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Duration of Effective Tuberculosis Treatment, Not Acid-Fast Bacilli (AFB) Smear Status, as the Determinant for De-isolation in Community Settings

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For decades, multiple public health and clinical tools have been used to prevent tuberculosis (TB) transmission. Two of these tools are directly discussed in the document by the National Tuberculosis Coalition of America (NTCA) in this issue of *Clinical Infectious Diseases*: (1) prompt and effective TB disease treatment and (2) isolation, or separating persons with TB disease from others until noninfectious. Use of nucleic acid amplification tests can facilitate rapid TB diagnosis, rapid detection of drug resistance, and early effective treatment [1, 2]; prompt TB treatment initiation is beneficial to both the person with TB and the community. The risk–benefit equation for isolation of persons with TB after treatment initiation, however, is not as straightforward; in this situation, persons with TB bear the burden of isolation, with potential benefit from preventing transmission accruing to the community.

While the US Centers for Disease Control and Prevention (CDC) has issued guidelines for discontinuation of TB isolation in healthcare settings [3] and congregate settings such as correctional facilities [4], there are currently no parallel national guidelines for community settings, such as the home where a person with TB on treatment is awaiting clearance for return to work or school. Recognizing that state TB programs and TB medical directors have the most familiarity with local TB epidemiology, public health resources, and healthcare systems, as well as other state or local priorities, CDC defers to state and local authorities to make and enforce policies regarding TB isolation within their jurisdictional boundaries. Federal authorities apply in the context of international arrivals at US ports of entry or

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interstate travel, including the authority to issue isolation orders for persons with infectious TB, which is a federally quarantinable communicable disease in the United States [5–7].

Isolation policies and guidance for people in community settings garnered increased attention during the coronavirus disease 2019 (COVID-19) pandemic, with public health officials aiming to strike the balance between individual restrictions and community benefit. In this same time frame, TB survivors organized to share publicly their experiences with the harms of prolonged isolation while on treatment [8, 9]. Specifically, persons undergoing treatment for TB disease face negative consequences from isolation due to stigma, mental health impacts, loss or interruption of employment or schooling, and issues accessing and maintaining housing. Persons with TB are disproportionately represented among people from racial and ethnic minority groups, non–US-born persons, low-income persons, and persons with barriers to accessing healthcare. Health equity concerns have also led to re-examination of the public health benefits of averting possible transmission by persons with TB on treatment weighted against the harms of isolation.

Many public health TB programs, extrapolating from national healthcare facility guidelines, have required that individuals with TB have negative acid-fast bacilli (AFB) sputum smears prior to discontinuation of isolation in community settings. It is not unusual for persons with TB, particularly those with extensive or cavitary pulmonary disease, to have persistently positive AFB sputum specimens for weeks to months. Consequently, persons with TB often cannot work for prolonged periods and may be separated from their families. Isolation from family, friends, and other in-person social support networks is associated with depression and anxiety [10, 11]. Many persons with TB who have jobs without sick leave, who work in jobs that cannot be done remotely, or who work in the informal economy, such as day laborers, experience immediate income loss during isolation; some are unable to pay for housing and become at risk of eviction or homelessness. The cumulative impacts of prolonged isolation on persons with TB and their families can be catastrophic.

The most important recommendation made in the NTCA guidance document is for TB programs to assess and update how local isolation discontinuation policies are implemented in community settings after persons with TB initiate treatment. By summarizing evidence on limited benefits along with known harms of isolation after treatment initiation, the NTCA guidance document provides a practical framework for more cautious and limited use of isolation for persons with TB on treatment as a strategy for US TB programs during a time when rapid molecular diagnostics and effective TB treatments are widely available. The emphasis on treatment-as-prevention while de-emphasizing isolation and other behavioral interventions for persons on treatment is in line with similar patient-centered public health initiatives for other infectious diseases, such as human immunodeficiency virus (HIV) and hepatitis C [12, 13].

Prior to the initiation of effective treatment, the likelihood of TB transmission is influenced by many factors, including the following: anatomic site of involvement; bacillary burden (indicated by cavitary disease on chest radiograph, extensive bilateral pulmonary or disseminated TB disease, or presence and number/grade of AFB on sputum smear microscopy at diagnosis); cough frequency; amount of cough aerosol generated; mask

use by the person with TB; use of personal protective equipment by exposed persons; ventilation, proximity, and number of persons in the environment in which the person with TB interacts with others; duration of exposure; and age or immunocompromising conditions of exposed persons [11, 14, 15].

However, a key evidence-based point in the NTCA guidelines is that, after initiation of effective TB treatment, AFB smear grade in sputum—relied on historically as a sole laboratory predictor of infectiousness for isolation discontinuation decisions—is no longer a useful indicator of infectiousness. Even the presence of culturable *Mycobacterium tuberculosis* complex bacilli in sputum may not have the direct correlation with infectiousness previously assumed. Rather, evidence summarized in the NTCA guidelines (Table 1) demonstrates that effective treatment is the critical factor in rendering persons with TB rapidly noninfectious. Importantly, interruption of effective therapy may cause persons with TB to become infectious again.

The key conclusion of the evidence review used to formulate the NTCA guidelines is that most persons with pulmonary TB in US community settings likely have little or no infectious potential after 5 days of effective treatment and therefore can be taken out of isolation accordingly, regardless of sputum AFB smear or culture status. Treatment duration prior to de-isolation may be extended beyond 5 days due to several factors that are known to be associated with transmission. These include circumstances of the person's living situation and workplace; presence of vulnerable contacts, such as children less than 5 years of age or immunocompromised persons; lack of adequate ventilation or crowding of environments; or plans to travel by public conveyance. Individual characteristics to consider in decisions to extend isolation are baseline burden of disease, clinical confidence that TB treatment is effective, adherence to therapy, and comorbid medical conditions that are associated with TB drug malabsorption. The guidelines recommend additional consultation or expert review if isolation in community settings is extended beyond 14 days to develop treatment plans that minimize harms to individuals and their communities.

Additionally, the NTCA guidelines recommend that isolation no longer be an all-or-none strategy but instead be considered a more dynamic nonpharmaceutical intervention. The guidelines recommend tailoring restrictions to the person's specific situation. For example, persons with TB who work outdoors and are willing to wear masks during brief times indoors could continue to work, even during the initial days of treatment.

These recommendations rest on some crucial underpinnings, as follows:

1. Access to and capacity to undertake individual case review to allow careful evaluation of individual details and social context to inform isolation discontinuation decisions.
2. Availability of rapid molecular testing for drug resistance to ensure effective treatment, particularly for persons with risk factors for drug-resistant TB.
3. Ability to evaluate the success of "effective treatment" administration, via assessment of directly observed therapy (DOT) and evaluation for clinical improvement (eg, symptomatic well-being, fever, and cough frequency).

4. Availability of expert consultation for persons with complicated or drug-resistant TB or with complex clinical considerations from state or local TB medical consultant(s) or a CDC-supported TB Center of Excellence.

The NTCA isolation guidelines, in summary, guide public health isolation decisions for outpatients with TB in community settings and emphasize that effective TB treatment is the key factor in persons with TB becoming noninfectious. It is important to note that these guidelines are distinct from CDC TB isolation guidance intended specifically for persons in healthcare facilities and congregate settings. If carefully applied, with local TB expertise involved in decision-making about isolation duration, the NTCA guidelines have the potential to improve quality of life for persons with TB and minimize the harms of unnecessarily lengthy isolation.

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Table 1.

Summary of Key Evidence That Effective TB Treatment Rapidly Renders Persons With TB Noninfectious

Type of Evidence	Brief Summary	Location and Date
Randomized trial	Persons with TB randomized to sanatorium versus home-based treatment with INH and PAS; no difference in LTBI or TB disease among household contacts over 5 y; "major risk to contacts resulted from exposure to patient before diagnosis"	Madras, India, 1956–1959 [16]
Retrospective cohort	Persons with TB discharged from the hospital on treatment while still TB culture positive (majority also AFB smear positive) compared with persons with TB who were AFB smear and culture negative at discharge from hospital; no difference in TST conversion among household contacts	Arkansas, 1967–1971 [17]
Experiment	Guinea pigs susceptible to TB infection exposed to air vented from a TB ward; treatment of persons with TB with INH, PAS, and SM reduced transmission to guinea pigs by 98% immediately compared with untreated persons with TB	Baltimore VA TB Ward, 1959–1961 [18]
Experiment	Guinea pigs susceptible to TB infection exposed to air vented from MDR TB ward; TST conversions in guinea pigs showed infection of 1 (1%) of guinea pigs after 3 mo of exposure to 27 persons with MDR (most AFB smear positive) on treatment with regimen of levofloxacin, kanamycin, ethionamide, and either ethambutol or prothionamide	South Africa, ~2007–2012 [19]
Transcriptomic analysis	Analysis of TB isolates from respiratory aerosols of 7 persons with drug-susceptible TB on TB treatment with rifampin, INH, PZA, and ethambutol showed immediate downregulation of transcription of genes involved in TB virulence and infectiousness after 1 d of treatment	Mumbai, India, 2018–2020 [20]

Abbreviations: AFB, acid-fast bacilli; INH, isoniazid; MDR, multidrug resistant; LTBI, latent tuberculosis infection; PAS, para-aminosalicyclic acid; PZA, pyrazinamide; SM, streptomycin; TB, tuberculosis; TST, tuberculin skin test.