention and control suits their setting best is acknowledged.

As indicated by the ISTC [2] and ESTC [4], all providers of care for patients with TB (or suspected TB) or LTBI (or suspected LTBI) are assuming an important public health responsibility to prevent ongoing infection transmission. It is therefore important that the responsibilities are clearly defined; that the relevant healthcare provider involves the necessary health services, has adequate resources to perform contact investigation, and obtains a comprehensive individual risk assessment of each identified MDR TB or XDR TB contact.

Evidence and background documents

The expert opinions for responsibilities and involved health providers are of a general nature, therefore availability of evidence is not relevant.

Expert opinions

These opinions are valid for both MDR TB and XDR TB contacts.

Who should be responsible for the investigation of MDR TB and XDR TB contacts?

Contact investigation of MDR TB or XDR TB patients should be performed within a public health structure according to national guidelines.

How should identified MDR TB and XDR TB contacts with LTBI, or individuals suspected to have TB, be managed in their initial contact with the healthcare system?

Contacts with LTBI or individuals suspected of disease should be referred to a physician with experience in TB, particularly MDR TB and XDR TB.

For case management of children in contact with patients with MDR TB or XDR TB, ideally either a national consultant for clinical TB or experienced paediatric infectious disease or paediatric pulmonologist specialist should be consulted.

The MDR TB or XDR TB contacts diagnosed with LTBI should receive the contact details of a, preferably named, healthcare worker from the local TB clinic, whom they can consult in case of symptoms suggestive of TB or if adverse events occur.

To what information should the physician responsible for an identified MDR TB and XDR TB contact have access?

The physician in charge of the contact diagnosed with LTBI or TB disease should be informed about the relevant results of the contact investigation and about the current national guidelines.

3.3 Clinical consultation and information to the contact

General considerations

- As indicated by the ISTC [2] and ESTC [4], all healthcare providers responsible for a patient with TB (or suspected TB) should ensure that contacts of the TB patient are evaluated and managed in line with national and international recommendations. The care and preventive measures should be tailored to the individual patient's circumstances and include an assessment of adherence to treatment and promote full adherence of TB treatment [2, 4].
- Evaluation of identified contacts should follow a comprehensive individual risk assessment.

Evidence and background documents

The expert opinions on clinical consultation and information to the contact or to the parent or other caregiver of a contact are of a general nature, therefore availability of evidence is not relevant.

Expert opinions

These opinions are valid for both MDR TB and XDR TB contacts.

What should be included in the clinical assessment of MDR TB and XDR TB contacts?

Assessment should cover the complete medical history of the exposed contact (previous contacts, previous LTBI or TB disease, previous preventive therapy or TB treatment, country of birth, BCG vaccination, age of BCG vaccination, other medical conditions, medication, etc.). If indicated, a physical examination and interpretation of TST, IGRA and chest radiograph (or other imaging techniques) should be performed.

An extensive evaluation of risk factors for the development of TB disease in the contact should be carried out. Special attention should be given to contacts at very high risk, such as children and immunocompromised persons.

What information should be provided to the MDR TB and XDR TB contact diagnosed with LTBI?

If a contact has been identified as having LTBI (and TB disease has been excluded), the contact should be provided with consultation, information and health education by a physician or other healthcare worker experienced in the management of LTBI and TB disease.

Contacts should receive information regarding the risk of disease and symptoms of TB disease, and should receive specific instructions on further management during or after the period of preventive therapy or follow-up observation.

The information provided should take into account the individual risk factors (close and/or prolonged exposure, age, persons with immunodeficiency, risk factors for drug-related adverse events). The contact should receive information about the benefits and risks of preventive treatment and the likelihood of LTBI developing into TB disease.

The contact should also receive information about the possibility of developing TB after potential immune-suppression in the future. Contacts should be informed that the TB clinic should be contacted in case of possibly relevant complaints during and after the period of follow-up.

When the contacts do not speak the local language, an interpreter should be found to explain all relevant information to the contacts.

What information should parents and other caregivers of MDR TB and XDR TB contacts be given?

Parents of children with diagnosed LTBI should receive information and health education from a healthcare worker experienced in the diagnosis and treatment of LTBI and TB. Caregivers should receive information regarding risk of disease, symptoms of TB disease and they should receive specific instructions on further management during or after the period of follow-up.

3.4 Management of identified MDR TB and XDR TB contacts considered to have LTBI

General considerations

- The guidance given here focuses on those individuals who have been identified as MDR TB or XDR TB contacts and by clinical assessment are considered to have LTBI.
- An individual is considered to have LTBI when an overall risk assessment indicates so. The risk assessment should consider the individual's history of *M. tuberculosis* exposure, clinical history and risk factors, or presence of an immunological response by TST or IGRA (if applicable).
- Accessibility to healthcare for MDR TB or XDR TB contacts needs to be taken into account when developing national guidelines for the management of these contacts.

Options to consider in the management of contacts

Even with the available evidence collected in three recent systematic reviews on the benefit of preventive therapy and adverse events (see below) it is not possible to either support or reject preventive therapy at this stage. There are therefore two valid options to consider for the further management of MDR TB and XDR TB contacts. These are discussed here. Because of the inconclusive evidence and the lack of new studies on the topic, there is a range of recommendations provided in national and international guidelines and policy documents. In this chapter, we discuss the two options for preventive treatment or follow-up by careful clinical observation; further we present the most up-to-date information on the benefits and risks associated with these options. Finally, the expert panel provides an opinion on what to consider in the individual risk assessment of contacts and proposes how a contact should be managed given the available options.

Preventive therapy

Support of the concept

The purpose of preventive therapy is to prevent the progression of LTBI to TB disease in an individual who has been exposed to TB. The concept of preventive therapy has been shown to be effective for LTBI after contact with drug-susceptible TB (see 2.4). The corresponding evidence for preventive therapy of MDR TB and XDR TB contacts is very scarce, although for children there are indications of a positive effect of preventive therapy (see below). For other groups of contacts, the necessary body of evidence has yet to be generated, and there are ongoing studies to collect evidence in support of the use of preventive therapy in contacts of MDR TB cases. One of these studies involves the provision of second-line preventive therapy for MDR TB contacts from two outbreaks in Micronesia, which seems to point towards a positive effect of preventive therapy in a general population of MDR TB contacts. However, as this study is not yet published in a peer-reviewed journal, some sources of bias cannot be excluded at this stage and these findings have to be confirmed in larger trials and other settings.

General considerations

- MDR TB and XDR TB are two definitions based on distinct and specific drug susceptibility patterns. There is, however, a multitude of other resistance patterns, and the feasibility of preventive therapy will depend on the number of drugs available for the specific infecting strain of *M. tuberculosis*.
- To inform the management of a MDR TB or XDR TB contact and as part of the care of the source case, the drug susceptibility pattern of the infecting organism (the source of infection) should be determined and rapid tests for drug resistance should be used, provided that local resources allow this.
- The efficacy of any regimen will depend on treatment adherence and completion by the contact, which could be influenced by adverse events during the specific drug regimen. Thus, to ensure the efficacy of preventive therapy, treatment adherence support, and a close dialogue between contact and healthcare provider needs to be in place so that adverse events and compliance can be addressed appropriately.

Information and observation

Support of the concept

The purpose of providing information and follow-up with careful clinical observation for those who have been in contact with an infectious MDR TB or XDR TB case, is to detect signs of TB disease early so that prompt treatment can be provided to cure the patient and stop further transmission of MDR TB and XDR TB in the community. So far, this option has been the preferred one in many national recommendations in the EU/EEA, as there is a lack of evidence supporting alternatives to giving preventive therapy. In contacts where the risks outweigh the benefits of preventive therapy, close observation is thus the only alternative, particularly in contacts at high risk of adverse events or contacts who are most likely infected with a *M. tuberculosis* strain for which there is no reasonable preventive drug regimen available.

General considerations

- There is scarce evidence for a best practise for follow-up observation of contacts of susceptible TB, MDR TB and XDR TB.
- It is essential to have a close dialogue with the contact (or parent/caregiver in case of a child contact) on the risks of developing TB disease and to regularly perform careful clinical evaluations to ensure prompt and early detection of TB disease.

Evidence and background documents

Benefit of preventive therapy of MDR TB contacts

The KNCV/DCC/ECDC systematic review assessing the effectiveness of preventive therapy identified three eligible studies [9].

Attamna et al. [54] described the incidence of MDR TB disease in close contacts (n=476) of patients with pulmonary MDR TB (n=78) after preventive therapy, compared to the incidence in close contacts that did not receive preventive therapy. The study was performed in Israel between 1998 and 2006. Follow-up was provided for a minimum of three years, with a maximum of eight years. In this study, no cases of TB occurred in either the treated or the untreated group, therefore this study provides very limited evidence (Table 5).

Kritski et al. [55] retrospectively studied (1988 and 1992) close contacts (n=218) of retreated patients with MDR TB (n=64). The study was performed in Brazil. Some contacts received isoniazid preventive therapy while others did not. The risk of developing active TB disease was lower in the treated group, but the risk difference was not significant, with a risk difference of 4% (95% CI: -3% to 12%) in favour of preventive therapy (Table 5). Note that the two contacts who developed TB were afflicted by a strain resistant to isoniazid and rifampicin, and their index cases had *M. tuberculosis* isolates of same resistance pattern.

Schaaf et al. [56] performed a prospective cohort study in infected (n=61) and non-infected (n=44) children below five years of age in household contact with adults with pulmonary MDR TB (n=73). The study was conducted in South Africa between 1994 and 2000. All infected children and all children below two years of age who had received no previous treatment or preventive therapy of any kind for TB were offered preventive therapy. This study is the only one that provides evidence that preventive therapy – taking into account the resistance profile of the index case – may prevent TB disease in children (under the age of five years) who are in contact with MDR TB patients [56]. The risk of developing TB disease was lower in the treated group, but the risk difference was not significant, with a risk difference of 5% (95% CI -2% to 11%) in favour of preventive therapy. The study found a significant risk difference of 15% (95% CI -27% to -4%) (Table 5) between treated and untreated children when assessing confirmed and probable TB. All three culture-confirmed TB cases occurred in children not receiving preventive therapy.

Risk of bias assessment

In all studies, the untreated contacts were a selected group, either because they had received previous TB treatment or preventive therapy [56]. In all cases, the decision of treatment was in the discretion of the physician [54] or not reported and thus unclear [55]. This type of selection bias, however, is inherent to the observational nature of these studies.

The results of the studies were not adjusted for confounders, which puts them also at high risk of bias. For example, in Schaaf et al., the children who received preventive therapy were the group with the higher risk for developing disease since they were significantly younger, had more sputum smear-positive index cases, had a higher rate of infection, and had less often received previous treatment or preventive therapy [56]. Kritski et al. provided insufficient information on the comparability of the treated and untreated groups and the duration of follow-up [55]. Attamna et al. did not provide information on the comparability of the exposed and non-exposed [54].

Summary

The existing studies provide little evidence for special risk groups as contacts were not stratified in any particular risk groups, except for the study on children by Schaaf et al. Consequently, there is no specific evidence available relating to the benefit of preventive therapy in immunocompromised MDR TB contacts. Please note that because of the low number of events, the confidence intervals are wide. Also, there is a considerable source of bias in these observational studies, owing to the relatively small sample sizes in the included studies that provide the collected evidence base. More on this can be found in the full KNCV/DCC/ECDC systematic review [9].

Conclusions

The systematic review concludes that it is not possible with the available evidence to support or reject preventive therapy. Only a limited amount of evidence supports the effectiveness of preventive therapy. More research and particularly clinical trials are warranted before any recommendations in favour of (or against) preventive therapy can be made.

Table 5: Description and results of the studies assessing the effectiveness of preventive therapy in MDR TB contacts

Study	Sample size (n)	Active TB disease (n, %)		Prophylaxis regimen (n)	Risk difference (95% CI)	Odd ratio (95% CI)
		Preventive therapy	No preventive therapy			
Attamna 2009 Contacts	476 adults	0/89 (0)	0/387 (0)	Tailored regimen (mainly ciprofloxacin and pyrazinamide) (12), isoniazid, (71), other treatments (6)	0.00 (-0.02; 0.02)	-
Kritski 1996 Contacts[1]	218 adults	2/45 (4.4) 1.2/1000 pm	15/173 (8.7) 1.7/1000 pm	Isoniazid	-0.04 (-0.12; 0.03)	0.49 (0.11-2.23)
Kritski 1996 Infected contacts[2]	188 adults	2/45 (4.4)	13/145 (9.0)	Isoniazid	-0.05 (-0.12; 0.03)	0.46 (0.07-2.32)
Schaaf 2002 Contacts	61 infected[3] children 44 uninfected[4] children	Confirmed TB[5] 0/41 (0) Confirmed+ probable TB[6] 2/41 (4.9)	Confirmed TB 3/64 (4.7) Confirmed+ probable TB 13/64 (20.3)	Individualised treatment[7].	Confirmed TB -0.05 (-0.11; 0.02) Confirmed+ probable TB -0.15 (-0.27;-0.04)	0.21 (0.01-4.21) 0.20 (0.04-0.94)

[1] *Persons living in the same household as the index case during the entire five previous years.*

[2] *Persons living in the same household as the index case during the entire five previous years with a TST result ≥10 mm.*

[3] *TST of ≥ 15 mm, symptomatic, normal chest radiograph or only calcifications in the lung parenchyma of regional lymph nodes on the chest radiograph.*

[4] *Asymptomatic, nonsignificant (<15 mm induration) TST, normal chest radiograph, and negative cultures for* M. tuberculosis.

[5] *Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on chest radiograph; or adenopathy compressing airways identified by bronchoscopy and culture-positive for* M. tuberculosis *or acid-fast bacilli on microscopy.*

[6] *Well-defined hilar or mediastinal adenopathy, miliary or endobronchial TB on chest radiograph; or adenopathy compressing airways identified by bronchoscopy.*

[7] *High dose isoniazid 15-20 mg/kg/d, pyrazinamide 25-35 mg/kg/d, ethionamide 10-15 mg/kg/d and/or ethambutol 15-20 mg/kg/d and/or ofloxacin 15 mg/kg/d. The administration of the latter two drugs depends on the susceptibility pattern of the strain isolated from the index case. Children who had received previous TB treatment or chemoprophylaxis with isoniazid (with or without rifampicin/pyrazinamide) were not routinely prescribed another course of chemoprophylaxis except when it was preferred by the parent instead of a follow-up.*

Preventive therapy in contacts of MDR TB in two outbreaks in Chuuk, Federated States of Micronesia

An intervention with second-line preventive therapy for MDR TB contacts in two outbreaks in Chuuk, Federated States of Micronesia, showed the benefit of preventive therapy in MDR TB contacts (provisional unpublished data). The associated studies are awaiting publication, but the outbreaks have been previously described in short reports [57-60]. For the purpose of this guidance document, we have received the approval from the investigators to briefly describe the outbreaks and the preliminary outcome findings.

In July 2008, the US CDC responded to a request from the Federated States of Micronesia to investigate two distinct and simultaneous MDR TB outbreaks. This is a summary of the latest findings as of February 2012, after the final evaluation of all identified infected and uninfected contacts was completed. In these outbreaks, a total of five MDR TB patients infected with two different strains were identified. Contact tracing was initiated, and 232 contacts were identified. One strain (A) was resistant to isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin; the other strain (B) displayed resistance to isoniazid, rifampicin and ethionamide. A complete evaluation of the MDR TB contacts was performed. Fifteen were diagnosed with MDR TB disease, five were diagnosed with drug-susceptible TB disease, and 119 were considered to have LTBI with positive TST and therefore offered LTBI preventive therapy. 14 of the 119 cases refused the treatment. After exclusion of TB disease, LTBI preventive therapy was initiated in a total of 105 contacts considered to have LTBI. All therapy was directly observed, and a fluoroquinolone-based regimen was chosen: fluoroquinolone alone or in combination with ethionamide for one strain (A), fluoroquinolone with ethambutol for the other (B). The two-drug regimen was used in children were mono-therapy was not regarded to be sufficient. Ninety-three of the 105 completed the MDR LTBI therapy. There are so far no cases of MDR TB disease among those who initiated MDR LTBI therapy. In total, 28 contacts (15 contacts of the original five MDR TB patients, plus 11 additionally linked MDR TB cases in persons not previously identified as contacts, and two of the 14 who refused MDR LTBI therapy) developed MDR TB disease or were treated as MDR TB clinical cases between July 2008 and February 2012.

This data document the safety and tolerability of the fluoroquinolone-based regimen (twelve contacts discontinued treatment, but only four of those due to adverse events; four other patients interrupted treatment due to adverse events, but ultimately were able to complete treatment). Fifty-two patients reported adverse events but completed the preventive therapy. These patients reported side effects at 159 (15%) of 1 038 monthly DOT visits, with the most frequent adverse events being nausea, headache or dizziness.

Adverse events in anti TB treatment

A systematic review assessed the adverse events of preventive therapy (anti TB drugs other than isoniazid or rifampicin) in healthy individuals [10].

Twenty eligible studies were identified: 14 randomised controlled trials (RCTs) with a total of 20 study arms with anti TB drugs and six non-comparative observational studies, of which four case series described the occurrence of adverse events during preventive therapy of MDR TB. The following anti TB drugs were used in the included studies: levofloxacin, moxifloxacin, ofloxacin, rifabutin, pyrazinamide and ethambutol.

Levofloxacin

For levofloxacin (six studies; eight study arms) no severe adverse events were reported, i.e. no adverse events that needed treatment, and the reason for drop-out was not related to adverse events. The dosage of levofloxacin varied between 400 and 1000 mg per day. Seven out of eight study arms had a duration of one week. The studies' sample size included at maximum of 20 participants.

Moxifloxacin

For moxifloxacin (five studies) one severe adverse event that needed treatment was reported in 41 participants in one study. In another study, one in 76 participants discontinued treatment because of adverse events. The dosage of moxifloxacin was 400 mg per day in all studies. Three out of five studies reported treatment duration of one week. The sample size varied between 10 and 76 participants.

Ofloxacin

For ofloxacin (four studies with ofloxacin given as a single drug; six study arms) three participants (out of 40 participants, one study) needed treatment of an adverse event, which was also a reason for discontinuation of treatment. In another study, two out of 12 participants discontinued treatment because of adverse events. The dosage of ofloxacin ranged between 200 and 400 mg per day. Three out of four studies provided treatment of one week. The sample size varied between 12 and 40 participants.

Rifabutin

For rifabutin (two studies; three study arms), three participants (two out of 13, and one out of 20 participants, from one study with two study arms) discontinued treatment because of adverse events. The dosage of rifabutin was 300 mg per day. The duration of treatment was 10 and 13 days, respectively, for the two studies. The sample size varied between 13 and 20 participants.

Pyrazinamide combinations in MDR TB contacts

Four case series reported on the preventive therapy of (possible) LTBI of MDR TB contacts. Combination therapy was prescribed for six to 12 months. All used pyrazinamide with another drug (ofloxacin in two studies, ethambutol in one, and levofloxacin in another study), i.e. pyrazinamide without isoniazid.

All these studies reported a high frequency of adverse events. Treatment was discontinued in 58% to 100% of the subjects due to adverse events ranging from mild adverse events such as nausea and dizziness to serious effects requiring treatment.

Risk of bias

The following risks of bias in the studies described above were identified:

For the RCTs, the risk of bias for random sequence generation was unclear in all studies except one. Allocation concealment was not described in any of the trials. Six of the 14 trials were at high risk of bias because of lack of blinding. All trials were actively controlled. Beforehand knowledge about the potential adverse events may have caused bias in reporting adverse events, although the direction of the bias (under- or overreporting) remains unclear.

The single-arm intervention studies in healthy volunteers had some methodological problems. For Van Saene et al., there was no demonstration that the volunteers were healthy, and the target population from which the volunteers were selected was not described [61]. Furthermore, outcome assessment was not described, which was the same for Zhang et al. [62].

Summary

For all four of the drug treatments mentioned above, minor adverse events like dizziness, headache and gastrointestinal disorders were reported relatively frequently. However, similar symptoms were also seen in the comparator groups. Only four placebo-controlled studies mentioned the presence or absence of differences in the frequency of adverse events between groups, and only three of these tested these potential differences statistically.

Levofloxacin does not seem to evoke more adverse events than placebo treatment. The data suggest that gastrointestinal symptoms occur more frequently in those treated with moxifloxacin than in placebo-treated persons, but this potential difference was not tested in four out of five studies. Gastrointestinal symptoms also seem to be more prevalent in those receiving ofloxacin than in placebo-treated persons. For rifabutin no conclusion can be drawn since only one study arm compared rifabutin treatment to placebo treatment.

Conclusions

The available evidence on adverse events of anti TB drugs other than isoniazid or rifampicin in healthy individuals come from those RCTs which provide indirect evidence, but their sample sizes were small and the number of adverse events low. The available evidence on adverse events of preventive therapy in MDR TB contacts stems from those case-series studies which provide a direct answer, but since all are observational studies there is a considerable risk of bias. In conclusion, adverse events need to be taken into account in the individual risk assessment when evaluating an MDR TB contact for preventive therapy or follow-up. The available evidence on adverse events is not strong enough to support or reject preventive therapy.

Follow-up

There is currently no evidence available on the optimal follow-up time in contacts of MDR TB or XDR TB with regard to patient benefits and costs of the intervention. However, the lifetime risk of developing tuberculosis disease in immunocompetent adults is about 10%, with half of this risk within the first one to two years after infection [26, 63]. The risk of progressing to TB disease remains after the first two years after infection, but no cut-off point exists as to when follow-ups for the detection of TB can be discontinued, as there are no medical benefits. In young children under five years of age the majority (>90%) of TB disease will develop within 12 months of infection [49]. Infants and children under five years of age [29], immunocompromised individuals due to HIV infection [25] or TNF-antagonist treatment [64, 65] are at increased risk of progression from LTBI to TB disease. These individuals as well as other identified risk groups require special attention as part of the individual risk assessment.

Expert opinions

The opinions expressed below are specific in respect to MDR TB and XDR TB contacts, as special consideration has to be given to XDR TB contacts. The opinions expressed are in relation to the currently available anti TB drugs and the available evidence on benefits and adverse events of preventive therapy, as of November 2011.

Which factors should be evaluated to inform the decision whether to provide preventive therapy to MDR TB contacts considered to have LTBI?

When evaluating an MDR TB contact and deciding between the two options (to provide preventive therapy and/or careful clinical observation and information), an overall individual risk assessment should be conducted, taking into consideration the following: the MDR TB contact's risk for progression to TB disease; the drug susceptibility pattern of the source case of infection; and the contact's risk for adverse drug events if initiating preventive therapy.

Are there any specific risk groups to whom special attention should be paid?

Children below the age of five years and immunocompromised persons in close contact with MDR TB patients and considered to have LTBI are at particular risk of progressing to TB disease. These risk groups might benefit from preventive therapy. The preventive therapy may be interrupted if, based on further examination, infection is found to be unlikely.

Persons over five years of age in close contact with MDR TB patients and considered to have LTBI could also be considered for preventive therapy if the individual risk assessment indicates this course of action.

If the decision is made to put an individual on preventive therapy, the selection of the drugs should be based on:

- the drug susceptibility pattern of the source case's likely infecting strain;
- local patterns of drug resistance;
- the potential adverse events in individual patients, taking into account age and other risk factors;
- the selection of single or multiple drugs and the duration of treatment will depend on the availability of drugs with bactericidal activity for the particular infecting strain; alternatively, the decision can follow national guidelines.

Which arrangements should be in place if preventive therapy is considered?

If preventive therapy is considered by the expert physician or other healthcare provider, national legislation should ensure that the treatment costs for the patient are covered.

If preventive therapy is considered to be relevant for a particular individual, careful clinical monitoring and follow-up is essential for the detection of drug-adverse events and signs of TB disease if the preventive therapy is not effective.

Specific opinions for XDR TB contacts

As the currently available treatment options are very limited for XDR TB, it is likely that the risks of preventive therapy outweigh the benefits for contacts of XDR TB patients. Thus, the option to inform and observe the contacts will be preferable, given the currently available drugs and evidence.

How should health authorities conduct follow-ups for MDR TB and XDR TB contacts suspected to have LTBI?

All MDR TB and XDR TB contacts considered to have LTBI who, after a comprehensive individual risk assessment, are not given preventive therapy should be followed-up by careful clinical observation.

Follow-ups should be performed according to existing national guidelines.

All persons in contact with MDR TB or XDR TB (after exclusion of TB disease) should be informed about the risks and symptoms, carefully observed, and provided with easy access to a specialised TB clinic in case of symptoms between assessments. No specific time period for follow-up or periodicity of clinical assessments is recommended, but regular systematic, clinical observation is essential for the early detection of TB disease (see also 3.4).

Individuals repeatedly in contact with infectious MDR TB or XDR TB cases (e.g. healthcare workers) should be re-examined periodically.

4 Future research needs

There is a need for further research in this area. The following research priorities were identified by ECDC and the expert panel:

Tracing of MDR TB contacts is important to prevent TB disease and further transmission. Studies are needed:

- to identify the most effective contact-tracing procedures for close contacts;
- to identify the most effective follow-up procedures in healthcare workers constantly exposed to MDR TB.

As part of the management of MDR TB contacts, studies on specific groups are needed, e.g. on children below the age of five years, children with HIV infection, immunocompromised individuals, pregnant women, and the elderly. In particular, studies are needed:

- for treated contacts: (randomised) clinical trials:
  - to determine which drugs and which drug combinations and dosages are optimal for preventive therapy;
  - to assess the effectiveness of the different regimens;
  - to determine the duration of preventive therapy;
- to assess the effectiveness of preventive therapy in conjunction with antiretroviral treatment;
- to assess the risk of development of new drug resistance in contacts receiving (inadequate and adequate) preventive therapy;
- for untreated contacts, and healthcare workers constantly exposed to MDR TB:
  - to identify the optimal follow-up period for different groups of individuals;
  - to identify the optimal frequency of testing for LTBI during the follow-up period.

In order to increase adherence to treatment of MDR TB contacts (and reduce the risk of development of new drug resistance in contacts), studies are needed:

- to identify new drugs with less adverse events and to explore possible (positive and negative) interactions between combined drugs;
- to identify biomarkers indicating the risk of progression from LTBI to TB disease; and
- to assess operational management to shorten preventive therapy.

Cost-effectiveness and cost-benefit studies are needed: as the provision of preventive therapy has economic implications (as well as logistic ones) at the national and community level, cost-effectiveness and cost-benefit studies are of value to inform the decision whether to implement policies such as the systematic provision of preventive therapy.

Data modelling studies are needed: detailed dynamic transmission models can underpin the health economic data and allow generalisability to different settings.

Basic research studies are needed:

- to assess whether MDR TB is more or less infectious and/or transmissible than drug-susceptible TB; and
- to assess if individuals infected with MDR TB develop TB later than individuals infected with drug-susceptible TB.

References

1. van der Werf MJ, Sandgren A, Manissero D. Management of contacts of multidrug-resistant tuberculosis patients in the European Union and European Economic Area. Int J Tuberc Lung Dis. 2012 Mar;16(3):426.
2. Gagneux S. Fitness cost of drug resistance in *Mycobacterium tuberculosis*. Clin Microbiol Infect. 2009 Jan;15 Suppl 1:66-8.
3. Migliori GB, Sotgiu G, Blasi F, Zumla A, Loddenkemper R, Raviglione MC, et al. Towards the development of EU/EEA standards for tuberculosis care (ESTC). Eur Respir J. 2011 Sep;38(3):493-5.
4. Migliori GB, Zellweger JP, Abubakar I, Ibraim E, Caminero JA, De Vries G, et al. European Union standards for tuberculosis care. Eur Respir J. 2012; in press.
5. Passannante MR, Gallagher CT, Reichman LB. Preventive therapy for contacts of multidrug-resistant tuberculosis. A Delphi survey. Chest. 1994 Aug;106(2):431-4.
6. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep. 2000 Jun 9;49(RR-6):1-51.
7. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: World Health Organization; 2008.
8. National Institute for Health and Clinical Excellence. NICE clinical guideline 117. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: National Institute for Health and Clinical Excellence; 2011.
9. van der Werf MJ, Langendam MW, Sandgren A, Manissero D. Lack of evidence to support policy development for management of contacts of MDR TB patients: two systematic reviews. Int J Tuberc Lung Dis. 2012 Mar;16(3):288-96(9).
10. Langendam MW, Tiemersma EW, van der Werf MJ, Sandgren A. Adverse effects of anti-tuberculosis drugs in healthy individuals: a systematic review. Unpublished manuscript. 2012.
11. WHO. Global tuberculosis control: WHO report 2011. Geneva: World Health Organization; 2011.
12. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2009. Stockholm: ECDC; 2011.
13. WHO. Multidrug and extensively drug-resistant TB (M/XDR TB): 2010 global report on surveillance and response. Geneva: World Health Organization; 2010.
14. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2008. ECDC: Stockholm; 2010.
15. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax. 2006 Feb;61(2):158-63.
16. Eurosurveillance editorial team. New WHO Europe action plan to fight MDR TB. Euro Surveill. 2011;16(37).
17. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2011.
18. Sotgiu G, D'Ambrosio L, Centis R, Bothamley G, Cirillo DM, De Lorenzo S, et al. TB and M/XDR TB infection control in European TB reference centres: the Achilles' heel? Eur Respir J. 2011 Nov;38(5):1221-3.
19. Migliori GB, Sotgiu G, D'Ambrosio L, Centis R, Lange C, Bothamley G, et al. TB and MDR/XDR TB in European Union and European Economic Area countries: managed or mismanaged? Eur Respir J. 2012 Mar;39(3):619-25.
20. Barry CE, 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nature reviews. 2009 Dec;7(12):845-55.
21. Gideon HP, Flynn JL. Latent tuberculosis: what the host 'sees'? Immunologic research. 2011 Aug;50(2-3):202-12.
22. Marciniuk DD, McNab BD, Martin WT, Hoeppner VH. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Chest. 1999 Feb;115(2):445-52.
23. Schaaf HS, Beyers N, Gie RP, Nel ED, Smuts NA, Scott FE, et al. Respiratory tuberculosis in childhood: the diagnostic value of clinical features and special investigations. Pediatr Infect Dis J. 1995 Mar;14(3):189-94.
24. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm: ECDC; 2011.
25. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 Mar 2;320(9):545-50.

26. Poulsen A. Some clinical features of tuberculosis. 1. Incubation period. Acta Tuberc Scand. 1950;24(3-4):311-46.
27. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008 Jul 15;5(7):e152.
28. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009 Jan 1;48(1):72-82.
29. World Health Organization Stop TB Partnership Childhood TB Subgroup. Chapter 4: childhood contact screening and management. Int J Tuberc Lung Dis. 2007 Jan;11(1):12-5.
30. Fox GJ, Dobler CC, Marks GB. Active case finding in contacts of people with tuberculosis. Cochrane database of systematic reviews (Online). 2011;9:CD008477.
31. Bothamley GH, Ditiu L, Migliori GB, Lange C. Active case finding of tuberculosis in Europe: a Tuberculosis Network European Trials Group (TBNET) survey. Eur Respir J. 2008 Oct;32(4):1023-30.
32. Erkens CG, Kamphorst M, Abubakar I, Bothamley GH, Chemtob D, Haas W, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. Eur Respir J. 2010 Oct;36(4):925-49.
33. Andersson DI, Levin BR. The biological cost of antibiotic resistance. Current opinion in microbiology. 1999 Oct;2(5):489-93.
34. von Groll A, Martin A, Stehr M, Singh M, Portaels F, da Silva PE, et al. Fitness of Mycobacterium tuberculosis strains of the W-Beijing and Non-W-Beijing genotype. PloS one. 2010;5(4):e10191.
35. Borrell S, Gagneux S. Infectiousness, reproductive fitness and evolution of drug-resistant Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009 Dec;13(12):1456-66.
36. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane database of systematic reviews (Online). 2000(2):CD001363.
37. Gray DM, Zar H, Cotton M. Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children. Cochrane database of systematic reviews (Online). 2009(1):CD006418.
38. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane database of systematic reviews (Online). 2010(1):CD000171.
39. Menzies D, Al Jahdali H, Al Otaibi B. Recent developments in treatment of latent tuberculosis infection. Indian J Med Res. 2011 Mar;133(3):257-66.
40. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. Jama. 1999 Mar 17;281(11):1014-8.
41. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS (London, England). 2007 Jul 11;21(11):1441-8.
42. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011 May 7;377(9777):1588-98.
43. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. The New England journal of medicine. 2011 Jul 7;365(1):11-20.
44. Hsu KH. Thirty years after isoniazid. Its impact on tuberculosis in children and adolescents. Jama. 1984 Mar 9;251(10):1283-5.
45. Holty JE, Sista RR. Mycobacterium tuberculosis infection in transplant recipients: early diagnosis and treatment of resistant tuberculosis. Current opinion in organ transplantation. 2009 Dec;14(6):613-8.
46. WHO. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011.
47. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. The New England journal of medicine. 2011 Dec 8;365(23):2155-66.
48. Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med. 2006 Apr 15;173(8):922-6.
49. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2011 Dec 9;60:1650-3.
50. Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf HS, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ (Clinical research ed. 2007 Jan 20;334(7585):136.
51. WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2006.

52. Centers for Disease Control and prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Atlanta: CDC; 2010.
53. WHO and The International Union Against tuberculosis and Lung Disease. Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach. Paris, France2010.
54. Attamna A, Chemtob D, Attamna S, Fraser A, Rorman E, Paul M, et al. Risk of tuberculosis in close contacts of patients with multidrug resistant tuberculosis: a nationwide cohort. Thorax. 2009 Mar;64(3):271.
55. Kritski AL, Marques MJ, Rabahi MF, Vieira MA, Werneck-Barroso E, Carvalho CE, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 1996 Jan;153(1):331-5.
56. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. Pediatrics. 2002 May;109(5):765-71.
57. Two simultaneous outbreaks of multidrug-resistant tuberculosis--Federated States of Micronesia, 2007-2009. MMWR Morb Mortal Wkly Rep. 2009 Mar 20;58(10):253-6.
58. Bamrah S, Brostrom R, Setik L, Fred D, Kawamura M, Mase R. Abstracts of the 41th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (IUATLD). Berlin, Germany, 11-15 November, 2010. Int J Tuberc Lung Dis. 2010 Nov;14(11 Suppl 2):S11-387.
59. Brostrom R, Fred D, Heetderks A, Desai M, Song R, Haddad M, et al. Islands of hope: building local capacity to manage an outbreak of multidrug-resistant tuberculosis in the Pacific. Am J Public Health. 2011 Jan;101(1):14-8.
60. Fred D, Desai M, Song R, Bamrah S, Pavlin BI, Heetderks A, et al. Multi-drug resistant tuberculosis in Chuuk State Federated States of Micronesia, 2008-2009. Pac Health Dialog. 2010 Apr;16(1):123-7.
61. van Saene HK, Lemmens SE, van Saene JJ. Gut decontamination by oral ofloxacin and ciprofloxacin in healthy volunteers. J Antimicrob Chemother. 1988 Sep;22 Suppl C:127-34.
62. Zhang L, Li JT, Lu Y, Li MN, Zhang YL, Liu Y, et al. Pharmacokinetics of multiple intravenous instillation of levofloxacin in Chinese healthy subjects. Acta Pharmacol Sin. 2002 Apr;23(4):381-4.
63. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibliotheca tuberculosea. 1970;26:28-106.
64. Salgado E, Gomez-Reino JJ. The risk of tuberculosis in patients treated with TNF antagonists. Expert Rev Clin Immunol. 2011 May;7(3):329-40.
65. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J. 2010 Nov;36(5):1185-206.