

Tuberculosis in Switzerland

Guidance for healthcare professionals



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Background

This text is based on current international guidelines for the diagnosis and management of tuberculosis. This version updates the 2014 edition of the publication "Tuberculosis in Switzerland – Guidance for Health Care Professionals" and at the same time replaces the 3rd edition (4 / 2011) of the "Handbuch Tuberkulose".

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1 Role of the physician

1 Role of the physician

Clinicians play the central role in the management of tuberculosis, both in terms of provision of care for the individual affected by tuberculosis and from the perspective of public health: the physician is the indispensable link between individual and public health.

The duties of the physician are:

- To **“think TB”** in a patient with signs and / or symptoms compatible with tuberculosis, particularly if the patient belongs to a group known to be at high risk of tuberculosis (e.g. born in a high-incidence country, recent contact with a case of transmissible tuberculosis, compromised immunity).
- To rapidly carry out the necessary **diagnostic examinations (radiograph** of the chest, microbiological examinations and other targeted testing according to clinical presentation) or to **refer** the patient to an experienced colleague or a specialised centre.
- To **immediately notify** the local health department of any case of tuberculosis at treatment initiation.
- To ensure that the **persons (contacts) with prolonged exposure to a patient** with a transmissible form of tuberculosis are **examined**. The contact investigation is performed in coordination with the Cantonal Medical Officer and in cooperation with the designated local tuberculosis office, usually the cantonal Lung Association.
- To ensure that the patient **adheres to and tolerates the prescribed treatment** until its scheduled completion, and to immediately notify the Cantonal Medical Officer of any interruptions, failure to comply with treatment, or loss of the patient to follow-up.
- To **facilitate adherence and treatment completion**. To this end, the social environment of the patient is taken into account and all persons concerned with the restoration of health of the patient should provide the necessary assistance if and where needed.
- To **confirm that the case of tuberculosis has been cured** by performing or ordering the necessary examinations to be carried out for all cases and informing the Cantonal Medical Officer of the outcome of treatment.

2 Epidemiology

2 Epidemiology

Tuberculosis in Switzerland has decreased for at least 150 years as in many other countries in Western Europe. The number of notified cases dropped to a nadir of 478 in 2007, then increased slightly over the subsequent years to drop again in 2017 (554 cases) resulting in a notification rate of 6.5 incident cases per 100'000 population. Of these, 77% were of foreign origin, defined as foreign citizenship and /or born outside Switzerland (**Figure 2-1**). In 2015, the last year these data were collected, 34% of all reported cases occurred among asylum seekers or refugees.

Tuberculosis was pulmonary in 70% (year 2017). Of the pulmonary cases, 91% were confirmed by culture and 50% were reported by laboratories to be positive on microscopic examination of a respiratory specimen.

Patients of foreign origin were mostly young adults, reflecting migration patterns and, to some extent, also the commonly prevailing epidemiologic situation in their country of origin.

Figure 2-2 shows the age distribution of cases separated by origin (foreign vs. Swiss). In the 5 years from 2012 to 2016, there were 52 cases younger than 5 years. 37 were of foreign origin (foreign citizenship and /or born abroad). Seven of these children were born abroad and 28 were born in Switzerland (country of birth unknown in two).

In Switzerland reporting of drug susceptibility test results is mandatory. The proportion of multidrug-resistant (MDR) tuberculosis among all notified and tested cases had been around 2% for many years and has been 3% since 2013.

Globally, the World Health Organization (WHO) estimates that the incidence of tuberculosis has been slowly decreasing for several years. As outlined in the Global Tuberculosis Report 2018, the WHO now estimates that 10 million new cases occurred in the year 2017, of which 9% are accounted for by people living with HIV [1]. The annual number of new tuberculosis cases per

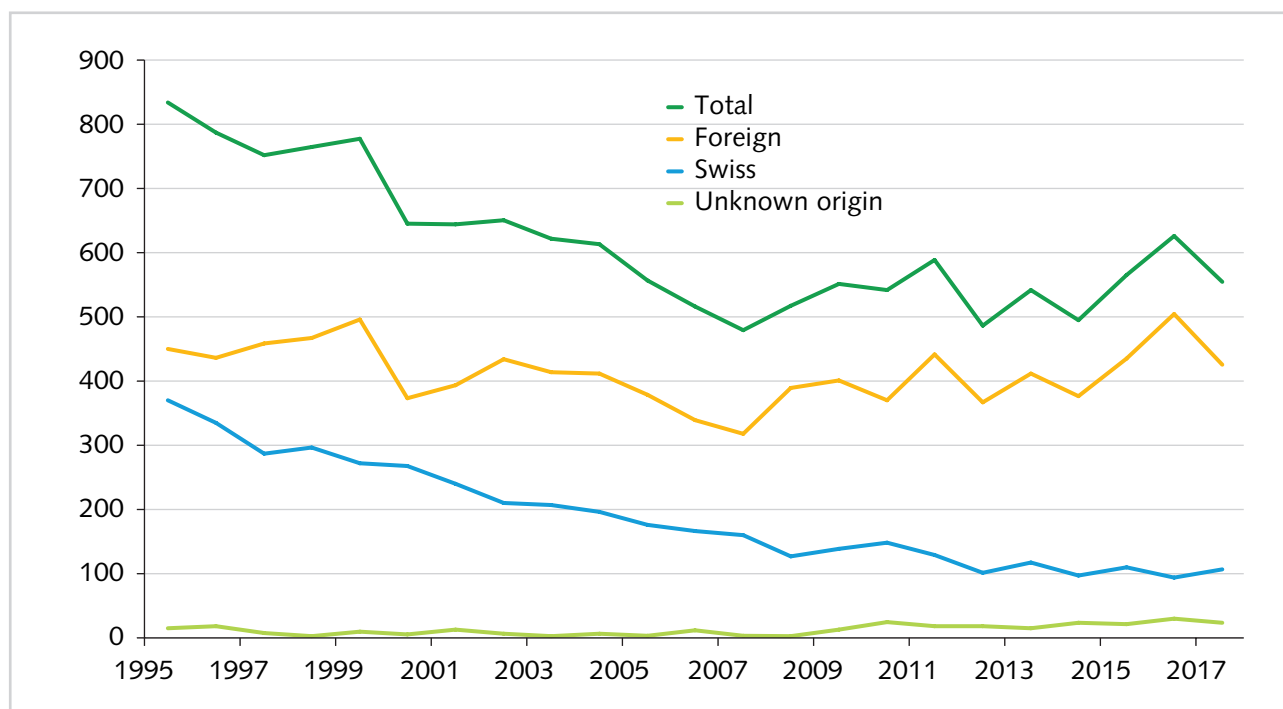


Figure 2-1. Tuberculosis cases notified to the Federal Office of Public Health, by origin, Switzerland, 1995–2017

100'000 population (the incidence rate) varies widely among countries. While the estimated incidence rate was below 10 in most of the highly developed countries (as low as 3.1 in the USA), it is higher in the vast majority of countries. It is above 500 (as high as 665) in some countries of Southern Africa and Asia (Figure 2-3). The number and proportion of cases estimated to have drug-resistant tuberculosis is worrisome (Figures 2-4 and 2-5) and funding gaps for global tuberculosis care and control remain critical.

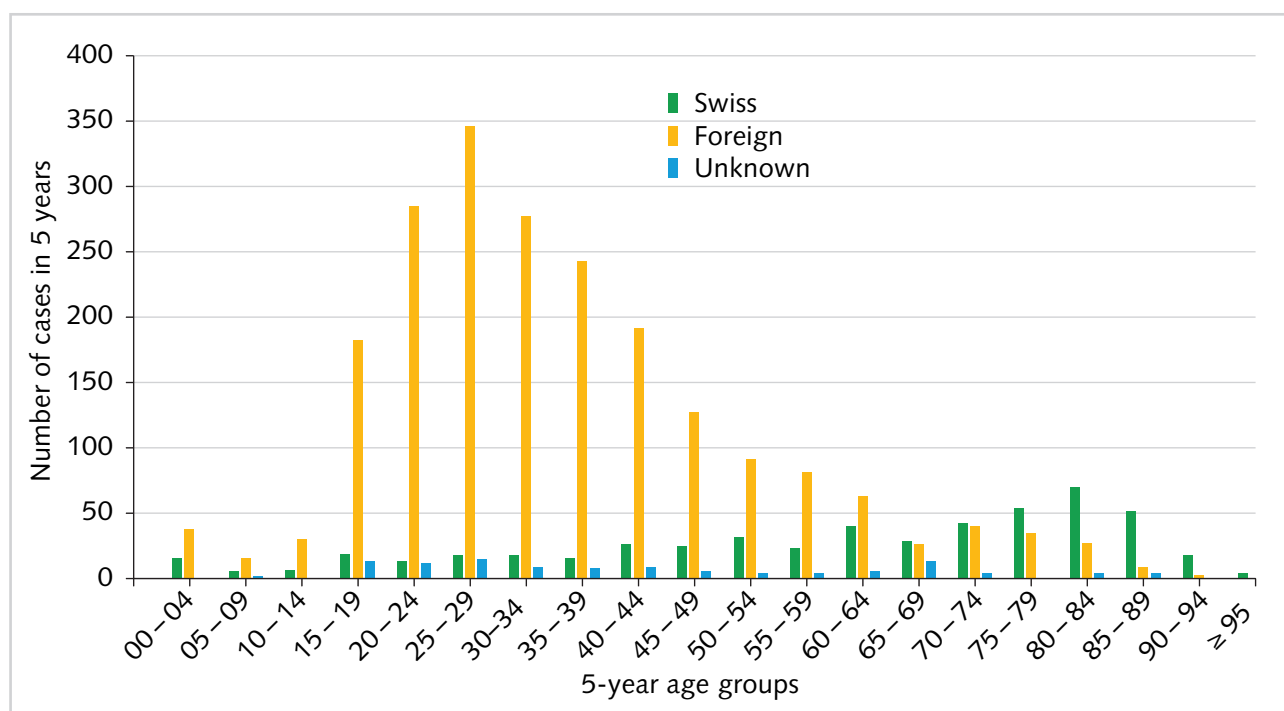


Figure 2-2. Ages and origins of cases notified to the Federal Office of Public Health, Switzerland, in 2012–2016 (total n=2716).

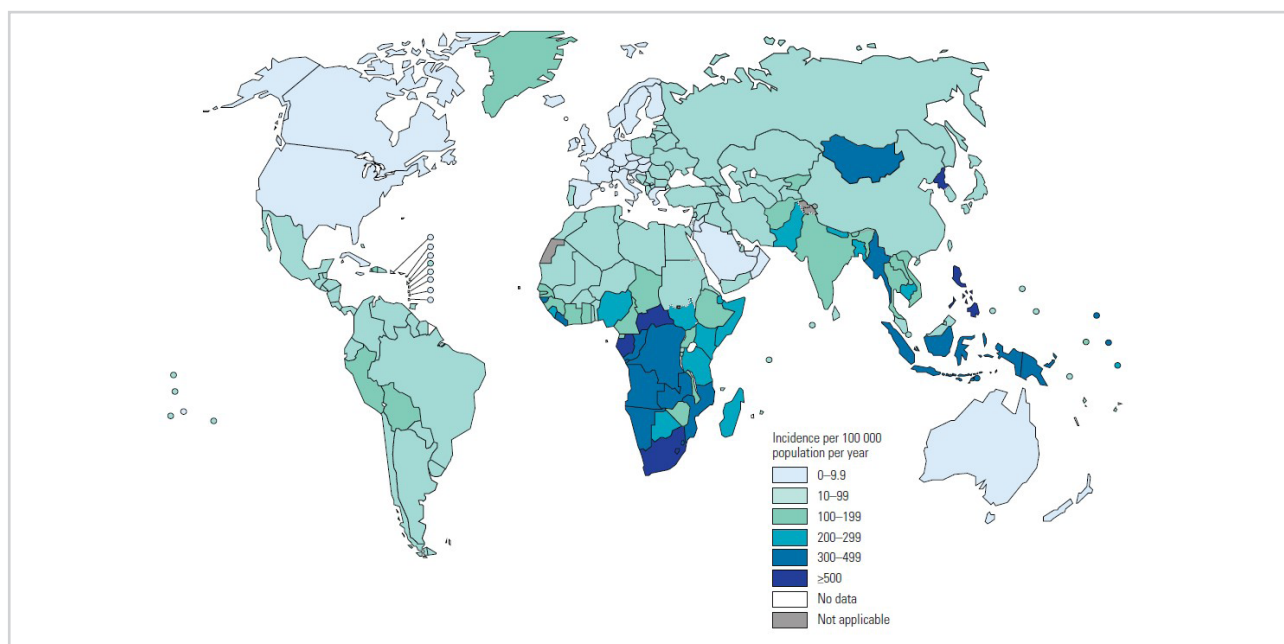


Figure 2-3. Number of new tuberculosis cases per 100'000 population and year (incidence rate), 2019. World Health Organization, Global Tuberculosis Report 2020 [1].

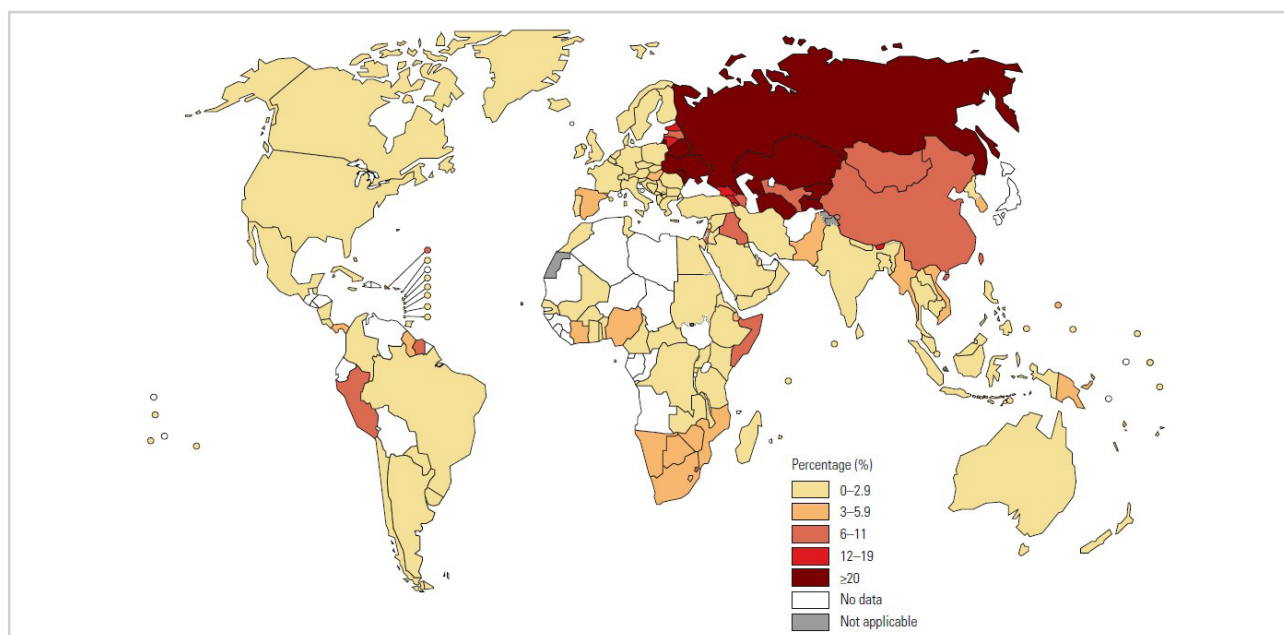


Figure 2-4. Distribution of the proportion of multidrug-resistant tuberculosis among patients with no history of prior treatment. World Health Organization, Global Tuberculosis Report 2020. Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2005–2020.

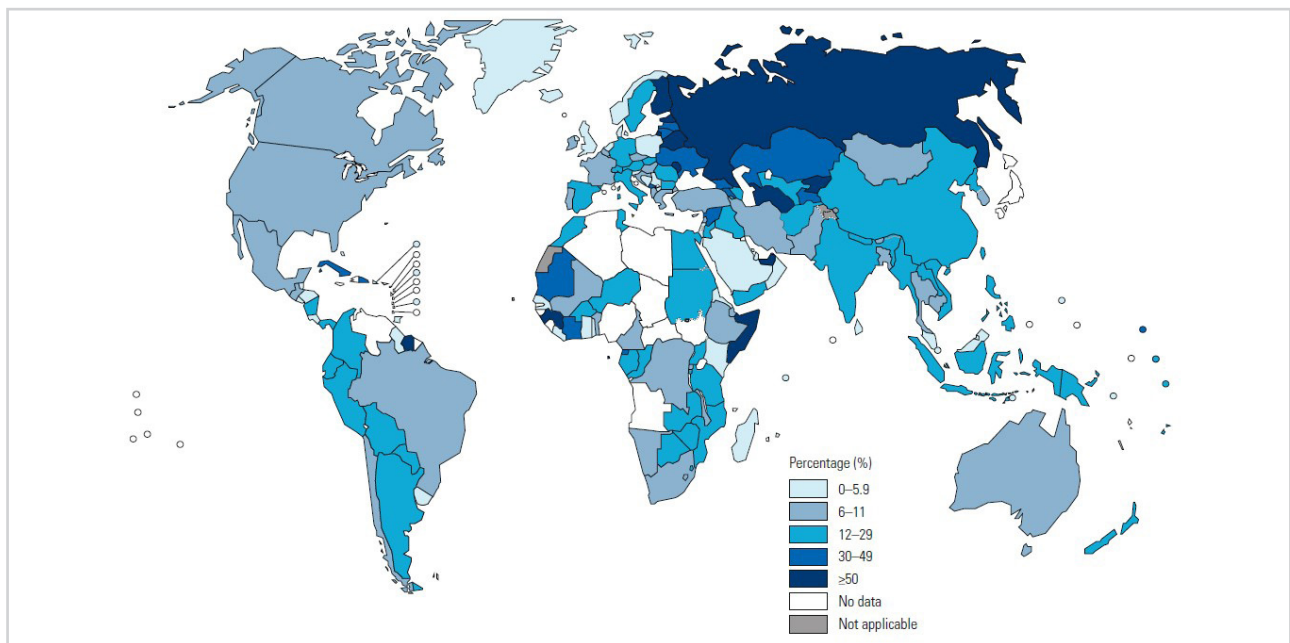


Figure 2-5. Distribution of the proportion of multidrug-resistant tuberculosis among patients with a history of prior treatment. World Health Organization, Global Tuberculosis Report 2020 [1].
Figures are based on the most recent year for which data has been reported, which varies among countries. Data cover the period 2005–2020. The high percentages of previously treated TB cases with RR-TB in Belize, Guam and Sao Tomé and Príncipe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases).

3

Transmission, pathogenesis and clinical presentation

- 3.1 Transmission
- 3.2 Pathogenesis
- 3.3 Clinical presentation
- 3.4 Radiological presentation

3 Transmission, pathogenesis and clinical presentation

Throughout this text and in line with contemporary scientific literature, the term “infection with *Mycobacterium tuberculosis*” (abbreviated *M tuberculosis*), refers to a state without signs and symptoms of tuberculosis (except for positive tests for infection with *M tuberculosis*) (chapter 4) while the term “tuberculosis” refers to the disease (signs and / or symptoms present).

3.1 Transmission

Tuberculosis is caused by a pathogenic species of the *Mycobacterium tuberculosis* complex (*M tuberculosis*, *M bovis*, *M africanum*, and *M canettii* [the species *M bovis* BCG and *M microti*, which are rarely pathogenic for humans, also belong to the complex]). Transmission of *M tuberculosis* is airborne by droplet nuclei containing live bacilli. Patients with tuberculosis of the respiratory tract produce droplets of various sizes and in various quantities through their respiratory manoeuvres (notably coughing and talking). The smallest droplets remain suspended in the air and evaporation turns them into suspended nuclei containing one or more tubercle bacilli. These droplet nuclei are sufficiently small to remain suspended in the air for a prolonged period of time (hours). They have a high probability of reaching the alveoli when inhaled where they might adhere to the cell wall to be engulfed by tissue macrophages. Indoors there is thus no safe distance between the patient and the exposed persons as room air can contain aerosolized bacilli even at a distance or after the patient has left the room. Assessing the risk of transmission in a specific situation is crucial for planning a contact investigation (chapter 5).

The rare cases of tuberculosis due to *M bovis* (1.3% of the cases in Switzerland in 2008–2017) are usually transmitted by ingestion of bacilli with unpasteurised milk originating from a cow with tuberculous mastitis. Air-borne transmission is also possible. They occur mostly (60%) among Swiss patients above the age of 65 years while most of the remainder occur in adult patients of any age with an origin abroad. In the elderly Swiss, these cases are a result of a reactivation of an infection acquired long in the past.

3.2 Pathogenesis

M tuberculosis may successfully prevent macrophages from destroying engulfed bacilli. Bacilli may thus multiply within the macrophage, then be released upon bursting of the cell, provoke a local inflammatory response, be engulfed again by other macrophages, which may act as antigen presenting cells, and ultimately lead to sensitization of lymphocytes. This may be followed either by:

- eradication of the mycobacteria; or
- persistence of mycobacteria and formation of granulomas.

Persons thus said to be latently infected with *M tuberculosis* due to a positive immunologic test (chapter 4.1) are neither ill nor able to transmit *M tuberculosis*. The overwhelming majority of such latently infected persons will never develop tuberculosis. An immunologic response can be elicited by appropriate test systems (a tuberculin skin test or an interferon-gamma release assay). It is the only sign of a prior acquired infection with *M tuberculosis*.

In a minority of persons, the subclinical or latent infection with *M tuberculosis* will progress to tuberculosis (i.e. the clinically and / or radiographically manifest disease due to *M tuberculosis*), the risk being highest within the first two years following infection. The risk of progression from infection to disease is greatly increased among the very young (infants and young children), in HIV infection and in drug-induced immunosuppression, e.g. after solid organ transplantation. The risk is also increased in other chronic disorders affecting immune response such as silicosis, chronic renal failure, diabetes, cigarette smoking, malnutrition, etc., and in adolescence to young adulthood.

Only patients with untreated tuberculosis of the lungs and airways can expectorate bacilli and thus potentially infect others. This is rare in children under the age of ten years. The potential of transmission is increased if the patient is coughing and produces sputum, if the expectorations contain large numbers of bacilli (which is typically the case in cavitary lung disease), and if there is a physical force producing large numbers of small-sized droplets (cough being the primary force in tuberculosis patients).

3.3 Clinical presentation

Tuberculosis is mostly located in the lung parenchyma (pulmonary tuberculosis) but may also affect other organs (extrapulmonary tuberculosis) due to lymphatic or haematogenous spread. The most frequently affected extrapulmonary sites are lymphatic, pleural and osteoarticular. Disseminated forms (miliary tuberculosis, multi-organ disease) and meningitis are mainly observed among immunocompromised patients and at the extremes of age.

Tuberculosis clinically manifests commonly as a slowly progressive illness with local (for pulmonary forms: cough, scanty sputum) and constitutional (fever, malaise, fatigue, night sweats, loss of appetite and weight) signs and / or symptoms. The symptoms are frequently mild during the early phase of the disease and paucity of symptoms may be misleading. No specific clinical sign or symptom is pathognomonic for tuberculosis. Elderly patients often have fewer and more atypical symptoms while children may present with prolonged fever and failure to thrive. The clinical suspicion therefore relies on epidemiological and clinical factors increasing the likelihood for tuberculosis such as the origin of the patient, the duration of symptoms, the history of a prior exposure to the disease, and on radiological findings. Decreasing interest in, and knowledge about, tuberculosis carries the risk of delayed diagnosis with an increased frequency of advanced forms of the disease.

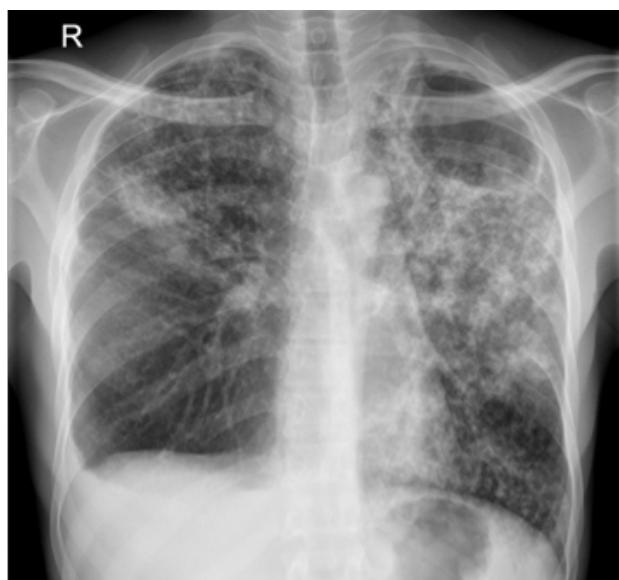


Figure 3-1. Chest radiograph of a patient with sputum smear-positive pulmonary tuberculosis. Extensive bilateral disease with asymmetric infiltrates, mottling, and cavitation.

3.4 Radiological presentation

Pronounced abnormalities on a (conventional or computed) radiological chest image are usually the most conspicuous sign of pulmonary tuberculosis. Asymmetric infiltrates in the upper fields (**Figure 3-1**) are highly suggestive, particularly if they contain cavities or show a micronodular pattern. Atypical localizations (infiltrates in the lower fields) can be present more frequently among elderly and immunocompromised patients. In children, hilar lymphadenopathy and pulmonary infiltrates are common radiological findings of pulmonary tuberculosis. Although there are no specific recommendations for its systematic use, computed tomography imaging (CT) (conventional or low-dose) may be a useful adjunct to conventional chest radiography (**Figure 3-2**). CT has a considerably higher sensitivity for detecting small cavitary lesions, tree-in-bud infiltrations or opacities in the apical or retro-cardiac parts of the lung parenchyma and images may be suggestive of pulmonary tuberculosis. Miliary patterns are easier to detect on CT and mediastinal or hilar adenopathy with inhomogeneous density suggestive of necrosis are characteristic findings in mediasti-

nal lymph node tuberculosis. Small peripheral and hilar nodules (calcified or not) may be found after a primary infection that may lie long in the past. Ruling out active tuberculosis may be necessary if symptoms are present or a treatment for infection with *M tuberculosis* is considered. No radiological presentation is specific for tuberculosis. The radiological findings do not allow distinguishing between bacteriologically active (replicating bacteria), inactive (dormant bacteria), or healed (no or dead bacteria) pulmonary tuberculosis. Before infiltrates are considered purely scars of tuberculosis based on radiological grounds, a clinical history has to be taken, symptoms and signs of tuberculosis be ruled out, and respiratory specimens have to be negative.



Figure 3-2. Chest computed tomography of a patient with pulmonary tuberculosis. Thickwalled cavity in the upper segment of the right lower lobe with tree-in-bud alterations.

4

Latent infection with *M tuberculosis*

- 4.1 Infection and progression to disease
- 4.2 Indications to test for latent infection in asymptomatic persons
- 4.3 Indirect immunodiagnostic tests to diagnose latent infection with *M tuberculosis*
- 4.4 Test type selection
- 4.5 Treatment options for latent infection with *M tuberculosis*

4 Latent infection with *M tuberculosis*

4.1 Infection and progression to disease

The interval between acquisition of infection with *M tuberculosis* and clinical manifestation of tuberculosis may vary from months to years or even decades: tuberculosis has an ill-defined incubation period. Conversely, it may not be deduced from such observation that “once infected, always infected” applies. Substantial bacteriologic, histopathologic, immunologic, and epidemiologic evidence has accumulated that lifetime persistence of live bacilli may be not the rule but rather an important exception.

None of the available tests can determine whether live bacilli are actually present in a clinically healthy person suspected of having latent infection with *M tuberculosis*. The tests at our disposal make use of memory immune cells that *M tuberculosis* induces. Immunological memory may persist lifelong. This is evidenced by the persistently positive test after bacteriologically cured tuberculosis and also by the prolonged perseverance of tuberculin skin test reactivity and its only gradual waning following BCG vaccination.

M tuberculosis and other mycobacteria (such as environmental mycobacteria and notably *M bovis* BCG) induce a delayed cellular immune response mediated by sensitized T lymphocytes. This sensitization can be detected either by:

- a tuberculin skin test (sensitive to an array of mycobacterial species); or
- a blood test: interferon-gamma release assay (IGRA) (sensitive to a limited number of mycobacterial species, but not to *M bovis* BCG).

The tuberculin skin test measures the in-vivo accumulation of memory T cells at the site of injection of a purified protein derivative (PPD) as an antigen. The IGRA measures the in-vitro release of interferon-gamma from memory T cells in the presence of mycobacterial cell wall antigens of mycobacteria of the *M tuberculosis* complex.

A positive response to either of these tests is indicative of prior contact with mycobacterial antigens or infection with mycobacteria, but not evidence for the continued presence of live mycobacteria. For this reason, neither the tuberculin skin test nor IGRAs can distinguish between infection with *M tuberculosis* and tuberculosis.

Applying the term **latent infection with *M tuberculosis*** (also denoted as “latent tuberculosis infection” or “LTBI”, notably in the US) to a person with a positive tuberculin skin test or IGRA is thus somewhat misleading: what we are able to measure is the immunological imprint left by **prior acquisition of mycobacterial antigens or prior infection with a mycobacterium**. It is thus not definitive evidence of persisting infection with live bacilli. The risk of progression to tuberculosis requires, however, the presence of live bacilli. It is thus not particularly surprising that both the tuberculin skin test and IGRAs are relatively poor predictors of future tuberculosis (the vast majority of positive reactors will never develop tuberculosis). Conversely, the negative predictive value (the probability that a person with a negative tuberculin skin test or a negative IGRA [except in the presence of anergy] does not develop tuberculosis) improves with a decrease of the true prevalence of *M tuberculosis* infection.

An assessment of the risk of a latently infected person to progress to tuberculosis will take into account:

- the person's age;
- the time elapsed since acquisition of infection;
- the integrity of the cellular immune system;
- chest radiological findings suggesting scars after tuberculosis, e.g. calcified thoracic granulomas or lymph nodes (in persons not treated for tuberculosis previously).

Given persisting infection, the risk of progression to tuberculosis depends on the quality of the immune response of the infected person. Recently infected persons, especially if they are children below the age

of 5 years or immunocompromised persons (HIV, anti-TNF-alpha treatment, etc.) or persons with diabetes, renal failure, or silicosis are at increased risk of progression to tuberculosis. They are thus prime candidates for preventive drug treatment. The risk of tuberculosis is highest during the first 2 years following infection, and decreases thereafter but never quite disappears (see Figure 4-1).

4.2 Indications to test for latent infection in asymptomatic persons

Any testing for latent infection should only be made if a positive test will be followed by treatment for latent infection, a recommendation to be discussed with the patient before applying the test.

Testing for latent tuberculosis infection is indicated for the identification of possible infection with *M tuberculosis*:

- in persons recently exposed to an index case with transmissible tuberculosis (contact investigation);

- in immunocompromised persons (initial check-up in persons with HIV infection, before initiating immunosuppressive treatment [e.g. before anti-TNF-alpha therapy], or before organ transplantation);
- in persons with an elevated risk of occupational exposure (healthcare workers, laboratory staff, social workers) according to a risk assessment, to have a baseline result before taking up employment in such an environment.

Screening for latent infection by systematic testing is currently not indicated for any situation not listed above (poor predictive value of a positive test in non-targeted screening).

4.2.1 Repeat testing of health care workers

In every institution of the health service and other institutions with tuberculosis risk, the employer is responsible for a risk assessment. In occupations with substantially increased risk of exposure to transmissible tuberculosis, adequate protective measures must be taken (chapter 7.5). In addition, a baseline test should

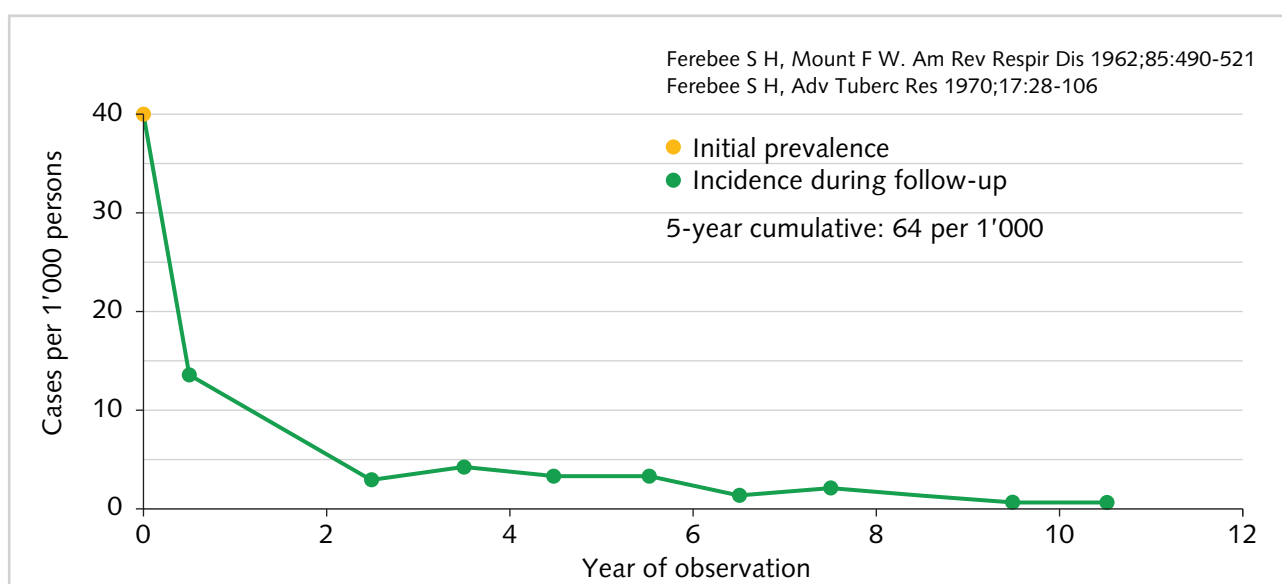


Figure 4-1. Prevalence and incidence of tuberculosis among recently infected household contacts, by time elapsed since identification of index case, United States Public Health Service trial.

be obtained among employees at risk. Repeat routine testing of health care workers is generally not recommended (see chapter 4.3.2, last paragraph). Testing should be carried out after an exposure to a potentially infectious case, i.e. when a contact investigation (see chapter 5) takes place, and only in persons who had a negative baseline test.

4.2.2 Migrant children below the age of 5 years from countries with a high prevalence of tuberculosis

A controversial issue are asylum seekers below the age of 5 years immigrating to Switzerland. A working group of the Paediatric Infectious Disease Group in Switzerland (PIGS) has issued a guideline in 2016 suggesting screening for tuberculosis (active disease) with a tuberculin skin test when such children are seen for the first time in the health care system [2]. The aim is to find tuberculosis at an early stage. According to this recommendation, a child with a positive tuberculin test should be referred to a specialist for appropriate evaluation and treatment of tuberculosis or preventive treatment of infection with *M tuberculosis*. Screening of asymptomatic immigrant children for infection with *M tuberculosis* outside of contact tracings (see chapter 5) is controversial because of a lack of data.

4.3 Indirect immunodiagnostic tests to diagnose latent infection with *M tuberculosis*

4.3.1 Tuberculin skin test

In Switzerland, shortages in supplies with tuberculin are frequent. It is thus preferred to use IGRAs, with the exception of children below the age of 5 years (see below).

Tuberculin contains a large number of different mycobacterial peptides, most of which are also present in *M bovis* BCG and to a lesser extent in several species of environmental mycobacteria.

The intradermal technique is the only recommended route of administration. A dose of 0.1 mL of PPD RT23 tuberculin (containing 2 tuberculin units) is injected intradermally to the volar aspect of the forearm. For injection, a 1 mL syringe fitted with a

short-bevel needle (26 G) is used, with the opening of the bevel facing upwards, into the superficial layer of the skin.

The induration is measured 48 to 72 hours after administration. The transverse diameter (in millimetres) of the induration is measured, i.e. the diameter perpendicular (transverse) to the long axis of the arm. Importantly, the possible presence of any oedema or erythema is not taken into consideration for the measurement, solely the induration.

The chosen cut-off point to denote a “significant” or “positive” reaction is a balance between test sensitivity and specificity.

Tuberculin skin test sensitivity is more consistent than test specificity which depends on cross-reactions with other mycobacteria. Excluding anergic or partially anergic individuals (unable to react appropriately to tuberculin despite infection with *M tuberculosis*), an induration of 10 or more millimetres has about 90% sensitivity, and an induration of 5 or more millimetres about 99%, in identifying all non-zero reactors. However, it has to be kept in mind that the trade-off for higher sensitivity is a lower specificity, with more individuals being classified as being infected while in fact they are not.

In a targeted contact investigation, it is recommended to consider an induration size of 5 and more millimetres in contacts as “positive” requiring investigations for tuberculosis and preventive therapy. The more targeted a contact investigation is (i.e., the more it focusses on the most exposed contacts), the higher the predictive value of a positive tuberculin skin test will be as the prevalence of true infection can be expected to be higher.

Such low cut-off points have also been recommended for other persons at particularly high risk of tuberculosis (such as patients with HIV infection).

4.3.2 Interferon-gamma release assays (IGRAs)

The IGRAs (two commercial tests are currently registered by Swissmedic) use only two (or three) distinct peptides present in pathogenic species of the *M tuberculosis* complex. These peptides are not present in

M bovis BCG and *M microti* (but they are present in *M marinum*, *M kansasii* and *M szulgai*). The IGRA blood tests are thus not influenced by prior vaccination with BCG or most other environmental mycobacteria. Test sensitivity is comparable to that of the tuberculin skin test, but specificity is higher. IGRAs assess the levels of interferon-gamma released from the lymphocytes after incubation of a blood sample with specific peptides. The result is expressed in IU / mL (QuantiFERON-TB® Gold In-Tube) or in the number of sensitized lymphocytes per 250'000 cells (T-SPOT®.TB). In addition to the specific peptides, IGRA test kits also include control assays for negative (background interferon) and positive (mitogen stimulation) reactions. The technical instructions issued by the manufacturer must be strictly adhered to when collecting and transporting samples. In particular, the blood samples should not be exposed to low temperatures (inhibition of lymphocytes). In infants and children less than 5 years of age, the proportion of indeterminate test results is increased. The place of IGRAs in infants and young children remains unresolved. IGRAs are generally more specific than the tuberculin skin test, but they have other drawbacks such as fluctuation in responsiveness over time, i.e. "conversions" and "reversions" are more frequent than with tuberculin skin testing. Findings of poor specificity of IGRAs in serial testing call for a review of cut-off points and better definitions of "grey zones" (cf. chapter 4.2.1). In addition, the diagnostic performance of IGRAs is lower in children compared to adults.

4.4 Test type selection

Rationale for the recommendations

The recommendations formulated in this section reflect actual practice in Switzerland, current deficiencies in knowledge, and the discordance in recommendations by international expert societies (e.g. United Kingdom NICE guidelines, Canadian Thoracic Society). As more information accumulates, these recommendations will possibly have to be adapted accordingly.

For the time being, three strategies may be used to test for latent infection:

- Using an IGRA as the only test.
- Using the tuberculin test as the only test (< 5 years old contacts).
- A tuberculin skin test followed by an IGRA if the tuberculin skin test is positive.

However, in the future, it is possible that non-availability of tuberculin will preclude its use.

Using an IGRA as the only test

Generally, the sensitivity of an IGRA is comparable to the tuberculin skin test and the IGRA is more specific than the tuberculin test, particularly in BCG-vaccinated subjects. Thus, among adults, there is an increasing tendency to rely solely on an IGRA.

Among BCG-vaccinated children under the age of 5 years, using solely an IGRA might appear particularly desirable. However, due to a relatively high frequency of indeterminate results and the challenge of drawing venous blood from small children (see below), IGRAs cannot generally be recommended to replace the tuberculin skin test in this age group, but may be used in selected cases and when TST is not available.

Using the tuberculin test as the only test

The tuberculin skin test is preferred in the evaluation of children aged less than five years in whom the robustness of IGRAs has not been sufficiently demonstrated and some studies have shown an excess frequency of indeterminate results among younger compared to older children.

In immunocompetent patients, the tuberculin skin test is sufficient as sole test and equivalent to an IGRA whenever the test is negative. In contacts below the age of 5 years, it is acceptable to not confirm a positive TST with an IGRA and start preventive therapy after excluding tuberculosis disease.

A tuberculin skin test followed by an IGRA if the tuberculin skin test is positive

An IGRA is used here following a positive tuberculin skin test and is expected to exclude persons with a false-positive tuberculin skin test to avoid unnecessary

preventive therapy. The drawbacks of sequential testing are the costs for two tests and the limited knowledge about the operating characteristics of the two test systems. Prior BCG vaccination may affect the tuberculin skin test result depending on BCG strain, age at vaccination, time elapsed since vaccination, and potential boosting induced by infection with environmental mycobacteria. However, this two-step approach is resource intensive, not just because it requires two tests, but also because it requires at least two visits to arrive at a final result.

Tests performance is limited by immunosuppression

Both TST and IGRAs can be affected by various regimens of iatrogenic immunosuppression or immunosuppressive diseases. These situations will increase the number of false-negative tests (TST, IGRA) and of indeterminate tests (IGRA). The impact of immunosuppressive drugs on test results is unpredictable, and the impact of HIV infection seems to be related to the CD4 cell count. In immunosuppressed contacts with a high pre-test probability for infection but with an indeterminate test result, contacts should be treated as if infection was present.

4.5 Treatment options for latent infection with *M tuberculosis*

Persons judged to be infected with *M tuberculosis* and to be at increased risk of progression to tuberculosis should receive preventive therapy (also called "treatment of latent infection with *M tuberculosis*") if they have no symptoms or signs consistent with active tuberculosis. Based on clinical trials, the choice is among three regimens with similar efficacy:

- daily isoniazid for 9 months; or
- daily rifampicin for 4 months; or
- daily isoniazid and rifampicin for 3 months.

While trial efficacy of 6 months of isoniazid is inferior to longer durations, the World Health Organization and the British NICE guidance maintain a recommendation of 6 months' isoniazid as an alternative to the above regimens.

The largest body of trial evidence across age groups is available for isoniazid preventive therapy. Trials based on rifampicin have been largely limited to adults. Nevertheless, all regimens listed here are recommended for use in any person judged to require preventive therapy, irrespective of age. All regimens require precautionary measures among patients with acute or chronic liver injury which is an indication for consultation with a specialist.

A directly observed shorter treatment with isoniazid and rifapentine once weekly for 12 weeks is an equally effective regimen to treat latent infection with *M tuberculosis* used in the USA. However, rifapentine is not registered and not available in Switzerland (and in Europe).

Contacts judged to have become infected by a source known to have isoniazid-resistant tuberculosis should be offered one of the rifampicin-containing preventive therapy regimens and in case of exposure to MDR tuberculosis a specialist with relevant experience should be consulted.

If correctly followed, preventive treatment of latent infection with *M tuberculosis* can reduce the risk of progression to tuberculosis by up to 90%. Persons on preventive therapy must be regularly followed clinically to ensure their tolerance of, and adherence to, treatment. Baseline testing of liver enzymes is advocated by some experts particularly when a combination treatment with isoniazid and rifampicin is envisaged. If baseline liver testing is normal, monthly testing for liver enzymes is not recommended except in persons with pre-existing liver disease, a history of regular alcohol consumption or treatment with other medication known to cause drug-induced liver injury.

The risk of drug-induced liver injury must be balanced against the benefit of preventive therapy. Among persons with risk factors for progression to tuberculosis

(such as recently acquired infection), the expected risk of hepatitis is likely to be smaller than the risk of progression to tuberculosis at any age, provided that there is no pre-existing liver injury.

Possible interactions between treatments for LTBI and concurrent medication must be considered. Absorption of rifampicin is significantly decreased by food, mostly food with high lipid content, and anti-acid medication. Isoniazid interacts with most antiepileptic drugs (increases their serum level), oral anticoagulants (acenocoumarol), and glucocorticosteroids. Rifampicin, by induction of cytochromes, has a long list of interactions and reduces the efficacy of oral contraceptives, opiates, antiepileptic medication, glucocorticoids and other hepatically metabolized drugs. The treating physician must adjust the doses of these drugs and **women of child-bearing age must be reminded that hormonal contraception is not effective during treatment for LTBI with rifampicin and one month after completion of the treatment.**

It is recommended that all other medication taken by a patient put on rifampicin or isoniazid be checked for any type of interaction using a dedicated updated software or website.

Pregnancy is not a contraindication for treating LTBI, whatever the regimen chosen. There is a slightly increased risk of reactivation of tuberculosis in the peri- and post-partum period which further justifies treating the mother during her pregnancy. There are no teratogenic effects of isoniazid or rifampicin at any stage of pregnancy. In case of treatment with isoniazid, supplementation with vitamin B6 is recommended.

Breast-feeding is also compatible with isoniazid and / or rifampicin. In case of treatment with isoniazid, supplementation with vitamin B6 for the newborn is recommended. Small quantities of either drug pass into the milk.

5

Contact tracing and investigation

- 5.1 Principles for the approach to a contact investigation
- 5.2 Limitations of contact tracings

5 Contact tracing and investigation

The aim of contact tracing and investigation is to determine which person(s), among those in contact with an infectious case of pulmonary tuberculosis, may have been infected or may already have developed tuberculosis. The risk of progression to tuberculosis among recently infected persons can be reduced substantially by preventive therapy. The primary aim of contact tracing is for the individual contact to benefit from preventive therapy. While some epidemiological impact of contact tracing may also exist, this is not its primary rationale. Reasonable efforts at contact tracing should be made while coercive measures are not justified.

In some cases, especially if the tuberculosis case is a child below the age of 5 years, the aim of contact tracing is to find a source case. Suspected source cases are usually above the age of 12 years. They should be sent for examination with a chest radiograph, especially if the person is symptomatic.

The risk of acquiring infection with *M tuberculosis* is largely exogenous in nature and depends on:

- the concentration of *M tuberculosis* in the ambient air and
- the duration of exposure to that air (i.e. breathing time).

Sources of transmission of *M tuberculosis*

- Tuberculosis patients whose respiratory tract secretions contain *M tuberculosis* are potential transmitters, but not all are equally so. Practically, a potential source of transmission is defined as a patient whose respiratory specimens contain acid-fast bacilli visible on microscopic examination (smear positive). For practical reasons, this includes specimens produced spontaneously (sputum expectoration without induction), produced after sputum induction or collected by bronchoscopy (bronchial aspiration or bronchoalveolar lavage). It was further agreed, without a clear evidence base, by a European consensus group that a significant risk of acquiring infection with *M tuberculosis* exists only for contacts who have been exposed

indoors to the air shared with a smear positive patient for **more than 8 cumulative hours** during the 3 months prior to treatment initiation [3].

- Tuberculosis patients whose respiratory tract secretions are microscopically smear negative and positive only on culture or only by nucleic acid amplification techniques (including Xpert® MTB/RIF assay) represent a lower risk. In such cases, only close contacts (such as family members, or people sharing a same room / apartment / home) are considered to be at significant risk, together with any other person whose total indoor exposure time exceeds **40 cumulative hours** during the 3 months prior to treatment initiation.

The risk of progression to tuberculosis is largely endogenous in nature. It is described in chapter 4.1.

The Cantonal Medical Officer is responsible for ensuring that the contact investigations are carried out. Well-trained, experienced staff (commonly of the cantonal Lung Association or the hospital infection control unit) in close cooperation with the treating physician and the Cantonal Medical Officer carry out contact investigations.

Indications for the initiation of a contact investigation:

- Patients with pulmonary tuberculosis who are microscopically smear positive on direct or induced sputum or on a bronchoalveolar lavage or bronchial aspiration specimen.
- Patients with pulmonary tuberculosis who are microscopically sputum smear negative and positive only on a nucleic acid amplification test or culture of a respiratory specimen. For such index cases contact investigation is limited to close contacts (or those exposed for cumulatively more than 40 hours) and children below the age of 5 years.

5.1 Principles for the approach to a contact investigation

Firstly, a list is established of persons who were in close or prolonged contact (as described in the boxes above, in chapter 3.1, and in [3]) with the index case during up to three months preceding the diagnosis or the initiation of tuberculosis treatment. The list of contact persons is prepared with the input from the index patient. This requires trust-building, expertise, tact, repeated visits, and may need the help of interpreters or community representatives. The anonymity of the index case must be preserved as much as possible. If the index patient lives in an institution (nursing home, centre for asylum seekers, shelter for the homeless, etc.), the list is prepared with the assistance of a staff member from the institution. In acute care hospitals, contact investigations in health care workers and roommate patients are planned in coordination with the infection control departments and occupational health services.

The list is prepared as expediently as possible (in the days immediately following treatment initiation and notification) to allow rational planning of the contact investigation. Wherever possible, the contact persons are grouped by exposure gradient (i.e. duration and intensity of exposure, the intensity depending mainly on the concentration of mycobacteria in the room air as described in the boxes above and in chapter 3.1).

Secondly, all persons on the list of contacts will be contacted regarding symptoms. If symptoms compatible with tuberculosis are present, appropriate investigations (see below) must be performed promptly. If no symptoms are present, children under the age of 12 years and immunocompromised individuals are examined within days with a tuberculin skin test or an IGRA. In all other contacts, testing will take place after at least 2 months. Although conversion of these tests from negative to positive may occur as early as 2 weeks after exposure, waiting 2 months will ensure that the majority of converters are detected. Risk of progression to active disease in the 2 months following exposure is very low except for infants and immunocompromised individuals, and thus waiting 2 months to perform an IGRA or a TST is acceptable.

Irrespective of the intensity and duration of exposure, contacts will be grouped as those requiring immediate examination and those in whom examination is deferred.

5.1.1 Contacts requiring examination without delay (Table 5-1)

- **All contacts with signs or symptoms compatible with tuberculosis** require a medical examination (including a chest radiograph) as quickly as possible. Immunocompromised individuals should also be swiftly referred to their treating physician for clinical assessment.
- **Children under 12 years of age and immunocompromised persons** are given priority for contact examination and testing without delay. If asymptomatic this can be done within days.
- **Children under 5 years of age** must always be examined clinically and by conventional chest radiograph swiftly. If a contact child of an index case with known *M tuberculosis* susceptibility is symptomatic, has a positive tuberculin skin test, and / or an alteration in the radiological examination, a full course of tuberculosis treatment will be initiated. If the drug susceptibilities of the index case's mycobacterial strain are not known, collection of up to three respiratory samples (gastric aspirates, induced sputum or bronchoalveolar lavage) for microbiological examination including Xpert® MTB / RIF (see chapter 6) is recommended. Stool examinations with Xpert® MTB / RIF may also be considered in addition. **If tuberculosis is excluded, preventive treatment is initiated immediately** since, after recent infection, the rate of progression to tuberculosis in infants below the age of one year is estimated at 30 to 40%, and conversely, preventive treatment is well tolerated.
- If an initial tuberculin skin test is negative, the test is repeated after at least 2 months following the last effective exposure to the index case (pragmatically defined as the last contact before treatment was initiated in the index case). If a tuberculin test or an IGRA is still negative at this point in time, infection can likely be excluded and preventive treatment is stopped.

- Other contacts to be examined promptly are potential source cases of children under 5 years of age with tuberculosis. Source cases are usually adults (or at least 12 years old). A chest radiograph is the test of choice.

5.1.2 Contacts in whom examination is deferred (Table 5-1)

All other contacts may be examined on a single occasion at least 2 months after the last effective exposure (see also Table 5-1 for the rationale of the choice). It is advisable to start with the contacts most exposed in terms of duration and intensity of exposure and expand testing to less exposed persons after tests have been positive in the more exposed group.

Only contacts with a positive test result or with symptoms by that time require further examination (symptoms, clinical examination, and chest radiograph). Tuberculosis must be excluded before preventive therapy for latent infection with *M tuberculosis* (see chapter 4.5) is started. Treatment of tuberculosis is discussed in chapter 7.

5.1.3 Information of the public

On occasion, media reports on the occurrence of a case of tuberculosis may be a source of confusion and insecurity among the public. In such a case, it can be expedient and effective for the Cantonal Medical Officers in charge to swiftly dispense information and to put the procedures applied into proper perspective.

Tuberculosis may still be associated with irrational images and fears. Identification of a case of active tuberculosis in a community, whatever the level of education and background, may lead to anxiety, panic, and stigmatisation of the index case. It is thus very important to:

- identify professionals for providing appropriate information and answering questions;
- identify and inform close contacts of the index; patient
- proactively inform on site at schools, work places, and other communities to explain, reassure, and

clarify the contact tracing procedures, repeatedly if necessary;

- provide written information in appropriate languages (see chapter 12).

5.2 Limitations of contact tracings

There may remain some degree of uncertainty in each step of a contact investigation. This relates to infectiousness of the index case, intensity of exposure, the possibility of pre-existing test positivity in contacts, the possibility of immunosuppression as an explanation for test negativity, problems in retrieving the contacts, refusal of testing, refusal to be treated, non-adherence to treatment. Data of the Swiss Lung Association for contact tracing in Switzerland show that, of all contacts found test positive in 2013–2017, approximately half started treatment for infection with *M tuberculosis* and approximately one third completed it. Taking into account the above uncertainties, the efforts of contact tracing should therefore be targeted to persons in which the chain of actions will most likely have an effect.

An exemplary situation is a pulmonary tuberculosis case in a centre for asylum seekers: by the time the contact investigation starts, contacts may already have been transferred to other centres which makes the task more complicated. A reasonable target are usually family and other close persons who are likely to still be found where the index case is staying. Additionally, as in other settings, children and the immunosuppressed should have priority. A culturally sensitive approach is needed, and often the presence of an interpreter. An assessment of the situation by specialized staff (e.g. of the Lung Associations) and knowledge about the different stages of asylum procedures can define a balanced approach, bearing in mind that the primary aim of the contact investigation is to detect and treat newly infected contact persons. Persons with pre-existing infection with *M tuberculosis* have a lower risk of progression to disease. They may also benefit from preventive treatment but the expected benefit is lower as the period with the highest risk of progression to disease is likely to lie in the past.

In practice, contacts with a presumed recent infec-

tion identified by a **positive tuberculin skin test** or **IGRA** are at risk of progression to tuberculosis. So are immunocompromised contacts and small children with a significant exposure who may have false negative immunological tests. **These persons must be informed about the risk of developing tuberculosis and, unless contra-indicated, should be offered preventive therapy. Before starting preventive therapy,** it is important to exclude tuberculosis.

Contacts with a **negative test** result > 2 months after the last effective exposure and no signs and symptoms of tuberculosis have a negligible risk of developing tuberculosis unless they are immunocompromised (resulting in a possibly false negative test result).

The recommended procedure does not take into account BCG vaccination status because it is often uncertain whether and when the exposed person was vaccinated.

Table 5-1. Specific procedures for the contact investigation according to age and immune status**A. Procedure for asymptomatic contacts aged 12 years and older without immunosuppression**

At least two months after contact 2 months is the approximate maximum latency window for cell-mediated immune response			IGRA or tuberculin skin test
Tuberculin skin test	Negative result	→	No further examination
	Positive result	→	IGRA to confirm
IGRA	Positive result	→	History of tuberculosis, medical examination and chest radiograph
Medical examinations to exclude pulmonary and extrapulmonary tuberculosis, including a chest radiograph	Normal chest radiograph and asymptomatic	→	Preventive therapy if not contraindicated
	Abnormal chest radiograph	→	Further examination (including specimens taken for culture) Anti-tuberculosis treatment if indicated

Contacts aged ≥ 12 years of children with tuberculosis aged < 5 years: Initiate search for infectious tuberculosis disease among the contacts by taking a patient history and carrying out a clinical examination and a chest radiograph.

B. Procedure for asymptomatic contacts aged less than 12 years and for the immunocompromised**Children aged 5 to less than 12 years:**

Prompt testing within days. Children with a negative initial test are given a second test 2 months later.

Children under 5 years of age:

Prompt medical examination including a chest radiograph by a specialist within days. Asymptomatic children under 5 years of age with a negative first test and without evidence of possibly active tuberculosis (after radiography) should receive isoniazid treatment (unless there is demonstrated resistance to isoniazid) and have a second test at least 2 months later. If the second test remains negative, treatment is stopped. If the second test is positive (conversion), the child must be re-examined. After tuberculosis has been excluded again, isoniazid therapy for infection with *M tuberculosis* should be continued for a total of 9 months.

Newborns up to 1 month of age:

Must be promptly examined by a specialist within days.

Immunocompromised persons:

Immunocompromised persons (HIV infection, medication-induced immunosuppression¹, transplantation, renal failure, etc.) should be tested within days (preferably with an IGRA). Because both tuberculin test and IGRA may be false negative, immunocompromised patients must also always be examined clinically and radiologically. If there is no evidence of tuberculosis and the immunologic test is negative, the latter should be repeated at least 2 months later. If the second test is positive, the presence of active tuberculosis should again be excluded (by clinical and radiological examination) before prescribing preventive therapy. A high probability of exposure and infection may override a negative IGRA and warrant preventive treatment in an immunosuppressed individual.

¹ Such drugs include tumor necrosis factor-alpha inhibitors, azathioprine, methotrexate, cyclophosphamide, and other immunosuppressive drugs used in solid organ and stem-cell transplantation reported to increase the risk of progression from latent infection to tuberculosis.

6

Diagnosis of tuberculosis

- 6.1 Considerations in patients with possible tuberculosis
- 6.2 Sample collection in patients with possible tuberculosis
- 6.3 Microbiological techniques

6 Diagnosis of tuberculosis

6.1 Considerations in patients with possible tuberculosis

Tuberculosis should be suspected based on clinical (chapter 3.3) and epidemiological grounds (chapter 2). After history taking and examination, a chest radiograph is performed even if an extrathoracic form of tuberculosis is suspected. Any radiological finding compatible with tuberculosis will then lead to microbiological investigations. A definitive diagnosis of tuberculosis is based on the identification of a pathogenic species of the *M tuberculosis* complex from a biological sample (sputum, bronchial secretion, lymph node puncture, pleural or tissue biopsy, stools or gastric aspirate in children, etc.), i.e. positive culture and / or nucleic acid amplification test. In exceptional situations, it may be appropriate to treat patients (especially children) on the basis of symptoms, clinical signs, or radiological abnormalities alone (approximately 20% of all notified tuberculosis cases in Switzerland).

Immunological tests (tuberculin skin test and IGRAs) are indirect tests for determining the immunologic response to a pre-existing mycobacterial infection only. They neither prove current disease (tuberculosis) nor the persistence of live bacilli in the asymptomatic host (infection). They have limited value in the diagnosis of tuberculosis when symptoms are present, sensitivity as well as specificity are insufficient. With a sensitivity around 70–80%, more than 20% of patients with tuberculosis have negative IGRAs, and a positive IGRA does not necessarily explain symptoms and mean that the patient has tuberculosis. In children with suspected tuberculosis, however, paediatricians find immunological tests helpful, as cultures from respiratory samples may remain negative in paucibacillary disease. However, a positive immunological test cannot distinguish between tuberculosis and infection with *M tuberculosis* and a negative immunological test cannot rule out tuberculosis (sensitivity 70 to 80%).

6.2 Sample collection in patients with possible tuberculosis

In suspected pulmonary tuberculosis, a first sputum sample is collected on the spot to immediately perform a direct nucleic acid amplification test (e.g. Xpert® MTB/RIF, COBAS® TaqMan® MTB), see chapter 6.3. A second sputum specimen is collected after one hour, a strategy recently proven to be not inferior to the collection of a next day early morning specimen. This strategy avoids delay to treatment initiation and unnecessary isolation time until tuberculosis is ruled out with further test results since **aerosol isolation of a patient with a negative direct PCR** for the presence of *M tuberculosis* (MTB) **is not necessary**. In this situation, alternative diagnoses, including malignancy or other infections mimicking tuberculosis, must be considered and further tests including bronchoscopy with biopsies are recommended. In such cases, biopsies taken should always be sent to the microbiological laboratory without previous immersion in formalin, in parallel to work-up in pathology and cytology laboratories.

In patients unable to produce spontaneous sputum, sputum induction with an aerosol containing hypertonic saline (with salbutamol) facilitates sputum production. This procedure can frequently replace bronchoscopy. It is also appropriate for children of school age. Children < 5 years of age are not able to produce sputum: the recommended standard is the collection of gastric aspirate samples for PCR testing, microscopy and culture, and in addition the examination of stool with PCR. Bronchoscopy with the collection of bronchial washings, bronchoalveolar lavage, transbronchial biopsies (in suspected miliary disease), aspiration of mediastinal lymph nodes by endobronchial ultrasound as well as the collection of postbronchoscopy sputum are other diagnostic techniques with a good yield to detect *M tuberculosis*.

6.3 Microbiological techniques

6.3.1 Microscopy

The microscopic examination of stained sputum smears by bright-field microscopy (using the Ziehl-Neelsen staining technique) or by fluorescence microscopy (using auramine O or a modification thereof) provides a presumptive diagnosis in pulmonary tuberculosis with a high load of bacilli. It is also a means for assessing the relative potential of infectiousness of the patient and thus an indicator for the required extent of a contact investigation. Microscopy has a lower sensitivity in identifying *M tuberculosis* than nucleic acid based amplification tests and particularly culture. Microscopy must always be supplemented by nucleic acid amplification tests to exclude nontuberculous mycobacteria (in case of positive microscopy) and by culture to increase diagnostic sensitivity and to conduct resistance testing. Follow-up sputum microscopy and culture is used to document response to treatment and, towards the end of treatment, treatment success.

6.3.2 Nucleic acid amplification techniques and Xpert® MTB/RIF assay

Nucleic acid amplification techniques, based on polymerase chain reactions of specific gene sequences of *M tuberculosis*, have been used in mycobacteriology for more than 20 years. Since 2010, the Xpert® MTB/RIF test using clinical samples without pre-processing and with a run-time of less than 2 hours has been used to detect *M tuberculosis* complex (MTB) with high sensitivity. The MTB component of Xpert® MTB/RIF has a higher sensitivity than sputum smear microscopy for detecting the presence of MTB. As a rule, microscopically sputum smear-positive pulmonary tuberculosis cases are Xpert® MTB/RIF positive. Microscopically positive sputum smears with negative Xpert® MTB/RIF tests are usually caused by nontuberculous mycobacteria.

A second generation of the Xpert® MTB/RIF assay, Xpert® MTB/RIF **Ultra** has been introduced. The test requires a larger sputum volume and seems to result in a higher sensitivity, especially in paucibacillary specimens (smear negative or HIV patients), but at the expense of a lower specificity for detecting the presence of *M tuberculosis*.

Nucleic acid amplification techniques are also useful to detect resistance mutations. The Xpert® MTB/RIF automatically runs a highly sensitive assay for rifampicin resistance (RIF component) starting from unprocessed clinical samples. Nevertheless, given the low prevalence of true rifampicin resistance in strains generally detected in Switzerland, Xpert® MTB/RIF overall has a relatively low positive predictive value. In practice, a substantial proportion of positive results for rifampicin resistance by Xpert® MTB/RIF are false positive. The positive predictive value improves substantially if the patient is at increased risk of drug resistance (history of prior treatment, treatment failure, relapse, contact with cases with known rifampicin resistance, originating from a region with a high prevalence of drug resistance). In the Swiss setting, a positive RIF resistance result in Xpert® MTB/RIF must always be confirmed with a different resistance test system before a treatment schedule to treat MDR-TB is started. All rifampicin-resistant strains are required by law to be sent to the National Reference Laboratory in Zurich (cf. 6.3.3) and confirmation by this laboratory is warranted before a complex treatment for MDR-TB is initiated. Close collaboration with this laboratory, with the MDR-TB expert group of the Competence Centre for Tuberculosis of the Swiss Lung Association, and with an expert centre for MDR-TB treatment is strongly recommended in these cases (see below).

Fig. 6-1 (courtesy Hans Rieder) illustrates the often limited positive predictive value (PPV) of a positive Xpert® MTB/RIF result for rifampicin resistance. The predictive value of the test depends not only on the sensitivity (95.8%) and the specificity (98.1%) of the test, but also on the prevalence of rifampicin resistance among tuberculosis cases of the respective population (e.g. country of origin, asylum seekers, etc.; cf. Figures 2-4 and 2-5):

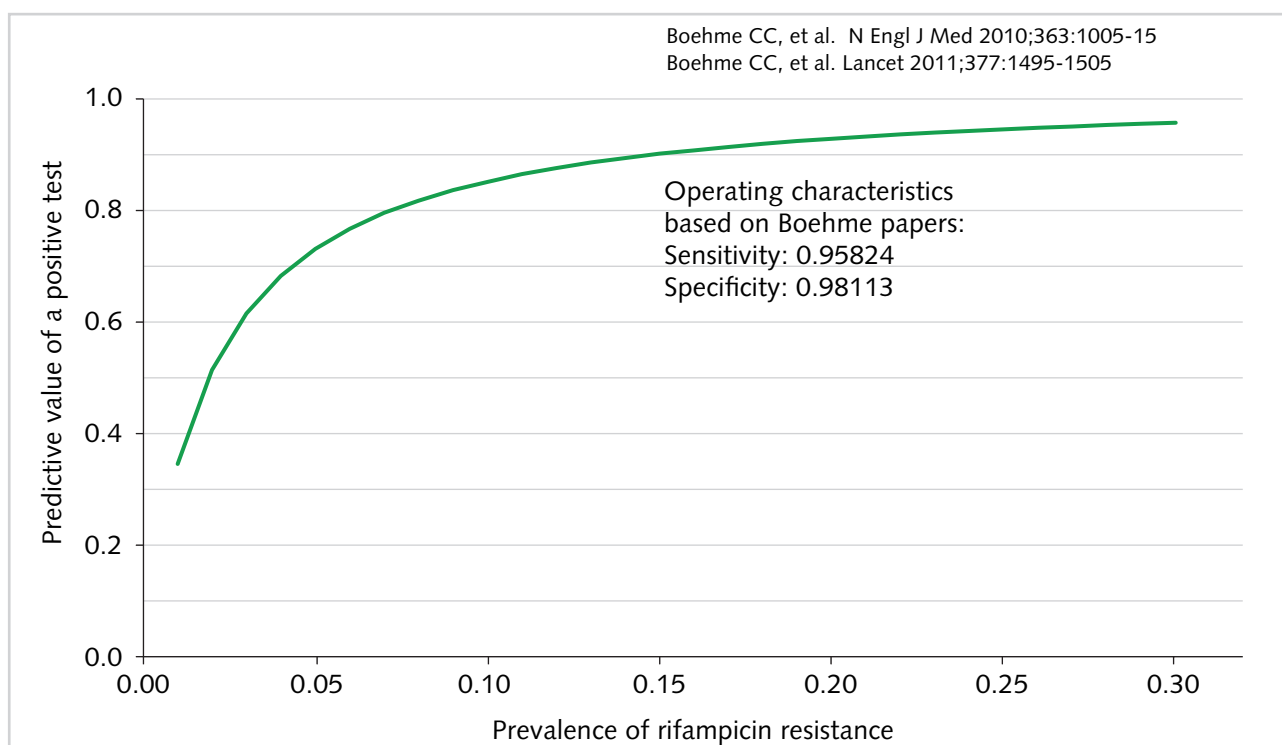


Fig. 6-1. Predictive value of a “rifampicin resistant” result with Xpert MTB/RIF, given prevalence of rifampicin resistance. The negative predictive value for the RIF component of Xpert MTB/RIF (i.e. no *rpoB* mutation detected) is usually very high and a treatment for drug-susceptible tuberculosis can be started.

Key clinical considerations concerning the direct PCR (Xpert® MTB/RIF test system)

- Xpert® MTB/RIF in sputum has been endorsed by WHO as the primary test for all cases of suspected pulmonary tuberculosis in all settings.
- **Untreated cases that are Xpert® MTB/RIF positive** for the presence of MTB are considered infectious and **isolation is recommended** (at home or in the hospital) until effective tuberculosis treatment has been given for 5–15 days (longer if *rpoB* mutation is present).
- Patients with possible tuberculosis but with respiratory specimens that are **Xpert® MTB/RIF negative** for the presence of MTB are considered non-infectious and do not need isolation.

- For patients with respiratory specimens that are **Xpert® MTB/RIF positive for MTB and negative for RIF** (no *rpoB* mutation detected and thus at very low risk for drug resistance), the standard treatment regimen **HRZE for 2 months followed by HR for 4 months** can be initiated. However, isoniazid resistance needs to be ruled out, either directly by PCR assays or later from cultured isolates.
- Xpert® MTB/RIF is helpful in specimens collected with biopsy, needle aspiration or stools, but has a lower yield in pleural and pericardial effusions and meningeal fluid.
- Xpert® MTB/RIF should not be used as an indicator of response to treatment or in suspected relapse cases because of persistence of positive results in successfully treated cases.

- Xpert® MTB/RIF is costly and should not be performed after tuberculosis diagnosis is formally established (except to verify a positive result for rifampicin resistance).
- Xpert® MTB/RIF does not replace smear microscopy for follow-up on treatment nor does it replace mycobacterial culture for resistance testing.

Alternative genetic strategies have been developed for detection of drug-susceptible and drug-resistant *M tuberculosis*, e.g. a combination of COBAS® TaqMan® MTB with line-probe assays.

6.3.3 Mycobacterial culture and resistance testing

In general, culture using a combination of solid and liquid media is more sensitive than nucleic acid amplification and is required for phenotypic drug susceptibility testing. Since mycobacteria grow very slowly, definitive negative results are only available after several weeks. However, data from the National Reference Laboratory and recent data from other international reference centres indicate that, for respiratory samples, rapid molecular-based methods may largely replace culture in the future as they compare favourably in terms of sensitivity and resistance detection.

Since 2016, laboratories are required to send rifampicin-resistant strains to the National Reference Laboratory. There, additional genotypic and phenotypic susceptibility testing (including for second-line drugs) is carried out. Most important is testing for second-line drugs (fluoroquinolones and others) with determination of the minimum inhibitory concentration. Such results can offer critical guidance for the treatment regimen for multidrug-resistant tuberculosis, gauging the usefulness of some drugs. Molecular analyses including whole genome sequencing also allow for the detection of resistance mutations and for the monitoring of transmission of MDR-TB.

7

Treatment of tuberculosis

- 7.1 Standard treatment regimen
- 7.2 Treatment of drug-resistant tuberculosis
- 7.3 Special situations
- 7.4 Treatment follow-up
- 7.5 Isolation

7 Treatment of tuberculosis

7.1 Standard treatment regimen

Before initiating tuberculosis treatment, it is essential to:

- Complete all recommended diagnostic procedures, notably obtaining the appropriate specimens for microbiological examinations.
- Assess the risk of drug resistance, in particular to rifampicin (the key drug determining curability with first-line drugs and a proxy for combined rifampicin-isoniazid resistance, i.e. multidrug resistance [MDR]).
- Assess the immunological status of the patient (HIV test).
- Assess liver and renal function.

Tuberculosis is treated with a combination of anti-tuberculosis drugs administered over a period of several months. The four commonly used first-line anti-tuberculosis drugs are isoniazid, rifampicin, pyrazinamide, and ethambutol. The dosages currently recommended by the World Health Organization are summarized in [Table 7-1](#) [4].

Standard treatment of tuberculosis

Initial or intensive phase (months 1–2):

4 drugs: Isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) for 2 months*

Continuation phase (months 3–6):

2 drugs: Isoniazid (H) and rifampicin (R) for 4 months

Short notation: 2HRZE / 4HR

* While most guidelines advocate HRZE for two months, E may be discontinued in fully susceptible isolates (as mentioned in guidelines of the American Thoracic Society ATS) [5].

The best established efficacious treatment regimen is a daily regimen throughout the six months. All anti-tuberculosis drugs are administered once daily, if possible in the morning. Intermittent treatment during the intensive phase is strongly discouraged. An intermittent continuation phase (thrice weekly) is only recommended if all drugs are given under direct observation. High-fat meals reduce absorption of rifampicin and, thus, peak blood levels and the area under the curve. If drugs are taken with breakfast, this meal should thus be dominated by carbohydrates (and protein), keeping fat to a minimum ([Figure 7-1](#)).

	Daily dose (range) in mg per kg		Intermittent (thrice-weekly) continuation phase
	Adults	Children*	Adults only
Isoniazid	5 (4–6)	10 (7–15)	10 (8–12)
Rifampicin	10 (8–12)	15 (10–20)	10 (8–12)
Pyrazinamide	25 (20–30)	35 (30–40)	Not applicable
Ethambutol	15 (15–20)	20 (15–25)	Not applicable

* up to a body weight of 25 kg

For combination tablets see: compendium.ch

To simplify the administration of treatment, the use of fixed-dose combination preparations is recommended (HRZE in one tablet and HR in one tablet). Tuberculosis patients on treatment need support from the caring team. If treatment interruptions occur, it is suggested to resume treatment according to guidance by the American Thoracic Society [5, table 6]. Pyridoxine (vitamin B6) is given with isoniazid to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons infected with human immunodeficiency virus [HIV]; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age) [5].

All forms of tuberculosis are treated with the same standard regimen, with the following exceptions:

- Some authorities (American Thoracic Society / US Centers for Disease Control and Prevention / Infec-

tious Diseases Society of America) note that expert opinion suggests an advantage in prolongation of the continuation phase to 7 months (total duration 9 months) in the presence of cavitory disease that is still culture positive after the intensive phase. Yet, they also suggest to consider clinical factors and the HIV status before deciding on the need for prolongation of treatment [5].

- Tuberculous meningitis: the continuation phase is extended to 10 months (12 months total), with the addition of corticosteroids during the first few weeks.
- Tuberculous pericarditis and severe (septic) tuberculosis: adjunct treatment with corticosteroids during the first few weeks is recommended.

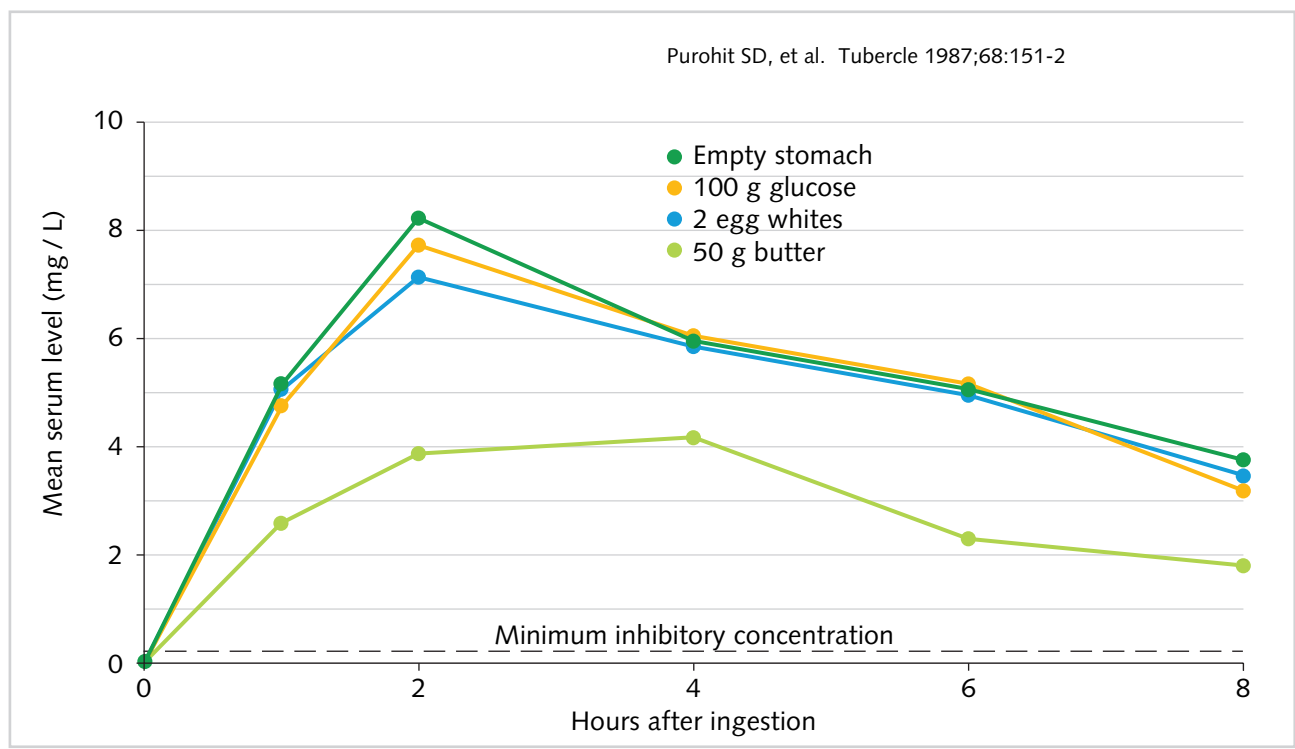


Figure 7-1. The impact of a meal containing carbohydrates, protein, or fat on the pharmacokinetics of rifampicin.

- Tuberculosis due to *M bovis* is naturally resistant to pyrazinamide and thus requires a treatment duration of 9 months (with extension of the continuation phase to 7 months, i.e. 2HRE/7HR).
- The treatment regimen for strains resistant to isoniazid only is given in chapter 7.2. The treatment regimen for strains resistant to rifampicin is always elaborated with a specialist.

7.2 Treatment of drug-resistant tuberculosis

Inappropriate treatment of patients with drug-resistant *M tuberculosis* can lead to the acquisition of additional resistance (amplification). It is thus important to estimate the likelihood of resistance before initiating tuberculosis treatment.

The risk of drug resistance is particularly elevated in patients who have at least one of the following:

- received antituberculosis drug treatment in the past for one or more months before this treatment episode. The risk is particularly high if the treatment was administered for several months without success (treatment failure), or if the treatment regimen did not comply with current recommendations;
- been in contact with a patient with known drug resistance;
- arrived from a region with a high prevalence of drug resistance (such as most countries of the former Soviet Union, cf. Figures 2-4 and 2-5, chapter 2).

For the treatment of *M bovis*, naturally resistant to pyrazinamide, see chapter 7.1. While low-level isoniazid mono-resistance may be overcome by the recommended standard treatment regimen, it is primarily rifampicin resistance (with or without concurrent isoniazid resistance – which in itself is the most common occurrence) that determines the adequacy of the chosen regimen: the treatment outcome of rifampicin-

resistant tuberculosis is frequently poor if treated solely with first-line drugs.

The recommended standard procedure for Switzerland is thus, at least in patients with an elevated risk for drug resistance, to perform a molecular test for a mutation of the *rpoB* gene associated with rifampicin resistance (cf. chapter 6.3.2). If no mutation is present, the standard treatment regimen is initiated. If the strain is later found to be resistant to isoniazid or pyrazinamide, treatment schedules need to be adapted (see box below for isoniazid resistance alone).

In the case of a high suspicion or demonstration of rifampicin resistance, confirmed by the National Reference Laboratory in Zurich (see above), MDR tuberculosis is likely and an alternative treatment regimen must be selected according to most recent international guidelines [6]. The advice of a specialist must always be sought. A presentation and internet-based discussion of the case in the “MDR-TB expert group” of the Swiss Lung Association facilitates the exchange of expert advice.

Treatment regimen for tuberculosis in the presence of resistance to isoniazid alone:

For any isoniazid mono-resistance, WHO recommends a regimen of rifampicin, pyrazinamide, and ethambutol (RZE) with levofloxacin for a duration of 6 months [7]. This regimen should be started as soon as isoniazid resistance is discovered and it is pursued until 6 months of levofloxacin have been given. The 4-drug fixed-dose combination with isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) may be used instead of Z+RH to limit the need for using single drugs.

Treatment regimen for tuberculosis resistant to rifampicin, without or with concomitant isoniazid resistance (the latter is known as multidrug-resistant [MDR] tuberculosis):

Before defining the treatment regimen in consultation with a specialist, make sure the strain is sent

to the National Reference Laboratory in Zurich for confirmation of resistance results and for additional molecular and conventional resistance testing. Treatment is always defined with a specialist taking into account recent international guidelines [6].

7.3 Special situations

Children: The treatment regimen for tuberculosis in children is the same as for adults. Children metabolize drugs faster than adults. For that reason, WHO recommends higher doses for all first-line drugs in children up to 25 kg of body weight (**Table 7-1**). The treatment of tuberculous meningitis and pericarditis may require the addition of an injectable drug and corticosteroids. It should be supervised by a specialist. Treatment of extrapulmonary disease and complicated pulmonary disease in children should be supervised by a paediatric specialist.

Pregnancy and breast-feeding: The standard treatment regimen (2HRZE/4HR) is recommended.

The immunocompromised patient: The standard treatment regimen is recommended. Interactions between rifampicin and certain antiretroviral drugs have to be taken into account. In patients on certain antiretroviral drugs, rifabutin, less prone to interactions, might be used as a substitute for rifampicin. All interactions should be checked or discussed with an expert, and antiretroviral or tuberculosis treatment adapted accordingly. Closer monitoring of clinical and laboratory parameters may be warranted for these patients.

Hepatic failure: In hepatic failure, pyrazinamide should be omitted and treatment prolonged to 9 months. In patients with elevated liver enzymes at treatment initiation, liver enzymes must be measured more frequently after initiation of the standard regimen. HRZ can cause drug-induced liver injury which is suspected if hepatitis symptoms are present and the ALT level is ≥ 3 times the upper limit of normal, or ≥ 5 times the upper limit of normal in the absence of symptoms. In either situation, hepatotoxic drugs must be stopped until liver tests recover. Treatment combining moxifloxacin, ethambutol, and amikacin

(15 mg/kg i.v. daily in one dose) may be used before a stepwise re-introduction of rifampicin and isoniazid is attempted. A fluoroquinolone might be added to the regimen.

Renal failure: The use of ethambutol and pyrazinamide must be spaced to a thrice weekly dosage if the creatinine clearance is < 30 mL/min. The drug may entirely be omitted from the regimen if no resistance to other first line drugs is present. A fluoroquinolone may be added to the regimen. For patients on haemodialysis, all drugs should be given after dialysis.

7.4 Treatment follow-up

Direct observation of drug intake: A first assessment of expected treatment adherence is to be made at treatment start. A key to success is the subsequent continuous assessment of adherence throughout the entire treatment duration. In order to ensure adherence, WHO recommends direct observation of drug intake by a third person (directly observed treatment: DOT). DOT reduces the risk of acquisition of drug resistance. Fixed-dose drug combinations reduce prescription errors but do not by themselves reduce the risk of acquisition of drug resistance if self-administered (patients may be selective in the number of ingested tablets leading to sub-inhibitory concentrations, notably of drugs with a narrow therapeutic range, i.e. ethambutol and pyrazinamide).

For these reasons, DOT is recommended in certain situations, in particular:

- For patients with whom communication is impaired.
- For patients who are in socially unstable situations or who have mental health or cognitive problems.
- For patients who previously had one or more treatment episodes or who receive treatment for multi-drug-resistant tuberculosis.

Some Swiss tuberculosis centres (e.g. Geneva) initiate treatment with DOT for almost all of their patients and switch to self-administered treatment after a few

weeks. Because DOT can be difficult to accept for some patients, it may be presented as an opportunity to have easy access to healthcare providers, with an advantage e.g. in the case of adverse drug reactions. DOT may be provided in specialized centres, cantonal lung associations, pharmacies, or by home care nurses.

Clinical follow-up during treatment: To rapidly ascertain the occurrence of possible adverse drug events and to ensure patient adherence with treatment, the organization of regular clinical visits is essential. Such visits should take place fortnightly during the intensive phase and at least monthly during the continuation phase of treatment.

Adverse drug events: Adverse antituberculosis drug events are fairly frequent among adult patients. The most common are gastrointestinal (abdominal pain, nausea), hepatic (increases in liver enzymes), neurological (dizziness, fatigue, paraesthesias) and cutaneous (itching, rashes). Minor adverse events can be managed by modifications of the dosing schedule or the use of appropriate drugs. Severe adverse drug events (such as drug-induced hepatitis) require at least temporary interruption of one or more drugs, sometimes with subsequent drug substitution. A specialist should be consulted in such a situation.

Drug-drug interactions: Interactions are particularly frequent between rifampicin and a host of other drugs because rifampicin is a potent inducer of the hepatic cytochrome P450 system which increases the metabolism of many drugs (such as **oral contraceptives**, opiates, **antiepileptic drugs**, **corticosteroids**, **anticoagulants** and many others). It is essential to obtain a thorough history of medications the patient is taking and to take the necessary precautionary measures and actions. Specific websites on drug-drug interactions should be consulted.

Control of liver enzymes: Because antituberculosis treatment includes three potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide), liver enzymes should be tested at treatment start and monthly (or more frequently if clinically indicated) thereafter among patients with known liver disease or conditions

predisposing to liver disease (such as alcohol abuse).

Examination of sputum during treatment: The effect of treatment and the possible acquisition of drug resistance can be assessed by regular follow-up of all patients with initially culture-positive pulmonary tuberculosis. Examination of the spontaneous expectorations by direct microscopic examination and culture is therefore recommended:

- at the end of the intensive phase (end of the second month); and
- before the end of the continuation phase (end of the fifth month).

If sputum smear and culture are still positive at 2 months, examination of monthly sputum until smear and culture become negative are recommended. If the emergence of drug resistance during treatment is suspected, a search for rifampicin resistance with the RIF test included in Xpert® MTB/RIF may be considered. As noted previously, the MTB test included in Xpert® MTB/RIF during treatment is expected to stay positive for more than 6 months and is therefore useless during treatment or in suspected relapses after treatment completion (**Figure 7-4**).

Radiographic follow-up: Conventional chest radiography or low-dose computed tomography may be useful for indirectly assessing the effect of tuberculosis treatment, but it is not indispensable. However, making use of an imaging technique is justified:

- at the end of the intensive phase;
- at treatment completion.

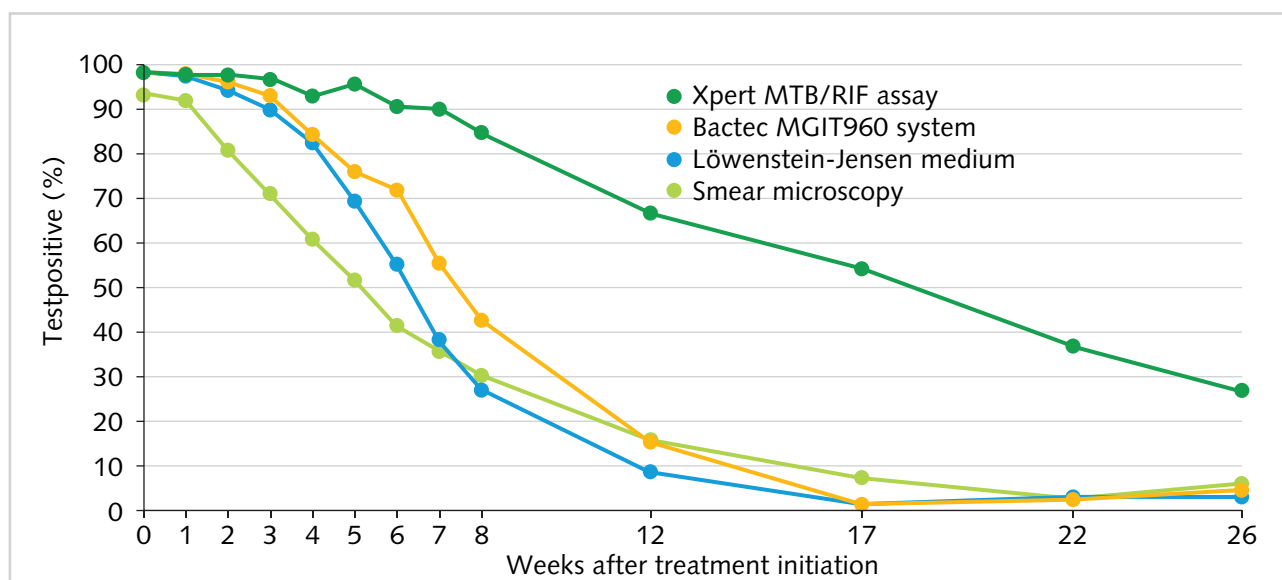


Figure 7-4. Consecutive sputum smear, culture and Xpert® MTB/RIF results in 221 patients successfully treated for pulmonary tuberculosis (Lancet Respir Med 2013;1:462–70).

7.5 Isolation

7.5.1 Isolation of patients with a suspicion of tuberculosis

The aim of isolating patients – exceptionally in the hospital, preferably at home (whenever the patient's physical and social conditions permit) – is to prevent transmission of *M tuberculosis* to third persons. In hospital settings, untreated patients with a clinical or radiological suspicion of infectious pulmonary tuberculosis should be isolated until one respiratory specimen is negative by PCR (see box airborne isolation in chap. 7.5.2). The sensitivity of PCR assays is higher compared to the sensitivity of three microscopic sputum smear examinations and the result is obtained much more rapidly. In patients with a high pre-test probability for tuberculosis and a negative first PCR assay, examination of a second specimen is recommended. If negative again, isolation can be lifted to investigate other differential diagnoses further.

7.5.2 Isolation of patients with confirmed tuberculosis on treatment

If a nucleic acid amplification test result of a respiratory specimen is positive, the patient is put on tuberculosis treatment. Isolation (at the hospital or at the patient's home) is maintained until tuberculosis treatment is established and the patient is clinically improving: reduction of cough and sputum, no more fever, improved general condition and appetite, no side effects of drugs (usually 5 to 15 days).

Of note, virtually all transmissions that ever occur have taken place before initiation of appropriate antibiotic therapy. With therapy, transmissibility rapidly diminishes, and there is no documented man-to-man transmission of mycobacteria after treatment initiation.

Whenever clinically permissible (the patient is not too ill), the safest procedure is to maintain adequate therapy and discharge the patient from hospital to home as quickly as possible. With appropriate chemotherapy, transmissibility rapidly diminishes. However, to allow the patient to adapt to therapy and to minimise unnecessary exposures, patients isolated in home set-

tings should not be allowed to go to public settings or to work for the first 2 weeks of effective therapy.

If hospitalization of a confirmed pulmonary tuberculosis (or extrapulmonary tuberculosis with draining lesions with the potential of producing aerosols) is warranted for the patient's sake and cannot be avoided, airborne isolation is required to prevent nosocomial transmission.

Airborne isolation (in the hospital or chronic care facility) includes the following:

- **A single patient room with toilet and shower and with closed doors**, ideally equipped with special air handling and high ventilation capacity: Monitored negative pressure relative to the surrounding area, six air exchanges per hour, air exhaustion directly to the outside or recirculated after HEPA filtration before return. These technical specifications are **recommended** for patients with non-resistant tuberculosis (i.e. should be used if available), and **mandatory** for patients with multidrug resistant tuberculosis (i.e. patients are transferred to an institution with available technicalities).
- If negative pressure or ventilation with HEPA filtration is unavailable, regular air exchange by hourly opening of windows is recommended as an alternative.
- For **nursing staff and visitors**, wearing a mask type N95 or a Filtering Face Piece FFP2 (according to Norm EN 149) or higher-level respirators (Filtering Face Piece FFP3 mandatory if multidrug-resistant tuberculosis), fitted properly prior to room entry and removed after leaving the room, is recommended.
- **Patients leaving the isolation room**, e.g. for examinations or for a walk outside the hospital, should wear a surgical mask (EN 14683 Type II or Type IIR) inside the institution for source containment.

- Every medical institution treating patients with tuberculosis is obligated to implement all protective measures against transmission of tuberculosis that are necessary according to the state of the art. The employer bears the overall responsibility for occupational safety and health protection (Ordinance on the Prevention of Accidents and Occupational Diseases and other regulations on safety and health at work)².

The patient should be discharged for ambulatory treatment at home whenever possible. However, if "home" is a communal setting (e.g. asylum centre or shelter for the homeless), several conditions should be met (see below). Discharge is possible after 5 to 15 days (more when drug resistances are present) of effective and well-tolerated treatment with clinical improvement. Conversion of sputum smears or Xpert[®] MTB/RIF assay from positive to negative is **not** a prerequisite for hospital discharge, because these tests are expected to stay positive for prolonged periods of time after treatment initiation (Figure 7-4).

A special situation is preschool children. They are less contagious as they cannot produce an effective cough, have paucibacillary disease and they usually have no caverns. Therefore isolation is most commonly not required. However, family members accompanying such a child in a hospital setting may have transmissible tuberculosis and should wear surgical masks in this setting until pulmonary tuberculosis has been excluded in them.

7.5.3 Duration of isolation

Isolation (in the hospital or at home) for **patients on treatment** is stopped if the following conditions are met:

- The medications are well tolerated.
- Treatment adherence and stable accommodation are assured.

- The continuation of treatment has been organized and the necessary arrangements have been made.
- Cough has been decreasing in frequency and is now rare or absent.
- There is a clinically observable response to treatment.
- There is no evidence or suspicion of drug resistance (unless treated accordingly).

In coughing patients with sputum smear-positive multidrug-resistant tuberculosis (MDR-TB), modalities of isolation may have to be prolonged and discussed with expert centres. This is also the case for the duration of MDR-TB isolation at the patient's home.

² For more detailed information regarding protective measures: Jost M, et al. Tuberculosis in the workplace – hazards and prevention. 3rd edition, Suva 2010, order number 2869/35 (German, French, Italian).

8

Notification system, surveillance and treatment

- 8.1 Notification system and surveillance
- 8.2 Monitoring of outcome of tuberculosis treatment

8 Notification system, surveillance and treatment

8.1 Notification system and surveillance

Notification of any case of tuberculosis is mandatory (Epidemics Act). This generally applies to cases diagnosed as tuberculosis disease who started treatment with at least three drugs. Treatments for latent infection with *M tuberculosis* should not be notified.

The Cantonal Medical Officer where the patient is resident or, if the place of residence is not in Switzerland or not known, where the patient is being treated or has been diagnosed, must be notified:

- **By the physician** for any case of tuberculosis for which antituberculosis treatment has been initiated with at least 3 drugs and /or whose cultures are positive. It also applies to patients who should have started treatment but did not because they died or disappeared before. The following form is to be completed: **Notification of clinical findings** within one week³.
- **By the laboratory** in the case of identification of acid-fast bacilli or of mycobacteria of the *M tuberculosis* complex by amplification or in culture in any specimen. A copy of the form **laboratory notification** must be sent directly to the Federal Office of Public Health and, in parallel, to the Cantonal Medical Officer (within 24 hours).

The Cantonal Medical Officer checks the information contained on the physicians' notification form, signs it, and transmits it to the Federal Office of Public Health. He or she may forward a copy to the cantonal Lung Association.

The Cantonal Medical Officer or, if mandated by the latter to do so, the cantonal Lung Association decides whether or not to carry out a contact investigation. In most cantons, contact investigations and collection of follow-up information on treatments including their outcomes are performed by the cantonal Lung Association on behalf of the Cantonal Medical Officer. If a contact investigation is requested, the cantonal Lung Association should receive, from the Cantonal Medical Officer or directly from the microbiology laboratory,

the results of the bacteriological examinations of the index case (to decide on the extent of the contact investigation and on a recommendation for preventive therapy).

The Federal Office of Public Health publishes weekly preliminary notifications in its Bulletin. It periodically publishes a summary of the final data.

8.2 Monitoring of outcome of tuberculosis treatment

The outcome of treatment of all cases of tuberculosis uses categories compatible with those defined by WHO. Notification of outcome has become mandatory as of 2016. The Federal Office of Public Health sends a reminder to the Cantonal Medical Officers to collect the information from the treating physicians. The Cantonal Medical Officers of many cantons mandate their cantonal Lung Associations with the task of collecting the information. A regular follow-up with the treating physicians during the course of the treatment, by the Cantonal Medical Officers or the Lung Association, helps to have more complete information on treatment outcomes.

1. **Cure**
Full treatment course with documented culture conversion from positive to negative (applies for cases with initially culture-positive pulmonary tuberculosis).
2. **Treatment completed**
Treatment has been completed without documented culture conversion.
3. **Default / failure to comply with treatment**
Interruption of treatment by the patient for two consecutive months or more.
4. **Treatment failure**
Persistence of positive cultures after 5 months of treatment or later.

5. Death while on antituberculosis treatment or before the start of treatment

Because of the difficulty in determining the cause of death, WHO requires only reporting of death while on treatment (or before) due to whatever cause. In Switzerland, it is recommended to distinguish 1) “death due to tuberculosis” from 2) “death due to a cause other than tuberculosis”. “Cause” is defined here as the underlying cause of death, i.e. the condition present at the beginning, setting off the chain of events.

6. Transfer out

Patients transferred to continue treatment in another jurisdiction and treatment outcome remained unknown. In practice, this commonly concerns patients who continue treatment abroad, which complicates information retrieval. However, a reasonable effort should be made to gather the information even in these cases.

7. Other/unknown

E.g. patient still under treatment 12 months after the start. This should not be a frequent event and an effort is made at the FOPH to classify these outcomes in one of the categories above.

The outcome of MDR-tuberculosis treatment is collected in a similar fashion⁴.

³ www.bag.admin.ch/tuberculose

⁴ For details collected on outcomes, see notification forms on www.bag.admin.ch/tuberculose.

9

Vaccination with BCG

9 Vaccination with BCG

Vaccination with BCG is no longer recommended for any permanent resident of Switzerland.

The 2018 Swiss Vaccination Schedule (www.bag.admin.ch/plandevaccination), issued by the Federal Office of Public Health and the Federal Commission for Immunizations (EKIF/CFV), states:

“BCG vaccination is only recommended for new-borns and infants below the age of 12 months with an increased risk of exposure. They are at risk of developing a disseminated form of tuberculosis. At risk of exposure are infants whose parents originate from a country with a high incidence of tuberculosis and who will return to this country. A threshold incidence of > 50 cases per 100'000 population per year is recommended to define a high-incidence country (www.who.int/tb/country/data/profiles/en/). Stays of a limited duration (e.g. vacations) in high incidence countries are not an indication for BCG vaccination.”

Vaccination with the attenuated strain *M bovis* BCG has been shown, in retrospective studies, to give substantial protection against tuberculous meningitis (Figure 9-1) and disseminated tuberculosis.

Protection of young children against other forms of tuberculosis is less but still considerable, while protection of older children or adults has been much poorer on average, but with a substantial range from none to 80% protection among adults. The reasons for the incomplete and often varying protection remain unclear but it is apparent that they are more related to the type of protection that mycobacteria induce (effector T cell immunity rather than central memory T cell immunity) and perhaps also to interactions with various environmental species of mycobacteria rather than vaccine ineffectiveness. The WHO recommends to give BCG, as part of the Expanded Programme on Immunization, at birth or as early in life as possible in countries with a high burden of tuberculosis.

Several Western European countries that have used BCG in the past have changed their vaccination policy in the past two to three decades. Many have discontinued BCG, sometimes with the exception of some population segments (www.bcgatlas.org).

The rationale behind discontinuation is the change in the epidemiologic situation that has resulted in a very small risk for children to become infected with

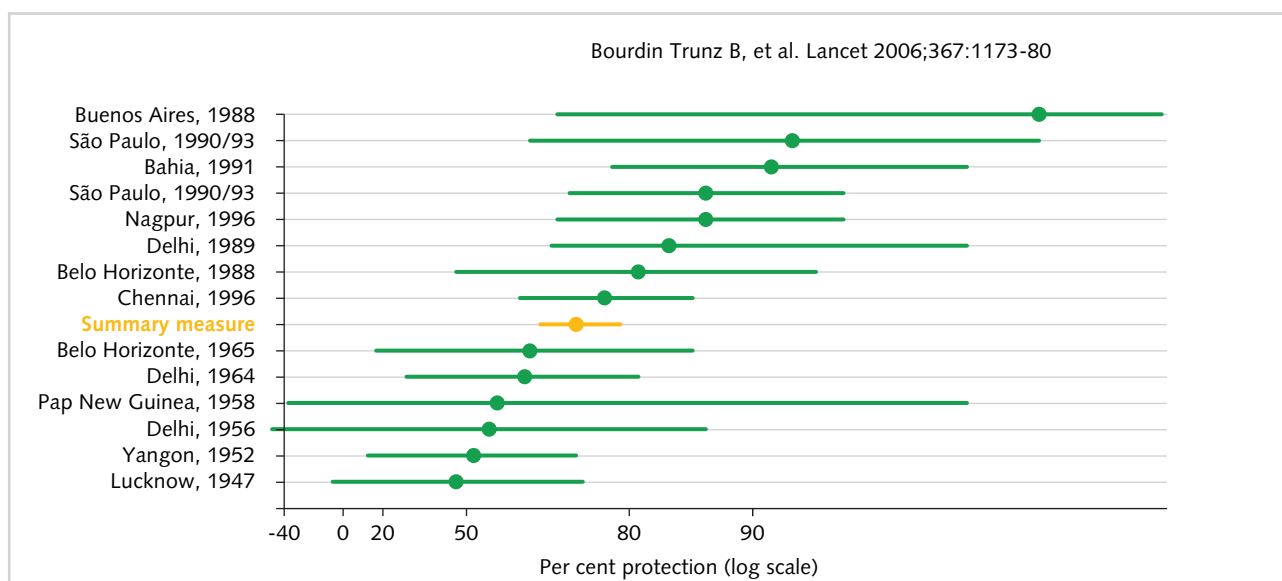


Figure 9-1. Protection from BCG vaccination against tuberculous meningitis in retrospective studies.

M tuberculosis in these countries. Resulting is a small risk of childhood tuberculosis and an even smaller risk of meningeal tuberculosis among infants, the primary target of BCG vaccination. When weighed against the (albeit small) risk of adverse vaccine events (such as disseminated BCG in infants with HIV infection or specific underlying congenital immunodeficiency or local lesions, abscess, adenitis), the choice has increasingly been in favour of improving contact tracing, diagnosis and treatment.

Treatment of BCG complications may require expert advice. All BCG strains are resistant to pyrazinamide. Information of the particular BCG strain used for vaccination and immunity of the host helps to guide regimens.

Treatment may also be warranted when BCG used as immunotherapy for bladder carcinoma causes local or even disseminated disease.

10 Tuberculosis and asylum seekers

10 Tuberculosis and asylum seekers

The vast majority of incident tuberculosis cases in Switzerland are reported among persons of foreign origin (chapter 2). After 2005 and until the end of 2017, asylum seekers were the only population group among them subject to screening (based on geographic origin, history and symptoms) for tuberculosis at the time of requesting asylum. A generic version of the screening tool used is available on www.tb-screen.ch. Since 2018, a systematic screening is not mandatory in federal reception centres. The tool (tb-screen) is integrated into a comprehensive questionnaire (mmcheck.ch). It is used for most asylum seekers in the context of a voluntary consultation carried out by a health care professional.

The screening system (tb-screen itself or integrated in mmcheck) identifies persons with prevalent symptomatic tuberculosis at the time of requesting asylum. However, cases may be detected even before screening when arriving overtly ill at the reception centres. However, the majority of cases ever occurring in this population are discovered in the months or years following entry into the country. The later appearance of tuberculosis can be attributed to different possible reasons: further progression from a stage that had been missed at initial screening, reactivation of a latent infection with *M tuberculosis* present at the time of immigration, or progression of a recent infection acquired after arrival, usually as a result of transmission from one migrant to another. Continuous vigilance remains thus of critical importance. Maintenance of a high index of suspicion is always required, but particularly so in any person originating from a country with a much higher tuberculosis incidence than Switzerland. If symptoms are identified, a chest radiograph needs to be taken swiftly, followed by a sputum examination in the case of any radiological abnormality compatible with tuberculosis.

In principle, asylum seekers with tuberculosis are allowed to complete their treatment in Switzerland provided that the treating physician reports the case to the State Secretariat for Migration (SEM)⁵ in a timely fashion.

This agreement between the FOPH and the SEM does not influence a decision on whether to grant asylum

or not but leads to a postponement of any measure of deportation until after completion of tuberculosis treatment. The agreement applies only to tuberculosis and not to infection with *M tuberculosis*. It may not apply if the date of deportation to a country of the European Union under the terms of the Dublin Convention has already been established. In such a case, the physician in charge of the treatment should require from the SEM that the patient be referred to a pre-identified tuberculosis treatment centre in the country of destination in order to facilitate transmission of medical information and to avoid treatment interruption. Medical counselling for persons returning home (Return Counselling Services) might be useful in such situations⁶.

⁵ <http://www.tbinfo.ch/fr/formulaires/rapport-medical-sem.html>

⁶ https://www.sem.admin.ch/sem/fr/home/publiservice/weisungen-kreisschreiben/asylggesetz/rueckkehr_und_wiedereingliederung.html and <https://www.sem.admin.ch/sem/en/home/rueckkehr/rueckkehrhilfe.html>

11 Financial issues and legal background

- 11.1 Health insurance
- 11.2 Accident insurance
- 11.3 Public health authorities
- 11.4 Employers
- 11.5 Private persons
- 11.6 Special situations

11 Financial issues and legal background

The Epidemics Act (Federal Act on Combating Communicable Human Diseases) of 2012 constitutes the legal basis for tuberculosis control. The Federal Act on Health Insurance (LAMal) with its Ordinance (OAMal) and the Federal Act on Accident Insurance (LAA) govern the financing of the prevention and control of tuberculosis.

Depending on the individual circumstances and the services provided, five distinct parties share responsibilities in covering the costs involved:

- The health insurance
- The accident insurance
- The Cantonal Medical Officer
- The employer
- The concerned individual

Particular attention has to be paid to the entity responsible for covering the costs incurred by persons without a valid residence permit, including former asylum seekers. This is notably of importance if treatment is directly observed. It is not only in the interest of the Cantonal Medical Officer but an obligation under the Federal Constitution for the canton and / or community of the place of residence to ensure tuberculosis diagnosis and treatment (cf. 11.6.2). If there is no official place of residence in Switzerland, the place of stay applies.

11.1 Health insurance

As a rule (exception described in chapter 11.2), after identification of a latent infection with *M tuberculosis*, the health insurance is responsible for assuming the costs resulting from complementary medical investigations (for the exclusion of tuberculosis disease) as well as treatment costs for latent infection. When a diagnosis of tuberculosis has been established, the health insurance covers the cost for appropriate examinations and treatment. The patient shares the costs and no exemption from cost sharing is granted for tuberculosis.

The health insurance covers the costs which exceed a defined deductible (which is at least CHF 300 per year, depending on the insurance scheme a person chose). Additionally, patients have to pay 10 % of all medical care costs out of their own pocket up to a maximum of CHF 700 per year for adults and CHF 350 for children.

11.2 Accident insurance

All employees in Switzerland are mandatorily insured against accidents and occupational diseases either by the Swiss National Accident Insurance Fund (Suva) or by a private accident insurance. In addition, the Suva is the supervisory body for the prevention of occupational diseases in all enterprises in Switzerland according to Articles 50 paragraph 1 and 70 ff. OPA (Ordinance on the Prevention of Accidents and Occupational Diseases) [8].

A latent tuberculosis infection (LTBI) or tuberculosis may be suspected to be related to the occupation, commonly after a contact with a contagious tuberculosis case on the job. Such a suspicion should be individually declared to the accident insurance. The accident insurance evaluates each case and determines whether it recognizes it as an “occupational disease” (be it tuberculosis or LTBI).

Tuberculosis and LTBI caused by an occupational activity in health care institutions are recognized as “occupational diseases” according to article 9 paragraph 1 of the Accident Insurance Act (LAA) and annex 1 of the Accident Insurance Ordinance (OLAA). The treatment after a conversion of a test for LTBI from negative to positive will usually be covered in this setting.

However, workers outside health care institutions, such as in immigration services, prisons, or social services, can also acquire tuberculosis or LTBI. These workers are accepted as having an “occupational disease” if the terms of article 9.2 of LAA are met. According to this specific regulation, it must be shown that the disease is caused “exclusively or very predominantly” by the professional activity. The decision to recognize a claim always lies with the insurer. While settings or

jobs with a typically increased risk of exposure to *M tuberculosis* are usually covered by this regulation, other suspected cases of professionally acquired LTBI or tuberculosis but without a typical job-specific elevated risk of *M tuberculosis* exposure require a more convincing set of arguments to be recognized as “occupational diseases”.

If the accident insurance recognizes a case of tuberculosis or a LTBI as an “occupational disease”, it will cover the medical costs (investigation and treatment) incurred. If the result of testing for tuberculosis or LTBI is negative, the insurer will likewise cover the costs of testing if the reason for testing was a legitimate suspicion of LTBI or tuberculosis and if the individual claim is recognized according to the above-mentioned principles. However, initial tests (whatever the result) and regularly repeated tests with negative results that may be carried out in institutions with an elevated risk of exposure according to chapter 4.2 are not covered.

11.3 Public health authorities

As defined in the provisions of the Epidemics Act, contact investigations are epidemiological investigations under the responsibility of the Cantonal Medical Officers. The Epidemics Act explicitly obliges the cantons to pay for the investigations it orders to be carried out. Other sources of funding, e.g. the employer, may agree to share costs. A contact investigation usually follows the notification of a case of tuberculosis considered to be transmissible. It should only be undertaken by a healthcare provider if instructed to do so by the Cantonal Medical Officer or the cantonal Lung Association (in the cantons where the latter has the mandate to do so). Cantons are not obliged to cover the costs of the consequences of a positive test for infection with *M tuberculosis*, or of tuberculosis, found in a contact investigation. Further investigations and treatments are covered by the health insurance (chapter 11.1).

11.4 Employers

In healthcare institutions and other institutions which test employees for infection with *M tuberculosis* without a defined specific exposure, the employer bears the associated costs.

11.5 Private persons

Individuals requesting a screening test for latent infection on their own, for personal or other reasons (schooling, employment, etc.), must, as a general rule, bear these costs in full.

11.6 Special situations

11.6.1 Tuberculosis among asylum seekers

When tuberculosis has been diagnosed in an asylum seeker in the care of the federal government, the State Secretariat for Migration bears the cost for diagnosis and treatment, directly or by providing insurance coverage. It also pays the cantons a lump sum for each asylum seeker attributed as well as a monthly allowance. These payments are also meant to maintain health insurance coverage.

Asylum seekers who have lost their status as such and stay on illegally in the country lose their insurance coverage.

11.6.2 Illegal residents

Access to medical care should be guaranteed for any patient suspected of or diagnosed with tuberculosis, whatever his or her legal status.

According to the terms of the provisions laid down in article 3, paragraph 1 of the LAMal, any person residing in Switzerland is legally required to take out health insurance within three months of taking up residence in the country. Similarly, health insurance must be taken out within three months after birth for a child born in Switzerland. Legally, this also applies for people without a valid residence permit (illegal aliens) who stay in Switzerland. Health insurers are therefore obliged to insure persons at their request

(the definitions of residency of article 24 of the Civil Code apply). This request can also be presented after disease is diagnosed, with retroactive effect (articles 7 [paragraph 8] and 8 of the OAMal).

In pursuance of the provisions of article 12 of the Federal Constitution, a constitutional right to assistance in emergency situations exists. In fact, whoever finds himself or herself in a situation of distress and is not capable of looking after himself or herself has the right to be aided and assisted and to receive the means necessary to lead an existence that is in keeping with human dignity. This right also applies to illegal aliens. The canton and / or community of residence or stay ultimately bears the costs.

“The national platform for medical services for sans-papiers” provides more extensive information on health for illegal aliens:

<https://www.tbinfo.ch/fr/centre-de-connaissances/migration/sans-papiers.html>

11.6.3 Directly observed therapy

Under certain circumstances (see above), directly observed therapy (DOT) is indicated.

The Cantonal Medical Officer can order the use of DOT. In most cantons, a healthcare worker of the cantonal Lung Association will organize DOT. However, the administration per se of the medication may be delegated to another body (for example, a pharmacy, a cantonal centre for asylum seekers, the social services, the treating physician, home nurses).

Pharmacies may be much more convenient for patients requiring DOT than tuberculosis treatment centres or cantonal Lung Association offices. A well-defined agreement must be made between the body mandating the DOT and the pharmacy on the other hand. When DOT is delegated, it is mandatory that the physician in charge of antituberculosis treatment be clearly identified. Whoever organized the DOT must be informed rapidly if the patient becomes irregular in attending or fails to attend.

The cantonal Lung Association charges the canton for the time spent on administrative tasks according to the instructions given, and to the extent mentioned, in a service order. For the body administering the medication to the patient (i.e. the cantonal Lung Association or the delegated body), there are the two following invoicing possibilities:

1. The cantonal Lung Association's services are invoiced to the canton. In the event that a fixed amount has been agreed upon between the cantonal Lung Association and the body that administers the medications, this payment is generally invoiced to the canton via the cantonal Lung Association.
2. The service is invoiced to the patient for reimbursement by his or her health insurance. However, this is only possible if the body that administers the medications is a physician or a recognized service provider as laid down in the provisions of the LAMal (nursing staff, auxiliary personnel and organizations providing their services based on a physician's mandate as defined in articles 49 and 51 of the OAMal). For the administration of medications in the physician's office as a delegated activity by personnel other than physicians, a position (00.0150 as of 2019) of the Tarmed tariff of medical fees can be used. However, the patient must participate in the cost of treatment through an annual deductible and a 10% participation in any bill charged to the patient and / or the insurer (up to the maximum stated in chapter 11.1).

12 Information and useful addresses

- 12.1 Brochures and other printed matter
- 12.2 The internet
- 12.3 Tuberculosis hotline for medical staff

12 Information and useful addresses

12.1 Brochures and other printed matter

A list of the publications available at the Tuberculosis Competence Centre is given below:
www.tbinfo.ch/fr/centre-de-connaissances/publications.html

For healthcare professionals

- Tuberculosis in Switzerland – Guidance for healthcare professionals, 2019 update (F/G/I/E), the present publication
- Helbling P, et al. Tuberculosis in the workplace – hazards and prevention. Revised edition, Suva 2020, order number 2869/35d (German, French, Italian)
- Scales for reading the skin test (intra-dermal reaction to tuberculin)

For the general public

- Information brochure on tuberculosis (F/G/I) (also available electronically)
- Information sheet on tuberculosis in 19 languages, entitled “Frequently Asked Questions about tuberculosis and their answers” (available electronically only)

12.2 The internet

On www.tbinfo.ch you can find the following continuously updated information:

List of addresses

www.tbinfo.ch/fr/adresses-utiles.html

- Cantonal services specialized in tuberculosis
- Persons to contact for the supra-cantonal contact investigations
- Persons to contact at the federal reception centres for asylum seekers

- List of addresses of the Cantonal Medical Officers
- Community interpreters
- Unit for health consultations and for providing assistance to illegal immigrants
- Units for tuberculosis in the countries of the European Union
- Laboratories that carry out IGRA tests
- List of antituberculosis drugs available in Switzerland

Other services provided

www.tbinfo.ch/fr/centre-de-connaissances.html

- Answers to frequently asked questions (question forum)
- Offers for training programmes
- Presentations made at recent tuberculosis symposia
- Database of reference works
- Database of iconographic data
- Films
- Statistics
- Collection of internet links on tuberculosis

12.3 Tuberculosis hotline for medical staff

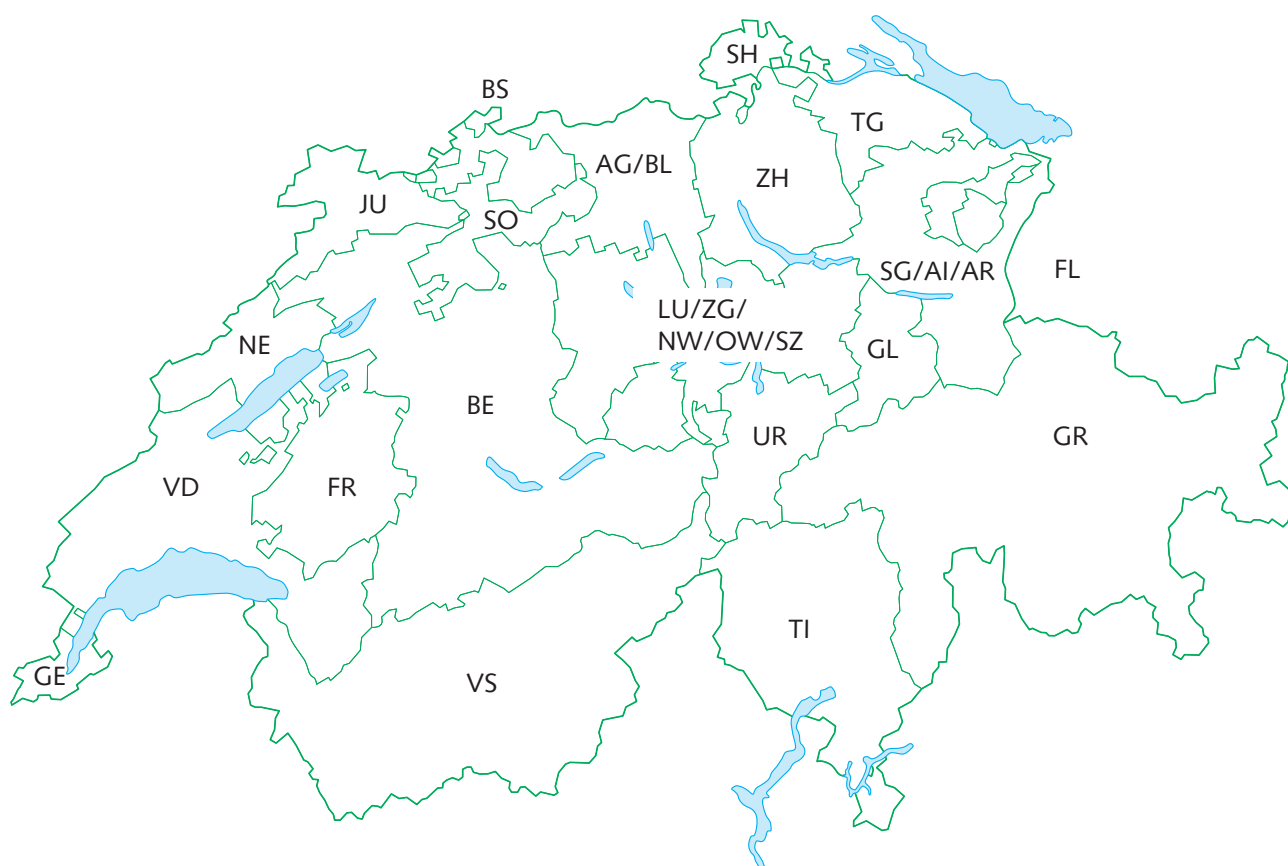
At telephone **0800 388 388**, experts reply to questions asked by medical staff regarding the treatment of tuberculosis. This information is provided in French, German or Italian and is free of charge. The tuberculosis hotline is open on workdays (from Monday to Friday from 8 a.m. to 12 a.m. and from 2 p.m. to 5 p.m.).

13 Bibliography

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Specialized services for tuberculosis



Specialized services for tuberculosis

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tuberkulose@llag.ch
www.lungenliga-ag.ch

Basel-Stadt

Tel. 061 267 95 26
gsd@bs.ch
www.gesundheitsdienste.bs.ch

Bern

Tel. 031 632 60 69
tb.info@insel.ch
www.infektiologie.insel.ch

Fribourg

Tél. 026 426 02 70
info@liguepulmonaire-fr.ch
www.liguepulmonaire-fr.ch

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www.hug-ge.ch/pneumologie/
tuberculose

Glarus

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