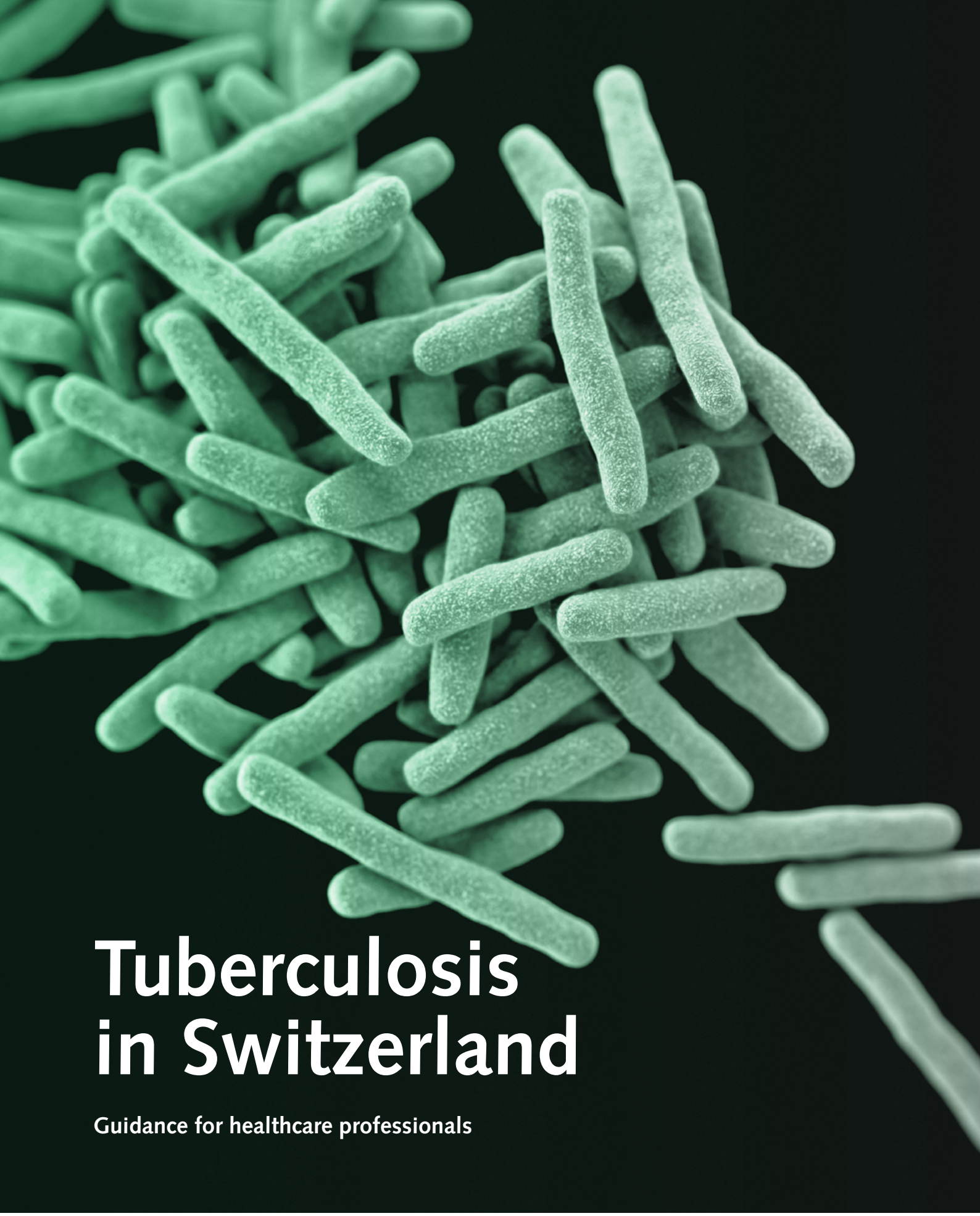

Tuberculosis in Switzerland

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 2021 edition of the publication "Tuberculosis in Switzerland – Guidance for Health Care Professionals".

Tuberculosis in Switzerland

Guidance for healthcare professionals

Glossary

Cantonal services specialized in tuberculosis		The cantonal medical officer has a mandated tuberculosis office, which is the local lung association in most cantons
Directly observed therapy	DOT	Direct observation of tablet swallowing during the course of a tuberculosis treatment
Interferon-gamma release assay	IGRA	Blood test indicating immunological contact with *M. tuberculosis*
Latent tuberculosis infection	LTBI	Historical term for TBI. Following WHO recommendation the term is now being discarded given that infection cannot always be considered to be dormant
Multidrug-resistant tuberculosis	MDR-TB	A form of TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid
Mycobacterium tuberculosis	*M. tuberculosis*	Acid fast bacilli causing tuberculosis
Tuberculin skin test	TST	Skin test indicating immunological contact with *M. tuberculosis*
Tuberculosis	TB	Disease caused by *M. tuberculosis*
Tuberculosis infection	TBI	A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TB disease
World Health Organization	WHO	A specialized agency of the United Nations responsible for international public health

Contents

1 Role of the physician

1 Role of the physician

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

The tasks 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, asylum seekers)
- **To rapidly carry out the necessary diagnostic examinations** (radiograph of the chest, sputum PCR and other targeted testing according to clinical presentation) **or to refer** the patient to an experienced colleague or a specialized centre.
- **To immediately notify** the Cantonal Medical Officer of any case of tuberculosis at treatment initiation with the corresponding notification form[1]. The Cantonal Medical Officer decides whether or not to conduct a contact investigation.
- **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 ensure adherence and treatment completion** in cooperation with the cantonal services specialized in tuberculosis. To this end, the social environment of the patient is taken into account (e.g. stigma, home environment, mental health aspects) and all persons concerned with the restoration of health of the patient should provide the necessary assistance if and where needed.
- **To notify the treatment outcome** to the Cantonal Medical Officer according to the WHO protocol: treatment failure, cured, treatment completed, died, lost to follow up, not evaluated [1].
- **To perform follow-up assessments** after treatment completion to detect early relapses and to assess post-tuberculosis sequelae.

1 *https://www.bag.admin.ch/bag/de/home/krankheiten/infektionskrankheiten-bekaempfen/meldesysteme-infektionskrankheiten/meldepflichtige-ik/meldeformulare.html*

2 Epidemiology

2 Epidemiology

2.1. Epidemiology in Switzerland and worldwide

The incidence of tuberculosis has been declining in Switzerland, as in many other Western European countries, for at least 150 years. In 2022, this downward trend was confirmed again with 365 reported cases and an incidence of 4.16 cases per 100,000 inhabitants. Of those affected, 73% were of non-Swiss origin, i.e. they were born abroad or, if this was not known, had foreign citizenship **(Figure 2-1)**. The most recent data for asylum seekers and refugees were made available in 2015. 34% of all reported cases occurred among these persons at that time.

The lungs were affected in 94% of tuberculosis cases in 2020. Of these cases with lung involvement, 87% were culturally confirmed; in 41%, laboratories reported a positive microscopic result from a respiratory specimen. The foreign-born were predominantly young adults, reflecting migration patterns and, to some extent, the prevailing epidemiological conditions of the countries of origin. **Figure 2-2** shows the age distribution of cases by origin (foreign vs. Switzerland/FL). In the five-year period from 2018 to 2022, 53 cases involved children under the age of five and the majority of cases in the Swiss- or FL-born occurred in the age groups of over 50 year-olds. In the group of children under 5 years of age, 8 were of non-Swiss origin (born abroad or, if this was not known, with foreign citizenship). In two cases, neither country of birth nor citizenship were known.

In Switzerland, the results of resistance testing are subject to mandatory reporting. The proportion of multidrug-resistant tuberculosis (MDR tuberculosis) in all reported and tested cases has been 1% in 2022. According to estimates by the World Health Organisation (WHO), the global incidence of tuberculosis has been slowly decreasing for several years. In the Global Tuberculosis Report of 2023, the WHO estimates a worldwide total of 10.6 million new cases of tuberculosis for 2022 [2]. The annual number of new cases of tuberculosis per 100,000 inhabitants (the incidence) varies greatly from country to country. While the estimated incidence is below ten in most highly developed countries (as low as 3.1 in the USA), it is higher in the vast majority of countries. In some countries in Southern Africa and Asia, it is above 500 and ranges up to 665. In 2022, 87% of new tuberculosis cases were reported in 30 high-incidence countries, of which two-thirds of new cases were reported in eight countries (India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and South Africa) **(Figure 2-3)**.

Both the number and proportion of estimated drug-resistant tuberculosis cases are worrying **(Figure 2-4)**, with considerable funding gaps in global tuberculosis control. For example, the number of reported multi- or rifampicin-resistant tuberculosis (MDR-TB, RR-TB) cases increased by 10% in 2019 compared to 2018.

Strategic objectives in Switzerland

In Switzerland, the strategic objectives are the adequate control of tuberculosis, of its transmission and of its medical and social consequences:

- Persons with tuberculosis who use the health care system in Switzerland must be detected at an early stage and treated adequately and completely. To this end, maintaining an appropriate level of expertise of health professionals is central.
- At-risk groups must receive appropriate information on early detection
- Contact investigations for infectious cases, and care of persons with tuberculous infections, should be carried out in a standardized and efficient manner.
- Tuberculosis should be controlled effectively, expediently and economically in Switzerland. To this end, defined standards must be adhered to. Measures to control tuberculosis must be regularly monitored regarding effectiveness meeting the objectives.
  Three framework conditions are fundamental for greater efficiency in the fight against tuberculosis: harmonization, standardization and coordination of practices and activities.
  The strategic objectives should contribute to the WHO End TB Strategy goal of ending the global TB epidemic.

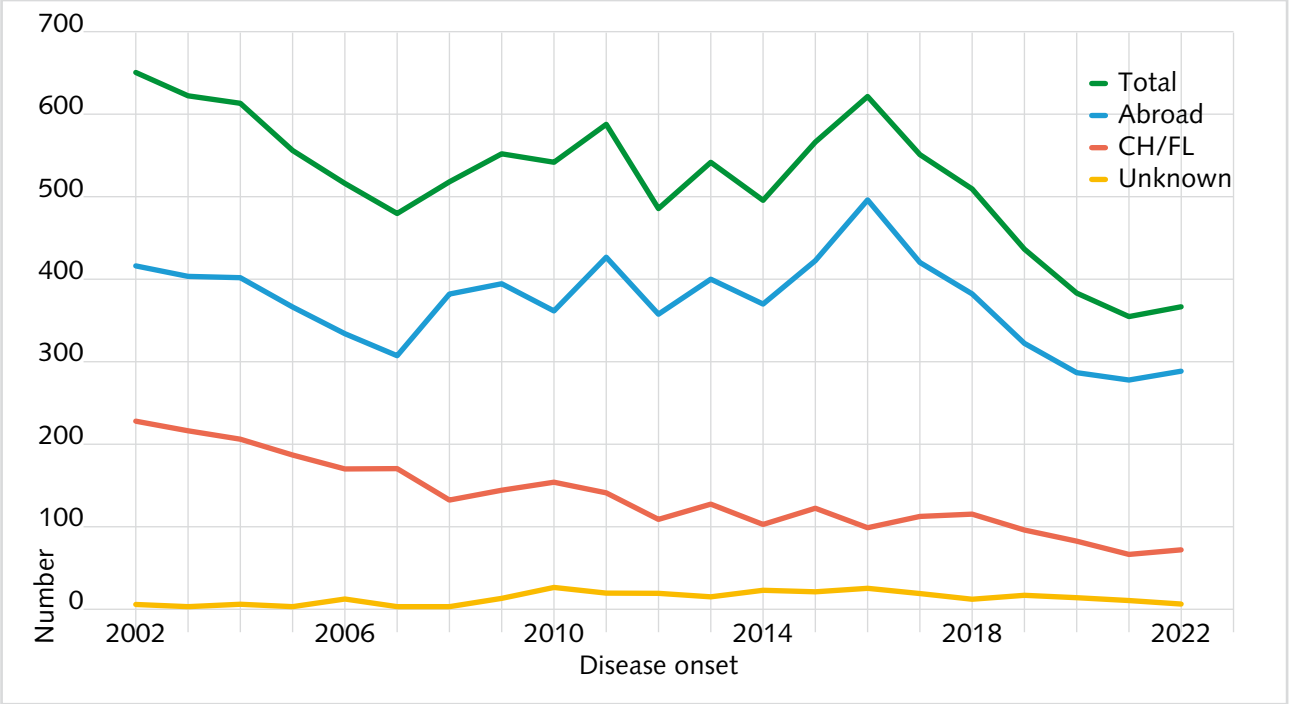

Figure 2-1. **Tuberculosis cases in Switzerland reported to the Federal Office of Public Health, by origin, 2002-2022.**

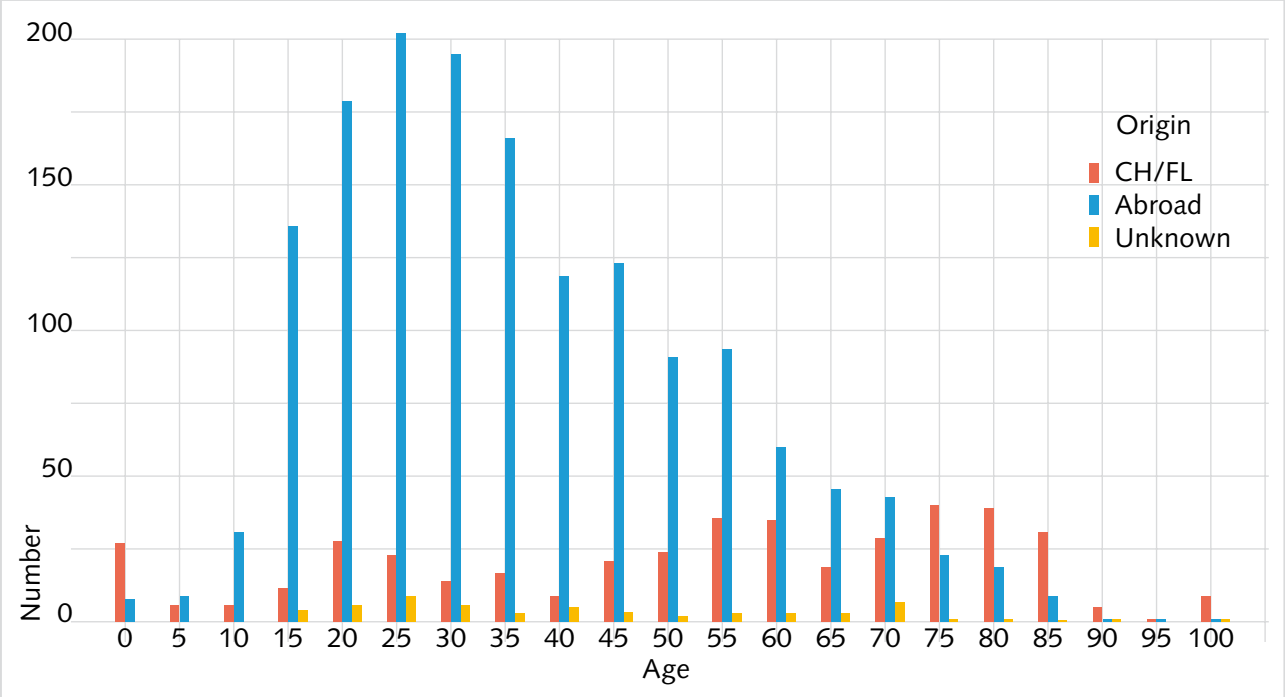

Figure 2-2. **Tuberculosis cases reported to the Federal Office of Public Health from 2018 to 2022 by age and origin (n=2521)**

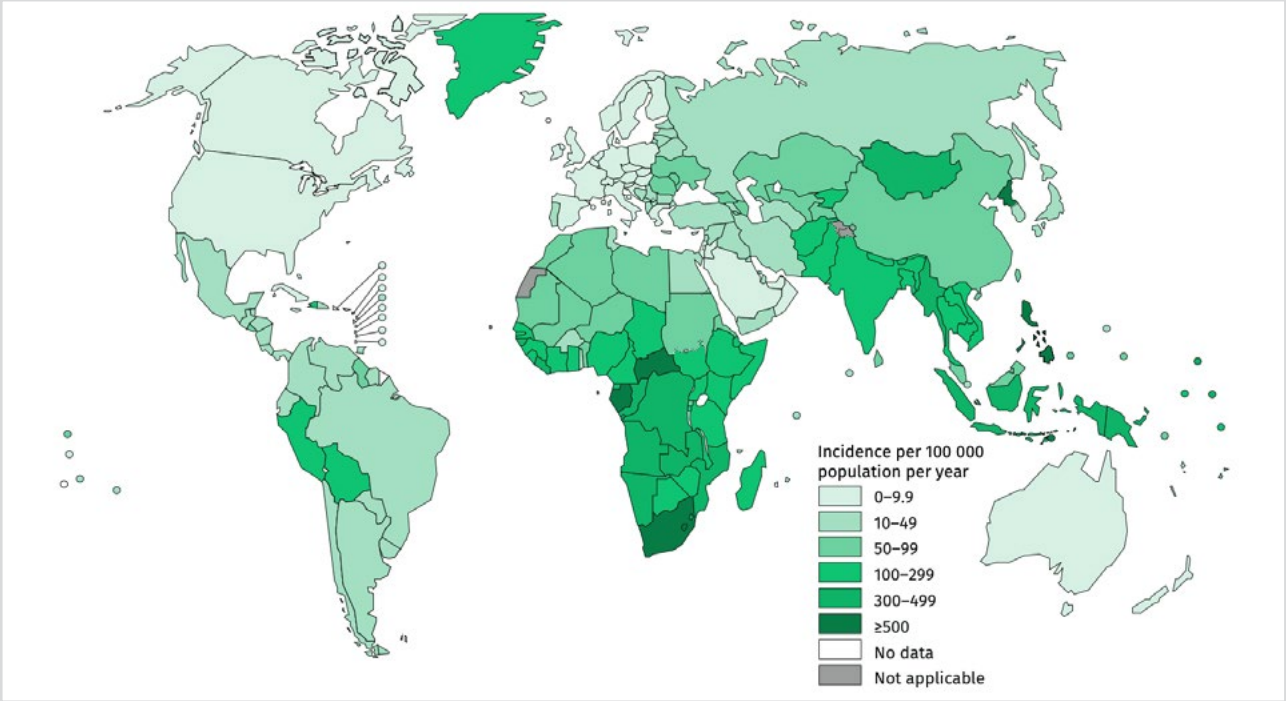

Figure 2-3. **Number of new tuberculosis cases per 100'000 population and year (incidence rate), 2022. World Health Organization, Global Tuberculosis Report 2023** [1].

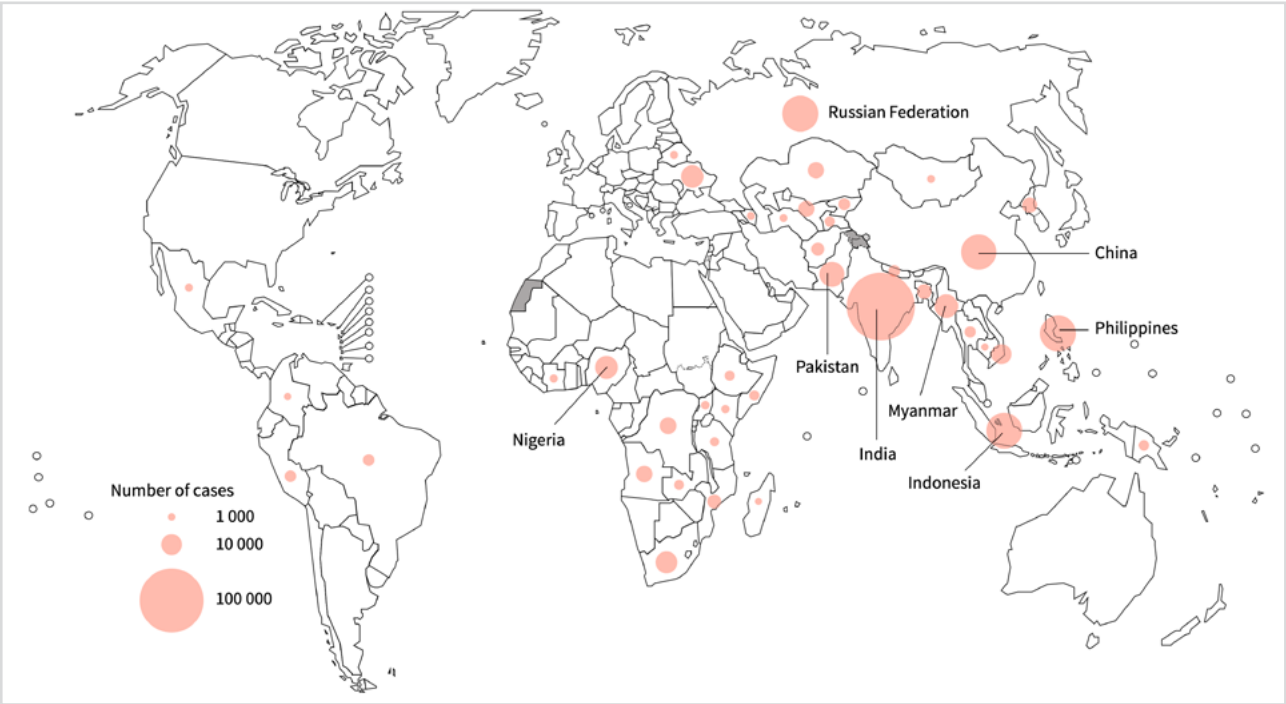

Figure 2-4. **Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases**

2.2 Impact of the COVID-19 pandemic on tuberculosis

Worldwide, the COVID-19 pandemic has had a severe impact on tuberculosis care. New cases recorded by WHO dropped by 18% between 2019 and 2020, while mortality increased: indeed, figures for 2020 are similar to those of 2017 (ca. 1.5 million deaths). This was the first year-to-year increase in tuberculosis deaths since 2005. Access to treatment has also been jeopardized: according to the WHO, the number of cases treated between 2019 and 2020 decreased by 21%, whereas MDR-TB treatments dropped by 15%. This most probably reflects a combination of decreased access to health care and tuberculosis services, as a result of confinement measures, lock-downs, and redistribution or lack of resources [3]. It may also reflect the impact of stigma of symptoms such as cough, common to both tuberculosis and COVID.

The COVID-19 pandemic also had severe economic consequences: according to the UN an estimated 100 million people have been pushed into poverty. This may impact the future burden of tuberculosis.

A sudden decline in tuberculosis case detection (including MDR-TB) after March 2020 has been noted worldwide [4], with a few local exceptions, and was reported in all 6 WHO regions; 16 countries were responsible for 93% of the decline between 2019 and 2020, including India, Indonesia, The Philippines and China. In these countries testing for tuberculosis infection, contact tracing, initiation of treatment for infection and BCG vaccination in children decreased.

In Switzerland, the number of new tuberculosis cases also dropped substantially between 2019 (429 cases), 2020 (371 cases, -13%) and 2021 (361 cases, -15.8%) with a decrease of incidence from 4.96 to 4.14/100'000 inhabitants. Changes were similar in male and female subjects. However, there are presently no data suggesting an increase in mortality or hospital admissions for more severe tuberculosis cases. Migration patterns remained stable during this period. The absolute number of asylum seekers decreased at the beginning of the pandemic and rose again to pre-pandemic figures after the pandemic.[1]

While confinement and "barrier" measures may have had an impact on transmission, most cases of tuberculosis in Switzerland are considered as reactivation of a previously acquired infection. Studies and a longer observation period are required for a better understanding of this phenomenon, which differs from what is observed in middle and high incidence countries.

1 *https://tradingeconomics.com/switzerland/asylum-applications*

3 Transmission, pathogenesis and clinical presentation

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 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 maneuvers (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 macrophages. In closed, poorly ventilated rooms 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).

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 with *M. tuberculosis* infection (previously called "latently infected") demonstrating a positive immunologic test (chapter 4.1) are neither ill nor able to transmit *M. tuberculosis*. The overwhelming majority of such 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 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. Recent concepts point out the fact that there is a spectrum of disease with a considerable portion of tuberculosis cases with mild or no symptoms (subclinical tuberculosis). 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.

In general, 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 12 years. Transmission is increased if the patient coughs 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). Invasive procedures such as bronchoscopy and intubation also increase the risk of transmission.

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. The WHO provides an annual up-date of tuberculosis incidence worldwide according to their most recent estimates: this is a helpful component of a priori risk assessment for tuberculosis (pre-test-probability)[2]. Decreasing awareness and knowledge about tuberculosis carries the risk of delayed diagnosis with an increased frequency of advanced forms of the disease. Authorities and health care workers responsible for the management of facilities with a high number of vulnerable and high-risk populations, such as asylum centres should be aware of the risks tuberculosis cases could pose.

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 retrocardiac 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 mediastinal 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 tuberculosis may be necessary if symptoms are pre- sent 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),

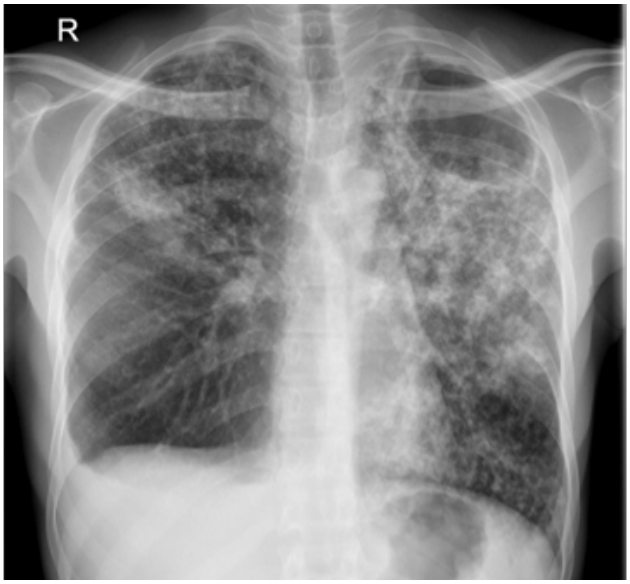

Figure 3-1. Chest radiograph of a patient with sputum smear-positive pulmonary tuberculosis. Extensive bilateral disease with asymmetric infiltrates, mottling, and cavitation.

inactive (dormant bacteria), or healed (no or dead bacteria) pulmonary tuberculosis. Before infiltrates can be 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 by PCR, microscopy and culture. Comparing images with earlier radiographs or CTs is also helpful.

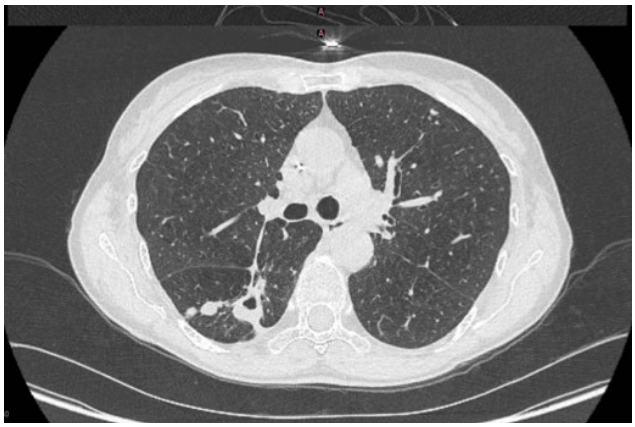

Figure 3-2. Chest computed tomography of a patient with pulmonary tuberculosis. Thickwalled cavity in the upper segment of the right lower lobe with tree-in-bud alterations.

2 *https://www.who.int/teams/global-tuberculosis-programme/data*

4 Infection with *M. tuberculosis*

4 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 suggesting that lifetime persistence of live bacilli is not the rule but rather an important exception. Furthermore, the immunological activity of the host against *M. tuberculosis* bacilli may result in a "continuous disease spectrum" from infection to disease [5].

None of the currently available tests can determine whether live bacilli are actually present in a clinically healthy person suspected of having infection with *M. tuberculosis*. The tests at our disposal search for memory immune cells that *M. tuberculosis* induces. Immunological memory may persist lifelong. This is evidenced by the persistence of positive tuberculin skin test reactivity and positive IGRA after bacteriologically cured tuberculosis, and also by only gradual waning of tuberculin skin test reactivity 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 **infection with *M. tuberculosis*** to a person with a positive tuberculin skin test or IGRA is 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).

An assessment of the risk of an 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 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 2 years or immunocompromised persons (HIV, anti-TNF-alpha treatment, etc.) are at highest risk of progression to tuberculosis, while in persons with diabetes, renal failure, or silicosis the risk of progression is moderately increased. 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 completely disappears **(Figure 4-1)**.

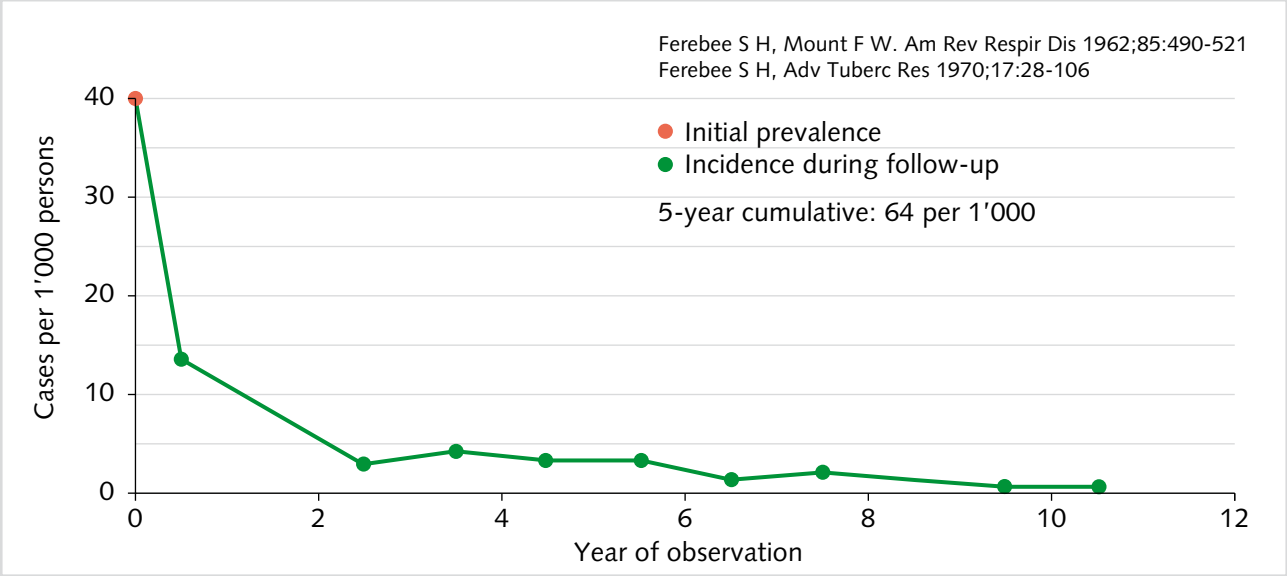

Figure 4-1. Prevalence and incidence of tuberculosis among recently infected household contacts, by time elapsed since identification of index case, United States Public Health Service trial.

A novel approach to inform individual patients about their personal risk of developing tuberculosis after infection is the use of a personalised risk predictor for incident tuberculosis (personalised risk predictor for incident tuberculosis, «PERISKOPE-TB» [6]). which was developed through a large international collaboration, led by researchers at University College London. They pooled individual level data from 15 previous studies done in 20 countries. These studies tested people for tuberculosis infection, and then followed them up to identify which participants developed tuberculosis. These datasets were used to develop the prediction model, and to validate its use for clinical practice. The tool can be easily used online at http://periskope.org. It provides an estimation of 2-year risk of tuberculosis with or without preventive treatment as well as an estimation of the number of persons needed to be treated to prevent one case of tuberculosis. Results are indicative and must be integrated in local diagnostic and preventive strategies (see also chapter 5).

4.2 Indications to test for infection in asymptomatic persons

Generally, any testing for tuberculosis infection should only be made if a positive test will be followed by treatment for infection, a recommendation ideally discussed with the patient before applying the test.

Testing for tuberculosis infection is indicated:

- **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 infection by systematic testing is currently controversial for situations not listed above and is not generally recommended (poor predictive value of a positive test in non-targeted screening). However, taking into account the rapidly increasing list of immuno-impacting drugs for which it is too early to have data as to the risk of tuberculosis reactivation, it is the clinician together with the patient who should decide if the treatment and/or condition justifies testing for tuberculosis infection and, in case of a positive test, preventive treatment. Another controversial issue is the screening for infection in young migrants arriving from high tuberculosis prevalence countries (see chapter 10).

4.2.1 Repeat testing of health care workers

In every institution of the health services and other institutions with a risk of exposure to tuberculosis, 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 be obtained among employees at risk for infection. However, repeat routine testing of health care workers is 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 working group of the Paediatric Infectious Disease Group in Switzerland (PIGS) has issued a guideline in 2016 suggesting screening for tuberculosis with a tuberculin skin test when such children are seen for the first time in the healthcare system [7]. In addition an update for refugees from Ukraine was published in 2022 [8]. The aim is now to find infection and tuberculosis at an early stage by screening with an IGRA or skin tests, depending on availability of the tests. A child with a positive test should then be referred to a specialist for appropriate evaluation and treatment of tuberculosis or preventive treatment of infection.

However, screening of asymptomatic immigrant children for infection remains challenging in the migrant setting and outside of contact tracings (see chapter 5), and the recommendation remains controversial as data supporting evidence of general screening in migrant children is limited.

4.3 Immunodiagnostic tests to diagnose infection with *M. tuberculosis*

4.3.1 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. 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 millimeters) of the induration is measured, i.e. the diameter perpendicular (transverse) to the long axis of the arm. Importantly, the possible presence of erythema is not taken into consideration for the measurement, solely the induration.

In a targeted contact investigation, it is recommended to consider an induration size of 5 and more millimeters in contacts as "positive" requiring investigations for tuberculosis or preventive therapy.

4.3.2 Interferon-gamma release assays (IGRAs)

The IGRAs (two commercial tests are currently registered by Swissmedic) use 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 Plus) 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 IGRAs are age dependent and therefore false negative or indeterminate test results may occur [9] more frequently. 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).

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

- Using an IGRA as the only test.
- Using the tuberculin skin test as the only test
- Using both tests concurrently to increase sensitivity (only recommendable in young children)

In Switzerland, shortages in supplies with tuberculin are frequent and 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, there is an increasing tendency to rely solely on an IGRA.

Using the tuberculin test as the only test
The tuberculin skin test is preferred in the evaluation of BCG-unvaccinated younger, not BCG vaccinated children, in whom lower interferon gamma production may lead to false negative or indeterminate IGRA results 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 younger children it is acceptable to not confirm a positive skin test with an IGRA and start preventive therapy after excluding tuberculosis disease.

Using both tests concurrently to increase sensitivity
This strategy is limited to young children, where a positivity in one or the other of the tests applied is followed by a recommendation for a preventive therapy.

Tests performance is limited by immunosuppression
Both TST and IGRAs can be affected by various regimens of 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 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 infection with *M. tuberculosis*") if they have no symptoms or signs consistent with tuberculosis.

Based on clinical trials, the choice is among three regimens with similar efficacy (for dosage of the drugs see chapter 7):

- Daily isoniazid for 6 (or 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 of 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.

An option would be the directly observed shorter treatment with isoniazid and rifapentine once weekly for 12 weeks. The regimen is equally effective to treat infection and is widely used in the USA [10]. However, rifapentine is not registered and not available in Switzerland (and in Europe). Moreover, the costs are not covered by health insurances.

Contacts judged to have become infected by a person 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 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 necessary 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 and is smaller with rifampicin than with isoniazid. 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 tuberculous infection 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 tuberculous infection 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 infection, 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 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 but coercive measures are not justified.

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

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 .
- 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 services specialized in tuberculosis 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.

The "source finding" aspect of contact tracing

At the first encounter with any person newly diagnosed with tuberculosis, but especially in children below the age of 5 years, an extended history concerning symptoms and signs of tuberculosis in contacts of the patient is taken to potentially find someone who could have transmitted tuberculosis to the index patient.

5.1 Principles for the approach to a contact investigation

Firstly, a list of persons is established who were in close or prolonged contact (as described in the boxes above, in chapter 3.1, and in [11]) 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, center for asylum seekers, shelter for the homeless, prison etc.), the list is prepared with the additional 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 and must have a tuberculin skin test or an IGRA performed. 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 disease in the 2 months following exposure is very low except for infants and immunocompromised individuals, and thus waiting 2 months to perform a test 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,** immunocompromised individuals and children under 5 years of age require a medical examination (including a chest radiograph) as quickly as possible.

- **Children under 5 years of age** must always be examined within days, regardless of symptoms. This includes a clinical examination, chest radiography and a tuberculin skin test or IGRA. If a contact child of an index case with known *M. tuberculosis* susceptibility is symptomatic rapid examination is important. If the contact child has a positive tuberculin skin test or IGRA or an alteration in the radiological examination, a full course of tuberculosis treatment may be initiated. If tuberculosis can be excluded, treatment for TB infection is initiated immediately since the rate of progression to tuberculosis in infants below the age of five years is estimated at 30 to 40% , and conversely, preventive treatment is very well tolerated.

- If an initial tuberculin skin test or IGRA is negative preventive treatment with isoniazid is started, and the test is repeated after 2 months. If a tuberculin test or an IGRA remains negative at this point in time, preventive treatment is stopped.

- **Children 5-12 years of age** and immunocompromised persons are given priority for contact examination and testing without delay. If asymptomatic this can be done within 1-2 weeks. If symptomatic this should be done within a few days. This includes a clinical examination, conventional chest radiography and a tuberculin skin test or IGRA.

Other contacts to be examined promptly are potential source persons of children with tuberculosis under 5 years of age. Source persons are usually above the age of 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 this 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. With larger groups (open-plan offices, roommates in prisons etc.) it may be advisable to first test the very close contact persons (e.g. the next table neighbors) and only then expand the circle if a considerable number of contacts test positive in the first circle.

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 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. Approximately three quarters of the contacts with *M. tuberculosis* infection started treatment and treatment completion was reported for at least one third (however, this figure is probably an underestimation and reflects lacking information). 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.
For the individual risk assessment for tuberculosis and the respective risk reduction by treatment in persons tested positive for infection, it may be informative to

make use of the personalized risk predictor for incident tuberculosis (PERISKOPE-TB, see chapter 4), used online at http://periskope.org [6]. It provides an estimation of 2-year risk of tuberculosis with or without preventive treatment as well as an estimation of the number of persons needed to be treated to prevent one case of tuberculosis.

An exemplary situation is a pulmonary tuberculosis case in a center for asylum seekers: by the time the contact investigation starts, contacts may already have been transferred to other centers which makes the task more complicated. A reasonable target group is usually family and/or 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 and be examined as mentioned above (see chapter 5.1.1). For all other close contacts with no symptoms, screening for tuberculosis infection (e. g. IGRA) is reasonable only in settings with a stable environment and thus a high likelihood for adherence to treatment of tuberculosis infection. This is often not the case at federal asylum centres, but may be given at a later stage, e.g. in cantonal asylum centres or other circumstances. It is therefore important that the exposure is noted in the medical file of the asylum seeker so that the person will be tested after 8 weeks, if appropriate. For more information about screening for infection in asylum seekers see chapter 10.5.2.

Contacts with a presumed recent infection identified by a positive IGRA or tuberculin skin test 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 should be informed about the risk of developing tuberculosis and, unless contraindicated, 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 contra-indicated
	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 6 (or 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 immunosuppression*, 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.

* *Such drugs include tumor necrosis factor-alpha inhibitors, azathioprine, methotrexate, cyclophosphamide, and other immunosuppressive drugs used in solid organ transplantation. Data concerning the risk of progression from tuberculosis infection to disease of novel targeted immune-modulatory drugs are often insufficient, thus a high index of suspicion for tuberculosis is warranted in such patients.*

6 Diagnosis of tuberculosis

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 or CT scan (low dose often sufficient for tuberculosis diagnosis) is performed even if an extrathoracic form of tuberculosis is suspected (because many patients with extrapulmonary forms of tuberculosis also have a pulmonary involvement). 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. If positive, IGRA or tuberculin skin test results may support a diagnosis of tuberculosis with a reported sensitivity of 70 to 80% [9] for children. In exceptional situations, it may be appropriate to treat patients (especially children) based on 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%, depending on the form of tuberculosis, the immune status of the patient and other underlying characteristics, more than 20% of patients with tuberculosis have negative IGRAs. Vice versa, a positive IGRA does not necessarily explain symptoms and mean that the patient has tuberculosis. In children with suspected tuberculosis, however, pediatricians find immunological tests helpful, as cultures from respiratory samples may remain negative and children display asymptomatic or oligosymptomatic forms. However, it is important to note that a positive immunological test cannot distinguish between tuberculosis and infection with *M. tuberculosis* and a negative immunological test cannot rule out tuberculosis.

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 Ultra, BD MAX® MDR-TB, 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, provided the sputum sample is adequate. 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* **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 and bronchoalveolar lavage 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. This applies also in particular to extrapulmonary samples.

In patients unable to produce spontaneous sputum, sputum induction with an aerosol containing hypertonic saline (with or after 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 30 years and are endorsed as a highly sensitive and specific technology by WHO. 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

Assay Information

Assay	Assay Version	Assay Type
Xpert MTB-RIF Ultra	4	In Vitro Diagnostic

Test Result: MTB DETECTED VERY LOW;
RIF Resistance NOT DETECTED

Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	23.4	160	NA	PASS
IS1081-IS6110	19.8	621	NA	PASS
rpoB1	28.4	333	POS	PASS
rpoB2	28.6	212	POS	PASS
rpoB3	29.8	147	POS	PASS
rpoB4	31.8	108	POS	PASS

Fig. 6-1. Results from Xpert® MTB/RIF Ultra. The analysis indicates the presence of a low amount of *M. tuberculosis* (nucleic acids) without indications for RIF resistance.

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 analyses a larger sputum volume and results in a higher sensitivity due to amplification of multicopy targets, especially in paucibacillary specimens (smear negative or HIV patients).

Nucleic acid amplification techniques detect the presence of mycobacterial DNA, which need not originate from viable mycobacteria. Therefore, the tests may remain positive for prolonged time periods in patients during and after tuberculosis treatment and cannot be used to document the cure of tuberculosis.

Nucleic acid amplification techniques are not only useful for the detection of the pathogen but also to detect resistance mutations. The Xpert® MTB/RIF Ultra automatically runs a highly sensitive assay for rifampicin resistance (RIF component) starting from unprocessed clinical samples **(Figure 6-1)**. It probes the resistance determining region of the *rpoB* gene with four probes but does not analyze loci associated with isoniazid resistance. The Xpert® MTB/XDR detects resistance for isoniazid, fluorquinolones and amikacin directly from sputum. Alternatively, the presence of widespread resistance conferring mutations may be probed by line probe assays (e.g. Genotype MTBDRplus or sl, Hain), or in selected cases by next generation sequencing **(Figure 6-2)**.

All rifampicin-resistant strains are required by law to be sent to the National Reference Laboratory hosted by the Institute of Medical Microbiology, University of 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[3], and with an expert center for MDR-TB treatment is strongly recommended in these cases (see below).

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

- Direct PCR 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 direct PCR 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 direct PCR negative for the presence of MTB are considered non-infectious and do not need isolation.
- For Patients with respiratory specimens that are direct PCR 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 or later from cultured isolates by molecular tests and/or phenotypic drug susceptibility testing.
- Direct PCR is helpful in specimens collected with biopsy, needle aspiration or stools, but has a lower yield in pleural and pericardial effusions and meningeal fluid.
- Direct PCR 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.
- Direct PCR is costly and should not be performed after tuberculosis diagnosis is formally established (except to verify a positive result for rifampicin resistance).
- Direct PCR does not replace smear microscopy for follow-up on treatment nor does it replace mycobacterial culture for resistance testing.

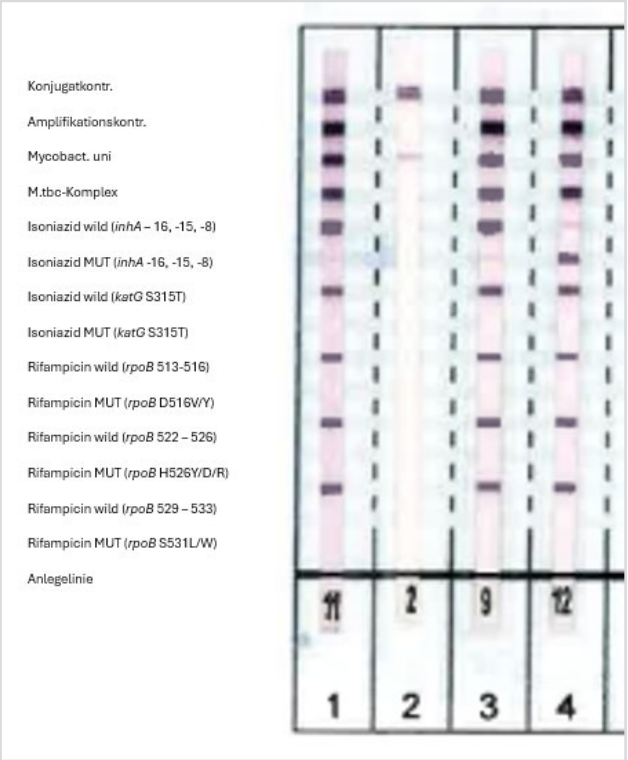

Fig. 6-2. Detection of isoniazid (INH) and rifampicin (RIF) resistance mutations by line probe assay (AID Diagnostika). Probes in lanes 1 and 3 show wild-type bands for *inhA promotor, katG and rpoB* at positions frequently associated with INH resistance and RIF resistance, respectively. The pattern therefore indicates INH and RIF susceptibility. Probe in lane 2 not interpretable (low amount of DNA). The probe in lane 4 shows a band pattern indicative of an *inhA* promoter mutation which is associated with INH resistance.

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 centers indicate that, for respiratory samples, rapid molecular-based methods may largely replace culture in the future as they compare favorably 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 drug susceptibility testing for first-line drugs and susceptibility testing for second-line drugs such as fluoroquinolones, bedaquiline and linezolid. The results can offer critical guidance for the treatment regimen for multidrug-resistant tuberculosis, gauging the usefulness of some drugs. In depth molecular analyses including whole genome sequencing allow the detection of resistance mutations, lineage typing and epidemiological investigations for the monitoring of transmission of tuberculosis.

3 *https://www.lungenliga.ch/kompetenzzentrum-tuberkulose/dienstleistungen*

7 Treatment of tuberculosis

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]) (see 7.2. risk of drug resistance).
- Assess the immunological status of the patient (HIV test).
- Assess liver and renal function.
- Have a complete list of medications taken regularly

Standard treatment of tuberculosis

Initial or intensive phase (months 1–2):
4 drugs: Isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) daily for 2 months*

Continuation phase (months 3– 6):
2 drugs: Isoniazid (H) and rifampicin (R) daily for 4 months

Short notation: 2HRZE / 4HR

Tuberculosis is treated with 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** [13].

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) in case of not very extensive disease. [14].

The best-established efficacious treatment regimen is a daily regimen throughout the six months. All antituberculosis drugs are administered once daily, if possible in the morning. In some patients with drug intolerance in the mornings, taking the drugs >1.5 hours after a meal may be alternative. Intermittent treatment during the intensive phase is strongly discouraged. An intermittent continuation phase (thrice weekly) may only be considered if all drugs are given under direct observation. High-fat meals reduce absorption

Table 7-1. **Recommended (World Health Organization) dosages for four first-line drugs** [14,15]

	Daily dose (range) in mg per kg	
	Adults	Children*
Isoniazid	5 (4–6)	10 (7–15)
Rifampicin	10 (8–12)	15 (10–20)
Pyrazinamide	25 (20–30)	35 (30–40)
Ethambutol	15 (15–20)	20 (15–25)

* up to a body weight of 25 kg
For combination tablets see: compendium.ch

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)**.

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 [13, table 6]. Pyridoxine (vitamin B6) is given with isoniazid to all persons to minimize the risk of neuropathy.

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 / Infectious 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 cavitary 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 [13].
- 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.
- Tuberculosis due to *M bovis* is naturally resistant to pyrazinamide and thus requires a treatment

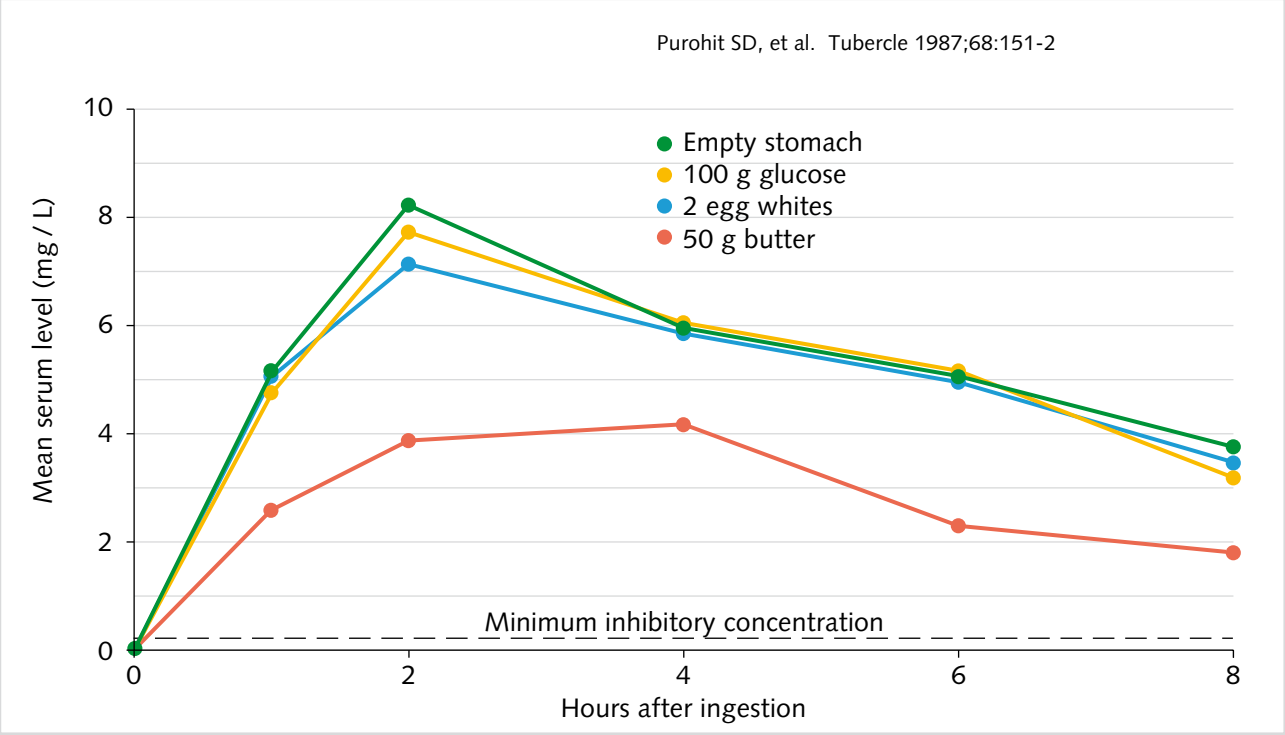

Figure 7-1. The impact of a meal containing carbohydrates, protein, or fat on the pharmacokinetics of rifampicin.

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.

Evidence from several recent studies suggests that patients can be cured with a shorter than the recommended 6 months duration of treatment. Such studies were able to achieve equivalence of a shorter 4-month treatment duration, using additional active drugs (rifapentine high dose – currently not available in Europe; moxifloxacin). Currently, the possible benefit of a shortened treatment duration can not be applied due to the missing access to rifapentine. Hence, the standard therapy and the recommended standard treatment duration of 6 months does not change.

Rifampicin doses have historically increased since the middle of the last century to 10 mg/kg body weight based on cost and tolerability analyses. Various rifampicin doses have been tested, both in models in vitro and in vivo and in clinical studies. While the in vitro and in vivo models clearly show an advantage for higher concentrations regarding resistance development and sterilization, this advantage could not be clearly reproduced in clinical studies. For example, increasing the dose to >20mg/kg shows earlier culture conversion, but with no effect on all-cause mortality. In summary, high-dose rifampicin therapy is thus only recommended in specific clinical situations such as tuberculous meningitis or large caverns and should be discussed with tuberculosis experts.

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 and initiate adequate resistance diagnostics.

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).

Sputum examination with e.g. Xpert® MTB/RIF Ultra is recommended (see chapter 6.3.2.). If the PCR is positive but no mutation is present, the standard treatment regimen is initiated. If resistance to isoniazid or pyrazinamide is detected at a later date, treatment schedules need to be adapted (see box below for isoniazid resistance alone).

In the case of of rifampicin resistance or its demonstration, 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 . The advice of a specialist must always be sought. A presentation and internet based discussion of the case in the "MDR-TB expert group[4]" 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) and levofloxacin for a duration of 6 months . 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:

Before defining the treatment regimen in consultation with a specialist, make sure the strain is sent to the National Reference Laboratory in Zurich. Currently, in accordance with WHO and the German tuberculosis guideline, three treatment regimens for MDR-tuberculosis may be recommended:

- Six months of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) as a fixed drug combination. For some patients, extending the treatment beyond 6 months can be appropriate. (this regimen is currently recommended for >14 year-old persons only)
- At least 18 months of individualized MDR-TB treatment with bedaquiline + levofloxacin or moxifloxacin + linezolid and at least 1 drug of WHO-Gruppe B (clofazimine, terizidone), adapted to the results of resistance testing.
- At least 9 months with a 4 months intensive phase of bedaquiline, levofloxacin, prothionamide (may be replaced by linezolid 600mg/d for 2 months), ethambutol, pyrazinamide, high dose Isoniazid and clofazimine and a 5 months continuation phase with levofloxacin, pyrazinamide, ethambutol and clofazimine.
- New treatment regimens for drug resistant tuberculosis are evolving and recommendations may rapidly change or alter. We thus recommend to always contact a specialist or the MDRTB expert group.

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 (3 months to 16 years) up to 25 kg of body weight **(Table 7-1)**. WHO now recommends for non-severe TB in children 2 months of RHZ(E) and and 2 months of RH [17]. The treatment of tuberculous meningitis and pericarditis may require the addition of corticosteroids, usually for 6 to 8 weeks. It should be supervised by a specialist. For tuberculosis meningitis, because of low penetration of rifampicin and ethambutol in the cerebrospinal fluid, new treatment regimens and drug dosages are under evaluation, with options such as much higher dosages of rifampicin and an on-going 6 months trial of rifampicin/levofloxacin/pyrazinamide. WHO also proposes a 6 months intensive regimen with the addition of ethionamide (6HRZEto) as a possible alternative to the 12 months regimen (2HRZE/10HR) for children without HIV co-infection [2]. Treatment of extrapulmonary disease and complicated pulmonary disease in children should be supervised by a pediatric 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 this case, 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 also 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. Most cases tolerate the reintroduction of the first-line regimen. Nevertheless a TB-expert should be consulted. Patients not tolerating rifampicin should be treated with a regimen used for MDR-TB treatment (see chapter 7.2.).

Renal failure: The use of ethambutol and pyrazinamide must be spaced to a thrice weekly dosage if the creatinine clearance is < 30 mL / min. Ethambutol 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
- For patients who receive treatment for multi-drug-resistant tuberculosis.

Some Swiss tuberculosis centers (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 centers, cantonal lung associations, pharmacies, or by home care nurses. Video-observed therapy (VOT) using a cellphone and sending daily short videos to a secured platform has been shown as a promising time-saving alternative to DOT and is currently being tested in Switzerland.

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. Specific websites on drug-drug interactions should be consulted (e.g. Up-to-date, DynaMed McGill).

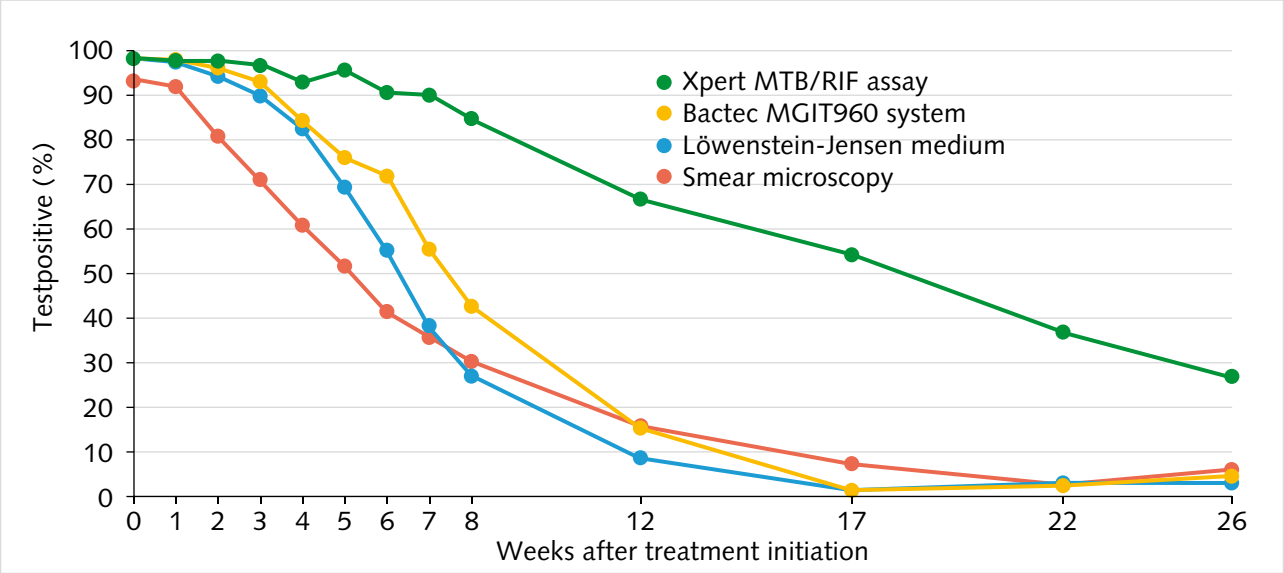

Figure 7-2. Consecutive sputum smear, culture and Xpert® MTB / RIF results in 221 patients successfully treated for pulmonary tuberculosis (Lancet Respir Med 2013;1:462–70).

Control of liver enzymes: Because antituberculosis treatment includes three potentially hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide), liver enzymes should be tested at treatment start, after 7-10 days 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). For children routine liver function testing is not mandatory if the baseline liver function testing is normal but should be done when liver injury is suspected clinically.

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 Ultra and other genotypic or phenotypic resistance testing methods should be performed (i.e.Xpert® MTB/XDR). As noted previously, the MTB test included in Xpert® MTB / RIF Ultra during treatment is expected to stay positive for more than 6 months and is therefore useless for treatment monitoring or in suspected relapses after treatment completion **(Figure 7-2)**.

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 and should not be done if an initial radiograph was normal. However, making use of an imaging technique is justified

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

7.5 Isolation

7.5.1 Isolation of patients with presumed 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. The clinician presuming or diagnosing pulmonary tuberculosis is responsible for the decisions on isolation.
In hospital settings, untreated patients with a clinical or radiological suspicion of infectious pulmonary tuberculosis should be isolated until at least one first respiratory specimen is negative by PCR (see box airborne isolation in chapter 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 human-to-human 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 therapy, transmissibility rapidly diminishes. However, to allow the patient to adapt to therapy and to minimize unnecessary exposures, patients isolated in home settings should not be allowed to go to public settings or to work for the first 15 days of effective therapy.

If hospitalization of a confirmed pulmonary tuberculosis or extrapulmonary with aerosol producing interventions (e.g surgery of infected bone, suction/drainage of infected tissue) 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 is mandatory in patients with multidrug resistant tuberculosis, whereas for patients with non-resistant tuberculosis regular air exchange is sufficient.
- Training on respiratory hygiene and cough etiquette for patients wearing surgical masks further reduces aerosol emission.
- 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 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. 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).

The patient should be discharged for ambulatory treatment at home whenever possible. However, if "home" is a communal setting (e.g. asylum center or shelter for the homeless), several conditions should be met (see below). Discharge is possible after 5 to 15 days (more when drug resistance is 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 **(Figure 7-2)**.

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 cavitation. 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 centers. This is also the case for the duration of MDR-TB isolation at the patient's home. Prolonged isolation may be traumatous for the patient.

4 *https://www.lungenliga.ch/kompetenzzentrum-tuberkulose/dienstleistungen*

8 Notification system, surveillance and treatment

8 Notification system, surveillance and treatment

8.1 Notification system and surveillance

Notification of any case of tuberculosis is mandatory (Epidemic Act and its regulations). This generally applies to cases diagnosed as tuberculosis disease who started treatment with at least three drugs. Treatments for 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 week.[5]
- 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 should forward a copy to the cantonal services specialized in tuberculosis.

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 services specialized in tuberculosis 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 Cantonal Medical Officers of many cantons mandate their cantonal services specialized in tuberculosis 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 cantonal services specialized in tuberculosis, helps to have more complete information on treatment start and outcomes.

5 *https://www.lungenliga.ch/kompetenzzentrum-tuberkulose/formulare-vorlagen*

9 Vaccination with BCG

9 Vaccination with BCG

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

The 2024 Swiss Vaccination Schedule[6], issued by the Federal Office of Public Health and the Federal Commission for Immunizations (EKIF/CFV), states:

"BCG vaccination is only recommended for newborns and infants below the age of 12 months (risk of developing disseminated tuberculosis) with an increased risk of exposure. These are infants who will live permanently in a country with a high incidence of tuberculosis. A threshold incidence of > 50 cases per 100'000 population per year is recommended to define a high-incidence country. As long as the vaccine is not available in Switzerland, it is recommended that the vaccination is carried out in the country of destination. 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 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 decades. Many have discontinued BCG, sometimes with the exception of some population segments[7].

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 or local lesions, abscess, adenitis), the choice has increasingly been in favour of improving contact tracing, diagnosis and treatment.

Treatment of BCG complications require expert advice from a pediatric infectious disease specialist. 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 disseminated disease.

6 *https://www.bag.admin.ch/plandevaccination*
7 *https://www.bcgatlas.org*

10 Tuberculosis screening in asylum seekers

10 Tuberculosis screening in asylum seekers

10.1. Introduction

Tuberculosis screening in asylum seekers and migrants is a major challenge and there is no universally accepted approach. Screening policies are influenced by numerous factors, including historical aspects, and hence, differ between countries. Each approach has its advantages and disadvantages. Factors to be considered include local tuberculosis epidemiology, health system and overall health priorities [18]. Switzerland has a low incidence of tuberculosis (2022: 4.16/100,000) and the vast majority of tuberculosis cases are reported among persons of foreign origin (see chapter 2). In 2022, 73% of the reported cases were of non-Swiss origin.
Screening needs to be cost-effective. For instance, chest radiography was used for most of the asylum seekers (except for children aged <15 years and pregnant women) until the end of 2005 as the basic method for screening for pulmonary tuberculosis in Switzerland. Because the cost-effectiveness was not optimal, the routine chest radiography was replaced by an interview-based screening system in 2006 which offers advantages in terms of cost and the burden of medical procedures on the population being examined. With the revision of the Epidemics Act and the corresponding Epidemics Ordinance in 2016, the border sanitary service in the asylum centres has been reorganized. Although the interview-based screening system is no longer mandatory, it is still offered to asylum seekers at arrival and frequently used.

10.2. Time frames of tuberculosis screening in asylum seekers

As soon as an asylum seeker has registered at a federal asylum centre with processing facilities, a decision is made as to whether their asylum procedure will be conducted there or at another federal centre[8]. Depending on the situation, asylum seekers may therefore be accommodated in several federal asylum centres before being expelled or transferred to cantonal accommodation. The maximum length of stay of an asylum seeker in the federal asylum centres is 140 days and access to healthcare must always be ensured by the operator of the accommodation. It is recommended that the interview-based tuberculosis screening is conducted within 72 hours after arrival of a new person at a federal asylum centre.

10.3. Objectives

The objectives are the adequate control of tuberculosis cases, of its transmission and of its medical and social consequences (see chapter 2). As different countries have different health systems, the accommodation of asylum seekers is organized differently and they differ in other local circumstances. Therefore, screening methods from other countries cannot be uncritically extrapolated to Switzerland. Moreover, the differences between the federal asylum centres and the subsequent accommodation (cantonal asylum centre or other facilities) must be taken into account. This chapter provides recommendations to address the majority of challenges. However, whether or not these recommendations are sufficient for a single case must be determined by the local team responsible for conducting the interview and physical examination. In addition, the recommendations have to be put into the infrastructural context and the available staff in each asylum centre. An important objective remains unchanged, namely, the one of minimizing the number of missed pulmonary tuberculosis cases.

10.4. Screening at federal asylum centers

10.4.1. Comprehensive health questionnaire

The most important goal is the detection and treatment of pulmonary tuberculosis cases without delay to reduce the period of infectiousness and therefore to limit onward transmission.
In federal asylum centres, an interview-based screening system based on geographic origin, history and symptoms was implemented in 2006 [19]. Today, systematic screening questions for tuberculosis are

integrated into a comprehensive health questionnaire (mmcheck.ch). It is used for most asylum seekers in the context of a voluntary consultation carried out by a health care professional. Although the questionnaire is not mandatory, it is frequently used. It is estimated that approximately 75% of asylum seekers participated in 2022. This falls just short of the target value of 80% and federal asylum centres below this value should make efforts to ensure that more asylum seekers take up the offer.
The interview-based screening system identifies persons with prevalent symptomatic tuberculosis at the time of requesting asylum, but cases may be detected even before screening when arriving overtly ill at the reception centres.

10.4.2. Limitations of the health questionnaire

It is known that the questionnaire has its limitations and it may miss cases of pulmonary tuberculosis, in particular in individuals with no or few symptoms or in individuals that are not willing to admit symptoms. The yield of catching pulmonary tuberculosis at arrival may be improved by the following approaches:

- All care and nursing staff at the asylum centre should complete the E-Learning courses provided by the Swiss Lung Association, which include a tuberculosis module[9]. This aids to increase the awareness of tuberculosis symptoms among personnel.

- Cultural differences and possible misunderstanding of symptom expression in the interview must be addressed. For example, migrants may not understand the difference between cough and sputum. In addition, cough or sputum is regarded as impolite behavior or associated with stigma in certain regions of the world, and individuals may be reluctant to admit these symptoms.

- A clinical examination by experienced staff following the interview can be performed in order to identify signs and symptoms for tuberculosis that would have been missed by the questionnaire only (e.g., wasting syndrome). Therefore, it is recommended to obtain consent for both the comprehensive health questionnaire and the clinical examination prior to starting the interview. It is reasonable that pulmonary tuberculosis is less frequently missed when both investigations are performed than when only conducting the interview. However, even with both methods, there is not a 100% certainty (and no method has a 100% sensitivity) that no single case of pulmonary tuberculosis is missed. Therefore, continuous vigilance and teaching of asylum seekers on tuberculosis symptoms are necessary. In addition, the threshold for performing a chest radiograph should be low if there are clinical or patient history hints suggestive for pulmonary tuberculosis, even when the responses in the questionnaire were unremarkable.

10.4.3. Reactivation of tuberculosis infection to pulmonary disease

The majority of pulmonary tuberculosis cases occurring in migrants and asylum seekers are discovered in the months or years following entry into the country. The later appearance of tuberculosis can be attributed to different possible reasons: reactivation of an 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. Thus, it is possible that in some cases, pulmonary tuberculosis was yet not apparent at arrival but the infection reactivated at the federal asylum centres during the waiting time before being expelled or transferred to cantonal accommodation. Therefore, continuous vigilance and high suspicion remains of critical importance.

10.4.4. Examinations in persons with presumed tuberculosis

If symptoms are identified, a chest radiograph needs to be taken swiftly (if possible directly after the interview-based screening), followed by a microbiological examination of a respiratory specimen in the case of any radiological abnormality compatible with tuberculosis. To avoid delays in diagnosis, every asylum centre should ensure fast and easy access to radiographs in the event of presumed tuberculosis. Moreover, in cases where radiograph cannot be analyzed immediately after being taken, it is advisable to take a sputum sample at the same time as the radiograph in persons with

high suspicion for tuberculosis (e.g.; several symptoms consistent with tuberculosis). This may avoid delays in diagnosis.

10.4.5. Interferon-Gamma Release Assays (IGRA)

Systematic screening for infection is not recommended in federal asylum centres (see chapter below). The main objective at the federal asylum centre is to not miss pulmonary tuberculosis. The treatment of *M. tuberculosis* infection is not a priority at the federal asylum centre. Treatment is only meaningful when the compliance is assured and the treated individual understands the rationale and the reasoning of the approach. Both factors are unlikely present in this scenario.

10.5. Screening beyond the federal asylum centers (cantonal asylum centre or other facilities)

10.5.1. Pulmonary tuberculosis should not be missed

As mentioned above, health care professionals should be aware of the risk for reactivation of *M. tuberculosis* infection as the majority of the tuberculosis cases in the European Union (EU) and European Economic Area (EEA) are due to reactivation of tuberculosis infection (acquired in the country of origin or newly acquired e.g. during travel) particularly within the first few years of arrival. In low-incidence countries the number of incident tuberculosis cases (developing after arrival in the country of settlement) is up to 10 times higher than the number of prevalent tuberculosis cases (detected at or immediately after arrival). Reactivation rate or rapid progression are particularly high in young children and young adults between 15 and 24 years.
Since reactivation can also occur between the transfers to other centres (e.g. another federal asylum centre or cantonal centre) or there may be a further progression from a stage that had been missed at initial screening, the measures should be implemented to ensure that no pulmonary tuberculosis cases are missed. Therefore, new symptoms or findings suggestive for pulmonary disease have to be assessed without delay, even if a prior examination in another center was considered normal.

10.5.2. Screening for tuberculosis infection, IGRA

In order to prevent the development of tuberculosis among migrants, some European countries have implemented a policy of screening for tuberculosis infection soon after arrival with the provision of preventive treatment for individuals found to be infected. Individual screening for tuberculosis infection is not universally recommended but may be considered for a highly selected population in specific settings. For example, screening for tuberculosis infection is only reasonable if the treatment can be initiated and completed in infected patients. Hence, adherence to treatment must be assured. Migrants have been reported to have lower treatment completion rates than other groups due to lack of motivation, competing interests, and language barriers. In a very selective group with long-term monitoring in a stable housing condition, it seems feasible to ascertain a high adherence using a short course of treatment. Therefore, screening for tuberculosis infection should only be considered in settings with stable environment, highly probable adherence to treatment and well-informed asylum seekers who understand the benefits and risks of treatment. This setting is not present at federal asylum centres but may be present at a later stage in cantonal housing centers. For cost-effectiveness reasons, screening is usually restricted to young migrants originating from regions of the world with very high incidence rate of tuberculosis (for instance >100/100‘000/year). Although the incidence in the country of origin can be a useful index, health care professionals should be aware that routes of migration are associated with higher risk of transmission (e. g. residing in overcrowded accommodations or detention centers or travelling in crowded vehicles) and therefore asylum seekers can have an increased tuberculosis risk that is more affected by their migration journey than by the incidence in their country of origin. In addition to the incidence rate in the origin of country or travel in congregate settings, history of tuberculosis contact (e. g. recent exposure in a federal asylum centre (see chapter 5.2)), imprisonment and comorbidities or other risk factors increasing the risk of development of

tuberculosis (HIV infection, immune deficiency, young age) may be considered when selecting the patients to be screened. As the costs of screening for tuberculosis infection are not covered by health insurance, prior consultation with the cantonal authorities is necessary to ensure that the costs are covered.

Completion of tuberculosis treatment

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) in a timely fashion[10].

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[11]. 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 center in the country of destination in order to facilitate transmission of medical information and to avoid treatment interruption. Medical counseling for persons returning home (Return Counseling Services) might be useful in such situations[12].

8 *https://www.sem.admin.ch/sem/en/home/asyl/asylverfahren/asylregionen-baz/verteilung-regionen.html*

9 *Übertragbare Krankheiten im Asylbereich (https://communicablediseases.asyl.lungenliga.ch)*

10 *https://www.sem.admin.ch/sem/de/home/publiservice/service/formulare.html*

11 *https://www.bag.admin.ch/dam/bag/de/dokumente/mt/infektionskrankheiten/tuberkulose/tuberkulose-merkblatt-aerzte-sem.pdf.download.pdf/tuberkulose-merkblatt-aerzte-sem-de.pdf*

12 *https://www.sem.admin.ch/sem/de/home/international-rueckkehr/rueckkehrhilfe/individuelle-rkh.html*

11 Financial issues and legal background

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 an 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 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 for adults, depending on the insurance scheme a person chose, while for children the deductible is CHF 0). 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. OPA (Ordinance on the Prevention of Accidents and Occupational Diseases) [23].

According to Article 9 paragraph 1 of the Accident Insurance Act (UVG), occupational diseases are diseases caused exclusively or predominantly by harmful substances or specific work in the course of occupational activity. Work-related diseases within the meaning of this article of the law are infectious diseases caused by work in hospitals, laboratories, experimental stations and the like.

Occupational tuberculosis diseases and tuberculosis infection (TBI) in health care facilities are recognised as "occupational diseases" in accordance with Art. 9 para. 1 of the Accident Insurance Act and Annex 1 of the Accident Insurance Ordinance (UVV). Usually, this covers treatment following conversion of a test for a tuberculosis infection from negative to positive.

However, workers outside the health sector, e.g. in immigration services, correctional services or social services, can also contract a tuberculosis disease or tuberculosis infection. In the case of these employees, an "occupational disease" is recognised if the criteria according to Art. 9.2 UVG are fulfilled. According to this relevant regulation, it must be proven that the illness is "exclusively or very predominantly" caused

by the occupational activity. The decision on the recognition of a claim always lies with the insurance company. While environments or workplaces with typically increased risk of exposure to *M. tuberculosis* are usually covered by this regulation, other suspected cases of occupationally acquired TBI or tuberculosis disease, where there is not the classic occupation-specific increased risk of exposure to tuberculosis, require more compelling arguments for recognition as an "occupational disease".

Every suspected case of tuberculosis infection or tuberculosis disease **in an occupational context** should be reported individually to the accident insurance. The accident insurance assesses each individual case and decides whether it should be recognised as an "occupational disease" (be it tuberculosis or TBI). Any costs for further clarifications requested by the accident insurance prior to a decision to recognise the claim shall be borne by the accident insurance if there is a well-founded suspicion of an occupational disease. If a tuberculosis disease or infection (IGRA test conversion from negative to positive) is recognised as an occupational disease, the costs of the investigations and treatment shall be borne by the accident insurance. In all other respects, the same benefits shall continue to be paid as in the case of an accident.

For clarifications of contact persons of cases of tuberculosis that have been assessed as contagious, an agreement should be made with the cantonal medical office.

More detailed information about this topic can be found in the Suva brochure[13] (available in German, French and Italian).

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 infection to M. tuberculosis 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 Persons with irregular residence status

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 (persons with irregular residence status) 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 persons with irregular residence status.[14]

11.6.3 Directly observed therapy and video-observed therapy

Under certain circumstances, directly observed therapy (DOT) is indicated (see chapter 7.4.). The Cantonal Medical Officer can order the use of DOT. For every DOT it must be assured that the patient has been given all the needed information by excellent communication and if necessary, with the assistance of a translator. In most cantons, a healthcare worker of the cantonal services specialized in tuberculosis will organize DOT. However, the administration per se of the medication may be delegated to another body (for example, a pharmacy, a cantonal center for asylum seekers, the social services, the treating physician, home nurses). Pharmacies may be much more convenient for patients requiring DOT than tuberculosis treatment centers 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. As an alternative to DOT, video observed therapy (VOT) has been tested successfully in several countries and is presently being evaluated in Switzerland. Costs involved are related to time spent by the nurses to follow on the dedicated web platform the videos sent by the patients to monitor their treatment.

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, in accordance with the applicable tariff. 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 (or 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). 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).

13 *https://www.suva.ch/de-ch/download/dokument/tuberkulose-am-arbeitsplatz---gefaehrdung-und-praevention--2869-35.D*

14 *https://www.sante-sans-papiers.ch*

12 Information and useful addresses

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12.1 Brochures and other printed matter

All available publications can be found on the website of the Competence Centre for Tuberculosis: www.lungenliga.ch/kompetenzzentrum-tuberkulose

For healthcare professionals

- Tuberculosis in Switzerland – Guidance for healthcare professionals, 2024 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)

For the general public

- Information brochure on tuberculosis (F/G/I) (also available electronically)
- Information sheet on tuberculosis in 20 languages, entitled "Frequently Asked Questions about tuberculosis and their answers" (only digital)

12.2 Online resources

On www.lungenliga.ch/kompetenzzentrum-tuberkulose you can find the following continuously updated information

- 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
- Form for international contact tracing
- Unit for health consultations and for providing assistance to illegal immigrants
- Laboratories that carry out IGRA and diagnostic TB tests
- Further education courses for health care professionals
- Free eLearning about the disease tuberculosis
- Recent national and international statistics

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 and public health aspects. 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

13 Bibliography

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Specialized services for tuberculosis

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

Basel-Stadt
Tel. 061 267 27 96
epi-bs@hin.ch
www.gesundheitsdienste.bs.ch

Bern
Tel. 079 514 91 09
tb.info@insel.ch
www.insel.ch

Fribourg
Tél. 026 426 02 70
lpf-responsables@liguessantefr.ch
www.liguepulmonaire-fr.ch

Genève
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tuberculose@lpge.ch
www.hug-ge.ch/pneumologie/tuberculose

Graubünden
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Jura
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