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Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis

Recommendations from the National Tuberculosis Controllers Association and CDC

Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting *Mycobacterium tuberculosis* Infection, United States

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis

Recommendations from the National Tuberculosis Controllers Association and CDC

Summary

In 1976, the American Thoracic Society (ATS) published brief guidelines for the investigation, diagnostic evaluation, and medical treatment of TB contacts. Although investigation of contacts and treatment of infected contacts is an important component of the U.S. strategy for TB elimination, second in priority to treatment of persons with TB disease, national guidelines have not been updated since 1976.

This statement, the first issued jointly by the National Tuberculosis Controllers Association and CDC, was drafted by a working group consisting of members from both organizations on the basis of a review of relevant epidemiologic and other scientific studies and established practices in conducting contact investigations. This statement provides expanded guidelines concerning investigation of TB exposure and transmission and prevention of future cases of TB through contact investigations. In addition to the topics discussed previously, these expanded guidelines also discuss multiple related topics (e.g., data management, confidentiality and consent, and human resources). These guidelines are intended for use by public health officials but also are relevant to others who contribute to TB control efforts. Although the recommendations pertain to the United States, they might be adaptable for use in other countries that adhere to guidelines issued by the World Health Organization, the International Union against Tuberculosis and Lung Disease, and national TB control programs.

Introduction

Background

In 1962, isoniazid (INH) was demonstrated to be effective in preventing tuberculosis (TB) among household contacts of persons with TB disease (*1*). Investigations of contacts and treatment of contacts with latent TB infection (LTBI) became a strategy in the control and elimination of TB (*2,3*). In 1976, the American Thoracic Society (ATS) published brief guidelines for the investigation, diagnostic evaluation, and medical treatment of TB contacts (*4*). Although investigation of contacts and treatment of infected contacts is an important component of the U.S. strategy for TB elimination, second in priority to treatment of persons with TB disease, national guidelines have not been updated since 1976.

This statement, the first issued jointly by the National Tuberculosis Controllers Association (NTCA) and CDC, was drafted by a working group consisting of members from both organizations on the basis of a review of relevant epidemiologic and other scientific studies and established practices in conducting contact investigations. A glossary of terms and abbreviations used in this report is provided (Box 1 and Appendix A).

This statement provides expanded guidelines concerning investigation of TB exposure and transmission and prevention of future cases of TB through contact investigations. In addition to the topics discussed previously, these expanded guidelines also discuss multiple related topics (e.g., data management, confidentiality and consent, and human resources). These guidelines are intended for use by public health officials but also are relevant to others who contribute to TB control efforts. Although the recommendations pertain to the United States, they might be adaptable for use in other countries that adhere to guidelines issued by the World Health Organization, the International Union Against Tuberculosis and Lung Disease, and national TB control programs.

Contact investigations are complicated undertakings that typically require hundreds of interdependent decisions, the majority of which are made on the basis of incomplete data, and dozens of time-consuming interventions. Making successful decisions during a contact investigation requires use of a complex, multifactor matrix rather than simple decision trees. For each factor, the predictive value, the relative contribution, and the interactions with other factors have been incompletely studied and understood. For example, the dif-

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BOX 1. Terms* and abbreviations used in this report

Acid-fast bacilli (AFB)
Anergy
Associate contact
Bacille Calmette-Guérin (BCG)
Boosting
Bronchoscopy
Bronchoalveolar lavage (BAL)
Case
Cavity (pulmonary)
Contact
Contagious
Conversion
Delayed-type hypersensitivity (DTH)
Directly observed therapy (DOT)
Disseminated TB
Drug-susceptibility test
Enabler
Exposure
Exposure period
Exposure site
Immunocompromised and immunosuppressed
Incentive
Index
Induration
Infection
Infectious
Isoniazid (INH)
Laryngeal TB
Latent *M. tuberculosis* infection (latent tuberculosis infection [LTBI])
Mantoux method
Meningeal TB
Miliary TB
Multidrug-resistant TB (MDR TB)
Mycobacterium bovis
Mycobacterium tuberculosis
Nucleic acid amplification (NAA)
Purified protein derivative (PPD) tuberculin
QuantiFERON®-TB test (QFT)
QuantiFERON®-TB Gold test (QFT-G)
Radiography
Secondary (TB) case
Secondary (or "second-generation") transmission
Smear
Source case or patient
Specimen
Sputum
Suspected TB
Symptomatic
TB disease
Treatment for (or of) latent (*M. tuberculosis*) infection
Tuberculin
Tuberculin skin test (TST)
Tuberculin skin test conversion
Tuberculosis (TB)
Two-step (tuberculin) skin test

* Terms listed are defined in the glossary (Appendix A).

ferences between brief, intense exposure to a contagious patient and lengthy, low-intensity exposure are unknown.

Studies have confirmed the contribution of certain factors: the extent of disease in the index patient, the duration that the source and the contact are together and their proximity, and local air circulation (*5*). Multiple observations have demonstrated that the likelihood of TB disease after an exposure is influenced by medical conditions that impair immune competence, and these conditions constitute a critical factor in assigning contact priorities (*6*).

Other factors that have as yet undetermined importance include the infective burden of *Mycobacterium tuberculosis*, previous exposure and infection, virulence of the particular *M. tuberculosis* strain, and a contact's intrinsic predisposition for infection or disease. Further, precise measurements (e.g., duration of exposure) rarely are obtainable under ordinary circumstances, and certain factors (e.g., proximity of exposure) can only be approximated, at best.

No safe exposure time to airborne *M. tuberculosis* has been established. If a single bacterium can initiate an infection leading to TB disease, then even the briefest exposure entails a theoretic risk. However, public health officials must focus their resources on finding exposed persons who are more likely to be infected or to become ill with TB disease. These guidelines establish a standard framework for assembling information and using the findings to inform decisions for contact investigations, but they do not diminish the value of experienced judgment that is required. As a practical matter, these guidelines also take into consideration the scope of resources (primarily personnel) that can be allocated for the work.

Methodology

A working group consisting of members from the NTCA and CDC reviewed relevant epidemiologic and other scientific studies and established practices in conducting contact

investigations to develop this statement. These published studies provided a scientific basis for the recommendations. Although a controlled trial has demonstrated the efficacy of treating infected contacts with INH (*1*), the effectiveness of contact investigations has not been established by a controlled trial or study. Therefore, the recommendations (Appendix B) have not been rated by quality or quantity of the evidence and reflect expert opinion derived from common practices that have not been tested critically.

These guidelines do not fit every circumstance, and additional considerations beyond those discussed in these guidelines must be taken into account for specific situations. For example, unusually close exposure (e.g., prolonged exposure in a small, poorly ventilated space or a congregate setting) or exposure among particularly vulnerable populations at risk for TB disease (e.g., children or immunocompromised persons) could justify starting an investigation that would normally not be conducted. If contacts are likely to become unavailable (e.g., because of departure), then the investigation should receive a higher priority. Finally, affected populations might experience exaggerated concern regarding TB in their community and demand an investigation.

Structure of this Statement

The remainder of this statement is structured in 13 sections, as follows:

- **Decisions to initiate a contact investigation.** This section focuses on deciding when a contact investigation should be undertaken. Index patients with positive acid-fast bacillus (AFB) sputum-smear results or pulmonary cavities have the highest priority for investigation. The use of nucleic acid amplification (NAA) tests is discussed in this context.
- **Investigating the index patient and sites of transmission.** This section outlines methods for investigating the index patient. Topics discussed include multiple interviews, definition of an infectious period, multiple visits to places that the patient frequented, and the list of contacts (i.e., persons who were exposed).
- **Assigning priorities to contacts.** This section presents algorithms for assigning priorities to individual contacts for evaluation and treatment. Priority ranking is determined by the characteristics of individual contacts and the features of the exposure. When exposure is related to households, congregate living settings, or cough-inducing medical procedures, contacts are designated as high priority. Because knowledge is insufficient for providing exact recommendations, cut-off points for duration of exposure are not included; state and local program officials should determine cut-off points after considering published results, local experience, and these guidelines.
- **Diagnostic and public health evaluation of contacts.** This section discusses diagnostic evaluation, including specific contact recommendations for children aged <5 years and immunocompromised persons, all of whom should be evaluated with chest radiographs. The recommended period between most recent exposure and final tuberculin skin testing has been revised; it is 8–10 weeks, not 10–15 weeks as recommended previously (*4*).
- **Medical treatment for contacts with LTBI.** This section discusses medical treatment of contacts who have LTBI (*6,7*). Effective contact investigations require completion of therapy, which is the single greatest challenge for both patients and health-care providers. Attention should be focused on treating contacts who are assigned high or medium priority.
- **When to expand a contact investigation.** This section discusses when contacts initially classified as being a lower priority should be reclassified as having a higher priority and when a contact investigation should be expanded. Data regarding high- and medium-priority contacts inform this decision.
- **Communicating through the media.** This section outlines principles for reaching out to media sources. Media coverage of contact investigations affords the health department an opportunity to increase public knowledge of TB control and the role of the health department.
- **Data management and evaluation of contact investigations.** This section is the first of three to address health department programmatic tasks. It discusses data management, with an emphasis on electronic data storage and the use of data for assessing the effectiveness of contact investigations.
- **Confidentiality and consent in contact investigations.** This section introduces the interrelated responsibilities of the health department in maintaining confidentiality and obtaining patient consent.
- **Staffing and training for contact investigations.** This section summarizes personnel requirements and training for conducting contact investigations.
- **Contact investigations in special circumstances.** This section offers suggestions for conducting contact investigations in special settings and circumstances (e.g., schools, hospitals, worksites, and congregate living quarters). It also reviews distinctions between a contact investigation and an outbreak investigation.
- **Source-case investigations.** This section addresses source-case investigations, which should be undertaken only when more urgent investigations (see Decisions to Initiate a

Contact Investigation) are being completed successfully. The effectiveness and outcomes of source-case investigations should be monitored critically because of their general inefficiency.

- **Other topics.** This section reviews three specialized topics: cultural competency, social network analysis, and recently approved blood tests. Newly approved blood tests for the diagnosis of *M. tuberculosis* infection have been introduced. If these tests prove to be an improvement over the tuberculin skin test (TST), the science of contact investigations will advance quickly.

Decisions to Initiate a Contact Investigation

Competing demands restrict the resources that can be allocated to contact investigations. Therefore, public health officials must decide which contact investigations should be assigned a higher priority and which contacts to evaluate first (see Assigning Priorities to Contacts). A decision to investigate an index patient depends on the presence of factors used to predict the likelihood of transmission (Table 1). In addition, other information regarding the index patient can influence the investigative strategy.

Factors that Predict Likely Transmission of TB

Anatomical Site of Disease

With limited exceptions, only patients with pulmonary or laryngeal TB can transmit their infection (*8,9*). For contact investigations, pleural disease is grouped with pulmonary disease because sputum cultures can yield *M. tuberculosis* even when no lung abnormalities are apparent on a radiograph (*10*). Rarely, extrapulmonary TB causes transmission during medical procedures that release aerosols (e.g., autopsy, embalming, and irrigation of a draining abscess) (see Contact Investigations in Special Circumstances) (*11–15*)

TABLE 1. Characteristics of the index patient and behaviors associated with increased risk for tuberculosis (TB) transmission

Characteristic	Behavior
Pulmonary, laryngeal, or pleural TB	Frequent coughing
AFB* positive sputum smear	Sneezing
Cavitation on chest radiograph	Singing
Adolescent or adult patient	Close social network
No or ineffective treatment of TB disease	

* Acid-fast bacilli.

Sputum Bacteriology

Relative infectiousness has been associated with positive sputum culture results and is highest when the smear results are also positive (*16–19*). The significance of results from respiratory specimens other than expectorated sputum (e.g., bronchial washings or bronchoalveolar lavage fluid) is undetermined. Experts recommend that these specimens be regarded as equivalent to sputum (*20*).

Radiographic Findings

Patients who have lung cavities observed on a chest radiograph typically are more infectious than patients with noncavitary pulmonary disease (*15,16,21*). This is an independent predictor after bacteriologic findings are taken into account. The importance of small lung cavities that are detectable with computerized tomography (CT) but not with plain radiography is undetermined. Less commonly, instances of highly contagious endobroncheal TB in severely immunocompromised patients who temporarily had normal chest radiographs have contributed to outbreaks. The frequency and relative importance of such instances is unknown, but in one group of human immunodeficiency virus (HIV)–infected TB patients, 3% of those who had positive sputum smears had normal chest radiographs at the time of diagnosis (*22,23*).

Behaviors That Increase Aerosolization of Respiratory Secretions

Cough frequency and severity are not predictive of contagiousness (*24*). However, singing is associated with TB transmission (*25–27*). Sociability of the index patient might contribute to contagiousness because of the increased number of contacts and the intensity of exposure.

Age

Transmission from children aged <10 years is unusual, although it has been reported in association with the presence of pulmonary forms of disease typically reported in adults (*28,29*). Contact investigations concerning pediatric cases should be undertaken only in such unusual circumstances (see Source-Case Investigations).

HIV Status

TB patients who are HIV-infected with low CD4 T-cell counts frequently have chest radiographic findings that are not typical of pulmonary TB. In particular, they are more likely than TB patients who are not HIV-infected to have mediastinal adenopathy and less likely to have upper-lobe infiltrates and cavities (*30*). Atypical radiographic findings increase the potential for delayed diagnosis, which increases transmission. However, HIV-infected patients who have pul-

monary or laryngeal TB are, on average, as contagious as TB patients who are not HIV-infected (*31,32*).

Administration of Effective Treatment

That TB patients rapidly become less contagious after starting effective chemotherapy has been corroborated by measuring the number of viable *M. tuberculosis* organisms in sputa and by observing infection rates in household contacts (*33–36*). However, the exact rate of decrease cannot be predicted for individual patients, and an arbitrary determination is required for each. Guinea pigs exposed to exhaust air from a TB ward with patients receiving chemotherapy were much more likely to be infected by drug-resistant organisms (*8*), which suggests that drug resistance can delay effective bactericidal activity and prolong contagiousness.

Initiating a Contact Investigation

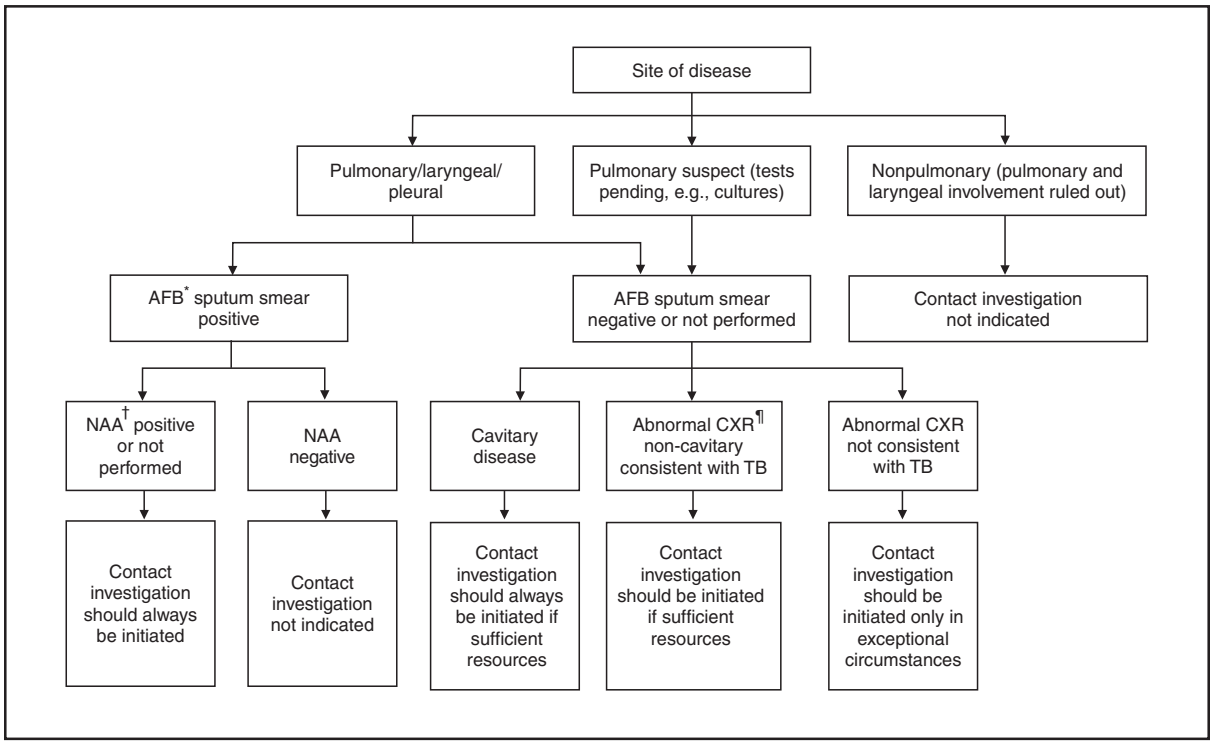
A contact investigation should be considered if the index patient has confirmed or suspected pulmonary, laryngeal, or pleural TB (Figure 1). An investigation is recommended if the sputum smear has AFB on microscopy, unless the result from an approved NAA test (Amplified *Mycobacterium tuberculosis* Direct Test [MTD], GenProbe,® San Diego, California, and Amplicor® *Mycobacterium tuberculosis* Test [Amplicor], Roche® Diagnostic Systems Inc., Branchburg, New Jersey) for *M. tuberculosis* is negative (*37*).

If AFB are not detected by microscopy of three sputum smears, an investigation still is recommended if the chest radiograph (i.e., the plain view or a simple tomograph) indicates the presence of cavities in the lung. Parenchymal cavities of limited size that can be detected only by computerized imaging techniques (i.e., CT, computerized axial tomography scan, or magnetic resonance imaging of the chest) are not included in this recommendation.

When sputum samples have not been collected, either because of an oversight or as a result of the patient's inability to expectorate, results from other types of respiratory specimens (e.g., gastric aspirates or bronchoalveolar lavage) may be interpreted in the same way as in the above recommendations. However, whenever feasible, sputum samples should be collected (through sputum induction, if necessary) before initiating chemotherapy.

Contact investigations of persons with AFB smear or culture-positive sputum and cavitary TB are assigned the highest priority. However, even if these conditions are not present, contact

FIGURE 1. Decision to initiate a tuberculosis (TB) contact investigation



* Acid-fast bacilli.
† Nucleic acid assay.
§ According to CDC guidelines.
¶ Chest radiograph.

investigations should be considered if a chest radiograph is consistent with pulmonary TB. Whether to initiate other investigations depends on the availability of resources to be allocated and achievement of objectives for higher priority contact investigations. A positive result from an approved NAA test supports a decision to initiate an investigation. Because waiting for a sputum or respiratory culture result delays initiation of contact investigations, delay should be avoided if any contacts are especially vulnerable or susceptible to TB disease (see Assigning Priorities to Contacts).

Investigations typically should not be initiated for contacts of index patients who have suspected TB disease and minimal findings in support of a diagnosis of pulmonary TB. Exceptions can be justified during outbreak investigations (see Contact Investigations in Special Circumstances), especially when vulnerable or susceptible contacts are identified or during a source-case investigation (see Source-Case Investigations).

Investigating the Index Patient and Sites of Transmission

Comprehensive information regarding an index patient is the foundation of a contact investigation. This information includes disease characteristics, onset time of illness, names of contacts, exposure locations, and current medical factors (e.g., initiation of effective treatment and drug susceptibility results). Health departments are responsible for conducting TB contact investigations. Having written policies and procedures for investigations improve the efficiency and uniformity of investigations.

Establishing trust and consistent rapport between public health workers and patients is critical to gain full information and long-term cooperation during treatment. Good interview skills can be taught and learned skills improved with practice. Workers assigned these tasks should be trained in interview methods and tutored on the job (see Staffing and Training for Contact Investigations and Contact Investigations in Special Situations).

The majority of TB patients in the United States were born in other countries, and their fluency in English often is insufficient for productive interviews to be conducted in English. Patients should be interviewed by persons who are fluent in their primary language. If this is not possible, health departments should provide interpretation services.

Preinterview Phase

Background information regarding the patient and the circumstances of the illness should be gathered in preparation for the first interview. One source is the current medical record (*38*). Other sources are the physician who reported the case and (if the patient is in a hospital) the infection control nurse. The information in the medical record can be disclosed to public health authorities under exemptions in the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (http://aspe.hhs.gov/admnsimp/pl104191.htm) (*39*). The patient's name should be matched to prior TB registries and to the surveillance database to determine if the patient has been previously listed.

Multiple factors are relevant to a contact investigation, including the following:

- history of previous exposure to TB,
- history of previous TB disease and treatment,
- anatomical sites of TB disease,
- symptoms of the illness,
- date of onset,
- chest radiograph results,
- other results of diagnostic imaging studies,
- diagnostic specimens that were sent for histologic or bacteriologic analysis (with dates, specimen tracking numbers, and destinations),
- current bacteriologic results,
- anti-TB chemotherapy regimen (with dates, medications, dosages, and treatment plan),
- results from HIV testing,
- the patient's concurrent medical conditions (e.g., renal failure implies that a renal dialysis center might be part of the patient's recent experience),
- other diagnoses (e.g., substance abuse, mental illness, or dementia) that impinge directly on the interview, and
- identifying demographic information (e.g., residence, employment, first language, given name and street names, aliases, date of birth, telephone numbers, other electronic links, and next-of-kin or emergency connections).

Determining the Infectious Period

Determining the infectious period focuses the investigation on those contacts most likely to be at risk for infection and sets the timeframe for testing contacts. Because the start of the infectious period cannot be determined with precision by available methods, a practical estimation is necessary. On the basis of expert opinion, an assigned start that is 3 months before a TB diagnosis is recommended (Table 2). In certain circumstances, an even earlier start should be used. For example, a patient (or the patient's associates) might have been aware of protracted illness (in extreme cases, >1 year). Information from the patient interview and from other sources should be assembled to assist in estimating the infectious period. Helpful details are the approximate dates that TB

TABLE 2. Guidelines for estimating the beginning of the period of infectiousness of persons with tuberculosis (TB), by index case characteristic

Characteristic			
TB symptoms	AFB* sputum smear positive	Cavitary chest radiograph	Recommended minimum beginning of likely period of infectiousness
Yes	No	No	3 months before symptom onset or first positive finding (e.g., abnormal chest radiograph) consistent with TB disease, whichever is longer
Yes	Yes	Yes	3 months before symptom onset or first positive finding consistent with TB disease, whichever is longer
No	No	No	4 weeks before date of suspected diagnosis
No	Yes	Yes	3 months before first positive finding consistent with TB

SOURCE: California Department of Health Services Tuberculosis Control Branch; California Tuberculosis Controllers Association. Contact investigation guidelines. Berkeley, CA: California Department of Health Services; 1998.
* Acid-fast bacilli.

symptoms were noticed, mycobacteriologic results, and extent of disease (especially the presence of large lung cavities, which imply prolonged illness and infectiousness) (*40,41*).

The infectious period is closed when the following criteria are satisfied: 1) effective treatment (as demonstrated by *M. tuberculosis* susceptibility results) for ≥2 weeks; 2) diminished symptoms; and 3) mycobacteriologic response (e.g., decrease in grade of sputum smear positivity detected on sputum-smear microscopy). The exposure period for individual contacts is determined by how much time they spent with the index patient during the infectious period. Multidrug-resistant TB (MDR TB) can extend infectiousness if the treatment regimen is ineffective. Any index patient with signs of extended infectiousness should be continually reassessed for recent contacts.

More stringent criteria should be applied for setting the end of the infectious period if particularly susceptible contacts are involved. A patient returning to a congregate living setting or to any setting in which susceptible persons might be exposed should have at least three consecutive negative sputum AFB smear results from sputum collected ≥8 hours apart (with one specimen collected during the early morning) before being considered noninfectious (*42*).

Interviewing the Patient

In addition to setting the direction for the contact investigation, the first interview provides opportunities for the patient to acquire information regarding TB and its control and for the public health worker to learn how to provide treatment and specific care for the patient. Because of the urgency of finding other infectious persons associated with the index patient, the first interview should be conducted ≤1 business day of reporting for infectious persons and ≤3 business days for others. The interview should be conducted in person (i.e., face to face) in the hospital, the TB clinic, the patient's home, or a convenient location that accommodates the patient's right to privacy.

A minimum of two interviews is recommended. At the first interview, the index patient is unlikely to be oriented to the contact investigation because of social stresses related to the illness (e.g., fear of disability, death, or rejection by friends and family). The second interview is conducted 1–2 weeks later, when the patient has had time to adjust to the disruptions caused by the illness and has become accustomed to the interviewer, which facilitates a two-way exchange. The number of additional interviews required depends on the amount of information needed and the time required to develop consistent rapport.

Interviewing skills are crucial because the patient might be reluctant to share vital information stemming from concerns regarding disease-associated stigma, embarrassment, or illegal activities. Interviewing skills require training and periodic on-the-job tutoring. Only trained personnel should interview index patients.

In addition to standard procedures for interviewing TB patients (*43*), the following general principles should be considered:

- **Establishing rapport.** Respect should be demonstrated by assuring privacy during the interview. Establishing respect is critical so rapport can be built. The interviewer should display official identification and explain the reasons for the interview. The interviewer should also discuss confidentiality and privacy (see Confidentiality and Consent in Contact Investigations) in frank terms that help the patient decide how to share information. These topics should be discussed several times during the interview to stress their importance. Sufficient time should be allocated, possibly >1 hour, for a two-way exchange of information, although the patient's endurance should be considered.

- **Information exchange.** The interviewer should confirm information from the preinterview phase, obtain missing information, and resolve disparities. Obtaining information regarding how to locate the patient throughout treatment is crucial. The beginning of the infectious period should be set from the information derived from this exchange.
- **Transmission settings.** Information regarding transmission settings that the patient attended during the infectious period is needed for listing the contacts and assigning priorities (see Investigating the Index Patient and Sites of Transmission). Topics to discuss include where the patient spent nights, met with friends, worked, ate, visited, and sought health care. The interviewer should ask specifically regarding congregate settings (e.g., high school, university, correctional facility, homeless shelter, or nursing home). The interviewer also should inquire regarding routine and nonroutine travel. Contacts not previously identified might have been exposed during the patient's infectious period while the patient was traveling. Routine travel modes (e.g., carpool) could also be settings in which contacts were exposed.
- **Sites of transmission.** The key to efficient contact investigations is setting priorities. The investigator must constantly balance available resources, especially staff time, with expected yield. However, the interview with the patient should be as comprehensive as possible. All possible sites of transmission should be listed, regardless of how long the patient spent at the sites. Priorities should be set on the basis of the time spent by the index patient, and decisions regarding investigation of the sites and contacts should be made after all the information has been collected (see Assigning Priorities to Contacts and When to Expand a Contact Investigation).
- **List of contacts.** For each transmission setting, the interviewer should ask for the names of contacts and the approximate types, frequencies, and durations of exposure. Ideal information regarding each contact includes full name, aliases or street names, a physical description, location and communication information (e.g., addresses and telephone numbers), and current general health. The interviewer might need to spend more time asking regarding contacts who are difficult for the patient to remember. Recent illnesses among contacts should be discussed.
- **Closure.** The interviewer should express appreciation, provide an overview of the processes in the contact investigation, and remind the patient regarding confidentiality and its limits. The patient especially should be told how site visits are conducted and confidentiality protected. An appointment for the next interview should be set within the context of the schedule for medical care.
- **Follow-up interviews.** The best setting for the second and subsequent interviews is the patient's residence. If the original interviewer senses incomplete rapport with the index patient, a second interviewer can be assigned. The follow-up interviews are extensions of the initial interview. If the interviewer senses resistance to meeting in certain places or discussing those places, making site visits to those places might facilitate identification of additional contacts whom the index patient had not remembered or wanted to name.

Proxy Interview

Proxy interviews can build on the information provided by the index patient and are essential when the patient cannot be interviewed. Key proxy informants are those likely to know the patient's practices, habits, and behaviors; informants are needed from each sphere of the patient's life (e.g., home, work, and leisure). However, because proxy interviews jeopardize patient confidentiality, TB control programs should establish clear guidelines for these interviews that recognize the challenge of maintaining confidentiality.

Field Investigation

Site visits are complementary to interviewing. They add contacts to the list and are the most reliable source of information regarding transmission settings (*17*). Failure to visit all potential sites of transmission has contributed to TB outbreaks (*25,44*). Visiting the index patient's residence is especially helpful for finding children who are contacts (*17,38*). The visit should be made ≤3 days of the initial interview. Each site visit creates opportunities to interview the index patient again, interview and test contacts, collect diagnostic sputum specimens, schedule clinic visits, and provide education. Sometimes environmental clues (e.g., toys suggesting the presence of children) create new directions for an investigation. Certain sites (e.g., congregate settings) require special arrangements to visit (see Contact Investigations in Special Circumstances). Physical conditions at each setting contribute to the likelihood of transmission. Pertinent details include room sizes, ventilation systems, and airflow patterns. These factors should be considered in the context of how often and how long the index patient was in each setting.

Follow-Up Steps

A continuing investigation is shaped by frequent reassessments of ongoing results (e.g., secondary TB cases and the estimated

infection rate for groups of contacts). Notification and follow-up communications with public health officials in other jurisdictions should be arranged for out-of-area contacts.

The following organizations provide resources to make referrals for contacts and index patients who migrate across the U.S.-Mexican border between the United States and Mexico:

- Cure TB (http://www.curetb.com), a referral program provided by the County of San Diego for TB patients and their contacts who travel between the United States and Mexico;
- Migrant Clinicians' Network (TB Net) (http://www.migrantclinician.org/network/tbnet), a multinational TB patient tracking and referral project designed to work with mobile, underserved populations; and
- Referral System for Binational TB Patients Pilot Project (http://www.borderhealth.org/files/res_329.doc), a collaborative effort between CDC and the National Tuberculosis Program in Mexico to improve continuity of care for TB patients migrating across the border (see Contact Investigations in Special Circumstances).

Specific Investigation Plan

The investigation plan starts with information gathered in the interviews and site visits; it includes a registry of the contacts and their assigned priorities (see Assigning Priorities to Contacts and Medical Treatment for Contacts with LTBI). A written timeline (Table 3) sets expectations for monitoring the progress of the investigation and informs public health officials whether additional resources are needed for finding, evaluating, and treating the high- and medium-priority contacts. The plan is a pragmatic work in progress and should be revised if additional information indicates a need (see When to Expand a Contact Investigation); it is part of the permanent record of the overall investigation for later review and program evaluation. Data from the investigation should be recorded on standardized forms (see Data Management and Evaluation of Contact Investigations).

Assigning Priorities to Contacts

The ideal goal would be to distinguish all recently infected contacts from those who are not infected and prevent TB disease by treating those with infection. In practice, existing technology and methods cannot achieve this goal. For example, although a relatively brief exposure can lead to *M. tuberculosis* infection and disease (*45*), certain contacts are not infected even after long periods of intensive exposure. Not all contacts with substantial exposure are identified during the contact investigation. Finally, available tests for *M. tuberculosis* infection lack sensitivity and specificity and do not differentiate between persons recently or remotely infected.

Increasing the intensity and duration of exposure usually increases the likelihood of recent *M. tuberculosis* infection in contacts. The skin test cannot discriminate between recent and old infections, and including contacts who have had minimal exposure increases the workload while it decreases the public health value of finding positive skin test results. A positive result in contacts with minimal exposure is more likely to be the result of an old infection or nonspecific tuberculin sensitivity (*46*). Whenever the contact's exposure to the index TB patient has occurred <8–10 weeks necessary for detection of positive skin tests, repeat testing 8–10 weeks after the most recent exposure will help identify recent skin test conversions, which are likely indicative of recent infection.

For optimal efficiency, priorities should be assigned to contacts, and resources should be allocated to complete all investigative steps for high- and medium-priority contacts. Priorities are based on the likelihood of infection and the potential hazards to the individual contact if infected. The priority scheme directs resources to selecting contacts who

TABLE 3. Time frames for initial follow-up of contacts of persons exposed to tuberculosis (TB)

Type of contact	Business days from listing of a contact to initial encounter*	Business days from initial encounter to completion of medical evaluation†
High-priority contact: index case AFB§ sputum smear positive or cavitary disease on chest radiograph (see Figure 2)	7	5
High-priority contact: index case AFB sputum smear negative (see Figure 3)	7	10
Medium-priority contact: regardless of AFB sputum smear or culture result (see Figures 2–4)	14	10

SOURCE: California Department of Health Services Tuberculosis Control Branch; California Tuberculosis Controllers Association. Contact investigation guidelines. Berkeley, CA: California Department of Health Services; 1998.

* A face-to-face meeting that allows the public-health worker to assess the overall health of the contact, administer a tuberculin skin test, and schedule further evaluation.

† The medical evaluation is complete when the contact's status with respect to *Mycobacterium tuberculosis* infection or TB disease has been determined. A normal exception to this schedule is the delay in waiting for final mycobacteriologic results, but this applies to relatively few contacts.

§ Acid-fast bacilli.

- have secondary cases of TB disease,
- have recent *M. tuberculosis* infection and so are most likely to benefit from treatment, and
- are most likely to become ill with TB disease if they are infected (i.e., susceptible contacts) or who could suffer severe morbidity if they have TB disease (i.e., vulnerable contacts).

Factors for Assigning Contact Priorities

Characteristics of the Index Patient

The decision to initiate a contact investigation is determined on the basis of the characteristics of the index patient (see Decisions to Initiate a Contact Investigation). Contacts of a more infectious index patient (e.g., one with AFB sputum smear positive TB) should be assigned a higher priority than those of a less infectious one because contacts of the more infectious patient are more likely to have recent infection or TB disease (*19,40,47–50*).

Characteristics of Contacts

Intrinsic and acquired conditions of the contact affect the likelihood of TB disease progression after infection, although the predictive value of certain conditions (e.g., being underweight for height) is imprecise as the sole basis for assigning priorities (*51,52*). The most important factors are age <5 years and immune status. Other medical conditions also might affect the probability of TB disease after infection.

Age. After infection, TB disease is more likely to occur in younger children; the incubation or latency period is briefer; and lethal, invasive forms of the disease are more common (*53–58*). The age-specific incidence of disease for children who have positive skin test results declines through age 4 years (*56*). Children aged <5 years who are contacts are assigned high priority for investigation.

A study of 82,269 tuberculin reactors aged 1–18 years who were control subjects in a Bacille Calmette-Guérin (BCG) trial* in Puerto Rico indicated that peak incidence of TB occurred among children aged 1–4 years (*56*). Infants and postpubertal adolescents are at increased risk for progression to TB disease if infected, and children aged <4 years are at increased risk for disseminated disease (*57*). The American Academy of Pediatrics also recommends primary prophylaxis for children aged <4 years (*57*). Guidelines published by ATS and CDC recommend primary prophylaxis for children aged <5 years (*6,59*). These guidelines are consistent with previous CDC recommendations in setting the cut-off at age <5 years for assigning priority and recommending primary prophylaxis (*6,59*).

* The age-cohort effect was strong in this study, but this factor is beyond the scope of these guidelines.

Immune status. HIV infection results in the progression of *M. tuberculosis* infection to TB disease more frequently and more rapidly than any other known factor, with disease rates estimated at 35–162 per 1,000 person-years of observation and a greater likelihood of disseminated and extrapulmonary disease (*60–64*). HIV-infected contacts are assigned high priority, and, starting at the time of the initial encounter, extra vigilance for TB disease is recommended.

Contacts receiving >15 mg of prednisone or its equivalent for >4 weeks also should be assigned high priority (*6*). Other immunosuppressive agents, including multiple cancer chemotherapy agents, antirejection drugs for organ transplantation, and tumor necrosis factor alpha (TNF-α) antagonists, increase the likelihood of TB disease after infection; these contacts also are assigned a high priority (*65*).

Other medical conditions. Being underweight for their height has been reported as a weakly predictive factor promoting progression to TB disease (*66*); however, assessing weight is not a practical approach for assigning priorities. Other medical conditions that can be considered in assigning priorities include silicosis, diabetes mellitus, and status after gastrectomy or jejunoileal bypass surgery (*67–76*).

Exposure. Air volume, exhaust rate, and circulation predict the likelihood of transmission in an enclosed space. In large indoor settings, because of diffusion and local circulation patterns, the degree of proximity between contacts and the index patient can influence the likelihood of transmission. Other subtle environmental factors (e.g., humidity and light) are impractical to incorporate into decision making. The terms "close" and "casual," which are frequently used to describe exposures and contacts, have not been defined uniformly and therefore are not useful for these guidelines.

The most practical system for grading exposure settings is to categorize them by size (e.g., "1" being the size of a vehicle or car, "2" the size of a bedroom, "3" the size of a house, and "4" a size larger than a house [*16*]). This has the added advantage of familiarity for the index patient and contacts, which enables them to provide clearer information.

The volume of air shared between an infectious TB patient and contacts dilutes the infectious particles, although this relationship has not been validated entirely by epidemiologic results (*15,77–79*). Local circulation and overall room ventilation also dilute infectious particles, but both factors can redirect exposure into spaces that were not visited by the index patient (*80–83*). These factors have to be considered.

The likelihood of infection depends on the intensity, frequency, and duration of exposure (*16,17,40,84*). For example, airline passengers who are seated for ≥8 hours in the same or adjoining row as a person who is contagious are much more likely to be infected than other passengers (*85–88*). One set

of criteria for estimating risk after exposure to a person with pulmonary TB without lung cavities includes a cut-off of 120 hours of exposure per month (*84*). However, for any specific setting, index patient, and contacts, the optimal cut-off duration is undetermined. Administratively determined durations derived from local experience are recommended, with frequent reassessments on the basis of results.

Classification of Contacts

Priorities for contact investigation are determined on the basis of the characteristics of the index patient, susceptibility and vulnerability of contacts, and circumstances of the exposures (Figures 2–4). Any contacts who are not classified as high or medium priority are assigned a low priority. Because priority assignments are practical approximations derived from imperfect information, priority classifications should be reconsidered throughout the investigation as findings are analyzed (see When to Expand a Contact Investigation).

Diagnostic and Public Health Evaluation of Contacts

On average, 10 contacts are listed for each person with a case of infectious TB in the United States (*50,59,89*). Approximately 20%–30% of all contacts have LTBI, and 1% have TB disease (*50*). Of those contacts who ultimately will have TB disease, approximately half acquire disease in the first year after exposure (*90,91*). For this reason, contact investigations constitute a crucial prevention strategy.

Identifying TB disease and LTBI efficiently during an investigation requires identifying, locating, and evaluating high- and medium-priority contacts who are most at risk. Because they have legally mandated responsibilities for disease control, health departments should establish systems for comprehensive TB contact investigations. In certain jurisdictions, legal measures are in place to ensure that evaluation and follow-up of contacts occur. The use of existing communicable disease laws that protect the health of the community (if applicable to contacts) should be considered for contacts who decline examinations, with the least restrictive measures applied first.

Initial Assessment of Contacts

During the initial contact encounter, which should be accomplished within 3 working days of the contact having been listed the investigation, the investigator gathers background health information and makes a face-to-face assessment of the person's health. Administering a skin test at this time accelerates the diagnostic evaluation.

The health department record should include:

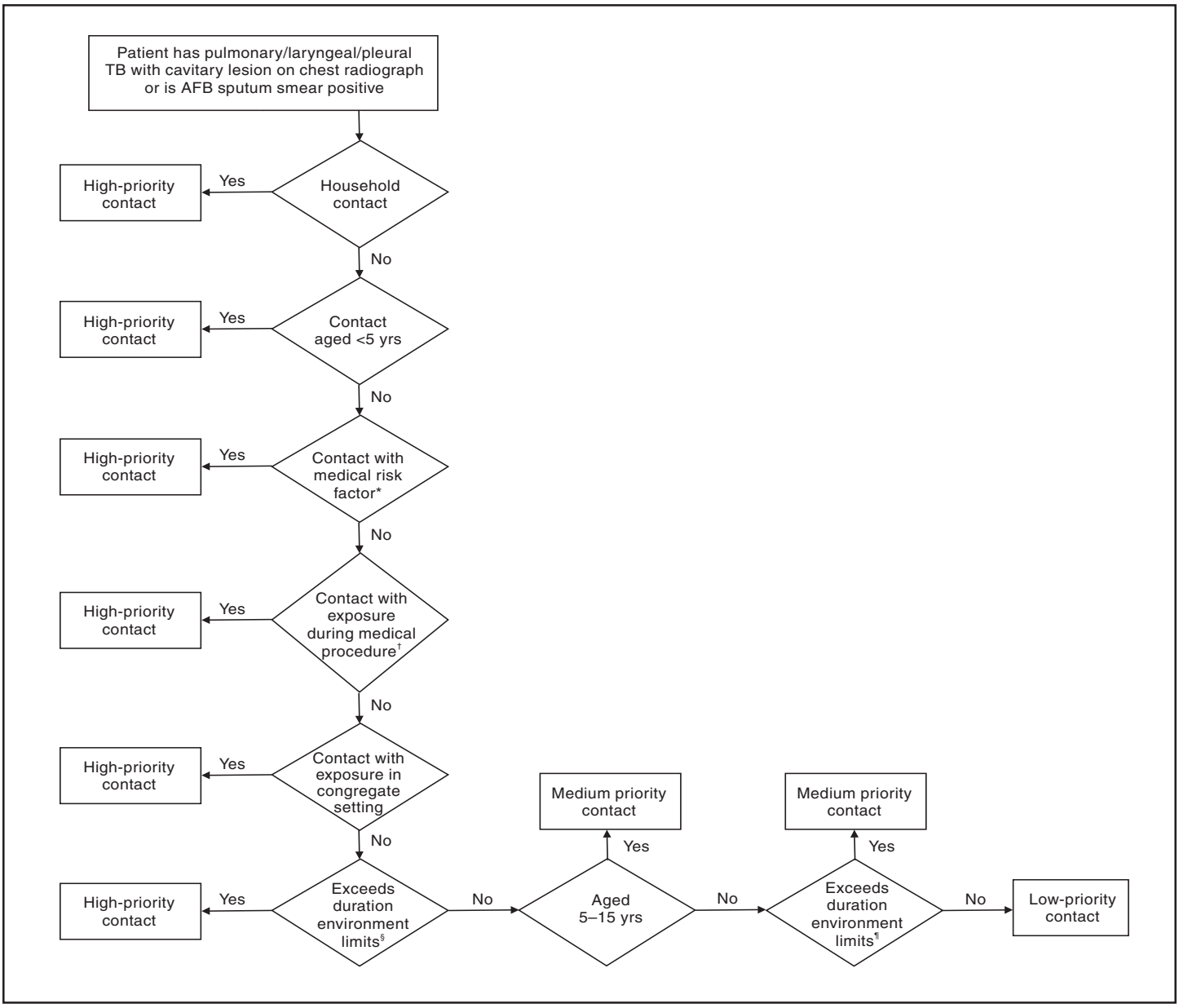
- previous *M. tuberculosis* infection or disease and related treatment;
- contact's verbal report and documentation of previous TST results;
- current symptoms of TB illness (e.g., cough, chest pain, hemoptysis, fever, chills, night sweats, appetite loss, weight loss, malaise, or easy fatigability);
- medical conditions or risk factors making TB disease more likely (e.g., HIV infection, intravenous drug use, diabetes mellitus, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, head or neck cancer, hematological and reticuloendothelial diseases, end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, or low body weight);
- mental health disorders (e.g., psychiatric illnesses and substance abuse disorders);
- type, duration, and intensity of TB exposure; and
- sociodemographic factors (e.g., age, race or ethnicity, residence, and country of birth) (see Data Management and Evaluation of Contact Investigations).

Contacts who do not know their HIV-infection status should be offered HIV counseling and testing. Each contact should be interviewed regarding social, emotional, and practical matters that might hinder their participation (e.g., work or travel).

When initial information has been collected, priority assignments should be reassessed for each contact, and a medical plan for diagnostic tests and possible treatment can be formulated for high- and medium-priority contacts. Low-priority contacts should not be included unless resources permit and the program is meeting its performance goals.

In 2002, for the first time, the percentage of TB patients who were born outside the United States was >50%; this proportion continues to increase (*92*). Because immigrants are likely to settle in communities in which persons of similar origin reside, multiple contacts of foreign-born index patients also are foreign born. Contacts who come from countries where both BCG vaccination and TB are common are more likely than other immigrants to have positive skin tests results when they arrive in the United States. They also are more likely to demonstrate the booster phenomenon on a postexposure test (*17,40*). Although valuable in preventing severe forms of disease in young children in countries where TB is endemic, BCG vaccination provides imperfect protection and causes tuberculin sensitivity in certain recipients for a variable period of time (*93,94*). TSTs cannot distinguish reactions related to remote infection or BCG vaccination from those caused by recent infection with *M. tuberculosis*; boosting related to BCG or remote infection compounds the interpretation of positive results (*95*).

FIGURE 2. Prioritization of contacts exposed to persons with acid-fast bacilli (AFB) sputum smear-positive or cavitary tuberculosis (TB) cases



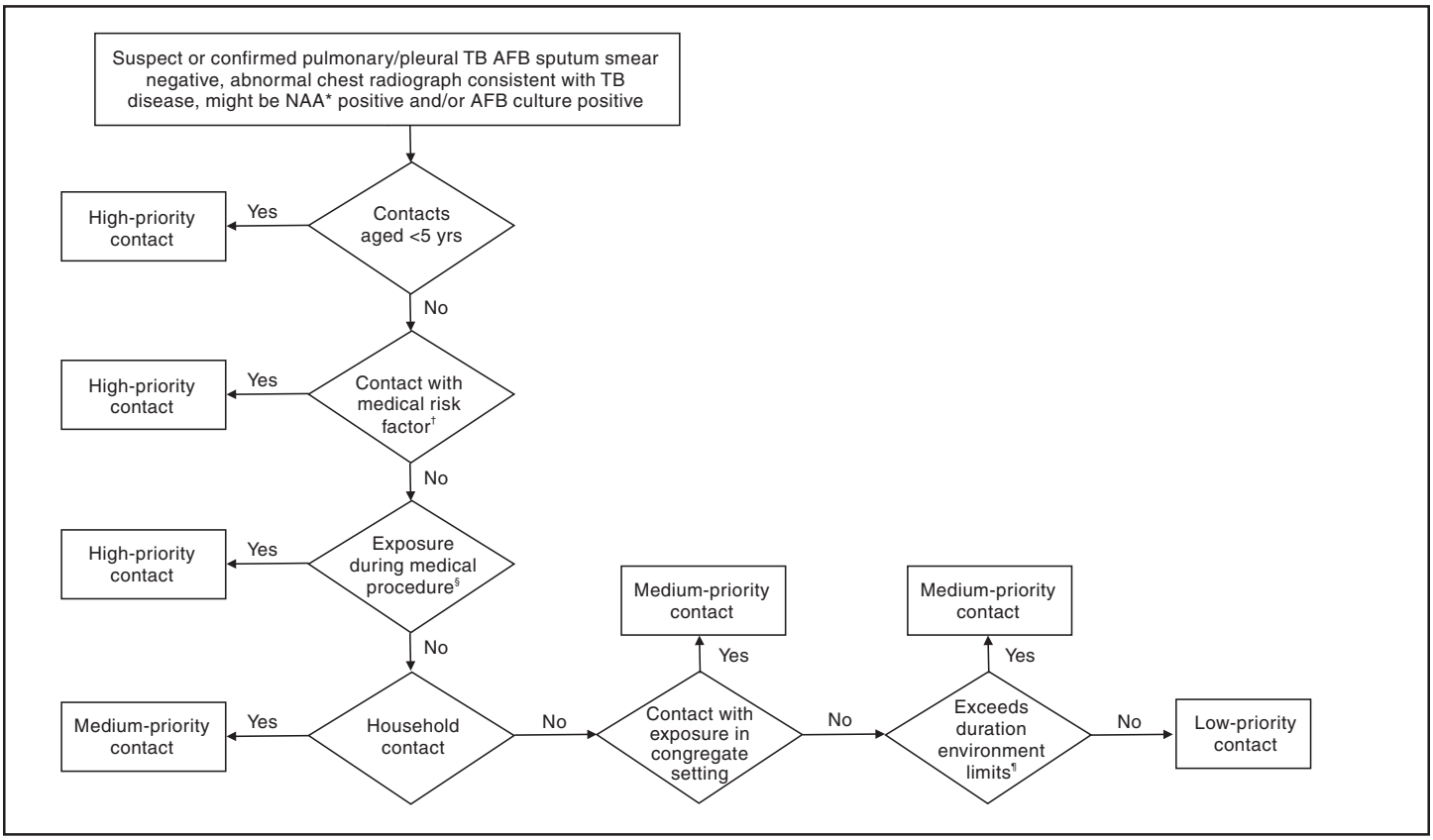
* Human immunodeficiency virus or other medical risk factor.
† Bronchoscopy, sputum induction, or autopsy.
§ Exposure exceeds duration/environment limits per unit time established by the health department for high-priority contacts.
¶ Exposure exceeds duration/environment limits per unit time established by the health department for medium-priority contacts.

A positive TST in a foreign-born or BCG-vaccinated person should be interpreted as evidence of recent *M. tuberculosis* infection in contacts of persons with infectious cases. These contacts should be evaluated for TB disease and offered a course of treatment for LTBI.

Voluntary HIV Counseling, Testing, and Referral

Approximately 9% of TB patients in the United States have HIV infection at the time of TB diagnosis, with 16% of TB patients aged 25–44 years having HIV infection (*96*). In addition, an estimated 275,000 persons in the United States are unaware they have HIV infection (*97*). The majority of

FIGURE 3. Priority assignments for contacts exposed to persons with acid-fast bacilli (AFB) sputum smear-negative tuberculosis (TB) cases



* Nucleic acid assay.
† Human immunodeficiency virus or other medical risk factor.
§ Bronchoscopy, sputum induction, or autopsy.
¶ Exposure exceeds duration/environment limits per unit time established by local TB control program for medium-priority contacts.

TB contacts have not been tested for HIV infection (*98*). Contacts of HIV-infected index TB patients are more likely to be HIV infected than contacts of HIV-negative patients (*99*).

Voluntary HIV counseling, testing, and referral for contacts are key steps in providing optimal care, especially in relation to TB (*100,101*). Systems for achieving convenient HIV-related services require collaboration with health department HIV-AIDS programs. This also can improve adherence to national guidance for these activities (*100*).

Tuberculin Skin Testing

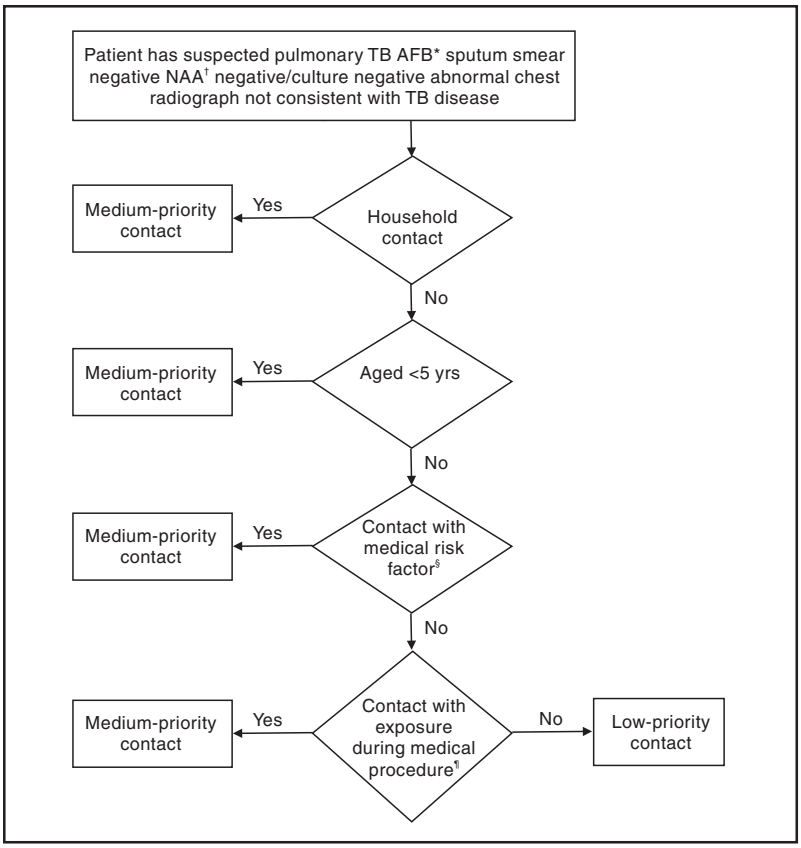
All contacts classified as having high or medium priority who do not have a documented previous positive TST result or previous TB disease should receive a skin test at the initial encounter. If that is not possible, then the test should be administered ≤7 working days of listing high-priority contacts and ≤14 days of listing medium-priority contacts. For interpreting the skin test reaction, an induration transverse diameter of ≥5 mm is positive for any contact (*1*)

Serial tuberculin testing programs routinely administer a two-step test at entry into the program. This detects boosting of sensitivity and can avoid misclassifying future positive results as new infections. The two-step procedure typically should not be used for testing contacts; a contact whose second test result is positive after an initial negative result should be classified as recently infected.

Postexposure Tuberculin Skin Testing

Among persons who have been sensitized by *M. tuberculosis* infection, the intradermal tuberculin from the skin test can result in a delayed-type (cellular) hypersensitivity reaction. Depending on the source of recommendations, the estimated interval between infection and detectable skin test reactivity (referred to as the window period) is 2–12 weeks (*6,95*). However, reinterpretation of data collected previously indicates that 8 weeks is the outer limit of this window period (*46,102–106*). Consequently, NTCA and CDC recommend that the window period be decreased to 8–10 weeks after

FIGURE 4. Prioritization of contacts exposed to persons with suspected tuberculosis (TB) cases with abnormal chest radiographs not consistent with TB disease



* Acid-fast bacilli.
† Nucleic acid assay.
§ Human immunodeficiency virus infection or other medical risk factor.
¶ Bronchoscopy, sputum induction, or autopsy.

exposure ends. A negative test result obtained <8 weeks after exposure is considered unreliable for excluding infection, and a follow-up test at the end of the window period is therefore recommended.

Low-priority contacts have had limited exposure to the index patient and a low probability of recent infection; a positive result from a second skin test among these contacts would more likely represent boosting of sensitivity. A single skin test, probably at the end of the window period, is preferred for these contacts. However, diagnostic evaluation of any contact who has TB symptoms should be immediate, regardless of skin test results.

Nonspecific or remote delayed-type hypersensitivity (DTH) response to tuberculin (PPD in the skin test) occasionally wanes or disappears over time. Subsequent TSTs can restore responsiveness; this is called boosting or the booster phenomenon (*95,107*). For contacts who receive two skin tests, the booster phenomenon can be misinterpreted as evidence of recent infection. This misinterpretation is more likely to occur for foreign-born contacts than it is for those born in the United States (*17,108*).

Skin test conversion refers to a change from a negative to a positive result. To increase the relative certainty that the person has been infected with *M. tuberculosis* in the interval between tests, the standard U.S. definition for conversion includes a maximum time (2 years) between skin tests and a minimum increase (10 mm) in reaction size (*6,34*). With the 5 mm cut-off size used for interpreting any single skin test result obtained in contact investigations, the standard definition for conversion typically is irrelevant. For these guidelines, contacts who have a positive result after a previous negative result are said to have had a change in tuberculin status from negative to positive.

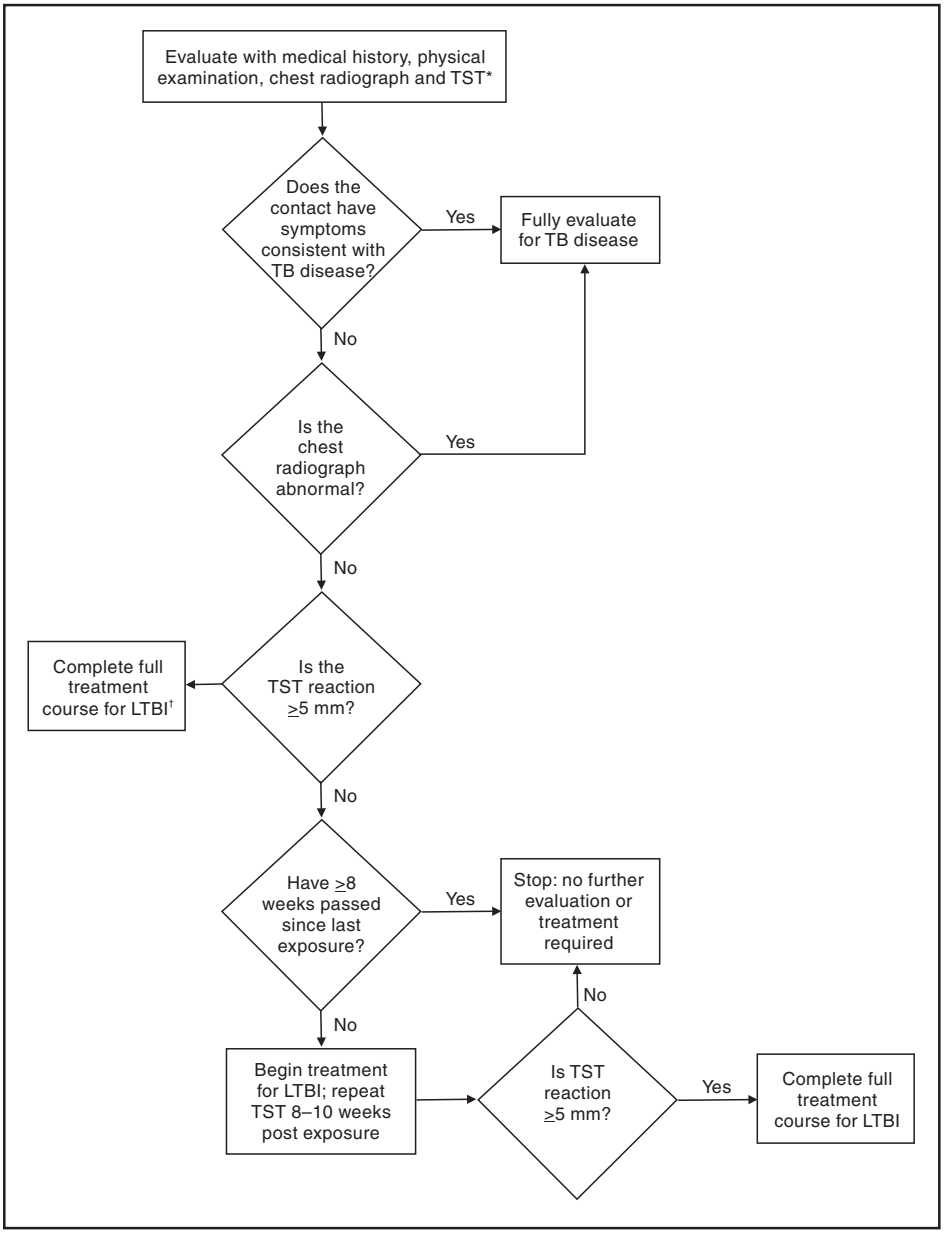
Medical Evaluation

All contacts whose skin test reaction induration diameter is ≥5 mm or who report any symptoms consistent with TB disease should undergo further examination and diagnostic testing for TB (*6*), starting typically with a chest radiograph. Collection of specimens for mycobacteriologic testing (e.g., sputa) is decided on a case-by-case basis and is not recommended for healthy contacts with normal chest radiographs. All contacts who are assigned a high priority because of special susceptibility or vulnerability to TB disease should undergo further examination and diagnostic testing regardless of whether they have a positive skin test result or are ill.

Evaluation and Follow-Up of Specific Groups of Contacts

Because children aged <5 years are more susceptible to TB disease and more vulnerable to invasive, fatal forms of TB disease, they are assigned a high priority as contacts and should receive a full diagnostic medical evaluation, including a chest radiograph (Figure 5). If an initial skin test induration diameter is <5 mm and the interval since last exposure is <8 weeks, treatment for presumptive *M. tuberculosis* infection (i.e., window prophylaxis) is recommended after TB disease has been excluded by medical examination. After a second skin test administered 8–10 weeks postexposure, the decision to treat is reconsidered. If the second test result is negative, treatment should be discontinued and the child, if healthy, should be discharged from medical supervision. If the second result is

FIGURE 5. Evaluation, treatment, and follow-up of tuberculosis (TB) contacts aged <5 years



* Tuberculin skin test.
† Latent TB infection.

positive, the full course of treatment for latent *M. tuberculosis* infection should be completed.

Contacts with immunocompromising conditions (e.g., HIV infection) should receive similar care (Figure 6). In addition, even if a TST administered ≥8 weeks after the end of exposure yields a negative result, a full course of treatment for latent *M. tuberculosis* infection is recommended after a medical evaluation to exclude TB disease (*16*). The decision to administer complete treatment can be modified by other evidence concerning the extent of transmission that was estimated from the contact investigation data.

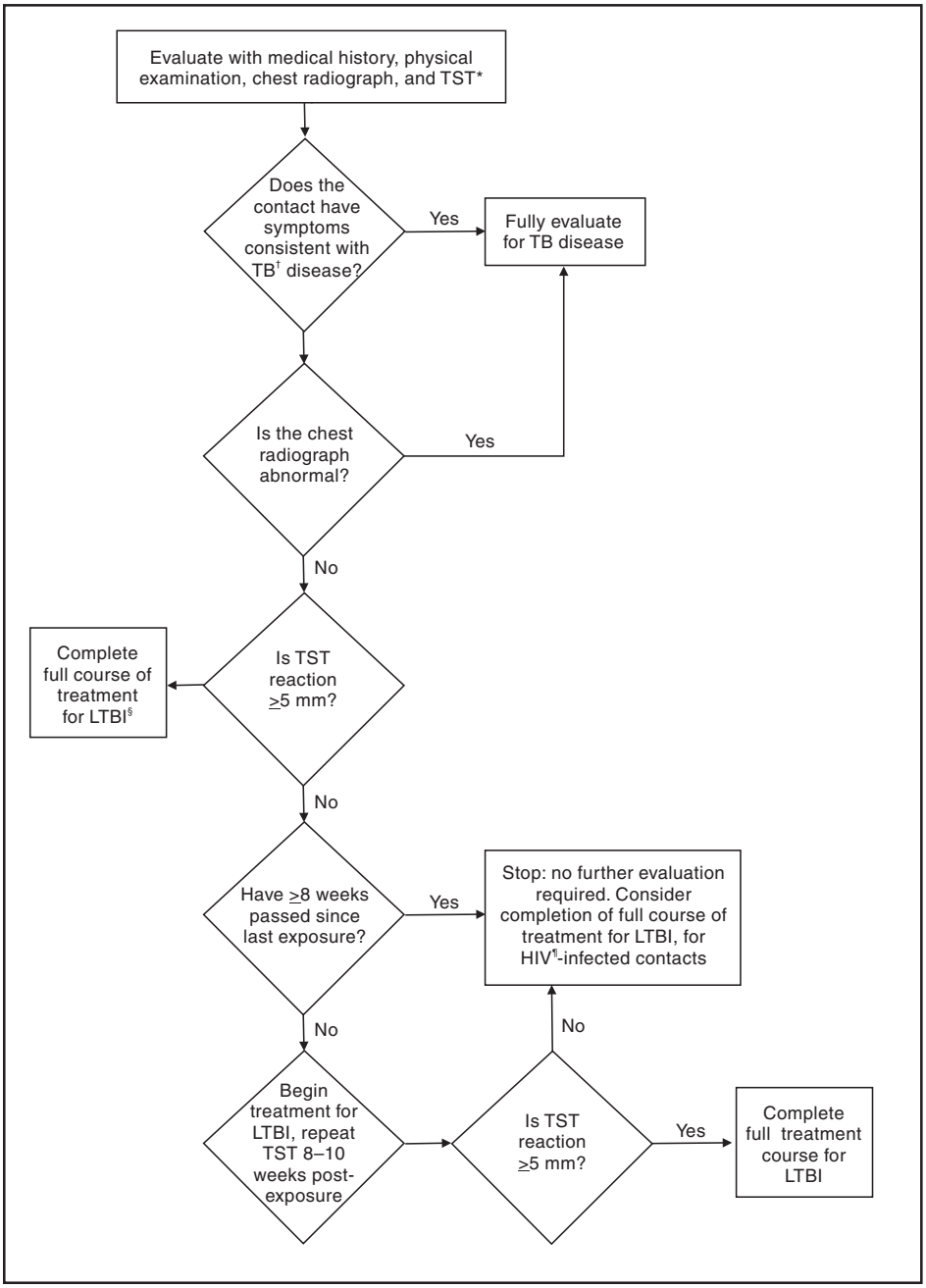
The majority of other high- or medium priority contacts who are immunocompetent adults or children aged ≥5 years can be tested and evaluated as described (Figure 7). Treatment is recommended for contacts who receive a diagnosis of latent *M. tuberculosis* infection.

Evaluation of low-priority contacts who are being tested can be scheduled with more flexibility (Figure 8). The skin test may be delayed until after the window period, thereby negating the need for a second test. Treatment is also recommended for these contacts if they receive a diagnosis of latent *M. tuberculosis* infection.

The risk for TB disease is undetermined for contacts with documentation of a previous positive TST result (whether infection was treated) or TB disease (Figure 9). Documentation is recommended before making decisions from a contact's verbal report. Contacts who report a history of infection or disease but who do not have documentation are recommended for the standard algorithm (Figure 8). Contacts who are immunocompromised or otherwise susceptible are recommended for diagnostic testing to exclude TB disease and for a full course of treatment for latent *M. tuberculosis* infection after TB disease has been excluded, regardless of their previous TB history and documentation. Healthy contacts who have a documented previous positive skin test result but have not been treated for LTBI can be considered for treatment as part of the contact investigation. Any contact who is to be treated for LTBI should have a chest radiograph to exclude TB disease before starting treatment.

Certain guidance regarding collecting historic information from TB patients or contacts stipulates confirmation of previous TST results (e.g., a documented result from a TST) (*4*). The decision regarding requiring documentation for a specific detail involves a subtle balance. Memory regarding medi-

FIGURE 6. Evaluation, treatment, and follow-up of immunocompromised contacts



* Tuberculin skin test.
† Tuberculosis.
§ Latent TB infection.
¶ Human immunodeficiency virus.

cal history might be weak or distorted, even among medically trained persons. However, the accuracy of details reported by a TB patient or contact might not be relevant for providing medical care or collecting data. For previous TST results, patients can be confused regarding details from their history; routine skin tests sometimes are administered at the same time as vaccinations, and foreign-born patients might confuse a skin test with BCG vaccination or streptomycin injections. For contacts (but not patients with confirmed TB), a skin test result is critical, and documentation of a previous positive result should be obtained before omitting the skin test from the diagnostic evaluation.

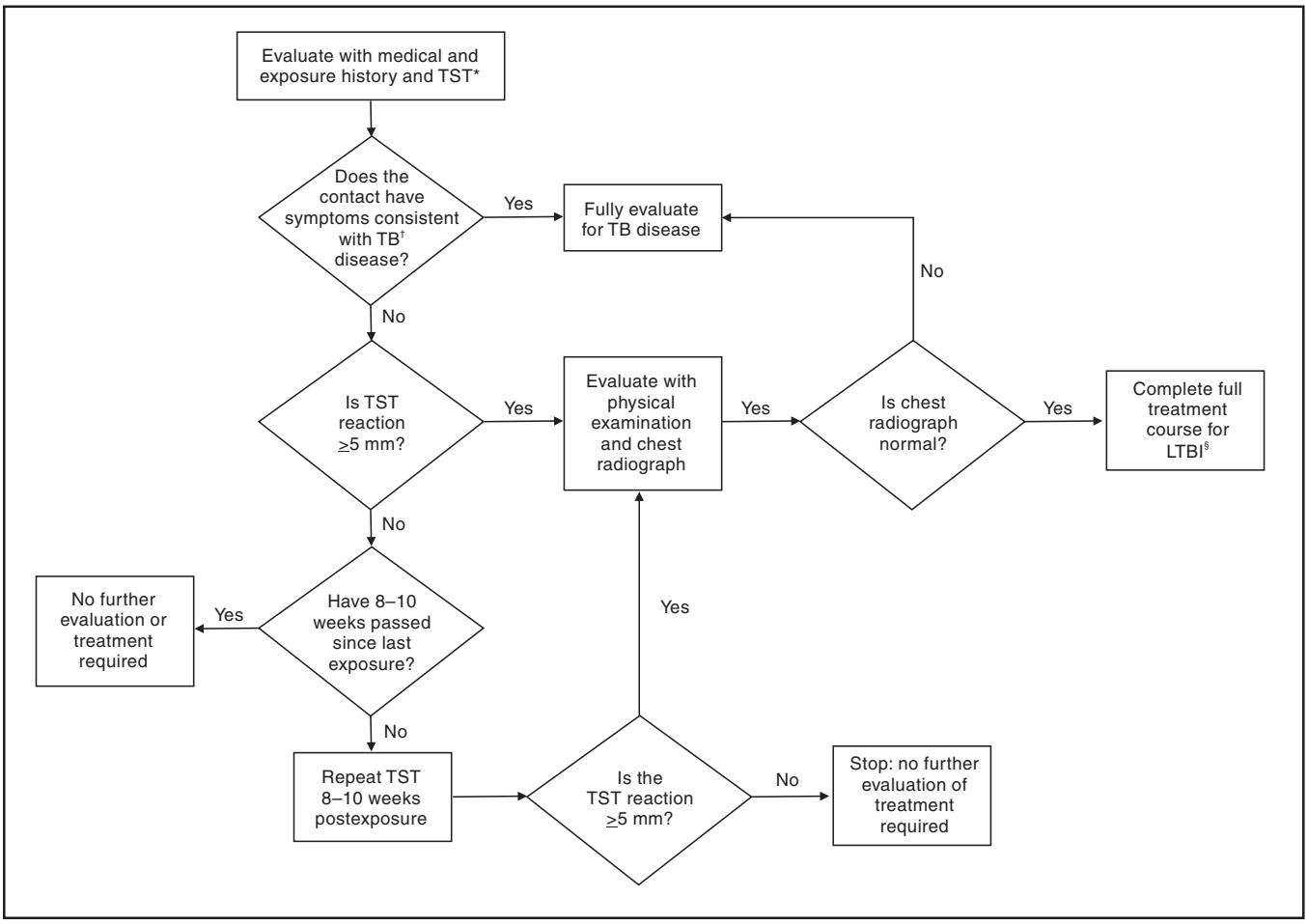
Treatment for Contacts with LTBI

The direct benefits of contact investigations include 1) finding additional TB disease cases (thus potentially interrupting further transmission) and 2) finding and treating persons with LTBI. One of the national health objectives for 2010 (objective no. 14-13) is to complete treatment in 85% of contacts who have LTBI (*107*). However, reported rates of treatment initiation and completion have fallen short of national objectives (*17,50,109,110*). To increase these rates, health department TB control programs must invest in systems for increasing the numbers of infected contacts who are completely treated. These include 1) focusing resources on the contacts most in need of treatment; 2) monitoring treatment, including that of contacts who receive care outside the health department; and 3) providing directly observed therapy (DOT), incentives, and enablers.

Contacts identified as having a positive TST result are regarded as recently infected with *M. tuberculosis*, which puts them at heightened risk for TB disease (*6,7*). Moreover, contacts with greater durations or intensities of exposure are more likely both to be infected and to have TB disease if infected. A focus first on high-priority and next on medium-priority contacts is recommended in allocating resources for starting and completing treatment of contacts.

Decisions to treat contacts who have documentation of a previous positive skin test result or TB disease for presumed LTBI must be individualized because their risk for TB disease is unknown. Considerations for the decision include previous

FIGURE 7. Evaluation, treatment, and follow-up of immunocompetent adults and children aged ≥5 years (high- and medium-priority contacts)



* Tuberculin skin test.
† Tuberculosis.
§ Latent TB infection.

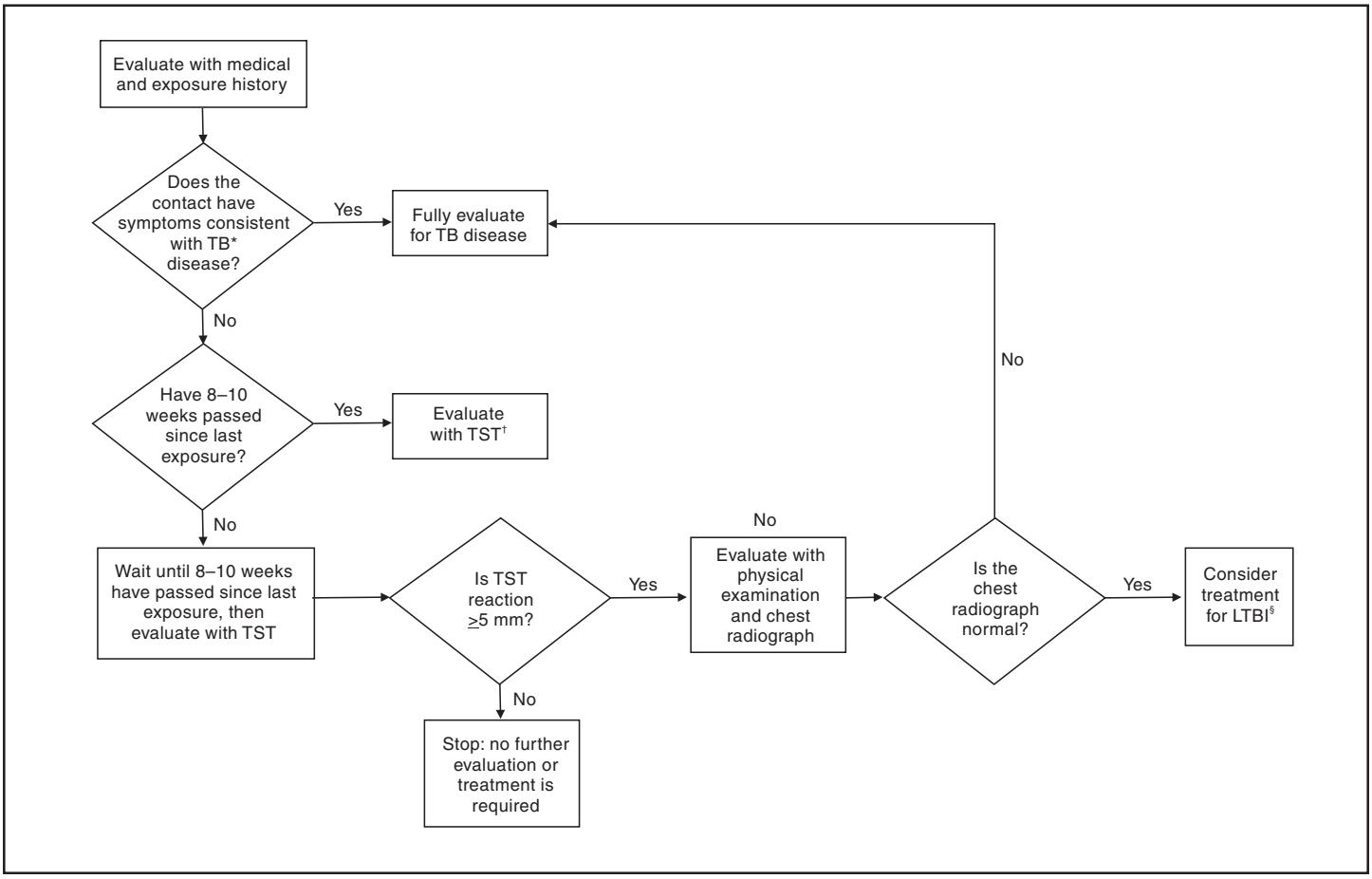
treatment for LTBI, medical conditions putting the contact at risk for TB disease, and the duration and intensity of exposure. Treatment of presumed LTBI is recommended for all HIV-infected contacts in this situation (after TB disease has been excluded), whether they received treatment previously.

Window-Period Prophylaxis

Treatment during the window period (see Diagnostic and Public Health Evaluation of Contacts) has been recommended for susceptible and vulnerable contacts to prevent rapidly emerging TB disease (*4,6,56,61,111*). The evidence for this practice is inferential, but all models and theories support it. Groups of contacts who are likely to benefit from a full course of treatment (beyond just window-period treatment) include those with HIV infection, those taking immunosuppressive therapy for organ transplantation, and persons taking TNF-α antagonists (*6,61,62,65*). The risks for TB are less clear for patients who chronically take the equivalent of >15 mg per day of prednisone (*6*). TB disease having been ruled out, prophylactic treatment of presumed *M. tuberculosis* infection is recommended as an option for all these groups. The decision as to whether to treat individual contacts who have negative skin test results should take into consideration two factors:

- the frequency, duration, and intensity of exposure (even brief exposure to a highly contagious TB patient in a confined space probably warrants the same concern as extended exposure to less contagious patients); and
- corroborative evidence of transmission from the index patient (a substantial fraction of contacts having positive skin test results implies contagiousness).

FIGURE 8. Evaluation, treatment, and follow-up of low-priority contacts



* Tuberculosis.
† Tuberculin skin test.
§ Latent TB infection.

Treatment after Exposure to Drug-Resistant TB

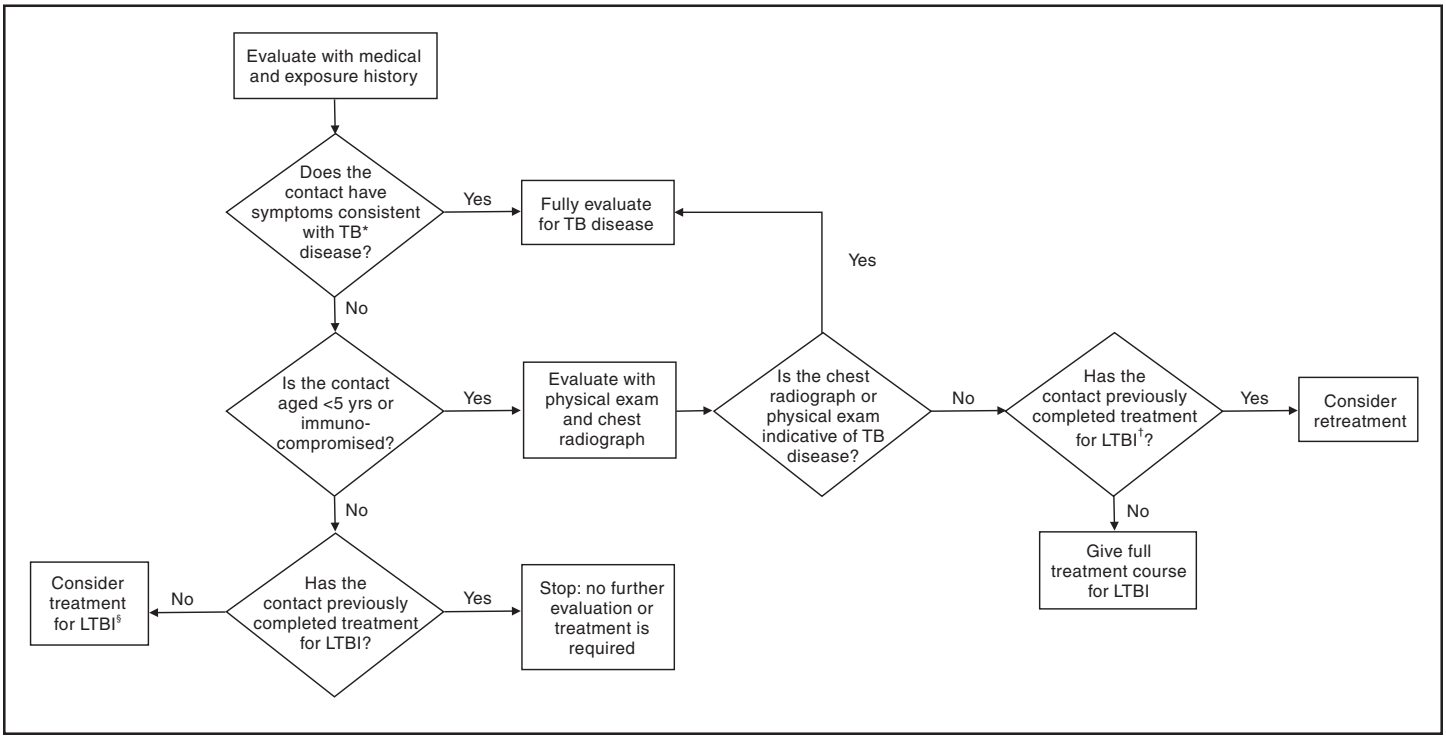
Guidelines for providing care to contacts of drug-resistant TB patients and selecting treatment regimens have been published (*6,7,112*). Drug susceptibility results for the *M. tuberculosis* isolate from the index patient (i.e., the presumed source of infection) are necessary for selecting or modifying the treatment regimen for the exposed contact. Resistance only to INH among the first line agents leaves the option of 4 months of daily rifampin. Additional resistance to rifampin constitutes MDR TB. None of the potential regimens for persons likely infected with MDR TB has been tested fully for efficacy, and these regimens are often poorly tolerated. For these reasons, consultation with a physician with expertise in this area is recommended for selecting or modifying a regimen and managing the care of contacts (*6*). Contacts who have received a diagnosis of infection attributed to MDR TB should be monitored for 2 years after exposure; guidelines for monitoring these contacts have been published previously (*6*).

Adherence to Treatment

One of the national health objectives for 2010 is to achieve a treatment completion rate of 85% for infected contacts who start treatment (objective no. 14-13) (*107*). However, operational studies indicate that this objective is not being achieved (*17,110*). Although DOT improves completion rates (*17*), it is a resource-intensive intervention that might not be feasible for all infected contacts. The following order of priorities is recommended when selecting contacts for DOT (including window-period prophylaxis):

- contacts aged <5 years,
- contacts who are HIV infected or otherwise substantially immunocompromised,
- contacts with a change in their tuberculin status from negative to positive, and

FIGURE 9. Evaluation, treatment, and follow-up of contacts with a documented previously positive tuberculin skin test



* Tuberculosis.
† Latent TB infection.
§ Before initiation of treatment, contacts should be evaluated fully for TB disease.

- contacts who might not complete treatment because of social or behavior impediments (e.g., alcohol addiction, chronic mental illness, injection-drug use, unstable housing, or unemployment).

Checking monthly or more often for adherence and adverse effects of treatment by home visits, pill counts, or clinic appointments is recommended for contacts taking self-supervised treatment. All contacts being treated for infection should be evaluated in person by a health-care provider at least monthly. Incentives (e.g., food coupons or toys for children) and enablers (e.g., transportation vouchers to go to the clinic or pharmacy) are recommended as aids to adherence. Incentives provide simple rewards whereas enablers increase a patient's opportunities for adherence. Education regarding TB, its treatment, and the signs of adverse drug effects should be part of each patient encounter.

When to Expand a Contact Investigation

A graduated approach to contact investigations (i.e., a concentric circles model) has been recommended previously (*4,5,113*). With this model, if data indicate that contacts with the greatest exposure have an infection rate greater than would be expected in their community, contacts with progressively less exposure are sought. The contact investigation would expand until the rate of positive skin test results for the contacts was indistinguishable from the prevalence of positive results in the community (*5*). In addition to its simplicity and intuitive appeal, an advantage to this approach is that contacts with less exposure are not sought until evidence of transmission exists. Disadvantages are that 1) surrogates for estimating exposure (e.g., living in the same household) often do not predict the chance of infection, 2) the susceptibility and vulnerability of contacts are not accommodated by the model, and 3) the estimated prevalence for tuberculin sensitivity in a specific community generally is unknown. In addition, when the prevalence for a community is known but is substantial (e.g., >10%), the end-point for the investigation is obscured.

Recent operational studies indicate that health departments are not meeting their objectives for high- and medium-priority contacts (*17,50,109*). In these settings, contact investigations generally should not be expanded beyond high- and medium-priority contacts. However, if data from an investigation indicate more transmission than anticipated, more contacts might need to be included.

When determining whether to expand the contact investigation, consideration of the following factors is recommended:

- achievement of program objectives with high- and medium-priority contacts; and
- extent of recent transmission, as evidenced by
  - — unexpectedly high rate of infection or TB disease in high-priority contacts (e.g., 10% or at least twice the rate of a similar population without recent exposure, whichever is greater),
  - — evidence of secondary transmission (i.e., from TB patients who were infected after exposure to the source patient),
  - — TB disease in any contacts who had been assigned a low priority,
  - — infection of contacts aged <5 years, and
  - — contacts with change in skin test status from negative to positive between their first and second TST.

In the absence of evidence of recent transmission, an investigation should not be expanded to lower priority contacts. When program-evaluation objectives are not being achieved, a contact investigation should be expanded only in exceptional circumstances, generally those involving highly infectious persons with high rates of infection among contacts or evidence for secondary cases and secondary transmission. Expanded investigations must be accompanied by efforts to ensure completion of therapy.

The strategy for expanding an investigation should be derived from the data obtained from the investigation previously (*4,5,43*). The threshold for including a specific contact thereby is decreased. As in the initial investigation, results should be reviewed at least weekly so the strategy can be reassessed.

At times, results from an investigation indicate a need for expansion that available resources do not permit. In these situations, seeking consultation and assistance from the next higher level in public health administration (e.g., the county health department consults with the state health department) is recommended. Consultation offers an objective review of strategy and results, additional expertise, and a potential opportunity to obtain personnel or funds for meeting unmet needs.

Communicating Through the Media

Routine contact investigations, which have perhaps a dozen contacts, are not usually considered newsworthy. However, certain contact investigations have potential for sensational coverage and attract attention from the media. Typical examples include situations involving numerous contacts (especially children), occurring in public settings (e.g., schools, hospitals, prisons), occurring in workplaces, associated with TB fatalities, or associated with drug-resistant TB.

Reasons for Participating in Media Coverage

Media coverage can provide both advantages and drawbacks for the health department, and careful planning is recommended before communicating with reporters. Favorable, accurate coverage

- educates the public regarding the nature of TB,
- reminds the public of the continued presence of TB in the community,
- provides a complementary method to alert exposed contacts of the need for seeking a medical evaluation,
- relieves unfounded public fears regarding TB,
- illustrates the health department's leadership in communicable disease control,
- ensures that constructive public inquiries are directed to the health department, and
- validates the need for public resources to be directed to disease control.

Potential drawbacks of media coverage are that such coverage can

- increase public anxiety, especially after alarmist or inaccurate messages,
- lead unexposed persons seeking unnecessary health care because of a perceived threat,
- contribute to unfavorable views of the health department (e.g., because of perceived delays in responding to the TB problem),
- contribute to spread of misinformation regarding the nature of TB,
- trigger unconstructive public inquiries, and
- lead to disclosure of confidential information (e.g., patient identity).

Strategy for Media Coverage

Anticipatory preparation of clear media messages, coordinated among all parties for clarity and consistency, is recommended. The majority of health departments have formal policies and systems for arranging media communications, and TB control officials are advised to work with their media-communications services in securing training and preparing media messages anticipating news coverage. In certain instances, this will require coordination among local, state, and federal public health organizations. Issuing a press release in advance of any other media coverage is recommended so as to provide clear, accurate messages from the start. Waiting

until a story reaches the media through other sources leaves the health department reacting to inaccuracies in the story and could lend credence to a perception that information is being withheld from the public.

Certain newsworthy contact investigations involve collaborators outside of the health department because of the setting (e.g., a homeless shelter). The administrators of these settings are likely to have concerns, distinct from the public health agenda, regarding media coverage. For example, a hospital administrator might worry that reports of suspected TB exposures in the hospital will create public distrust of the hospital. Collaboration on media messages is a difficult but necessary part of the overall partnership between the hospital (in this example) and the health department. Early discussions regarding media coverage are recommended for reducing later misunderstandings. In addition, development of a list of communication objectives also is recommended in preparing for media inquiries.

Data Management and Evaluation of Contact Investigations

Data collection related to contact investigations has three broad purposes: 1) management of care and follow-up for individual index patients and contacts, 2) epidemiologic analysis of an investigation in progress and investigations overall, and 3) program evaluation using performance indicators that reflect performance objectives. A systematic, consistent approach to data collection, organization, analysis, and dissemination is required (*114–117*).

Data collection and storage entail both substantial work and an investment in systems to obtain full benefits from the efforts. Selecting data for inclusion requires balancing the extra work of collecting data against the lost information if data are not collected. If data are collected but not studied and used when decisions are made, then data collection is a wasted effort. The most efficient strategy for determining which data to collect is to work back from the intended uses of the data.

Reasons Contact Investigation Data Are Needed

For each index patient and the patient's associated contacts, a broad amount of demographic, epidemiologic, historic, and medical information is needed for providing comprehensive care (Tables 2, 4, and 5). In certain instances, such care can last >1 year, so information builds by steps and has numerous longitudinal elements (e.g., number of clinic visits attended, number of treatment doses administered, or mycobacteriologic response to treatment). Data on certain process steps are necessary for monitoring whether the contact investigation is keeping to timeline objectives (e.g., how soon after listing the skin test is administered to a contact).

Aggregated data collected during an investigation inform public health officials whether the investigation is on time and complete. The ongoing analysis of data also contributes to reassessment of the strategy used in the investigation (e.g., whether the infection rate was greater for contacts believed to have more exposure).

Data from a completed investigation and from all investigations in a fixed period (e.g., 6 months) might demonstrate progress in meeting program objectives (Box 2). However, these core measurements for program evaluation cannot directly demonstrate why particular objectives were not

TABLE 4. Minimal recommended data concerning the index patient

Identifiers and demographic information
Case manager
Name and aliases
For minors and dependents, guardian information
Date of birth*
Social security number
Current locating information and emergency contacts
Residences during infectious period if unstably housed
RVCT number* and local case number
Sex*
Race*
Ethnicity*
Country of birth*
If foreign born, length of time in United States*
Primary language and preferred language
Methods of translation or interpretation
Settings in which index patient might have transmitted tuberculosis (TB) and associated timeframes
Living situation(s)
Employment or school
Social and recreational activities
Congregate settings (e.g. jail or homeless shelter)*
Substance abuse with social implications (e.g., crack cocaine)*
TB information
Health-care provider for TB (e.g., public health, private, both, other)*
Anatomic site of disease*
Symptoms and their dates
Chest radiograph results, including presence of cavity*
TB medications with start and stop dates*
Bacteriologic results (sputum smear, culture, and drug susceptibility) with dates*
Previous history of TB disease and treatment*
Previous history of exposure to other persons diagnosed with TB
Infectious period (updated as new information arrives)
HIV infection status*
HARS† number
Contact investigation
Date of initial interview with index patient
Dates of follow-up interviews with the index patient

* Data items collected on the Report of a Verified Case of Tuberculosis (RVCT) form.
† HIV/AIDS Reporting System.

TABLE 5. Minimal data recommended concerning each contact of persons with tuberculosis (TB)

Investigator and dates
Contact manager or investigator
Date listed
How or why contact was listed (e.g., named by index patient)
Dates of interviews
Start and end dates for exposure (updated as new information arrives)
Identifiers
Name and aliases
For minors and dependents, guardian information
Social security number
Date of birth
Locating information and emergency contacts
Sex
Race
Ethnicity
Country of birth
If foreign born, length of time in the United States
Primary language and preferred language
Methods of translation or interpretation
Relationship or connection to index patient
Social affiliations (e.g., work, school, church, clubs, or activities)
Environmental information about exposure settings (e.g., size or ventilation)
Frequency, duration, and time frame of interactions
Previous history of TB disease or latent infection, and documentation
BCG† vaccination and date
Medical risk factors for progression of infection to TB disease*
Population risk factors for prevalent *Mycobacterium tuberculosis* infection*
Evaluation for TB disease and latent infection
Health-care provider for TB (e.g., public health, private, both, or other)
Symptoms suggesting TB disease
Tuberculin skin tests, with dates, reagents, and lot numbers, and reaction measurement
Chest radiograph results with dates
Bacteriologic results with dates
HIV infection status
Final diagnostic classifications for latent *M. tuberculosis* infection or disease
Treatment information for contacts with latent *M. tuberculosis* infection
Dates of treatment
Treatment regimen (medication, dosing schedule, and any changes to these)
Methods of supervising treatment (e.g., directly observed treatment.)
Adverse effects (specify each)
Interruptions in regimen and dates
Outcome of treatment (e.g., completion, consistent with ARPE*)
If treatment not completed, reason*

* Aggregate report for program evaluation.
† Bacille Calmette-Guérin.

achieved. If the data are structured and stored in formats that permit detailed retrospective review, then the reasons for problems can be studied. CDC's Framework for Program Evaluation in Public Health is recommended for assessing the overall activities of contact investigations (*118*).

BOX 2. Recommended objectives for contact investigations, by key indicators

Key indicator	Objective
Infectious index patients with at least one contact listed	90%
Contacts who are evaluated for tuberculosis disease and latent infection	90%
Infected contacts who begin treatment for latent infection	85%
Treated contacts who complete treatment for latent infection	75%

Data definitions are crucial for consistency and subsequent mutual comprehension of analytic results. However, detailed definitions that accommodate every contingency defeat the simplicity required for an efficient system. Data definitions are best when they satisfy the most important contingencies. This requires a trade-off between completeness and clarity. As with the initial selection of data, working back from the intended uses of the data is helpful in deciding how much detail the data definitions should have.

Routine data collection can indicate whether the priority assignments of contacts were a good match to the final results (e.g., infection rates and achievement of timelines). These data cannot determine whether all contacts with substantial exposure were included in the original list (i.e., whether certain contacts who should have been ranked as high priority were missed completely because of gaps in the investigation).

Methods for Data Collection and Storage

Direct computer entry of all contact investigation data is recommended. Systems designed to increase data quality (e.g., through use of error checking rules) are preferred. However, technologic and resource limitations are likely to require at least partial use of paper forms and subsequent transfer at a computer console, which requires a greater level of data quality assurance because of potential errors in the transfer. Security precautions for both paper copy and electronically generated data should be commensurate with the confidentiality of the information. Ongoing training concerning systems is recommended for personnel who collect or use the data.

A comprehensive U.S. software system for contact investigation data collection and storage has not been implemented. Health department officials are advised to borrow working systems from other jurisdictions that have similar TB control programs. Any system should incorporate these recommendations.

Computer storage of data offers improved performance of daily activities because a comprehensive system can provide reminders regarding the care needs of individual contacts (e.g., notification regarding contacts who need second skin tests and recommended dates). A system also can perform interim analysis of aggregate results at prescheduled intervals. This contributes both to reassessment of the investigative strategy (see When to Expand a Contact Investigation) and to program evaluation.

Confidentiality and Consent in Contact Investigations

Multiple laws and regulations protect the privacy and confidentiality of patients' health care information (*119*). Applicable federal laws include Sections 306 and 308(d) of the Public Health Service Act; the Freedom of Information Act of 1966; the Privacy Act of 1974, which restricts the use of Social Security numbers; the Privacy Protection Act of 1998; and the Privacy Rule of HIPAA, which protects individually identifiable health information and requires an authorization of disclosure (*39*). Section 164.512 of HIPAA lists exemptions to the need to obtain authorization, which include communicable diseases reported by a public health authority as authorized by law (*120*). Interrelationships between Federal and State codes are complex, and consultation with health department legal counsel is recommended when preparing policies governing contact investigations.

Maintaining confidentiality is challenging during contact investigations because of the social connections between an index patient and contacts. Constant attention is required to maintain confidentiality. Ongoing discussions with the index patient and contacts regarding confidentiality are helpful in finding solutions, and individual preferences often can be accommodated. Legal and ethical issues in sharing confidential information sometimes can be resolved by obtaining consent from the patient to disclose information to specified persons and by documenting this consent with a signed form.

The index patient might not know the names of contacts, and contacts might not know the index patient by name. With the patient's consent, a photograph of the patient or of contacts might be a legal option to assist in identifying contacts. In certain places, separate consent forms are required for taking the photograph and for sharing it with other persons. In congregate settings, access to occupancy rosters might be necessary to identify exposed contacts in need of evaluation.

In their approach to confidentiality and consent issues for contact investigations, TB control programs will need to address the following:

- **Policies and training.** Policies explicitly regarding TB contact investigations are recommended for inclusion in the health department's overall policies for protecting confidentiality and breaking it when needed. Consultation with legal counsel improves the utility and validity of the policies. Periodic training in the policies is recommended for all staff who participate in contact investigations, including receptionists, interpreters, and clerical personnel.
- **Informed consent.** Consent for disclosure of information in the patient's primary language is recommended. Refusal to grant consent can threaten public health and requires documentation and sometimes legal consultation for determining acceptable interventions. Any deliberate breach of confidentiality by the health department should be authorized by law and documented. Accidental breaches should be brought to the attention of the legal counsel for advice on remediation. Obtaining informed consent presents the opportunity for learning patient preference for confidentiality. Frequent discussions between health department workers and patients regarding confidentiality can allay mistrust.
- **Site investigations.** Especially in congregate settings (e.g., the workplace), maintaining confidentiality during a TB contact investigation is threatened by site visits. Anticipatory discussions with the patient can lead to solutions for safeguarding confidentiality, and a patient's preferences should be honored when consistent with laws and good practices (*121*). In addition, to the extent that onsite administrators already know confidential information regarding an index patient or contacts, they can be asked to respect confidentiality even if they are not legally bound to do so. Employee and occupancy rosters are often shared with health department personnel to facilitate identification of contacts who should be evaluated. Confidentiality of these records also must be safeguarded.
- **Other medical conditions besides TB.** Legal and ethical concerns for privacy and confidentiality extend beyond TB. All personal information regarding an index patient and contacts is afforded the same protections.

Staffing and Training for Contact Investigations

The multiple interrelated tasks in a contact investigation require personnel in the health department and other healthcare-delivery systems to fulfill multiple functions and skills (Box 3). Training and continuous on-the-job supervision in all these functions help ensure successful contact investigations.

BOX 3. Specialized functions for contact investigations

- Interviewing
- Data collection and management
- Epidemiologic analysis
- Medical record review
- Tuberculin skin testing
- Exposure environment assessment
- Case management
- Media relations and public education
- Patient education
- Medical evaluation and assessment
- Medication procurement and management
- Program evaluation
- Site visits
- Patient reception
- Protocol development
- Social assessment
- Investigation coordination

SOURCES: CDC. Essential components of a tuberculosis prevention and control program. MMWR 1995;44(No. RR-11):1–17; CDC. Core curriculum on tuberculosis: what the clinician should know. 4th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2000.

Job titles of personnel who conduct contact investigations vary among jurisdictions (Box 4). State licensing boards and other authorities govern the scope of practice of health department personnel, and this narrows the assignment of functions. Reflection of these licensure-governed functions is recommended for personnel position descriptions, with specific references to contact investigations as duties.

Contact Investigations in Special Circumstances

Contact investigations frequently involve multiple special circumstances, but these circumstances typically are not of substantive concern. This section lists special challenges and suggests how the general guidance in other sections of this document can be adapted in response.

Outbreaks

A TB outbreak indicates potential extensive transmission. An outbreak implies that 1) a TB patient was contagious, 2) contacts were exposed for a substantial period, and 3) the interval since exposure has been sufficient for infection to progress to disease. An outbreak investigation involves several overlapping contact investigations, with a surge in the need for public health resources. More emphasis on active case finding is recommended, which can result in more contacts than usual having chest radiographs and specimen collection for mycobacteriologic assessment.

BOX 4. Positions and titles used in contact investigation literature

- Tuberculosis (TB) program manger
- DOT (directly observed therapy) worker
- Case manager
- Nurse epidemiologist
- Public health nurse (PHN)
- Public information/media relations officer
- Disease investigation specialist
- Physician (health department/hospital or private)
- Contact investigation worker
- TB medical consultant
- Medical epidemiologist
- HIV counselor
- Outreach worker
- Department of Health:
  - Investigator
  - TB control manger
  - Contact investigation interviewer
- Regional nurse consultant
- Community health worker
- Licensed practical nurse
- Assessment unit epidemiologist
- Public health team
- Local health jurisdiction:
  - Field staff
  - Health officer
  - Public health worker
  - TB control/public health nurse
  - Nursing supervisor
  - Manager
  - Medical interpreter

SOURCE: CDC. Core curriculum on tuberculosis: what the clinician should know. 4th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2000.

Definitions for TB outbreaks are relative to the local context. Outbreak cases can be distinguished from other cases only when certain association in time, location, patient characteristics, or *M. tuberculosis* attributes (e.g., drug resistance or genotype) become apparent. In low-incidence jurisdictions, any temporal cluster is suspicious for an outbreak. In places where cases are more common, clusters can be obscured by the baseline incidence until suspicion is triggered by a noticeable increase, a sentinel event (e.g., pediatric cases), or genotypically related *M. tuberculosis* isolates.

On average in the United States, 1% of contacts (priority status not specified) have TB disease at the time that they are

evaluated (*50*). This disease prevalence is ≥100 times greater than that predicted for the United States overall. Nonetheless, this 1% average rate is not helpful in defining outbreaks, because substantial numbers of contacts are required for a statistically meaningful comparison to the 1% average.

A working definition of "outbreak" is recommended for planning investigations. A recommended definition is a situation that is consistent with either of two sets of criteria:

- during (and because of) a contact investigation, two or more contacts are identified as having active TB, regardless of their assigned priority; or
- any two or more cases occurring ≤1 year of each other are discovered to be linked, and the linkage is established outside of a contact investigation (e.g., two patients who received a diagnosis of TB outside of a contact investigation are found to work in the same office, and only one or neither of the persons was listed as a contact to the other).

The linkage between cases should be confirmed by genotyping results if isolates have been obtained (*122*). Any secondary case that is unexpectedly linked to a known index patient represents a potential failure of certain contact investigation, and therefore the strategy for the original investigation should be reassessed to determine whether the strategy for finding contacts was optimal and whether the priorities were valid or if additional contacts must be sought. If a secondary case occurred because treatment for a known contact with LTBI was not started or completed, then the strategies for treatment and completion should be reviewed.

An outbreak increases the urgency of investigations and places greater demands on the health department. Therefore, whenever possible, a suspected linkage between cases should be corroborated by genotyping results before intensifying an investigation. Even if genotypes match, an epidemiologic investigation is required for determining probable transmission linkages (*122–125*).

In an outbreak, contacts can be exposed to more than one case, and cases and contacts can be interrelated through multiple social connections which complicate efforts to set priorities. Social network analysis offers an alternative framework (see Other Topics) (*126*). The risk factors contributing to a specific outbreak should be determined, because these findings will affect the investigation and inform the strategy.

Contagious TB undiagnosed or untreated for an extended period, or an extremely contagious case. The challenges created by the extended infectious period include the patient's inability to remember persons and places and a greater number of contacts in a greater number of places. Social network techniques (see other topics) and setting-based investigations are proxy methods for finding contacts. A highly contagious case, sometimes with several pulmonary cavities or laryngeal disease, suggests a greater number of high-priority contacts. If an outbreak has been discovered, and if the patient has one of these forms of TB, any contacts who have indeterminate exposure data should be classified as high priority.

Sometimes a delay in treating TB is caused by failure to suspect TB or to report it. Opportunities for educating the providers should be pursued immediately, especially if contacts are likely to seek health care from the same providers.

Multidrug resistance can cause prolonged contagiousness if a standard treatment regimen for drug susceptible TB is being administered. This problem can be prevented by obtaining initial susceptibility results, by monitoring the patient's condition and response to therapy, and by suspecting MDR TB when the patient has treatment failure, relapse, or slow recovery from illness (*127*).

Source patient visiting multiple sites. A TB patient who has an active, complex social life and who frequents multiple sites where transmission of *M. tuberculosis* could occur is also less likely to be able to name all contacts. Proxy interviews (see Investigating the Index Patient and Sites of Transmission) and setting-based investigations are methods that supplement the patient's recall.

Patient and contacts in close or prolonged company. When an outbreak has been discovered, high priority is recommended for contacts having close or prolonged exposure.

Environment promoting transmission. A small interior space with poor ventilation can act as the focus of intense transmission of *M. tuberculosis*. High priority is recommended for all contacts who spent time with an outbreak source patient in such spaces, even if the periods of exposure were brief or unknown.

Certain larger environments (e.g., a warehouse worksite or a school bus [*128,129*]) have been reported as sites of intensive transmission when patients were highly contagious or when patients and contacts were in prolonged company. If the evidence from the investigation indicates a link between the site and transmission in an outbreak, the contacts in such a site should be designated as high priority, regardless of the site's characteristics.

Contacts very susceptible to disease after *M. tuberculosis* infection. Urgency is required when outbreak cases are diagnosed in contacts who are relatively more susceptible to progression from *M. tuberculosis* infection to TB disease. Other contacts with similar susceptibility should be sought. If such an outbreak includes children aged <5 years, a source-case investigation should be undertaken if the contagious source is unknown initially (see Source-Case Investigations). Intensified methods for active case finding among contacts are recommended.

Gaps in contact investigations and follow-up. Omissions, errors, and system failures can resurface later in the form of

secondary TB cases (i.e., an outbreak). Tracing back cases in an outbreak indicates whether prevention opportunities were missed in previous contact investigations or other prevention activities (e.g., targeted testing).

Extra-virulent strain of *M. tuberculosis*. The existence of such strains has not been demonstrated. Determining which strains are more infective or pathogenic for humans is not yet possible, and the relevance of greater/faster pathogenicity of certain strains in laboratory animals is not fully understood yet (*58,128,130*).

Congregate Settings

Overall concerns associated with congregate settings include 1) the substantial numbers of contacts, 2) incomplete information regarding contact names and locations, 3) incomplete data for determining priorities, 4) difficulty in maintaining confidentiality, 5) collaboration with officials and administrators who are unfamiliar with TB, 6) legal implications, and 7) media coverage. Certain settings require intensified onsite approaches for ensuring that contacts are completely evaluated and for meeting objectives for treating LTBI. Requests for supplemental resources are recommended when the scope or duration of an investigation is expected to disrupt other essential TB control functions.

Maintaining confidentiality for an index patient is difficult if the patient was conspicuously ill or was absent from the setting while ill (see Data Management and Evaluation of Contact Investigations). Permission should be sought from the index patient before sharing information with any officials (e.g., supervisors, managers, or administrators) at the setting. Collaboration with officials at the setting is essential for obtaining access to employee and occupancy rosters, ascertaining contacts, performing onsite diagnostic evaluations or treatment, and offering education to associates (e.g., classmates, friends, or coworkers) of the index patient.

For congregate settings, the types of information for designating priorities are site specific, and therefore a customized algorithm is required for each situation. The general concepts of source-case characteristics, duration and proximity of exposure, environmental factors that modify transmission, and susceptibility of contacts to TB should be included in the algorithm (see Decisions to Initiate a Contact Investigation, Index Patient and Sites of Transmission, and Assigning Priorities to Contacts).

The optimum approach for a setting-based investigation is to interview and test contacts on site. If this is not possible, then the contacts should be invited for evaluation at the health department, which should consider having additional personnel or extended hours. As a last resort, contacts can be notified in writing to seek diagnostic evaluation with their own health-care providers. In this case, the letter should inform health-care providers regarding the TB exposure (including drug susceptibility results), diagnostic methods (including a 5 mm skin test cut point), treatment recommendations for LTBI, and a reference telephone number at the health department for obtaining consultation. Health-care providers also should receive a form for each contact that can be used to return diagnostic results and treatment decisions to the health department.

Certain congregate settings create opportunities for efficient onsite supervision of treatment for numerous contacts. Treatment can be delivered by having health department personnel visit the setting twice weekly for intermittent therapy, or by collaborating with a health professional hired by the setting. Arrangements are needed to maintain confidentiality with this approach. Officials and administrators at the setting are likely to be concerned regarding liability, which can be addressed in advance with legal counsel.

For constructive media coverage, the health department should collaborate with the setting in focusing on clear, consistent information. News reports that are factually accurate and that correctly describe the role of the health department can facilitate the investigation (see Communicating Through the News Media).

Correctional Facilities

The Advisory Council for the Elimination of Tuberculosis (ACET) has issued guidance on preventing and controlling TB in correctional facilities (*131*). Jails and prisons have been implicated in TB outbreaks (*132–135*). Multiple factors can hinder contact investigations. The best preparation for conducting contact investigations in jails and prisons is preexisting formal collaboration between correctional and public health officials. If collaboration has not been established before a contact investigation is needed, creating it as part of the investigation is necessary.

Certain correctional populations have a high prevalence of HIV infection, and reviewing the HIV testing policies, procedures, and aggregate statistics is recommended. If inmates have not been offered voluntary counseling, testing, and referral for HIV infection, and TB exposure is suspected, offering voluntary HIV counseling, testing, and referral is strongly recommended.

Inmates move about within correctional facilities on both daily and weekly schedules that can affect TB exposures. In addition, inmates are transferred within and between jails or prisons. Certain correctional settings have convenient, comprehensive longitudinal records for the locations of inmates that are essential for drawing up contact lists, estimating ex-

posure periods, and assigning priorities to contacts. A tour of exposure sites within each setting helps in estimating exposure intensity.

Prisons typically have onsite health services, but jails might not. Certain prisons and jails test new inmate admissions and employees for *M. tuberculosis* infection, and certain prisons have periodic surveillance testing of employees, inmates, or both. Health-care providers in an onsite system can provide invaluable assistance in reviewing health records and evaluating and treating contacts. If medical record data (e.g., previous exposure and skin test results) cannot be retrieved rapidly, health department officials should consider requesting additional resources.

Investigations in jails can be especially challenging because of rapid turnover of inmates and crowding. The number of contacts who had close proximity to an index patient/inmate can be great, and yet exposure might be brief. This complicates the process of assigning priorities. Unless tracking records for inmates who were in a confined space with an infectious TB patient allow a determination that aggregate exposure was brief (e.g., <8 hours), these contacts should be assigned high priority. High-priority contacts who are transferred, released, or paroled from a correctional facility before medical evaluation for TB should be traced.

Unless they have been released or paroled, prison inmates with LTBI can complete a treatment regimen while incarcerated. In contrast, inmates in jails who are contacts are unlikely to be able to complete treatment while incarcerated. A low completion rate is anticipated when inmates are released or paroled unless follow-through supervision can be arranged.

Workplaces

A substantial number of persons spend the majority of their waking hours in their workplaces, which can be crowded. Duration and proximity of exposure can be greater than for other settings. Details regarding employment, hours, working conditions, and workplace contacts should be obtained during the initial interview with the index patient (see Investigating the Index Patient and Sites of Transmission), and the workplace should be toured after accounting for confidentiality and permission from workplace administrators or managers. Employee lists are helpful for selecting contacts, but certain employees might have left the workplace and thus been omitted from current employee lists.

Occasional customers of a business workplace (e.g., intermittent visitors to a fast-food restaurant) should be designated as low-priority contacts. Customers who visit a business workplace repeatedly should be assigned priorities as in other investigations (see Assigning Priorities to Contacts), especially susceptible or vulnerable contacts.

Workplace administrators or managers are likely to express concern regarding liability, lost productivity, and media coverage. In addition, they might have limited obligations to protect patient confidentiality. All these issues can be addressed during planning. For example, the assistance of the health department's media relations specialist can be offered to the workplace. For questions of liability and requirements under law, discussions between the health department's and the workplace's legal counsels are recommended.

Hospitals and Other Health-Care Settings

Nearly every type of health-care setting has been implicated in transmission of *M. tuberculosis*, and guidance on preventing transmission has been provided by CDC, the Healthcare Infection Control Practices Advisory Committee, and other organizations (*42,136*). State governments have different degrees of regulatory authority over health-care settings. Personnel collaborating with hospitals and other health-care entities should have knowledge of applicable legal requirements.

Infection control practitioners, although vital partners in these settings, might not be familiar with TB contact investigations. Multiple settings have engineers who can describe and test the environmental systems. Such an investigation should be planned jointly as a collaboration between the setting and the health department. Initial discussions should include data sharing and divisions of responsibilities. Liability, regulations, confidentiality, media coverage, and occupational safety are complex for health-care settings. Occupational Safety and Health Administration rules, which are interpreted differently by different jurisdictions, might require hospital administrators to report when employees are reported to be infected from occupational exposure. Public health officials should consider inviting legal counsel to the initial planning sessions with health-care administrators.

The majority of health-care settings have policies for testing employees for *M. tuberculosis* infection at the time of employment and, in settings where exposure is anticipated, periodically thereafter. Test results are helpful as baseline data. The availability of baseline results for contacts who were patients or clients of the setting is variable; long-term care facilities might have these data.

Schools

This category includes child care centers, preschools, primary through secondary schools, vocational schools that replace or immediately follow secondary school, and colleges or universities. Contact investigations at juvenile detention centers and adult education systems should be managed along the same lines as investigations conducted in correctional settings and in workplaces, respectively.

Early collaboration with school officials and community members is recommended when considering an investigation related to a school, even if preliminary information suggests that an investigation is unnecessary. The typical features of contact investigations in schools are the potentially substantial numbers of contacts and difficulties in assigning priorities to contacts who have undetermined durations and proximities of exposure. The potential is great for controversies among public health officials, school officials, and the guardians of the children.

The presence of TB in schools often generates publicity. Ideally, the health department should communicate with the school and parents (and guardians) before any media report a story. TB control officials should anticipate media coverage and plan a collaborative strategy (see Communicating Through the News Media).

Consent, assent, and disclosure of information are more complex for nonemancipated minors than for adults. Each interaction with a minor is also a potential interaction with the family. The health department typically has limited alternatives for evaluating a minor if permission is not granted. Anticipatory legal consultation is recommended.

Public health officials should visit the school to check indoor spaces, observe general conditions, and interview maintenance personnel regarding ventilation. Class assignment records help in listing contacts, estimating durations of exposure, and setting priorities. However, certain schools purge these files at the end of each school year, in which case interviews with students and personnel are necessary to list contacts.

Extramural activities add other exposure sites and contacts. Clubs, sports, and certain classes require additional information gained from interviewing the patient, the patient's guardians, and school personnel. For patients who ride school buses, a bus company might keep a roster of riders with addresses.

The strategy for contact investigations in child care centers, preschools, and primary schools depends on whether the index patient is a child (i.e., preadolescent) or an adult (e.g., a teacher or caregiver). The potential infectiousness of an adult in the school should be determined (see Decisions to Initiate a Contact Investigation and Investigating the Index Patient and Sites of Transmission).

In a source-case investigation of a child aged <5 years who has TB and who attends preschool or child care, all adults in these settings should be included if the source case has not been located in the family or household (see Source-Case Investigations). Certain home-based child care centers include adults who do not provide child care but who still share airspace with the children. Source-case investigations should not be pursued in primary and higher-level schools unless other evidence points to the school as the focus.

In secondary and higher levels of education, students usually have adult-form TB, and infectiousness can be estimated by the standard criteria (see Decisions to Initiate a Contact Investigation and Investigating the Index Patient and Sites of Transmission). With advancing education, academic schedules and extramural social schedules become more complex, and the information reported by the index patient is more important for a thorough investigation than it is for younger children.

Multiple jurisdictions have pre-employment requirements for TB clearance screening (e.g., a test for *M. tuberculosis* infection) at schools or daycare settings, and certain jurisdictions require TB clearance for entering students. Certain colleges and universities also have these requirements. These baseline data are helpful for interpreting results from the investigation.

Schools that have onsite health services can administer DOT to students with LTBI, or the health department can send workers twice weekly to provide intermittent therapy. This approach should be coordinated with the annual school cycle.

School breaks, vacations, graduations, and transfers disrupt the contact investigation. In collaboration with school officials, the health department can notify, by mail, students and other contacts who will be unavailable at the school. These contacts should be referred for evaluation at the health department. Contacts seeking care from their own health-care providers should receive written instructions to give their providers.

Shelters and Other Settings Providing Services for Homeless Persons

ACET and CDC have provided guidance for providing TB control services to homeless persons and for preventing TB transmission at settings providing services to them (*137*). The challenges that can be anticipated for a contact investigation involving a homeless TB patient include difficulty locating the patient and contacts if they are mobile, episodic incarceration, migration from one jurisdiction to another, psychiatric illnesses (including chemical dependency disorders) that hinder communication or participation, and preexisting medical conditions (in particular, HIV infection). When names or locations of specific contacts are unknown, interviews with the patient and potential contacts should focus on social networks and settings, including correctional facilities.

One surrogate for degree of exposure at an overnight shelter is the bed/cot assignment. The proximity and duration of overlap should be estimated as closely as possible for selecting high-priority contacts. Certain daytime-use settings keep sign-in lists, but these might lack information regarding overlap of visits.

Homeless persons frequently seek health care from multiple volunteer providers, halfway houses, chemical dependency treatment programs, community clinics, urgent care centers,

and hospital emergency departments. Consultation and assistance from health-care providers in these systems can be helpful. This also creates an opportunity for collaboration, contact ascertainment, and mutual education.

Site visits and interviews are crucial, because the social communities of homeless persons are likely to vary by situation. A contact investigation presents an opportunity to review the screening and testing services and to offer assistance with these and other means of decreasing transmission of *M. tuberculosis* (e.g., environmental controls). However, transmission also could occur at sites besides shelters (e.g., jails, taverns, abandoned buildings, and cars).

Settings providing services to homeless persons are affected by policies, laws, and regulations according to their service population, location, and funding sources, and certain of these issues are relevant for the contact investigation. Access to visitation and occupancy rosters (or logs) and to other information regarding persons, vital for listing contacts and determining priorities, might be restricted by law (e.g., at settings that provide treatment for substance-abuse disorders), and the terms of access should be negotiated.

Low treatment-completion rates have been reported for treatment of LTBI diagnosed at homeless shelters (*137–140*). TB control officials should work with setting administrators to offer onsite supervised intermittent treatment. Sites with more stable populations are likely to benefit most from this approach.

Transportation Modes

Transmission of *M. tuberculosis* has been confirmed on military vessels at sea, commercial aircraft, passenger trains, and school buses (*85,129,141–144*). However, transmission is unlikely unless ventilation is restricted or exposure is long or repetitive. Investigations for these settings should be assigned low priority unless ventilation is restricted or single-trip exposure time is >8 hours (cumulative if the trip has multiple segments) as currently recommended for commercial airline travel, or at least two separate trips were taken with the index patient (*145*).

Drug or Alcohol Usage Sites

Shared sites of drug or alcohol usage (e.g., taverns and crack houses), have been implicated as sites of *M. tuberculosis* transmission (*146,147*). Potential factors are close person-to-person proximity, repetitive exposure, and poor ventilation. Routine interviews might not generate a complete contact list for these settings, and the patient's social network should be explored for other information sources. Connections to correctional settings should be sought. HIV infection is associated with multiple forms of substance abuse, and HIV counseling, testing, and referral services are recommended.

Special Sites Not Under Jurisdiction

Examples of sites that are not under the jurisdiction of the local or state health department are those under the jurisdiction of the U.S. government (e.g., military bases), diplomatic missions, or reservations for American Indian/Alaska Native tribes. If these sites have their own health-care systems, the health department can offer technical consultation and can request data from contact investigations. At sites that do not have health-care systems, agreements can be made between local TB control officials and the onsite authorities to delegate the public health response to the health department.

Index Patient Unable to Participate

Approximately 8% of pulmonary TB patients with AFB detected on sputum microscopy have no contacts listed (*17,50*). TB patients who have few or no contacts listed are more likely to be homeless or to have died (i.e., before an interview could be conducted). This implies that the patients might have had contacts, but learning who the contacts were is difficult. Social-network information, setting-based investigations, and proxy methods are recommended to supplement the contact list. In addition, any person in whom a case of pulmonary TB was diagnosed at death indicates that a possible delay in diagnosis has occurred, which could infer increased and prolonged infectiousness and a need to increase the scope of the investigation.

MDR TB

The occurrence of MDR TB does not change recommendations for assigning contact priorities. Special consideration should be given to instances when resistance is acquired during treatment or when drug resistance was detected late during the treatment course, because these patients might have had prolonged periods of infectiousness. Treatment regimens for infected contacts require expert consultation (see Treatment for Contacts with LTBI) (*6*).

Interjurisdictional Contact Investigations

Contact investigations that overlap multiple jurisdictional areas require joint strategies for finding contacts, having them evaluated, treating the infected contacts, and gathering data. A different solution usually is required for each situation.

Multiple jurisdictions within the United States. The index patient and associated contacts might have stable residences, but travel among sites in different jurisdictions. The health department that counts the index patient is responsible

for leading the investigation and notifying the health departments in other jurisdictions regarding contacts residing in those jurisdictions. Notifications should include requests for follow-through results of contact evaluation and treatment. A team of representatives from the multiple health departments can increase the efficiency of such an investigation by planning the overall strategy together and monitoring the progress.

Migratory workers. ACET has issued specific TB prevention and control recommendations for migratory agricultural workers (*148*). An investigation for any migratory workers requires a strategy that is adjusted to their migration and work schedule. The workers' itinerary should be ascertained during initial planning, and health departments in successive destinations should be notified. A selection from among three general types of contact record management is recommended: 1) the transfer of patient records from one health department to the next on the itinerary; 2) the continual referral of information to a single coordinating health department throughout the investigation; or 3) patient ownership of records, with each patient responsible for keeping information while moving. Because of the duration of treatment, treating LTBI is the most difficult phase. Certain seasonal workers remain in one place as long as several months during off-season, and this period should be used to deliver as much treatment as possible.

Contagious TB patient traveling within the United States. Officials from the health department that initially encountered the patient should interview the patient to gather as much identifying and locating information as possible for contacts who were visited during the patient's travels. These data should be referred to the jurisdictions in which the contacts are located. The jurisdiction that counts the index patient is assigned responsibility for managing the contact investigation overall.

International contact investigations. The United States and Mexico participate in the Referral System for Binational TB Patients Pilot Project, which coordinates follow-up care when a TB patient moves between these two countries, mainly between participating jurisdictions. Cure TB also contributes to continuity of care in other regions of the two countries. Neither of these systems includes contact investigations at present. TBNet is a health-care system for migratory agricultural workers who are receiving treatment for LTBI and thus includes contacts. For cases or contacts in Canada, U.S. health departments should notify TB control coordinators in provincial health departments.

Unusual Events Causing Exposure to *M. tuberculosis* Complex

The normal mode of transmission is person to person by the airborne route. Unusual events (e.g., laboratory accidents) also can cause *M. tuberculosis* transmission. In contrast, *M. bovis* transmission usually occurs via infected dairy products, which is preventable by pasteurization.

Animals with human-type or bovine TB. Multiple mammalian and certain nonmammalian species are susceptible to human-type TB, presumably through exposure to persons with TB who are contagious. Multiple animal hosts also can contract bovine TB (i.e., infection with *M. bovis*), probably from exposure to other infected animals or from consuming infected dairy products or contaminated feed.

Standard methods for diagnosing *M. tuberculosis* infection and disease have not been described for the majority of species. Evaluation and management of an animal exposed to *M. tuberculosis* should be referred to a veterinarian, who can consult with the state veterinarian. Animal-to-human transmission of human TB in a household has not been confirmed, and the human contacts should be designated as low priority. However, determining the source of *M. tuberculosis* infection for an animal with TB is recommended.

The degree of risk for aerosol-inducing procedures (e.g., intubation, bronchoscopy, or necroscopy) performed on an animal having TB is unknown. However, these procedures are likely to create infectious aerosols. If infection control precautions for preventing *M. tuberculosis* transmission were not implemented during the procedures, then in-room contacts are assigned high priority.

The evaluation and management of animals exposed to *M. bovis* should be referred to a veterinarian. Cases of *M. bovis* in animals should be reported to the state veterinarian. Animal-to-human transmission of *M. bovis* from necropsy procedures has been confirmed (*149*).

Patients who acquire *M. bovis* infection from ingestion are more likely to have extrapulmonary TB (e.g., scrofula or peritonitis), but pulmonary disease is possible. Contact investigations regarding persons who have pulmonary TB caused by *M. bovis* should be planned according to the guidelines provided in this report. However, the potential for transmission is less clear. Current and proposed tests for infection (e.g., the TST and QuantiFERON®-TB Gold [QFT-G, manufactured by Cellestis Limited, Carnegie, Victoria, Australia]) detect *M. bovis* infection, but the tests are not approved specifically for this indication. After active *M. bovis* disease has been excluded by symptom review, examination, and tests as indicated by findings, suspected latent *M. bovis* infection should be treated as ordinary *M. tuberculosis* infection.

Multiple laboratory mammals, especially nonhuman primates, are highly susceptible to human-type TB. Federal animal welfare regulations administered by the U.S. Department of Agriculture (http://www.nal.usda.gov/awic/legislat/awicregs.htm) apply to laboratory animals and certain animals used in exhibi-

tions. If such animals are exposed to infectious TB, consultation with the state veterinarian is recommended.

Microbiology laboratory accidents. Routine laboratory procedures for manipulating either patient specimens or cultured isolates of *M. tuberculosis* generate infectious aerosols. Unintentional events (e.g., spills outside containment areas) and system failures can cause exposure. A contact investigation for such scenarios should be based on the location of persons in the room at the time of the event and the airflow in the room. Consultation with a microbiologist is recommended. In general, baseline skin test results are available for workers in laboratories in which *M. tuberculosis* is cultured or kept.

Surgical wounds, abscesses, embalming, and autopsies. Diseased tissues are not typical sources of infection unless procedures create aerosols: water-jet irrigation, dripping fluids, electrical cauterization, and cutting with power tools. If procedures were performed on infected tissues before infection control precautions were instituted, then persons in the room at the time should be designated as high-priority contacts.

Percutaneous inoculations. *M. tuberculosis* can cause infection and local disease in skin or deeper tissue after direct inoculation by a contaminated object. Percutaneous exposure would be highly unusual in anyone except a health-care worker, who should have a previous result from baseline testing for infection. A 9-month INH treatment regimen should be started if the *M. tuberculosis* is likely to be susceptible to it. Treatment should be stopped if a repeat test for *M. tuberculosis* is negative ≥8 weeks after exposure, and treatment should be extended to the full course if the test result is positive. If the baseline test result was positive, the full 9 months of treatment is recommended. During treatment, the person should be examined monthly for signs of local infection or spread to regional lymph nodes.

Source-Case Investigations

A source-case investigation seeks the source of recent *M. tuberculosis* infection, perhaps newly diagnosed TB disease (*43*). TB disease in children aged <5 years typically indicates that the infection must be recent. For this reason, it is a sentinel public health event. Young children usually do not transmit TB to others, and their contacts are unlikely to be infected because of exposure to them (*150*). A source-case investigation moves in the opposite direction of contact investigation, but the principles used in contact investigation apply. Source-case investigations concerning adults with TB disease are not discussed in this report (*42,131,151*).

Source-case investigations typically have low yield for the effort required. They are not recommended unless a TB control program is achieving its objectives (in particular, treatment of infected contacts) when investigating infectious cases.

Source-Case Investigation for a Child with TB Disease

The yield of source-case investigations for children who have TB disease varies, typically <50% on average (*152–156*). Source-case investigations can be considered for children aged <5 years. A younger age cut-off might be advisable because the focus would be on more recent transmission. An investigation may be started before the diagnosis of TB is confirmed because waiting for confirmation can decrease the chances of finding associates.

Source-Case Investigation for a Child with Latent *M. tuberculosis* Infection

A search for the source of infection for a child who has LTBI is unlikely to be productive (*157–159*). These kinds of investigations are recommended only regarding infected children aged <2 years and only if data are monitored to determine the value of the investigation.

Procedures for Source-Case Investigation

Seeking a source case follows the same overall procedures as a standard contact investigation. Parents or guardians usually are the best informants. Such persons are termed associates. Attention focuses on ill associates who have symptoms of TB disease. A source-case investigation should begin with the closest associates (e.g., household members).

Limited data are needed for assessing the productivity of source-case investigations. These data include the number of index patients investigated for their sources, the number of associates screened for TB disease, and the number of times that a source is found.

Other Topics

Cultural Competence

Culture refers to the integrated pattern of knowledge, beliefs, and behavior that is passed from one generation to another (*160*), including how persons act and interact. If contact investigations are to be productive, cultural differences must be respected and understood. Cultural competence is the knowledge and interpersonal skills that allow health-care providers to appreciate and work with persons from cultures other

than their own. It involves awareness of cultural differences, self-awareness, and sensitivity to a patient's culture and adaptation skills.

Language and culture are important factors in TB contact investigations. The ability to understand cultural norms and to bridge the gaps that exist between cultures requires training and experience. Influencing patients to participate in a contact investigation increasingly depends on the cultural competency of the health-care worker. Training that is derived from the National Standards for Culturally and Linguistically Appropriate Services in Health Care is recommended (*161*).

Language interpreters need basic knowledge regarding TB, transmission, contact investigations, and the medical care of contacts. Patient confidentiality is a critical element of training. The use of family-member interpreters is discouraged. The majority of family members do not have a medical orientation. Patients might feel reluctant to reveal contacts of a family member.

Social Network Analysis

Social network analysis might offer an effective way to list TB contacts and assign priorities to them (*162–166*). Social network analyses have been tested retrospectively on TB outbreak investigations (*126,167–170*) and contact investigations (*171,172*). However, the use of social network analysis to improve contact investigations has not been tested prospectively, the methods might require additional labor, and further operational research is needed.

Use of Blood Tests for the Detection of Latent *M. tuberculosis* Infection

The majority of experience with diagnosing *M. tuberculosis* infection, especially LTBI, in contacts has been with the TST. Newly released blood tests now have potential use for this purpose. The initial QuantiFERON®-TB test (QFT) is a whole blood assay that measures IFN-γ release in response to purified protein derivative (PPD). Good agreement was reported with the skin test in healthy adults being tested for LTBI, and QFT was approved by the U.S. Food and Drug Administration (FDA) (*173,174*). Data are insufficient to demonstrate the accuracy of QFT test for testing contacts, and it was not recommended for this situation (*175*).

Recently, QFT-G was approved by FDA for use as an in vitro diagnostic to aid in diagnosing *M. tuberculosis* infection, including both LTBI and TB disease. This test detects the release of IFN-γ from lymphocytes of sensitized persons when their blood is incubated with peptide mixtures simulating two *M. tuberculosis* proteins called ESAT-6 and CFP-10. These proteins are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains, but are absent from all BCG vaccine strains and commonly encountered non-tuberculous mycobacteria. Therefore, QFT-G offers the possibility of detecting *M. tuberculosis* infection with greater specificity than has been possible previously with tests that used tuberculin PPD as the TB antigen (*175,176*).

CDC recommends that QFT-G can be used in all circumstances in which the TST is currently used, including contact investigations (*177*). QFT-G can be used in place of and not in addition to the TST. A positive QFT-G result should prompt the same evaluation and management as a positive TST. No reason typically exists to follow a positive QFT-G with a TST. For persons with recent contact to infectious TB, negative QFT-G results typically should be confirmed with a repeat test performed 8–10 weeks after the end of exposure. Studies to identify the most appropriate times to re-test contacts with QFT-G have not been reported. Until more specific data are available, the timing of QFT-G testing should be similar to that used for the TST.

Concern has been expressed that the QFT-G test might be somewhat less sensitive than the TST in detecting LTBI (*177*). As with a negative TST, a negative QFT-G result alone should not be used to exclude *M. tuberculosis* infection in severely immunosuppressed adults, children aged <5 years, or patients about to undergo treatment with TNF-α inhibitors, in whom the consequences of accepting a false-negative result could be especially severe.

Another blood test for detection of infection, the ELISPOT test (marketed as T-SPOT-TB), is similar in principle to QFT ELISPOT results correlate with TB exposure risk better than skin test results for contacts of pulmonary TB patients), and like QFT-G, it appears able to differentiate between BCG vaccination and *M. tuberculosis* infection (*178,179*). ELISPOT has not yet been approved for use in the United States.

Additional resources regarding tuberculosis (TB) contact investigations are available from the following organizations:

- CDC, National Center for HIV, STD, and TB Prevention, Division of Tuberculosis Elimination (available at http://www.cdc.gov/nchstp/tb)
  - — Self-Study Modules on Tuberculosis 6–9 [Module 6: Contact Investigations]
  - — Effective TB Interviewing for TB Contact Investigations
  - — Effective TB Interviewing for Contact Investigation: Facilitator-Led Training Guide
  - — Effective TB Interviewing for Contact Investigation: Facilitator-Self-Study Modules
  - — Patient Education Booklet, "Contact Investigations" (Languages: English, Tagalog, Vietnamese, and Spanish)

— TB Education and Training resources Web Site (available at http://www.findTBresources.org);
- Northeastern National Tuberculosis Center (available at http://www.umdnj.edu/ntbcweb)
  — Performance Guidelines for Contact Investigation: The TB Interview—A Supervisor's Guide for the Development and Assessment of Interviewing Skills
  — TB Interviewing for Contact Investigation: A Practical Resource for the Healthcare Worker
  — TB Simulated Patients: A Training Resource for the Contact Investigation Interview
  — Performance Guidelines: A Supervisor's Guide for the Development and Assessment of Field Investigation Skills
  — TB Field Investigation: A Resource for the Investigator
  — Conducting a TB-Education Session as Part of the Congregate Setting Investigation
  — Evaluating Congregate Setting Investigations in Tuberculosis Control;
- Charles P. Felton Model TB Center (available at http://www.harlemtbcenter.org)
  — Addressing HIV/AIDS Issues in TB Contact Investigations;
- Francis J. Curry National Tuberculosis Center (available at http://www.nationaltbcenter.edu)
  — Contact Investigation in a Worksite Toolbox
  — Quality Improvement for TB Case Management: An Online Course
  — Making the Connection: An Introduction to Interpretation Skills for TB Control
  — Facilitating TB Outreach: Community Workers and Hard-To-Reach TB Populations;
- Southeastern National Tuberculosis Center (available at http://http://SNTC.medicine.ufl.edu); and
- Heartland National Tuberculosis Center (available at http://www.heartlandtbcenter.edu).

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Appendix A

Glossary

The following terms and abbreviations are used in this report.

Acid-fast bacilli (AFB). Microorganisms that are distinguished by their retention of specific stains even after being rinsed with an acid solution. The majority of AFB in patient specimens are mycobacteria, including species other than *Mycobacterium tuberculosis* complex. A positive nucleic acid amplification (NAA) or culture result is needed for confirmation of *M. tuberculosis* complex. The relative concentration of AFB per unit area on a slide (the smear grade) is associated with infectiousness.

Anergy. A condition wherein a person has diminished ability to exhibit delayed T-cell hypersensitivity reaction to antigens because of a condition or situation resulting in altered immune function. When referring to inability to react to a skin test, the correct term is cutaneous anergy. Skin tests for anergy (i.e., control antigens) have poor predictive value and are not recommended.

Associate contact. A person who is somehow affiliated with a patient who has noninfectious tuberculosis (TB) or with another contact. Often used in connection with source-case investigations; does not imply an *M. tuberculosis* transmission pathway.

Bacille Calmette-Guérin (BCG). A vaccine for tuberculosis named after the French scientists Calmette and Guérin. The vaccine is effective in preventing disseminated and meningeal TB disease in infants and young children. It might have approximately 50% efficacy for preventing smear-diagnosed pulmonary TB in adults. It is used in multiple countries where TB disease is endemic.

Boosting. When nonspecific or remote sensitivity to tuberculin (purified protein derivative [PPD] in the skin test) wanes or disappears with time, subsequent tuberculin skin tests can restore the sensitivity. This is called boosting or the booster phenomenon. An initially limited reaction size is followed by a larger reaction size on a later test, which can be confused with a conversion or a recent *M. tuberculosis* infection. Two-step testing is used to distinguish new infections from boosted reactions in infection-control surveillance programs, but this method is not recommended for testing contacts.

Bronchoscopy. A procedure for examining the lower respiratory tract that requires inserting the end of an endoscopic instrument through the mouth or nose (or tracheostomy) and into the respiratory tree. It can be used to obtain diagnostic specimens. It also creates a high risk for *M. tuberculosis* transmission to health-care workers if it is used on a patient who has TB (even if the patient is smear negative), because the procedure induces coughing.

Bronchoalveolar lavage (BAL). A procedure for collecting respiratory specimens from the airway, typically during bronchoscopy. Sterile saline is flushed through an airway, and the resultant mixture of cells, secretions, and saline is aspirated for studies (e.g., microscopy and culture).

Case. A particular instance of a disease (e.g., TB). A case is detected, documented, and reported.

Cavity (pulmonary). A hole in the lung parenchyma, typically not involving the pleural space. Although multiple causes can account for a lung cavity, and its appearance is similar regardless of its cause, in pulmonary TB, it results from the destruction of pulmonary tissue by direct bacterial invasion and an immune interaction triggered by *M. tuberculosis*. A tuberculous cavity large enough to see with a normal chest radiograph predicts infectiousness.

Contact. Refers to someone who has been exposed to *M. tuberculosis* infection by sharing air space with a person with infectious TB.

Contagious. Refers to TB disease of either the lungs or the throat that has been demonstrated to have caused transmission to other persons or the patient who has TB disease.

Conversion. A change in the result of a test for *M. tuberculosis* infection that is interpreted to indicate a change from being uninfected to infected. With the tuberculin skin test, an increase of $\geq$10 mm in induration size during $\leq$2 years is defined as a conversion. A conversion is presumptive evidence of new *M. tuberculosis* infection and poses an increased risk for progression to TB disease. The term is applied to contacts only when previous skin test results are available. A change in tuberculin status during the window period is not necessarily consistent with this definition.

Delayed-type hypersensitivity (DTH). Cell-mediated inflammatory reaction to an antigen that is recognized by the immune system, typically because of previous exposure to the same or similar antigens. Cell-mediated reactions are contrasted with an antibody (or humoral) response. DTH typically peaks 48–72 hours after exposure to the antigen.

Directly observed therapy (DOT). An adherence-enhancing strategy in which a health-care worker or other trained person watches a patient swallow each dose of medication and is

accountable to the public health system. DOT is the preferred method of care for all patients with TB disease and is a preferred option for patients under treatment for latent infection.

Disseminated TB. See Miliary TB.

Drug-susceptibility test. A laboratory determination to assess whether an *M. tuberculosis* complex isolate is susceptible or resistant to anti-TB drugs that are added to mycobacterial growth medium. The results predict whether a specific drug is likely to be effective in treating TB disease caused by that isolate.

Enabler. A practical item given to a patient for making adherence (e.g., to treatment or to clinic appointments) easier.

Exposure. The condition of being subjected to something (e.g., an infectious agent) that could have an effect. A person exposed to *M. tuberculosis* does not necessarily become infected. Much of the work in a TB contact investigation is dedicated to learning who was exposed and, of these, who became infected.

Exposure period. The coincident period when a contact shared the same air space as a person with TB during the infectious period.

Exposure site. A location that the index patient visited during the infectious period (e.g., a school, bar, bus, or residence).

Immunocompromised and immunosuppressed. Conditions in which at least part of the immune system is functioning at less than normal capacity. According to some style experts, immunocompromised is the broader term, and immunosuppressed is restricted to conditions with iatrogenic causes, including treatments for another condition. Some immunocompromised conditions increase the likelihood that *M. tuberculosis* infection will progress to TB disease. Certain conditions also make TB disease or infection from *M. tuberculosis* more difficult to diagnose because manifestations of TB disease differ, and tests for infection rely on an intact immune system.

Incentive. A gift given to patients to encourage or acknowledge their adherence to treatment.

Index. The first case or patient that comes to attention as an indicator of a potential public health problem. Contrast with Source.

Induration. The firmness in the skin test reaction. Induration is produced by immune-cell infiltration in response to tuberculin antigen that was introduced into the skin. It is measured by palpation transversely, and the result is recorded in millimeters (mm). The measurement is compared to guidelines to determine whether the test result is classified as positive or negative.

Infection. A condition in which microorganisms have entered the body and typically have elicited immune responses. *M. tuberculosis* infection might progress to TB disease. The expression *M. tuberculosis* infection includes both latent infection and TB disease. Latent *M. tuberculosis* infection or latent tuberculosis infection (LTBI) is an asymptomatic condition that follows the initial infection; the infection is still present but is dormant (and believed not to be currently progressive or invasive). TB disease is determined by finding anatomic changes caused by advancing infection (e.g., shadows from infiltrates on a chest radiograph) or by noting symptoms (e.g., malaise, feverishness, or cough), and typically by both. Positive culture results for *M. tuberculosis* complex typically are interpreted as both an indication of TB disease and its confirmation, but infecting organisms can be obtained from patients who have no other evidence of disease.

Infectious. Refers either to TB disease of the lungs or throat, which has the potential to cause transmission to other persons, or to the patient who has TB disease.

Isoniazid (INH). A highly active anti-TB chemotherapeutic agent that is a basis of treatment for TB disease and latent infection.

Laryngeal TB. A highly infectious form of TB disease, with erosive, exudative invasion of the larynx.

Latent *M. tuberculosis* infection (or latent tuberculosis infection [LTBI]). See Infection.

Mantoux method. A skin test performed by intradermally injecting 0.1 mL of PPD tuberculin solution into the volar or dorsal surface of the forearm. This is the recommended method for tuberculin skin testing.

Meningeal TB. A highly dangerous and difficult-to-diagnose form of TB disease with infectious invasion of the tissues covering the brain. Often indolent but uniformly fatal if untreated, at times it is diagnosed too late to save the patient's life or prevent permanent disability.

Miliary TB. Sometimes referred to as disseminated TB. A dangerous, and difficult to diagnose, form of rapidly progressing TB disease that extends throughout the body. Uniformly fatal if untreated, sometimes it is diagnosed too late to save a life. Derives its names from a pathognomonic chest radiograph, but certain patients with this condition have normal findings or ordinary infiltrates on the chest radiograph.

Multidrug-resistant TB (MDR TB). TB disease caused by an *M. tuberculosis* strain that is resistant to at least INH and rifampin. Treatment regimens for curing MDR TB are long, expensive, and difficult to tolerate. The cure rate depends on the susceptibility of *M. tuberculosis* to alternative chemotherapy.

***Mycobacterium bovis* (*M. bovis*).** A member organism of *M. tuberculosis* complex and the causative infectious agent of TB in cattle. It also causes infection and disease in humans, who become infected by consuming unpasteurized dairy products from tuberculous cows. Human *M. bovis* TB disease has certain distinctive characteristics but in practical terms is indistinguishable from human-variant TB. Human pulmonary *M. bovis* TB disease probably is transmissible to other humans by the airborne route, and secondary cases can result, especially among vulnerable contacts.

***Mycobacterium tuberculosis* (*M. tuberculosis*).** The namesake member organism of *M. tuberculosis* complex, and the most common causative infectious agent of TB disease in humans. At times, the species name refers to the entire *M. tuberculosis* complex, which includes *M. bovis* and five other related species.

Nucleic acid amplification (NAA). A laboratory method used to target and amplify a single DNA or RNA sequence for detecting and identifying (typically) a microorganism. NAA tests for *M. tuberculosis* complex are sensitive and specific; they can accelerate confirmation of pulmonary TB disease.

Purified protein derivative (PPD) tuberculin. A material used in diagnostic tests for *M. tuberculosis* infection. In the United States, PPD solution (5 tuberculin units per 0.1 mL) is approved for administration as an intradermal injection as a diagnostic aid for *M. tuberculosis* infection (latent infection or TB disease). PPD tuberculin also was one of the antigens in the first-generation QuantiFERON-TB test.

QuantiFERON®-TB test. An in vitro cytokine assay that detects cell-mediated immune response (see also DTH) to *M. tuberculosis* in heparinized whole blood from venipuncture. This test requires only a single patient encounter, and the result can be ready ≤1 day. In 2005, QuantiFERON®-TB is being replaced by QuantiFERON®-TB Gold, which has greater specificity because of its synthetic antigens. QuantiFERON®-TB Gold appears capable of distinguishing between the sensitization caused by *M. tuberculosis* infection and that caused by BCG vaccination.

Radiography. The diagnostic imaging techniques (including plain-film chest radiographs and computerized tomography) that rely on degrees of X-radiation transmission related to differences in tissue densities.

Secondary (TB) case. A new case of TB disease that is attributed to recent (i.e., <2 years) transmission as part of a scenario under investigation. Technically, all cases are secondary, in the sense that they arise from other cases that are contagious.

Secondary (or "second-generation") transmission. Transmission of *M. tuberculosis* from persons with secondary cases (see Secondary (TB) case). This creates a chain of transmission, and if secondary transmission is identified as part of a contact investigation, the scenario can be classified as an outbreak.

Smear. A laboratory technique for preparing a specimen so bacteria can be visualized microscopically. Material from the specimen is spread onto a glass slide (and typically dried and stained). Smear, stain, and microscopy methods for mycobacteria are specific to this genus (see AFB). The slide can be scanned by light or fluorescent high-power microscopy. These methods require ongoing quality assurance for prompt and reliable results. The results for sputum AFB smears typically are reported as numbers of AFB per high-powered microscopy field, or else as a graded result, from no AFB to 4+ AFB. The quantity of stained organisms is associated with degree of infectiousness.

Source case or patient. The case or person that was the original source of infection for secondary cases or contacts. The source case can be, but is not necessarily, the index case.

Specimen. Any bodily fluid, secretion, or tissue sent to a laboratory for testing.

Sputum. Mucus containing secretions coughed up from within the lungs. Tests of sputum (e.g., smear and culture) can confirm pulmonary TB disease. Sputum is different from saliva or nasal secretions, which are unsatisfactory specimens for detecting TB disease. However, specimens suspected to be inadequate should still be processed because positive cultures can still be obtained and may be the only bacteriologic indication of disease.

Suspected TB. A tentative diagnosis of TB that will be confirmed or excluded by subsequent testing. Cases should not remain in this category for >3 months.

Symptomatic. A term applied to a patient with health-related complaints (i.e., symptoms) that might indicate the presence of disease. At times, the term is applied to a medical condition (e.g., symptomatic pulmonary TB).

TB disease. See discussion under Infection.

Treatment for LTBI. Treatment that prevents the progression of infection into TB disease.

Tuberculin. A precipitate made from a sterile filtrate of *M. tuberculosis* culture medium.

Tuberculin skin test (TST). A diagnostic aid for finding *M. tuberculosis* infection. A small dose of tuberculin (see also Mantoux method and PPD) is injected just beneath the surface of the skin by the Mantoux method, and the area is

examined for induration by palpation 48–72 hours after the injection. Indurated margins should be read transverse (perpendicular) to the long axis of the forearm.

Tuberculin skin test conversion. See Conversion.

Tuberculosis (TB). A clinically active, symptomatic disease caused by infection with a member of the *M. tuberculosis* complex.

Two-step (tuberculin) skin test. A procedure used for baseline skin testing of persons who will periodically receive TSTs (e.g., health-care workers or residents of long-term–care facilities) to reduce the likelihood of mistaking a boosted reaction for a new infection. If an initial TST result is classified as negative, a second test is repeated 1–3 weeks later. If the reaction to the second TST is positive, it probably represents a boosted reaction, indicating that the infection was most likely in the past and not recent. If the second TST is also negative, the person is classified as not being infected. Two-step skin testing has no place in contact investigations or in other circumstances in which ongoing transmission of *M. tuberculosis* is suspected.

Appendix B

Recommendations for the Investigation of Contacts of Persons with Infectious Tuberculosis (TB)

Decision to Initiate a Contact Investigation

- The features of the TB case under investigation inform decisions about whether to perform a contact investigation (see Figure 1). An investigation (i.e., seeking and evaluating contacts) is recommended for the following forms of suspected or confirmed TB because they are likely to be infectious: pulmonary, laryngeal, or pleural TB disease with 1) pulmonary cavities, 2) respiratory specimens that have acid-fast bacilli (AFB) on microscopy, or 3) both.
- As time and resources permit and as recommended investigations are completed successfully, other pulmonary TB cases may be investigated if they are confirmed by culture of respiratory secretions.
- Pulmonary TB cases without positive mycobacteriology results should not be investigated unless circumstances indicate otherwise (e.g., if mycobacteriologic results are absent because of an error or if a priori information raises suspicion that contacts have been infected).
- The only forms of purely extrapulmonary TB (i.e., cases without pulmonary disease) that should be investigated are laryngeal or pleural disease. For other forms, source-case investigations can be considered under special circumstances (see Source-Case Investigations).

Investigating the Index Patient and Sites of Transmission

- Written policies and procedures for these tasks improve uniformity and efficiency.
- Tasks should be assigned to trained and experienced public health workers.
- Interviews should be in the index patient's primary language and be conducted by persons fluent in that language or in conjunction with fluent interpreters.
- The index patient should be interviewed in person (i.e., not by telephone) ≤1 business day after notification for cases indicating infectiousness and ≤3 business days for others. For patients who have died or who are inaccessible, alternative sources of information regarding contacts should be sought.
- The place of residence for the index patient should be visited ≤3 business days of initiating the contact investigation.
- All potential settings for transmission should be visited ≤5 working days of initiating the contact investigation.
- The contact list and priority assignments (see Assigning Priorities to Contacts) should be written into an investigative plan.
- Information regarding the index patient should be reassessed at least weekly until drug-susceptibility results are available for the *Mycobacterium tuberculosis* isolate, for 2 months after notification, or until infectiousness has diminished, whichever is longer.
- At 1–2 weeks after the first interview, the index patient should be interviewed again as necessary for clarification and additional information.

Assigning Priorities to Contacts

- Priorities for ranking contacts for investigation are set on the basis of the characteristics of the index patient, the duration and circumstances of exposure, and the vulnerability or susceptibility of the contact to disease progression from *M. tuberculosis* infection.
- The optimal exposure cut-off durations for assigning priorities to contacts have not been determined because available data lack this level of precision. The National Tuberculosis Controllers Association work group did not reach consensus on cut-off durations. On the basis of local experience and adjusting for resource limitations, public health officials should set local standards for the durations of exposure that define high, medium, and low priority.

Diagnostic and Public Health Evaluation of Contacts

General

- Health departments are responsible for ensuring that TB contacts are medically evaluated and treated.
- Communicable disease regulations or laws in certain jurisdictions apply to contacts who are not responsive to requests to be examined. The least restrictive means should be applied first.

- Each high- and medium-priority contact should be assessed initially ≤3 working days after being listed.
- Each high- and medium-priority contact should be evaluated medically to determine whether TB disease and latent infection with *M. tuberculosis* are present or absent.
- The same diagnostic methods are recommended for all contacts except when they have medical or constitutional conditions making TB more likely or more difficult to diagnose. A contact's country of origin and Bacille Calmette-Guérin (BCG) vaccination status are not included in algorithms for diagnosis or treatment.

Voluntary HIV Counseling, Testing, and Referral

- Inform all contacts that HIV infection is the greatest known risk factor for TB disease progressing from *M. tuberculosis* infection, and ask whether they have been tested for HIV infection.
- Offer voluntary HIV counseling, testing, and referral to TB contacts who do not know their HIV infection status. Collaboration with HIV-AIDS programs is recommended for establishing systems that are convenient and flexible for patients.
- Voluntary HIV counseling, testing, and referral are recommended for contacts of HIV-infected infectious TB patients.

Tuberculin Skin Testing

- A tuberculin skin test (TST) is recommended for all contacts who do not have a documented prior positive test result or documented prior TB disease. The skin test can be administered at the time of the initial assessment. High-priority contacts should receive a test ≤7 days after they are listed, and medium-priority contacts ≤14 days.
- A two-step TST as defined for infection control surveillance is not recommended for contact investigations.

Evaluation of Children Aged <5 Years

- Contacts aged <5 years exposed to an infectious index patient are assigned a high priority.
- Contacts aged <5 years should be medically examined and have a chest radiograph regardless of the result of the current or prior skin tests or history of prior TB disease.

Evaluation of HIV-infected or Other Immunocompromised Contacts

- HIV-infected or other immunocompromised contacts are high-priority contacts.
- In addition to a medical history, examination, and a TST, a chest radiograph is recommended for all these contacts. Sputum collection for AFB microscopy and culture is recommended if the contact has symptoms consistent with TB disease or if the chest radiograph has abnormalities that could be caused by TB.

Any Contacts Being Evaluated

- Contacts who have a positive TST result (≥5 mm) should be medically examined, including a chest radiograph, to rule out TB disease. Contacts who have symptoms consistent with TB also should be medically evaluated, including a chest radiograph, to rule out TB, regardless of the results of the skin test, history of a prior positive result, or history of prior TB disease.
- During the infectious period, those high- and medium-priority contacts who have a negative skin test result <8 weeks after their most recent exposure should have a second skin test 8–10 weeks after that exposure.
- For low-priority contacts, the initial skin test may be delayed until 8–10 weeks after the most recent exposure if the contact does not have symptoms suggestive of TB disease. If the test is administered <8 weeks after the most recent exposure, the decision to give a second, postexposure skin test can be made on a case-by-case basis.

Treatment for Contacts with *M. tuberculosis* Infection

- Treating contacts who have latent *M. tuberculosis* infection through completion is a health department responsibility to prevent communicable diseases.
- High- and medium-priority contacts with positive TSTs who come from countries with prevalent TB should be treated, regardless of whether they have had routine BCG vaccination.
- Treatment for latent infection should be offered to all contacts who have a positive tuberculin skin test result, after active TB is excluded. The emphasis of the program should be on completing treatment in high- and medium-priority contacts.

- Window-period prophylaxis (see Diagnostic and Public Health Evaluation of Contacts) is recommended as an option for contacts aged <5 years who have a negative skin test result <8 weeks after the end of exposure, after TB disease has been excluded. If a second skin test result 8–10 weeks after the end of exposure is negative, treatment can be stopped.
- A full course of treatment for presumptive *M. tuberculosis* infection is recommended for HIV-infected or otherwise notably immune-suppressed contacts, after TB disease has been excluded, even if skin test results are negative >8 weeks after the end of exposure.
- The decision to treat contacts who have documentation of a previous positive skin test result or TB disease should be made on an individual basis. Treatment is recommended for HIV-infected contacts in this category, even if infection has been treated previously.
- Rifampin treatment is recommended for contacts who, after TB disease has been excluded, have infection presumed to be isoniazid (INH)-resistant, rifampin-susceptible *M. tuberculosis* after exposure to an index patient with such an isolate.
- Expert consultation is recommended for selecting treatment for a latent infection with presumed INH- and rifampin-resistant *M. tuberculosis*. Contacts with such an infection should be monitored with periodic examination for at least 2 years.
- Directly observed therapy (DOT) for latent infection is preferred over self supervised. DOT preference should be assigned to these groups, in this general order:
  - — confirmed or suspected TB disease;
  - — latent *M. tuberculosis* infection in contacts aged <5 years;
  - — latent *M. tuberculosis* infection in contacts who have HIV infection or other conditions that limit immune response to TB;
  - — latent *M. tuberculosis* infection in contacts with documented change in tuberculin sensitivity, from a negative to a positive result; and
  - — latent *M. tuberculosis* infection in contacts who might not complete treatment because of social or behavioral impediments (e.g., alcohol addiction, chronic mental illness, injection-drug use, unstable housing, unemployment).
- Monitoring for adherence and adverse effects by home visits, pill counts, or clinic appointments monthly or more often is recommended for contacts on self-administered treatment.
- Use of enablers and incentives and establishment of a positive rapport with contacts who are taking treatment are recommended for enhancing adherence.

When to Expand a Contact Investigation

- Inclusion of lower-priority contacts generally is not recommended unless objectives for high- and medium-priority contacts are being met.
- Consider expanding the scope (i.e., number of contacts) of an investigation if any one or more of the following criteria exist:
  - — unexpectedly large rate of infection or TB disease in high-priority contacts,
  - — evidence of second-generation transmission,
  - — TB disease in any contacts who had been assigned low priority,
  - — infection in any contacts aged <5 years, and
  - — contacts with change in skin test status from negative to positive.
- After reviewing the results from the investigation to date (i.e., for high- and medium-priority contacts), select the additional contacts by extrapolating the risks for infection as shown by the data.
- When results from an investigation indicate that it should be expanded, but resources are insufficient, seeking assistance from the next higher public-health administrative level is recommended.

Communicating Through the Media

- Anticipatory media communication (e.g., with a press release) for large or highly visible TB contact investigations is recommended to capitalize on the opportunity for constructive public communications.
- Coordination of media communications, both within the health department and with collaborating partners outside the health department, improves the clarity and consistency of media messages.
- For efficiency, use of media message templates for contact investigations is recommended.

Data Management and Evaluation of Contact Investigations

- Collection of specific data elements on index patients and their contacts is recommended. The data elements should permit calculation of program performance indices.
- Data should be collected on standardized (paper or electronic) forms.
- Data definitions and formats for use by persons who collect, use, and interpret contact investigation data are recommended.
- Whenever feasible, data definitions and formats should be standard among jurisdictions.
- Electronic data storage is recommended for quick analysis of interim results.
- Policies for data management and storage are recommended, with assignment of responsibilities.
- Training and policies for data accuracy, completeness, and security are recommended. Part of a staff-person's time should be dedicated to reviewing and monitoring contact investigation data.
- Periodic summarization and review of data are recommended during a particular contact investigation and overall.
- Program evaluation for contact investigation activities, at least annually, is recommended. It is an integral part of TB program responsibility.
- Beyond standard data elements shown in these guidelines, specific additional elements can contribute to local program management.

Confidentiality and Consent in Contact Investigations

- Specific policies for release of confidential information related to contact investigations are recommended. These policies should be consistent with the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Sections 306 and 308(d) of the Public Health Service Act and be developed in consultation from health department legal counsel. These policies typically include instructions for obtaining consents and for breaking confidentiality when required for public health as authorized by laws.
- Patient confidentiality is a core element integrated with all activities in contact investigations, and training in its laws and practice is recommended for all personnel who participate.
- Discussion with the index patient and contacts regarding their confidentiality beliefs and concerns is recommended. TB control program staff should explain to the index patient the measures that will be taken to maintain confidentiality.
- Preparations for protecting confidentiality are recommended for each site visit during an investigation. Anticipatory discussions with any patients who might be affected contribute to the preparations.
- Confidentiality applies to all private information and medical conditions in addition to TB.

Staffing and Training for Contact Investigations

- Certain functions in contact investigations require state licensure. Delineation of these functions is recommended for preparing personnel position descriptions.
- Specialized functions and related skills are needed during contact investigations; they might be provided by sources outside of the health department (Box 3).
- Preparatory training and detailed on-the-job supervision as each function is encountered by new health department personnel establish the basis for expertise.
- Direct observation by experienced personnel and opportunities for practicing skills are essential when any personnel assume new functions for contact investigations.
- Clerical personnel, receptionists, and managers who help with contact investigations need to understand the overall purpose and methods of contact investigations.
- When sources outside the health department serve essential functions in a contact investigation, the health department is responsible for assessing whether the skills are sufficient and offering training so that the functions are met correctly.

Contact Investigations in Special Circumstances

- A cluster of TB cases (i.e., a presumed outbreak) indicates potential lapses in TB control which should be investigated along with the outbreak. Assistance should be requested if the scope of the investigation exceeds local capacity or disrupts key activities of TB control.
- When secondary TB cases are discovered unexpectedly (e.g., outside of a contact investigation), this indicates a

potential outbreak. Review of the investigative strategy is recommended.
- When contact investigations include congregate settings, officials or administrators at the setting should be enlisted as collaborators. Access to employee and occupancy rosters should be sought. Sensitivities and needs of the setting and its populace should be accommodated to the extent permitted by good public health practice.
- When few contacts are listed because information cannot be obtained from an index TB patient, alternative or proxy methods, such as interviews in the extended social network, are recommended.
- Contact investigations for multidrug-resistant TB do not require a change in procedures, but the reasons for the drug resistance should be explored.
- Interjurisdictional contact investigations should be planned collaboratively from the inception. Assistance in coordinating such investigation should be sought from the next higher public-health administrative level.
- Unusual exposures to *M. tuberculosis*-complex, such as laboratory accidents or tuberculous animals, should be investigated on site, and contacts should be selected in accordance with the event, in consultation with subject-matter experts.

Source-Case Investigations

- Source-case investigations are not recommended unless investigations of infectious cases have been successfully completed and program objectives for investigating contagious patients and treating their infected contacts are being met.
- Source-case investigations, if conducted, are recommended for TB disease in children aged <5 years.
- Data on source-case investigations should be reviewed for determining the value of these investigations in the local context.
- Searching for a source of unexplained latent *M. tuberculosis* infection is not recommended, and if conducted, should be reserved for infected children aged <2 years.

Other Topics

Cultural Competency

- Systems for providing culturally and linguistically acceptable care during contact investigations are recommended.
- Training in cultural and linguistic sensitivity is recommended for personnel who conduct contact investigations.

Social Network Analysis

- The methods of social network analysis are recommended for further research. However, certain concepts (e.g., setting-based investigations) are also applicable to current efforts.

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports | December 16, 2005 / Vol. 54 / No. RR-15

Continuing Education Activity Sponsored by CDC

Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis
Recommendations from the National Tuberculosis Controllers Association and CDC

EXPIRATION — December 16, 2008

You must complete and return the response form electronically or by mail by **December 16, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.75 hours Continuing Medical Education (CME) credit; 0.25 Continuing Education Units (CEUs); 3.2 contact hours Continuing Nursing Education (CNE) credit; or 2.5 contact hours National Commission for Health Education Credentialing (NCHEC) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

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1. Read this *MMWR* (Vol. 54, RR-15), which contains the correct answers to the questions beginning on the next page.
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1. Read this *MMWR* (Vol. 54, RR-15), which contains the correct answers to the questions beginning on the next page.
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   Fax: 770-488-8555
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   Division of Scientific Communications
   Coordinating Center for Health Information and Service, MS K-95
   Centers for Disease Control and Prevention
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   Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report provides expanded guidelines concerning the investigation of tuberculosis (TB) exposure and transmission and prevention of future cases of TB through contact investigations. The goal of this report is to provide standard and comprehensive guidance for this public health activity that will lead to improved outcomes for persons exposed to infectious TB. Upon completion of this educational activity, the reader should be able to 1) discuss when to initiate a contact investigation; 2) discuss how to prioritize the evaluation of contacts; 3) discuss the diagnostic evaluation of contacts, including children aged <5 years old and immunocompromised contacts; 4) discuss the medical treatment of contacts who have latent tuberculosis infection [LTBI]; and 5) discuss when to expand a contact investigation.

To receive continuing education credit, please answer all of the following questions.

1. What factors predict transmission of TB?
A. Anatomical site of disease.
B. Sputum bacteriology.
C. Radiographic findings.
D. Administration of effective treatment.
E. All of the above.

2. The infectious period is usually determined to be 3 months before the diagnosis of TB.
A. True.
B. False.

3. The most important characteristics of contacts for assigning priority are age and immune status.
A. True.
B. False.

4. Two-step tuberculin skin tests (TSTs) are recommended for the evaluation of foreign-born contacts.
A. True.
B. False.

5. Contacts with TST reactions ≥5 mm should undergo further medical evaluation, including a chest radiograph.
A. True.
B. False.

6. Which contacts should be considered for window prophylaxis?
A. Children aged <5 years.
B. Healthy adults
C. Contacts who are immunocompromised.
D. College students.
E. All of the above.
F. A and B.
G. A and C.

7. Source-case investigations are recommended for adults with TB disease.
A. True.
B. False.

8. Which best describes your professional activities:
A. Physician.
B. Nurse.
C. Health educator.
D. Office staff.
E. Other.

9. I plan to use these recommendations as the basis for…(*Indicate all that apply.*)
A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

10. Overall, the length of the journal report was…
A. much too long.
B. a little too long.
C. just right.
D. a little too short.
E. much too short.

11. After reading this report, I am confident I can discuss when to initiate a contact investigation.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

12. After reading this report, I am confident I can discuss how to prioritize the evaluation of contacts.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

13. After reading this report, I am confident I can discuss the diagnostic evaluation of contacts, including children aged <5 years and immunocompromised contacts.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

14. After reading this report, I am confident I can discuss the medical treatment of contacts who have LTBI.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can discuss when to expand a contact investigation.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. The learning outcomes (objectives) were relevant to the goals of this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. The instructional strategies (text, tables, boxes, figures, and appendices) used in this report helped me learn the material.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. The content was appropriate given the stated objectives of the report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

***MMWR* Response Form for Continuing Education Credit**
December 16, 2005/Vol. 54/No. RR-15

Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis
Recommendations from the National Tuberculosis Controllers Association and CDC

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Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	14. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
2. [ ]A	[ ]B				15. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
3. [ ]A	[ ]B				16. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
4. [ ]A	[ ]B				17. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
5. [ ]A	[ ]B				18. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
6. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E [ ]F [ ]G	19. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
7. [ ]A	[ ]B				20. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
8. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	21. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
9. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	22. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
10. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	23. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E
11. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	24. [ ]A	[ ]B			
12. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E	25. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E [ ]F
13. [ ]A	[ ]B	[ ]C	[ ]D	[ ]E					

Signature ***Date I Completed Exam***

22. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

23. The *MMWR* format was conducive to learning this content.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. Do you feel this course was commercially biased? (*Indicate yes or no; if yes, please explain in the space provided.*)

A. Yes.
B. No.

25. How did you learn about the continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–7:
1. E; 2. T; 3. T; 4. F; 5. T; 6. G; 7. F.

Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting *Mycobacterium tuberculosis* Infection, United States

Prepared by
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Summary

On May 2, 2005, a new in vitro test, QuantiFERON®-TB Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia), received final approval from the U.S. Food and Drug Administration as an aid for diagnosing Mycobacterium tuberculosis *infection. This test detects the release of interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides representing two proteins present in* M. tuberculosis: *early secretory antigenic target–6 (ESAT-6) and culture filtrate protein–10 (CFP-10). These antigens impart greater specificity than is possible with tests using purified protein derivative as the tuberculosis (TB) antigen. In direct comparisons, the sensitivity of QFT-G was statistically similar to that of the tuberculin skin test (TST) for detecting infection in persons with untreated culture-confirmed tuberculosis (TB). The performance of QFT-G in certain populations targeted by TB control programs in the United States for finding latent TB infection is under study. Its ability to predict who eventually will have TB disease has not been determined, and years of observational study of substantial populations would be needed to acquire this information. In July 2005, CDC convened a meeting of consultants and researchers with expertise in the field to review scientific evidence and clinical experience with QFT-G. On the basis of this review and discussion, CDC recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control (e.g., those for health-care workers). This report provides specific cautions for interpreting negative QFT-G results in persons from selected populations. This report is aimed at public health officials, health-care providers, and laboratory workers with responsibility for TB control activities in the United States.*

Background

On May 2, 2005, a new in vitro test, QuantiFERON®-TB Gold (QFT-G, manufactured by Cellestis Limited, Carnegie, Victoria, Australia), received final approval from the U.S. Food and Drug Administration (FDA) as an aid in diagnosing *Mycobacterium tuberculosis* infection, including both latent tuberculosis infection (LTBI) and tuberculosis (TB) disease. This enzyme-linked immunosorbent assay (ELISA) test detects the release of interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: early secretory antigenic target–6 (ESAT-6) and culture filtrate protein–10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all Bacille Calmette-Guérin (BCG) vaccine strains and from commonly encountered nontuberculous mycobacteria (NTM) except *M. kansasii*, *M. szulgai*, and *M. marinum* (*1*), QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin purified protein derivative (PPD) as the antigen.

QFT-G represents one type of IFN-γ release assay (IGRA) (*2*). Tests such as QFT-G measure the IFN-γ released by sensitized white blood cells after whole blood is incubated with antigen. Tests such as ELISpot enumerate cells releasing IFN-γ after mononuclear cells recovered from whole blood are incubated with similar antigens. Two IGRAs have been approved by FDA for use in the United States: the original QuantiFERON®-TB test (QFT) and the recently approved QFT-G. The two tests use different antigens to stimulate IFN-γ release, different methods of measurement, and different approaches to test interpretation. QFT was approved as an aid for diagnosing LTBI, whereas QFT-G is approved as an aid for diagnosing both LTBI and TB disease. QFT is no longer commercially available.

The material in this report originated in the National Center for HIV, STD, and TB Prevention, Kevin Fenton, MD, PhD, Director, and the Division of Tuberculosis Elimination, Kenneth G. Castro, MD, Director.
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Before QFT was approved in 2001, the tuberculin skin test (TST) was the only test available for detecting LTBI (*3*). QFT-G is intended to replace QFT. QFT-G results can be available <24 hours after testing without the need for a second visit, whereas a TST requires a second encounter to read the result 48–72 hours after administration of the test. As a laboratory-based assay, QFT-G is not subject to biases and errors of TST placement and reading. However, errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of QFT-G. Related to the uncertainty in interpreting a test result, including that of the TST, when the test's measurement approaches a fixed cut-off point, the reproducibility of QFT-G is less when the measured amount of IFN-γ is near the test's cut-off point. Detection of substantial amounts of released IFN-γ in the nil sample disallows arriving at a negative test result.

Each of the three tests (TST, QFT, and QFT-G) relies on a different immune response and differs in its relative measures of sensitivity and specificity. The TST assesses in vivo delayed-type hypersensitivity (Type IV), whereas QFT and QFT-G measure in vitro release of IFN-γ. The TST and QFT measure response to PPD, a polyvalent antigenic mixture, whereas QFT-G measures response to a mixture of synthetic peptides simulating two specific antigenic proteins that are present in PPD. The agreement between TST and QFT results in persons at increased risk for LTBI facilitated approval and acceptance of QFT (*3,4*). Results of similar studies using QFT-G testing for persons at increased risk have not been published, but less agreement between TST and QFT-G results is predictable because fewer and more specific antigens are used in QFT-G. QFT-G is not affected by prior BCG vaccination (*1*) and is expected to be less influenced by previous infection with nontuberculous mycobacteria (*5*). TSTs are variably affected by these factors. QFT-G does not trigger an anamnestic response (i.e., boosting) because it does not expose persons to antigen. Injection of PPD for the TST can boost subsequent TST responses, primarily in persons who have been infected with NTM or vaccinated with BCG. Compared with the TST, QFT-G might be less affected by boosting from a previous TST.

Assessment of the accuracy of QFT-G and other indirect tests for *M. tuberculosis* infection (including TSTs) is hampered by the lack of confirmatory tests to diagnose LTBI and culture-negative TB disease (*6*). This lack is partially addressed by observing the proportion of negative tests among persons who are unlikely to have *M. tuberculosis* infection because they lack risks (this approach approximates specificity); by observing the proportion positive among persons with culture-confirmed TB disease (this approach approximates sensitivity); and by determining factors associated with discordance between a new test and the TST. One limitation of the first approach is that certain persons who have no recognized risks might be infected with *M. tuberculosis*, which causes specificity to be underestimated. A broad limitation is that the TST and any newer tests might not perform the same for detecting LTBI as they do for detecting *M. tuberculosis* infection during TB disease. For example, reduction of in vitro IFN-γ release has been attributed to suppressive cytokines associated with TB disease (*7*). When comparing an IGRA with a TST, variations in methods also must be considered (e.g., use of different antigens or risk-stratified cut-off points for interpreting results).

Studies assessing QFT-G with these approximation methods have been published (*5,8,9*). A specificity of 98.1% was reported in 216 BCG-vaccinated Japanese nursing students who were entering their training and who were at low risk for *M. tuberculosis* infection, and a sensitivity of 89.0% was reported in 118 patients with culture-confirmed TB (*5*). However, QFT-G results were derived slightly differently than the methods approved by FDA. In another study (*8*), QFT-G was compared with TST by using two tuberculin units of RT-23 (*8,10*). In a group of 99 healthy, BCG-vaccinated medical students in Korea, the specificity of QFT-G was 96%, compared with 49% for the TST. Among 54 patients with pulmonary TB disease, the sensitivity of the QFT-G was 81%, compared with 78% for the TST (*8*). QFT-G and the TST were compared in an unselected population of 318 hospitalized patients (*9*). QFT-G had greater sensitivity for TB disease (67%) than did TST (33%), but indeterminate QFT-G responses were common (21%) among patients with negative TST results, the majority of whom were thought to be immunocompromised or immunosuppressed.

The antigens or laboratory methods in other studies have varied (*2*). Although the findings are informative, how QFT-G will perform in the same circumstances is unknown. In an investigation of contacts in a high school in Denmark in which a student had infectious TB, the same ELISA used with QFT-G was employed, but with recombinant ESAT-6 and CFP-10 antigens used rather than the mixtures of synthetic peptides used with QFT-G (*11*). The IGRA used in that study agreed well with the TST in non-BCG–vaccinated contacts. BCG-vaccinated contacts were not skin tested, but their IGRA results closely paralleled those for the nonvaccinated contacts, which suggested that BCG vaccination was not affecting the results of this IGRA.

Methodology

During July 11–12, 2005, CDC convened a meeting in Atlanta, Georgia, of consultants and researchers with expertise in the field to review studies and assess experience with

QFT-G. Unpublished data from studies of QFT-G were considered in preparing these guidelines. Expert consultants (see Membership List), researchers, TB control public health practitioners, and representatives of FDA, other federal agencies, and the manufacturer reviewed the evolving data on QFT-G. Data from ongoing studies evaluating QFT-G in U.S. Navy recruits, correctional facility inmates, persons with suspected TB disease, contacts of persons suspected to have TB disease, and health care workers were reviewed. For developing these guidelines, CDC considered the scientific evidence and the opinions of the consultants. Their opinions did not represent endorsement from their organizations.

This report provides interim guidance for use and interpretation of QFT-G. Confirming or excluding TB disease and assessing the probability of LTBI require a combination of epidemiologic, historic, physical, and diagnostic findings that should be considered when interpreting QFT-G results. This report is intended to assist public health officials, clinicians, and laboratorians in their efforts to understand the use of QFT-G for TB control.

Indications for QFT-G

FDA approved QFT-G as an in vitro diagnostic aid using peptide mixtures simulating ESAT-6 and CFP-10 proteins to stimulate cells in heparinized whole blood. Detection of IFN-γ by ELISA is used to identify in vitro responses to ESAT-6 and CFP-10 that are associated with *M. tuberculosis* infection (*12*). From a medical and public health perspective, QFT-G testing is indicated for diagnosing infection with *M. tuberculosis*, including both TB disease and LTBI. Whenever *M. tuberculosis* infection or disease is being diagnosed by any method, the optimal approach includes coordination with the local or regional public health TB control program.

How QFT-G Testing is Performed and Interpreted

Instructions for the QFT-G assay are in the package insert (*13*). Aliquots of heparinized whole blood are incubated with the test antigens for 16–24 hours. The blood must be incubated with the test antigens ≤12 hours after collection. Test kits include two mixtures of synthetic peptides representing ESAT-6 and CFP-10 as test antigens, phytohemaglutinin (a mitogen used as a positive assay control), and saline (used as a nil sample to measure the background level of IFN-γ). After incubation, the concentration of IFN-γ in the plasma is determined by ELISA by using the reagents included in the test kit. The amount of IFN-γ released is determined by subtracting the amount in the nil from the amount in the ESAT-6, CFP-10, or mitogen-stimulated plasma. QFT-G test results can be calculated by using software provided by the manufacturer. This report provides guidelines for interpreting test results (Table). Laboratory reports should include interpretation of QFT-G test results and indicate the concentration of IFN-γ in each plasma sample.

Cautions and Limitations

Certain limitations of QFT-G are similar to those of the TST, but these limitations have not been studied extensively for QFT-G. Whereas the sensitivity of QFT-G for detecting *M. tuberculosis* infection in persons with untreated culture-

TABLE. Interpretation of QFT-G* results, from IFN-γ† concentrations in test samples

ESAT-6–nil§ or CFP-10–nil¶ or both	Nil	Mitogen–nil**	QFT-G result	Interpretation
≥0.35 IU/mL†† and >50% above nil	Any	Any	Positive	*Mycobacterium tuberculosis* infection likely
<0.35 IU/mL	≤0.7	≥0.5	Negative	*M. tuberculosis* infection unlikely but cannot be excluded, especially when illness is consistent with TB§§ disease and likelihood of progression to TB disease is increased
<0.35 IU/mL	Any	<0.5	Indeterminate	QFT-G results cannot be interpreted as a result of low mitogen response
≤50% above nil	>0.7	Any	Indeterminate	QFT-G results cannot be interpreted as a result of high background response

* QuantiFERON®-TB Gold test.
† Interferon-gama.
§ The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating early secretory antigenic target–6 (ESAT-6) minus the IFN-γ concentration in blood incubated with saline.
¶ The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating culture filtrate protein–10 (CFP-10) minus the IFN-γ concentration in blood incubated with saline.
** IFN-γ concentration in blood incubated with mitogen minus the IFN-γ concentration in blood incubated with saline.
†† International units per mL.
§§ Tuberculosis.

confirmed TB is approximately 80% in published studies (*5,8*), its sensitivity for particular groups of TB patients (e.g., young children and immunocompromised patients) has not been determined.

QFT-G sensitivity for LTBI might be less than that of the TST, although the lack a confirmatory test makes this difficult to assess. Estimating the sensitivity of any indirect test for LTBI by testing patients who have TB disease might be inaccurate because of differences between these conditions. The ability of QFT-G to predict risk for LTBI progressing subsequently to TB disease has not been determined.

QFT-G, as with the TST, cannot differentiate infection associated with TB disease from LTBI. A diagnosis of LTBI requires that TB disease be excluded by medical evaluation, which should include checking for suggestive symptoms and signs, a chest radiograph, and, when indicated, examination of sputum or other clinical samples for the presence of *M. tuberculosis*.

Similar to any other diagnostic test, the predictive value of QFT-G results depends on the prevalence of *M. tuberculosis* infection in the population being tested. Each QFT-G result and its interpretation should be considered in conjunction with other epidemiologic, historic, physical, and diagnostic findings.

As with a negative TST result, negative QFT-G results should not be used alone to exclude *M. tuberculosis* infection in persons with symptoms or signs suggestive of TB disease. The presence of symptoms or signs suggestive of TB disease increases the likelihood that *M. tuberculosis* infection is present, and these circumstances decrease the predictive value of a negative QFT-G or TST result. Medical evaluation of such persons should include a history and physical examination, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus (HIV), and, when indicated, other tests or studies.

The performance of QFT-G, in particular its sensitivity and its rate of indeterminate results, has not been determined in persons who, because of impaired immune function, are at increased risk for *M. tuberculosis* infection progressing to TB disease. Impaired immune function can be caused by HIV infection or acquired immunodeficiency syndrome (AIDS); current treatment with immunosuppressive drugs including high-dose corticosteroids, tumor necrosis factor-alpha (TNF-α) antagonists, and drugs used for managing organ transplantation; selected hematologic disorders (e.g., myeloproliferative disorders, leukemias, and lymphomas); specific malignancies (e.g., carcinoma of the head, neck, or lung); diabetes; silicosis; and chronic renal failure (*6*). Each of these conditions or treatments is known or suspected to decrease responsiveness to the TST, and they also might decrease production of IFN-γ in the QFT-G assay. Consequently, as with a negative TST result, negative QFT-G results alone might not be sufficient to exclude *M. tuberculosis* infection in these persons.

Published data are relatively limited concerning the use of QFT-G among persons recently exposed to TB (e.g., contacts) and other populations at high risk for LTBI. No published data document the performance of QFT-G in children aged <17 years.

With any of the testing methods, persons who have a negative test result can still have LTBI. Those who have a negative result but who are likely to have LTBI and who are at greater risk for severe illness or poor outcomes if TB disease occurs might need treatment or closer monitoring for disease (*6*). Potential examples include close contacts who are aged <5 years, those who are immunocompromised because of HIV infection, or those who will undergo treatment with TNF-α antagonists (which increase the risk for progression from LTBI to TB disease) (*14–16*).

QFT-G has practical limitations that include the need to draw blood and to ensure its receipt in a qualified laboratory in time for testing. The blood must be incubated with the test antigens ≤12 hours after collection, while the lymphocytes are viable. After the blood is incubated with antigens for 16–24 hours, plasma must be collected and either properly stored or tested promptly by ELISA. Collecting the required 5-mL blood sample from younger children might not be possible or acceptable.

Additional Considerations and Recommendations in the Use of QFT-G in Testing Programs

QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health-care workers and others undergoing serial evaluation for *M. tuberculosis* infection. QFT-G usually can be used in place of (and not in addition to) the TST.

A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. No reason exists to follow a positive QFT-G result with a TST. Persons who have a positive QFT-G result, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed. At a minimum, a chest radiograph should be examined for abnormalities consistent with TB disease. Additional medical evaluation would depend on clinical judgment on the basis of findings from history (including exposure to infectious TB), physical examination, and chest radiography. HIV counseling, testing, and referral is recommended because HIV infection increases the suspicion for TB and the urgency of treating LTBI. After TB has been excluded, treatment of LTBI should be considered (*6*).

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation. However, for persons with recent contact with persons who have infectious TB, negative QFT-G results should be confirmed with a repeat test performed 8–10 weeks after the end of exposure, as is recommended for a negative TST result. Studies to determine the best time to retest contacts with negative QFT-G results have not been reported. Until more information is available, the timing of QFT-G testing should be the same as that used for the TST (*17,18*).

When "window period" prophylaxis (i.e., treatment for presumed LTBI) is indicated for contacts aged <5 years or severely immunocompromised persons who are exposed to highly contagious TB, repeat testing for LTBI is recommended 8–10 weeks after contact has ended (*18*). With either TST or QFT-G, negative results of the test at the end of the window period should be interpreted by considering all available epidemiologic, historic, clinical, physical, and diagnostic information, including the findings for the other contacts in the investigation. A full course of treatment should be considered even with a negative result from either test at the end of the window period when the rate of *M. tuberculosis* transmission to other contacts was high or when a false-negative result is suspected because of a medical condition (*18*).

A greater rate of positive results has been reported with TST than with QFT-G in persons with and without recognized risks for *M. tuberculosis* infection, except for patients who have culture-confirmed TB disease (*5,8*). This tendency might be explained by either greater specificity with QFT-G, greater sensitivity with TST, or both. For this reason, all information must be considered when making treatment decisions for persons with increased risk for progression from LTBI to TB or in whom TB disease is associated with increased risk for severe illness or poor outcomes.

An indeterminate QFT-G result does not provide useful information regarding the likelihood of *M. tuberculosis* infection. The optimal follow-up of persons with indeterminate QFT-G results has not been determined. The options are to repeat QFT-G with a newly obtained blood specimen, administer a TST, or do neither. For persons with an increased likelihood of *M. tuberculosis* infection who have an indeterminate QFT-G result, administration of a second test, either QFT-G or TST, might be prudent. The potential for TST to cause boosting and the need for two-step testing in settings conducting serial testing should be considered. For persons who are unlikely to have *M. tuberculosis* infection, no further tests are necessary after an indeterminate QFT-G result. Laboratories should report the reason that the QFT-G result was indeterminate (e.g., high background levels of IFN-γ in the nil sample or inadequate response to mitogen). In one report, inadequate response to mitogen was associated with immunosuppressive conditions (*9*).

As with the TST, if TB disease is suspected, additional diagnostic evaluations should be performed before or at the same time as the QFT-G and should not be delayed while awaiting QFT-G results. These evaluations should include chest radiography, bacteriologic studies, serology for HIV, and, as indicated by the illness, additional tests and studies. At present, as with the TST, the results of indirect tests for *M. tuberculosis* (e.g., QFT-G) usually would not influence the selection of additional tests and studies in such patients.

TB control programs can use QFT-G for investigating contacts of persons with potentially infectious TB disease. Because QFT-G does not require a second visit to complete, test results probably will be available from a greater percentage of contacts than would be available using TST. Because of its greater specificity, QFT-G is expected to indicate a smaller proportion of contacts as infected than the TST would indicate. Public health resources that previously were devoted to completion of testing can instead be concentrated on full evaluation and complete treatment of contacts who have positive QFT-G results. In contrast to the TST, initial QFT-G testing of contacts will not boost subsequent test results, which avoids uncertainty about interpreting follow-up results. However, QFT-G might be less sensitive for LTBI than the TST, and its ability to predict subsequent development of TB disease is undetermined.

QFT-G might represent a cost-effective alternative to the TST in testing programs which are part of the TB infection control program in institutions such as health care settings, correctional facilities, or homeless shelters. In these settings, false-positive reactions to the TST pose a problem. This problem is compounded in settings with BCG-vaccinated persons born in countries where TB is prevalent. Follow-up visits for reading the TST also pose substantial operational challenges; the second visit for reading requires extra effort and leads to inefficiency. The greater specificity of the QFT-G and the requirement for only one visit are compelling advantages. General recommendations on the use of QFT-G as part of the infection control program in health-care settings have been included in the most recent revision of the TB infection control guidelines (*19*). In situations with serial testing for *M. tuberculosis* infection, initial two-step testing, which is necessary with the TST, is unnecessary with QFT-G and is not recommended.

TB control programs or institutions that elect to use QFT-G should consult and collaborate with laboratories in their system to ensure that specimens are properly obtained, handled, and processed prior to and after arrival in the laboratory.

Information concerning the assay is in the package insert (*13*). Training of laboratory staff will be necessary. Certain facilities might elect to refer specimens for testing. The Clinical Laboratory Improvement Amendments (CLIA) regulations for quality systems of all phases of the total testing process (preanalytic, analytic, and post-analytic) and for general laboratory systems must be followed, including, but not limited to, the requirements for test system, equipment, instruments, reagents, materials and supplies (42 CFR Part 493.1252), and the establishment or verification of performance specifications (42 CFR Part 493.1253) (*20*). In addition, under CLIA, documentation of all quality systems, including laboratory proficiency and staff competency, is required.

Future Research Needs

Additional studies to assess the performance of the QFT-G test under program conditions should be conducted. Further research is needed regarding use of QFT-G in multiple clinical circumstances. Studies of test performance should assess specificity, sensitivity, reproducibility, and association of test results with risk for infection and risk for progressing to TB disease. Comparisons among different IGRAs and TSTs are encouraged. Questions to be addressed include the following:

- performance of QFT-G in young children, especially those aged <5 years;
- performance of QFT-G in persons with impaired immune systems, including persons with HIV/AIDS, those who will be treated with TNF-α antagonists, and others;
- performance and practicality of use of QFT-G in substantial numbers of persons who undergo periodic screening;
- determination of the subsequent incidence of TB disease after LTBI has been either diagnosed or excluded with QFT-G;
- length of time between exposure, establishment of infection, and emergence of a positive QFT-G test result;
- economic evaluation and decision analysis comparing QFT-G with TST;
- changes in QFT-G results during therapy for both LTBI and TB disease;
- ability of QFT-G to detect reinfection after treatment for both LTBI and TB disease; and
- performance of QFT-G in targeted testing programs (e.g., for recent immigrants from high-incidence countries) and contact investigations.

In collaboration with FDA and the manufacturer, CDC will establish mechanisms for postmarketing surveillance. Providers should use FDA's MedWatch (available at http://www.accessdata.fda.gov/scripts/medwatch) to report instances of a contact having all of the following criteria:

- a negative QFT-G or TST result >6 weeks after the end of exposure,
- culture-confirmed TB disease <2 years after the end of exposure, and
- an *M. tuberculosis* isolate that has a genotype identical to that of the presumed source case.

Certain instances consistent with these criteria might require further study of the circumstances. However, reliance on postmarketing surveillance is not a substitute for research targeted at the above-noted questions. Research in these areas and others should therefore be conducted through prospective studies.

The optimal methods for ensuring quality in laboratory implementation of QFT-G testing should be determined. Educational materials are needed that can be widely disseminated to educate physicians regarding the use of the QFT-G assay. CDC will work with partners and the manufacturer to ensure the development of such materials.

Other IGRA tests and test formats might become available in the United States over the next several years (*21,22*). Users of any of these products should anticipate the need for periodic modifications in practice, with resulting improvements in utility of these testing technologies.

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CDC Expert Consultation on QuantiFERON®-TB Gold

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