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# Appendix B: De-isolation review and recommendations

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ADDENDUM



# Appendix B: De-isolation review and recommendations

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## Summary

- The preponderance of data suggests that appropriate treatment rapidly renders people with tuberculosis (TB) non-infectious, perhaps within a few days of treatment initiation, even for initially smear-positive cases.
- These studies also suggest that sputum smear and culture status are less predictive of infectiousness once patients are established on effective therapy.
- Nevertheless, there remains some uncertainty as to when, precisely, people with TB on treatment are rendered completely non-infectious.
- The insistence on smear conversion before lifting airborne precautions may unnecessarily prolong isolation and cause patient harm with little public health benefit.
- For people with TB that are medically well enough, ambulatory treatment and home isolation is to be preferred over prolonged hospital isolation. This will attenuate some but not all harms of prolonged isolation.

## Preamble

Treatment of TB disease quickly reduces infectivity and is thus a fundamental component of TB public health management.[1–4] Just how quickly people with TB become non-infectious after initiating effective therapy, and what biomarkers best predict this, remains controversial.[5,6]

A recent systematic review commissioned by the World Health Organization (WHO) to inform the 2019 WHO TB infection Control Guidance update did not find definitive clinical data on the precise number of days or weeks of treatment required to render all people with TB non-infectious. As a result, WHO could not provide explicit guidance on safe timing of patient de-isolation.[1,7]

Perhaps reflecting the lack of definitive data, infection control guidelines on de-isolation from low-burden countries vary and often equivocate in their specific recommendations[6] (see Table 1).

Until 1990, prior to the dual threats of human immunodeficiency virus (HIV) and multidrug-resistant (MDR-TB), the "2-week rule" was common practice and guided duration of isolation for people with pulmonary TB post-treatment initiation.[8] This rule was informed by human-to-guinea pig studies and observational clinical data. However, in 1994, following high-profile nosocomial MDR-TB outbreaks, the Centers for Disease Control and Prevention changed tack to recommend continuing isolation until at least sputum smear conversion was achieved (demonstrated by 3 consecutive negative sputum samples on microscopy).[9] The requirement to confirm bacteriologic response helped to avoid premature de-isolation of patients with unrecognized MDR-TB. Bacteriologic response, usually expressed as sputum smear conversion, following TB treatment start is now a commonly used convention to guide de-isolation and has been incorporated into many recent TB and Infection and Prevention Control guidelines (see Table 1).

However, sputum smear conversion in response to treatment can take weeks, even in drug-susceptible cases, and can prolong duration of isolation significantly.[10] In a systematic review of 8 clinical studies, more than 50% of people with pulmonary TB remained smear-positive 3 weeks into treatment and 20% remained smear-positive for more than 2 months.[7] Sputum culture conversion on treatment can take even longer (40 days median). Up to 40% of initially smear-positive cases will remain culture positive after 2 months of effective treatment. Thus, these patients were presumably still excreting culturable bacilli for weeks after isolation precautions were lifted.

Against the current convention to isolate until sputum smear conversion, there are several lines of evidence suggesting that people with pulmonary TB may be non-infectious (or at least minimally infectious) very soon after initiation of effective treatment and long before smear conversion is achieved. And, although degree of infectiousness prior to treatment start correlates with sputum smear positivity,[11] there is evidence that relative contagiousness, once on TB treatment, is no longer predicted by sputum smear status or culture status.

The evidence-base used to examine these questions can be classified into the following groups: observation of people on treatment and subsequent rates of transmission to contacts, human-to- guinea pig exposure experiments, direct measurements of viable bacilli in patient-produced aerosols, in vitro early bactericidal assays and studies assessing the potential harms of prolonged isolation.

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**Table 1.** Summary of infection control guidance documents from low-incidence countries.

| Country/ Organization | Publication | Year | Type of pulmonary TB | Recommendation for de-isolation (provided clinical response is documented, patient is receiving and tolerating a treatment regimen likely to be effective, and drug-resistance is not present) | Reference |
|---|---|---|---|---|---|
| United States of America | Morbidity and Mortality Weekly Report: Hospital Infection Control Guidelines | 2005 | Smear-positive<br>Smear-negative<br>MDR-TB | Minimum 2 weeks **and** 3 sputum samples are smear-negative<br>Minimum 2 weeks of treatment<br>Until sputum culture conversion on treatment documented | Jensen et al.[9] |
| Europe | European Respiratory Society/ European Centre for Disease Prevention and Control Statement: European Union standards for tuberculosis care | 2017 | Smear-positive | Until sputum smear conversion on treatment achieved (Standard 20) | European Centre for Disease Prevention and Control[43] |
| Europe | Reducing tuberculosis transmission: a consensus document from the World Health Organization (WHO) Regional Office for Europe | 2019 | All patients | Sputum smear status should not be used to guide de-isolation. However, specific guidance on duration of infectious cannot be made. | Migliori et al.[5] |
| WHO | WHO guidelines on tuberculosis infection prevention and control: 2019 Update | 2019 | All patients | No specific duration of isolation or parameter provided. Guidelines state that "deisolation should be based on the likely infectivity of the individual case and the availability of other supportive systems (in particular, decentralized models of care)" | Christof et al.[1] |
| United Kingdom | The National Institute for Health and Care Excellence Tuberculosis: management and infection control in hospital | 2020 | Drug-susceptible, pulmonary TB, regardless of smear-status | Consider de-isolation after 2 weeks of therapy if rifampin-resistance is not suspected and treatment response well-documented. | NICE[44] |
| New Zealand | Guidelines for Tuberculosis Control in New Zealand | 2019 | Drug-susceptible cases | "A pragmatic approach may be to isolate cases of pulmonary TB until the full susceptibility results are back from the laboratory. This would mean that most patients are in airborne isolation for up to two weeks, by which time infectivity of even heavily smear-positive patients will have fallen to negligible levels."<br>"Default de-isolation occurs at two weeks" in hospitalized patients. | Ministry of Health[45] |
| Australia | Infection control guidelines for the management of patients with suspected or confirmed pulmonary tuberculosis in healthcare settings | 2016 | Drug-susceptible cases | "Should remain isolated in a negative pressure room with airborne precautions applied until criteria are met. In principle these criteria should include: a reduction in or absence of cough; reduced smear burden or smear negativity; assured treatment by direct observation; and an appropriate discharge plan. | Coulter and National Tuberculosis Advisory Committee[46] |

## 1. Narrative review of the evidence

### 1.1. Clinical studies

To our knowledge, there are no controlled clinical trials in low-incidence settings that directly address rates of transmission to susceptible contacts in the first weeks following TB treatment initiation.

However, 1 large, randomized control trial conducted in the late 1950s in Chennai compared TB transmission from people with TB treated under segregation in a sanitorium until sputum culture negative with those treated entirely at home without isolation precautions.[12] Of those contacts who were tuberculin skin test (TST) negative at initial testing, rates of subsequent TST conversion after one year of follow-up was 25% in contacts of patients treated at home and 23% in contacts of patients treated in the sanitorium. Incident active disease at 1 year and 5 years of follow-up occurred in 8.1%/10.5% in contacts of patients treated at home and 8.0%/11% in contacts of patients treated in sanitoria. A strength of the study was the meticulous and thorough evaluation of most known patient contacts and the excellent degree of follow-up over 5 years. However, the trial was conducted in a high-incidence community, with contacts in both arms exposed to substantial risk of transmission from other source cases; this could have obscured an important difference in transmission rates. This makes it difficult to exclude the possibility that prolonged isolation might prevent some occurrences of transmission.

A subsequent analysis of the Chennai study found no relationship between duration of culture positivity following initiation of effective therapy and the rate of transmission to contacts.[13,14] The treatment regimens employed in this study did not include rifampin or pyrazinamide (PZA) and thus sputum culture conversion took much longer than it does with current regimens. However, despite slow bacteriologic response, people on TB treatment were unlikely to infect contacts. The authors suggested that once source cases are established on treatment, the sputum bacteriologic status of the host does not predict infectiousness.

### 1.2. Observational clinical studies

A few retrospective, observational studies have tried to address the question of infectivity post-treatment start in low-incidence settings and are discussed in this section. Several review articles have also summarized the findings.[5,14–18] Indeed, there may be more review papers on the topic than there are primary data sets.

Gunnels et al. analyzed contact tracing data from 155 patients admitted to hospital in Arkansas for treatment of pulmonary TB in the early 1970s.[19] Transmission from patients on treatment who were de-isolated despite persistent sputum smear and culture positivity (86 patients) were compared to those kept in isolation until sputum culture negativity was achieved (69 patients). In this frequently cited study, transmission, as judged by TST positivity of contacts, did not differ by sputum bacteriologic status at time of de-isolation. Tuberculin reactivity was found in 64% and 60% of contacts in each group. Skin-test conversion occurred in 26% of contacts of those discharged with smear and culture positivity and in 20% of contacts of those discharged with negative sputum smear and culture. It is important to note that the median time on treatment prior to de-isolation in both groups was about 5 weeks. Furthermore, this study was not randomized, and it is possible that patients allowed to come off isolation by their treating physicians despite persistent sputum smear positivity might have differed in other factors associated with transmission compared to those kept in hospital.

In a study from Baltimore, 25 people with pulmonary TB and their 70 contacts were closely followed with serial TST post-contact.[20] Some of the patients were treated at home and others were treated in hospital. Although 23% of all contacts were eventually found reactive to tuberculin, based on the timing of TST reaction, it was judged that none were infected after the source case had started treatment and was at home without isolation. Although this study performed detailed study of a relatively large number of contacts, early discharge home on treatment occurred for only a subset of patients, as determined by their treating physician and this likely introduced some selection bias.

In another non-comparative study from early 1970s, transmission rates from 21 people with smear-positive pulmonary TB treated in Cincinnati were evaluated.[21] These people with TB were admitted to hospital under isolation for an average of 15 days post-treatment initiation before being de-isolated and discharged home. At the time of discharge, nearly all patients remained sputum smear positive (19/21) and sputum culture positive (20/21). Of 70 tuberculin negative household contacts, no skin-test conversions occurred. and no secondary cases were detected after the source was placed on treatment. It is important to note that 30% of the tuberculin negative contacts in this study were prescribed "gap prophylaxis" prior to de-isolating the source case. This would have reduced the power of the study to detect meaningful transmission rates. Furthermore, the provision of preventative therapy to some contacts at the discretion of provider may have introduced selection bias.

There is a relative paucity of observational studies examining infectivity of people with pulmonary TB on treatment in the modern era.[22,23] An observational study to test this question would likely require large number of people with infectious TB cases assigned different durations of isolation post-treatment start. The appropriate use of primary prevention for tuberculin negative contacts under 5 years of age would be expected to further reduce transmission post-treatment in the modern era. To our knowledge, epidemiologic studies that incorporate the use of DNA fingerprinting technology to clarify transmission events have not yet been employed to explore this question.

### 1.3. Human-to-Guinea pig transmission studies

Guinea pigs are susceptible to TB infection through aerosol exposure. Much of our understanding of factors associated with TB transmission were elucidated using a

human-to-guinea pig experimental transmission model first developed by Riley in the 1950s.[24] In this model, guinea pigs were exposed to exhausted air drawn from isolation rooms containing people with pulmonary TB. Infection of the guinea pigs is detected through skin test conversion and culture of active lesions.

A recent WHO commissioned systematic review of animal studies identified four published reports with enough data to assess infectiousness following initiation of TB treatment.[11,25–27] Overall, the studies demonstrate that people with TB on effective treatment are much less infectious than people with TB not on effective treatment, even prior to sputum smear or culture conversion. Furthermore, most transmission to guinea-pigs appears to stop within a day or 2 of treatment initiation, even in patients who were smear-positive disease at treatment start. A separate review of these same studies came to a similar conclusions.[25]

In the Riley studies, people with TB on effective treatment for drug-susceptible disease were 98% less likely as those not on treatment to transmit in the human-to-guinea pig model. He showed that 29 animals were infected from untreated patients and only one animal was infected by people on TB treatment for less than 48 hours.[11] The temporal relationship between infectiousness and time on treatment could not be precisely determined as the people were started on treatment at the same time as they entered the specially constructed experimental facility. It should be noted that the people in these studies were treated with isoniazid combined with streptomycin and para-amino-salicylic acid (PAS); neither rifampin nor PZA were employed.

In a similarly design series of experiments conducted in South Africa, people identified with drug-resistant tuberculosis were transferred to a specialized unit equipped to conduct human-to-guinea-pig transmission studies.[25] People were started on an empiric standardized MDR-TB treatment regimen the day of arrival, pending the results of phenotypic drug-susceptibility testing. In 1 study, 27 people started on what was later found to be effective treatment based on drug-susceptibility testing (ie, regimens containing a fluoroquinolone, injectable and ethionamide for patients infected with isolates confirmed susceptible to these agents). These 27 people appeared to infect only 1% of guinea pigs over a mean duration of exposure of 3 months. For people subsequently found to have extensively-drug resistant TB or who discontinued treatment due to adverse effects, and were thus not on effective treatment, rate of infected guinea pigs was substantially higher.

The design of the guinea pig studies included in the systematic review did not allow precise determination of the speed of the effect of treatment on infectiousness.[7] Although substantial reductions in infectiousness were observed within 1 to 2 days of effective treatment, it is not clear how many days of treatment would be needed to render all patients entirely non-infectious.

Further guinea pig exposure studies that are specifically designed to answer the question of how many days of effective treatment are needed to eliminate potential transmissibility in all patients would be useful.

### 1.4. Cough aerosol sampling studies

Specialized cough aerosol sampling devices allow investigators to selectively capture respirable droplet nuclei excreted through cough and then perform quantitative mycobacterial cultures. This allows measurement of the number of aerosols containing viable bacilli produced by a given patient's cough.[28]

Subsequent field studies have shown that less than one-third people with sputum smear-positive pulmonary TB are able to generate cough aerosols containing viable bacilli.[29] The ability to generate infectious aerosols may partly explain the observed heterogeneity in infectiousness of pulmonary TB patients in epidemiologic studies. Indeed, 2 large cohort studies have shown that the measures of culturable cough aerosols predicts subsequent infectiousness to contacts better than other patient factors including the smear positivity of expectorated sputum.[30,31]

More recent cough-aerosol captures studies have examined the impact of treatment. For example, in prospective cohorts of 233 people with culture positive pulmonary TB from Brazil and Uganda, treatment with effective anti-TB therapy for as little as 1-2 days dramatically reduced, but did not eliminate, the number of infectious aerosols produced.[32] This study did not repeat sampling beyond 2 days of treatment and thus could not determine how soon after treatment had started all potentially infectious aerosols are eliminated.

In a cohort recruited from a South African clinic, effective treatment of drug-susceptible TB again rapidly reduced culturable cough aerosols substantially.[33] After 8 days of first-line treatment, none of the drug-susceptible cases (N = 38) could produce cough aerosols with viable bacilli. Few patients with MDR-TB on effective treatment were included in this study.

Overall, cough aerosol data support the notion that effective treatment rapidly reduces infectivity of patients, even as traditional sputum samples remain smear and/or culture positive. More data is needed to confirm the clinical relevance of the culturable aerosol model and to measure impact of treatment more precisely over the first weeks.

### 1.5. In vitro data

In vitro data to guide duration of infectiousness for drug-susceptible TB is best described in a review by Menzies[17] where the early bactericidal activity of first-line anti-TB agents used in combination are described.[34] With a standard TB regimen consisting of three drugs, concentration of viable TB bacilli in sputum is expected to drop by 3 logs within 2 weeks. This implies that for sputum smear-negative TB, less than 100 viable bacilli per mL of sputum would survive after 2 weeks of therapy, and accordingly people could be judged non-infectious. For people with heavily smear positive sputum, 2 weeks of therapy would still leave more than 10,000 viable bacilli per mL, meaning that patients would remain smear positive and likely still infectious.

However, judgements about infectiousness that are derived from in vitro data assume that microbes that can be cultured

from sputum samples have the same ability to survive in cough aerosols and to establish infection in another host — with or without treatment. However, the data from epidemiologic, cough aerosol and human-to-guinea pig studies suggests that treatment does make a difference.

Early bactericidal activity of the fluroquinolones levofloxacin (1000 mg daily) and moxifloxacin (400 mg daily) is considered comparable to that of isoniazid.[35] The early bactericidal activity of bedaquiline (dosed at 400 mg daily) and linezolid (600 mg daily) appear less than that of isoniazid but comparable to rifampin.[36,37] Modern MDR-TB treatment regimens are expected to have substantial early bactericidal activity that may render patients non-infectious relatively quickly compared to older MDR regimens. Implications for de-isolation of patients receiving modern MDR-TB treatment regimens are not yet well established.

### *1.6. Potential harms of prolonged isolation*

There are potential harms associated with prolonged time in isolation.[1,6,8] Isolation for TB has been associated with significant anxiety, fear and mood dysfunction.[38] In one Canadian study, people with TB had a 25% higher rate of depression than people without TB, and that length of stay in hospital was an independent predictor of developing depression.[39]

Studies of hospitalized patients under isolation for infection with nosocomial bacterial pathogen have shown that people in hospital isolation receive less nursing attention and experience higher rates of medication errors and hospital adverse events than patients not in isolation.[40] People in isolation often have less visitors than other patients, too.[40]

A survey of members of a Canadian indigenous community with experience in TB sanitoriums highlighted the trauma and stigma associated with prolonged hospitalization away from home.[41]

While many people with infectious TB receive treatment under home isolation, inadequately housed people with TB must remain isolated in hospital away from the support of family and friends until deemed non-infectious. Thus, the harms of prolonged isolation disproportionately affect those from disadvantaged populations.

Recent qualitative studies in people with MDR-TB and their family indicate a strong preference for early de-isolation over prolonged hospitalization.[42]

Many providers feel obligated to test sputum more frequently during the intensive phase of treatment to demonstrate smear-negativity as soon as possible and allow a patient to come off isolation as quickly as possible. This likely adds to treatment costs. Some physicians may add anti-mycobacterial agents (eg, fluoroquinolones) to the initial standard treatment regimen in an effort to hasten sputum smear conversion and thus shorten isolation. However, this "treatment intensification" may add risk of toxicity without improving overall treatment results (see Chapter 5: Treatment of Tuberculosis Disease).

## 2. De-isolation recommendations

The following recommendations for discontinuation of isolation and airborne precautions (de-isolation[a]) are intended for patients in the community and in healthcare settings. The decision to de-isolate remains subject to expert clinical and public health judgment. TB treatment providers or infection control professionals may prolong isolation beyond the recommended minimal times; this is described further in the caveat section.

**Recommendations:**

**Smear-negative[b], rifampin-susceptible pulmonary TB[c]:**

- **We conditionally recommend that airborne precautions can be discontinued (and person de-isolated) once there is clinical evidence of improvement and a minimum of 2 weeks of effective therapy[d,e] has been completed** (poor evidence).

**Smear-positive, rifampin-susceptible pulmonary TB:**

- **We conditionally recommend that airborne precautions can be discontinued once there is clinical evidence of improvement[f], a minimum of 2 weeks of effective therapy has been completed and there are 3 consecutive negative acid-fast bacilli sputum smears.[g] Airborne precautions may be discontinued if there is clinical evidence of improvement after completing a minimum of 4 weeks[h] of effective therapy, even if the sputum smears are persistently positive (poor evidence).**

**Confirmed or suspected rifampin-resistant pulmonary TB:**

- **We conditionally recommend that airborne precautions may be discontinued once there is clinical improvement, second-line drug susceptibility results are available, and a minimum of 4 weeks of effective therapy has been completed. In addition, for those initially smear positive, 3 consecutive sputum smears must be negative** (poor evidence).

***Definitions/Footnotes:***

a. *De-isolation: Airborne precautions can be discontinued and/or lifting of home-isolation restrictions. People de-isolated would be allowed to return to school and work and enter indoor public spaces without restriction unless otherwise stipulated by public health professionals.*
b. *Smear-negativity can be re-confirmed at the time of treatment start, to exclude progression to smear-positive disease during the time from initial specimen collection to culture positivity. However, repeat sampling at the end of 2 weeks of therapy is not required.*
c. *Rifampin susceptibility for the purposes of this protocol can be determined by genotypic or phenotypic methods.*
d. *Two weeks refers to 14 doses of daily administered treatment or 2 calendar weeks of 5 days per week of direct-observed therapy.*

e. *Effective treatment: For the purposes of de-isolation, effective therapy for rifampin-susceptible cases (based on genotypic and/or phenotypic testing) consists of at least 3 drugs, one of which is rifampin. For rifampin resistant TB, effective therapy consists of at least 3 drugs to which the isolate is confirmed susceptible or highly likely to be susceptible to.*
f. *Treatment Response: Clinical evidence of improvement refers to a broad range of symptoms, including but not limited to improvement in cough, resolution of fevers, or decreased night-sweats.*
g. *Sputum smear conversion: This is confirmed when at least 2 consecutive sputum samples (collected at least 1 hour apart) are smear-negative on fluorescent microscopy.*
h. *Four weeks refers to 28 doses of daily administered therapy or 4 calendar weeks of 5 days per week direct-observed therapy.*

**Important Additional Caveats**

Before allowing de-isolation, ensure that the person is tolerating the treatment regimen and that an acceptable treatment plan with supported adherence is established.

The decision to de-isolate remains subject to expert clinical and public health judgment. TB treatment providers or infection control professionals may prolong isolation or apply restriction beyond the aforementioned guidelines under certain circumstances. For example, longer de-isolation might be warranted for people with pulmonary TB who reside or work in congregate settings together with immunologically vulnerable individuals (such as day care facilities, neonatal or pediatric intensive care units, hospital wards and clinics for transplant recipients or those under treatment for hematologic malignancies).

Sputum samples used to guide de-isolation should be of adequate volume and sputum induction may be required. Bronchoscopy should not be employed simply to obtain respiratory tract samples that are used to guide duration of isolation. In the event follow-up sputum samples cannot be obtained, de-isolation should be performed in consultation with TB expert and/or public officer of health.

**Home Isolation:**

For people with TB that are medically well enough, ambulatory treatment and home isolation is preferred over hospital isolation.

Home isolation is acceptable when the following conditions are met:

- First, the person is tolerating the treatment regimen and an acceptable treatment plan with supported adherence is established.
- Second, the person does not share a common airspace with non-household members (eg, rooming house) and the household air is not being recirculated to other housing units (eg, as seen in some apartment complexes).
- Third, all household members have been previously exposed to the person. If any household members are TST negative, they should be informed and understand the potential risks of ongoing exposure.
- Fourth, any children under the age of 5 or persons with immunocompromising conditions present in the home are receiving treatment for active TB disease or latent TB infection.

When on home-isolation, no visitors should be allowed in the home except for health care workers wearing appropriate personal protective equipment (see Chapter 14: Prevention and Control of Tuberculosis Transmission in Healthcare Settings). The person on home isolation should not go to work, school or any other public indoor environment and should not use any form of public transportation (if absolutely necessary, a taxi can be used to attend essential healthcare appointments provided the person is wearing a mask). While on home isolation, the person can ambulate outdoors.

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