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Guiding Principles to Reduce Tuberculosis Transmission in the WHO European Region

Giovanni Battista Migliori, Lia D'Ambrosio, Rosella Centis,
Martin Van Den Boom, Soudeh Ehsani, Masoud Dara

ABSTRACT

Evidence-based guidance is needed on (i) how tuberculosis (TB) infectiousness evolves in response to effective treatment and (ii) how the TB infection risk can be minimized to help countries to implement community-based, outpatient-based care while reducing TB-related suffering and improving TB treatment outcomes. This document aims to 1) review the available evidence on how TB infectiousness evolves in response to effective treatment and which factors can lower or boost infectiousness; 2) present policy options on the infectiousness of TB patients relevant to the WHO European Region; 3) define the limitations in the available evidence and 4) provide recommendations for further research. The document aims to target all professionals dealing with TB (e.g. TB specialists, pulmonologists, infectious disease specialists, primary health care professionals, and other clinical and public health professionals), as well as health staff working in settings where TB transmission may occur.

Keywords

Tuberculosis - diagnosis, drug therapy, epidemiology, prevention and control, transmission
Tuberculosis, Multidrug-resistant - diagnosis, drug therapy, epidemiology, prevention and control, transmission
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Abbreviations

ACH	air changes per hour
EQA	external quality assurance
DOT	directly observed therapy
DST	drug-susceptibility testing
FAST	Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely and Treat effectively based on rapid drug-susceptibility testing
HBC	high-burden countries
IGRA	interferon gamma release assay
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
OR	odds ratio
PAS	*para*-aminosalicylic acid
TB	tuberculosis
TST	tuberculin skin test
UV	ultraviolet
UVGI	upper room ultraviolet germicidal irradiation
XDR-TB	extensively drug-resistant tuberculosis

Contributors

Authors

Giovanni Battista Migliori
WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italy

Lia D'Ambrosio
WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italy

Rosella Centis
WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italy

External peer reviewers

Edward Nardell
Division of Global Health Equity, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Marina Tadolini
Unit of Infectious Diseases, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Italy

Giovanni Sotgiu
Clinical Epidemiology and Medical Statistics Unit, Department of Clinical and Experimental Medicine, University of Sassari, Italy

Askar Yedilbayev
Partners In Health, Boston, Massachusetts, United States of America

Masoud Dara
Joint Tuberculosis, HIV and Viral Hepatitis programme, WHO Regional Office for Europe, Copenhagen, Denmark

Martin van den Boom
Joint Tuberculosis, HIV and Viral Hepatitis programme WHO Regional Office for Europe, Copenhagen, Denmark

Soudeh Ehsani
Joint Tuberculosis, HIV and Viral Hepatitis programme WHO Regional Office for Europe, Copenhagen, Denmark

WHO Regional Office for Europe

Masoud Dara
Joint Tuberculosis, HIV and Viral Hepatitis programme

Martin van den Boom
Joint Tuberculosis, HIV and Viral Hepatitis programme

Soudeh Ehsani
Joint Tuberculosis, HIV and Viral Hepatitis programme

Executive summary

More evidence-based guidance is needed on (i) how tuberculosis (TB) infectiousness evolves in response to effective treatment and (ii) how the TB infection risk can be minimized. This will help countries to move away from mainly providing traditional hospital-based, hospital-oriented treatment and care towards more community-based, outpatient-based care, in an effort to ultimately contribute to reducing TB-related suffering and improve TB treatment outcomes.

This document aims to:

- review the available evidence on:
  - how TB infectiousness evolves in response to effective treatment;
  - which factors can lower TB infectiousness; and
  - which factors contribute to increasing TB infectiousness;
- present policy options on the infectiousness of TB patients relevant to the WHO European Region; and
- define the limitations in the available evidence; and
- provide recommendations for further research.

The document aims to target all professionals dealing with TB (e.g. TB specialists, pulmonologists, infectious disease specialists, primary health care professionals, and other clinical and public health professionals), as well as health staff working in settings where TB transmission may occur.

Answers to the following six questions are crucial to inform policy guidance.

1. Which patients are infectious and which factors favour transmission?
2. When does an infectious patient become non-infectious after starting treatment?
3. What can render the patient non-infectious more rapidly?
4. What can limit the rapid decline in a patient's infectiousness?
5. Which patients need hospital admission (and respiratory isolation) because of their infectiousness?
6. What are the research needs?

Relevant scientific documents published in English in the grey literature were identified using the following keywords in the Google search engine: "Tuberculosis"; "MDR-TB" (including extensively drug-resistant-TB (XDR-TB)); "infectiousness"; "contagiousness"; "'transmission" and "infection control".

The following main policy elements are derived from the present review:

- infection control planning is needed at the national/subnational and facility levels;
- three groups of actors should be considered – patients, health care workers and visitors;
- in the absence of stronger evidence, the cut-off value of 8-h exposure is not useful to activate contact tracing. In children and other vulnerable groups, a shorter exposure time will probably be sufficient for infection to occur. Criteria related to the intensity, frequency and duration of exposure should guide the contact-tracing plan following exposure to an infectious TB patient based on the concentric circle approach;
- sputum smear microscopy is a quick, cheap tool for assessing pretreatment infectiousness, although it has limitations. Up to one fifth of untreated sputum smear-positive cases can transmit *M. tuberculosis*. Sputum culture is useful to demonstrate the viability of bacilli, although results take two to three weeks and it cannot predict infectiousness once the treatment starts;
- although sputum smear and culture tests can still be positive more than two weeks after treatment starts, the available evidence shows that infectiousness drops very rapidly if adequate treatment is implemented – however, this is difficult to quantify;
- it is easier to provide adequate treatment when the *M. tuberculosis* strain is drug susceptible. The real risk is infection from undetected multidrug-resistant TB (MDR-TB) or XDR-TB cases;
- new rapid molecular diagnostic techniques (i.e. Xpert MTB/RIF, line probe assays (LPAs)) should be systematically used to promptly identify drug-resistant patients so that adequate treatment can be rapidly started, thus reducing the period of infectiousness;
- stringent isolation criteria are necessary for presumed and confirmed XDR-TB patients for whom treatment does not rapidly prevent transmission. Existing community-based programmes have shown that MDR-TB patients can also be managed at home because effective treatment rapidly reduces their infectiousness; and
- although outpatient management is recommended in principle, a proportion of TB patients (e.g. clinically severe cases) will need hospital admission. Any hospital admitting TB patients should offer adequate infection control and quality patient-centred management;

The key criteria for hospitalization are:

- complications of TB (e.g. respiratory failure and conditions requiring surgical interventions such as haemorrhage, pneumothorax and pleural effusion);

- severe forms of TB (i.e. TB meningitis) and/or severe clinical manifestations of comorbidities (e.g. liver disease, renal disease and uncontrolled diabetes); and
- life-threatening and serious medical events resulting from adverse reactions to anti-TB drugs (e.g. life-threatening arrhythmias, psychosis, renal failure and hearing loss).

Additional criteria (to be applied in rare and exceptional cases) are:

- patients for whom effective and safe anti-TB treatment cannot be ensured in an outpatient, community or home setting (i.e. homelessness, overcrowding, exposure of children aged under 5 years, and pregnant women in the household);
- when there are accessibility problems (i.e. patient lives far from an outpatient facility); and
- where there is non-adherence to treatment – can be considered as a last resort once all other care options have been used/applied exhaustively.

Any hospital or health facility admitting TB patients should offer adequate infection control measures in addition to high quality core services, including:

- clinical expertise on TB and M/XDR-TB management (including for directly observed therapy (DOT));
- laboratory results from laboratories with external quality assurance (EQA) and control systems in place (may be located elsewhere);
- respiratory isolation capacity and adequate infection control measures (including the recommended 12 air changes per hour (ACH));
- adequate and regular maintenance of their infection control equipment (i.e. ventilation systems, UVGIs etc.)
- personal protection measures (i.e. respirators) available within well-designed personal protection programmes that include staff awareness training/education and respirator fit testing;
- open spaces to allow patients to socialize without the risk of TB transmission;
- adequate numbers of staff trained and supervised to adhere to administrative and personal protection measures for infection control; and
- a people-centred approach (e.g. psychological support, palliative care, link with home care and social services for the post-discharge home care phase).

Introduction

Scope, purpose and target audience

More evidence-based guidance is needed on (i) how TB infectiousness evolves in response to effective treatment and (ii) how the TB infection risk can be minimized. This will help countries to move away from mainly providing traditional hospital-based, hospital-oriented treatment and care towards more community-based, outpatient-based care, in an effort to ultimately contribute to reducing TB-related suffering and improve TB treatment outcomes.

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1. Which patients are infectious and which factors favour disease transmission?
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Background

The 2011–2015 Roadmap to prevent and combat drug-resistant tuberculosis *(1)*, endorsed by the WHO Regional Committee for Europe, estimated that 250 000 new MDR-TB patients and 13 000 XDR-TB patients would be prevented; 225 000 MDR-TB patients would be diagnosed (of which, 127 000 would be successfully treated); and approximately 120 000 lives and US$ 5 billion would be saved by implementing the plan. In 2011, the approach of many countries to drug-resistant TB was based on small-scale pilot projects; however, in 2015, the vast majority of countries developed comprehensive national plans.

Between 2012 and 2016, TB notification rates declined from 40.8 per 100 000 population to 32.8 per 100 000 population *(2)*. Moreover, treatment success rates increased from 73% to 77% in new and relapsed patients and from 49% to 55% in rifampicin-resistant TB (RR-TB) and MDR-TB patients. In 2016, 73% of all estimated RR-TB and MDR-TB cases were detected, a notable increase from the baseline value of 62% documented in 2014. Furthermore, treatment coverage (including for MDR-TB) became universal, starting from a 63% baseline. The TB incidence and mortality decreased annually by 4.3% and 8.5%, respectively, over this period *(2)*. Additionally, drug stock-outs decreased, coverage of drug-susceptibility testing (DST) increased and electronic health records for individual surveillance largely replaced paper-based data collection. In parallel, TB awareness and its health implications, as well as political commitment, increased in the WHO European Region.

In 2016, the total number of TB cases notified in the Region was 297 132 (251 625 in the 18 high-burden countries (HBCs)), corresponding to a notification rate of 32.8 cases per 100 000 population (64.2 per 100 000 population in HBCs). Between 2012 and 2016, the average annual decline in notifications was 5.3% (5.6% in HBCs). This remarkable progress, on top of economic savings, prevented TB-related deaths and suffering and improved the Regional capacity for early TB diagnosis and effective treatment and follow-up.

However, the Region still has the highest prevalence of MDR-TB in the world, at approximately one in five new patients and one in two previously treated patient suffers from MDR-TB. Therefore, we need to rapidly improve our capacity to diagnose MDR-TB, treat cases adequately (based on the individual drug-resistance pattern) and ensure that patients successfully complete a full course of anti-TB treatment.

Among TB cases, the prevalence of MDR-TB remains high, at 17.7% of new cases and 51.9% of retreatment cases (51.9% and 53.5%, respectively, in HBCs). Among MDR-TB cases, the prevalence of XDR-TB is 13.1% *(2)*. However, MDR-TB treatment success rate has only marginally increased from 48% to 51% during the 2011–2015 period. In the last evaluated cohort (patients who started MDR-TB treatment in 2014 and completed it in 2016), the success rate has increased further to 54.7% over the Region and 54.8% in the 18 HBCs. TB/HIV coinfection and mortality rates have actually been increasing by 6.2% and 3.6% annually, respectively, over the same period, further fuelling the TB and MDR-TB epidemic.

The problems of addressing MDR-TB are manifold: they cannot be simply solved by introducing new drugs and shorter treatment regimens. Given the high complexity and the social nature of the disease, intensified efforts are needed to provide comprehensive people-centred approaches in the Region, in line with people's needs and preferences, to improve treatment adherence and, ultimately, treatment outcomes.

To this end, Member States need to fully understand the infectiousness of TB patients and the risk of infection once effective treatment has been started. Therefore, evidence-based guidance is needed on how infectiousness evolves in response to effective treatment and how the risk of infection can be minimized to reduce TB-related suffering and improve treatment outcomes.

Methodology

Literature search

Owing to the difficulty of summarizing the six questions within an overarching research question, it was necessary to use a research methodology incorporating a wide search of scientific manuscripts and documents using different search engines. It was particularly important to assess the current grey literature, along with studies preceding the Internet era.

Relevant scientific documents published in English (in Google Scholar and other grey literature sources) were identified using the Google search engine and the following keywords: "Tuberculosis"; "MDR-TB" (including extensively drug-resistant-TB (XDR-TB)); "infectiousness"; "contagiousness"; "'transmission" and "infection control". As a systematic review covering these topics was published in 2013 *(3)*, the search focused on the 2013–2017 period. Historical articles were retrieved from WHO and the International Union against Tuberculosis and Lung Disease

documents *(4,5)*, including both observational and clinical trial studies. A non-systematic approach was adopted because of the short period since the last published systematic review and the large time span from historical studies to the more recent ones.

All retrieved documents were evaluated based on the aim of the project. Information useful to address the six scientific questions was obtained from text and using references retrieved from the main articles. This highly sensitive search strategy reduced the risk of missing important documents not included in classic scientific search engines.

Limitations

A limitation of the review process is that documents published in language other than English were not considered.

Probability of TB transmission

To better understand the concepts discussed in this document, this section summarizes the probabilistic aspects of TB transmission, that is, what happens when an uninfected individual is exposed to an infectious index case.

TB infection is a probabilistic phenomenon, involving many different factors (*4*). For TB infection to occur, the inhalation of at least one viable and virulent *M. tuberculosis* droplet nucleus must reach the alveolar macrophages within the lung. Owing to structural barriers in the lung and to innate or adaptive immunity, droplet nuclei are generally successful in inducing infection. Therefore, the host needs to inhale multiple droplet nuclei during either a single exposure or repeated exposures to become infected. The source strength (number of droplet nuclei generated) is therefore an important factor: this can be influenced by factors such as cough strength and frequency, presence of lung cavities, sputum viscosity, ventilation and air dilution. There is no "average" infectious patient: each patient is different, although "hyper-transmitters" (i.e. highly infectious, undiagnosed cases) probably account for most TB transmission. Features of the host are also very important: for instance, immunosuppressed people or those with comorbidities are more likely to be infected. To minimize exposure side, it is extremely important that the index case should receive effective treatment so as to rapidly become non-infectious. Given these factors, it is impossible to define a minimum exposure duration that will result in transmission. Several core factors that might reduce the patient's infectiousness will be discussed in later sections.

Current WHO guidance on TB infection control

The WHO Policy on TB infection control in health care facilities, congregate settings and households provides comprehensive guidance on the main issues related to infection control *(6)*. Managerial activities (Table 1) are necessary to support infection control through implementing an airborne infection control committee, evaluating the structural features of the building, and ensuring that surveillance, advocacy, monitoring and evaluation, and operational research activities are in place. Three main activities are classically used to achieve TB/airborne infection control: administrative controls; environmental controls; and personal protection. All of the main guidelines in force follow this approach *(7–11)*.

Table 1. Measures for TB infection control in health care settings: managerial activities

No.	Managerial activity
1	Identify and strengthen a coordinating body for TB infection control and develop a comprehensive budgeted plan that includes human resource requirements for implementing TB infection control at all levels
2	Ensure the appropriate design, construction, renovation, maintenance and use of health facilities
3	Conduct TB surveillance among health workers and assessment at all levels of the health system and in congregate settings
4	Address TB infection control advocacy, communication and social mobilization, including engagement of civil society
5	Monitor and evaluate the set of TB infection control measures
6	Enable and conduct operational research

Source: adapted from World Health Organization (2009) *(6)*.

The principles of a refocused, intensified, administrative TB transmission control strategy, known as FAST (Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely and Treat effectively based on rapid DST), have also been used in developing this document *(12,13)*. The pilot experience in different countries (including Bangladesh, Nigeria, Peru, Russian Federation and Vietnam) showed a high proportion of undetected TB patients among hospitalized cases: they were correctly managed by implementing the FAST approach *(14)*.

The following sections will discuss the available evidence, which suggests that transmission mainly occurs from undiagnosed TB patients (i.e. before they start an effective treatment regimen) or from

unrecognized M/XDR-TB patients (who are therefore not being correctly treated with a regimen adapted to the resistance profile).

For example, in countries of the former Soviet Union (and elsewhere), many patients are diagnosed with TB based on chest radiography and sputum smear microscopy. Patients are then treated with the category 1 regimen for drug-susceptible TB cases (i.e. two months of rifampicin, isoniazid, pyrazinamide and ethambutol; followed by four months of rifampicin and isoniazid). As WHO recommended, rapid molecular diagnostic techniques (e.g. Xpert MTB/RIF and LPA based technologies) are not used in all settings on a routine basis and culture based DST results may only be available after a certain time delay. A high risk of disease transmission in the interim exists, which might contribute to the further spread and development of drug resistance *(15)*.

Administrative controls

Administrative controls are policies and work practices to reduce the risk of exposure, infection and disease (summarized in Table 2).

Table 2. Measures for TB infection control in health care settings: administrative controls

No.	Administrative control
1	Promptly identify people with TB symptoms (triage), separate infectious patients, control the spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in health care facilities
2	Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral therapy and isoniazid preventive therapy for HIV-positive health workers

Source: adapted from World Health Organization (2009) *(6)*.

Environmental controls

Environmental controls are equipment or practices to reduce the concentration of infectious bacilli in the air in areas where contamination is likely (summarized in Table 3).

Table 3. Measures for TB infection control in health care settings: environmental controls

No.	Environmental control
1	Use ventilation systems (natural and mechanical ventilation)
2	Use UVGI fixtures with ensured adequate fixture and air mixing by means of low velocity ceiling fans
3	Adequate design, construction, renovation, maintenance and use of the health facility are also important

Source: adapted from World Health Organization (2009) *(6)*.

The importance of the type of ventilation on air circulation was demonstrated in a historical study following a TB outbreak in a United States Navy ship *(16,17)*. The study found that living in the same compartment with an infectious TB patient or sharing air from a close circuit ventilation system was the core determinant of TB transmission.

It is not yet possible to culture human-generated *M. tuberculosis* strains from ambient air. Molecular detection methods have so far proven inadequate to detect the number of bacilli and measure their viability and infectivity *(18)*. The time from droplet nuclei generation to infection can be brief (a few seconds). Two laboratory studies have evaluated *M. tuberculosis* survival time ($T_{½}$) in a Goldberg drum (used for aerosol survival studies), with differing results: 6 h in the Loudon study of 1969 and 20 min in the 2003 study by Lever and colleagues *(19–21)*. Therefore, it is yet not possible to define the average aerosol survival time with confidence and certainty.

A comprehensive systematic review highlighted the importance of ventilation in determining aerosol dispersal *(22)*. The importance of mechanical ventilation in protecting health care workers from infection *(23)* and the protective role of natural ventilation (e.g. opening windows and using extractors such as roof turbines) have been also reported *(24,25)*. All of these studies reported the ACH by evaluating carbon dioxide decay. Such environmental controls are also important to prevent transmission in settings where HIV coinfection is rampant *(26)*.

Natural ventilation has limitations, especially since buildings are usually not specifically designed to optimize this: wind speed and direction are often unpredictable (as are temperature and humidity) and windows often cannot be left open (e.g. for security reasons or cold periods). Furthermore, the necessary outdoor waiting areas are not always suitable in cold climates or are difficult to provide in a city environment *(13)*.

Mechanical ventilation can overcome some of these difficulties, although it can be expensive and involves technical and maintenance difficulties which might hamper its use in some countries. A recent comprehensive review on environmental controls by Nardell *et al.* discussed the role of air cleaners (that recycle room air) and upper room ultraviolet (UV) germicidal irradiation (UVGI) or germicidal UV fixtures in environmental control *(13)*. Air cleaners, while potentially effective, often underperform (usually adding only a few ACH); in contrast, UVGI was recently demonstrated to have an efficacy of 72% in Peru *(27)* and 80% in South Africa *(28)*. However, UVGI fixtures must be adequately designed and built with adequate air mixing by low velocity ceiling fans, to be

effective *(13)*. The new approaches to design fixture technology, UV dosing and the potentialities of light-emitting diode UV technology make UVGI approach an increasingly attractive option *(29)*. A recent study found that in Vladimir Oblast, Russian Federation the annual operational cost of a room was $126 for mechanical ventilation, $143–287 for an air cleaner and as low as $14 for UVGI (G. Volchenkov, Vladimir TB Regional Control Centre, Vladimir, Russian Federation; personal communication, 2 December 2014), suggesting that this technology might be cost-effective *(12,13)*),

In view of the prevailing weather conditions in the WHO European Region, natural ventilation alone is unlikely to represent a solution to environmental control: UVGI is the best and most cost-effective environmental control system currently available.

Personal protection

The aim of personal protection is to protect personnel working in environments with contaminated air (Table 4).

Table 4. Measures for TB infection control in health care settings: personal protection

No.	Personal protection
1	Surgical masks prevent infectious particles being expelled by the wearer
2	Particulate respirators protect health care worker from inhaling infectious particles
3	When used with administrative and environmental controls, type N95, FFP2 or FFP3 respirators provide additional protection for health care workers caring for infectious TB patients
4	Whenever respirators are used, a respirator programme is necessary

Source: adapted from World Health Organization (2009) *(6)*.

The WHO Policy on TB infection control includes a single chapter on personal protection, Surgical masks and respirators *(6)*. However, it is important to note that surgical masks are indicated for patients (to reduce the spread of droplet nuclei in the air through cough hygiene and source control), while respirators are indicated to protect staff and visitors from inhaling droplet nuclei *(11)*. Surgical masks worn by infectious human beings can reduce the transmission to guinea pigs by 56% *(30)*.

The importance of respirators to protect from inhaling droplet nuclei is highlighted in several guidelines *(7,8,31,32)* and a recent study *(33)*. It should be emphasized that to be effective portable N95/FFP2 respirators need to be fit tested and that for various reasons (e.g. failure of different

type/size of respirator to fit the face, lack of respirator fit testing) the estimated effectiveness of respirators does not exceed 70–80% *(15)*.

Need for national/subnational and facility planning

The Policy on TB infection control underlines the importance of developing adequate infection control plans covering airborne diseases at the national and subnational levels *(6)*. Detailed facility-level plans are also necessary to ensure that administrative controls, environmental controls and personal protection are properly implemented. Basu et al. have attempted to estimate the extent to which a combination of the early diagnosis, effective treatment, isolation of patients and personal protection for staff can prevent TB transmission *(33)*. The study investigated the effect of administrative, environmental and personal protection infection control measures on the M/XDR-TB epidemic in the rural community of Tugela Ferry, South Africa using a mathematical model incorporating longitudinal inpatient and community-based data collected over two years. In the absence of new infection control interventions, approximately 1300 XDR-TB cases were predicted to occur in the area by the end of 2012, with 50% due to nosocomial transmission. The use of masks (for patients) and respirators (for health staff) alone was predicted to avert less than 10% of cases (as well as preventing transmission among health staff). A combination of masks and reduced hospitalization time, with a shift to outpatient treatment, was predicted to prevent up to one third of XDR-TB cases. Improved ventilation, the use of rapid drug-resistance testing, and ensuring HIV treatment and isolation of TB patients was predicted to prevent about 48% of XDR-TB cases (range 34–50%). Notably, this study was based on modelling and not on real experimental data. The main limitation of this approach is that the results depend on the assumptions made. Of relevance to the current document, the study assumed high ACH values, which is not applicable in eastern Europe.

A recent large programmatic evaluation of infection control measures adopted in 88 hospitals in China *(34)* described the results of a survey on implementation of the principles of the WHO Policy on TB infection control *(6)*. Unfortunately, the descriptive review does not provide evidence on the appropriateness or effectiveness of the measures.

Question 1. Which patients are infectious and which factors favour disease transmission?

The actors: patients, health staff and visitors

According to the WHO Policy on TB infection control *(6)*, the actors who play a role in TB transmission are the patients, health staff and visitors. Although patients are traditionally seen as index cases that transmit the infection and the health care workers as the potential victims to be protected, visitors (and other patients) also need to be considered, both as potential index cases or as individuals who might be infected. All three types of actors can either transmit or acquire *M. tuberculosis* infection. Although health care workers are known to be at risk of infection *(35)*, recent reports underline the possibility that they can both infect patients *(36)* and be infected by them *(37)*. Interestingly, a recent report followed disease transmission in a microepidemic originating from a highly infectious sputum smear-positive/culture-positive MDR-TB woman who gave birth in a maternity ward in Modena, Italy. Of the 92 contacts, 88 only had nosocomial contact, whereas the other four had had both nosocomial and household contact: 41 were neonates, 42 were mothers and nine were visiting relatives (four husbands and five grandparents).

Who is infectious?

There is clear evidence that the source of transmission in hospitals is patients (or health staff) with undetected, untreated TB or patients with known TB, but unknown drug resistance (and thus receiving ineffective therapy). Several studies have documented the prevalence of undetected TB (for example, in Lima, Peru *(38)* and Zambia *(39)*). Gelmanova et al. documented the impact of undiagnosed MDR-TB on the emergence of MDR-TB in Tomsk, Siberia, Russian Federation *(40)* – a large territory almost the same size as Poland. The core problem is that most transmission control efforts focus on patients with known TB, most of whom are on effective therapy and therefore no longer infectious any more, while most transmission sources are elsewhere *(12,13)*.

Three historical studies were performed in Bedfordshire, United Kingdom (1948–1952) *(41)*, Rotterdam, the Netherlands (1967–1969) *(42)* and Saskatchewan, Canada (1966–1971) *(43)*. They clearly show that untreated sputum smear-positive/culture-positive individuals are much more infectious to household contacts compared with sputum smear-negative individuals (either sputum culture negative or positive) prior to beginning of effective anti-TB treatment. Interestingly, there was not much difference in tuberculin skin test (TST) conversion among the contacts of culture-positive/sputum smear-negative and culture-negative/sputum smear-negative cases, underlining that

sputum smear positivity is responsible for infection. These studies show that 25–65% of household contacts exposed to sputum smear-positive/culture-positive cases undergo TST conversion compared with less than 10% of those exposed to sputum smear-negative index cases (either sputum culture negative or positive).

Similarly, Gunnel et al. reported no difference in infection among household contacts of 86 culture-positive cases (52 were sputum smear-negative/culture-positive) and 69 culture-negative cases undergoing anti-TB chemotherapy (with 284 and 216 contacts, respectively,) *(44)*. This provides further confirmation of the effectiveness of treatment in reducing infectiousness independent of the sputum smear/culture status. A more recent Finnish study found that among 609 contacts of 134 index cases (sputum culture positive with positive or negative sputum smear findings), four developed TB within four years. All had been in contact with untreated sputum smear-positive index cases *(45)*.

A large Brazilian study of 160 index cases and 934 household contacts reported the rates of TB infection and secondary TB cases among the household contacts of sputum smear-positive/culture-positive cases related to the intensity and location of the exposure before treatment had started *(46)*. The sleeping proximity (same bed, room or house), biological (father, mother) or social relationship (spouse), and the average number of days per month of contact, or hours per day nursing the index case and number of meals shared per day were evaluated as significant variables. A proximity score was developed, consisting of clinical variables correlating with an increased risk of TB infection (presence of cough, pulmonary TB, sputum smear positivity, being index case's caregiver or mother; sleep location, living in the same house). For intense exposure, TST and interferon gamma release assay (IGRA) positivity rates were similar (81% vs 77%, respectively, for contacts sleeping in the same bed; 69% vs 67%, respectively, for contacts sleeping in the same room); for milder exposure, the TST positivity rate was higher than the IGRA positivity rate. The rate of both TST and IGRA positivity increased with the proximity score. Of the 710 individuals who underwent both IGRA and TST, 69% of contacts sleeping in the same bed were positive for both IGRA and TST compared 62% of contacts sleeping in the same room, 54% of those sleeping in the same house and 39% of those sleeping in another house *(46,47)*. The rates of secondary TB cases and TB incidence among household contacts increased with the proximity score. The proximity score was also associated with microbiologically confirmed TB disease (sputum smear positive/culture positive). The findings suggest that TB transmission before treatment was due to sputum smear-positive/culture-positive cases, although the study design did not generate information on how

many infections or TB cases were specifically due to sputum smear-positive (only) or culture-positive cases.

In a fingerprinting study in Californian, United States of America, 17% of transmission occurred among contacts of sputum smear-negative index cases before their treatment had started *(48)*. The relative transmission rate from sputum smear-negative versus sputum smear-positive cases was 0.22 (or one fifth).

In summary, transmission is multifactorial, relating to the concentration of airborne droplet nuclei but also to the source strength, ventilation, proximity, susceptibility and, most importantly, the administration of effective treatment. Until effective treatment is provided, sputum smear positivity can be used to evaluate infectiousness. We describe below that this is no longer true when the patient starts treatment, as long as the regimen is effective (i.e. there is no undetected resistance when a regimen for susceptible cases is administered) *(12,18)*.

Implications for policy

Although 30–40% of contacts of untreated sputum smear-positive cases acquire a TB infection (49), and therefore sputum smear-positive cases are mainly responsible for transmission, the possibility that untreated sputum smear-negative cases may transmit the disease cannot be excluded.

Exposure time needed to generate infection?

Various factors can influence the effectiveness of TB transmission, including factors related to the index case and the contact (discussed below) *(4,6)*. Other important factors include the proximity, frequency and duration of contact. The Rotterdam study demonstrated the importance of proximity in TB transmission: 35% of close contacts of a sputum smear-positive index case were infected versus 10% of casual contacts. For sputum smear-negative cases, the proportions were lower (10% and under 10%, respectively) *(43)*. The core question remains: what are the minimum frequency and duration of contact for infection to occur?

Historical studies in animal models enabled the study of airborne *M. tuberculosis* in droplet nuclei *(50–52)*. In Riley's studies, a TB ward with single rooms of known dimension hosting TB untreated patients was connected via a controlled, calibrated close ventilation circuit to a large chamber containing (exposed) guinea pigs *(51,52)*. The animals were monitored and their organs were

examined if signs of disease developed. This method allowed the number of infectious droplets in the air leading to effective transmission to be quantified. On average, one infectious droplet nucleus is present in 340 m^3 of air. The authors also estimated that the time needed for a nurse to breathe in this volume of air and become infected (i.e. have TST conversion) was 12–18 months on average.

A cut-off time of 8 h for exposure to an index case is used in several countries to initiate contact tracing; this can result from multiple shorter exposures *(53–56)*. The cut-off time is based on modest evidence from transmission in airplanes and other closed settings *(8,9,31,53,57,58)*. According to recommendations from the United States of America, for index cases without pulmonary cavities, the proposed cut-off time for contact tracing is equivalent to 180 h of exposure per month *(7,53)*. The 2015 Australian guidelines suggest different cut-off values depending on the dimensions of the room where exposure has taken place *(31)*: 8 h for small spaces (e.g. car, small room); 24 h for a classroom or meeting room; 50 h for a cafeteria or small church; and 100 h for a large space (auditorium, gymnasium) 100 h. These estimates need to be seen as procedural efforts that are not based on experimental evidence. As already mentioned, many variables can play a role in determining infection for a given exposure (e.g. source strength, strain virulence, air dilution, proximity, host resistance). For some of these, the available evidence is so weak that an estimate of the duration of exposure needed for infection or cannot be determined.

In airplanes, two major episodes of transmission occurred in a study of 2600 passengers on 191 flights (in nine different aircraft models). The first episode involved the transmission of *M. tuberculosis* from a crew member to colleagues in a flight lasting over 12 h *(54,59)*. The second episode involved a few passengers seated close to the index case in a flight lasting over 8 h *(59,60)*. However, the specific conditions in airplanes (i.e. a small volume, overcrowded, with pre-defined ventilation and no possible air exchange while in flight) cannot be extrapolated to other settings.

In the MDR-TB microepidemic in a maternity ward in Modena, Italy, Richeldi et al. reported an average exposure time of 6.05 h for the 88 main contacts, and of over 8 h for 15 contacts *(37)*. Of the 88 contacts, 17 became IGRA (ELISPOT) positive. This study was the first to demonstrate the importance of casual nosocomial contacts and a correlation between exposure and TST and IGRA conversion. The sputum smear-positive/culture-positive index case (highly infectious, undiagnosed) remained for four days in the maternity ward (with six beds per room) postnatally, alongside other babies and mothers. The mothers slept in the same room and the babies slept separately in a nursery, with no specific infection control measures.

The risk of children becoming TST positive following exposure to sputum smear-positive adults at day care or after-school care facilities was considered low in a Norwegian study: under 3% of children underwent TST conversion after a median contact period of 6.9 h *(61)*. However, a recent Italian study demonstrated that children can become infected within a rather shorter exposure time, whereas the same was not true for adults. A highly contagious paediatrician transmitted *M. tuberculosis* (resulting in several TB cases) in children undergoing vaccination against non-TB diseases, with an exposure time of only 15–20 min *(36)*. This study confirmed previous findings of rapid transmission in children exposed for less than 8 h *(62)*.

In a recent household contact study of sputum smear-positive/culture-positive cases performed in Brazil in a setting with a moderate TB incidence, the intensity of exposure and sleep location in relation to the TB index case were directly related to the TST/IGRA response and incidence of secondary TB *(46)*. The proximity score (a modified version of the Mandalakas score) *(46)* provided a standardized way to capture the cumulative risk factors of proximity from 10 different variables. These included cough features, existence of pulmonary TB, microbiological status, sleep location and living in the same house.

In summary, the available evidence does not allow the establishment of a cut-off time to allow infection to occur: it is not possible to define a lower time limit to exclude the possibility of *M. tuberculosis* transmission. The best approach available to establish infectiousness is the concentric circle approach *(57,63)*.

Implications for policy

The cut-off value of 8-h exposure is not useful to activate contact tracing. In children and other vulnerable groups, a shorter exposure period is likely to be sufficient for infection. Criteria including the intensity, frequency and duration of exposure should guide the contact-tracing plan following exposure to an infectious TB case based on the concentric circle approach.

Features that influence transmission

Various factors can influence transmission *(4,6)*: these can relate to the index case, the recipient, the bacterial strain or the environment.

Index case: factors already described include age, immune status, sputum smear positivity, presence of pulmonary cavities, the force and frequency of cough, and adherence to cough etiquette principles.

Recipient: factors influencing disease transmission include immune status and the presence of comorbidities and for the bacterium include its intrinsic virulence *(11)*.

Bacterial strain: a recent systematic review suggested that clinical MDR-TB strains are likely to have the same transmission potentialities as drug-susceptible TB strains *(64)*, thus contradicting previous dogma that assigned lower pathogenicity to mutant strains *(15,65,66)*.

Environment: the fixed characteristics of the building (type, location, structure) and other variable characteristics (temperature, humidity, rain, (over)crowding, resources, regular maintenance of UVGI installations and ventilation systems, availability of policies to implement administrative measures and ventilation practices) are important factors in disease transmission *(6)*.

Implications for policy

Efforts are needed to reduce modifiable determinants favouring transmission while strengthening those protecting against transmission.

Features of the index case

Initial assessment

All factors that favour transmission deserve to be adequately evaluated by the clinician, including cough, clinical signs and symptoms, microbiological status (sputum smear, sputum culture, resistance pattern determined by both DST and rapid Xpert MTB/RIF testing), and radiological features.

Active versus passive screening of at-risk groups

As the FAST approach shows, the most dangerous TB cases are the unknown/undiagnosed cases. Therefore, health staff must keep a high level of clinical suspicion when dealing with patients reporting signs and symptoms compatible with TB. A cough lasting for over two weeks is the most important clinical sign although, via the "think TB" approach, other nonspecific signs and symptoms (general malaise, night sweats, fever, haemoptysis, weight loss) should trigger an adequate chain of events *(32,67)*. The patient should undergo bacteriological examinations (rapid diagnostic tests, sputum smear, sputum culture and DST to confirm TB and exclude MDR-TB) and chest X-ray radiography *(32,68–70)*.

In the case of positive sputum smear findings and Xpert MTB/RIF confirmation of TB, the patient should be rapidly started on an effective TB treatment. If Xpert MTB/RIF testing confirms RR-TB, the patient should be treated as for MDR-TB. LPA based technology for second-line drugs is useful to rapidly diagnose MDR-TB and exclude XDR-TB to avoid "blind" treatment with insufficient active drugs, while phenotypic DST will enable fine-tuning of the treatment *(32,67)*.

The contacts of a TB case should undergo epidemiological evaluation according to the so-called stone-in-the-pond principle *(63)* and those infected (as evaluated by TST and/or IGRA, in line with national or subnational policy) should be treated for latent TB infection, as recommended by WHO, after active TB is ruled out *(32,67,71–73)*.

Question 2. When does an infectious patient become non-infectious after starting treatment?

We have reviewed the evidence on the infectiousness of untreated patients based on sputum smear and culture status and on the role of treatment in reducing it. The core question for developing a policy on isolation, discharge and management at home for patients is: how long does it take anti-TB chemotherapy to render a patient non-infectious? We will provide evidence showing that effective treatment essentially stops transmission, so that interventions such as isolation, air disinfection, wearing a mask (for patients) or respirator (for health staff and visitors), although important, are less important *(13)*.

What is the effect of treatment on infectiousness?

Rapid diagnosis and effective treatment are the core factors to reduce the infectiousness of TB patients *(11,13,15)*. Clearly, adequate therapy should be given, in terms of drugs/regimens based on drug susceptibility, administration route, dose, duration, adherence and drug absorption *(32,74,75)*.

Studies done before the spread of drug resistance demonstrated that anti-TB chemotherapy can rapidly render patients non-infectious *(44,49,51,52,76–79)*. Based on this evidence, the rule of the two weeks after starting treatment was established (as the time needed for adequately treated patients to be considered non-infectious) *(49)*. It is important to emphasize that this rule was achieved through consensus among experts, who did not consider the important results of Riley's studies (although these were available at the time) *(51,52,78)*.

In the first study, Riley observed three to four guinea pig infections per month following exposure to sputum smear-positive, chronic, previously treated TB patients by means of a specially constructed TB ward *(78)*. When newly diagnosed, previously untreated cases were admitted to the ward, the infections in guinea pigs stopped; they re-started when chronic patients were admitted to the ward. These results were interpreted to indicate that the action of starting treatment for susceptible cases on the day of admission to the ward was very effective for stopping transmission.

In the second study, Riley exposed guinea pigs to drug-sensitive and drug-resistant TB patients (MDR-TB did not exist at the time) who had been untreated or treated since diagnosis and admission *(78)*. The rather weak regimen used at the time (streptomycin, isoniazid and *para*-aminosalicylic acid (PAS)) reduced infectiousness by 98% with immediate effect. However, given the small number of drug-resistant cases, no firm conclusions could be made.

Fennelly et al. cultured bacilli from a sample of cough aerosols using a novel method *(50)*. They found that aerosol cultures from four MDR-TB patients who were being adequately treated declined exponentially, much faster than results from sputum smear microscopy and smear culture. This result confirms the core role of treatment in reducing infectiousness and the unreliability of sputum smear/culture assays to monitor infectiousness after treatment starts.

Escombe et al. studied guinea pigs exposed to exhausted air from a ward admitting TB/HIV-coinfected patients. They showed that transmission occurs from patients inadequately treated because of underlying drug resistance (i.e. nine MDR-TB patients, whose status was not known at the time treatment started) *(80)*. A total of 292 guinea pigs were exposed over 505 days to exhaust air from 97 TB/HIV-coinfected patients with pulmonary TB. Of these patients, 66 were sputum culture positive and 35 were sputum smear positive. Of 125 infected guinea pigs, 122 (98%) were infected by nine MDR-TB patients who were inadequately treated or whose treatment was delayed. Only three drug-susceptible TB patients infected one guinea pig each: two had delayed treatment and one had stopped treatment due to adverse events. In summary, most TB patients on effective anti-TB treatment did not infect guinea pigs: only patients with undetected MDR-TB infected guinea pigs. This study confirms the power of effective treatment to prevent transmission regardless of sputum smear and culture status.

In a more recent study, guinea pigs were exposed to exhaust air from rooms hosting presumed MDR-TB cases *(81)*. In different human-to-guinea pig transmission experiments, the proportion of

guinea pigs infected ranged from 1% to 77%. The reasons for the marked inter-experimental variation in transmission rates were unclear: patients had been selected based on similar characteristics associated with transmission (cough, sputum smear positivity, lung cavities); and all were receiving standard South African MDR-TB treatment regimen. However, the explanation became evident when several guinea pig isolates matched human isolates of XDR-TB, but not of MDR-TB. In one experiment, a cohort of 27 patients with similar transmission characteristics had infected just one out of 90 guinea pigs subjected to three months of continuous exposure. As in Riley's studies, in most patient's treatment started at the same time that the patient entered the experimental ward (not weeks earlier), again suggesting that effective treatment stops transmission almost immediately, including for MDR-TB. However, the same may not be true for XDR-TB, as effective drugs such as fluoriquinoloes and injectables are ineffective. A recent unpublished study showed that supplementing a failed South African MDR regimen with bedaquiline and linezolid (according to the South African protocol) did not reduce transmission to guinea pigs over a 13-day period (E. Nardell, Harvard Medical School, Boston, Massachusetts, United States of America, unpublished data, 13 July 2018).

Based on these considerations, Dharmadhikari et al. *(81)* and Farmer & Raviglione *(82)* concluded that the standard MDR-TB treatment used in South Africa rapidly and effectively suppresses disease transmission, regardless of the sputum smear and culture status – similar to the results of Riley and of Escombe et al. for drug-susceptible TB *(79,80)*. These studies show the importance of rapidly detecting XDR-TB using rapid genetic tests and the timely initiation of appropriate treatment.

The evidence that disease transmission in hospital mostly results from undiagnosed patients and patients with undetected drug resistance and that effective treatment stops transmission has been translated into a refocused, intensified approach to TB transmission control called FAST. We have described how the early results of FAST application in the field suggest that reducing the time from hospital entry to diagnosis reduces the exposure time. Studies to document reduced nosocomial transmission are currently under way. Unpublished findings show that in Russian Federation rapid diagnosis of MDR-TB by Xpert MTB/RIF is resulting in a lower incidence of MDR-TB in the population – presumably due to decreased transmission and reinfection in hospitals (Dr Grigory Volchenkov, Vladimir TB Regional Control Centre, Vladimir, Russian Federation, personal communication, 2 December 2014). These findings have been confirmed by further evidence showing that prolonged infectiousness in a patient under treatment can be due to inadequate

chemotherapy, drug resistance and lack of treatment adherence *(83–85)*. We have been unable to find case reports of transmission from patients under effective treatment *(13,15)*.

Fitzwater et al. studied 95 drug-susceptible and drug-resistant TB cases in Lima, Peru, treated with standardized short-course chemotherapy under strict DOT *(86)*. The median time to convert sputum culture to a negative result was 38.5 days for the whole cohort. It was not affected by the sputum smear status at baseline. The median time to sputum culture conversion among drug-susceptible TB cases was 37 days; of these, 10% were still culture positive at day 60, which predicts the existence of MDR-TB. The results of this study should be interpreted as confirmation that conversion of sputum smear and culture might take time (particularly for MDR-TB cases) and that these outcomes cannot be used to predict transmission once effective treatment has started *(13,15)*.

Menzies performed a systematic review of available experimental and epidemiological evidence on the contagiousness of treated patients *(87)*. The main results of the review are presented and discussed below.

Experimental evidence

Approximately 30–50% of pan-susceptible TB cases that were initially sputum smear positive/culture positive and treated with modern rifampicin-containing regimens underwent sputum culture conversion within one month *(88,89)*. In 5–10% of cases, the sputum remained smear positive/culture positive after three months. In MDR-TB cases, more time was needed to achieve bacteriological conversion. Therefore, although sputum smear and sputum culture conversion are used as indicators of effective treatment, they cannot be used to evaluate infectiousness *(13,15)*.

Importantly, Kim et al. reported that 20–30% of cases treated with rifampicin-based regimens became culture negative while remaining sputum smear positive *(90)*. When sputum from 20 patients remaining sputum smear positive/culture positive after one month of treatment was administered intraperitoneally to guinea pigs, all developed TB. However, this funding does not mean that sputum smear-positive/culture-positive patients undergoing effective treatment are infectious by the airborne route. Aerosolization may play a key role in limiting the spread of disease from patients on effective treatment, as demonstrated by Loudon and colleagues *(19,20)*. In a trial to investigate the mechanism determining the rapid fall in infectiousness of patients after starting treatment, Loudon theorized that evaporation of the droplet nuclei could increase the drug

concentration around bacilli *(20)*. This mechanism might inactivate the bacilli or hamper their capacity to successfully infect human hosts. Although the drug concentration must increase as droplets evaporate, this phenomenon was never confirmed experimentally to reduce the transmission rate.

Epidemiological evidence

Only a few studies have evaluated the possibility that index cases under treatment might infect their contacts and only five studies have reported epidemiological evidence *(44,76,77,79,91)*. The best known is the Madras study, which is the only randomized study to our knowledge *(77)*. The other four studies, performed in the United States of America, might have allocated less severe cases to the ambulatory arm *(44,76,79,91)*. The main limitation of all five studies is that 30–65% of household contacts were already infected at the time treatment started. The proportion of the remaining contacts who remained uninfected ranged from 18% to 70% in the different studies. The microbiological status and settings were different, as was treatment duration before exposure *(44,76,77,79,91)*. The Madras study found that fewer contacts (both TST positive and negative) of patients treated at home developed TB compared with contacts of patients treated at a sanatorium *(77)*. Another important finding was that most of the contacts who developed TB did so within the first three months (irrespective of whether the index case was treated at home or in the sanatorium). This strongly suggests that these contacts were probably already infected and, therefore, that patients undergoing adequate treatment are unlikely to infect their contacts. The other four studies had consistent results *(44,76,79,91)*.

Which tools do we have to monitor treatment and assess infectiousness?

Sputum smear microscopy and smear culture are the classic surrogate markers for monitoring and assessing infectiousness *(92)* and form the basis of decisions on the patient's infectiousness *(93)*. Early bactericidal activity is still used as an important measure in controlled clinical trials *(92)*. Note that sputum smear and culture findings can predict infectiousness before the start of effective treatment, but not afterwards. Colony numbers (in smear cultures) can also be used to assess the treatment response and infectiousness *(94)*. Radiology (number and extension of pulmonary cavities) can also contribute to treatment monitoring. Although pharmacokinetic/pharmacodynamic and therapeutic drug monitoring are not considered treatment monitoring tools, they represent additional resources to ensure adequate dosing, thus aiding effective treatment. They have been recently recommended, for the first time, in the North American TB guidelines *(74,95)*.

Unfortunately, genetic tests cannot be used to monitor infectiousness due the high rate of false positive results (genetic materials belonging to dead bacilli are also detected) *(96–98)*.

In acknowledging the limitations of sputum smear as initial diagnostic tool and to guide treatment decisions, Behr et al. suggested that interpretations of infectiousness need to be guided by clinical suspicion and the HIV serostatus of contacts *(48)*. The study also revealed that treatment was prescribed 12 days later to sputum smear-negative patients than to sputum smear-positive patients. Again, effective treatment of TB patients is the key factor in determining infectiousness.

Fortún et al. measured the time to sputum smear and culture conversion (34 and 38 days after the start of treatment, respectively) and found that 53% of patients underwent culture conversion within the first four weeks of treatment *(99)*. Thus, the time to sputum smear and culture conversion is useful to evaluate treatment effectiveness but not the patient's infectiousness. Hernández-Garduño et al. found that one sixth of the overall disease transmission occurred in the contacts of untreated sputum smear-negative patients *(100)*. The factors associated with persistent culture positivity in treated cases are high colony counts (odds ratio (OR) 2.86), lung cavities (OR 4) and a prolonged symptomatic period (OR 3.57), in addition to drug resistance *(100)*.

Older guidelines tend to focus mainly on the two-week rule and still rely on sputum smear and culture conversion results, irrespective whether effective treatment has been initiated. For example, Infection control guidelines of the American Thoracic Society, United States Centers for Disease Control and Prevention and Infectious Diseases Society of America state that patients with pulmonary TB can be considered non-infectious when: (i) they have received adequate chemotherapy for two to three weeks; (ii) they show clinical improvement; and (iii) there is a negligible chance of MDR-TB *(7)*. The criteria for infectiousness need to be more stringent for hospitalized patients, who should stay in respiratory isolation until they have three consecutive negative results for sputum smear microscopy. If managed at home, the same criteria should be applied in case children or immunosuppressed individuals (e.g. people living with HIV) are present.

As already discussed, new evidence demonstrates that once effective treatment starts, infectiousness drops rapidly. Sputum smear and culture results are useful to monitor treatment effectiveness but are no longer suitable to predict infectiousness. The availability of rapid diagnostics allows tailored MDR-TB treatment to start on the same day as diagnosis. All of these factors modify the indications for isolation, as discussed in the following sections.

Implications for policy

Sputum smear microscopy is a quick and cheap tool to assess infectiousness, but has a major limitation when (only) used as initial diagnostic tool . Up to one fifth of sputum smear-positive patients can transmit M. tuberculosis when untreated. Sputum culture is useful to demonstrate the viability of bacilli, although the results take two to three weeks: it cannot predict infectiousness once treatment has started.

Although sputum smear and culture findings can remain positive for more than two weeks after the start of treatment, the available evidence shows that infectiousness drops very rapidly if adequate treatment is administered. This is easier to achieve when the strain is drug susceptible. The real risk is represented by undetected MDR-TB or XDR-TB cases.

New rapid diagnostic methods (Xpert MTB/RIF, LPA) should be routinely used to promptly identify drug-resistant TB patients for whom adequate treatment can be rapidly started, thus reducing their infectiousness.

Question 3. What can render the patient non-infectious more rapidly?

Several factors influence the patient's response to treatment, and these need to be coupled to the infection control measures.

Bacterial load: patients with extensive lesions and a high bacterial load remain infectious for longer.

Disease site: for example, patients with laryngeal TB are highly infectious as the source of bacilli is near the mouth, facilitating transmission.

Nutrition/immunity status: the roles of nutrition and immunity in combating the disease have been well known since TB was mainly treated in sanatoria. Interventions to improve nutrition and to restore immunity when necessary (i.e. antiretroviral treatment for TB/HIV-coinfected patients) are likely to help, although their contribution has never been quantified *(101)*. Moreover, although a relationship between nutrition/immunity and transmission is biologically plausible, there is no evidence to support it.

People-centred approach: interventions included in this approach, by enhancing treatment adherence (DOT/video-observed treatment have a role here), can improve the patient's response to treatment *(32,102)*. Here again, although plausible (adherence is likely to reduce

infectiousness, given the core role of effective treatment), no evidence is currently available to support a relationship between a people-centred approach and the treatment response.

Immunotherapy, host-directed therapies: new approaches in this area have been proposed, but there is insufficient evidence on their clinical utility *(101)*.

Bactericidal potentialities of treatment regimens: the bactericidal capacity of the anti-TB regimen in use is likely to reduce the infectiousness period, although there is no experimental evidence to support this. Bactericidal drugs can reduce the number of colonies, but this may not be the only mechanism involved in reducing infectiousness (e.g. the bacilli growing in culture may be not infectious) *(75,103)*.

Improved treatment programmes: all efforts to improve the quality of treatment (e.g. high-quality drugs, correct doses and regimens, use of therapeutic drug monitoring) are likely to be useful in reducing infectiousness, although there is no formal evidence to support this.

Implementation of WHO guidance: sustainable implementation of administrative, environmental and personal protection measures to reduce the duration and degree infectiousness are pre-requisites for health units admitting MDR-TB patients (see below for details) *(6,102,104)*.

Active screening: of the available transmission control interventions, the administrative approach of active screening for undetected TB and drug resistance followed by prompt effective therapy is most likely to result in sustainable reductions of transmission.

Question 4. What can limit the rapid decline in a patient's infectiousness?

The following factors (among others) have the potential to limit the rapid decline in a patient's infectiousness and, therefore, enhance transmission *(33,102)*:

- insufficient and unsustainable application of administrative, environmental and personal protection measures;
- a hospital-based approach and funding schemes that encourage admission; and
- suboptimal home care services and community care approach.

Due to these limitations, the model of TB and MDR-TB care in some countries is still based on long-term hospital admission, which has a high risk of transmission (discussed extensively in this document).

Question 5. Which patients need hospital admission (and respiratory isolation) because of their infectiousness?

We have already discussed the criteria for defining an infectious patient. There is evidence that even patients who remain infectious can be managed at home if adequate infection control measures are ensured *(102)*. More and more evidence is becoming available on the effectiveness (and cost–effectiveness *(105)*) of decentralized and ambulatory-based programmes to manage MDR-/XDR-TB *(106–111)*. Through the use of visiting nurses, these patient-centred programmes have improved case detection rates, continuity of care and treatment outcomes *(112)*. This section will revise the available evidence to clarify, to the fullest extent, which patients really need hospital admission *(113)*.

The historical Madras study and subsequent ones demonstrated that there were no differences in the proportion of TST negative contacts who developed TB following index case's hospital admission versus home care *(44,77,114,115)*.

In the Madras study, the effect of treatment (isoniazid and PAS) was compared in patients treated under good conditions in a sanatorium (good quality accommodation, nursing care, a nutritious diet, prolonged bed rest) versus those treated under poorer conditions at home *(77)*. Treatment results were similar in terms of radiological (reduction in pulmonary cavity size and cavity closure), microbiological outcomes and the proportion of relapses after four years. The rate and speed of bacteriological conversion were also similar (90% sputum smear and culture conversion within four months): at two months, 45% of home-based patients underwent sputum smear and culture conversion versus 49% of sanatorium-based patients, while at four months the proportions were 89% and 93%, respectively. Close family contacts were followed up for five years: there was no difference in TB incidence between hospital and family contacts. The TB rate among contacts within five years was: TST positivity, nine out of 86 (10.5%) home contacts versus 10 out of 87 (11.5%) sanatorium contacts; TST negativity, 15 out of 159 (9.4%) home contacts versus 28 out of 177 (15.8%) sanatorium contacts. Notably, at the time MDR-TB was not yet widespread, around half of the contacts were already TST positive at the time of index case diagnosis and the bactericidal capacity of the treatment regimen was low compared with modern regimens.

Brooks et al. reported no conversions among household contacts following the home management of 21 patients discharged after 23 days of initial hospital treatment; 19 out of 21 were still sputum smear positive when discharged *(76)*. Menzies and colleagues recommended that patients should at

least show initial signs of clinical improvement (clinical, radiological and microbiological improvements, with reduced bacilli count in sputum smear microscopy) before being discharged for outpatient management *(87,116)*. Experiences in the Russian Federation *(40)* and other countries (including South Africa) *(33,106–109,111,117)* show the dangers of in-hospital transmission and the advantages of home care. Home care can be initiated at the start of treatment if the main condition that effective treatment has been promptly initiated within community-based TB or MDR-TB programmes has been satisfied. Bassili et al. performed a systematic review on the effectiveness of MDR-TB management that included 35 studies (25 in hospital and eight in the home) and 14 478 patients treated between 1973 and 2007 (with data published between 1993 and 2010) *(118)*. The pooled treatment success rate was 65.5% for hospital care and 66.7% for home care, with no differences for any treatment outcomes related to the care model. Simonovska & Ilievska-Popovska found no difference in sputum smear conversion rates and treatment outcomes for ambulatory-managed versus hospital-managed patients in the former Yugoslav Republic of Macedonia *(119)*.

Boyd et al. investigated the time to treatment for rifampicin-resistant in a systematic review and meta-analysis covering 53 studies, 83 cohorts and 13 034 patients *(93)*. In all, 76% of diagnosed cases had started treatment with second-line anti-TB drugs. The weighted mean time from sputum collection to treatment was 81 days (95% confidence interval (CI) 70–91 days), and was shorter for patients managed in an ambulatory setting versus a hospital setting (57 days vs 86 days). The treatment delay was much shorter when rapid genetic methods were used compared with phenotypic DST (38 days vs 108 days). These findings highlight the need to implement the FAST approach, which, by reducing the delay between detection and the initiation of effective treatment through active case-finding, makes an important contribution to reducing transmission.

In a qualitative study, Horter et al. showed that both MDR-TB patients and health staff preferred home-based to hospital-based care *(120)*. In advocating for an alternative management model for M/XDR-TB cases, Padayatchi & Friedland underlined that simple, cheap strategies (e.g. opening windows, sitting in the open, covering the mouth when coughing, using respirators) might reduce transmission *(121)*. However, all of these interventions, although important, are less effective than the prompt initiation of effective treatment *(13,15,122)*.

In a multisite South African study, Loveday et al. provided further evidence on the advantage of treating TB at home, even in settings where HIV infection is highly prevalent *(108)*. The results of a non-randomized, observational, prospective cohort study comparing community-based (736

patients) versus centralized (813 patients) case management for MDR-TB patients demonstrated higher success rates with the community approach, although results varied across the four study sites.

Van Cutsem et al. emphasized the importance of early diagnosis and treatment to reduce infectiousness and of decentralized models of care to reduce transmission *(122)*. They also described barriers to adherence to infection control principles, including interpersonal factors and those related to the health facility and health system. Similar arguments were raised in a recent review by Yuen et al. that supported active case-finding and prompt treatment to reduce transmission (core elements of the FAST approach) *(123)*.

In a study in the Republic of Moldova, Jenkins et al. demonstrated that MDR-TB can appear rapidly during treatment: between 7.2% and 9.2% of TB cases (initially non-MBR-TB) acquired this status during treatment (half within three months of starting treatment) *(124)*. The findings are alarming: at least 80% of MDR-TB patients in the Republic of Moldova are currently hospitalized. Two main reasons for the increasing MDR-TB epidemic were identified: reinfection (from undetected sources); and a delay in adequately treating patients after diagnosis (i.e. a delay in DST is delaying the initiation of effective MDR-TB treatment). In confirming the results of the Tomsk study *(40)* and of another Russian experience (Dr Grigory Volchenkov, Vladimir TB Regional Control Centre, Vladimir, Russian Federation; personal communication, December 2014) the authors concluded that ambulatory care and universal access to rapid diagnostic testing would reduce nosocomial transmission. A systematic review by Weiss et al. summarizes the available evidence on MDR-TB community care programmes *(111)*.

A useful summary of these arguments is included in a recently published WHO document *(102)*, emphasizing the lack of significant differences in treatment outcomes between inpatient and outpatient models of care. Given the current evidence, unless there is a clinical or public health need, people with presumably infectious TB or confirmed pulmonary TB should not be admitted to hospital for diagnostic test or care.

Theoretically, in low TB incidence countries (with a low MDR-TB case burden), individual patients may be accommodated in single negative-pressure ventilation rooms; however, this is impossible in countries with a high TB incidence (e.g. in countries of the former Soviet Union, as far as Europe is

concerned). Therefore, hospital admission should be reserved for those TB or MDR-TB cases that really need it.

Criteria for hospital admission

A proportion of cases still need to be admitted for medical reasons, including severe cases, life-threatening conditions, comorbidities, psychiatric problems, adverse drug reactions and, in specific other cases, for social reasons *(125)*.

The WHO document, A people-centred model of tuberculosis care, suggests the following key criteria for hospitalization *(102)*:

- complications of TB (e.g. respiratory failure and conditions requiring surgical interventions such as haemorrhage, pneumothorax and pleural effusion);
- severe forms of TB (i.e. TB meningitis) and/or severe clinical manifestations of comorbidities (e.g. liver disease, renal disease and uncontrolled diabetes); and
- life-threatening and serious medical events resulting from adverse reactions to anti-TB drugs (e.g. life-threatening arrhythmias, psychosis, renal failure and hearing loss).

Additional criteria (to be applied in rare and exceptional cases) include:

- patients for whom effective and safe anti-TB treatment cannot be ensured in an outpatient, community or home setting (i.e. homelessness, overcrowding, exposure of children aged under 5 years, and pregnant women in the household);
- when there are accessibility problems (i.e. patient lives far from an outpatient facility); and
- where there is non-adherence to treatment – this can be considered in some settings as a last resort once all other care options have been used/applied exhaustively, based on the legal framework in force *(126,127)*.

Features of an hospital admitting TB and MDR-TB patients

A patient admitted to hospital should never represent a source of transmission to other patients, health staff and visitors. Therefore, the hospital needs to offer adequate infection control measures in addition to core services including:

- clinical expertise in TB and M/XDR-TB management (including for DOT);
- laboratory results from laboratories with a robust EQA system in place;

- respiratory isolation capacity and adequate infection control measures (including the recommended 12 ACH);
- personal protection measures (i.e. respirators) available within well-designed personal protection programmes, including staff awareness/education and respirator fit testing;
- open spaces that allow patients to socialize without the risk of *M. tuberculosis* transmission *(128)*;
- an adequate number of staff trained and supervised to adhere to administrative and personal protection measures of infection control; and
- a patient-centred approach (psychological support, palliative care, link with home care and social services for the post-discharge home care phase).

The WHO document, A people-centred model of tuberculosis care, suggests that people deemed to be at a low risk of RR-TB and /MDR-TB should be placed in single rooms and that those at a high risk should ideally be accommodated in a negative-pressure room while rapid diagnostic tests are urgently performed *(102)*.

Implications for policy

Although, in principle, outpatient management is recommended for TB patients, a certain proportion of severe and/or social cases will need to be admitted to hospital. Any hospital admitting TB cases should offer a range of services to ensure adequate infection control and quality patient-centred management.

Question 6. What are the research needs?

As more than half of MDR-TB cases result from transmission and the remainder from the selection of drug-resistant mutants, the two core research priorities are to reduce transmission and prevent drug resistance. Both are included in the FAST approach *(11,13,129)*.

More information is needed on how drugs stop disease transmission, apart from their bactericidal effects, particularly in MDR- and XDR-TB cases. It is also important to discover (cost)-effective screening approaches for undetected TB (e.g. active screening through cough surveillance, digital X-rays and breathe tests that do not require sputum). Host-directed therapy is also an emerging area of research: for example, evaluating the role of statins or metformin in preventing or limiting TB in the household contacts of highly drug-resistant patients.

Finally, MDR-TB treatment will inevitably generate XDR-TB cases among treatment failures; unfortunately, some of these patients will be incurable and need palliative care. More research is needed to identify models to ensure that untreatable XDR-TB patients receive the necessary level of comfort (while preventing transmission) in palliative care institutions.

Conclusions

This document on TB infectiousness and infection control provides useful, comprehensive guidance on the specific policy adaptations suitable for the WHO European Region, focusing on three main pillars: administrative controls, environmental controls and personal protection. Other elements such as a people-centred approach, nutritional support, rapid diagnosis and effective treatment are also important in limiting transmission. Other elements might need to be added as new evidence becomes available.

The following main policy elements are derived from the present review:

- infection control planning is needed at the national/subnational and facility levels;
- three groups of actors should be considered – patients, health staff and visitors;
- in the absence of stronger evidence, the cut-off value of 8-h exposure is not useful to activate contact tracing. In children and other vulnerable groups, a shorter exposure time will probably be sufficient for infection to occur. Criteria related to the intensity, frequency and duration of exposure should guide the contact-tracing plan following exposure to an infectious TB patient based on the concentric circle approach;
- sputum smear microscopy is a quick, cheap tool for assessing pretreatment infectiousness, although it has limitations. Up to one fifth of untreated sputum smear-positive cases can transmit *M. tuberculosis*. Sputum culture is useful to demonstrate the viability of bacilli, although results take two to three weeks and it cannot predict infectiousness once the treatment starts;
- although sputum smear and culture tests can still be positive more than two weeks after treatment starts, the available evidence shows that infectiousness drops very rapidly if adequate treatment is implemented – however, this is difficult to quantify;
- it is easier to provide adequate treatment when the *M. tuberculosis* strain is drug susceptible. The real risk is infection from undetected multidrug-resistant TB (MDR-TB) or XDR-TB cases;

- new rapid molecular diagnostic techniques (i.e. Xpert MTB/RIF, LPAs) should be systematically used to promptly identify drug-resistant patients so that adequate treatment can be rapidly started, thus reducing the period of infectiousness;
- stringent isolation criteria are necessary for presumed and confirmed XDR-TB patients for whom treatment does not rapidly prevent transmission. Existing community-based programmes have shown that MDR-TB patients can also be managed at home because effective treatment rapidly reduces their infectiousness; and
- although outpatient management is recommended in principle, a proportion of TB patients (e.g. clinically severe cases) will need hospital admission. Any hospital admitting TB patients should offer adequate infection control and quality patient-centred management.

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World Health Organization
Regional Office for Europe

UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark
Tel: +45 45 33 70 00 Fax: +45 45 33 70 01
Email: eurocontact@who.int
Website: www.euro.who.int