Eur Respir J 2010; 36: 925–949
DOI: 10.1183/09031936.00201609


**SERIES "UPDATE ON TUBERCULOSIS"**
**Edited by C. Lange, M. Raviglione, W.W. Yew and G.B. Migliori**
**Number 1 in this Series**

# Tuberculosis contact investigation in low prevalence countries: a European consensus

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**ABSTRACT: Contact investigation to identify individuals with tuberculosis and latent infection with *Mycobacterium tuberculosis* is an important component of tuberculosis control in low tuberculosis incidence countries. This document provides evidence-based and best-practice policy recommendations for contact tracing among high- and medium-priority contacts in a variety of settings. It provides a basis for national guidelines on contact investigation and tuberculosis outbreak management, and should support countries and tuberculosis control managers in evaluating and revising national policies. A review of existing guidelines, a literature search, several meetings and consultation with experts were used to formulate and grade recommendations for action during contact investigation.**

**Available tests to identify individuals with latent infection with *M. tuberculosis* are designed to identify immune response against mycobacterial antigens and have variable predictive value for the likelihood to develop active tuberculosis in different populations. Contact investigation should therefore be limited to situations with a clear likelihood of transmission or to those with a higher probability of developing active tuberculosis, for instance, young children and immunocompromised persons. A risk assessment-based approach is recommended, where the need to screen contacts is prioritised on the basis of the infectiousness of the index case, intensity of exposure and susceptibility of contacts.**

**KEYWORDS: Active case finding, contact investigation, consensus statement, latent tuberculosis infection, preventive chemotherapy, tuberculosis**

The primary objective of any tuberculosis control activity is prompt identification and adequate treatment of newly emerging tuberculosis cases. Timely identification and adequate treatment of those with transmissible tuberculosis reduces the risk of exposure of community members. As a result, the future incidence of tuberculosis is diminished, as the prevalence of infection with *Mycobacterium tuberculosis* declines in the cohort with the passage of time. The Stop TB Strategy and World Health Organization (WHO) guidelines for effective tuberculosis control [1] provide a framework for tackling tuberculosis, largely for countries with a high tuberculosis incidence.

Low-incidence countries in the European region have, in addition, addressed the goal of tuberculosis elimination [2–5], requiring a substantially broader approach. In particular, in addition to case identification among contacts of newly identified potential sources of infection, emphasis is also given to adequate preventive therapy or, as a minimum if the latter is contraindicated, follow-up of persons with recent *M. tuberculosis* infection. Identification of infected contacts thus targets an important subset of the prevalently infected who had escaped the focus on the prevention of infection. Contact investigation is the most readily available intervention to identify recently infected individuals and has been

**For editorial comments see page 714.**

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Received:
Dec 23 2009
Accepted after revision:
March 18 2010

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

identified as an essential component of the tuberculosis control and elimination strategy in most low-incidence countries.

Since 1990, WHO, the International Union Against Tuberculosis and Lung Disease (The Union), and the KNCV Tuberculosis Foundation have jointly organised a series of workshops, aimed at reorienting tuberculosis control in the European region of WHO, formulating guidelines and standards to foster consensus on a commonly agreed approach. Consensus building has emphasised wide consultation among tuberculosis control experts, national correspondents of EuroTB, and representatives of ministries of health. These workshops have become known as ''Wolfheze Conferences'', christened after the location in the Netherlands where the first meetings took place. From these meetings a series of consensus documents, position papers and recommendations has emerged [2, 6–11].

In 2006, a survey was undertaken to determine the contact investigation policies and practices in Europe, the results of which were presented and discussed at the Wolfheze Conference in Vilnius (Lithuania) in September 2006. In addition, a more comprehensive survey of national policies on active case finding across the WHO European region was conducted by the Tuberculosis Network European Trials Group (TBNET) [12]. Both surveys revealed some variation in active case-finding policies and strategies in Europe, although all countries screened close contacts of cases of sputum smear-positive tuberculosis. This suggested both the need and potential usefulness of a common evidence-based policy, both for countries moving towards eliminating tuberculosis, and for those transiting from an intermediate- to low-incidence epidemiology. More importantly, there was no consensus of what constituted a positive tuberculin skin test. A consensus statement should support countries and national tuberculosis control managers in evaluating and, where indicated, revising national policy.

The consensus document presented here aims to serve as a basis for national guidelines on contact investigation and outbreak management in tuberculosis prevention and control/elimination programmes in the countries of the WHO European Region. It fits with, and specifically supplements, the principles of the framework for an action plan to fight tuberculosis in the European Union from the European Centre for Disease Control (ECDC) [13] and those of the Berlin Declaration on Tuberculosis [14].

## METHODS

A draft consensus document was prepared for discussion at the 2008 Wolfheze Conference by representatives from European low-incidence countries. It took recourse to published guidelines for contact investigations from the USA [15], the UK [16], Canada [17], Germany [18] and the Netherlands [19], and additional material published subsequently through November 2009. The available evidence and recommendations in each section were graded using a letter code in parentheses, in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) grading system advocated by the European Respiratory Society (see Appendix), primarily by the coauthor with responsibility for the concerned section, and finalised in concordance with the first and the senior author.

### *Definitions*

In this document, ''tuberculosis'' refers to clinically, bacteriologically, histologically and/or radiologically active disease. ''Latent infection with *M. tuberculosis*'' is usually defined as presumptive infection with *M. tuberculosis* complex, as evidenced by a ''positive'' tuberculin skin test reaction and/or a positive interferon-$\gamma$ release assay (IGRA), without any sign of clinically or radiologically manifest disease. However, the biological nature of latent infection with *M. tuberculosis* is controversial [20]. Direct identification of individuals who are latently infected with live *M. tuberculosis*, without active tuberculosis, is currently not possible. The tests available in clinical practice to identify individuals with latent *M. tuberculosis* infection, the *in vivo* tuberculin skin test and the *ex vivo* IGRA are designed to identify a memory of an adaptive immune response against mycobacterial antigens, rather than to identify true latent infection [21]. The proportion of individuals with a persistently positive immune response against *M. tuberculosis* by tuberculin skin test or IGRA who are truly latently infected with live mycobacteria is unknown. The acronym ''LTBI'' is commonly used synonymously to describe latent infection with *M. tuberculosis*, and is adapted from the American Thoracic Society (ATS) terminology ''latent tuberculosis infection'' [22]. It is used pragmatically to describe those individuals with a positive adaptive immune response in the tuberculin skin test or in a *M. tuberculosis*-specific IGRA, who are potentially infected with *M. tuberculosis*.

## GOAL AND OBJECTIVES OF CONTACT INVESTIGATION

The yield of secondary cases among contacts of newly identified tuberculosis cases is largely determined by source characteristics, the definition of a ''contact'', and the duration of exposure of contacts to the index (putative source) case. If the net is cast wide, the yield may be infinitesimally small [23]. More typically, if investigations focus on contacts of cases with bacteriologically confirmed tuberculosis of the respiratory tract in settings with a generally well functioning tuberculosis program, such as in the USA, and investigations are conducted according to priority settings, ~1% of such identified contacts may be expected to be identifiable secondary cases in routine practice [24].

The risk of progression to tuberculosis is highest immediately following a median incubation period of ~6 weeks that is required for a first-manifest immunological response [25]. The subsequent risk follows an approximately exponential decline during the first ~7 yrs [26, 27]. After this period, the incidence levels off and appears to persist for many years or even decades. In placebo recipients in preventive therapy trials in the USA, the incidence of tuberculosis beyond ~7 yrs following infection was ~1 per 1,000 person-yrs [26]. This is remarkably identical to the incidence observed in the placebo group in the Bacille Calmette Guérin (BCG) trial in the UK [27]. The early incidence is, importantly, determined by the age at which infection is acquired [28]. It may be as large as 30–40% among infants, to as low as 2% among primary school children [29]. Among primary school children who were tuberculin skin test-positive at recruitment into a BCG trial in Puerto Rico, case incidence was as low as 0.8 per 100 person-yrs [30]. However, the applicability of the latter findings to the current situation in Europe from this tropical setting (relative contribution to

cross-reactions with the tuberculin skin test resulting from prior infection with environmental mycobacteria) with a different epidemiology, remains questionable. Among those who did develop tuberculosis subsequent to infection within the first 7 yrs, ~60% did so within the first, and cumulatively 80% <2 yrs subsequent to tuberculin skin test conversion in the placebo group in the BCG trial in the UK [31, 32]. Thus, the lifetime risk of developing active tuberculosis after conversion of the tuberculin skin test is determined by the risk during the first few years, plus the cumulative incidence during the low-incidence period that follows it, which, in turn, is determined by remaining life expectancy. COMSTOCK *et al.* [30] estimated the lifetime risk of a child (beyond the highest risk period) to be cumulatively 10%. VYNNYCKY and FINE [33] estimated the age-weighted average for England and Wales (UK) at 12%, and HORSBURGH [28] at ~10–20%. A study from Germany estimated the two-year progression rate to active tuberculosis in healthy contacts with positive IGRA responses to be close to 15% [34]. Thus, there is a fairly large variation in the estimates for the incidence immediately following infection but much less so for the cumulative lifetime incidence, the explanation for which remains at least partially elusive.

The objectives of contact investigation are as follows: 1) to reduce morbidity and fatality due to tuberculosis by early identification and adequate treatment of contacts with tuberculosis; 2) to arrest further transmission by early detection of possible (secondary) source cases; 3) to contribute to the elimination of tuberculosis through prevention of future cases of tuberculosis in the population by detection and preventive therapy of infected contacts at risk of developing tuberculosis.

In some situations, a source case investigation is conducted to identify an infectious person who might be the source case of someone with tuberculosis or latent infection with *M. tuberculosis* [35, 36]. This is usually done when recent transmission is likely as in the following cases: 1) a child aged <5 yrs of age is found with tuberculosis or infection with *M. tuberculosis* without a known source of infection; 2) a person with tuberculosis likely due to recent infection with *M. tuberculosis* (primary tuberculosis) is found without a known source of infection; 3) a cluster of persons with tuberculin skin test or IGRA conversion is found in a high-risk institution.

## LIKELIHOOD AND RISK OF TRANSMISSION

### *Relative infectiousness of index patient and infectious period*

Every tuberculosis patient should be interviewed promptly after diagnosis to assess the need for, and the urgency of, contact investigation. The extent of contact investigation will depend on the degree of infectiousness of the index patient, the period of infectiousness, the putative location(s) of transmission, the likelihood of the contacts to develop tuberculosis if infected, and the proportion of persons found to be infected.

With few exceptions, only patients with tuberculosis of the lung parenchyma or airways transmit tubercle bacilli. In patients with mediastinal or hilar lymphadenopathy due to tuberculosis, in individuals infected with HIV who have low numbers of circulating CD4 T-cells, and in patients with pleural effusions concealing the lung parenchyma, sputum cultures may yield *M. tuberculosis* even when the lung parenchyma on chest radiography appears normal [37]. Anecdotal case reports point to the possibility of aerosol-producing procedures among cases with extrapulmonary tuberculosis resulting in transmission [38–41]. Isolated extrapulmonary tuberculosis does not warrant contact investigations, but any patient with extrapulmonary tuberculosis requires radiological and bacteriological examinations to exclude concomitant pulmonary disease.

The potential of infectiousness is related to the patient's ability to aerosolise bacilli and to the number of bacilli that are aerosolised [42–44]. Any respiratory manoeuvre (talking, singing, coughing, sneezing) produces aerosols. The larger the physical force of the manoeuvre, the larger the number of expelled droplets and the smaller their size; the smaller the size, the quicker they evaporate to droplet nuclei [45–47]. However, the frequency of the event, especially coughing, is of practical relevance for the transmission of *M. tuberculosis*. The number of bacilli contained in expelled droplets is determined by the underlying lesions in the respiratory tract and their access to the airways. The largest number of bacilli is found in cavitary lesions, where they may number in excess of 100 million colony-forming units [48]. If spontaneously produced sputum is positive on direct microscopic examination, even a weak positive result points to a minimum concentration of 5,000–10,000 bacilli per mL sputum [49, 50]. In contrast, more sensitive methods, such as culture, may detect as few as 10–100 bacilli per mL sputum [51]. The fraction attributable to transmission from sputum smear-negative, culture-positive tuberculosis will vary depending on the disease extent prevalent in the community before the diagnosis is made [52]. For example, in a recent survey, patients with smear-negative, culture-positive tuberculosis have been estimated to be responsible for 13 % of all transmissions resulting in secondary cases in The Netherlands [53]. In industrialised countries, the direct examination of spontaneously produced sputum by microscopy has become the exception, rather than the rule. Instead, sputum is commonly concentrated by centrifugation and, where it cannot be obtained directly, sputum induction, bronchoalveolar lavage or other techniques are employed to obtain a specimen, to increase the sensitivity of diagnosis. Thus, ''sputum smear-positive'' has attained a substantially different meaning from that used in historical publications. As a result, the fraction of transmissions attributable to culture-only positive patients has reduced for this reason as well. Nevertheless, certain characteristics (table 1) that identify the most potent transmitters still hold. Even where concentration of specimens has become the rule, there are still laboratories which continue to perform direct sputum smear examinations, and they should be encouraged to do so, as this will always assist in rapidly identifying those patients with the highest potential of being transmitters.

Because of the change in the way bacteriological examinations are performed and the relatively increasing contribution to transmission by cases positive by means other than microscopic examination, a pragmatic approach is to define as a potential transmitter of tubercle bacilli any patient in whom acid-fast bacilli have or *M. tuberculosis* has been isolated from a respiratory specimen other than from biopsy alone.

**TABLE 1** Parameters to assess the infectiousness of the index patient

| |
|---|
| Anatomical site: pulmonary tuberculosis [54] |
| The production of sputum [54] |
| Results of sputum smear examination [55] |
| Results of sputum culture [55] |
| Cavitations [55, 56] |
| Coughing [45, 57, 58] |

### *Infectious period*

Diagnostic delay (both by the patient and the healthcare system) is an important determinant of the period of infectiousness. There is a substantial body of information on the decline of infectiousness subsequent to treatment initiation [59–61], an observation supported by bacteriological evidence of the early bactericidal activity of antituberculosis medications [62].

In contrast, onset of infectiousness cannot be determined objectively; thus, guidance to estimate the duration of infectiousness prior to diagnosis must be defined pragmatically. Expert opinion commonly uses onset of cough as a proxy measuring point for when transmissibility began. In the absence of cough, the time of onset of any respiratory tract symptom attributable to tuberculosis has been proposed as a substitute to define onset of infectiousness [15].

The number of identified infected contacts naturally raises a question about the duration for which the index case had been infectious. To determine the period of infectiousness during which contacts will have to be identified, the following rules may be used (level of evidence: D; see Appendix) [15]. 1) Pulmonary cases with a positive sputum smear should be considered to have been potentially infectious for the period the patient is known to have been coughing (initially to a maximum of 3 months). The presence of radiologically identifiable cavitations increases the assumed degree of infectiousness. 2) Pulmonary cases with culture-positive pulmonary tuberculosis and two negative sputum smears may be considered potentially infectious for a period of 1 month before the date of tuberculosis diagnosis, where the presence of cough or a cavity increases the assumed degree of infectiousness. 3) A person with drug-susceptible pulmonary tuberculosis should be considered potentially infectious until the person has completed $\geqslant$2 weeks of appropriate treatment [60] in the absence of any suspicion or proof of multidrug-resistant tuberculosis and has improvement from symptoms [63].

Nevertheless, the ''two-week'' observation [60] cannot always be taken at face value. Some patients never transmit, while others may do so for a prolonged period of time. Furthermore, and perhaps most importantly, that study [60] was conducted by ascertaining the increment of transmissions among contacts. As a large proportion of susceptible contacts may have been infected prior to initiation of chemotherapy, any subsequent increment may be difficult to ascertain. However, in the context of patients who are hospitalised and are potentially exposing other, more vulnerable persons, it would be dangerous to assume that all infectiousness has ceased in an initially sputum smear-positive patient after just 2 weeks of chemotherapy, as most of these still excrete viable bacilli. Such patients should be discharged as soon as possible to their home environment where little further damage can be safely assumed or if, among patients living in precarious situations, their follow-up can be assured. Should prolonged hospitalisation be required, however, every precaution must be taken to reduce the risk of nosocomial transmission for the prolonged period of time it takes until the cough frequency is diminished and excretion of viable bacilli ceases. In case of drug-resistant tuberculosis, the commonly associated prolongation of infectiousness must be considered. Some hospitals with the necessary infrastructure thus opt for prolonging hospitalisation of such patients in negative-pressure rooms until clear bacteriological and clinical evidence emerges that the potential of transmissibility has been substantially reduced.

### *Locations of transmission*

Environmental characteristics are key determinants for transmission probability. Outdoors, transmission is highly improbable unless source and susceptible person are in talking distance. Bacillary dispersion is immediate and sunlight or even skyshine exert rapid killing of any viable bacilli [64, 65]. In contrast, indoors, bacilli are potentially trapped, disperse within a room, and may remain viable and suspended in the air for a prolonged period of time [66–69]. Proximity is thus of much lesser importance.

Room size, air (re)circulation and, particularly, ventilation play an overriding role in dispersion of bacilli and dilution of their concentration in the ambient air. Therefore, only specific investigation, preferably including a visit to the putative locations where transmission may have occurred, will provide additional information to estimate the risk of tuberculosis transmission, and may also assist in identifying additional contacts.

### *Susceptibility of the contacts*

Contacts at highest risk of tuberculosis following infection and who will benefit most from preventive therapy are listed in table 2. Such persons are accorded a higher priority for evaluation. Tuberculin skin test and IGRA may be falsely negative in immunocompromised patients (see Diagnostic tools to evaluate contacts of tuberculosis patients). Young children ($<$2 yrs of age) have a higher risk of progression to tuberculosis, while children aged 2–4 yrs have a comparatively low risk for progression of tuberculosis (table 3). However, all children $<$5 yrs of age are at increased risk of meningeal and/or disseminated tuberculosis compared with adults. As in adults, the majority of disease manifestations in children occur in the first 6–12 months following primary infection. Furthermore, the longer remaining life expectancy adds to a cumulatively larger lifetime risk in children [30]. Therefore, children $<$5 yrs of age are a main target group for contact investigation.

## DIAGNOSTIC TOOLS TO EVALUATE CONTACTS OF TUBERCULOSIS PATIENTS

The diagnosis of tuberculosis requires a high index of suspicion raised by medical history, physical examination, imaging studies and laboratory results for tuberculosis. Laboratory confirmation must always be sought and relies on studying the morphology of micro-organisms (microscopy), culture techniques determining the viability through metabolic

**TABLE 2** Conditions increasing the risk for progression to tuberculosis and OR (from retrospective studies) or relative risk (RR; from prospective studies)

| Condition | [Ref.] | OR or RR |
|---|---|---|
| **Immune suppression** | | |
| HIV-positive and tuberculin skin test-positive | [71–73] | 50–110 |
| AIDS | [74, 75] | 110–170 |
| Solid organ transplantation related to immunosuppressant therapy | [76–78] | 20–74 |
| Receiving anti-TNF-α treatment | [79–81] | 1.5–17 |
| Corticosteroids >15 mg prednisolone equivalent per day for >2–4 weeks# | [82, 83] | 4.9 |
| **Malignancy** | | 4–8 |
| Haematological malignancy (leukemias, lymphomas) | [84] | 16 |
| Carcinoma of the head or neck and lung | [85] | 2.5–6.3 |
| **Gastrectomy** | [86, 87] | 2.5 |
| **Jejunoileal bypass** | [88, 89] | 27–63 |
| **Silicosis** | [90–92] | 30 |
| **Chronic renal failure/haemodialysis** | [93, 94] | 10–25 |
| **Diabetes mellitus** | [95–98] | 2–3.6 |
| **Smoking** | [99–103] | 2–3 |
| **Excessive alcohol use** | [104, 105] | 3 |
| **Underweight** | [106, 107] | 2.0–2.6 |
| **Age <5 yrs (table 3)** | [29] | 2–5 |

Level of evidence generally B or C. TNF: tumour necrosis factor. #: the adjusted RR of corticosteroids for the development of tuberculosis has not been convincingly established. Table adapted and updated from various sources [17, 22, 70].

activity of *M. tuberculosis*, and profiling the genome or components thereof by nucleic acid amplification. This may be supplemented by visualising the interaction between host and pathogen (histopathology) or measuring an immunological response (*e.g.* delayed-type hypersensitivity skin reaction or cytokines). Specimens from various sites, respiratory and other secretions, blood, and various body fluids or tissues, might have to be obtained to arrive at a definitive diagnosis (A) [108, 109].

In contrast to tuberculosis, latent infection with *M. tuberculosis* has traditionally been diagnosed by a delayed-type hypersensitivity response in the tuberculin skin test using the antigen mixture contained in the so-called purified protein derivative (PPD). IGRAs are novel *ex vivo* blood tests that have a superior specificity to the tuberculin skin test, while, importantly, comparative test sensitivity varies across study settings for the diagnosis of a recent *M. tuberculosis* infection (C) [110, 111]. Nevertheless, in tuberculosis contact investigations, positive IGRA results generally correlate better with exposure to an index case than positive tuberculin skin test results [112–116].

Neither IGRAs nor the tuberculin skin test are designed to diagnose tuberculosis as they do not distinguish between latent infection and tuberculosis (A) [110]. Nevertheless, given the high predictive value of a negative test result in a healthy population with a low expected prevalence, the use of a negative IGRA may be justifiable to support exclusion of tuberculosis [117, 118]. A negative response in an IGRA should nevertheless not dissuade a clinician to diagnose and treat presumptive tuberculosis, especially in immunosuppressed individuals and children [119, 120].

Most desirable is a test for the diagnosis of latent infection with *M. tuberculosis* with the highest prediction of subsequent disease. Some studies do suggest that an IGRA performs tangibly superior in that respect than the tuberculin skin test [34] while others have found this not to be the case [121, 122].

### *The tuberculin skin test*

The tuberculin skin test is widely used as a screening method for the identification of persons with a positive immune response against *M. tuberculosis* [12]. As a consequence of the development of an immunological memory against mycobacterial antigens, the intradermal administration of tuberculin results in a delayed-type hypersensitivity reaction represented by a local skin induration reaching a maximum ~48–72 h following antigen injection. A positive reaction is detectable after a median of ~6–8 weeks after acquisition of infection (C) [25, 123, 124]. The largest transverse diameter of the induration, perpendicular to the long axis of the forearm, is measured in millimetres [125]. The induration margin is either palpated or delineated with a ball-pen [126], neither of which provides assurance against the major source of error, terminal digit preference [127]. Terminal digit preference might be addressed by using inverted callipers instead of the commonly used transparent flexible rulers (C) [128].

The commercially most widely utilised tuberculin in Europe is PPD RT23 (Statens Serum Institut, Copenhagen), standardised against PPD-S [129]. The recommended dose of 2 TU has been demonstrated to be bioequivalent with the international standard dose of tuberculin (5 TU PPD-S) [130].

**TABLE 3** Risk of tuberculosis after infection in immune competent children (B)

| Age at primary infection | Risk of pulmonary disease or mediastinal lymphatic disease % | Risk of meningeal or disseminated tuberculosis % |
|---|---|---|
| **<12 months** | 30–40 | 10–20 |
| **12–24 months** | 10–20 | 2–5 |
| **2–4 yrs** | 5 | 0.5 |
| **5–10 yrs** | 2 | <0.5 |
| **>10 yrs** | 10–20 | <0.5 |

**TABLE 4** Proportion of patients with complete anergy (defined as 0 mm induration size) to the tuberculin skin test and sensitivity of the tuberculin skin test among patients with non-zero reaction sizes

| | Anergic % | [Ref.] |
|---|---|---|
| **Children with bacteriologically confirmed tuberculosis (including children with life-threatening disease manifestations)** | 14 | [133] |
| **Adults with culture-confirmed tuberculosis and no apparent immunosuppressive disorder** | 2–5 | [131, 134, 135] |
| **Adults with sputum smear-positive tuberculosis and HIV infection** | 25 | [135] |

*Test sensitivity*

The sensitivity of the tuberculin skin test, given a standard dose of tuberculin that is bioequivalent to 5 TU PPD-S (*e.g.* 2 TU PPD RT23) is fairly well characterised with a distribution belonging to the normal family and a mean of ~16–18 mm [131, 132]. From the distribution available from testing nonanergic tuberculosis patients, the sensitivity can be estimated for various cut-off points. In the absence of any relevant cross-reaction resulting from infection with environmental mycobacteria or prior *Mycobacterium bovis* BCG vaccination, it has be shown that the distribution among nonzero-reacting patients with bacteriologically confirmed tuberculosis is virtually identical to that among healthy children, presumably infected with *M. tuberculosis*, with non-zero reactions [132] and consistent across populations (tables 4 and 5).

However, the proportion of nonreacting patients, and likely healthy individuals infected with *M. tuberculosis*, is determined by various factors associated with relative cellular immunodeficiency or factors related to technical deficiencies in any step of the testing and reading procedure (table 6).

All these factors adversely impact on the otherwise well-characterised sensitivity of the tuberculin skin test. HIV infection is the strongest known factor in lowering reactivity to the tuberculin skin test in persons latently infected with *M. tuberculosis* or with tuberculosis [135].

*Test specificity*

In contrast to test sensitivity, specificity of the tuberculin varies greatly, due to cross-reactions resulting from prior infection with other mycobacteria. The antigens in tuberculin are specific for the genus *Mycobacterium* but not for the species *M. tuberculosis*. Most shared antigens are among the species of the *M. tuberculosis* complex, thus vaccination with BCG results in a virtually identical distribution among reactors shortly after vaccination but reactivity progressively wanes in subsequent years [148]. Different strains of BCG provide different levels of post-vaccinal allergy [149]. Both time elapsed since vaccination [150, 151] and age at vaccination [148, 152] influence the extent of cross-reactivity that might be seen in tuberculin skin testing, and reactions may be boosted by repeat testing (C) [153, 154]. Thus, the longer the time elapsed since vaccination and the larger the tuberculin reaction size, the higher the probability that the person is infected with *M. tuberculosis*, yet a discernible influence of BCG on reactivity may be retained for many years [155].

**TABLE 5** Sensitivity of the tuberculin skin test among patients with nonzero reaction sizes

| Cut-off value | Sensitivity % | Reference |
|---|---|---|
| **⩾5 mm** | 95–99 | [131, 136] |
| **⩾10 mm** | 91–95 | |
| **⩾15 mm** | 67–80 | |

Environmental mycobacteria share antigens to a various, but not well-characterised, extent with *M. tuberculosis*, and thus cross-react to different degrees with tuberculin [156–158]. This might be *M. bovis* BCG or environmental mycobacteria. The latter has been most convincingly demonstrated among the subset of lifetime, single-county residents in the largest ever conducted study among US Navy recruits [131]. In some areas (particularly in generally colder and low-humidity areas) there was very little, while in other areas (particularly in hot and humid areas) there was a large amount of sensitisation to environmental mycobacteria affecting tuberculin skin test specificity.

The prevalence of environmental mycobacteria is also known to vary greatly with soil characteristics [159, 160]. While in the USA, BCG has never been used on a large scale, in those areas in which it was used in a clinical trial, its lasting superimposed effect on test specificity can be seen, even many years after the trial.

**TABLE 6** Possible reasons for a false-negative tuberculin skin test (generally D)

Age <6 months
Age >65 yrs [137]
Cellular immune defects
(*e.g.* HIV infection, AIDS and lymphoproliferative disorders)
Acute or recent severe viral infection (*e.g.* rubella [138],
measles [139, 140] and mononucleosis [140]) and scarlet fever [140]
Immunisation with live vaccines within the past 6 weeks (*e.g.* measles,
poliomyelitis, yellow fever, mumps [141] and rubella [142])
Severe debilitating diseases (*e.g.* malignancies [143])
Systemic high-dose corticosteroid therapy (>15 mg prednisolone
equivalent) or treatment with immunosuppressants
Advanced pulmonary tuberculosis [133, 144],
central nervous system tuberculosis and disseminated tuberculosis [145]
Sarcoidosis [146]
Malnutrition [147]
Window period for manifest immune response to infection
with *Mycobacterium tuberculosis*
Application errors (incomplete or subcutaneous tuberculin injection,
incorrect quantity of tuberculin, inadequate storage of tuberculin)
Reading errors (too early or too late)

Given the same prevalence of latent infection with *M. tuberculosis*, balancing errors in sensitivity against those in specificity would require quite different cut-off points. Taking the example of the USA, a cut-off point of $\geqslant$5 mm to denote a positive test result would be highly predictive for true latent infection in most of the state of Montana but very poorly in most of Florida, taking two conspicuous examples, even if the true prevalence were exactly the same.

Above all, the predictive value will be driven by the underlying true prevalence, which is expectedly high among persons with a history of contact with a tuberculosis patient, while it will be low where no contact can be recalled. Using the data from the aforementioned US Navy recruit study, RUST and THOMAS [161] estimated the predictive value of a reaction size of 10 or more millimeters to be about 80% if there was, but only about 10% if there was not history of prior contact.

This makes it exceedingly difficult to define a uniformly applicable cut-off point to denote a positive tuberculin skin test result that optimises the balance between sensitivity and locally variable specificity. Epidemiological data on the prevalence of tuberculin skin test and IGRA test results in different populations and countries in Europe are clearly needed to better address this issue.

### *IGRA*

Two blood test assays have been developed and marketed for the immunodiagnosis of infection with *M. tuberculosis*. The QuantiFERON® -TB Gold and the QuantiFERON®-TB Gold In-Tube (Cellestis Ltd., Carnegie, Australia) as ELISA and the T-SPOT.*TB*® (Oxford Immunotec, Abingdon, UK) as an enzyme-linked immunospot assay (ELISPOT). Both types of assay aim to demonstrate the presence of antimycobacterial immune responses against region of difference (RD)-1-encoded early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10. The RD-1 is present in the genome of all members of the *M. tuberculosis* complex apart from the BCG substrains of *M. bovis*. The RD-1 sequences are not found in most environmental mycobacteria (also termed ''nontuberculous mycobacteria'') [162–167] except *Mycobacterium kansasii* [168], *Mycobacterium marinum*, and *Mycobacterium szulgai* [167, 169].

The QuantiFERON-TB® Gold In-Tube test includes an additional antigen, TB7.7 [170]. which is encoded by a phage-inserted region (ϕRv2) [171]. Both assays use the production of interferon-γ within the first day of incubation following antigen contact, compared with a negative control and a positive control as a readout. The cut-offs for the QuantiFERON-TB® Gold In-Tube test and the T-SPOT.*TB*® test to denote test positivity, test negativity or an indeterminate test result provided by the manufacturers are recommended.

An operational advantage of IGRAs over the tuberculin skin test is the additional performance of a negative control that allows assessment of nonspecific background reactivity, and a positive control (the lectin phytohaemagglutinin) of a mitogen stimulus, to assess general T-lymphocyte responsiveness. An absent mitogen response is formally scored as an ''indeterminate result'', but it provides meaningful information in immunocompromised patients [172]. Therefore, unlike the tuberculin skin test, *ex vivo* IGRAs may be able to discriminate true negative responses from anergy. Other causes for indeterminate results are technical laboratory errors (*e.g.* storage in a refrigerator or freezing before incubation resulting in cell anergy) and incorrect handling or transport.

The ELISA allows direct measurement of the concentration of interferon-γ in whole blood in stimulated and unstimulated assays. The ELISPOT allows the direct enumeration of the frequency of interferon-γ-secreting cells among a defined number of incubated peripheral blood mononuclear cells [170].

The sensitivity and specificity of IGRA are listed in tables 7 and 8 [109, 111].

In immunocompromised persons, *e.g.* individuals with HIV infection [173–175], immunosuppressive therapy [176, 177], or chronic renal failure [178], IGRAs are a more specific and more sensitive marker for a T-cell memory towards *M. tuberculosis* than the tuberculin skin test, but they appear to be less sensitive than in immunocompetent patients (B). The specificity of IGRAs is much superior to the specificity of the tuberculin skin test in individuals with prior BCG vaccination (B). IGRAs require a quality-assured laboratory, and the specifications for blood sampling and transport necessitate established logistic competence. As with the tuberculin skin test, antigen-specific responses in the IGRA are expected to be observed 2–8 weeks following *M. tuberculosis* infection (D) but sufficient data to support this assumption are still lacking. Studies have shown a boosting effect of the tuberculin skin test when given with an interval of >3 days on a subsequent IGRA (C) [179–181].

**TABLE 7** Summary sensitivity of interferon-γ release assays and the tuberculin skin test (TST)

| Series | Diagnostics | Subject | Studies n | Summary sensitivity (95% CI) | Sensitivity range |
|---|---|---|---|---|---|
| 1 | QFT-G | TB patients, adult | 21 | 0.80 (0.78–0.82) | 0.62–0.95 |
| 2 | QFT-G-IT | TB patients, adult | 6 | 0.74 (0.69–0.78) | 0.64–0.93 |
| 3 | QFT-G/G-IT | TB patients, child | 9 | 0.82 (0.75–0.87) | 0.53–1.00 |
| 4 | QFT-G/G-IT, T.SPOT | HIV-infected TB patients | 5 | 0.70 (0.60–0.79) | 0.63–0.85 |
| 7 | T.SPOT | TB patients | 13 | 0.90 (0.86–0.93) | 0.83–1.00 |
| 8 | TST | Healthy subjects | 20 | 0.77 (0.71–0.82) | 0.57–1.00 |

QFT-G: QuantiFERON®-TB Gold; QFT-G-IT: QuantiFERON®-TB Gold In-Tube; T.SPOT: T.SPOT-*TB*®; TB: tuberculosis. Data are taken from the meta-analysis in [109].

**TABLE 8** Summary specificity of interferon-γ release assays and the tuberculin skin test (TST)

| Series | Diagnostics | Subject | Studies n | Summary specificity (96% CI) | Specificity range |
|---|---|---|---|---|---|
| 1 | QFT-G/G-IT | Healthy young adults | 12 | 0.98 (0.97–0.99) | 0.92–1.00 |
| 2 | QFT-G/G-IT | Healthy young adults, $BCG^-$ | 8 | 0.99 (0.98–1.00) | 0.95–1.00 |
| 3 | QFT-G/G-IT | Healthy young adults, $BCG^+$ | 8 | 0.96 (0.94–0.98) | 0.89–0.99 |
| 4 | T.SPOT | Predominantly BCG vaccinated | 8 | 0.93 (0.86–1.00) | 0.85–1.00 |
| 5 | TST | BCG not vaccinated | 6 | 0.97 (0.95–0.99) | 0.93–1.00 |
| 6 | TST | BCG vaccinated | 6 | 0.59 (0.46–0.73) | 0.35–0.79 |

Several studies under series 1 are included in series 2 or 3. QFT-G: QuantiFERON®-TB Gold; QFT-G-IT: QuantiFERON®-TB Gold In-Tube; T.SPOT: T.SPOT-*TB*®; TB: tuberculosis. Data are taken from the meta-analysis in [109].

### *Other diagnostic tools*

#### *Chest radiography*

Chest radiography is a sensitive tool in identifying pulmonary tuberculosis. The reported proportion of normal chest radiographs among culture-proven pulmonary tuberculosis cases is commonly reported to be ⩽10% in the absence of recognised immunosuppression [182–184]. HIV infection may substantially alter radiographic findings [185, 186] and the proportion of patients with normal chest radiographs becomes larger with increasing immunosuppression (D) [183, 187]. A thoracic computed tomography image may be indicated in individual cases to improve the radiological diagnosis of tuberculosis. Even though some features on chest radiograph or thoracic computer tomography may be suggestive of tuberculosis, there are no images that are pathognomic for tuberculosis. In persons with latent infection with *M. tuberculosis*, the chest radiographs are usually normal, though abnormalities suggestive of prior tuberculosis such as calcification or fibrotic lesions may be present.

#### *History*

Each tuberculosis contact needs to be interviewed briefly to obtain more information on the factors summarised in table 9 (symptoms, the likelihood of a recently acquired infection, remote infection, prior tuberculosis, the susceptibility of the contact and the probability of treatment completion) in order to assess the individual's risk in relation to the previously established infectiousness of the source case and facilitate the interpretation of the results of the investigation.

#### *Physical examination*

Physical examination is indicated when the contact person presents with symptoms suggestive of tuberculosis, particularly if a chest radiograph is normal and a diagnosis of extrapulmonary tuberculosis with readily ascertainable signs (lymphatic, osteoarticular, cutaneous and other manifestations) must be considered.

#### *Sputum*

European standards for laboratory examinations have been published [188]. Any contact who has an abnormal chest radiograph or has symptoms suggestive of tuberculosis should have sputum specimens collected and examined. If no sputum is spontaneously produced, it is recommended to obtain an induced sputum specimen which has a similar yield as specimens obtained with bronchoalveolar lavage [189]. While gastric lavage is specific [190], it has poor sensitivity and is used as a last resort only in children from whom no direct respiratory specimen can be obtained (D).

#### *Nucleic acid amplification tests*

Nucleic acid amplification tests are expensive and complex. They have excellent specificity and may provide results within 3–24 h, but they have variable and often poor sensitivity in patients in whom sputum smears are negative for acid-fast bacilli [191, 192]. The main indication for nucleic acid amplification tests is thus to obtain a rapid identification of the species among bacteriologically positive specimens and determination of the strain's drug susceptibility pattern [192].

**TABLE 9** Information to be obtained during the interview of the tuberculosis contact

| |
|---|
| Degree of exposure to the index case and location of possible transmission |
| Risk of prior infection with *Mycobacterium tuberculosis* (*e.g.* foreign-born or prior tuberculosis contact) |
| BCG vaccination status |
| Previous TST and/or IGRA result |
| Age |
| Tuberculosis history (tuberculosis, latent infection with *M. tuberculosis*, previous antituberculosis chemotherapy or preventive therapy) |
| Medical history and comorbidity (immune status (table 2), risk of hepatitis or co-medication) |
| Symptoms of tuberculosis |
| Conditions associated with reduced adherence |

BCG: Bacille Calmette–Guérin; TST: tuberculin skin test; IGRA: interferon-γ release assay.

**TABLE 10** Degree of exposure

| | |
|---|---|
| **Intensity of exposure** | Degree of proximity (talking distance) between the contact and the index, if exposure was only outdoors |
| | Concentration of tubercle bacilli in the ambient indoor air, determined by cough intensity and bacillary load in the sputum |
| | The volume of air shared and quality of air circulation and ventilation indoors |
| **Duration of exposure** | Cumulative time of contact during the putative period of infectiousness period |

The information in this table is taken from [55, 194, 195].

## RISK ASSESSMENT AND PRIORITISATION OF TUBERCULOSIS CONTACTS

Various national guidelines agree on the basic approach to the organisation of contact investigation as an ordered sequence of priority decisions [15, 16, 18, 19]. The organisation of contact investigation is based on a risk assessment, for which the need to screen contacts is prioritised on the basis of the putative infectiousness of the index case, duration of exposure to the index case, and risk of tuberculosis among a contact in case infection had been acquired. There are two possible strategies: 1) identification and evaluation of high priority contacts with a prolonged exposure, and expansion of investigation according to the individual risk of progression to disease (risk group approach) [18]; and 2) identification and evaluation of high-priority contacts and expansion to medium-priority contacts according to evidence of transmission among high priority contacts and identification of those with a particularly high risk of progression to tuberculosis if infected (modified ''stone-in-the-pond'' principle) [193].

Contacts may be defined as ''high priority'' even in the absence of prolonged exposure, such as exposure to ambient air in a closed or poorly ventilated room, which is likely to still contain a high concentration of infectious droplet nuclei, even after the putative source case has left the room. A similar situation arises with brief exposure to a particularly high concentration of bacilli, such as might be the case during aerosol-producing manoeuvres like sputum induction, bronchoscopy, dental or otorhinolaryngolocial examination, or resuscitation measures [18].

The index patients should be interviewed about their social network and activities during the putative period of infectiousness in order to identify contacts who might have been subject to relevant exposure. Subsequently, contacts are grouped according to the degree of exposure and those at increased risk of progression to tuberculosis. This approach provides a framework for an ordered priority classification of individuals and groups from whom contact investigations are commenced and conducted.

The degree of exposure depends on the intensity and duration of exposure as shown in table 10. Contacts can be classified into groups around the source case according to the degree of exposure (tables 11 and 12). Contacts with conditions predisposing to a higher risk of progression to tuberculosis following infection (listed in table 2) will need to be identified and given priority for evaluation. When the different groups of contacts have been identified and located, the contacts can be classified into priority groups according to the degree of exposure and susceptibility (table 12).

**TABLE 11** Classification of contacts around the index case according to the degree of exposure

| **1st circle of contacts (inner circle)** | **Description** |
|---|---|
| Close household contacts | Those who live in the same household as the infectious case. Household contacts are considered, by definition, to share breathing space on a daily basis with the source case. |
| Close nonhousehold contacts | Close nonhousehold contacts may include those persons with short exposure times to direct face-to-face streams of air with a particularly high density of infectious droplet nuclei, such as may occur during bronchoscopy or otorhinolaryngeal examination of patients with hence untreated sputum smear-positive tuberculosis, and similar situations. For all other close nonhousehold contacts, an arbitrarily defined cumulative exposure time of 8 h, if the index is sputum smear-positive, or 40 h, if only sputum culture-positive has been recommended as a guiding principle [18]. This group also includes contacts with regular, prolonged contact with the source case, who share breathing space but do not live in the same household or who have spent time with the source case in a confined space, such as a car, sweatshop or prison cell. These may also include contacts, such as close friends and colleagues. |
| **2nd circle of contacts (middle circle)** | |
| Casual contacts | Those who spent less time with the infectious case. These may include frequent visitors to the home, friends, relatives, school or class mates, colleagues at work or leisure contacts, members of a club or team, or passengers in adjoining seats during aircraft travel of >8 h [201]. |
| **3rd circle of contacts (outer circle)** | |
| Community contacts | Those living in the same community or attending the same school, sports club or workplace who may have had sporadic contact. |

The information in this table is taken from [15, 16, 18, 22, 196–201].

**TABLE 12** Priority groups of contacts

| | |
|---|---|
| **High-priority contacts** | First-circle contacts at increased risk of developing tuberculosis following infection |
| | Other first-circle contacts |
| | Second-circle contacts at increased risk of developing tuberculosis following infection |
| **Medium-priority contacts** | Second-circle contacts |
| | Third-circle contacts at increased risk of developing tuberculosis following infection |
| **Low-priority contacts** | Third-circle contacts or outer circle |

## EVALUATION OF TUBERCULOSIS CONTACTS AND TIMING

To proceed in an orderly manner in a tuberculosis contact investigation, high-priority contacts are evaluated first for latent infection with *M. tuberculosis* and tuberculosis. Only once results from these examinations are known is a decision taken on how next to proceed. Figure 1 and table 13 give a schematic overview of when and how to evaluate the different priority groups.

In the event of a noninfectious index case likely due to recently acquired infection without a known source, a single evaluation of close contacts through a tuberculin skin test and/or IGRA and chest radiographic examination is advocated to identify the source with active pulmonary tuberculosis and other individuals infected with *M. tuberculosis* by the same source case among the close contacts.

### *Immediate evaluation of (vulnerable) high-priority contacts*

If the index case has a high potential of infectiousness, *e.g.* positive on direct sputum smear examination [202], an initial evaluation of first-priority contacts at particularly high risk of tuberculosis (table 2), and close contacts with symptoms suggestive of tuberculosis is indicated as swiftly as possible to reduce the risk of progression to tuberculosis by preventive intervention or, if present already, reduce morbidity and unnecessary delay in the diagnosis of secondary cases. For this purpose, all contacts should ideally be informed about the purpose and proceedings of the contact investigation <7 days after the identification of the index case. Immediate evaluation of the potentially most vulnerable contacts, specifically children aged <5 yrs, may uncover latent infection with *M. tuberculosis* or tuberculosis in a considerable proportion if the index case had been infectious for a prolonged period of time.

Immediate evaluation of other high priority contacts is recommended, *e.g.* in the Netherlands [19], as it is expected to provide preliminary empirical evidence on the actual infectiousness of the index patient and allow recent conversion to be distinguished from remote infection with *M. tuberculosis* by sequential tuberculin skin testing or IGRA. The highest priority should be given to a definitive assessment 2 months after adequate chemotherapy was initiated in the index case. Unless they have documented pre-existing latent infection

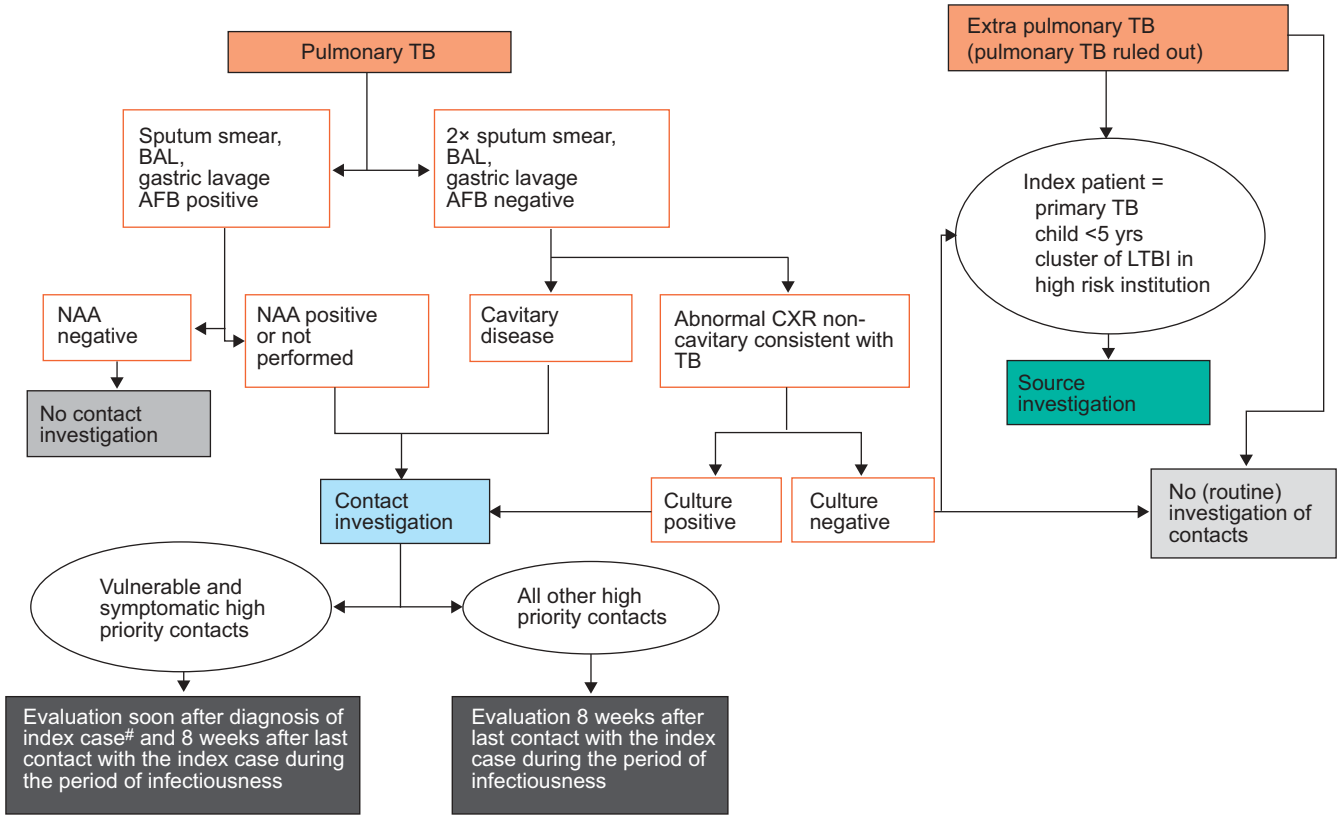


**FIGURE 1.** Need and timing of contact investigation. TB: tuberculosis; BAL: bronchoalveolar lavage; AFB: acid-fast bacilli; NAA: nucleic acid amplification; CXR: chest radiograph; LTBI: latent TB infection. #: first evaluation, other priority or vulnerable medium-priority contacts optional.

**TABLE 13** Organisation and timing of evaluation of contacts of infectious tuberculosis patients

| Contact group | Timing | |
|---|---|---|
| | <1 week after diagnosis (or as soon as possible) | After window period (8 weeks after last contact with the index case during the period of infectiousness) |
| **High-priority** | | |
| Vulnerable close contacts and contacts with symptoms of tuberculosis | TST[#]/IGRA and chest radiograph[¶] | TST/IGRA and chest radiography |
| Other close contacts | Optional or when proved transmission among (vulnerable) close contacts: TST[#]/IGRA and chest radiograph[¶] | TST/IGRA |
| **Medium-priority** | | |
| Vulnerable casual contacts | When proved transmission among high priority contacts: TST[#]/IGRA and chest radiograph | TST/IGRA |
| Other medium priority contacts | | When proved transmission among high priority contacts: TST/IGRA |
| **Low-priority** | | When proved considerable transmission among medium priority contacts: TST/IGRA |

TST: tuberculin skin test; IGRA: interferon-γ release assay. [#]: when there is a history of a previous positive tuberculin skin test, tuberculosis or latent infection with *M. tuberculosis*, no tuberculin skin test should be administered; [¶]: in bacille Calmette–Guérin-vaccinated patients, it is recommended not to use the tuberculin skin test in the first round of examination to avoid boosting in the second round.

with *M. tuberculosis* or previous or current tuberculosis, high-priority contacts should be evaluated for infection with *M. tuberculosis*. Some national guidelines give preference to primary testing by an IGRA test, in particular in immunocompromised patients [203], while others recommend an IGRA test for household contacts of sputum smear-positive cases who have a negative tuberculin skin test [16]. In the case of a history of prior tuberculosis or latent infection with *M. tuberculosis*, chest radiography is always indicated to exclude current tuberculosis. A radiograph may be supplemented by IGRA if prior infection is only documented by a tuberculin skin test. If the chosen test for latent infection is the tuberculin skin test, attention should be paid to the potential of boosting to repeat testing, which may be particularly important among BCG-vaccinated contacts. The tuberculin skin test may thus be postponed (where not in conflict with overriding circumstances as detailed above) until $\geqslant$8 weeks after the last relevant exposure to the index case. In individuals with a history of BCG vaccination, an IGRA is the preferred test for latent infection with *M. tuberculosis*. Chest radiography is indicated at the same time as the initial tuberculin skin test or IGRA if the contact: 1) has symptoms suggestive of tuberculosis; 2) is HIV-infected or has another immunosuppressive disorder or medications; 3) is <5 yrs of age; or 4) the tuberculin skin test reaction size exceeds 5 mm or the initial IGRA is positive.

High-priority contacts with a tuberculin skin test reaction of $\geqslant$5 mm should be evaluated by IGRA [11, 12]. A tuberculin skin test reaction size of such a small diameter has a relative high sensitivity but poor specificity, the latter of which is addressed by sequential testing with IGRA (D) [204]. In populations where the sensitivity and specificity of the tuberculin skin test is thought to be high such as in unvaccinated children, IGRA may not be superior to tuberculin skin testing [205], and thus the value added by a sequentially used IGRA limited.

Any contact who has an abnormal chest radiograph or symptoms compatible with tuberculosis should have a minimum of two sputum specimens collected for examination, regardless of the tuberculin skin test or IGRA result.

Once tuberculosis has been ruled out, primary prophylactic treatment (that is preventive therapy without definitive proof that latent infection has been acquired) should be initiated immediately in vulnerable high-priority contacts, namely children <5 yrs of age and contacts with HIV infection or other severe immunodeficiency, even if the result the of tuberculin skin test is <5 mm induration and/or an IGRA is negative.

### *Defining clinically workable cut-off points for the tuberculin skin test interpretation when IGRA are not available*

Where only the tuberculin skin test is available, a strategy different from the general recommendation that a positive reaction in a tuberculin skin test should be followed by an IGRA is in place. In this scenario, the general approach in screening using a sensitive test first, followed by a more specific test, is applied. In the first scenario, a balance of the errors resulting from deficiencies in both sensitivity and specificity at a given test criterion need to be applied.

Determining which cut-off points to choose to denote test positivity must take numerous factors into account concerning the variable sensitivity and specificity of the tuberculin skin test in different geographic settings, and variable levels of likelihood of infection as described before.

The problem is further compounded if there is a high likelihood of infection and the usually well-characterised test sensitivity is compromised, such as is the case among persons

with immunosuppressive disorders. An additional concern that enters the decision on making cut-off points is that the consequences of missing an infection (choosing high specificity over high sensitivity) are not the same for all persons concerned. For instance, not only is the risk of progression from latent infection to tuberculosis increased among infants and other very young children compared with children of *e.g.* primary school age; the risk of dissemination with a fatal or seriously disabling outcome is also much increased among the former, should they develop tuberculosis. In principle, this should also apply to the cut-off points for IGRAs and, indeed, the cutoff points recommended by the manufacturers have been questioned by some authors [179, 206, 207].

Furthermore, for clinical convenience, cut-off points are generally made, not along biological criteria, but to allow easy memorising, such as multiples of five. Such cut-off points have the additional disadvantage of being prone to digit preference [208]. What is proposed here is thus not an exact and unalienable recommendation, and may indeed be subject to improved modifications in various European countries that have better epidemiological background information, specific to the country, on prevalence of cross-reactions with environmental mycobacteria, extent of BCG vaccination, and, notably, background prevalence of infection with *M. tuberculosis*. The summary recommendations given in table 14 are thus meant to be a guidance for future European guidelines, and for countries not having their own, and perhaps superior recommendations, rather than an attempt to override pre-existing, epidemiologically defined criteria.

In situations with a low likelihood of infection, increasing the cut-off point to 15 mm will result in a substantial gain in specificity. However, for persons with a high risk of developing tuberculosis, such as close contacts of infectious tuberculosis patients, the cut-off point of 15 mm will result a loss of sensitivity (see table 5). Therefore, in the context of investigation of close contacts, a tuberculin skin test induration cut-off of $\geqslant$10 mm in immune-competent, non-BCG vaccinated hosts, $\geqslant$15 mm in immune-competent, BCG-vaccinated hosts, and $\geqslant$5 mm in immunocompromised hosts seem to be the most appropriate for the diagnosis of latent infection with *M. tuberculosis* based on tuberculin skin testing alone. In non-close contacts and when screening individuals with a low likelihood of infection, a tuberculin skin test induration cut-off of $\geqslant$15 mm in immune competent non-BCG vaccinated and $\geqslant$10 mm in the immunocompromized host is suggested for the diagnosis of latent infection with *M. tuberculosis* based on tuberculin skin testing alone. A negative tuberculin skin test is not reliable to exclude infection in HIV-seropositive individuals (table 14) [135].

### *Evaluation of high-priority contacts after the ''window period''*

The ''window period'' is the interval between acquisition of infection with *M. tuberculosis* and the point in time when an immunologic response becomes measurable as described previously. In all high-priority contacts, or in case of an initially negative tuberculin skin test or IGRA in a high priority contact, the evaluation should be performed or repeated when $\geqslant$8 weeks (1–2 weeks beyond the median window period) have passed since the last relevant exposure to the index case while infectious. If the index case was treated at home, the second tuberculin skin test in household contacts should be performed 8 weeks after the putative period of transmissibility has ended.

**TABLE 14** Recommended cut-off for tuberculin-skin test (TST) positivity in a contact investigation when interferon-$\gamma$ release assays are not available

| Likelihood of infection | TST induration cut-off | |
|---|---|---|
| | Non-BCG-vaccinated or BCG vaccination <12 months of age [153] | BCG vaccinated >12 months of age [152] |
| **High (close contact of smear-positive tuberculosis patient, expected prevalence of infection $\geqslant$10%)** | | |
| Immune competent | $\geqslant$10 mm [136] | $\geqslant$15 mm |
| Immunocompromised | | |
| HIV | Negative TST does not exclude infection [16, 135] | Negative TST does not exclude infection [16, 135] |
| Other conditions with increased risk of developing TB | $\geqslant$5 mm | $\geqslant$5 mm |
| **Low (other contacts of tuberculosis patient and (opportunistic) screening, expected prevalence of infection <10%)** | | |
| Immune competent | $\geqslant$15 mm [136] | TST not recommended [109] |
| Immunocompromised | | |
| HIV | Negative TST does not exclude infection | Negative TST does not exclude infection |
| Other conditions with increased risk of developing TB | $\geqslant$10 mm | $\geqslant$10 mm |

BCG: bacille Calmette–Guérin; TB: tuberculosis. Data taken from [16, 23, 109, 135, 136, 152, 153].

In children <5 yrs of age, primary prophylactic treatment may be stopped if the repeat tuberculin skin test remains negative. However, if the child is <6 months of age, a full course of prophylactic or preventive therapy should be completed, even when the second tuberculin skin test or IGRA remains negative. As a minimum, it should be continued until the child is old enough (>6 months of age) to mount a presumably more reliable response to a tuberculin skin test or IGRA. Contacts with HIV infection or other severe immunosuppressive disorders should be re-evaluated after completion of 2 months of preventive therapy. If tuberculosis can still be ruled out and the mandatory chest radiograph remains normal, they should complete the full course of preventive therapy.

#### *Assessing the need for expanding contact investigations*

In the risk group approach, other vulnerable contacts according to the individual risk of progression may be included in the evaluation. Other medium-priority contacts are usually not evaluated. In the concentric-circles approach, the contact investigation does not need to be expanded to the medium-priority groups, unless there is the following evidence of recent transmission among the high priority contacts. 1) Contacts with tuberculin skin test or IGRA conversions. 2) Young children with a positive tuberculin skin test reaction or IGRA. 3) Contact with tuberculosis detected. 4) The observed prevalence of infection is, importantly, higher than the expected age-specific background prevalence, (*e.g.* estimated to be ~10% in the USA [15], or at least twice the prevalence of a similar population without recent exposure, whichever is greater). However, this criterion may be difficult to implement in settings where information on background prevalence of infection with *M. tuberculosis* is unknown or cannot be reasonably estimated.

#### *Evaluation of medium-priority contacts*

In the concentric-circles approach, the need to investigate medium-priority contacts arises when there is evidence of transmission among high-priority contacts. Medium-priority contacts of sputum smear-negative tuberculosis patients should not be screened without evidence that transmission is likely to have occurred. Medium-priority contacts are usually evaluated only once after the window period and the investigation of high-priority contacts documents evidence of transmission. There are, however, circumstances where the pressure to act is high, such as when there has been exposure of vulnerable groups among medium-priority contacts, when there has been a long diagnostic delay in a patient considered to be highly infectious, or if secondary cases are found among medium-priority contacts. Under such circumstances, the evaluation of medium-priority contacts may be planned immediately after the first evaluation of the high-priority contacts.

Low-priority contacts are not evaluated unless there has been proven, considerable transmission among medium-priority contacts. When evaluated, they are only examined once after the window period.

For practical purposes, it is recommended to plan the evaluation of susceptible casual contacts only after evidence of transmission among close contacts has been found, except in situations where susceptible persons among casual contacts have been identified already, where a large group of susceptible casual contacts have been exposed, where the risk of infection and progression to disease of susceptible casual contacts is deemed high, or if the group of high-priority contacts identified is too small to reflect the infectiousness of the index patient.

## MANAGEMENT OF LATENT INFECTION WITH *M. TUBERCULOSIS*

#### *Treatment of latent infection with* M. tuberculosis

For the diagnosis of latent infection with *M. tuberculosis*, a positive tuberculin skin test and/or IGRA, a normal chest radiograph (or calcified lesions only, or as bacteriologically assured negative fibrotic lesions), and absence of signs or symptoms compatible with tuberculosis are required. Pursuing the identification of latent infection with *M. tuberculosis* is only justified if it results in an intervention where indicated, such as preventive therapy or, if contra-indicated, follow-up of those at risk of developing tuberculosis. It is also important to ensure that those not at risk do not receive unnecessary treatment [209, 210]. Where available, resources permit, the expected prevalence of infection is low, and/or prior BCG vaccination the rule, it is preferable to seek confirmation of a positive tuberculin skin test by an IGRA test, if the latter is not already the primary choice [203]. In general, a negative IGRA result overrules a positive tuberculin skin test result in adults. However, diverting IGRA and tuberculin skin test results should be carefully considered as an indication for preventive chemotherapy in vulnerable high-priority contacts.

An appropriate tuberculosis control and elimination strategy necessitates carefully weighing the benefits of preventing tuberculosis in the infected individual and in the community against the risk of drug-induced liver injury during the period of treatment. It also takes the risk of re-infection into account. Adverse drug events and nonadherence threaten the completion of treatment and treatment may be inefficacious if it does not match the drug susceptibility pattern of the source case's strain.

Table 15 summarises the evidence level for commonly used and recommended regimens for the treatment of latent infection with *M. tuberculosis*. The strongest evidence for a preventive therapy regimen is a choice between 12 months of isoniazid and 3 months of rifampicin plus isoniazid (A). Different recommendations on the optimum duration of isoniazid preventive therapy are based on a difference of opinion as to whether the regimen choice should be based on efficacy or effectiveness [21].

When the source case is unknown or when there are no drug susceptibility test results available, the probability that the contact has been infected by a resistant strain should be assessed and the choice of the preventive treatment regimen be made accordingly.

Adverse drug events may affect patient adherence. Patients must be fully informed both about minor inconveniences (such as orange discoloration of tears and urine from rifampicin) and potentially serious adverse events, such as drug-induced hepatic injury, and must be carefully evaluated for concomitant use of other medications to determine the potential of drug–drug interactions [219]. In particular, females using oral contraceptives must be advised about the potential of their failure when given rifampicin, and the alternative use of a

**TABLE 15** Treatment regimens for latent infection with *M. tuberculosis* [21]

| Treatment regimen | [Ref.] | | Efficacy/effectiveness | Level of evidence |
|---|---|---|---|---|
| **12 months isoniazid** | [26, 211] | 12H | 93%/75% | A |
| **9 months isoniazid** | [195, 212, 213] | 9H | ~90% | C |
| **6 months isoniazid** | [195] | 6H | 69%/65% | A |
| **4 months rifampicin** | [214–216] | 4R | Unknown (>3HR) | C |
| **3 months isoniazid-rifampicin** | [217, 218] | 3HR | Equivalent to 6H | A |

regimen based on isoniazid alone must be explored. In many European cultures, alcohol consumption is common, predisposing to liver injury prior to preventive therapy, the most important risk factor for toxic isoniazid hepatitis in preventive therapy [211]. Patients judged to have an increased risk of drug-induced liver injury should be offered regular evaluation of liver enzymes. There are indications that a shorter treatment regimen and offering the patient a choice between treatment regimens results in a lower proportion of patients interrupting the treatment [220]. To ensure treatment adherence, regular support visits and follow-up are advisable.

### *Alternatives to treatment*

When preventive therapy is prematurely discontinued or not even initiated, the contact should: 1) be educated thoroughly about symptoms and signs of tuberculosis, and the need for immediate medical evaluation if symptoms occur; 2) be educated thoroughly about the need for medical evaluation if they receive immunosuppressive therapy (such as tumour necrosis factor-$\alpha$ inhibitors, high-dose corticosteroid treatment, immunosuppressive therapy for malignancies, *etc.*) or if they have or develop other immunocompromising conditions.

Follow-up by annual or biannual radiographic evaluation among persons not receiving preventive therapy is used by some to ascertain the emergence of radiographically manifest tuberculosis. Such practice is of doubtful effectiveness if the experiences from the studies on periodic mass-screening are of any relevance, showing that the majority of new tuberculosis cases occur between screening rounds [221].

### *Management of contacts of cases with multidrug- and extensively drug-resistant tuberculosis*

Drug resistance is an important issue in the management of tuberculosis, as it may prolong the period during which patients are infectious and treatment efficacy may be compromised. There is no convincing evidence that drug resistance *per se* modifies the probability of transmission [222]. However, the consequences of acquiring an infection with a multidrug-resistant strain of *M. tuberculosis* are much more serious, and not all resistance-conferring mutations lower the fitness of *M. tuberculosis* [223, 224], and any lowered fitness is irrelevant in immunocompromised patients [225]. Furthermore, multidrug-resistant tuberculosis needs prolonged treatment with drugs that are generally less bactericidal then some of the first-line drugs. All this has repercussions on contact investigations. Despite the scarcity of information on how to deal with contacts putatively infected by such a case, the evaluation of contacts of patients with multidrug-resistant tuberculosis may be accorded higher priority. It may be necessary to re-examine contacts who have had ongoing exposure to the index case before adequate treatment was initiated and isolation measures were taken.

There are no randomised controlled trials assessing the efficacy of treatment of latent infection with multidrug-resistant *M. tuberculosis* or indeed extensively drug-resistant tuberculosis, and the scarce observational studies are hardly informative as to best practice [226]. Those who advocate preventive therapy in such cases recommend that the regimen should include two orally administered drugs, to which the putative infecting strain is susceptible. No specific preventive therapy regimen can currently be recommended because of lack of evidence and the high risk of drug-induced liver injury [227, 228].

Contacts presumably infected with a multidrug-resistant or extensively drug-resistant *M. tuberculosis* strain, whether receiving preventive therapy or not, should: 1) be thoroughly informed about symptoms and signs of tuberculosis and the need for immediate medical evaluation if symptoms occur; 2) be thoroughly informed about the need for medical evaluation if they would receive immunosuppressive therapy; 3) be assessed for risk factors for developing tuberculosis (table 2); and 4) receive regular and careful clinical follow-up for a period of $\geqslant$2 yrs. If tuberculosis develops, prompt initiation of treatment with a regimen designed to treat multidrug-resistant tuberculosis is recommended [229–231].

## OUTBREAK MANAGEMENT

The definition of an outbreak, agreed upon at the Wolfheze Workshop Conference ''the occurrence of two or more tuberculosis cases, outside the household setting, with an epidemiological and/or molecular link occurring within one year'' [232].

Various measures, beyond those usually undertaken during routine contact investigation of a single case, may be necessary once the occurrence of an outbreak has been determined. For the investigation of any outbreak, a case definition is required [233]. An outbreak control committee with all relevant stakeholders should be constituted (D). Membership of this committee will vary by country, but preferably includes a tuberculosis or respiratory physician, public health staff, a microbiologist and an administrative lead (D). This committee should decide on further action. Such action may include several overlapping contact investigations; coordination and proper communication to the exposed community, other healthcare providers and the media; analytical epidemiological studies; and additional public health resources. Early and

regular dissemination of information is critical to minimising levels of anxiety in the community, and is likely to result in improved cooperation and adherence to recommendations (D).

DNA fingerprint technology enables the identification of molecular clusters [234, 235, 236] and exclusion of pseudo-outbreaks due to laboratory cross-contamination [237] (C). Mycobacteriology laboratories have utilised DNA fingerprinting data, coupled to dates of specimen processing, to identify cases that are probably due to cross-contamination. Molecular evidence of clustering should always be combined with information on epidemiological and social relationships between clustered cases. This is an essential step in confirming known, and identifying previously unknown, spatial or temporal associations between outbreak cases. Secondary cases with an unexpected link to a known index case may represent a failure of conventional contact investigation in reaching the exposed population or may reveal previously unobserved transmission in the community. Continued occurrence of cases in clusters may suggest ongoing transmission that is not sufficiently controlled by conventional contact investigation and supports the use of other measures, such as screening of a subgroup with a high risk of infection.

In low-incidence settings, outbreak management through cluster surveillance may contribute to the prevention of transmission and provides a tool to evaluate the effectiveness of contact investigation practices [238].

## MONITORING AND EVALUATION OF CONTACT INVESTIGATION

Monitoring and evaluation of the results of a contact investigation will enable investigators to: 1) assess whether all persons with an increased risk of having become infected have been informed and/or screened; 2) assess whether other exposed groups need to be targeted for contact investigation; 3) evaluate the organisation, performance and effectiveness of contact investigation procedures; and 4) provide data for evidence-based guidelines on contact investigation. The evaluation of aggregated results on the yield of contact investigations may be useful to assess the efficacy of this intervention and the appropriate use of resources. Table 16 lists potential indicators and objectives for the evaluation of contact investigations as suggested by participants at the Wolfheze (The Netherlands) meeting in 2006 and recommended by the US Centers for Disease Control and Prevention [15].

For the purpose of evaluation, the results of each contact investigation should be reported to the appropriate authorities involved in the contact investigation. Data should be sent to a central coordinating health authority for further evaluation.

## CONTACT INVESTIGATIONS IN CONGREGATE AND OTHER SPECIAL SETTINGS

The occurrence of a tuberculosis case in congregate settings, such as schools, prisons, hospitals or other institutions where large groups of people are confined to areas with limited air circulation, requires a more tailored approach. Such institutions have a special responsibility towards the health of their communities and may feel the need to expand contact investigation at an early stage to a larger group of contacts, or contacts with a lower priority. The need for further investigation beyond routine contact tracing should, however, be determined by the infectiousness of the source case, the degree of overcrowding, and the susceptibility of the population (*e.g.* hospital, children). The decision-making process also takes into account any evidence of transmission and the effectiveness of interventions. Individuals travelling on ships, trains and aeroplanes may need contact investigation. Airborne transmission from animals [239], and humans with tuberculosis caused by *M. bovis* may occur rarely, and may require investigation [240].

### *Prisons*

Global guidelines for the management of tuberculosis in prisons focus on early detection and infection control, adequate treatment of susceptible and multidrug-resistant tuberculosis, and on case-holding after release from prison [241, 242]. In prison populations, the prevalence of tuberculosis is presumed to be higher than in the civilian population. While population groups with a high risk of infection with *M. tuberculosis* and tuberculosis, such as those addicted to alcohol or illicit drugs, the homeless, the mentally ill, foreign-born persons and former prisoners, often contribute a disproportionately high proportion of the incarcerated, there is remarkably little evidence of a considerably increased risk of infection with *M. tuberculosis* among occupations working in the prison system in low-incidence countries [243, 244]. Many low-incidence countries screen detainees for tuberculosis upon incarceration. Inmates and staff who are exposed to a case with bacteriologically confirmed respiratory tract tuberculosis should be investigated using the principles of risk assessment for contact investigation and outbreak management (D) [245]. Investigations should be pursued in close collaboration with the local public health and tuberculosis control authorities.

**TABLE 16** Recommended objectives for contact investigations, by key indicators

| Key indicator | Objective |
|---|---|
| **Proportion of infectious patients with at least one contact listed** | 90% |
| **Proportion of high-priority contacts who are evaluated for tuberculosis and latent infection with *M. tuberculosis*** | 90% |
| **Proportion of infected contacts who begin preventive therapy for latent infection with *M. tuberculosis*** | 85% |
| **Proportion of contact investigations concluded within 3–4 months after the diagnosis of the index patient** | 80% |
| **Proportion of contacts who complete preventive therapy for latent infection with *M. tuberculosis*** | 75% |

Adapted from [15].

Continuation of preventive and curative therapy should be ensured when contacts are released, transferred or paroled.

#### *Air travel*

The revision of International Health Regulations and the attention given to the emergence of multidrug- and extensively drug-resistant tuberculosis [246] also led to a renewed focus on air travel and airborne transmission on flights. The third edition of the WHO guidelines [200] outlines the procedures to follow and the responsibilities of various organisations and individuals when infectious tuberculosis is diagnosed in a patient who either has a history of recent air travel, or intends to undertake such. The need to evaluate exposed passengers should be assessed when a sputum smear-positive tuberculosis patient is known to have travelled on a flight of $\geqslant$8 h duration within the preceding three months (D). Where a decision has been taken to evaluate contacts, passengers sitting in the same row and the two rows ahead and behind the index patient should be assessed (D) [199]. The principles outlined in the WHO document summarise the current consensus on how to proceed, and supplement it to assist further adjustment of current guidelines. In particular, the investigation should be limited to instances where there is evidence of transmission from the screening of high priority contacts [201, 247]. Patients with infectious tuberculosis should not normally be allowed to travel on an airplane until they have been certified to be no longer infectious.

#### *Schools*

Contact investigation in schools is often complicated. While the principles of the organisation of contact investigation do not differ from other situations, young classmates or pupils of sputum smear-positive tuberculosis patients will generally be regarded as high- or medium-priority contacts, requiring a lower threshold for widening the investigation. In school outbreaks, transmission of *M. tuberculosis* can affect a substantial number of contacts [115]. Efforts should be made to conduct the investigation according to the strategies outlined in the previous sections and to prioritise students according to actual degree of exposure (hours shared in the same classroom per week) (C) [115]. Communication of prevention and control procedures to staff, parents and the general public is important to prevent anxiety and unwarranted media attention. Public health authorities should ensure that the media receive and disseminate correct information. If the index case is a pupil and the source of infection unknown, a source investigation as well as a contact investigation may be necessary (C) [248].

#### *Healthcare facilities*

Nosocomial transmission of *M. tuberculosis* is well recognised (B) [16]. Contact investigation is performed when a healthcare worker or in-patient has infectious tuberculosis following a risk assessment in accordance with the principles outlined in the present work (D). Special consideration should be given to the risk of exposure of immunocompromised patients (table 2) and hospital staff, including laboratory staff [249]. In addition, delays in diagnosis and failures in infection control should be taken into account during such risk assessment (D). The healthcare providers and tuberculosis control authorities should agree on who will coordinate the contact investigation and evaluate exposed patient groups and health staff (D). Vulnerable contacts, as well as their providers, need to be informed on the possibility of exposure and transmission of tuberculosis (D).

In contact investigations in nursing homes for elderly people, screening for latent infection with *M. tuberculosis* and prophylactic treatment with isoniazid are not routinely recommended because of the decreasing risk–benefit ratio with increasing age, unless there are additional risk factors [250, 251].

Recommendations for the management of these groups are: 1) evaluation of symptoms of disease, followed by chest radiography in the individual concerned or among all contacts (D); and 2) education of staff and affected residents thoroughly about symptoms and signs of tuberculosis and the need for immediate medical evaluation if symptoms occur (D).

#### *The homeless and persons living in shelters*

Incidence and prevalence of tuberculosis among the homeless and persons living in shelters is usually high and outbreaks amongst them have been widely recognised in low-incidence countries (C) [252–254]. Overcrowding in shelters for the homeless facilitates transmission. Screening following the diagnosis of a case of tuberculosis should be considered in such a setting. Unfortunately, contact addresses may not always be available (C) [255] and other measures such as mass chest radiography screening for tuberculosis may have to be used (C) [256].

#### *Exposure to animals with* M. bovis

Contact investigation should be limited to those in close contact with an infectious human case due to *M. bovis* (C) [240], those who have consumed raw milk or unpasteurised dairy products from a cow with tuberculous mastitis [257], and those with regular direct contact with an animal or carcass with pulmonary bovine tuberculosis or lesions of the udder, such as veterinary workers and farmers (D) [258, 259]. The same principles outlined in the management of *M. tuberculosis* exposure should be used.

## COMMUNICATION

Contact investigations will often confront the tuberculosis professional with opposing requests, particularly if the focus of investigation is on congregate settings. To adequately follow the outlined strategy for contact investigation, several days are needed and usually there is no ''medical emergency''. On the other hand, the anxiety of potential contacts and of their families often requires an ''urgent'' intervention in the form of correct information and reassurance. In addition, when the media are informed, the timing is reduced to a matter of hours only. This discrepancy is an additional reason why, in any contact investigation, it is important to provide correct information to the contacts and authorities involved as soon as possible. Particularly when contacts in congregate settings or the general public are involved, the timing is important to prevent the spread of incorrect information, in order to reduce the level of anxiety in the community. To reduce the negative impact of misleading and incorrect messages, health authorities should prepare a press release.

Prompt communication to healthcare services and contacts with a low risk of exposure may be helpful in the case of an outbreak, to promote early passive case finding.

## PREREQUISITES

### *Health system capacity*

Health systems delivering care and carrying out prevention and control activities are basic components of tuberculosis control. In Europe, they should be able to address the international, national and local challenges in the context of diverse epidemiological situations. The national health authorities involved in tuberculosis control should have a network in place to coordinate the local, regional and national levels, as well as public and private care providers.

The responsibilities of the appropriate public health authorities and healthcare providers at different stages and the components of contact investigations should be clear. However, competing demands restrict the resources that can be allocated to contact investigations. Therefore health authorities have to ensure that resources are allocated to the most cost-effective strategies controlling tuberculosis.

### *Laboratory services*

The appropriate standards for laboratory services for tuberculosis control programmes in low-incidence countries have been summarised [188]. On top of the required standards for microscopy, nucleic acid amplification, mycobacterial culture and susceptibility testing, standards for DNA fingerprinting techniques need to be agreed upon.

IGRAs offer new opportunities, but many questions remain unanswered. The manufacturers of the ELISPOT suggest that blood can be stored at room temperature for 8 h before analysis. New test systems that allow an extension of the storage period of blood for the ELISPOT IGRA for $\leqslant$24 h are advocated by the manufacturer, but clinical data on the performance of these assays are not available yet. The whole-blood ELISA IGRA is technically easier, but when routine phlebotomy services are used, overfilling of the tubes becomes more common (15% of samples taken), invalidating the test. Storage at room temperature for 16 h before incubation is permissible. Thereafter, standards of handling of biological materials apply and are routine in European laboratories.

## RESEARCH PRIORITIES AND RECOMMENDATIONS

Many of the controversies surrounding the usefulness of contact investigation practices are due to the lack of evidence on the (cost-)effectiveness of these interventions and their impact on the tuberculosis epidemic. Indeed, the only randomised controlled trials in this document relate to the efficacy of different preventive therapy regimens for latent infection with *M. tuberculosis*. It is important to realise that the number of patients to treat in order to prevent one tuberculosis case is the reciprocal of the following factors: 1) likelihood of latent infection with *M. tuberculosis*, 2) risk of tuberculosis given infection, 3) efficacy of the regimen, and 4) adherence to treatment [219].

Research should be directed towards answering two practical questions. 1) Who is likely to develop active tuberculosis and should, therefore, recieve preventive therapy? 2) What are the effective preventive therapy regimens and how can adherence to treatment be improved? The first question should preferably be answered before the second. It involves: 1) the relative importance of factors influencing transmission and infection; 2) the need for a test which will most reliably predict which *M. tuberculosis* infected individuals will develop tuberculosis; and 3) the cost-effectiveness of contact investigation strategies.

Prospective studies have shown that merely 2% of those with a positive tuberculin skin test, without concurrent HIV infection, will develop tuberculosis (a frequency that is nevertheless importantly modified by the age of the person) over 2–5 yrs if left untreated. In this situation, about 70 persons need to be treated to prevent one case of tuberculosis (A) [213]. Children and those with HIV co-infection have higher rates of tuberculosis after contact, but rates in a country with a high incidence of tuberculosis were 10% and 23%, respectively, after 2 yrs of follow-up [260].

Prior BCG vaccination and the integrity of the cellular immune system at the time of infection is clearly important. Those with concurrent HIV infection are more likely to develop tuberculosis, while those with prior BCG vaccination may benefit from a certain degree of protection.

Data regarding the predictive value of IGRA tests are awaited, but early indications suggest that those who show a T-cell response to the ESAT-6 and CFP-10 antigens may be more likely to develop tuberculosis (D) [12, 34, 121, 261, 262]. Examination of immune responsiveness in a prospective cohort of household contacts, comparing those who develop tuberculosis with matched controls who did not develop tuberculosis, would be valuable in reducing unnecessary treatment.

Strain characteristics may affect the likelihood of developing tuberculosis. *Mycobacterium africanum* appears to be less virulent than *M. tuberculosis*, and within the species, the Beijing strain family was associated with an increased risk of tuberculosis subsequent to acquisition of infection [263].

Strain typing, if routinely carried out, can add assurance that tuberculosis in a contact is related to the known index case and not due to reactivation of an earlier-acquired infection from another source.

Short-term studies will only address the problem of early progression to disease. The nature of late reactivation has not been fully elucidated. A long-term register, with a known identity of the initial strain of *M. tuberculosis*, should help in better clarifying the relative contributions of exogenous *versus* endogenous reinfection disease [264].

Adherence to preventive therapy is frequently poor and regimens are of equally long, if not longer, duration than tuberculosis treatment. There is an urgent need for the development of new drugs against latent infection with *M. tuberculosis* and for clinical trials with shorter regimens, using agents appropriate to the expected low-level metabolic activity of subclinical *M. tuberculosis* infection. Furthermore, effective preventive therapy regimens for the management of contacts of patients with multidrug-resistant tuberculosis are required.

## CONCLUSIONS

This consensus document provides evidence-based, best-practice recommendations for the performance of contact investigation among the persons exposed to tuberculosis patients. It stresses the importance of establishing the

**TABLE 17** Rating level of evidence according to the Scottish Intercollegiate Guidelines Network (SIGN)

| Rating | Study design | Special conditions | Level of evidence |
|---|---|---|---|
| 1++ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias | If directly applicable to target population | A |
| 1+ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias | If directly applicable to target population and overall consistency of results | |
| 1++ or 1+ | | Extrapolated evidence | B |
| 2++ | High quality systematic reviews of case–control or cohort or studies | If directly applicable to target population and overall consistency of results | |
| | High quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal | Extrapolated evidence | C |
| 2+ | Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal | If directly applicable to target population and overall consistency of results | |
| | | Extrapolated evidence | D |
| 3 | Nonanalytic studies, *e.g.* case reports, case series | | |
| 4 | Expert opinion | | |
| 1- | Meta-analyses, systematic reviews, or RCTs with a high risk of bias | | No supporting evidence |
| 2- | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal | | |

RCT: randomised controlled trial.

infectiousness of the source case, the likelihood of infection with *M. tuberculosis* among contacts and the risk amongst them to develop tuberculosis, the prioritisation of identified contacts, and the appropriate timing and use of diagnostic tests to diagnose infection with *M. tuberculosis*, and the primordial role in ruling out tuberculosis among identified contacts. Extension of the contact investigation to medium-and low-priority groups should be guided by the evidence of transmission from the source case. Infected contacts should be offered preventive therapy with an effective antimicrobial regimen, balancing risks and benefits of treatment. Outbreaks and the occurrence of tuberculosis cases in communities may necessitate special interventions, but the contact investigation should follow the principle of assessment of exposure risk through evidence of excess transmission to close contacts. Monitoring and evaluation of contact investigation practices will contribute to a better understanding and a more effective use of public resources. Further research must focus on the identification of those contacts with a high risk of developing tuberculosis, diagnostic tests with a high predictive value for the development of active disease, and effective, shorter preventive therapy regimens, including preventive therapy for contacts of patients with multidrug-resistant tuberculosis.

## APPENDIX

For Appendix, see table 17.

## STATEMENT OF INTEREST

Statements of interest for C. Lange and J-P. Zellweger can be found at www.erj.ersjournals.com/misc/statements.dtl

## ACKNOWLEDGEMENTS

The following national correspondents and tuberculosis experts are greatly acknowledged for their input and comments on various versions of the manuscript: D. Antoine (Institut de Veille Sanitaire, Paris, France), J.A. Caylà (Agència de Salut Pública de Barcelona, Barcelona, Spain), D. Che (Institut de Veille Sanitaire, Paris, France), B. Farrrugia (Chest Clinic, Public Health, Mater Dei Hospital, Malta), B. Hauer (Robert Koch Institute, Berlin, Germany), P. Helbling (Federal Office of Public Health, Bern, Switzerland), S. Keizer (Amsterdam Municipal Health Center, Amsterdam, The Netherlands), V. Kuyvenhoven (KNCV Tuberculosis Foundation, The Hague, The Netherlands), B. Winje (Norwegian Institute of Public Health, Oslo, Norway), E. Rodríguez Valín (National Center for Epidemiology, Carlos III Health Institute, Madrid, Spain), V. Romanus (Swedish Institute for Infectious Disease Control, Solna, Sweden), B. Schmidgruber (Tuberculosis Dept, Public Health Service, Vienna, Austria) and M. Wanlin (Belgian Lung and Tuberculosis Association, Brussels, Belgium).

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