Review

# De-isolation of patients with pulmonary tuberculosis after start of treatment — clear, unequivocal guidelines are missing

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A R T I C L E   I N F O

A B S T R A C T

The study review guidelines on isolation of patients with tuberculosis, TB, from the World Health Organization, WHO, Centers for Disease Control and Prevention, CDC, and the European Center for Disease Control, ECDC. The review found that unequivocal guidelines for removing patients out of negative-pressure isolation and de-isolation patients from either single rooms or isolation at home is needed. Studies show that the time of effective treatment is the key parameter to follow to determine if patients are contagious to others or not. This means that standard treatment of multi-drug resistant, MDR, TB will not result in the patient being non-infectious. Thus it is important right from the time of diagnosis to know if the patient is infected with MDR TB or not. Thus the early use of molecular techniques to reveal drug susceptibility is important. Clear guidelines stating if patient with microscopy negative sputum no matter infected with fully susceptible or MDR TB, no matter HIV positive or not is needed.

## Contents

## Introduction

Tuberculosis is now the commonest cause of death worldwide from an infectious disease.[1] Patients with sputum culture positive active pulmonary tuberculosis (TB) pose a risk of transmission to contacts both within- and outside of hospital. Multi-drug resistant

TB (MDR-TB) and extensive-drug resistant TB (XDR-TB) are now major global health challenges.[2] Currently, the infectiousness of patients with active TB is considered to be directly related to the number of aerosol droplets carrying *Mycobacterium tuberculosis* (*M.tb*) bacilli being propelled into the air.

Aerosol infection prevention and control procedures are important for reducing the risk of M.tb transmission in healthcare facilities and protection of healthcare workers, family and other patient contacts. Contact tracing and molecular genotypic susceptibility testing are important tools to ensure rapid identification, optimal treatment and adequate infection control measures to be instituted.

When a pulmonary TB diagnosis is considered patients should be isolated, preferably in a negative pressure room, until the diagnostic workup is complete. However, negative-pressure isolation rooms are not available in resource-limited settings and are a limited resource even in industrialized countries. In addition, being kept in isolation is psychologically stressful to patients and potentially hazardous to their health because of social isolation, poorer access to routine observation and less rigorous physical examination. It is therefore important that patients should be taken out of respiratory isolation once pulmonary tuberculosis has been ruled out, or discharged home as soon as the risk of transmission is reduced to very low levels and adequate treatment supervision measures are in place. Prolonged isolation of TB patients, especially those with MDR-TB or XDR-TB, is unnecessary once appropriate treatment has been initiated.

As part of the diagnostic work-up for susceptible TB, it is well established that isolation can be discontinued on the basis of a single negative spot PCR of sputum, (REF) but it is less clear on which basis isolation upon proven drug-resistant TB can be discontinued.[50]

For the majority of TB patients, infectiousness declines rapidly after commencement of appropriate TB treatment.[3,4] Early diagnosis and rapid initiation of optimal treatment, also for cases with drug resistant TB, is essential to minimize the transmission risk. Although the rate of decline in infectiousness varies from patient to patient, those established on effective treatment experience rapid declines (within days) in bacterial load and infectiousness. The most problematic cases are those with undiagnosed drug resistant TB who may remain infectious for months, since they respond poorly to standard first line treatment and may amplify resistance during the period of sub-optimal treatment. Current infection control recommendations are to ideally contain the patient in a negative pressure room, until the risk of transmission is low or negligible. However determining this is difficult in practice, and clear guidance is required to improve and standardize management practices.

The balance that should be struck needs to consider potential patient harms and health care costs from unnecessary isolation, while ensuring the safety of health care staff and the wider community. Careful consideration of this balance is of fundamental importance for rational utilization of the limited number of isolation rooms available. Discharge from isolation (de-isolation) sends a signal that the transmission risk to staff, family and members of the public is sufficiently low that respiratory containment is no longer required.

In this viewpoint we review isolation and infection control guidelines from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) and the European Center for Disease Control and Prevention (ECDC).

## Methods

The WHO, CDC and ECDC websites were searched using the search terms "tuberculosis, MDR-TB, isolation, infection control",

**Table 1**
Detection thresholds (bacteria per ml) for different diagnostic methods.[42]

| | |
|---|---|
| Microscopy | |
|   Ziehl-Neelsen | $10^4$-$10^5$ AFB/ml[43] |
|   Rhodamine | 5-10.000 AFB/ml[44] |
| PCR | |
|   GeneXpert | 100-130 CFU/ml[45] |
|   Others | 100-1000 CFU/ml[46] |
| Culture | |
|   Löwenstein-Jensen | (10)-100 bacilli/ml[47] |
|   Fluid Media | (Bactec a.o.) 10-(100) bacilli/ml[42] |

Whole genome sequencing is fast becoming a standard method for genotypic resistance testing.[48,49]

and the identified guidelines were evaluated by the authors specifically looking for recommendation for de-isolation criteria after initiation of treatment.

## Results

The detection threshold of microscopy, PCR and culture are shown in Table 1. This explains why there may be discordant results between methods and provides the background data to understand the methods in relation to infectiveness.

### WHO guidelines

The World Health Organization (WHO) treatment guidelines for drug-resistant tuberculosis 2016 contain no specific recommendations on isolation and hospital infection control.[5] It builds on the 2014 guidelines,[6] which states that "Smear positive TB patients should:

– spend as much time as possible outdoors; – sleep alone in a separate, adequately ventilated room; and if possible; – spend as little time as possible in congregate settings or in public transport", which all indicate that a "Smear positive" (Acid Fast Bacteria, AFB, microscopy positive) patient does not necessarily need isolation in negative pressure rooms in a hospital. The guideline states "Culture positive extensively drug-resistant TB (XDR-TB) patients should be in respiratory isolation at all times", which implies that even patients who are AFB-microscopy negative and PCR-negative but culture positive should be kept in isolation but not necessarily in a negative pressure room in hospital. This applies only to XDR patients, and isolation may be in the patient's own home provided he/she is kept in their own rooms and all contacts use N95 respirators when in contact with the patient.[5]

The WHO policy package for infection control includes managerial activities, administrative controls and environmental controls.[7] Managerial activities include implementation of infection control coordination bodies at hospital level and different activities including heath facilities construction and renovation.[7]

The administrative controls are aimed at regulating the flow of staff, visitors and patients through triage, separation of infectious cases and minimisation of the time spent at the health facility, while maximising prevention of transmission and minimising risks.

The environmental measures aim at enhancing ventilation (natural or mechanical) and investing in facility improvement, while applying strict personal protection measures including respirators for health staff (and visitors) and surgical masks for patients.[8,9]

The combination of different infection control strategies, including diagnosis of HIV infection and treatment with antiretroviral therapy, are able to avert a significant proportion of infections and, consequently, future cases.[10–12]

## CDC guidelines

Patients with TB disease can be sent home even if they do not have three negative sputum smears, provided that the patient is on standard TB treatment, and DOT has been arranged.[13] However, the CDC guidelines are more cautious concerning transmission from culture-positive cases with pulmonary TB,[14] referring to a study from 1985.[15] Yet, the guidelines do not directly address the risk of infection after the start of effective treatment, and refer to studies showing that HIV patients are more susceptible to infection than others.[16–18] The CDC state that: "for most patients, infectiousness appears to decline rapidly after adequate and appropriate treatment is started; however, the rate of decline varies from patient to patient". This is not helpful for the clinician managing a specific patient,[19] and the CDC guidelines can be interpreted to imply that the patient should remain isolated in a negative pressure room until sputum culture is negative. Given that a negative culture for M.tub. is usually not released as negative earlier than after 6 to 8 weeks, such practice will keep patients in hospitals for months.

## ECDC guidelines

The European Centre for Disease Prevention and Control (ECDC) and the European Respiratory Society (ERS) jointly developed the European Union Standards for Tuberculosis Care (ESTC) in 2011. These are based on The International Standards for TB Care (ISTC) developed by WHO, but are tailored specifically to the EU setting as global standards may not always adapt to EU settings and practices. Also, the majority of EU countries have the resources and capacity to implement higher standards for TB care.[20]

With regards to the decision on patient isolation, the EU standards state that TB patients should ideally be isolated until they achieve bacteriological conversion analogous to negative-sputum microscopy. The standards specifiy nothing further on isolation for drug-resistant tuberculosis, for which reason one must assume that a negative-sputum microscopy[50] applies for all cases of pulmonary TB regardless of the susceptibility pattern of the pathogenic tubercle bacilli.[20]

## Discussion

When assessing the need for isolation it is key to understand that "the rapid impact of effective chemotherapy on TB transmission, including drug-resistant strains, is the other critical information needed to reprioritize TB transmission control efforts. The impact of effective treatment on TB transmission is extremely rapid and profound, including that for MDR-TB. But transmission is on going if an ineffective regimen is used, for example when a first-line regimen is used in a case of MDR-TB or a MDR-TB regimen is used in a case of XDR-TB".[5,21]

The use of the Guinea-pig model where guinea pigs are kept with the TB patient is a widely accepted model for assessing transmission from patients with pulmonary TB. The study by Dharmadhikari AS et al. clearly demonstrates that patients on effective treatment rapidly lose infectivity even if they are AFB-microscopy and culture positive.[21]

Multidrug-resistant tuberculosis (MDR-TB) has been suspected of being infectious for a longer period than drug-susceptible TB, and this concern is a key feature behind most recommendations. The uncertainty about transmission hazard may keep patients in isolation for months while waiting for smear or culture conversion, but it is not well documented that a well-treated MDR-TB patient remains infective for a longer time period. The study by Dharmadhikari, A. S. et al. supports the EU isolation standards with their findings on the infectiousness of MDR-TB.[21] Based on transmission studies with guinea pigs they have found that on effective treatment, MDR-TB patients rapidly are rendered non-infectious.

This points toward the discordance of sputum smear and culture status and infectiousness of patients on therapy. It encourages that effective treatment is the dominant factor determining transmission. Mechanisms explaining the discordance may include the fact that organisms in culture do not undergo the stresses of aerosolization, drug exposure as well as innate and adaptive host defences. Instead, growth is supported to ensure optimal culture conditions. On the other hand, tubercle bacilli may be capable of undergoing massive transcriptional responses to moderate stresses, which could impact virulence or tolerance to aerosolization. This underlines that even though tuberculosis may be less infectious than so far feared caution should always be taken. Furthermore, treatment of XDR-TB is often ineffective in rapidly interrupting transmission making it infectious longer than theoretically necessary.[21]

The study also points out that it cannot be assumed that patients are infectious just because they are TB culture positive. The study confirms that the old "2-week-rule" correlates with a minimal transmission risk, provided that effective and fully adherent treatment can be guaranteed,[6,22] even though most patients on effective treatment will still be AFB-microscopy and culture positive by two weeks.[23] Persistent concerns, propagated by previous literature stating that patients remain infectious as long as they are sputum smear or culture positive justifying continued isolation,[24,25] seems to be unfounded.[26] The key to optimal infection control is rapid genotypic resistance testing to identify likely drug resistance at the earliest time point possible and to ensure that an effective treatment regimen is commenced from the very beginning.[27–29]

Isolation and infection control isolation confer hardship and anxieties for patients, healthcare workers and family members and may further perpetuate stigmatization of MDR-TB. In addition one must weigh the safety of the public and the patient's community contacts versus the morale and well being of the patient and the available resources required to isolate the patient beyond the recommended time frame.

A European study found pitfalls at European MDR-TB reference centres infection control level.[30,31] Although health care workers were sufficiently protected in the majority of cases (199/200, 99.5%) and respirators were always available (200/200, 100%), 20% of the cases (40/200) were not educated on cough etiquette and other important infection control practices, and no negative pressure rooms were available.[31] Furthermore, respirator fit testing was never performed, although infection control committees were generally in place.[30,31] According to European recommendations, sufficient respiratory isolation rooms for all new patients admitted (at least till the exact resistance pattern is identified and/or the patient is rendered non-infectious) and adequate isolation procedures need to be available in centres diagnosing and treating TB.[32,33]

However, much can be learned from South Africa on the programmatic implementation of infection control principles to manage MDR-TB.[34]

A combination of strict infection control measures both at hospital level (no admission without proper infection control) and at the patient's home reduced the cases of MDR and XDR-TB in Tugela Ferry between 2005 and 2015.[34–36]

South Africa shifted from recruiting hospital nurses and doctors to recruiting mobile team nurses and investing in vehicles to allow systematic home care both preparing the patient's family before discharge and following the patient at home after hospital discharge.

Infection control policies were systematically applied, with responsible staff at both facility and public health level. Health care workers underwent surveillance and adequate training.[5]

TB risk assessment, optimised case-finding and triage were systematically implemented at out-patient level.

Environmental measures focused on enhancing natural ventilation and investing in facility improvement, while applying strict personal protection measures.

The combination of different infection control strategies, including diagnosis of HIV infection and treatment with antiretroviral therapy, are able to avert a significant proportion of XDR-TB infections and, consequently, of future cases.

The South African experience is important also for Europe (Eastern Europe in particular), where unnecessary and longer hospitalizations still occur, increasing transmission to patients, visitors and staff. A comprehensive approach to infection control needs to include a paradigm shift from in-patient to out-patient care, as clearly recommended by WHO.[37–39]

These and similar experiences, available in other settings,[40,41] demonstrate the need to support adequate infection control policies both at the facility and at the public health level, as they are able to reduce transmission, and consequently prevent future M/XDR TB cases.

In conclusion, we propose that international guidelines provide clear advice concerning de-isolation of patients. De-isolation should be based on the length of effective treatment and not on bacteriological endpoints.

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