

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 abridged version complements and updates the "Manuel de la Tuberculose 2012" / "Handbuch Tuberkulose 2012" / "Manuale della tubercolosi 2012".

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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** (chest radiography, microbiological examinations) or to **refer** the patient to an experienced colleague or a specialized 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 with the agreement of the cantonal health authorities and in cooperation with the designated local antituberculosis office, usually the cantonal Lung Association
- To ensure that the patient **adheres to the prescribed treatment** until its scheduled completion, and to immediately notify the cantonal health authorities of any interruptions, failure to comply with treatment, or disappearance on the part of the patient. To facilitate adherence and treatment completion social aspects must be taken into consideration 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 health authorities of the outcome of treatment.

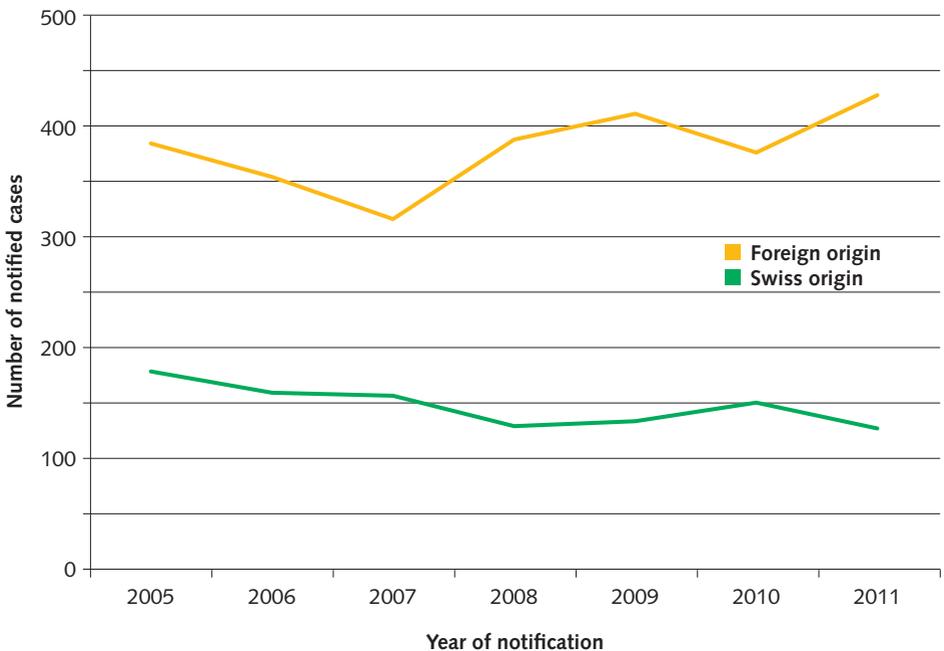
2 Epidemiology

Tuberculosis in Switzerland has decreased since at least the 19th century, 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. In 2011, the latest year with published final data, 577 cases were notified, resulting in a notification rate of 7.2 incident cases per

100,000 population. Of these, 127 (22 %) were of Swiss origin and 429 (74 %) were of foreign origin, including 131 (31 % of cases of foreign origin) asylum seekers or refugees (Figure 2-1).

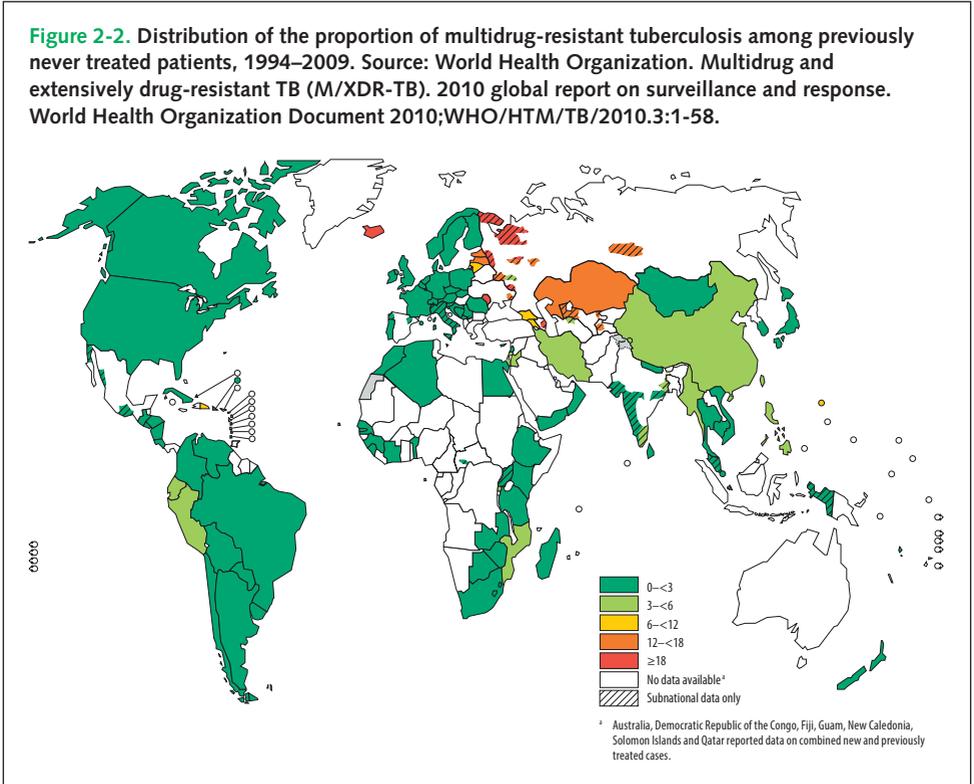
Tuberculosis was pulmonary in 71 %. Of the pulmonary cases, 84 % were confirmed by culture, and 31 % were positive on microscopic sputum smear examination.

Figure 2-1. Tuberculosis cases notified to the Federal Office of Public Health, by origin, Switzerland, 2005–2011.



Federal Office of Public Health. Bull FOPH 2013;(no 21):343-53

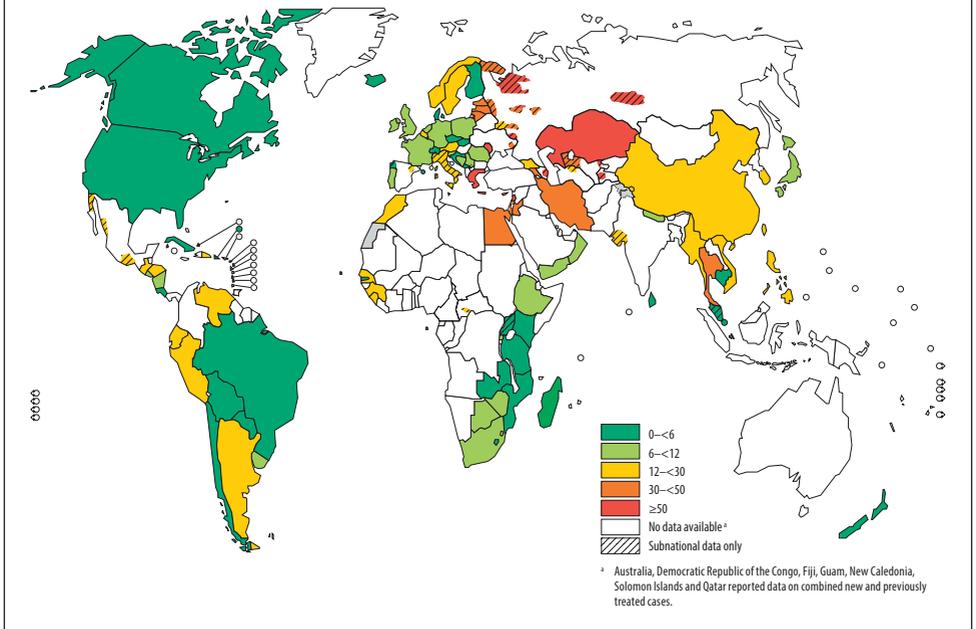
Figure 2-2. Distribution of the proportion of multidrug-resistant tuberculosis among previously never treated patients, 1994–2009. Source: World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB). 2010 global report on surveillance and response. World Health Organization Document 2010;WHO/HTM/TB/2010.3:1-58.



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. Switzerland mandates reporting of drug susceptibility test results. The prevalence of multidrug-resistant (MDR) tuberculosis

among newly notified cases has been constant for several years with about 1.5%. Globally, the World Health Organization (WHO) estimates that the incidence of tuberculosis has been slowly decreasing for several years, but the global burden remains enormous with an estimated 8.6 million new cases in the year 2012. The number and

Figure 2-3. Distribution of the proportion of multidrug-resistant tuberculosis among patients with a history of prior treatment, 1994–2009. Source: World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB). 2010 global report on surveillance and response. World Health Organization Document 2010;WHO/HTM/TB/2010.3:1-58.



proportion of cases estimated to have drug-resistant tuberculosis remains worrisome (Figures 2-2 and 2-3), and funding gaps for global tuberculosis care and control remain critical.

3 Transmission, pathogenesis, and clinical presentation

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 for humans non-pathogenic species *M bovis* BCG and *M microti* 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 sufficiently long in the air, before gravity pulls them to the ground, to allow evaporation in non-saturated air, becoming droplet nuclei containing one or more tubercle bacilli. Droplet nuclei are sufficiently small to remain suspended in the air for a prolonged period of time (hours) and have a high probability of reaching the alveoli when inhaled where they might adhere to the cell wall and be engulfed by tissue macrophages. The rarely occurring *M bovis* is usually transmitted by ingestion of bacilli with unpasteurised milk originating from a cow with tuberculous mastitis. The rare cases of tuberculosis due to *M bovis* are mostly either imported or, among elderly Swiss, the result of a reactivation of an infection acquired at times long in the past.

3.2 Pathogenesis

M tuberculosis may successfully prevent macrophages from exerting their non-specific destruction of engulfed bacilli. Bacilli may thus multiply within the macrophage, then be released upon destruction of the cell, provoke a local inflammatory response, be picked up by other macrophages, and ultimately lead to sensitization of lymphocytes. This may be followed either by:

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

Persons thus said to be latently infected with *M tuberculosis* are neither ill nor able to transmit *M tuberculosis*. The majority of such latently infected persons (estimated at around 90 %) 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 2 years following infection. The risk of progression from infection to disease is increased among the very young (infants and small children), in adolescence to young adulthood, and in any situation which de-

creases the integrity of the cellular immune system such as immunosuppressive treatment and disorders (notably HIV infection), diabetes, etc.

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 there is sputum production, if the expectorations contain large numbers of bacilli, and if there is a physical force producing large numbers of small-sized droplets (cough being the primary force in tuberculosis patients).

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. No specific clinical sign or symptom is pathognomonic for tuberculosis. Elderly patients often have fewer symptoms. The clinical suspicion for tuberculosis therefore additionally relies on a group of factors and indicators such as the origin of the patient, the duration of symptoms, a prior exposure to the disease, and radiological findings. Dwindling interest in, and knowledge about, tuberculosis carries the risk of delayed diagnosis with an increased frequency of advanced forms of the disease.

3.3 Clinical presentation

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

3.4 Radiological presentation

Abnormalities on a chest radiograph 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. No radiological presentation is specific for tuberculosis. The radiological findings do not allow distinguishing between bacteriologically active, inactive, or healed tuberculosis.

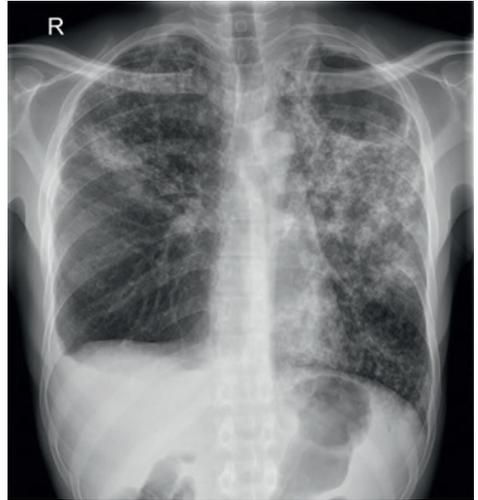


Figure 3-1. Chest radiograph of a patient with sputum smear-positive pulmonary tuberculosis. Extensive bilateral disease with asymmetric infiltrates, mottling, and cavitation.

Real case No. 1

A 27-year-old non-smoking Cameroonian patient with a progressive cough for 3 months and a persisting infiltrate in the right upper lobe is unlikely to suffer from viral bronchitis!

Real case No. 2

A 14-year-old Angolan girl with a 10 kg weight loss over the last 2 months and increasing cough on exertion suffers from more than adolescent depression.

4 Latent infection with *M tuberculosis*

The interval between acquisition of infection with *M tuberculosis* and clinical manifestation of tuberculosis can vary greatly, 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. In the 80 years since this was first opinionated, substantial bacteriologic, histopathologic, immunologic, and epidemiologic evidence has accumulated that lifetime persistence of live bacilli is more likely the exception than the rule.

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 the effector cell immunity that *M tuberculosis* induces and which persists for a decade or more. Such persistence of the immunologic response is perhaps best evidenced by the prolonged perseverance of tuberculin skin test reactivity and its waning following BCG vaccination.

M tuberculosis and other mycobacteria induce a delayed cellular immune response, expressing the sensitization of T lymphocytes. This sensitization can be detected by:

- a tuberculin skin test; or
- a blood test: interferon-gamma release assay (IGRA).

Both test systems assess the release of cytokines (mainly interferon-gamma) from sensitized T lymphocytes or their effects in the presence of mycobacterial antigens. A positive response to either of these tests

is indicative of prior acquisition of mycobacterial antigens or infection with a mycobacterium but not evidence for the continued presence of live mycobacteria. For this reason, neither the tuberculin skin test nor IGRAs can distinguish between past infection with *M tuberculosis*, persisting latent infection with *M tuberculosis*, and clinically or microbiologically manifest 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 for tuberculosis will take into account:

- the person's age;
- the time elapsed since acquisition of infection;
- the integrity of the cellular immune system.

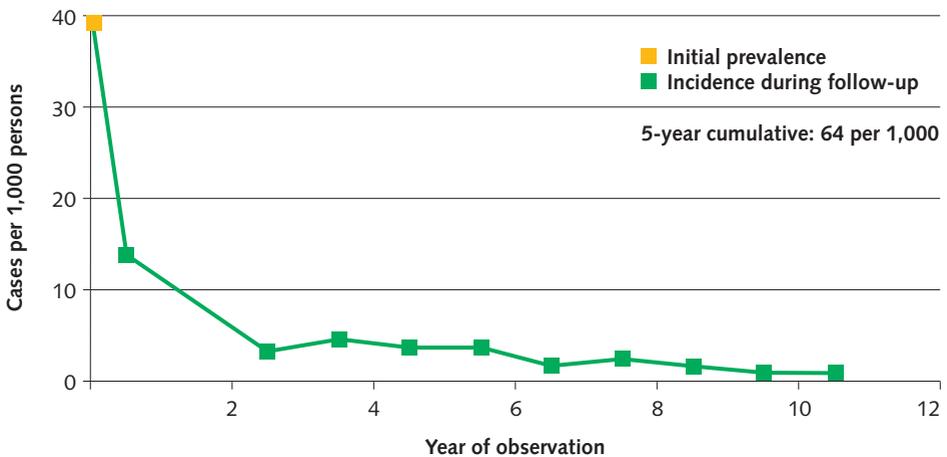
Given persisting infection, the risk of **progression to tuberculosis** depends on the quality of the immune defence of the infected person. Children below the age of 5 years, notably infants, other recently infected persons, and immunocompromised persons (HIV, anti-TNF-alpha treatment, etc.) are at 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 (Figure 4-1).

4.1 Tuberculin skin test

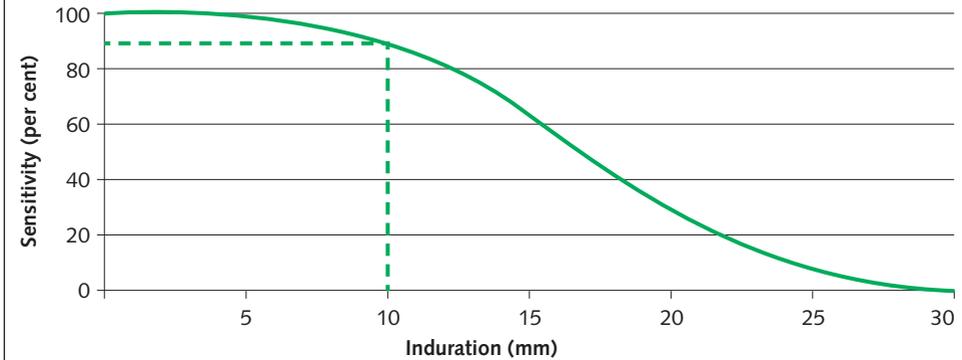
Tuberculin contains a large number of different mycobacterial peptides, most of which are also present in *M bovis* BCG and to a lesser extent in several species of environmental mycobacteria.

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.



Ferebee S H, Mount F W. *Am Rev Respir Dis* 1962;85:490-521
 Ferebee S H. *Adv Tuberc Res* 1970;17:28-106

Figure 4-2. Sensitivity of the tuberculin skin test by induration size among adults age 15 to 29 years old. Modelled by mixture analysis of Tumkur, India, tuberculin survey data.



Original data: Narain R, et al. Bull World Health Organ 1963;29:641-64

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, the skin is lightly stretched and the needle point is inserted, with the bevel facing upwards, into the superficial layer of the skin.

The reaction size is measured at the earliest 48 hours (preferably 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. Most 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 specificity varies more than test sensitivity as it depends on the variable prevalence of cross-reactions resulting from prior infection with other mycobacteria (*M bovis* BCG or various environmental mycobacteria) and time elapsed since infection with the latter.

Tuberculin skin test sensitivity is more consistent than test specificity. 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 (Figure 4-2).

There is a cost to increasing test sensitivity: the trade-off for higher sensitivity is a lower specificity that decreases with increasing sensitivity. Nevertheless, there is quite general agreement that, among contacts, preference is given to higher sensitivity, accepting that some individuals will be classified as being infected but who are in fact not. The predictive value of a positive tuberculin skin test increases with targeted contact investigation as the expected prevalence of true infection is larger. In a targeted contact investigation, it is recommended to consider an induration size of 5 and more millimetres in contacts not vaccinated with BCG as “positive” requiring preventive therapy. Such low cut-off points have also been recommended for other persons at particularly high risk of tuberculosis (such as patients with HIV infection). There is, however, evidence that the targeted sensitivity gain is relatively modest, while the specificity loss is more substantial.

4.2 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 (not present in *M bovis* BCG and *M microti*, but also present in *M marinum*, *M kansasii* and *M szulgai*). The IGRA blood tests are thus not influenced by prior vaccination with BCG or the most ubiquitous 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). The technical instructions issued by the manufacturer must be strictly adhered to. In particular, the blood samples should not be exposed to the cold (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.

4.3 Indications to test for latent infection in asymptomatic persons

- For the identification of possible infection with *M tuberculosis* in persons recently exposed to an index case with transmissible tuberculosis (contact investigation)
- For the identification of possible infection with *M tuberculosis* 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)
- For the identification of possible infection with *M tuberculosis* in persons who have been occupationally exposed (healthcare workers, laboratory staff, social workers) or to have a baseline result before taking up employment in an environment with an elevated risk of exposure.
- 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).

Through identification of infection with *M tuberculosis*, the tuberculin skin test and IGRAs can also provide supplementary information in certain clinical situations: they may add to the diagnostic work-up among patients with signs or symptoms compatible with tuberculosis in whom bacteriological confirmation of tuberculosis may be difficult to obtain (e.g. young children or patients with certain forms of extrapulmonary tuberculosis). Nevertheless, it must be kept in mind that IGRAs and the tuberculin skin test cannot distinguish between latent infection with *M tuberculosis* and (clinically manifest) tuberculosis.

While IGRAs are generally more specific than the tuberculin skin test, they have other drawbacks such as fluctuation in responsiveness, i.e. "conversions" and "reversions" are more frequent than with tuberculin skin testing. Recent findings with the poor specificity of IGRAs in serial testing call for a review of cut-off points and better definitions of "grey zones".

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 not least the discordance in recommendations by reputable bodies (e.g. United Kingdom NICE guidelines, Canadian Thoracic Society). As more information accumulates, these recommendations will possibly have to be adapted accordingly.

Three strategies are advocated to test for latent infection:

- A tuberculin skin test, followed by an IGRA if the tuberculin skin test is positive
- Using an IGRA as only test
- Using the tuberculin skin test as the only test.

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

This two-step approach is based on the concept of sequential testing choosing a test with high sensitivity as the first step, followed by a second step using a test with higher specificity. In other words, any person who possibly has the characteristic sought (here latent infection with *M tuberculosis*) is identified with the first test. The second test ensures the presence of the characteristic in order to prevent an unnecessary intervention (here 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. These might vary greatly by setting and person characteristics (notably age). The latter issue arises particularly among BCG-vaccinated persons up to possibly 15 years after vaccination. The influence of BCG on the tuberculin skin test result is related mainly to BCG strain, age at vaccination, time elapsed since vaccination, and potential boosting induced by infection with environmental mycobacteria. Thus, using a sequential testing strategy makes intuitively sense.

Using an IGRA as the only test

Generally, the sensitivity of an IGRA is not much challenged (comparable to tuberculin skin testing), and the test is commonly more specific than the tuberculin test. 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. Unfortunately, it is precisely among young children in whom IGRAs are not satisfactory either, due to a relatively high frequency of indeterminate results (see below).

Thus, the downside is that there are situations in which an IGRA cannot replace the tuberculin skin test. One such situation is serial testing for surveillance of nosocomial transmission among healthcare workers. Another important example is children, in whom many experts still advocate the tuberculin skin test.

Using the tuberculin skin test as the only test

There are two situations where this is the preferred approach.

First, in settings where serial testing of health care workers is in place (largely in North America). Several studies about such serial testing have now demonstrated an inordinately high frequency of apparently false-positive IGRA results suggesting conversion among persons in whom no exposure to a source of infection could be identified. A similar phenomenon was not shown for tuberculin skin testing used simultaneously in the same settings.

Second, in the evaluation of children (notably those aged less than 5 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.

Recommended test strategy in Switzerland when testing for latent infection is indicated

Here it is recommended that, among adults with exposure to an identified case with potentially transmissible tuberculosis, either approach is used, i.e., 1) the tuberculin skin test followed by an IGRA or 2) the IGRA as the only test system. Thus, the recommendations made in the first edition of these guidelines (2012) remain virtually unchanged.

An exception from the above recommendation is in testing children for latent infection

with *M tuberculosis*, notably those aged less than 5 years. Because of the relative frequency of indeterminate results with IGRAs in this age group, preference is given to the tuberculin skin test.

Recommended discontinuation of repeat testing of health care workers

Repeat, serial routine testing of health care workers without a specifically identified exposure to a potentially infectious case is no longer recommended in Switzerland. The rationale is the consideration of the general principle that any testing should only be performed in situations with an elevated risk of acquiring infection and a tangible benefit of preventive therapy.

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 (or, as it is now also commonly termed, treatment of latent infection with *M tuberculosis*). 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.

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, an indication for consultation with a specialist.

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.

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 to ensure their tolerance of, and adherence to, treatment. Monthly testing for liver enzymes is not mandatory in persons below the age of 35 years, unless the person has liver disease, a history of regular alcohol consumption or is receiving 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 a long-standing infection and no known additional risk factor, the risk of hepatitis becomes larger than the risk of tuberculosis above a certain (not very well-defined) age. Among persons with risk factors (such as recently acquired infection), the expected hepatitis risk in a person without pre-existing liver injury is likely to be smaller than the risk of progression to tuberculosis at any age.

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 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 (i.e. breathing time in) that air.

The risk of progression to tuberculosis is largely endogenous in nature and depends on:

- the age of the contact person;
- the time elapsed since acquisition of infection; and
- the integrity of the cellular immune system.

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). Such a specimen might have been produced spontaneously (sputum expectoration without induction), produced after sputum induction or collected by bronchoscopy (bronchial aspiration or broncho-alveolar lavage). It was further – somewhat arbitrarily – agreed 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 such a smear-positive patient for **more than 8 cumulative hours**.
- Tuberculosis patients whose respiratory tract secretions are 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) are considered to be at significant risk, together with any other person whose total indoor exposure time exceeds **40 cumulative hours**.

In Switzerland, the cantonal health departments are responsible for ensuring that the contact investigations are carried out. Well-trained, experienced staff (commonly the cantonal Lung Association or health department members) in close cooperation with the treating physician and public health authorities carry out contact investigations.

Indications for the initiation of a contact investigation:

- Tuberculosis patients diagnosed with pulmonary tuberculosis who are microscopically smear-positive on direct or induced sputum or on a broncho-alveolar lavage or bronchial aspiration specimen
- Tuberculosis patients with pulmonary tuberculosis who are positive on culture of directly obtained or induced sputum or on a broncho-alveolar lavage or bronchial aspiration specimen, or who have a specimen positive on a nucleic acid amplification test only. For such index cases contact investigation is limited to close contacts (or those exposed for cumulatively more than 40 hours) and small children.

5.1 Principles for the approach to a contact investigation

Firstly, a complete list is established of persons who were in close or prolonged contact with the index case during the 3 months preceding the diagnosis or the initiation of

antituberculosis treatment. The list of contact persons is prepared with the input from the index patient. If possible, the contact persons are grouped by exposure gradient. If the index patient lives in an institution (hospital, nursing home, shelter, immigrant centre, prison, etc.), the list is prepared with the assistance of a staff member from the institution.

The list must be prepared as expediently as possible (in the days immediately following treatment initiation and notification) to allow rational planning of the contact investigation.

Secondly, persons who were in close contact with the index case will be contacted regarding symptoms and given a tuberculin skin test or an IGRA.

Independently of the intensity and duration of exposure, children under 12 years of age and immunocompromised persons are given priority for contact examination and testing without delay. Children under 5 years of age must always be examined clinically and by chest radiograph as soon as possible. If disease is excluded, prophylactic treatment with isoniazid is initiated immediately. If an initial tuberculin skin test is negative, the test is repeated after 2 months after last effective exposure to the index case (pragmatically defined as the last contact before the index case initiated treatment). If still negative on a tuberculin test or an IGRA at this point in time, acquisition of infection can likely be excluded and prophylactic treatment may be stopped. All contacts with signs or symptoms compatible with tuberculosis require a medical examination (including a chest

radiograph) as swiftly as possible. All other contacts may be examined on a single occasion at least 8 weeks after the last effective exposure. Only contacts with a positive test result require further examination (chest radiograph) to exclude tuberculosis, which would require a full course of antituberculosis treatment.

In practice, only contacts with a putative infection identified by a positive tuberculin skin test or IGRA are at risk of progression to tuberculosis. These persons must be informed about the risk of developing tuberculosis and, unless contra-indicated, should be offered preventive therapy.

Contacts with a negative test result more than 8 weeks after the last effective exposure have a negligibly small risk of developing tuberculosis unless they are immunocompromised.

As frequently neither the BCG vaccination status nor the age at vaccination, if given, are known, the recommended procedure does not take into account BCG vaccination status.

5.2 Specific procedures for the contact investigation according to age and immune status

Procedure for contacts aged 12 years and older without immunosuppression

8 weeks after contact	(8 weeks is the approximate median latency window for specific cell mediated immune response)	Tuberculin skin test or IGRA
Tuberculin skin test	Negative result →	No further examination
	Positive result →	IGRA to confirm
IGRA	Positive result →	Medical examination and chest radiograph
Chest radiograph to exclude active TB	Normal →	Preventive therapy if not contra-indicated
	Abnormal →	Further examination (including specimens for culture) Antituberculosis treatment if indicated

Procedure for contacts up to the age of 12 years and for the immunosuppressed

Children aged 5 to less than 12 years of age:

- Immediate testing
- Children with an initially negative test are given a second test 8 weeks later.

Children under 5 years of age:

Immediate medical examination including chest radiograph by a specialist. Children under 5 years of age with a negative first test and without active tuberculosis should receive isoniazid treatment and have a second test 8 weeks later. If the second test remains negative, treatment may be stopped. If the second test is positive (conversion), the child should be re-examined and preventive therapy should be continued for a total of 9 months after active tuberculosis has been excluded.

Newborns up to 1 month of age:

Must be examined by a specialist.

Immunocompromised persons:

Immunocompromised persons (HIV infection, drug-induced immunosuppression, transplantation, renal failure, etc.) should immediately be tested (preferably with an IGRA). If the result is negative, the test should be repeated 8 weeks later. If the second test is positive, the presence of active tuberculosis should be excluded (by clinical and radiological examination) before prescribing preventive therapy.

6 Diagnosis of tuberculosis

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, pleural or other fluid, tissue, gastric aspirate in children). Such a patient is said to be a confirmed case of tuberculosis for the purpose of surveillance.

Patients with tuberculosis diagnosed on the basis of symptoms, clinical signs, or radiological abnormalities are considered as unconfirmed (other than definite) cases. They are also notifiable (as are cases of tuberculosis diagnosed at death).

Immunological tests (tuberculin skin test and IGRAs) are indirect tests for determining the immunologic response to a pre-existing mycobacterial infection. They neither prove current disease (tuberculosis) nor, necessarily, the persistence of live bacilli in the host. In patients clinically or radiographically suspected of having tuberculosis, it is important to obtain several samples (three are recommended as a minimum in Switzerland), at least one of which must be an early morning specimen (preferably upon wake-up). Sputum induction with an aerosol containing 3 % to 6 % hypertonic saline (with salbutamol) facilitates sputum production in patients not able to spontaneously produce a specimen. This procedure can frequently replace bronchoscopy, and is also appropriate for children of school age.

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]) is still

the fastest available technique for a presumptive diagnosis of multi-bacillary tuberculosis. It is also a rapid means for assessing the relative potential of infectiousness of the patient. It is an indicator for the required extent of contact investigation. Microscopy has a substantially lower sensitivity in identifying tuberculosis than culture. However, microscopy has a high sensitivity in identifying effective transmitters.

Microscopy must always be supplemented by culture of the specimen on solid and liquid media. This increases diagnostic sensitivity, allows obtaining a specific and definitive diagnosis of tuberculosis, and – in case of a positive culture – allows additional examinations such as drug susceptibility testing or molecular strain characterization. In cases with a high clinical suspicion of tuberculosis and a negative microscopy result, nucleic acid amplification techniques (such as the one built into the Xpert MTB/RIF[®] assay) can be used to provide a rapid and specific diagnosis of tuberculosis.

Real case No. 3

A 27-year-old Swiss bank employee develops a persistent cough with a cavitory infiltrate in the left upper lobe, slowly progressing in size. The first bacteriological examination of sputum is requested after 18 months by the family physician, and yields a strongly positive direct microscopy result. "Think TB!"

6 Diagnosis of tuberculosis

In patients at increased risk of drug resistance (history of prior treatment, treatment failure, relapse, contact with cases with known drug resistance, originating from a region with a high prevalence of drug resistance), rapid, sensitive, and specific genotypic testing for resistance to rifampicin is mandatory.

Whether or not a genotypic rifampicin drug susceptibility test result requires routine confirmation by a phenotypic test system is not entirely resolved and may depend on the test system. Phenotypic testing on some commercial liquid media systems has been shown to miss some clinically relevant mutations. The National Centre for Mycobacteria recommends confirmatory phenotypic testing also in the case of rifampicin. Genotypic test results for other drugs should always be confirmed phenotypically because the operating characteristics of genotypic systems still fall short of those with classic phenotypic testing.

The actual clinical correlate of drug susceptibility test results has been ascertained for some but not all antituberculosis drugs. It is known from the international network of supranational reference laboratories that both operating characteristics (sensitivity and specificity) and reproducibility for isoniazid and rifampicin are generally good. In contrast, all evaluated characteristics were poor for ethambutol and streptomycin. Less is still known about accuracy and reproducibility of susceptibility testing for second-line drugs. It is recognized that results for some of these drugs (such as e.g. cycloserine) may

be too unreliable to be considered by most experts.

For patients with tuberculosis due to a rifampicin-resistant strain, laboratories should be requested to perform tests for pyrazinamide (if not yet available as should be routine in Switzerland), at least one of the second-line injectable drugs (kanamycin, amikacin, capreomycin), and a fluoroquinolone (the latter most preferably including determination of the minimum inhibitory concentration) as such results can offer critical guidance on the recommendation for the treatment regimen for multidrug-resistant tuberculosis.

Real case No. 4

A young asylum seeker from Georgia enters Switzerland with long-lasting cough and weight loss. He indicates a prior treatment of unknown type and duration for tuberculosis in his country of origin. The chest radiograph discloses an infiltrate in the left upper lobe, interpreted as "scar of a healed tuberculosis" and no sputum examination is performed. Three weeks later, the patient is hospitalized with sputum smear-positive multidrug-resistant tuberculosis, after exposing roommates and staff. "Think TB!"

7 Treatment of tuberculosis

7.1 Standard treatment regimen

Before initiating antituberculosis 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 against rifampicin (the key drug determining curability with first-line drugs and a proxy for combined rifampicin-isoniazid resistance, i.e. multi-drug resistance [MDR])
- Assess the immunological status of the patient (HIV test).

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

Table 7-1. Recommended (World Health Organization) dosages for four first-line drugs.

	Daily dose (range) in mg per kg		Maximum daily dose (mg)	Intermittent (thrice-weekly) continuation phase
	Adults	Children		
Isoniazid	5 (4–6)	10 (7–15)	300	10 (8–12)
Rifampicin	10 (8–12)	15 (10–20)	600	10 (8–12)
Pyrazinamide	25 (10–30)	35 (30–40)	Not specified	NA
Ethambutol	15 (15–20)	20 (15–25)	Not specified	NA

Standard treatment of tuberculosis

Initial or intensive phase:

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

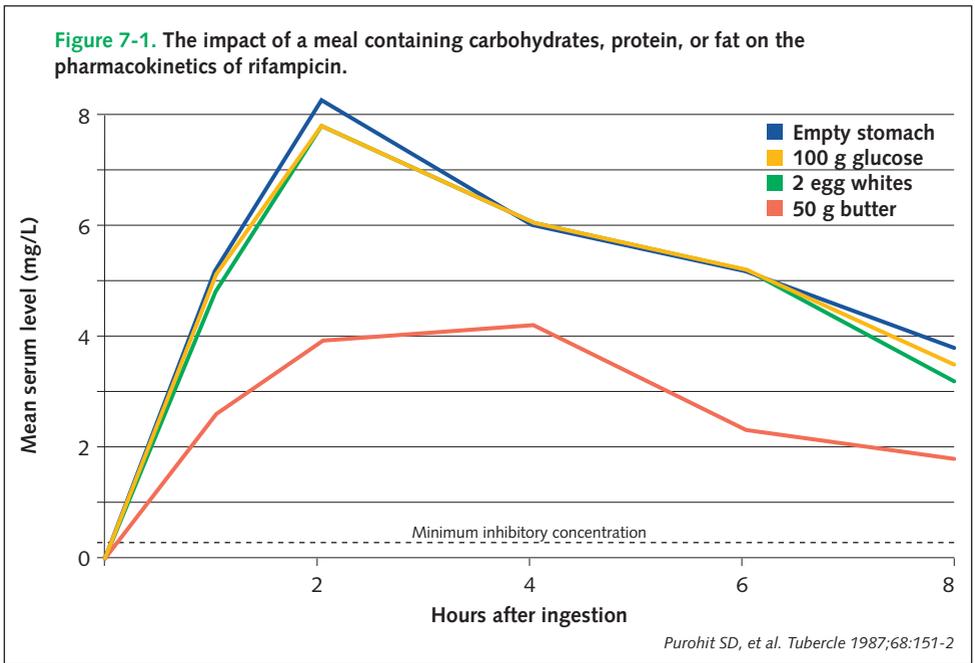
Continuation phase:

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

Short notation: 2 HRZE / 4 HR

The best established efficacious treatment regimen is a daily throughout regimen of 6 months duration. All antituberculosis drugs are administered once daily, if possible in the morning. Intermittent treatment during the intensive phase is not recommended. An intermittent continuation phase (thrice-weekly) is only recommended if all drugs are given under direct observation. High-fat meals reduce absorption and, thus, peak blood levels. If drugs are taken with breakfast, this meal should thus be dominated by carbohydrates (and protein), keeping the fat to a minimum (Figure 7-1).

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



Purohit SD, et al. Tubercle 1987;68:151-2

To simplify the administration of treatment, the use of fixed-dose combination preparations is recommended.

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

- Some authorities (American Thoracic Society) recommend prolongation of the continuation phase to 7 months (total duration 9 months) in the presence of cavitary disease that is still culture positive after the intensive phase.
- Tuberculous meningitis: the continuation phase is extended to 10 months (12 months total), with or without 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.
- Tuberculosis due to *M bovis* is naturally resistant to pyrazinamide and thus requires a treatment duration of 9 months (extension of the intensive phase to 7 months).
- Tuberculosis treatment due to organisms which are 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 development of further resistance (amplification). The risk of drug resistance is particularly elevated in patients who have at least one of the following:

- received prior antituberculosis drug treatment for one or more months. 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.

While isoniazid mono-resistance is usually overcome by the recommended standard treatment regimen, it is 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 disproportionately frequently poor if treated solely with first-line drugs.

7 Treatment of tuberculosis

In the case of a high suspicion or demonstration of rifampicin resistance, an alternative treatment regimen should be selected and MDR tuberculosis must be considered. This will require additional drug susceptibility testing to fluoroquinolones and at least one of the second-line injectable drugs (kanamycin, amikacin, capreomycin) to determine

the regimen most likely to result in treatment success. The advice of a specialist must always be sought. A notification of the case to the “closed user group” of the Swiss Lung Association facilitates the exchange of expert advice. See also WHO and Union Guidelines.

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

There is no observational or trial evidence available that a modification of the above recommended standard 6-month regimen is superior. Some experts nevertheless recommend the addition of ethambutol throughout the treatment. In any case, a patient should not ever be deprived of isoniazid based on a laboratory test result of resistance because low-level resistance (*inhA* gene mutations) is likely overcome given the large therapeutic margin of isoniazid. Some experts advocate the additional use of, or replacement with, a

fourth-generation fluoroquinolone in the presence of demonstrated high-level (*katG* gene mutations) isoniazid resistance.

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

Always consult a specialist and request drug susceptibility testing for pyrazinamide (if not available from routine initial testing), fluoroquinolones, and the preferred second-line injectable drug (kanamycin, capreomycin, or amikacin).

7.3 Special situations

Children: The treatment regimen for tuberculosis in children is the same as for adults. The drug metabolism is faster in children than in adults. For that reason WHO now recommends higher doses in pre-school children (see 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.

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

Hepatic failure: In hepatic failure, pyrazinamide should be omitted and treatment be prolonged to nine months. A fluoroquinolone might be added to the regimen.

Renal failure: The ethambutol dosage must be reduced (15–25 mg/kg) and spaced to thrice weekly dosage if the creatinine clearance is below 30 ml/min. The drug might be entirely omitted from the regimen. 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 about expected treatment adherence has 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 regular intake, WHO recommends direct observation of drug intake by a third person (directly observed treatment: DOT). Directly observed therapy 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, directly observed therapy is recommended in certain situations, in particular:

- For patients with whom communication is impaired
- For patients who are in socially unstable circumstances or who have mental health problems
- For patients with a second treatment episode or who receive treatment for multi-drug-resistant tuberculosis.

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 (gastralgia, 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.

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 the 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 expectorations (spontaneous or induced, if necessary) 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).

Radiographic follow-up: Chest radiography may be useful for indirectly assessing the effect of antituberculosis treatment, but it is not required. However, a chest radiograph may justifiably be taken:

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

7.5 Isolation of patients with tuberculosis

The aim of isolating patients – exceptionally in the hospital, preferably at home (whenever the patient's physical and social condition permits) – is to prevent transmission of *M tuberculosis* to third persons. It should be noted that most transmissions that will ever occur have actually taken place before initiation of appropriate chemotherapy. With appropriate chemotherapy, transmissibility rapidly diminishes.

Whenever clinically permissible (the patient is not too ill), the safest procedure is to discharge the patient from hospital as quickly as possible, place him or her on adequate chemotherapy, examine the family members for tuberculosis and put those for whom so indicated (see above) on preventive therapy. If hospitalization cannot be circumvented, isolation should be imposed if a microscopic examination or a nucleic acid amplification test result of any respiratory specimen is positive. Isolation is required in such a case to prevent nosocomial transmission. Isolation should be lifted as swiftly as possible and the patient be discharged for ambulatory treatment at home whenever possible.

Isolation might be eased or stopped (if indicated in the first place, see above) or the patient may be discharged from the hospital if all 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.

7.6 Outcome of antituberculosis treatment

The outcome of treatment of pulmonary tuberculosis is assessed according to the categories defined by the WHO. The Swiss Lung Association with its cantonal organizations (cantonal Lung Associations) requests this information from the treating physicians on behalf of the Cantonal Officer of Health.

1. Cure

Full treatment course with documented culture conversion in 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 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

Because of the difficulty in determining the cause of death, WHO requires only reporting of death while on treatment 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 reason that is at the beginning of 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, complicating information retrieval. However, a reasonable effort should be made to gather the information even in these cases.

7. Other

This should not be a frequent event. For instance, a patient switched to treatment for MDR who is still under treatment 12 months after the start.

Real case No. 5

An elderly patient with drug-susceptible tuberculosis conscientiously follows his treatment schedule but still coughs after several weeks of treatment. The physician then realizes that every morning the patient takes only one pill instead of four, because the prescription did not mention the daily dose!

The main cause of failure, relapse, or drug resistance is an error in the treatment regimen (the drug dosage is too low; the treatment combination is incomplete, too short, or intermittent) or a communication problem exists between the patient, the physician, the laboratory, the pharmacist, or the nursing staff.

8 Notification system and surveillance

Notification of any case of tuberculosis is mandatory (Law on Epidemics), irrespective of whether treatment had been initiated or not.

The Health Officer of the canton where the patient is resident or, if not a Swiss resident, where the patient is actually staying, 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. The following forms are to be completed: the Initial notification and the Complementary notification of tuberculosis within one week (www.tbinfo.ch/fr/formulaires/formulaires-de-declaration-tb-ofsp.html)
- **By the laboratory** in the case of identification of mycobacteria of the *M tuberculosis* complex by positive culture (any specimen) and/or microscopy of a respiratory 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 Officer of Health.

The Cantonal Officer of Health checks the information contained on the physician's notification forms and transmits them to the Federal Office of Public Health. He or she may forward a copy to the cantonal Lung Association.

The Cantonal Officer of Health and/or 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 treatment including its outcome are usually performed by the cantonal Lung Association. If a contact investigation is decided on, the cantonal Lung Association must be informed of the results of the bacteriological examinations (to inform the treating physicians of the infected contacts and to decide on the extent of the contact investigation and on the strategy for preventive therapy). These results are also necessary to ultimately organize the collection of treatment results.

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

Real case No. 6

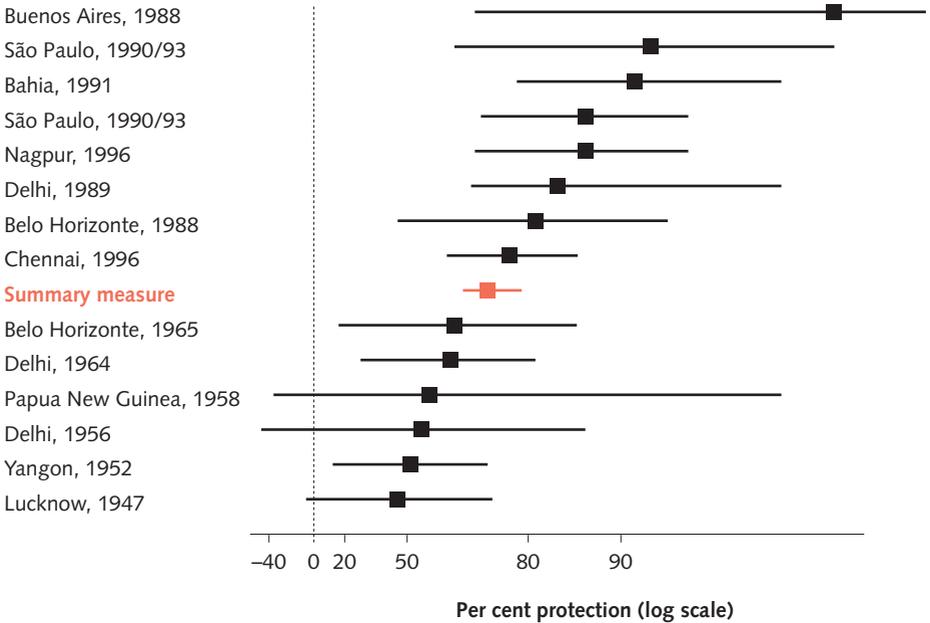
A Cantonal Officer of Health could not initiate a contact investigation because the physician failed to notify the health department about a case of tuberculosis. The complementary physician notification should always be made as soon as a decision to start treatment with a combination of at least 3 drugs is taken or the latest within one week.

9 Vaccination with BCG

Vaccination with BCG is no longer recommended for any permanent resident of Switzerland. The Federal Commission for Immunizations (EKIF/CFV) and the Federal Office of Public Health recommend that BCG immunization be only recommended to infants below the age of 12 months returning to live in countries where routine BCG immunization is recommended (www.bcgatlas.org).

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.

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



Bourdin Trunz B, et al. *Lancet* 2006;367:1173-80

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 and sometimes entirely absent. 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. Industrialized countries of Western Europe which have used BCG in the past (the Netherlands never used BCG systematically) have

changed their policy in the past two to three decades. Many have discontinued BCG, sometimes with the exception of some population segments. 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 *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), the choice has increasingly been in favour of improving contact tracing, diagnosis and treatment.

10 Tuberculosis among the foreign-born

The majority of incident tuberculosis cases in Switzerland are now reported among the foreign-born. Asylum seekers are currently the only population group subject to screening (based on history and symptoms) for tuberculosis at the time of requesting asylum. While the utilized screening system successfully identifies patients with overtly prevalent tuberculosis at the time of requesting asylum, the majority of cases ever occurring in this population are discovered in the months and 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 present at the time of immigration, or even progression of an infection actually acquired after arrival as a result of intra-group transmission. 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 bacteriological sputum examination in the case of any radiological abnormality.

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

In principle, asylum seekers with tuberculosis are allowed to complete their treatment in Switzerland provided that the treating physician reports the case to the Federal Office of Migration (www.tbinfo.ch/fr/formulaires/rapport-medical-odm.html) in a timely fashion.

This agreement between the Federal Office of Public Health and the Federal Office of Migration does not influence a decision on the asylum claim, but should lead to a postponement of any measure of expulsion until after tuberculosis treatment completion. The agreement applies only to tuberculosis and not to latent infection with *M tuberculosis*. It may not apply if the date of expulsion 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 that the patient be referred to a pre-identified tuberculosis treatment centre in order to facilitate transmission of medical information and to avoid treatment interruption.

Real case No. 7

A young Senegalese who coughs up blood every morning for 10 days is suffering from more than a nosebleed!

11 Financial issues and legal background

The Federal Law on Epidemics of 1970 and the Federal Law of 1928 on the fight against tuberculosis constitute the legal basis for tuberculosis control. The Health Insurance Law (LAMal) with its Ordinance (OAMal) and the Federal Law 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 public health department
- The employer
- The concerned individual.

Particular attention has to be paid to the guarantor for the costs incurred by persons without a valid residence permit, including former asylum seekers. This is notably of importance if treatment is directly observed.

11.1 Health insurance

As a rule, 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), as well as treatment costs for latent infection, unless it is judged to be occupational. When a diagnosis of tuberculosis has been established, the health insurance covers the cost for appropriate examinations

and treatment. The patient shares the costs (through the annual deductible and an expenditure-proportional charge). No exemption from cost sharing is granted.

11.2 Accident insurance

The national accident insurance deals with occupational safety and health. Article 9 of the LAA defines occupational diseases, summarized in Annex 1 of the Ordinance on Accident Insurance (OLAA). In fact, it is necessary to determine whether or not the infection (and resulting disease) was contracted while employed in a health care institution or not.

If the origin of an infection or a disease is suspected to be related to a healthcare occupation (e.g. tuberculin skin test or IGRA conversion, or the development of active tuberculosis after contact with a contagious index case on the job), this has to be declared to the accident insurance. The accident insurance will then evaluate the case and determine whether it is an occupational disease as defined in the clauses of the first or second paragraph of article 9 (LAA).

If the accident insurance recognizes tuberculosis as an occupational disease, it will cover the medical costs incurred. The same applies for medical investigations related to latent infection with *M tuberculosis* and its treatment, provided that latent infection results from occupational exposure (for example, demonstrated by a tuberculin skin test conversion).

11.3 Public health authorities

As defined in the provisions of the Law on Epidemics, contact investigations are epidemiological investigations under the responsibility of the cantonal public health authorities. Therefore, the cantonal public health department covers in principle the costs for contact investigations it orders to be carried out. This usually follows the notification of a case of tuberculosis considered to be transmissible. However, the aforementioned law does not contain any explicit provisions obliging the cantons to undertake such financing. Therefore, one should only proceed with contact investigations once instructed to do so by the Cantonal Officer of Health or the cantonal Lung Association, where the latter has the mandate to do so.

11.4 Employers

In healthcare institutions and other institutions which test employees for latent infection 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

Tuberculosis among asylum seekers

When tuberculosis has been diagnosed in an asylum seeker, the Federal Office of 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. This payment includes funds 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.

Illegal residents

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 a 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 him- or herself in a situation of distress and is not capable

of looking after him- 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 national platform for medical services for Sans-papiers” provides more extensive information on the subject of health prevention for illegal aliens (www.tbinfo.ch/fr/adresses-utiles/sans-papiers.html).

Directly observed therapy

Under certain circumstances, directly observed therapy is indicated.

The cantonal health authority can order the use of directly observed therapy. In most cantons, a healthcare worker of the cantonal Lung Association will organize directly observed therapy. 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).

Pharmacies may be much more convenient for patients requiring directly observed therapy than tuberculosis treatment centres or cantonal Lung Association offices. A well-defined agreement must be made between the physician in charge and the pharmacy. When directly observed therapy is delegated, it is mandatory that the physician in charge of antituberculosis treatment be clearly identified, and is informed rapidly if the patient becomes irregular in attending.

The healthcare worker 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 healthcare worker or the delegated body), there are the two following invoicing possibilities:

1. The health care provider's services are invoiced to the canton. In the event that a fixed amount has been agreed upon between the health care provider and the body that administers the drugs, this payment is generally invoiced to the canton.
2. The service is invoiced to the patient for the attention of the health insurance concerned. However, this is only possible if the body that administers the drugs is a physician or a recognized service provider as laid down in the provisions of the LAMal (nursing staff and auxiliary personnel and organizations providing their services upon medical prescription, cf. articles 49 and 51 of the OAMal). For the administration of drugs by non-medical personnel, the Tarmed tariff of medical fees 00.0150 can be used. However, the patient must participate in the cost of treatment through a deductible and by proportionate participation (contribution of 10 %).

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/publications.html):

For healthcare professionals

- The “Manuel de la Tuberculose” I “Handbuch Tuberkulose” (F/G/I; available electronically only as a PDF file)
- Abridged version of the “Manuel de la Tuberculose” (F/G/I/E; the present publication)
- “Tuberculosis: Risks and Prevention at the Workplace” (brochure No. 2869/35, SuvaPro)
- 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 18 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 Confederation reception centres for asylum seekers
- List of addresses of the cantonal physicians
- 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/prestations.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. The tuberculosis hotline is open on working days (from Monday to Friday from 8 a.m. to 12 a.m. and from 2 p.m. to 5 p.m.).

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Specialized services for tuberculosis

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