Tuberculosis Screening, Testing, and Treatment of US Health Care Personnel

ACOEM and NTCA Joint Task Force on Implementation of the 2019 MMWR Recommendations

Wendy Thanassi, MD, MA, Amy J. Behrman, MD, Randall Reves, MD, Mark Russi, MD, MPH, Melanie Swift, MD, MPH, Jon Warkentin, MD, MPH, Ryo Miyakawa, MD, Donna Wegener, MA, Lawrence Budnick, MD, MPH, Ellen Murray, RN, PhD, Ann Scarpita, BSN, MPH, Bobbi Jo Hurst, MBA, Sarah Foster-Chang, DNP, ANP-BC, Trini Mathew, MD, MPH, MaryAnn Gruden, MSN, COHN-S/CM, Julie Higashi, MD, PhD, and Thomas Warner Hudson III, MD

On May 17, 2019, the US Centers for Disease Control and Prevention and National Tuberculosis Controllers Association issued new Recommendations for Tuberculosis Screening, Testing, and Treatment of Health Care Personnel, United States, 2019, updating the health care personnel-related sections of the Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005. This companion document offers the collective effort and experience of occupational health, infectious disease, and public health experts from major academic and public health institutions across the United States and expands on each section of the 2019 recommendations to provide clarifications, explanations, and considerations that go beyond the 2019 recommendations to answer questions that may arise and to offer strategies for implementation.

The American College of Occupational and Environmental Medicine (ACOEM) fully supports implementation of the Unites States's (US) Centers for Disease Control and Prevention (CDC) and National Tuberculosis Controllers Association's (NTCA) Recommendations for Tuberculosis Screening, Testing and Treatment of Health Care Personnel, United States, 2019.[1] The new guidance updates the health care personnel-related sections of the Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005.[2] In particular, both ACOEM and NTCA endorse the discontinuation of routine annual tuberculosis (TB) testing in health care personnel (HCP) and the increased emphasis on the role of occupational health in encouraging treatment of persons with latent tuberculosis infection (LTBI) to prevent progression to active disease (reactivation) and to positively impact the public's health.

This document offers the collective effort and experience of occupational health, infectious disease, and public health experts from major academic and public health institutions across the US. It expands on each section of the 2019 Mortality and Morbidity Weekly Report (MMWR) CDC/NTCA Recommendations to provide clarifications, explanations, and considerations that go beyond the 2019 MMWR CDC/NTCA recommendations to answer questions that may arise and to offer strategies for implementation. This ''companion'' document was written to support the nation's occupational health providers, infection preventionists, public health officers, valued HCP, and the patients we serve.

The sections to follow closely mirror those of the 2019 MMWR CDC/NTCA Recommendations:

Introduction
Background with Literature Review
Baseline (post-offer/pre-placement) Screening and Testing
- Post-Offer/Pre-Placement (POPP) TB Risk Assessment and Symptom Review
- TB Testing for HCP Without Prior Positive Test
- Regarding Reversions
- TB Testing for HCP with Prior Positive Test
- Newly Confirmed Positive TB Test and/or Positive Symptom Review
- Considering Active TB Disease
- Compliance, Confidentiality, and Communication

Post-exposure TB Screening and Testing
- Overview
- Travel-Related Exposure
- Voluntary Testing for Self-assessed Potential Exposure
- Post-Exposure Testing Considerations and Interpretation

Serial Screening, Testing and Education for HCP
- Serial Screening and Testing
- Annual Education Requirement
- Annual Symptom Review for HCP with LTBI
- Transitioning a TB Screening Program for Health Care Personnel

Treatment and Education of Health Care Personnel with Positive Test Results
- Progression from LTBI to TB Disease (Reactivation TB)
- Educating HCP with LTBI
- Recommending Treatment

The 2019 MMWR CDC/NTCA recommendations shift the focus from routine serial testing to improving education and increasing LTBI treatment. Identifying, to the best of our ability, the presence of LTBI allows occupational health practitioners to encourage treatment and prevent future TB disease. Efforts to eliminate LTBI support workforce and workplace health locally, while moving us closer to a TB-free nation.

KEY POINTS – 2019 MMWR CDC/NTCA Recommendations

- The term health care worker has been replaced by HCP and refers to all paid and unpaid, part time, temporary, contract, student and full-time persons working in health care settings.
- At the point of hire or transfer into a clinical position, all HCP should have baseline TB screening that includes an individual risk assessment, symptom evaluation and (for those without LTBI or TB disease) a test for *M. tuberculosis* infection.
- Treatment to prevent progression to active TB disease (reactivation TB) is strongly encouraged for all HCP diagnosed with LTBI.
- HCP without LTBI should not undergo routine serial TB screening or testing at any interval after baseline (eg, annually)

From the American College of Occupational and Environmental Medicine, Elk Grove, Illinois.
The authors declare no conflicts of interest.
Supplemental digital contents are available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.joem.org).
Address correspondence to: Marianne Dreger, MA, ACOEM, 25 Northwest Point Blvd, Suite 700, Elk Grove Village, IL 60007 (info@acoem.org).

DOI: 10.1097/JOM.0000000000001904

in the absence of known exposure or evidence of ongoing TB transmission.
- HCP with untreated LTBI should receive a yearly symptom review, TB education, and treatment encouragement.
- The facility risk assessment, contained in the 2005 MMWR CDC Guidelines Appendix B,[2] continues to be required annually for the assessment and maintenance of environmental controls (Appendix 1, http://links.lww.com/JOM/A780).
- After known exposure to potentially infectious TB without adequate personal protection, HCP should have a symptom evaluation and timely TB testing.
- All HCP should receive TB education annually. Education should include information on TB risk factors, the signs and symptoms of TB disease, TB infection control policies and procedures, and LTBI treatment regimen options.

BACKGROUND WITH LITERATURE REVIEW

In the 1920s, US researchers began to recognize that HCP were at risk of contracting TB from patients.[3] By the 1950s, TB rates remained as high as 50 cases per 100,000 population and the increased risk of nosocomial TB in health care occupations became more clear.[3,4] Routine admission chest x-rays (CXR) were instituted and were shown to reduce TB risk among HCP.[4] By the 1980s, when TB rates decreased by 80% to under 10 cases per 100,000 population, the utility of such routine admission radiography was questioned.[5] There were occasional published reports of nosocomial transmission of TB to HCP from the 1960s and 1980s, usually attributed to diagnostic and/or treatment delays in environments with inadequate ventilation.[3]

The TB resurgence of 1985 to 1992, which mirrored the rise of human immunodeficiency virus (HIV) in the US, resulted in a concurrent rise in nosocomial TB transmission to HCP in urban hospitals and again highlighted their occupational risk. US TB rates increased from 9.3 to 10.4 per 100,000. Numerous investigations attributed facility-based transmission to administrative errors (inadequate infection control policies), clinical errors (missed and delayed diagnoses and delayed drug-resistance detection), and poor engineering controls (inadequate ventilation).[3,6,7] HCP tuberculin skin test (TST) conversions in the early 1990s ranged from less than 0.1% to 4.5% annually in hospitals in non-outbreak settings, but were as high as 20% in just 6 months in some institutions with outbreaks.[8] Annual TST conversions in hospitals with high TB admission rates were over 4% in the early 1990s but dropped to less than 1% within years of adopting improved administrative and engineering controls.[6–9]

Publications in this decade confirm annual US HCP TST conversion rates well below 1%. At a Midwest tertiary care medical center, 39,280 HCP with a baseline negative TB test underwent nearly 200,000 annual TSTs and only 123 (0.31%) conversions were detected over a 16-year period.[10] Most of the TST conversions appear to have been false-positive TSTs attributed to a delayed boosting effect since the positive TSTs occurred most frequently with the third TST placed during employment. In addition, only 9% of the 123 conversions were associated with known workplace or community TB exposure, 66% of these had negative interferon gamma release assay (IGRA) results, and no one developed active TB disease. These data, along with annual conversion rates of less than 1% in HCP at medical centers that care for patients with active TB disease, illustrate that the efficacy of TB infection control programs resulted in limiting the TB transmission to HCP.[6,9]

In a remarkable turn of events, effective TB infection control has led to such a low probability of HCP exposure that the TB rate in US HCP has dropped below that of the overall population. Two national studies published by CDC compared with TB rates among HCP to the total US population, one for the 5-year period 2003 to 2007[11] and the second for the 7-year period 2010 to 2016.[12] Both showed consistent evidence of lower TB incidence rates among HCP compared with the national population. The mean annual HCP TB rates for the 5-year period 2003 to 2007 and the 7-year period 2010 to 2016 were 4.2 and 2.5 per 100,000 persons, respectively. During these study periods, the US annual TB rates declined from 5.1 to 4.4, and from 3.6 to 2.9, respectively (Table 1). In addition to TB rate comparisons, the national genotyping data estimate the proportion of TB cases due to recent transmission was only 10% in HCP, compared with 14% in the population overall.[12]

The epidemiology of TB among HCP parallels the national pattern of predominately occurring in non-US-born persons.[11] Lambert et al[11] also described the features of TB disease over the 13-year period of 1995 to 2007 that included fatal outcomes among 3.1% of HCP reported TB cases, while fatal outcomes nationally were 10.9%. The relatively lower incidence and mortality rate from TB disease in the HCP population is not unexpected considering HCP are generally well-educated, employed, tend to have adequate housing and nutrition, and are in the middle of the age spectrum. These studies provide further evidence of very limited nosocomial or consequential transmission of TB to US HCP.

In this era of low TB incidence among US HCP, the high cost of maintaining annual testing and the burden of false-positive results has led to several revisions of recommendations for LTBI testing. The 2017 Clinical Practice Guidelines by Consensus of the American Thoracic Society, Infectious Diseases Society of America, and the CDC recommend the use of IGRAs over TSTs in low-risk persons who undergo mandatory testing.[14] IGRAs require only a single encounter, have higher specificity than the TST among individuals with prior bacille Calmette-Guérin (BCG) vaccination,[15,16] and are reported in many studies

TABLE 1. Mean Annual Numbers and Rates of Active TB Cases among Health Care Personnel (HCP) by Country of Birth during 2003–2007 and 2010–2016, Compared With the Total US Annual Numbers and Rates for 2005 and 2013

		HCP*			US†		
Study Period		US-born	Non-US-born	HCP Total	US-born	Non-US-born	US Total
2003–2007	Rate	1.7	17.9	4.2	2.5	22.3	4.8
	No. (%)	151 (35)	278 (65)	429 (100)	6,290 (45)	7,745 (55)	14,065 (100)
2010–2016	Rate	0.8	10.8	2.5	1.2	15.7	3.0
	No. (%)	90 (28)	262 (72)	352 (100)	3,330 (34)	6,222 (68)	9,561 (100)

*The mean annual numbers and rates for the 5- or 7-year periods were obtained from Lambert et al,[11] Mongkolrattanothai et al,[12] and via Lauren Lambert, personal communication.

†The comparison annual US numbers and rates for the two study periods are the data of 2005 and 2013, the mid-year of each study period when rates declined from 4.4 to 5.1 and 3.6 to 2.9, respectively.[13]

to be more cost-effective than TST for serial screening.[11,17–19] However, the specificities of both approved IGRAs appear lower than with TST when used for serial testing of low risk populations who did not have BCG vaccination.

A multicenter study comparing the performance of serial TST and of both of the IGRAs then approved by the US Food and Drug Administration (FDA) was conducted from 2008 to 2011 among HCP at four US hospitals with annual TST conversion rates of less than 1%. In this study, simultaneous TST, QuantiFERON®-TB-Gold In Tube (QFT-GIT) (QFT, Qiagen Inc.), and T-Spot®.TB (TSPOT, Oxford Immunotec) were obtained at baseline and repeated thrice at 6-month intervals. Among over 2100 HCP with baseline negative tests, the cumulative number of conversions was 21 (0.9%) for TST as expected but was 138 (6.1%) with QFT-GIT, and 177 (8.3%) using the T-Spot®.TB. There were no known TB exposures at the institutions. Only four HCP converted by both TST plus one IGRA, and 17 converted by TST alone. Repeat tests found reversion to negative in 65% of the TST converters and over 75% for converters with either IGRA, demonstrating the low positive predictive value of TB tests in US HCP.[20] These findings have been supported in other studies including a 2018 report of a retrospective cohort analysis of 40,142 tertiary care HCP who received a TST, showing 123 conversions over 16.4 years. Only nine (7%) of the converters had a suspected workplace TB exposure and none developed active TB. The majority (66%) of TST converters had a negative QuantiFERON-TB test result at the time of the TST conversion.[21]

In addition to reducing serial TB testing, the 2019 MMWR CDC/NTCA Recommendations emphasize the need to increase efforts to encourage treatment of LTBI, whether it was acquired in the community or in the workplace.[22] The emphasis on LTBI diagnosis, education, and treatment completion is an attempt to prevent reactivation and thereby reduce TB morbidity, mortality, and transmission to other HCP and patients.

BASELINE (POST-OFFER/ PRE-PLACEMENT) SCREENING AND TESTING

2019 MMWR CDC/NTCA Recommendation: ''All US health care personnel should have baseline TB screening, including an individual risk assessment, which is necessary for interpreting any test result. The 2005 guidelines state that baseline test results provide a basis for comparison in the event of a potential or known exposure to *M. tuberculosis*, facilitate detection and treatment of LTBI or TB disease in health care personnel before placement, and reduce the risk to patients and other health care personnel. The risk assessment and symptom evaluation help guide decisions when interpreting test results. For example, health care personnel with a positive test who are asymptomatic, unlikely to be infected with *M. tuberculosis*, and at low risk for progression on the basis of their risk assessment should have a second test (either an IGRA or TST) as recommended in the 2017 TB diagnostic guidelines of the American Thoracic Society, Infectious Diseases Society of America, and CDC. In this example, the health care personnel should be considered infected with *M. tuberculosis* only if both the first and second tests are positive.''[1]

Summary

The primary changes from the 2005 MMWR CDC Guidelines specific to the post-offer pre-placement process are the addition of an individual TB risk assessment with symptom review, and the recommendation to strongly encourage treatment of HCP with LTBI.[2]

Post-Offer/Pre-Placement (POPP) TB Risk Assessment and Symptom Review

The 2019 MMWR CDC/NTCA Recommendation states that all HCP should have a baseline POPP TB evaluation. An updated list of employees who are designated as ''HCP'' is included in Appendix 2, http://links.lww.com/JOM/A781.[2] For institutions where non-clinical new hires are not screened for TB, those employees should enter the pre-placement TB screening process if they transfer into a clinical position.

POPP TB screening is done in order to: (a) rule out active TB disease prior to placement; (b) identify LTBI and offer treatment or consultation for treatment as appropriate; and (c) establish a baseline to guide interpretation of future tests in the event of a new exposure or new symptoms suggesting active TB disease. POPP TB screening will always include a risk assessment, TB history, and a symptom review; will usually include testing by IGRA or TST; and may include imaging or additional evaluation to rule out active TB disease and guide treatment recommendations.

Individual risk assessments are necessary for interpreting test results. These should include:

- Risk factors for exposure, such as known exposure to person(s) with active TB disease or birth/residence in TB endemic countries (see 2019 MMWR CDC/NTCA Recommendations Risk Assessment[1]).
- Risk factors for progression to active TB disease (reactivation TB), such as immune-suppressing medications, diabetes, cancer, organ transplant, or HIV.[23] Note that diabetes is not a risk factor for acquiring TB, but having diabetes imparts a 2 to 4-fold increased risk for LTBI progressing to active TB disease.[24]

Additionally, obtaining the individual's TB history is important and could include:

- Documentation of prior TB test results (including dates and type of test where possible),
- History of LTBI or active TB disease, and
- Treatment history for active TB disease or for LTBI including location of treatment, length of treatment, medications taken (if known), whether treatment was completed, and any current symptoms consistent with active TB disease.

The symptom review should include:

- Questions regarding the presence of prolonged (more than 3 weeks), unexplained fever, prolonged cough or fatigue, hemoptysis, unintended weight loss, or drenching night sweats.

The individual risk assessments, including the TB history and symptom review questions (screening questionnaire), can be administered electronically, on paper, or by interview but should be standardized within an institution. Screening questionnaires should be consistent with national guidelines, evolving best practices, state/local health department requirements, and institutional policies. Since the HCP responses will include both health information and other protected personal information, completed TB screening questionnaires must be kept confidential. A licensed practitioner or qualified occupational health professional should review screening questionnaires and documentation of treatment. Clinical practices/institutions may opt for a single integrated screening questionnaire to streamline the onboarding process, or may use the risk assessment form included with the 2019 MMWR CDC/NTCA Recommendations,[1] in combination with a TB history and symptom review. A sample integrated questionnaire addressing all essential components of TB screening is appended and may be adapted to meet institutional needs (Appendix 3, http://links.lww.com/JOM/A782).

TB Testing for HCP Without Prior Positive Tests

Institutions may opt to accept recent, documented negative TB test results from other employers or training programs. The

decision to accept such results will vary based on reliability and remoteness of the report, workers' compensation considerations and facility policy. Institutions that accept prior negative IGRA or TST results for POPP clearance should use a consistent approach considering time interval, exposure risk, and medical history.

The initial TB test for HCP without a documented prior positive TB test can be either an IGRA (preferred) or a TST.[14] The choice of test may be influenced by a health care institution's specific cost, staffing, and logistical considerations. A single test type should be employed as much as possible in order to maintain consistency in interpretation. Current FDA-approved whole blood IGRA tests are the QuantiFERON®-TB Gold Plus (QFT, Qiagen Inc.),[25] an enzyme-linked immunoassay (ELISA), and the TSPOT®.TB (TSPOT, Oxford Immunotec),[26] a ficoll-separation assay (ELISPOT). Both tests utilize negative and positive controls, and both use the MTB-specific antigens ESAT-6 and CFP-10. Both assays are indirect measures of interferon gamma release in response to the TB-specific antigens. IGRAs have advantages over the TST during the onboarding process, including greater specificity in the BCG vaccinated and faster time-to-onboarding compared with the two-step TST.[27,28] Retesting indeterminate or invalid (QFT) and borderline or invalid (TSPOT®.*TB*) results is recommended. The intradermal TST utilizes purified protein derivative (PPD) tuberculin antigen solution and is sold in the US under the trade names Tubersol® (Sanofi Pasteur Ltd., Toronto, Canada) and Aplisol® (JHP Pharmaceuticals, LLC, Rochester, MI).

Intradermal TST placement and reading require annual training and competency. All tests should be placed consistent with CDC methodology and standards. Standardized training using validated resources is available (eg, CDC TST training video[29]). Institutions using TSTs to screen newly hired HCP should use the two-step methodology, with retesting ideally 1 to 3 weeks after the first TST.[2] Two-step TST is a recognized way of boosting an immune response that may have waned after a prior infection. HCP with a poorly documented prior positive TST may also benefit from two-step TST to confirm prior infection. A consistent approach for accepting documentation of prior TST results for either ''step'' should be adopted (recognizing that the evidence basis for cut-offs is limited). For instance, a policy might stipulate that a documented TST within a year prior to onboarding is acceptable.[2] The two-step TST process is recommended for clearance when more than 1 year has elapsed since the most recent TST.[2]

Test results should be interpreted in the context of the individual's TB risk assessment and current guidelines.[1,14] Usually, a single negative IGRA or a negative two-step TST is sufficient for TB clearance of HCP without TB risk factors. A positive TST is defined by the combination of induration and risk factors. For instance, a TST is considered positive at more than or equal to 5 mm for any person with either immunocompromising conditions (such as HIV infection) or with known, recent, unprotected TB exposure. The TST is considered positive with induration more than or equal to 10 mm for HCP without immunocompromising conditions and without a known, recent, unprotected TB exposure.[30] Finally, more than or equal to 15 mm induration is the positive ''cut-off'' for individuals (non-HCP) without immunosuppression or identified TB exposure. Note that CDC's positive cut-off induration for HCP, despite low rates of TB in HCP and data showing that most HCP do not have elevated risk compared with the general population, currently remains at more than or equal to 10 mm.[2]

Newly positive IGRA or TST results in HCP who have been negative in the past and are without risk factors for exposure to TB (ie, those with a low probability of true infection) should have a confirmatory/repeat TB test prior to radiography. If the repeat test is negative the result can, in the absence of clinical symptoms of TB, be regarded as negative and accepted for employment placement without radiographs.[14,16] When the repeat test is difficult to obtain, or when a significant delay may occur, a negative chest radiograph can be used for hiring clearance with the repeat test placed or drawn at the same time.

Regarding Reversions

The recommendation to repeat positive tests for confirmation in HCP without known exposure to active TB has been a CDC recommendation since 2010 and has been supported by extensive literature on serial testing of US HCP.[14,16,31–35] This recommendation has both operational and mathematical premises.

First, TST and both IGRAs are indirect measures of infection based on a skin induration or whole blood interferon gamma response to TB-specific antigens: they are not direct visualizations of the mycobacteria. Second, both IGRAs have cut-off values that were assigned by the FDA to maximize specificity, so that the likelihood of a false-negative result is minimized. On a scale of 0 to 10 international units per milliliter (IU/mL), the QFT is considered negative at less than 0.35 IU/mL, corresponding to 99% specificity.[25,36] Subsequent research, some of it summarized in a meta-analysis, has shown the QFT specificity to be closer to 95%, while that of the TST is roughly 97% in those with no prior exposure to BCG.[15] TST specificity is reduced to closer to 60% in those with a history of BCG vaccination.[15] For TSPOT, a negative result is returned when the number of spots counted (range 0 to 100s) is 0 to 4 in the US and 0 to 6 in Europe, equating to a 95% to 97% specificity.[14,26]

Mathematically, when highly specific tests for low-prevalence diseases are used in large populations that are at low-risk for the disease, false-positive rates rise due to mathematical principles of positive and negative predictive values. (PPV = True positives/(true positives + false positives) × 100. NPV = True negatives/(true negatives + false negatives) × 100). Therefore, positive results in this setting represent an indirect measurement of interferon-gamma release that may be just above the FDA-mandated cut-off point, but actually reflect only a minimally higher likelihood that the infection is present. Further, when tests in large populations are repeated, a repeated result will tend to more accurately represent the mean result of the entire population (known as regression to the mean), which in the case of US HCP and TB, is a negative result.[37] Therefore, repeating an unexpected test result in a population that has an overall low prevalence of the disease may yield a more accurate result than the original test provided.

TB Testing for HCP with Prior Positive TB Tests

Documentation should be obtained whenever possible for previous TB test results, imaging and TB treatment including compliance. For those with LTBI that was untreated or partially treated, further testing may be indicated. HCP with a previously positive TB test who have not completed treatment, or who report relevant symptoms regardless of treatment history, should undergo a focused physical examination to identify signs of TB disease including examination of the lungs and both cervical and supraclavicular lymph nodes.

Obtaining a new TB test in individuals with previously positive test results could be considered when additional test results are likely to alter management. Key examples include:

1. HCP with prior positive TSTs who have previously declined LTBI treatment may accept chemoprophylaxis to reduce the risk of progression to active TB disease when presented with confirmatory IGRA result.[38–42]
2. HCP who have received BCG vaccination and have a prior positive TST may benefit from the increased specificity of the IGRA.

3. HCP with an undocumented prior positive TST may benefit from a two-step TST to confirm prior infection. TST is considered safe in HCP with a history of positive TST results, except when a prior TST was associated with necrosis, blistering, ulceration, or anaphylaxis.[43]
4. HCP with low positive or unquantified results by an older generation IGRA and no history of TB treatment may benefit from retesting with a newer generation IGRA to clarify treatment recommendations.
5. HCP with IGRA results that are discordant or suggest reversion may benefit from a TST. TSTs should be avoided in HCP with a history of necrotic, blistering, ulcerated, or anaphylactic reactions to TST.[43]

Asymptomatic HCP with documented prior positive TB tests (IGRA and/or TST) do not require imaging for clearance if they have documentation of normal chest imaging after the prior positive TB test. A normal CXR is one with no radiographic evidence of TB disease or granuloma. Repeat imaging in the context of a normal baseline CXR is not recommended by the CDC but may be required by local workers' compensation or facility guidelines. If repeat imaging in this context is conducted, the facility should be consistent in the documentation and time frame requirements for prior CXR.

Re-imaging during the POPP TB evaluation can also be considered in HCP with a prior positive TB test and a prior normal CXR based upon review of their TB risk assessments:

1. When there has been known exposure to active TB since the prior image was obtained or extended time spent in regions with elevated TB rates,
2. When prior imaging is not well documented or is not normal,
3. When previous LTBI treatment was incomplete,
4. When the HCP was not treated for LTBI and has risk factors for progression to active TB disease (reactivation TB).

Newly Confirmed Positive TB Test and/or Positive Symptom Review

For low-risk HCP (defined as those "who are asymptomatic, unlikely to be infected with *M. tuberculosis*, and at low risk for progression on the basis of their risk assessment,")[1] a confirmed positive TB test is a test that is positive and when repeated is positive again. HCP with a history of necrotic, blistering, ulcerated, or anaphylactic reactions to TST, if retested, should be tested with an IGRA.[43] All HCP with confirmed positive TB tests should be counseled by a qualified provider regarding further evaluation and management. A major tenet of the 2019 MMWR CDC/NTCA Recommendations is that the onboarding process provides a crucial opportunity to offer counseling and to strongly encourage treatment for LTBI (see section on "Education and Treatment of Health Care Personnel with Positive Test Results" for further information).

The medical history, previous TB test results, identified TB exposures, and any prior TB or LTBI treatment should be evaluated to ascertain whether a positive test represents a new conversion or reflects a remote exposure. A history of time spent in any TB endemic country may also be relevant to establishing an infection timeline. A thorough work and volunteer history can also establish possible exposures. This timeline is important because active TB disease is most common in the first 2 years following exposure with conversion.[44]

The medical history should also elicit factors that would predispose the patient to progress to active TB disease such as HIV/AIDS, immune suppression (eg, cancer, solid organ transplant, biologic medications), recent significant weight loss, diabetes, smoking, or fibrotic lung disease. CDC recommends screening adults with LTBI for HIV in health care settings,[45] and the US Preventive Services Task Force recommends screening adults for diabetes.[46] Given the high risk of progression to active TB disease in patients with untreated comorbidities, this TB evaluation presents a logical opportunity to recommend diabetes and HIV screening if not previously done. Symptoms of pulmonary or extra-pulmonary TB should also be ascertained.

The physical examination should identify signs of active TB disease and include auscultation of the lungs, and palpation of both cervical and supraclavicular lymph nodes. Weighing the patient is useful to document weight stability, loss or gain.

All HCP with newly confirmed positive TB tests should be evaluated with a CXR. CXRs are reasonably sensitive for active pulmonary TB, and the vast majority of asymptomatic HCP with newly positive TB tests can be cleared safely for work placement based on a normal CXR alone. A single posterior-anterior (PA) view is usually adequate for employment clearance in asymptomatic individuals without TB risk factors.

Considering Active TB Disease

Active pulmonary tuberculosis is a serious, contagious disease: between 5% and 10% of people will die before or during their treatment for TB disease.[47] Active TB disease poses a disproportionately high risk of mortality to the elderly, young and immune compromised. Most states require prompt public health reporting of persons with suspected active TB disease, and confirmed active TB is reportable to the local health department in all states. Public health departments are responsible for contact screening in the community, for monitoring treatment of individuals with confirmed active TB disease, and for providing clearance for the treated employee to return to work. State and local public health departments can also offer valuable insights and resources for TB screening, diagnosis, and treatment in circumstances when guidance from this companion document cannot be directly applied due to unique characteristics of the HCP, local regulations, or limited available occupational health resources.

If imaging or clinical presentation suggests active pulmonary TB disease, further evaluation is necessary for work clearance. For HCP with possible infectious TB, occupational health clinicians should arrange for appropriate isolation precautions when necessary. Of note, neither the TST, IGRA, clinical examination, nor imaging alone can exclude active TB disease. False-negative IGRAs and TSTs occur in 10% to 30% of people with active TB disease and are more frequent among those with extra-pulmonary TB and those with immune suppression. Clinicians should not rely on these indirect tests for *M. tuberculosis* infection when active TB is suspected.[48]

Chest radiography is a mainstay of the initial evaluation for possible active pulmonary TB disease. While a single PA view is usually sufficient, adding a lateral view may improve sensitivity, particularly in immune compromised HCP who are more likely to have atypical radiographic presentations of active TB.[49,50] Additional imaging, including computed tomography (CT) scanning may be indicated based on clinical assessment or discussion with the radiologist. HCP with incidental findings of clinical significance on CXR should be counseled, given copies of their imaging, and confidentially referred for appropriate care.

Note that CXRs are likely to be normal in HCP with extra-pulmonary TB disease, so the absence of lung disease on CXR does not prove absence of either active TB disease or of infectiousness. Oropharyngeal and laryngeal TB are highly contagious, but not visible on CXR. Personnel with suspected oropharyngeal, laryngeal, or pulmonary TB should wear a mask and be restricted from work until their disease is determined by experts not to be infectious. Extra-pulmonary TB disease in the mediastinum, bones, lymph nodes, and abdomen is also not visible on CXR, but is not contagious. HCP with these

non-contagious conditions can remain at work during evaluation and treatment.

Clearance to work for HCP with possible infectious TB disease requires direct testing for *M. tuberculosis* and expert consultation. Testing may include serial sputum smear collection with acid-fast bacillus (AFB) staining, polymerase chain reaction (PCR), nucleic acid amplification testing (NAAT), or sputum culture. Such testing is sometimes completed in consultation with the facility's infection control, infectious diseases, or local public health services.

Return-to-work clearance is appropriate if initial smears or NAAT are negative on at least three high-quality sputum specimens, collected 8 to 24 hours apart with at least one collection obtained early in the morning, even though final culture results will not be available for several weeks.[2,51,52] Clinical judgment should always supersede test results.

Compliance, Confidentiality, and Communication

Information management requirements for occupational health practices that provide POPP TB screening and testing for HCP are complex. Minimum needs include:

- Ensuring that all newly onboarded HCP have met institutional policy requirements for work clearance specifically related to excluding active TB disease and documenting LTBI,
- Ensuring that HCP with positive test results are aware of their TB/LTBI status,
- Maintaining strict confidentiality of all medical and personal information,
- Ensuring that HCP have been educated on signs and symptoms of TB disease and are aware of when they should seek further medical evaluation, and
- Communicating clearance status to hiring managers without compromising protected health information. Occupational health staff should restrict their responses to the clearance status only, without revealing further testing needs.

An overarching goal of the 2019 MMWR CDC/NTCA Recommendations is to accurately identify and encourage the treatment of LTBI in order to prevent the devastating consequences that occur when HCP progress to active, infectious TB disease while working with vulnerable patients and colleagues. To that end, onboarding HCP who are confirmed to have LTBI should be strongly encouraged to undergo treatment. Occupational health staff can document treatment declination in the medical record and should revisit the treatment discussion and education on an annual basis. Appendix 4, http://links.lww.com/JOM/A783 contains a sample declination form.

POST-EXPOSURE TB SCREENING AND TESTING

2019 MMWR CDC/NTCA Recommendation: "After known exposure to a person with potentially infectious TB disease without adequate personal protection, health care personnel should have a timely symptom evaluation and additional testing, if indicated. Those without documented evidence of prior LTBI or TB disease should have an IGRA or TST performed. Health care personnel with documented prior LTBI or TB disease do not need another test for infection after exposure. These persons should have further evaluation if a concern for TB disease exists. Those with an initial negative test should be retested 8 to 10 weeks after the last exposure, preferably by using the same test type as was used for the prior negative test."[1]

Overview

While the US has one of the lowest incidence rates of TB in the world at 2.8 cases per 100,000 persons (2018), HCP cases in the US continue to experience exposures to persons with active pulmonary TB.[53] A contact investigation should be conducted for HCP exposed to persons with confirmed infectious TB disease or aerosolized *M tuberculosis* specimens. The timing and extent of contact investigation activities such as risk and exposure assessment, symptom screening, and testing should be dictated by the specific characteristics of the exposure. For most health care settings in the US, investigations may simply document the lack of significant exposure due to the appropriate engineering and administrative controls or use of personal protective equipment (PPE). The Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis by CDC and NTCA in 2005 contain information regarding environmental controls, data management, confidentiality, consent, and human resource considerations that are useful when structuring and operationalizing investigations.[54]

TB experts are also available for consultation through jurisdictional public health agencies and consultation and collaboration is encouraged. In most US jurisdictions, reporting and consultation with the public health department is required upon confirmation of a case of active TB disease in a health care setting.

Many of the principles used to determine whether a significant exposure occurred are similar to those with other infectious diseases, including influenza and the pandemic novel coronavirus. These considerations include the infectiousness of the patient, the location and duration of the HCP relative to the infected person, the activity being performed (eg, aerosol-generating), and the environmental controls that are in practice (eg, PPE and ventilation).

The 2019 MMWR CDC/NTCA Recommendations update the 2005 MMWR CDC Guidelines[2] in a few important ways:

1. The definition of TB exposure is refined by adding the language "without use of adequate personal protection" to qualify those who should be included in contact investigations. TB transmission generally requires prolonged exposure in a closed air space, but there is no static definition of what constitutes a TB exposure event. Table 2 lists factors that should be considered when gauging the clinical significance of an exposure. Also included in the table are factors that can mitigate *M. tuberculosis* transmission.
2. Contact investigations may be done with either IGRA or TST, though the collaborative 2017 CDC/ATS/IDSA Diagnostic Guidelines recommended IGRA over TST for exposure investigations.[13]
3. HCP with documented prior LTBI do not need another test for infection after exposure. This recommendation and exceptions to consider are explored further below.
4. The designation of a facility as medium risk, based on the 2005 MMWR CDC Guidelines Facility Risk Assessment Appendix B,[2] no longer establishes a requirement for annual HCP TB testing. However, medium risk facilities will continue to be guided by all of the environmental, administrative, and monitoring requirements that are outlined. Appendices 1, http://links.lww.com/JOM/A780 and 5, http://links.lww.com/JOM/A784 are the adapted versions of the 2005 MMWR CDC Guidelines' Appendices B and C,[2] with minor, bolded changes that reflect the 2019 MMWR CDC/NTCA Recommendations' guidance.

Travel-Related Exposure

Work, educational, and volunteer-related travel to TB endemic areas of the world merit special mention. The 2019 MMWR CDC/NTCA Recommendations identify any region other than Australia, Canada, New Zealand, and those countries in western or northern Europe as likely to have high rates of TB disease.[1] Clinical

TABLE 2. Factors that Affect Risk of TB Transmission to Health Care Personnel (HCP)

Factors that Decrease Risk for TB Transmission to HCP		
Patient Factors	**Environmental Factors**	**Time and Intensity of Exposure**
Early identification of possible TB disease of respiratory tract Early/prompt transfer of patient into respiratory isolation Early initiation of effective anti-TB regimen Effective antibiotic treatment of 3 days or more Patient is not coughing Surgical mask is worn by patient	Isolation room under negative air pressure Removal of infectious droplet nuclei by adequate air exchanges with exhaust to outside air Use of adequate ultraviolet germicidal irradiation (UVGI) Employee using appropriate personal protective equipment (PPE) (N95, powered air-purifying respirator [PAPR], or equivalent)	Risk of transmission is directly proportional to time and intensity of exposure Short exposure duration Infrequent exposure Absence of close physical contact
Factors that Increase Risk for TB Transmission to HCP		
Patient Factors	**Environmental Factors**	**Time and Intensity of Exposure**
Incorrect, lack of, or short duration of TB treatment High concentrations of acid-fast bacillus (AFB) on sputum smear Presence of cough Cavitation on CXR Oropharyngeal or laryngeal TB Failure to cover the mouth and nose while coughing (or not wearing a mask) Undergoing cough-inducing or aerosol-generating procedures (eg, bronchoscopy, sputum induction, autopsy) Culture or NAAT + regardless of AFB smear positivity	Sharing small, enclosed spaces Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplets Recirculation of air containing infectious droplet nuclei Inadequate cleaning and disinfection of medical equipment Improper procedures for handling specimens	Prolonged cumulative duration of exposure Frequent exposure Prolonged close physical proximity Intense exposure (eg, conducting aerosol-generating procedures)

Partially adapted from Centers for Disease Control and Prevention.[2]

rotations and overseas duties lasting a month or more in regions with high TB incidence (generally accepted to be more than 20 cases/100,000 people) may pose a risk for TB exposure to HCP. The 1-month timeframe derives from the 2018 California Department of Health Risk Assessment,[55] though studies regarding TB conversions in US HCP who travel for work are sparse. HCP who plan to engage in clinical or research activities with risk of exposure to active TB disease should undergo pre- and post-travel symptom screening and testing (more than 8 weeks after returning).[1] Serial TB screening and testing may be warranted for HCP who rotate on a regular basis to these regions.

Voluntary Testing for Self-assessed Potential Exposure

Employees may become exposed to TB disease if incarcerated, experiencing homelessness, have a family member/roommate from a high-risk country with a cough, or via other non-work-related situations, though the annual TB test conversion rate of less than 1% in US HCP supports that such conversions are uncommon.[56] Nonetheless, facilities or sections may decide that HCP can self-report a TB exposure concern and request a TB test with or without further inquiry by an occupational health provider into the potentially personal and private nature of that exposure. Alternatively, occupational health can encourage such HCP to seek testing from their primary care provider when such a concern arises. If the option for voluntary testing in the workplace is offered, notification of that option should be included in the annual education program.

Post-Exposure Testing Considerations and Interpretation

HCP who experienced unprotected exposure to active pulmonary or oropharyngeal TB should be enrolled in a contact investigation, ideally within 4 weeks of the first exposure event. This includes screening for (1) symptoms and signs of TB; (2) history of prior *M. tuberculosis* infection and treatment; and (3) risk of progressing to TB disease if infected with *M. tuberculosis.* This initial set of evaluations is to establish a baseline in the event of a change in symptoms or test conversion later. Persons with symptoms or signs suggestive of TB disease should be evaluated for active TB promptly. While this evaluation is ongoing, they should be restricted from work, instructed to avoid activities that could expose others, and reported to the public health department.

IGRAs are preferred for post-exposure testing of previously negative personnel because of the timeliness of the results, the obviation of the need for two-step testing, and for their higher sensitivity than the TST in contact investigations.[13,57–59] The two-step TST procedure typically used during the pre-placement process (to promote boosting for remote TB exposures) should not be used in contact investigations.[2]

If the HCP has a record of a previously positive TB test, the 2019 MMWR CDC/NTCA Recommendations state that the HCP does not require post-exposure testing. However, standard occupational health practice is to conduct testing in some of these personnel. A new TB test could prove useful in clarifying the pre-exposure status and protecting the worker in the event that the test is now negative. Untreated HCP with a previously positive TB test may be considered for new baseline/initial

TABLE 3. Management of HCP Exposed to Potentially Infectious Tuberculosis

Time Frame	Clinical Management	HCP TB Status Prior to Known TB Exposure			
		Negative IGRA or TST <3 Months Ago	Negative IGRA or TST ≥3 Months Ago or Unknown or Unavailable Results	Positive IGRA or TST, Untreated	Positive IGRA or TST, Treated
As soon as TB exposure is identified, up to 4 weeks after first exposure*	Step 1 TB symptom screen	Yes	Yes	Yes	Yes
	Step 2 Obtain initial post-exposure test (IGRA or TST)†	Optional‡	Yes	Conditional§	No
	Step 3 If initial post-exposure test is positive, or if TB symptoms are reported, obtain CXR and focused clinical examination‖	Yes	Yes	Yes	Yes
	Step 4 Recommend LTBI treatment if initial post-exposure test is positive without evidence of active TB disease‖	Yes	Yes	Yes	Rare**
At least 8 weeks after last exposure*,¶	Step 5 TB symptom screen	Yes	Yes	Yes	Yes
	Step 6 Obtain follow-up post-exposure test# if initial post-exposure test was negative or not obtained	Yes	Yes	Yes§	No
	Step 7 Obtain CXR and perform focused clinical examination if symptom screen or post-exposure test is positive‖	Yes	Yes	Yes	Yes
	Step 8 Recommend LTBI treatment if this post-exposure test is positive without evidence of active TB disease‖	Yes	Yes	Yes	Rare**

*Tests for TB infection obtained between 4 and 8 weeks after TB exposure serve neither as a valid baseline nor as a follow-up test, and are not recommended except, potentially, in the case of severe immunocompromised status or extenuating circumstance. If exposure identification was made after 4 weeks, commence with Steps 5 to 8 after 8 weeks using the last known test as the baseline.

†Some references may call this first post-exposure test a new ''baseline'' result. An interferon-gamma release assay (IGRA) is preferred over tuberculin skin testing (TST) for use in contact investigations. If TST must be used, note that if the previous TST result is >12 months old, two-step TST testing would be ideal, if feasible, for the 1st post-exposure test. IGRA is strongly preferred because this is difficult to accomplish in a timely manner and delays in the two-step testing process can cause confusing results.

‡The first post-exposure test may have limited value in HCP who had a negative IGRA or TST in the past 3 months, though it may be required by the facility or workers' compensation; check local policy. An IGRA could be useful for use in individuals who have only had TSTs.

§Obtain an IGRA for those with a previously positive test if (1) TST is the only test that was previously positive (particularly in BCG-vaccinated individuals) or (2) an earlier IGRA was positive on only one instance and not confirmed by a repeat test. If the LTBI diagnosis was confirmed, repeat testing is not necessary.

‖If there is any suspicion of active TB disease, expert consultation should be obtained.

¶HCP who are identified as TB contacts >8 weeks following last exposure to active TB disease should still be clinically managed as soon as possible as in Steps 5 to 8.

#Using the same test method as the first post-exposure test (if obtained) is preferred.

**Those with prior TB treatment may benefit from re-treatment, depending on exposure history, post-exposure test results, and risk factors, such as HIV infection, solid-organ transplant or ongoing treatment with a TNF-alpha inhibitor. Consultation with a specialist or the public health department is recommended.

post-exposure TB test in a few situations, including but not limited to when:

1. The HCP had a positive TST without a confirmatory IGRA, particularly if BCG-vaccinated;
2. An older generation IGRA with poorer quality control or reliability was used;
3. The TST or a single IGRA was positive in an HCP without TB risk factors; and
4. There is poor or absent documentation of the previous positive TB result.

In contrast, if it is determined during the course of taking the history that the HCP has had treatment for LTBI or active TB disease, testing may not be indicated (Table 3).

Management of contact investigations and interpretation of results for HCP can be nuanced. Table 3 offers a suggested workflow for such investigations. The interpretation of the initial test result (less than 4 weeks from first significant exposure) should be as follows:

- A negative test result should be retested more than 8 weeks following cessation of suspected exposure. A negative test result obtained less than 8 weeks after exposure is considered unreliable for excluding infection due to the time needed for the body to mount a reliable immune response.
- A positive test result indicates that a prior infection is likely. Evaluation and treatment are recommended. A follow-up TB test in more than 8 weeks is not indicated.

If the initial post-exposure TB test is negative or is not obtained within 4 weeks of the first exposure, contacts should undergo TB testing no sooner than 8 to

10 weeks after the last exposure, or as soon as possible if this time window is missed. Re-testing with the same method as the initial test is recommended to minimize variability in results. Re-testing after at least 8 weeks from the last exposure allows the immune system time to mount a reliable response to *M. tuberculosis* if sufficient exposure occurred. If either symptom screening or the TB test is positive, additional steps (such as physical examination and chest radiographs) are required to diagnose LTBI or active TB disease.

The interpretation of the follow-up test result (more than 8 weeks after last exposure) should be as follows:

- A negative TST or IGRA test result more than 8 weeks after the end of exposure indicates that *M. tuberculosis* infection is unlikely. A negative test result obtained less than 8 weeks after exposure is considered unreliable for excluding infection.
- A positive TST or IGRA result more than 8 weeks after the final exposure suggests that *M. tuberculosis* infection has occurred since prior testing (conversion). HCP with newly diagnosed *M. tuberculosis* infection should have a symptom review, CXR, and evaluation for progression to active TB. For those diagnosed with LTBI, treatment should be encouraged. If the recommendation for treatment is not accepted initially, annual symptom reviews should commence, and annual education should reinforce treatment options. The public health department should be notified of any suspected transmissions.

SERIAL SCREENING, TESTING, AND EDUCATION FOR HCP

2019 MMWR CDC/NTCA Recommendation: ''In the absence of known exposure or evidence of ongoing TB transmission, US health care personnel (as identified in the 2005 guidelines) without LTBI should not undergo routine serial TB screening or testing at any interval after baseline (ie, annually). Health care facilities might consider using serial TB screening of certain groups who might be at increased occupational risk of TB exposure (eg, pulmonologists or respiratory therapists) or in certain settings if transmission has occurred in the past (eg, emergency departments). Such determinations should be individualized on the basis of factors that might include the number of patients with infectious pulmonary TB who are examined in these areas, whether delays in initiating airborne isolation occurred, or whether prior annual testing has revealed ongoing transmission. Consultation with the local or state health department is encouraged to assist in making these decisions.

Health care personnel might have risks for TB exposure that are not related to work in the United States, or they might have risks for TB progression after baseline testing that necessitate special consideration. If these risks are unrecognized, these health care personnel might experience TB disease and transmit TB to patients, coworkers, or other contacts. Therefore, health care facilities should educate all health care personnel annually about TB, including risk factors, signs and symptoms; facilities also should encourage health care personnel to discuss any potential occupational or nonoccupational TB exposure with their primary care provider and occupational health clinician. The decision to perform TB testing after baseline should be based on the person's risk for TB exposure at work or elsewhere since that person's last test.''[1]

The 2019 MMWR CDC/NTCA Recommendations state that the risk assessment for health care settings (found in Appendices B and C in the Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005[2]) no longer forms the basis for determining a TB testing regimen for HCP, and that HCP without LTBI should not undergo routine serial TB screening or testing at any interval after baseline (ie, annually) in the absence of known exposure or evidence of ongoing TB transmission. This is part of the updated approach to TB elimination in US health care settings. Driving the new recommendation are current TB rates among HCP matching those of the general population,[11] the inherent limitations in predictive value of screening tests administered among low risk populations,[60] and the public health imperative to be proactive and treat LTBI. For more information regarding the supporting data, refer to ''Background with Literature Review'' section of this document.

Serial Screening and Testing

The 2019 MMWR CDC/NTCA Recommendations instruct not to conduct routine serial TB screening or testing at any interval after hire in the absence of known exposure, but state that health care facilities ''might consider'' serial TB screening for certain groups at increased occupational risk (citing pulmonologists or respiratory therapists as possible examples)[61] or for personnel working in settings with past documented transmission. Additionally, other HCP may have institutional or regulatory requirements for serial testing, such as laboratory personnel performing microbiological specimen testing for TB.[62,63] The new guidance further instructs that any decision to extend such serial testing should be individualized based upon criteria including:

1. The number of patients with infectious pulmonary TB examined;
2. Whether delays occurred in initiating airborne isolation;
3. Whether environmental controls and processes, such as patient masking and air handlers are in place and are functional; or
4. If prior serial testing has revealed ongoing transmission.

When there is any concern or uncertainty, consultation with public health is recommended. Current state and local regulations may be in conflict with this new federal guidance and may require routine TB testing for certain groups until such regulations change.

A specific threshold number of active TB cases that would trigger serial surveillance testing is not identified as it was in the 2005 MMWR CDC Guidelines (Appendix 5, http://links.lww.com/JOM/A784).[2] Instead, the recommendations advise that clinical staff involved in the direct care of patients with active pulmonary TB on a regular and ongoing basis may constitute personnel at increased risk. Examples of such increased risk would include HCP in a TB clinic who encounter patients with TB before initiation of airborne isolation, or individuals involved directly and frequently in cough-inducing or aerosol generating procedures on patients with active pulmonary TB. Staff involved in autopsy examinations in an area with high rates of TB, and laboratorians manipulating specimens or cultures with a large TB burden, may warrant further consideration for inclusion in serial screening or testing programs.[63–66] While there does not appear to be current published evidence in the US of higher LTBI incidence among those employees, such clinical settings have been associated with occupational transmissions in the past. Any extension of serial/annual testing to individual HCP should take into account the specific workplace clinical setting, its environmental and safety controls, and its volume of active TB cases seen where such precautions have or may fail. In situations where serial testing is considered, positive IGRA results should be confirmed (repeated) given the higher rates of conversions and reversions compared with the TST.[20,67] It is worth re-stating that there is a paucity of recent literature reporting occupational transmission of TB to any specific group of US hospital-based personnel.

The second criterion, delays in initiating airborne isolation, is largely addressed within the recommendations for post-exposure TB surveillance (see

preceding section, ''Post-Exposure Screening and Testing''). An instance in which such a delay occurs for a patient with active TB disease should generally be regarded as an exposure, triggering baseline, and follow-up TST or IGRA testing as per current guidance. Instances of delayed isolation should be identified and handled as specific exposure events. Settings in which such delays may be more likely and frequent would include patient care environments in regions of the world with high rates of active TB, to which US HCP may periodically rotate. Increased risk of TB among HCP continues to be a substantial hazard in such settings.[68,69] We recommend that a clinical rotation to TB-endemic regions of the world be considered an increased risk for TB exposure and thus warrant post-travel testing, and that serial screening be considered for the HCP who rotates on a regular basis to higher risk international settings. Those who rotate only rarely or intermittently to such settings should be considered for post-exposure TB surveillance upon return to the US, regarding the time in the higher risk setting as an interval of potential exposure.

The third criterion addresses settings in which the risk of TB exposure may be inadequately characterized but where past experience in monitoring LTBI conversion among HCP has suggested enhanced risk (as evidenced by annual testing that revealed ongoing transmission). Such settings offer the opportunity to better understand and mitigate risk factors for TB transmission (ie, enhanced environmental controls), and may benefit from continued serial surveillance in order to assess the impact of risk factor mitigation efforts. Encouragement in the new guidance to consult with local or state health departments prior to continuing any serial screening is sound, since ongoing screening is likely to be based on local factors rather than the general trends recognized in recent years for US HCP.

Annual Education Requirement

With implementation of the new guidance, rigorous annual TB education for HCP will take on greater importance. This is due both to the elimination of widespread serial surveillance testing and the intent of the guidance to encourage more treatment of LTBI in HCP. Educational programs should address the range of TB-related issues with which all staff should be familiar: exposure risks (both within and outside of the workplace), what to expect if a workplace TB exposure is identified, signs and symptoms of active disease, and which workplace-based and non-workplace-based medical resources to access if symptoms develop. Staff should be reminded of the option for voluntary TB testing if it is offered. Additional attention should be given to specific knowledge required by HCP who have untreated LTBI and to those who may be at increased TB risk due to work-related or non-work-related factors (such as immune suppression[70]; see Appendix 6, http://links.lww.com/JOM/A785).

Importantly, the 2019 MMWR CDC/NTCA Recommendations do not include the recommendation to conduct an annual individual risk assessment for HCP (eg, asking employees where they traveled outside of work). The recommendation to conduct the annual facility risk assessment (2005 MMWR CDC Guidelines Appendix B,[2]) does remain in place. Individuals with increased risk for occupational exposure (eg, engaging in aerosolizing procedures in facilities that routinely diagnose TB) should be identified by the facility risk assessment, and may be considered for serial testing. Serial testing for targeted staff can also be appropriate when environmental controls have been shown or are strongly suspected to have failed, as demonstrated by evidence of transmission without knowledge of a specific exposure.

Messages specifically directed at those with untreated LTBI to be aware of symptoms suggestive of active disease and to promptly report any such symptoms to occupational health should be folded into generally targeted educational modules. Annual education can help establish the knowledge base necessary to enhance personal awareness of potential signs and symptoms of TB. While such education could be accomplished with a widely directed teaching module, face-to-face encounters with occupational health providers do add value by providing the opportunity to teach, ask questions, and allay employee concerns. Most importantly, educating untreated staff regarding short-course treatments that are equally effective, have much higher compliance rates and are generally well tolerated can result in both individual and public health benefits (Fig. 1).

Annual Symptom Review for HCP with LTBI

The 2019 MMWR CDC/NTCA Recommendations do continue to support an annual symptom evaluation for those with untreated LTBI[1] (Appendix 7, http://links.lww.com/JOM/A786). This symptom survey should include education to help the HCP with treated or untreated LTBI understand which symptoms to monitor, whom to contact if symptoms of concern develop, and what LTBI treatment options to consider. While there is a paucity of literature showing efficacy of annual symptom surveys to detect active TB disease, the required annual symptom screening can be a useful point of contact to review the HCP's knowledge and understanding of TB and to encourage treatment of LTBI for those who have not previously accepted recommendations.

Importantly, the symptom assessments among those with LTBI should be carried out with an awareness of the possibly stigmatizing effect of singling out a specific group of HCP for serial surveillance due to LTBI positivity. Medical center occupational health clinics have often relied upon communication with managers to enforce adherence to serial TB surveillance programs, but this strategy could have the unintended consequence of suggesting the presence of TB infection to an individual's manager. To avoid this, adherence with annual symptom monitoring should be enforced to the extent possible through direct communication from occupational health to the HCP with LTBI rather than through the HCP's manager or supervisor. Options include regular mail, direct e-mail with a linked symptom survey, telephonic assessment, or in-person interview. If communication with a manager to enhance adherence is deemed necessary, it should state only that the employee has an occupational health requirement to be addressed.

Transitioning a TB Screening Program for Health Care Personnel

The vast majority of health care facilities will be able to eliminate serial TB testing thereby saving time and money that may be redirected to activities such as educating, identifying, tracking, and treating LTBI. Some programs will have transient impediments to getting to this future state that may include mandatory testing by localities and states, updating of hospital policies, contracts that specify TB testing, and general resistance to change. The transition will require consistent, reassuring communication that emphasizes that the safety of HCPs and patients should be improved by the pre-placement identification and treatment of LTBI, and identification and monitoring of those exposed to active TB cases. It is worth reiterating that the decades of serial TB screening program results, in conjunction with improvements in environmental controls, show the US has had a substantial reduction in TB burden.

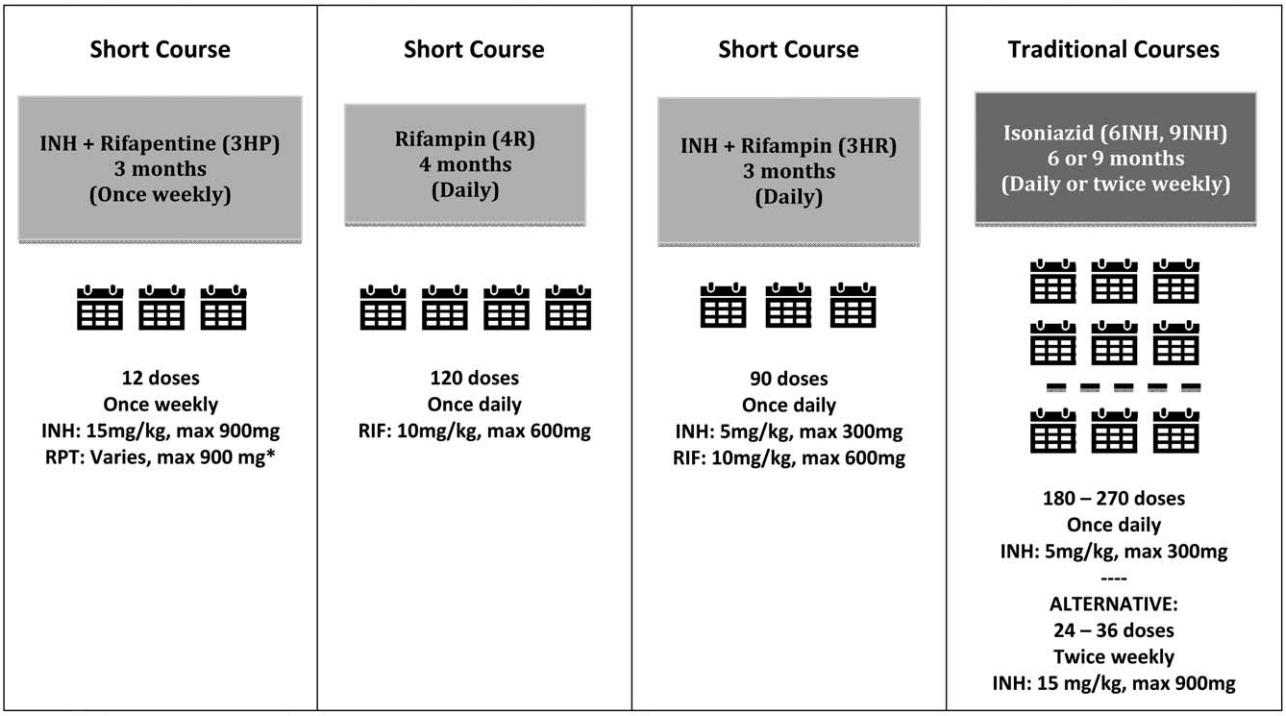


FIGURE 1. LTBI treatment options quick-reference guide, 2020. *Rifapentine: 25.1 to 32.0 kg, 600 mg; 32.1 to 49.9 kg, 750 mg; more than or equal to 50.0 kg, 900 mg maximum. See Table 4 for list of abbreviation meanings.

TREATMENT AND EDUCATION OF HEALTH CARE PERSONNEL WITH POSITIVE TEST RESULTS

2019 MMWR CDC/NTCA Recommendation: ''Health care personnel with a newly positive test result (with confirmation for those persons at low risk as described previously) should undergo a symptom evaluation and chest radiograph to assess for TB disease. Additional workup might be indicated on the basis of those results. Health care personnel with a prior positive TB test and documented normal chest radiograph do not require a repeat radiograph unless they are symptomatic or starting LTBI treatment. The local public health department should be notified immediately if TB disease is suspected.
Health care personnel with LTBI and no prior treatment should be offered, and strongly encouraged to complete treatment with a recommended regimen, including short-course treatments, unless a contraindication exists. Health care personnel who do not complete LTBI treatment should be monitored with annual symptom evaluation to detect early evidence of TB disease and to reevaluate the risks and benefits of LTBI treatment. These health care personnel also should be educated about the signs and symptoms of TB disease that should prompt an immediate evaluation between screening visits.''[1]

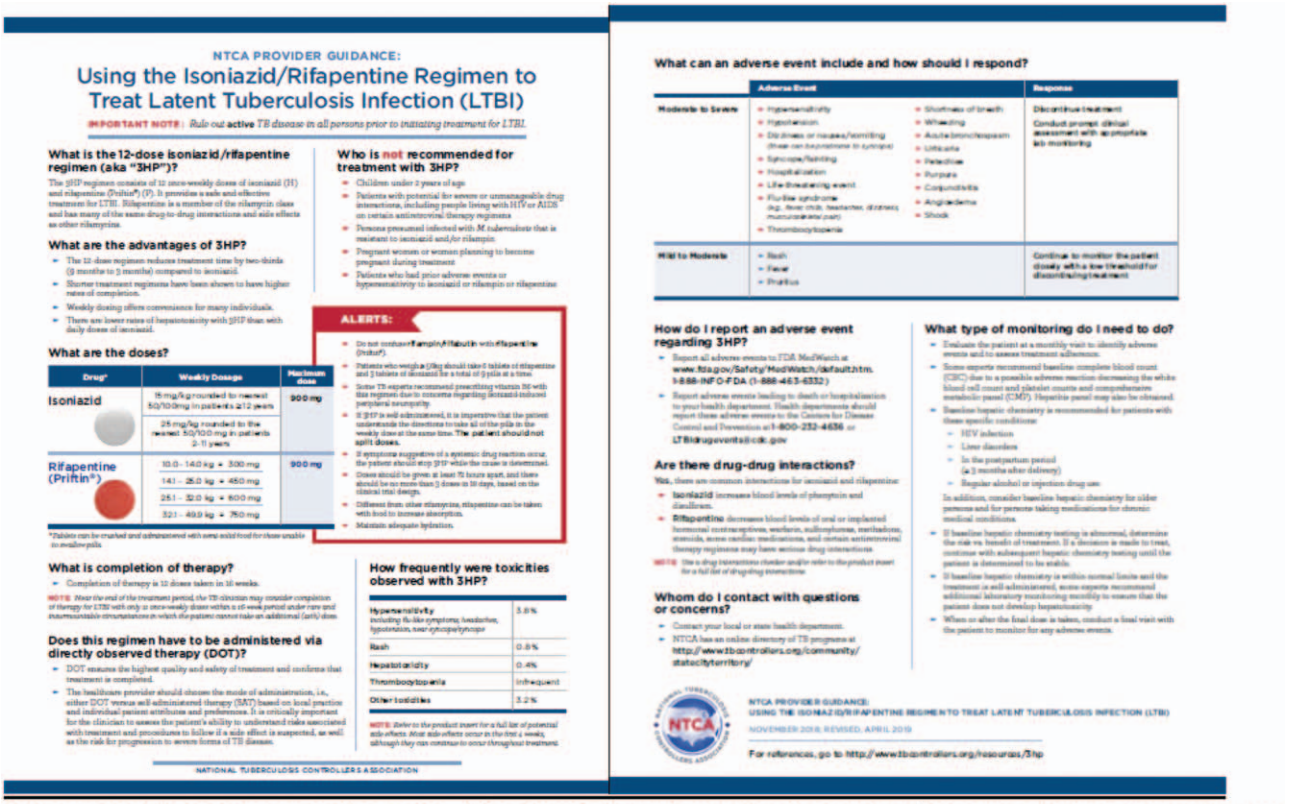
Progression from LTBI to TB Disease (Reactivation TB)

The vast majority of TB disease in the US is caused by the progression from latent infection to active disease (reactivation). Eighty-percent of the nearly 40,000 active TB cases reported in the US between 2006 and 2008 were reactivation TB, largely in non-US born persons.[47] Over 60% of these persons progressed more than 4 years after they arrived in the United States.[71] The rate of progression from LTBI to active TB disease was slightly higher among non-US born than US born persons.[72] Finding and treating LTBI, whether related to a contact investigation from an exposure or as identified during the POPP evaluation, both act to reduce the possibility of future cases. Preventing progression from LTBI to active TB disease in HCP merits particular attention because active disease often goes unrecognized for weeks to months and exposes large numbers of colleagues, vulnerable patients, and their families. Contact investigations associated with HCP who progress to TB disease can cost millions of dollars, result in negative media attention and cause significant harm.[73]

Educating HCP about LTBI

When HCPs with LTBI are evaluated at occupational health for consideration of treatment, the importance of education cannot be overstated. The goal is to teach HCP about their diagnosis, the risk of developing active TB disease, treatment options, and the benefits and risks of treatment. Once active TB disease is ruled out, the following key concepts should be clearly conveyed:

- You have LTBI, not active TB disease.
- The BCG vaccine does not interfere with the accuracy of the TB blood tests.
- When you have LTBI, it is not contagious so you cannot pass this to other people.
- You can be at work.
- You are at risk of developing active TB disease in the future.
- The risk of developing active TB depends on your health status and how recently you were infected.
- During the first 2 years after infection, the risk starts at about 5%, but can be much higher in some people.
- After the first 2 years the risk starts at about 1% per decade of life but can be much higher.
- Conditions and medications that you may have now or in the future could substantially increase that risk, including HIV infection, diabetes, cancer, lung disease, tobacco use, and immune suppression from medications and aging.
- If you develop active TB disease you may expose patients, coworkers, and


NTCA PROVIDER GUIDANCE:

Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI)

IMPORTANT NOTE: Rule out active TB disease in all persons prior to initiating treatment for LTBI.

What is the 12-dose isoniazid/rifapentine regimen (aka "3HP")?

What are the advantages of 3HP?

What are the doses?

Drug*	Weekly Dosage	Maximum dose
Isoniazid	15 mg/kg rounded to nearest 50/100 mg in patients ≥12 years 25 mg/kg rounded to the nearest 50/100 mg in patients 2–11 years	900 mg
Rifapentine (Priftin®)	10.0 - 14.0 kg = 300 mg 14.1 - 25.0 kg = 450 mg 25.1 - 32.0 kg = 600 mg 32.1 - 49.9 kg = 750 mg	900 mg

*Tablets can be crushed and administered with some solid food for those unable to swallow pills.

What is completion of therapy?

Does this regimen have to be administered via directly observed therapy (DOT)?

Who is not recommended for treatment with 3HP?

ALERTS:

How frequently were toxicities observed with 3HP?

Hypersensitivity including flu-like symptoms, headache, hypotension, near-syncope/syncope	3.8%
Rash	0.8%
Hepatotoxicity	0.4%
Thrombocytopenia	Infrequent
Other toxicities	3.2%

NATIONAL TUBERCULOSIS CONTROLLERS ASSOCIATION

What can an adverse event include and how should I respond?

	Adverse Event	Response
Moderate to Severe	• Hypersensitivity • Hypotension • Dizziness or nausea/vomiting (that can lead/relate to syncope) • Syncope/fainting • Hospitalization • Life-threatening event • Flu-like syndrome (e.g., fever, chills, headache, dizziness, myalgia/malaise, pain) • Thrombocytopenia • Shortness of breath • Wheezing • Acute bronchospasm • Urticaria • Petechiae • Purpura • Conjunctivitis • Angioedema • Shock	Discontinue treatment Conduct prompt clinical assessment with appropriate lab monitoring
Mild to Moderate	• Rash • Fever • Pruritus	Continue to monitor the patient closely with a low threshold for discontinuing treatment

How do I report an adverse event regarding 3HP?

Are there drug-drug interactions?

Whom do I contact with questions or concerns?

What type of monitoring do I need to do?

NTCA PROVIDER GUIDANCE:
USING THE ISONIAZID/RIFAPENTINE REGIMEN TO TREAT LATENT TUBERCULOSIS INFECTION (LTBI)
NOVEMBER 2019; REVISED: APRIL 2019

For references, go to http://www.tbcontrollers.org/resources/3hp

Source: Tuberculosis Controllers Association. *NTCA Provider Guidance: Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection*. November 2019; Revised April 2019. Available at: http://www.tbcontrollers.org/docs/resources/3hp/NTCA_Provider_Guidance_3HP_11918.pdf.[91]

FIGURE 2. NTCA provider guidance: using the Isoniazid/Rifapentine regimen to treat latent tuberculosis infection (LTBI). Source: Tuberculosis Controllers Association. NTCA provider guidance: using the Isoniazid/Rifapentine regimen to treat latent tuberculosis infection. November 2019; Revised April 2019. Available at: http://www.tbcontrollers.org/docs/resources/3hp/NTCA_Provider_-Guidance_3HP_11918.pdf.[74]

family. Some of these people may be at high risk of developing active TB and serious complications of the disease including death.
- Treatment of LTBI is safe, effective, and strongly recommended in most cases.
- Treatment of LTBI can be as short as 1 day per week for 12 weeks (Fig. 2).

Recommending Treatment

Since more than 80% of active TB cases in the US arise from previously untreated LTBI,[47] LTBI represents a unique opportunity to prevent a potentially devastating infectious disease via early treatment. For this reason, treatment of LTBI is now a cornerstone of the nation's TB elimination strategy.[75] Treatment is now strongly recommended for HCP with LTBI, unless risks of treatment outweigh the anticipated benefit for a particular patient. A CXR prior to the time of treatment initiation is recommended by the CDC; 3 to 6 months is a reasonable timeframe for needing to repeat a CXR prior to treatment.

The use of IGRAs increased acceptance of LTBI treatment compared with TST. In one study, that acceptance rate increased from 11% to 52% with positive results.[41] However, there is a concerning, consistent finding that HCP with LTBI are less likely than non-HCP to accept LTBI treatment.[38–40,42] Treatment acceptance rates vary but seem to cluster between 40% and 50% when all eligible HCP are included.[10,38,39,41,76,77] Acceptance rates as high as 90% with adherence have been reported with intensive clinic interventions including frequent follow-up visits. Selection bias may limit the reproducibility of these findings.[77,78]

The reasons for low HCP acceptance of treatment are unclear. Recent data suggest that physicians and HCP from high TB burden countries may be less likely to accept and complete treatment compared with other HCP.[76,79] One potential contributor may be greater familiarity with isoniazid (INH) treatment-associated adverse events. Newer regimens afford not only shorter, but safer courses of treatment, and therefore may be more acceptable to HCP. The consequences of active TB in HCP are potentially more serious than in the general population because they include not only personal illness but also costly and disruptive contact investigations, lost work time and an appreciable risk of exposing medically vulnerable patients.[80–84] Consideration of these factors may convince otherwise ambivalent HCP to accept treatment.

Occupational health programs should utilize strategies to reduce barriers to treatment and optimize treatment acceptance and completion. Such strategies may include:

- Offer treatment through an onsite occupational health clinic.
- Provide LTBI education appropriate to the HCP's knowledge base.
- Elicit and address the HCP's beliefs and concerns about LTBI and LTBI treatment.
- Subsidize the cost of treatment.
- Offer flexible, convenient mechanisms for follow-up care.

TABLE 4. Abbreviations

3HP	3 months INH + rifapentine (once weekly)
4RIF	4 months rifampin (daily)
6INH	6 months INH (daily)
9INH	9 months INH (daily)
AFB	Acid-fast bacillus
AIDS	Acquired Immunodeficiency Syndrome
BAMT	Blood assay for *M. tuberculosis*
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CXR	Chest radiograph, ''x-ray''
FDA	Food and Drug Administration
HCP	Health care personnel
HIV	Human Immunodeficiency Virus
IGRA	Interferon gamma release assay
INH	Isoniazid
LTBI	Latent tuberculosis infection
MMWR	Morbidity and Mortality Weekly Report
NAAT	Nucleic acid amplification testing
PA	Posterior-anterior
PAPR	Powered air purifying respirator
PCR	Polymerase chain reaction
POPP	Post-Offer/Pre-Placement
PPD	Purified protein derivative
PPE	Personal protective equipment
QFT-GIT	QuantiFERON®-TB-Gold In Tube
TB	Tuberculosis
TNF	Tumor necrosis factor
TST	Tuberculin Skin Test

- Follow up with HCP who do not accept treatment initially.
- Use a declination form to clearly document the offer of treatment and underscore the educational messages (Appendix 4, http://links.lww.com/JOM/A783).

Nine months of daily isoniazid (9INH) has long been a standard regimen used in the US for the treatment of LTBI. Clinical studies have indicated it can be highly effective in preventing progression to active TB, but adherence rates are typically suboptimal. Six months of daily INH (6INH) is another acceptable regimen, but again the high adherence rates required for optimal efficacy have been difficult to achieve. Both long course INH treatment regimens are associated with rare complications including mild-to-severe hepatocellular toxicity.

Currently, there are three short-course treatment regimens for LTBI that are recommended over 6INH and 9INH: 12 weeks of once-weekly INH and rifapentine (3HP), 3 months of daily INH plus rifampin (3HR), and 4 months of daily rifampin alone (4R). Each of these short regimens are now preferred first-line therapies, supplanting the long course INH options.[85–87] The short-course therapies have been shown to have equal or greater efficacy at preventing progression to active TB, significantly higher completion rates, and superior safety profiles when compared with 9INH.[88–90] Even shorter regimens continue to be studied.[91] When prescribing rifampin-based regimens, the potential for drug–drug interactions should be carefully considered and monitored. An LTBI treatment comparison table is offered in Fig. 1, and a 3HP user Guide is included in Fig. 2.

Some HCP who initially decline treatment may change their mind in subsequent years as medication regimens and influences in their personal lives also change. For those who decline or defer treatment, a mechanism to periodically reissue the offer and to educate them on new treatments as they become available is recommended and could be embedded in ongoing TB awareness education or respiratory fit testing. Resources for LTBI diagnosis, education, and treatment are available through CDC,[92] and its four regional TB Centers of Excellence for Training, Education, and Medical Consultation,[93] as well as the NTCA.[94]

CONCLUSION

The epidemiology of tuberculosis in the US is changing, and diagnostic tests and treatment regimens for TB are evolving. Occupational health providers should implement policies and protocols based on the current science. The 2019 MMWR CDC/NTCA Recommendations represent a philosophy and approach that focuses on educating all HCP and on treating HCP identified with LTBI to minimize the progression to active disease and infectiousness. In this companion document, we have sought to provide practical context for the recommendations. Occupational health practitioners should bear in mind that the 2019 MMWR CDC/NTCA Recommendations exist within the regulatory environment, and that some states or local governments may still have annual TB testing requirements for HCP. Over time, the regulations will evolve and allow this ACOEM/NTCA Companion Guidance to be used for occupational health practitioners who will implement work-based programs.

In addition to promoting health and preventing disease, the new recommendations should improve the efficiency and effectiveness of occupational health practices in health care facilities. The requirement for routine, serial, untargeted annual testing is no longer justified. This approach has generated tens of millions of negative TB test results and has occupied hundreds of thousands of hours of occupational health time, HCP time, and significant fiscal resources each year without providing significant improvement in either HCP or in-patient health. Policies that called for large-scale serial testing without attention to preventive treatment also generated many false-positive results and has resulted in additional unnecessary testing and treatment of people without TB. The waste and harm associated with tens of millions of negative TB tests annually also contributes both enormous medical waste and a substantial carbon footprint that negatively impact the planet as a whole.[95]

It is a true public health feat that the US is on its way to elimination of a disease that just 100 years ago killed one in seven Americans, and still kills 1.6 million people across the globe annually. The decline of TB in the US overall, and in HCP in particular, is remarkable in a country as large and as diverse as the US; the elimination of TB disease by proactively treating LTBI should be the US health care community's next collective priority. These are testaments to what we can do together when good science and good practice beget good policy.

ACKNOWLEDGMENTS

ACOEM and NTCA wish to thank the section leaders for this document: Randall Reves, MD (Background with Literature Review), Amy Behrman, MD (Baseline (post-offer/pre-placement) Screening and Testing), Jon Warkentin, MD, MPH (Post-exposure Screening and Testing), Mark Russi, MD, MPH (Serial Screening, Testing and Education for HCP), and Melanie Swift, MD, MPH (Education and Treatment of HCP with Positive Test Results). They also wish to thank the NTCA Board members and Paul J. Papanek MD, MPH, for their contribution as reviewers to this document.

REFERENCES

1. Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis Screening, Testing, and Treatment of US Health Care Personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:439–443.
2. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR Morb Mortal Wkly Rep*. 2005;54:1–141.
3. Sepkowitz KA. Tuberculosis and the health care worker: a historical perspective. *Ann Intern Med*. 1994;120:71–79.
4. Jacobson G, Hoyt DD, Bogen E. Tuberculosis in hospital employees as affected by an admission chest x-ray screening program. *Dis Chest*. 1957;32:27–38.
5. Tape TG, Mushlin AI. The utility of routine chest radiographs. *Ann Intern Med*. 1986;104:663–670.
6. Blumberg HM, Watkins DL, Berschling JD, et al. Preventing the nosocomial transmission of tuberculosis. *Ann Intern Med*. 1995;122: 658–663.

7. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Ann Intern Med*. 1995;122:90–95.
8. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. *Am J Infect Control*. 1995;23:352–356.
9. Welbel SF, French AL, Bush P, DeGuzman D, Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. *Am J Infect Control*. 2009;37:668–673.
10. Dobler CC, Farah WH, Alsawas M, et al. Tuberculin skin test conversions and occupational exposure risk in US Healthcare Workers. *Clin Infect Dis*. 2018;66:706–711.
11. Lambert LA, Pratt RH, Armstrong LR, Haddad MB. Tuberculosis among healthcare workers, United States, 1995–2007. *Infect Control Hosp Epidemiol*. 2012;33:1126–1132.
12. Mongkolrattanothai T, Lambert LA, Winston CA. Tuberculosis among healthcare personnel, United States, 2010–2016. *Infect Control Hosp Epidemiol*. 2019;40:701–704.
13. Centers for Disease Control and Prevention (CDC). *Reported Tuberculosis in the United States, 2016.* Atlanta, GA: US Department of Health and Human Services, CDC; 2017.
14. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64:e1–e33.
15. Diel R, Goletti D, Ferrara G, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Eur Respir J*. 2011;37:88–99.
16. Mazurek G, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection — United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59(RR05):1–25.
17. de Perio MA, Tsevat J, Roselle GA, Kralovic SM, Eckman MH. Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. *Arch Intern Med*. 2009;169:179–187.
18. Linas BP, Wong AY, Freedberg KA, Horsburgh Jr CR. Priorities for screening and treatment of latent tuberculosis infection in the United States. *Am J Respir Crit Care Med*. 2011;184:590–601.
19. Wrighton-Smith P, Sneed L, Humphrey F, Tao X, Bernacki E. Screening health care workers with interferon-gamma release assay versus tuberculin skin test: impact on costs and adherence to testing (the SWITCH study). *J Occup Environ Med*. 2012;54:806–815.
20. Dorman SE, Belknap R, Graviss EA, et al. Interferon-gamma release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med*. 2014;189:77–87.
21. Dobler C, Farah W, Alsawas M, et al. Tuberculin skin test conversions and occupational exposure risk in US healthcare workers. *Clin Infect Dis*. 2018;66:706–711.
22. Driver CR, Stricof RL, Granville K, et al. Tuberculosis in health care workers during declining tuberculosis incidence in New York State. *Am J Infect Control*. 2005;33:519–526.
23. Benoit SR, Gregg EW, Jonnalagadda S, et al. Association of diabetes and tuberculosis disease among US-bound adult refugees, 2009–2014. *Emerg Infect Dis*. 2017;23:543–545.
24. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: a systematic review and meta-analysis. *PLoS One*. 2017;12:e0187967.
25. QIAGEN. QuantiFERON®-TB Gold Plus (QFT®-Plus) Package Insert. Germantown, MD; 2019. Available at: https://www.quantiferon.com/us/wp-content/uploads/sites/13/2019/07/L1095849-R05-QFT-Plus-ELISA-IFU-USCA.pdf. Accessed June 15, 2020.
26. Oxford Immunotec, Inc. T-SPOT®.TB Package Insert. Marlborough, MA; 2015. Available at: http://www.tspot.com/wp-content/uploads/2012/01/PI-TB-US-v5.pdf. Accessed June 15, 2020.
27. Foster-Chang SA, Manning ML, Chandler L. Tuberculosis screening of new hospital employees: compliance, clearance to work time, and cost using tuberculin skin test and interferon-gamma release assays. *Workplace Health Saf*. 2014;62:460–467.
28. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev*. 2014;27:3–20.
29. Centers for Disease Control and Prevention. TST Training Video. Available at: https://tools.cdc.gov/podcasts/media/mp4/mantoux.mp4. Accessed June 15, 2020.
30. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Division of Tuberculosis Elimination, Centers for Disease Control and Prevention. TB Elimination Targeted Tuberculosis Testing and Interpreting Tuberculin Skin Test Results. Available at: https://www.cdc.gov/tb/publications/factsheets/testing/skintestresults_revised.pdf. December 2011.
31. Zwerling A, van den Hof S, Scholten J, Cobelens F, Menzies D, Pai M. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax*. 2012;67:62–70.
32. Thanassi W, Noda A, Hernandez B, Friedman L, Dorman S, Yesavage J. Negative tuberculin skin test and prediction of reversion of QuantiFERON interferon gamma release assay in US healthcare workers. *Infect Control Hosp Epidemiol*. 2016;37:478–482.
33. Thanassi W, Noda A, Hernandez B, et al. Delineating a retesting zone using receiver operating characteristic analysis on serial QuantiFERON tuberculosis test results in US healthcare workers. *Pulm Med*. 2012;2012:291294.
34. Fong KS, Tomford JW, Teixeira L, et al. Challenges of interferon-gamma release assay conversions in serial testing of health-care workers in a TB control program. *Chest*. 2012;142:55–62.
35. Ringshausen FC, Nienhaus A, Torres Costa J, et al. Within-subject variability of Mycobacterium tuberculosis-specific gamma interferon responses in German health care workers. *Clin Vaccine Immunol*. 2011;18:1176–1182.
36. Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. *Am J Respir Crit Care Med*. 2004;170:59–64.
37. Daley CL, Reves RR, Beard MA, et al. A summary of meeting proceedings on addressing variability around the cut point in serial interferon-gamma release assay testing. *Infect Control Hosp Epidemiol*. 2013;34:625–630.
38. Colson PW, Hirsch-Moverman Y, Bethel J, et al. Acceptance of treatment for latent tuberculosis infection: prospective cohort study in the United States and Canada. *Int J Tuberc Lung Dis*. 2013;17:473–479.
39. Gershon AS, McGeer A, Bayoumi AM, Raboud J, Yang J. Health care workers and the initiation of treatment for latent tuberculosis infection. *Clin Infect Dis*. 2004;39:667–672.
40. Horsburgh Jr CR, Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. 2010;137:401–409.
41. Sahni R, Miranda C, Yen-Lieberman B, et al. Does the implementation of an interferon-gamma release assay in lieu of a tuberculin skin test increase acceptance of preventive therapy for latent tuberculosis among healthcare workers? *Infect Control Hosp Epidemiol*. 2009;30:197–199.
42. Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. *BMC Infect Dis*. 2016;16:204.
43. Centers for Disease Control and Prevention. TB Elimination: Tuberculin Skin Testing. 2011. Available at: https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm. Accessed May 7, 2019.
44. Styblo K. Recent advances in epidemiological research in tuberculosis. *Adv Tuberc Res*. 1980;20:1–63.
45. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR–14):1–17. quiz CE11–14.
46. Siu AL, Force USPST. Screening for abnormal blood glucose and type 2 diabetes mellitus: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2015;163:861–868.
47. Flood J, Barry PM. Mainstreaming latent tuberculosis infection testing and treatment in the United States: who and how. *JAMA Intern Med*. 2017;177:1764–1765.
48. Kim YJ, Kang JY, Kim SI, Chang MS, Kim YR, Park YJ. Predictors for false-negative QuantiFERON-TB Gold assay results in patients with extrapulmonary tuberculosis. *BMC Infect Dis*. 2018;18:457.
49. Eisenberg RL, Romero J, Litmanovich D, Boiselle PM, Bankier AA. Tuberculosis: value of lateral chest radiography in pre-employment screening of patients with positive purified protein derivative skin test results. *Radiology*. 2009;252:882–887.
50. Meyer M, Clarke P, O'Regan AW. Utility of the lateral chest radiograph in the evaluation of patients with a positive tuberculin skin test result. *Chest*. 2003;124:1824–1827.
51. Luetkemeyer AF, Firnhaber C, Kendall MA, et al. Evaluation of Xpert MTB/RIF versus AFB smear and culture to identify pulmonary tuberculosis in patients with suspected tuberculosis from low and higher prevalence settings. *Clin Infect Dis*. 2016;62:1081–1088.
52. National TB Controllers Association (NTCA), Association of Public Health Laboratories (APHL). Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings; 2016. Available at: http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf. Accessed December 18, 2019.

53. Talwar A, Tsang CA, Price SF, et al. Tuberculosis - United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:257–262.
54. National Tuberculosis Controllers Association, Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Recomm Rep*. 2005;54(RR–15):1–47.
55. California Department of Public Health. California Adult Tuberculosis Risk Assessment and User Guide September; 2018. Available at: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-CA-TB-Risk-Assessment-and-Fact-Sheet.pdf. Accessed June 15, 2020.
56. Lobato MN, Hopewell PC. Mycobacterium tuberculosis infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. *Am J Respir Crit Care Med*. 1998;158:1871–1875.
57. Barcellini L, Borroni E, Brown J, et al. First evaluation of QuantiFERON-TB Gold Plus performance in contact screening. *Eur Respir J*. 2016;48:1411–1419.
58. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and positive predictive value of a whole-blood interferon-gamma release assay for developing active tuberculosis: an update. *Am J Respir Crit Care Med*. 2011;183:88–95.
59. Sester M, Sotgiu G, Lange C, et al. Interferon-gamma release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2011;37:100–111.
60. Mullie GA, Schwartzman K, Zwerling A, N'Diaye DS. Revisiting annual screening for latent tuberculosis infection in healthcare workers: a cost-effectiveness analysis. *BMC Med*. 2017;15:104.
61. Malasky C, Jordan T, Potulski F, Reichman L. Occupational tuberculous infections among pulmonary physicians in training. *Am Rev Respir Dis*. 1990;142:505–507.
62. Association of Public Health Laboratories (APHL). Mycobacterium Tuberculosis: Assessing Your Laboratory. Silver Spring, MD; 2019. Available at: https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Apr-TB-Toolkit.pdf. Accessed February 28, 2020.
63. Miller JM, Astles R, Baszler T, et al. Guidelines for safe work practices in human and animal medical diagnostic laboratories. Recommendations of a CDC-convened, Biosafety Blue Ribbon Panel. *MMWR Suppl*. 2012;61:1–102.
64. de Vries G, van Hunen R, Meerstadt-Rombach FS, et al. Analysing tuberculosis cases among healthcare workers to inform infection control policy and practices. *Infect Control Hosp Epidemiol*. 2017;38:976–982.
65. Holden KL, Bradley CW, Curran ET, et al. Unmasking leading to a healthcare worker Mycobacterium tuberculosis transmission. *J Hosp Infect*. 2018;100:e226–e232.
66. Seidler A, Nienhaus A, Diel R. Review of epidemiological studies on the occupational risk of tuberculosis in low-incidence areas. *Respiration*. 2005;72:431–446.
67. Zwerling A, Benedetti A, Cojocariu M, et al. Repeat IGRA testing in Canadian health workers: conversions or unexplained variability? *PLoS One*. 2013;8:e54748.
68. Apriani L, McAllister S, Sharples K, et al. Latent tuberculosis infection in health care workers in low and middle-income countries: an updated systematic review. *Eur Respir J*. 2019;53:1801789.
69. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS Med*. 2006;3:e494.
70. Murphy ME, Wilmore S, Satta G, et al. Occupational tuberculosis despite minimal nosocomial contact in a health care worker undergoing treatment with a tumor necrosis factor inhibitor. *Ann Am Thorac Soc*. 2016;13:2275–2277.
71. Centers for Disease Control and Prevention (CDC). Tuberculosis (TB): Data and Statistics; 2019. Available at: https://www.cdc.gov/tb/statistics/default.htm. Accessed December 18, 2019.
72. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh Jr CR. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am J Epidemiol*. 2014;179:216–225.
73. Muckenfuss M. *Health Warning: Loma Linda VA Employee Treated for TB*. Riverside, Calif: The Press-Enterprise; 2015.
74. Tuberculosis Controllers Association. NTCA Provider Guidance: Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI). November 2019 (Revised April 2019). Available at: http://www.tbcontrollers.org/docs/resources/3hp/NTCA_Provider_Guidance_3HP_11918.pdf. Accessed June 5, 2019.
75. Getahun H, Matteelli A, Abubakar I, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015;46:1563–1576.
76. Lee H, Koo GW, Min JH, et al. Factors associated with non-initiation of latent tuberculosis treatment among healthcare workers with a positive interferon-gamma releasing assay. *Sci Rep*. 2019;9:61.
77. Lal A, Al Hammadi A, Rapose A. Latent tuberculosis infection: treatment initiation and completion rates in persons seeking immigration and health care workers. *Am J Med*. 2019;132:1353–1355.
78. Shukla SJ, Warren DK, Woeltje KF, Gruber CA, Fraser VJ. Factors associated with the treatment of latent tuberculosis infection among healthcare workers at a midwestern teaching hospital. *Chest*. 2002;122:1609–1614.
79. Swift MD, Molella RG, Vaughn AIS, et al. Determinants of latent tuberculosis treatment acceptance and completion in healthcare personnel. *Clin Infect Dis*. 2019;ciz817. https://doi.org/10.1093/cid/ciz817.
80. Ahn JG, Kim DS, Kim KH. Nosocomial exposure to active pulmonary tuberculosis in a neonatal intensive care unit. *Am J Infect Control*. 2015;43:1292–1295.
81. Fraser TG, Kowalczyk J, Schmitt S, et al. Active tuberculosis in a healthcare worker: are you ready? *Infect Control Hosp Epidemiol*. 2009;30:80–82.
82. Nania JJ, Skinner J, Wilkerson K, et al. Exposure to pulmonary tuberculosis in a neonatal intensive care unit: unique aspects of contact investigation and management of hospitalized neonates. *Infect Control Hosp Epidemiol*. 2007;28:661–665.
83. Ohno H, Ikegami Y, Kishida K, et al. A contact investigation of the transmission of Mycobacterium tuberculosis from a nurse working in a newborn nursery and maternity ward. *J Infect Chemother*. 2008;14:66–71.
84. Schepisi MS, Sotgiu G, Contini S, Puro V, Ippolito G, Girardi E. Tuberculosis transmission from healthcare workers to patients and coworkers: a systematic literature review and meta-analysis. *PLoS One*. 2015;10:e0121639.
85. McClintock AH, Eastment M, McKinney CM, et al. Treatment completion for latent tuberculosis infection: a retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. *BMC Infect Dis*. 2017;17:146.
86. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379:440–453.
87. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69:1–11.
88. Arguello Perez E, Seo S, Schneider W, Eisenstein C, Brown A. Management of latent tuberculosis infection among healthcare workers: 10-year experience at a single center. *Clin Infect Dis*. 2017;65:2105–2111.
89. Stagg HR, Zenner D, Harris RJ, Munoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. *Ann Intern Med*. 2014;161:419–428.
90. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365:2155–2166.
91. Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380:1001–1011.
92. Centers for Disease Control and Prevention. Deciding When to Treat Latent TB Infection.; 2018. Available at: https://www.cdc.gov/tb/topic/treatment/decideltbi.htm. Accessed June 15, 2020.
93. Centers for Disease Control and Prevention. TB Centers of Excellence for Training, Education, and Medical Consultation.; 2018. Available at: https://www.cdc.gov/tb/education/tb_coe/default.htm. Accessed June 15, 2020.
94. National Tuberculosis Controllers Association. State, Big City, and Territory TB Program Contacts. Available at: http://www.tbcontrollers.org/community/statecityterritory/#.XadvbehKiM9. Accessed October 16, 2019.
95. Gluaser W, Petch J, Pendharkar S. Are disposable hospital supplies trashing the environment? In: *Healthy Debate*; 2016. Available at: https://healthydebate.ca/2016/08/topic/hospital-medical-waste.

