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Chapter 9: Pediatric tuberculosis

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KEY POINTS

- In Canada, pediatric tuberculosis (TB) is largely a disease of Canadian-born Indigenous children, foreign-born children and children of foreign-born parents.
- TB disease in young children (typically <5 years of age) is a sentinel event that should prompt a search for an infectious source case.
- Children under the age of 5 years are at high risk of progression to severe forms of TB disease after TB infection.
- Multiple sputum samples should be collected, as yield of sputum Acid-Fast Bacilli (AFB) smear microscopy and culture in children <10 years old is low.
- In children who are clinically stable who are unable to produce an expectorated sputum specimen, gastric aspirates or induced sputa should be collected before treatment for TB disease is initiated. In critically ill children, where the index of suspicion is high for TB disease, therapy should be initiated rapidly and collection of appropriate specimens should be completed as soon as possible.
- TB disease in children is most often a clinical diagnosis that is made using a combination of: (1) a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA); (2) contact with an infectious source case; (3) abnormal chest x-ray with typical findings of TB disease; and (4) compatible clinical signs or symptoms.
- A negative TST or IGRA is expected in up to 30% of children with TB disease and should not be used to exclude this diagnosis.
- Severe adverse events due to TB medications are rare in children. The onset of medication toxicity is vague in infants, toddlers and pre-teens and caregivers should be counseled about the risks of therapy and signs/symptoms for concerning side effects, and provided with support(s) to manage these.
- Targeted testing for TB infection is recommended based on likelihood of TB infection and progression to disease.
- For children less than 2 years, the recommended regimen for TB preventive therapy is 4 months of daily rifampin. Nine months of daily isoniazid is an acceptable alternative. In certain situations, 9 months of observed, twice-weekly isoniazid may be more appropriate (ie, issues of compliance, patient preference, directly observed therapy (DOT) worker availability etc).
- For children more than 2 years, the recommended regimens for TB preventive therapy are 4 months of daily rifampin or 12 weekly doses of combination isoniazid and rifapentine. Nine months of daily isoniazid is an acceptable alternative.
- For treatment of TB disease in children, daily therapy is strongly recommended over intermittent regimens.
- Ethambutol is now routinely used as part of initial empiric therapy of TB disease (pending sensitivities) in infants and children, unless contraindicated or if the source case if known to have fully drug-susceptible tuberculosis.

1. Introduction

In 2019, there were an estimated 1.2 million cases of childhood TB (defined as TB disease in those younger than 15 years old) around the globe, and TB remains a top-10 cause of childhood mortality.[1] There remains a need for better resources, improved diagnostic tools, new drugs and effective vaccines. While more than 60% of all Canadian TB disease occurs among the foreign-born population, more than half of childhood TB in Canada occurs in Canadian-born Indigenous children (Table 1), although they make up less than 10% of the Canadian pediatric population.[2,3] Among Indigenous children, the highest rates of TB are in the Inuit.[2] Foreign-born children and the children of foreign-born parents account for the rest of pediatric cases (see Chapter 1: Epidemiology of Tuberculosis in Canada).[2,4] A pediatric TB assessment should take into account the global and local epidemiology and the possibility of drug resistance, especially in foreign-born children and those who have traveled to TB endemic countries.

TB disease in children differs from that in adults in several ways: (1) diagnosis in children <10 years old may be difficult because signs and symptoms are often nonspecific; (2) TB disease is often paucibacillary; (3) TB disease in children <10 years old is often a sentinel event, indicating recent transmission; if an index case has not been identified, source case

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Table 1. Childhood TB cases in Canada, 2019 by population group.

Population group	AGE (years) <1	1-4	5-14	Total <15	% of all childhood cases
Inuit	4	9	22	35	31
First Nations	2	14	13	29	25
Metis	0	4	1	5	4
Total Indigenous	6	27	36	69	61
Canadian-born non-Indigenous	0	9	8	17	15
Total Canadian-born	7	37	45	89	78
Foreign-born	0	3	15	18	16
Unknown origin	1	2	4	7	6
Total cases	14	42	64	114	100

investigation is recommended for children <5 years old; (4) young children, especially infants, are at high risk of progressing from TB infection to disease, and predisposed to more severe forms of disease;[5,6] and (5) treatment may be more challenging due to issues with pill swallowing, drug palatability and dose adjustments for weight gain.

This chapter will cover the most important aspects of pediatric TB and highlight the differences in diagnosis and management in children compared with adults. Readers are encouraged to refer to other chapters for more detailed information.

2. Pathogenesis and definitions

Details of the pathogenesis of TB are outlined in Chapter 2: Transmission and Pathogenesis of Tuberculosis. Children inhale Mycobacterium tuberculosis (*M. tuberculosis)* from adults or adolescents with infectious pulmonary or laryngeal TB that has been aerosolized. Rarely, children have cough or multibacillary disease, and are infectious.[7,8] Primary infection generally consists of a parenchymal focus with regional intrathoracic lymph node enlargement. The parenchymal lesion may enlarge and caseate or nodes may enlarge and compress or erode through a bronchus, causing wheezing, segmental pneumonia or atelectasis. The primary infection is usually accompanied by an occult, subclinical bacteremia that seeds distant sites. This may rapidly lead to severe forms of disease, including miliary and central nervous system (CNS) TB. In general, the risk of progression to TB disease and of severe forms of TB disease after infection is highest in children younger than 5 years old (Table 2).[6] However, in most cases, the primary focus heals and the bacteria may survive in a state of immune containment that is referred to as TB infection.

Table 2. Average age-specific risk for disease development after untreated primary infection.

Age at primary infection	Manifestations of disease	Risk of disease (%)
<12 months	No disease	50
	Pulmonary disease	30-40
	TB meningitis or miliary disease	10-20
12-23 months	No disease	70-80
	Pulmonary disease	10-20
	TB meningitis or miliary disease	2-5
2-4 years	No disease	95
	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
5-10 years	No disease	98
	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
>10 years	No disease	80-90
	Pulmonary disease	10-20
	TB meningitis or miliary disease	<0.5

Source: Adapted from Marais et al.[9]

3. Clinical presentation of TB disease

Table 3 shows the sites of childhood TB as reported to the Public Health Agency of Canada (PHAC) for 2018-2020. In Canada, many children with TB disease are asymptomatic at presentation. They are often identified through active case finding as contacts of patients with infectious TB and are found to have abnormal chest x-rays. This is especially true of children under 5 years old.[10]

Children may also present with symptoms or signs suggestive of disease.[5] In high-burden countries, persistent cough, failure to thrive, unexplained prolonged fever or lethargy have all been identified as symptoms of concern. Many clinical diagnostic scoring systems have been developed, but they are not well validated and lack specificity.[11] In young infants, clinical features may be nonspecific: weight loss, hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, lethargy and/or irritability.[12,13] Poorly responding pneumonia at any age should prompt consideration of TB.[14] Clinical case definitions of childhood intrathoracic TB are intended for use in clinical research to evaluate diagnostic assays, and not for individual patient diagnosis or treatment decisions.[15] Older children and adolescents are more likely to present with adult-type disease and often endorse the classic triad of fever, night sweats and weight loss.[16] Those with pulmonary disease are also more likely to present with respiratory symptoms (productive cough and sometimes hemoptysis). Physical findings are often minimal relative to their chest x-ray abnormalities, which include lung infiltrates, typically but not always in the upper zone(s), sometimes with cavities.[17,18] TB disease in adolescents in Canada and other high-income countries is often extra-pulmonary.[10] Presentation may be protean: TB may mimic inflammatory bowel disease, brain or bone tumors, or involve almost any system in the body.[19] Delay in diagnosis of adolescents is common and may reflect a lack of suspicion by clinicians.[19] Failure to send sputa for mycobacterial smear and culture in adolescents with a productive cough and epidemiologic risk factors for TB contributes to this delay.

Table 3. Childhood TB by site of disease for the combined years 2018 and 2019.

Age group (yrs)	Pulmonary/ Intrathoracic (n)[a]	Extrathoracic (n)	Extrathoracic site		
			Peripheral lymph node (n)	CNS (n)	Bone and joint (n)
<1	14	1	0	0	1
1-4	81	3	3	0	0
5-14	91	21	8	4	3
All <15	186	25	11	4	4

Abbreviations: TB, tuberculosis; n, number.
[a]Includes pleural TB and intrathoracic lymphadenopathy.
Source: Public Health Agency of Canada.

Any extra-pulmonary site may be involved, most commonly extrathoracic lymph nodes. Mycobacterial cervical lymphadenitis in children is most commonly due to non-tuberculous mycobacteria. However, lymph node disease due to *M. tuberculosis* should be strongly considered in those with risk factors. TB lymphadenitis is more common in older children and adolescents (Table 3).[20] Miliary/disseminated disease and CNS disease, the most life-threatening forms of TB, are more likely to occur in children <2 years old, children who were not identified as contacts and the immunocompromised. In Canada, CNS TB has occurred more often in children ≥5 years old (Table 3), possibly reflecting the influence of contact tracing and contact management.

Epidemiologic risk factors and/or a clinical picture compatible with TB should prompt appropriate testing for TB.

4. Diagnosis of TB disease

Isolation of *M. tuberculosis* from culture of a clinical specimen confirms TB disease. In most children, microbiologic confirmation is difficult because they may be too young to spontaneously produce sputum or have paucibacillary disease. In Canada, diagnosis of TB disease in children is often based on a clinical case definition, which usually relies on the triad of (1) a positive TST or IGRA; (2) an abnormal chest x-ray and/or physical examination; and (3) discovery of a link to a known or suspected case of infectious TB. Some of these cases are also symptomatic.

4.1. Sample collection for TB disease

Pediatric TB disease, when compared with adult TB disease, is less likely to be microbiologically confirmed, due to its paucibacillary nature (less than 40% are culture positive); therefore, a negative microbiological test result should not be used to exclude TB disease.[21] Mycobacterial confirmation of the diagnosis should be attempted by collecting multiple specimens. This is particularly important when (1) an isolate from a source case is not available or there are multiple possible sources; (2) the source case has drug-resistant TB; (3) the child is immunocompromised; or (4) the child has extra-pulmonary disease.[22,23] In cases where pulmonary disease is minimal (ie, hilar adenopathy only), all other diagnoses have been excluded and only one drug-sensitive potential source case has been identified, then cultures are sometimes omitted and the source case sensitivities are used to guide management.

Gastric aspiration has been the collection procedure of choice in young children who are unable to produce sputum for the investigation of pulmonary TB. Some of the drawbacks of this technique are that it is more invasive, may be less tolerated by children and caregivers, may require hospitalization and has specific laboratory handling requirements.[24,25] Details about gastric aspiration, including links to online resources with videos, are available in Appendix 1.[26]

Alternate ways to collect sputum have been developed, including sputum induction and nasopharyngeal aspiration. A systematic review on alternative sputum collection methods for pediatric pulmonary TB found significant heterogeneity between studies and differences depending on the pretest probability of TB disease.[21] The study found that samples obtained from gastric aspiration or sputum induction had low positivity for both Gene Xpert and mycobacterial culture. The study showed a benefit in collecting at least two sputum specimens using either the same sample collection method or a different collection method. Regardless of the technique used, positive smear results do not differentiate between *M. tuberculosis* complex and non-tuberculous mycobacteria, which can cause false positive results.[23]

Sputum induction has been performed safely in infants as young as one month of age. Details about the procedure and a link to a video are available in Appendix 1. The advantages of sputum induction over gastric aspiration include a shorter period of fasting, no killing of the organisms by gastric acid and higher acceptability to staff and parents.[27] Attention to safety issues, including pretreatment with a bronchodilator and infection prevention control procedures to prevent nosocomial transmission, should be in place (see Chapter 14: Prevention and Control of Tuberculosis Transmission in Healthcare Settings).

The diagnostic yield from bronchoscopy is no higher than that of gastric aspiration or sputum induction.[28] Bronchoscopy may be useful in detecting tracheobronchial obstruction or for the exploration of alternative diagnoses.[29]

Other specimens can be collected if clinically indicated and include: bronchial washings, pleural fluid, cerebrospinal fluid (CSF), urine, other body fluids or tissue biopsy specimens. Fine-needle aspiration biopsy has been useful in children suspected of TB who present with palpable enlarged cervical nodes.[30,31] However, surgical excision (removal) has the advantage of improving clinical outcomes, as lymph nodes may continue to enlarge and drain despite therapy to which the organism is susceptible.[32] A lumbar puncture should be performed in cases of suspected congenital or neonatal TB and in infants with disseminated disease.[33,34]

Given the paucibacillary nature of childhood TB, the use of novel, noninvasive tests is being evaluated by some

laboratories, both in Canada and internationally. As sputum is swallowed, particularly during sleep in young children, *M. tuberculosis* has been shown to be detectable in the stool.[35,36] Systematic reviews evaluating stool Xpert (PCR) vs the microbiological reference standard have shown that the sensitivity ranges from 57-67% with a 98-99% specificity.[37,38] Stool has specific processing requirements and commercial stool processing kits and methods have been developed.

4.2. Other microbiological testing for TB disease

In addition to mycobacterial culture, nucleic acid amplification tests are useful in confirming the diagnosis of TB disease in children. A Cochrane review of Xpert MTB/RIF for TB disease in children demonstrated a pooled sensitivity of 46-73% and a specificity of 98-99% for sputum, nasopharyngeal aspirates, gastric aspirates and stool as compared with mycobacterial culture in pulmonary TB. The same Cochrane review evaluated a small number of studies employing Xpert Ultra on sputum and reported a pooled sensitivity of 73% and specificity of 98% as compared with mycobacterial culture.[39] The test characteristics of Xpert in CSF were similar at 54% sensitivity and 94% specificity, whereas the sensitivity increased to 90% in lymph node disease. Xpert Ultra assay on stool is being evaluated for diagnosing pulmonary TB in children and it appears promising in increasing the sensitivity, albeit at a cost of lower specificity.[40]

Recommendations

- **We strongly recommend that TB disease not be excluded in a child <10 years old with compatible clinical, epidemiological and/or radiographic features because of negative AFB cultures** (*good evidence*).
- **We strongly recommend collecting three sputum samples for microbiological testing because they have a higher yield than a single sample** (*good evidence*).
- **We strongly recommend sputum induction as an acceptable alternative to gastric aspirates in children <5 years old** (*good evidence*).
- **We conditionally recommend that pediatric body fluid samples be submitted only for AFB culture when total sample volumes are ≤1 mL; if sample volumes are >1 ml, then both AFB culture and nucleic acid amplification tests should be requested to expedite diagnosis** (*poor evidence*).

4.3. Diagnostic imaging

A chest x-ray is required for the initial evaluation of children with suspected intrathoracic TB.[41] In addition to an anterior-posterior view, a lateral radiograph is recommended to assess for hilar and mediastinal lymphadenopathy, the most frequent radiologic manifestations of intrathoracic TB in children.[42,43] Good-quality chest x-rays in children are essential because the common radiologic manifestations are more subtle than in adult-type disease and often located proximally to other structures in the mediastinum. This requires optimal positioning and cooperation of the child to avoid rotational and motion artifacts. Repeating chest x-rays with better positioning and inspiration may clarify questionable abnormalities and are always encouraged if the initial images are of suboptimal quality. Interpretation by a radiologist with experience in pediatric TB is important; there is a high level of inter-reader and intra-reader variability for detecting lymphadenopathy.[44,45] Computer-aided detection to improve the sensitivity of radiographs is an area of active research but not available in most settings at this time.[46,47]

Children are more susceptible to the long-term effects of the increased radiation exposure from computed tomography (CT) for intrathoracic disease.[48–51] The risk/benefits of CT scans and their impact on patient management should be assessed on a case-by-case basis. In general, we would only consider a chest CT in a child in very limited circumstances and only in children who have an abnormal initial chest x-ray. These may include diagnostic uncertainty in an ill child, a questionable radiograph in a child in contact with drug-resistant TB and planning for future diagnostic procedures. In adolescents with pulmonary disease, rapidly obtaining sputum for AFB smear and culture may reduce unnecessary CTs.[49] For extra-thoracic TB diagnosis, imaging should be performed according to clinical signs and symptoms, where the optimal modality is site specific (see Chapter 7: Extra-pulmonary Tuberculosis). However, for young children, considerations include the need for sedation, the ability of the child to cooperate and the risks of additional radiation exposure. For abdominal and lymph node TB, ultrasound is effective and as sensitive as CT.[52,53] CT may be more helpful in differentiating abdominal TB from other noninfectious pathologies.[54] For bone and joint TB, magnetic resonance imaging (MRI) is helpful in distinguishing osteoarticular from soft-tissue lesions. CNS TB is a significant concern in young children, who frequently present with hydrocephalus. Contrast enhancement is essential in identifying leptomeningeal enhancement and MRI is better at identifying both leptomeningeal enhancement and characteristic parenchymal disease (tuberculoma) than CT.[55,56] Finally, newer modalities such as positron emission tomography (PET)/CT scans may have a role in select cases of extra-pulmonary TB where available. They have the advantage of being quick (without need for heavy sedation) and can identify multiple sites of disease.[57]

Good practice statement

- **Good quality anterior-posterior and lateral chest x-rays are required for the initial evaluation of TB disease in children. Computed tomography is not routinely recommended.**

4.4. Tests for TB infection

In children, the TST and/or IGRA is an important part of the clinical case definition of TB disease, especially if there is a newly positive TST or IGRA. It should be noted that

a negative TST or IGRA does not exclude TB disease and may occur in up to 30% of culture-confirmed cases.[58] A positive TST or IGRA does not distinguish between TB infection and TB disease. Please see section on testing for infection and Chapter 4: Diagnosis of Tuberculosis Infection for details about TST and IGRA.

5. Management of TB disease

A diagnosis of TB disease in a young child, typically <5 years of age, should be considered a sentinel event and prompt the search for the source case, most likely an adult or adolescent in close contact with the child. Close caregivers should be promptly evaluated to rule out TB disease. To minimize nosocomial exposures upon admission of a child with suspected TB to a healthcare facility, parents/caregivers rooming in with the child should be assessed for TB symptoms and have a chest x-ray. Airborne precautions should be used until infectious TB is ruled out in both the patient and parents/caregivers (see Chapter 14: Prevention and Control of Tuberculosis Transmission in Healthcare Settings).

The principles and phases (intensive and continuation) of TB treatment are discussed in Chapter 5: Treatment of Tuberculosis Disease. A team approach is helpful in evaluating and treating children with TB disease. The team may include physicians, nurse practitioners, public health nurses, a social worker and an interpreter. Whenever possible, the team should include or involve a physician experienced with treating TB disease in children. Treatment is aimed at reducing morbidity and mortality, preventing acquired resistance and providing a lasting cure. Interruption of transmission is also important in adolescent patients with pulmonary TB who attend congregate settings, including schools. Prior to commencing therapy for TB disease, a baseline alanine aminotransferase and bilirubin level should be obtained. Human immunodeficiency virus (HIV) serology is recommended as standard of care for all children and adolescents being treated for TB disease, as TB is an opportunistic infection and the duration of treatment will be influenced by this result.

The most important element of the treatment of TB is the actual ingestion of the medication by the child.[24] Many children have difficulty with the pill burden and palatability. Child-friendly formulations in tablet form are available in many countries, avoiding the problems of compounding, but not in Canada.[59] In addition, some of these formulations are in fixed-dose combinations that are not recommended in Canada. If these fixed-dose combinations become available and are used (eg, for palatability), it should be with guidance from a pediatric TB specialist.

5.1. Individual drugs

The drugs used in the treatment of pediatric TB, including their doses and side effects, are summarized in Table 4. Only isoniazid (INH) is available as a commercial suspension. However, all others may be compounded into suspensions using published procedures (Table 4). Given the difficulties with taste (ethambutol is particularly unpalatable) and ability to swallow pills, administration of these medications to very young children may require multiple tries of different formulations (eg, crushed pills in different foods, suspensions, etc). More research is needed in this area for children, including the pharmacokinetics of newer TB drugs, the impact of mixing them with food and the stability of suspensions.[60]

In children under the age of 10 years, or weighing less than 30 kg, the recommended dose of INH is 10-15 mg/kg/day (maximum 300 mg).[23] Administration is affected by food and INH is better absorbed on an empty stomach. Fat and sugars reduce its absorption.[61] A sorbitol-based suspension avoids this problem but may cause diarrhea, especially in children weighing more than 5 kg.[62] Crushed pills are ideally mixed with water but few children will accept this and administration with small amounts of food/liquid is often suggested.[63] Doses of INH above 10 mg/kg/day are sometimes associated with pyridoxine deficiency. Pyridoxine supplementation should be given to children on meat and milk-deficient diets, breastfed infants, those with nutritional deficiencies, children with symptomatic HIV infection and adolescents who are pregnant or breastfeeding.[23] Breastfed infants of mothers who are taking INH with supplementary pyridoxine but who themselves are not receiving INH do not need supplementary pyridoxine.

Pyrazinamide (PZA) is an essential component of a 6-month regimen; without it, treatment should be at least 9 months. It is available as crushed tablets or compounded by some pharmacies. It frequently causes hyperuricemia, which occasionally manifests as joint pain. Of the first line TB drugs, it is the most frequently associated with drug-induced hepatotoxicity. In children, it can cause (though rarely does) intense itching, with or without a rash. Doses of 30-40mg/kg/day are recommended.[64]

Rifampin (RMP) capsules may be opened and sprinkled into food or compounded into suspension by pharmacists. The usual dose of RMP is 10-20 mg/kg/day. The suspensions may lose up to 10% of effective drug after 28 days. Higher RMP doses in children and adults is an area of active review. Doses of 30 mg/kg/day have been advised by some experts for treatment of TB meningitis.[23]

Ethambutol (EMB) is routinely used as part of initial empiric therapy of TB disease in infants and children unless otherwise contraindicated.[23] It should be discontinued once the strain is known to be fully drug-susceptible. It can cause a dose-dependent retrobulbar neuritis, which is very rare in children at usual doses but more likely to occur in patients with renal impairment. When possible, baseline ophthalmological assessment should be obtained and repeated if prolonged therapy is planned (as in drug-resistant TB cases). In accordance with World Health Organization (WHO) and American Academy of Pediatrics (AAP) guidance, 20 mg/kg/day should be used.[23] If higher doses are used, baseline vision and renal function should be tested and serially monitored.

Information on second-line drugs for MDR-TB used in pediatrics are available in Chapter 8: Drug-resistant tuberculosis and in various recent reviews.[67–70]

Table 4. Drugs used for treatment of TB in children.

	Daily dose (range)		Thrice-weekly dose[a](range)			
	By weight (mg/kg)	Max (mg)	By weight (mg/kg)	Max (mg)	Available dosage forms	Principal side effects
Isoniazid	10 (10-15)[b]	300	20-30	900	10 mg/mL suspension[c] 100 mg tablet 300 mg tablet	• Mild liver transaminase elevation • Hepatitis • Gastritis • Peripheral neuropathy • Hypersensitivity
Rifampin	Pulmonary: 15 (10-20) Meningitis/ Disseminated: 20-30	600, however if >60kg 10 mg/kg can be used up to 900 mg with close monitoring	10-20	600, however if >60kg 10 mg/kg can be used up to 900 mg with close monitoring	150 mg capsule 300 mg capsule Non-commercial suspension 25 mg/ mL[d]	• Orange discoloration of secretions • Vomiting • Hepatitis • Flu-like illness
Pyrazinamide	35 (30-40)	2000	70 (60-80)	see footnotes[e]	500 mg scored tablet Non-commercial suspension 100 mg/ mL	• Hepatotoxicity • Hyperuricemia • Arthralgia
Ethambutol	20 (15-25)	see foonotes[f]	40 (30-50)	see foonotes[g]	100 mg tablet 400 mg tablet Non-commercial suspension 50 mg/ mL	• Optic neuritis with decreased visual acuity and decreased red-green color discrimination • Gastrointestinal disturbance
Pyridoxine (Used to prevent isoniazid neuropathy: has no anti-TB activity)	1 mg/kg	25			25 mg. tablet 50 mg tablet	• Few

Table adapted from Red Book.
Abbreviations: TB, tuberculosis; INH, isoniazid; ATS, American Thoracic Society.
[a]Intermittent doses should be prescribed only when directly observed therapy is available. In general, daily therapy is definitely preferred over intermittent regimens.
[b]Hepatotoxicity is greater when INH doses are more than 10-15mg/kg daily.
[c]Only isoniazid is available as a commercial suspension in Canada.
[d]Rifampin, pyrazinamide (PZA) and ethambutol (EMB) may be compounded into suspensions using these published references (English)[65] and (French).[66]
[e]For PZA: 3000 mg according to ATS, 2000 mg according to Red Book.
[f]EMB: 1600 mg according to ATS, 2500 mg according to Red Book.
[g]For EMB: 2400 mg according to ATS, 2500 mg according to Red Book.

5.2. Initial treatment

Treatment should begin promptly when clinical, laboratory and radiographic indices support a presumptive diagnosis of TB disease. Therapy should be initiated while awaiting AFB smear, culture and susceptibility results. The susceptibility results of a known source case, if identified, may be used to guide empiric therapy, provided there is no possibility of an alternative source (eg, recent foreign travel).[62,71] Empiric therapy with INH, RMP, EMB, and PZA, unless contraindicated, is the recommended treatment of choice. If the source case is known to have fully drug-susceptible disease, EMB can be omitted. If there is a strong possibility of drug-resistant disease, expert consultation is strongly advised.

5.3. Treatment modification and duration

Once drug susceptibilities of the source case's or the child's isolate are available, treatment can be modified. In general, the higher the bacillary burden, such as in cavitary cases or smear-positive cases, the greater the need for more drugs and longer duration of therapy to prevent drug resistance and achieve relapse-free cure.

For fully susceptible intrathoracic TB, INH, RMP and PZA should be used for the first 2 months, followed by 4 months of INH and RMP. If RMP or PZA are discontinued because of side effects, longer durations of therapy are required. RMP is a cornerstone of anti-TB therapy and should not be discontinued because of minor side effects. The minimum duration of therapy is 6 months total, similar to adult TB-treatment recommendations. A recently presented, open-label trial compared a total of 4 months of therapy (2 months of INH, RMP and PZA followed by 2 months of INH and RMP) to the standard 6-month regimen for children with smear-negative, non-severe disease; further data are awaited to determine non-inferiority.[72] We continue to recommend a minimum of 6 months for treatment of childhood TB disease in Canada.

If hilar lymphadenopathy alone is present, treatment as for pulmonary TB disease should be used unless the isolate

is resistant. Please see Chapter 5: Treatment of Tuberculosis Disease for further details on dosing frequency, treatment duration(s), drug side effects and management of side effects.

5.4. Daily versus intermittent regimens

There are few randomized trials of TB treatment in children. Systematic reviews have found poorer cure rates with intermittent regimens, prompting the WHO to recommend daily therapy over intermittent regimens for treating pediatric TB disease, especially where HIV infection is common.[73–75]

5.5. Treatment adherence strategies

A decision to initiate treatment in a patient for TB disease implies a decision to monitor adherence, manage side effects, minimize risks of toxicity and ensure therapy is completed. All jurisdictions should have the capacity to provide daily, in person, comprehensive treatment support for children and adolescents with TB disease. The level and intensity of daily support should be individualized and may include DOT (see Chapter 5: Treatment of Tuberculosis Disease). If clinicians cannot provide this level of care, then they should refer the patient to programs that have this capacity. All patients should receive counseling about side effects and medication administration, and be provided with clinic contact information should side effects develop before the next scheduled appointment. Potential language and social barriers should be anticipated and appropriate accommodations be made to facilitate access to TB services. If DOT is used, it involves much more than simple observation of pills taken. Integrating a liaison public health nurse into the treatment team can facilitate medication administration, monitoring and follow-up for patients.

Although therapy generally is taken 7 days per week, it can also be taken as 5 observed doses per week. DOT is recommended for:

- disease due to suspected or proven drug-resistant strains;
- HIV co-infection or other significant immunocompromising condition;
- previous treatment failure for TB disease;
- re-treatment of disease;
- suspected nonadherence or previous nonadherence;
- reasonable doubts about the ability of the parents/guardians to supervise treatment for children;
- substance abuse in an adolescent; and
- psychopathology.[76,77]

For those not receiving daily direct observation, regular follow-up and supervision may help detect side effects, administration errors and barriers to adherence (see also Chapter 5: Treatment of Tuberculosis Disease).

5.6. Adjunctive therapy

For a more in-depth review of adjunctive therapies please see Chapter 7: Extra-pulmonary Tuberculosis. Corticosteroids are used as adjunctive therapy in select situations to prevent morbidity and mortality due to the inflammatory response. They are indicated for children with TB meningitis. In prospective, randomized trials they decreased mortality rates as well as neurologic and cognitive dysfunction.[78] Dexamethasone 0.3 mg-0.4 mg/kg/day for the first week and then tapered over six weeks or prednisone 1-2 mg/kg/day (maximum 60 mg) for three weeks tapered over the next three weeks have been used in those older than 14 years of age.[78,79] For children, the AAP and other experts have suggested that 2 mg/kg/day per day of prednisone (maximum 60 mg/day) or its equivalent for 4 to 6 weeks, and then tapered, is adequate.[23,80] Higher prednisone doses (4 mg/kg/day then tapered over 4-6 weeks) have been evaluated and can be considered if increasing intracranial pressure continues.[78] In selected cases of severe paradoxical reactions/immune reconstitution inflammatory syndrome (vision-threatening reactions), other immunomodulating, steroid-sparing agents, including infliximab, have been used.[81] Expert consultation is advised in these instances.

The use of corticosteroids in pleural TB is not supported by current evidence. Based on expert opinion, corticosteroids may have a role in endobronchial disease to relieve obstruction and atelectasis.[23] They may also be considered for children with pericardial effusions, severe miliary disease to mitigate alveolar-capillary block, and in the presence of severe immune reconstitution inflammatory syndrome reactions.[82] Corticosteroids should only be used in conjunction with effective anti-TB therapy and then tapered slowly over several weeks to avoid a rebound reaction. Generally, in non-meningitic conditions, 1-2 mg/kg/day of prednisone (maximum 60 mg/day) or its equivalent is recommended and then tapered over 6 to 8 weeks.

While several reports suggest that a high proportion of children with TB disease and infection may have low vitamin D levels, vitamin D supplementation does not clearly affect treatment outcomes or prevent TB infection or disease.[83–87] Existing recommendations regarding vitamin D supplementation for the population should be followed and additional supplementation should be considered in populations at increased risk of inadequate intake.[88–90]

5.7. Treatment of extra-pulmonary TB

Extra-pulmonary TB in children is treated with the same regimens as pulmonary disease, with the exception of CNS TB, disseminated/miliary TB and bone and joint TB, for which the recommended duration of treatment is 9 to 12 months. Please see Chapter 7: Extra-pulmonary Tuberculosis for further details.

5.8. Treatment of drug-resistant TB

Please see Chapter 8: Drug-resistant Tuberculosis. Children and adolescents at risk for drug-resistant TB include: (1) those with a history of treatment for TB disease; (2) contacts

of cases with infectious drug-resistant TB disease; (3) those born in, or who have resided in, countries with a high prevalence of drug-resistant TB; and (4) patients infected by a source case who has a positive AFB smear or culture after 2 months of appropriate therapy or is not responding to a standard treatment regimen (details of microbiologic isolation, speciation and drug-resistance testing are provided in Chapter 3: Diagnosis of Tuberculosis Disease and Drug-resistant Tuberculosis).[23] If a drug-resistant organism is isolated, obtain expert opinion from a physician experienced in the management of drug-resistant TB. There are also recent resources that discuss management of drug-resistant TB disease in children.[68–70]

5.9. TB and HIV

All children diagnosed with TB should be screened for HIV and all children diagnosed with HIV should be screened for TB at time of diagnosis of both. Children should be rescreened only if there are new exposures. Early antiretroviral therapy soon after diagnosis is now recommended for all children with HIV. The interactions between antiretroviral therapy and TB treatment are therefore important considerations in TB management.[91]

Given the numerous drug interactions between TB treatment and antiretroviral therapy, all cases of TB disease should be referred to a pediatric HIV center of expertise.[92] With the exception of CNS TB, antiretroviral therapy should ideally be initiated within 2 weeks of TB treatment being established. However, given the challenges of administering pediatric formulations of both TB drugs and antiretroviral therapy (taste and volume of multiple liquid suspensions), drug interactions and overlapping toxicities, delaying antiretroviral therapy for up to 8 weeks after TB treatment is initiated is reasonable for children without advanced HIV disease; in cases of CNS TB, a delay of at least 4 weeks is recommended for antiretroviral therapy initiation (see Chapter 10: Treatment of Active Tuberculosis in Special Populations). DOT should be used in these cases for the duration of TB treatment.[93]

Good practice statement

- **HIV-positive children who are treated for TB disease should have close adherence monitoring, (ie, directly observed therapy) for the entire duration of treatment.**

6. Diagnostic tests for TB infection

There is no confirmatory test for TB infection. Sensitivity of the TST or IGRA is measured in those with active TB disease as a proxy for TB infection. For practical purposes, a child with TB infection is considered to have no symptoms related to the infection, a positive TST or IGRA (see Chapter 4: Diagnosis of Tuberculosis Infection, Table 1, for TST interpretation guidelines), no clinical evidence of disease and a chest x-ray that is either normal or demonstrates evidence of remote infection, such as a calcified parenchymal nodule and/or a calcified intrathoracic lymph node.[94,95]

As with adults, the use of TST or IGRA needs to be interpreted in the clinical setting. This includes reason for testing, age, immunologic status, known contact with person(s) with infectious TB, place of residence, country of birth and foreign travel. The TST has been the most studied test in children that has some longitudinal data. Overall, the sensitivity of the TST or IGRA is similar, whereas the specificity of the IGRA is higher.[96] Previous recommendations were to use IGRA only in children older than 5 years due to a lack of data. More recently, data has been published in the younger pediatric population (see Table 5).

TST should be used in children under 2 years of age; however, there are increasing data showing similar sensitivity and negative predictive value of IGRAs in this age group and some experts recommend their use instead.[97] TST or IGRA can be used for children over 2 years of age. An IGRA is the preferred test in children who have received Bacille Calmette-Guérin (BCG) vaccine.

Recommendations

- **We strongly recommend that either an interferon-gamma release assay or tuberculin skin test be used to test for TB infection in children older than 5 years of age** (*good evidence*).
- **We conditionally recommend that either an interferon-gamma release assay or tuberculin skin test be used to test for TB infection in children 2-5 years of age** (*poor evidence*).
- **We conditionally recommend that an interferon-gamma release assay can be used in place of a tuberculin skin test to test for TB infection in children less than 2 years of age** (*poor evidence*).
- **We strongly recommend that an interferon-gamma release assay be used to test for TB infection in children older than 2 years of age who have received the Bacille Calmette-Guérin vaccine** (*good evidence*).

7. Targeted testing for TB infection

Resources should be devoted to the task of testing and treating children at high risk of TB infection or of progression of TB infection to TB disease, with the objective of providing health benefits to the individual child.[98] These children include: (1) contacts of a known/suspected case of TB disease; (2) children with suspected TB disease; (3) children with known risk factors for progression of TB infection to disease (see Chapter 4: Diagnosis of Tuberculosis Infection); (4) children traveling or residing for 3 months or longer in an area with a high incidence of TB, especially if the visit is anticipated to involve contact with the local population (see Chapter 13: Tuberculosis Surveillance and Tuberculosis Infection Testing and Treatment in Migrants); and (5) children who arrived in Canada from countries with a high TB incidence. The risk-benefit tradeoff of drug toxicity secondary to preventive treatment versus the development of TB disease more often favors preventive treatment in children compared to adults. In the United States, risk assessment questionnaires have been developed to identify

Table 5. IGRA in young children.

Author/ Year	Total population	Design	Tests	Duration of follow- up	Population description	Outcomes
Ho 2021[99]	2,088 children; 936 < 5 years of age	Prospective observational cohort	TST, QFT, T-SPOT in all	Cross sectional (Follow-up data for children is in Ahmed 2020, below)	US, at risk for TB	TST, QFT, T-SPOT + ve: **All** US-born: 11%, 12%, 8% Non-US born: 43%, 26%, 22% **<5 years old** US-born: 10%, 14%, 8% Non-US born 26%, 3.5%, 1.5%
Ahmed 2020[100]	3,593 children <15 years of age	Prospective cohort	TST, QFT, T-SPOT	2 years then cross referenced with TB registry	Born outside of US, 25% less than 5 years	• 4 developed TB disease • Concordance 80%, less in children younger than 2 years • 533 children TST positive and IGRA negative; none who were treated, none develop disease, including 54 under 2 years of age • Specificity TST 73%, QFT-GIT 90%, T-SPOT 92.9%
Wendorf 2020[101]	3,371 children <5 years of age	Comparison of database with TB registry	TST 24%, IGRA 56%	10,797 person-years, follow-up median 3 years in negative cases	California Refugee Health electronic information system; born in high-incidence countries	• No cases of TB • 1.4% IGRA positive • 13% TST positive
Kay 2018[97]	778 patients <18 years with laboratory confirmed	Registry	TST, IGRA vs TB disease (50% laboratory confirmed)		California TB registry for children	IGRA vs TST (sensitivity) • Less than 2 yrs: 80% vs 87% • 2-4 yrs: 91% vs 91% • 5-18 yrs: 96% vs 83%
Lombardi 2019[102]	226 children with TB disease	Retrospective multicenter study in Italy	QFT-IT vs TB disease (44% lab confirmed)	9 years	Majority foreign-born	TB disease: • <2 yrs – 93% • 2-5 yrs – 96% • 5-16 yrs 96% positive Lab confirmed: • 94, 100, 04% Overall sensitivity: • 98% in children vs 81% in adults

Abbreviations: TST, tuberculin skin test; QFT, quantiferon; T-SPOT, type of interferon-gamma release assay; IGRA, interferon-gamma release assay; QFT-GIT, Quantiferon Gold In-Tube type of IGRA; TB, tuberculosis.

children with risk factors for TB and TB infection who should undergo a TST.[103,104] Implementation of a similar strategy in Canada may help to better identify infected children here. Confining evaluation to children and adolescents from countries with a TB incidence >30/100,000 would likely capture more than 75% of those at risk for developing TB disease.[105,106]

8. Treatment for TB infection: TB preventive therapy

There are three different treatment regimens in regular use in Canada for TB preventive treatment in children and teens: (1) 3HP:12 weekly doses of INH and rifapentine (note that rifapentine can only be used in children ≥2 years old); (2) 4 R: four months of daily RMP; and (3) 9H: nine months of daily INH. (These regimens and their efficacy and safety profiles are also described in Chapter 6: Tuberculosis Preventive Treatment in Adults.) Parental and child preference should be strongly considered when choosing a TB preventive treatment regimen. The following information should be made available to the family to aid in decision-making: total pill burden per dose; frequency of doses; duration of treatment; need for treatment support with intermittent regimens; local public health supports; side effect profile; drug-drug interactions; and availability of liquid suspensions. In addition to these considerations, rifapentine is not currently available in many jurisdictions in Canada.

For children ≥2 years, the 3HP regimen or the 4 R regimen are the regimens of choice, as these are as effective as 9 months of INH and have higher completion rates, with no increase in adverse event rates.[107–109] However, the use of rifamycins may be contraindicated in certain pediatric subpopulations due to significant drug interactions (ie, adolescents on hormonal contraceptive agents). In these cases, 9 months of INH is a reasonable alternative.

For children <2 years, the preferred treatment option is 4 R, because of tolerability and total duration of therapy of

the treatment options available. It should be noted, however, that 9 months of INH has been the most studied regimen and historically the most widely used in children in this age group and can also be considered. Children in this age group do not have the same rates of hepatotoxicity with INH as adults. When choosing between regimens, this information should be considered in addition to the evidence available about completion rates and adverse events that favor the use of 4R in older children and adults. In some countries, 3 months of daily INH and RMP is used because it is available as a combination, dispersible tablet with no age restrictions.

Treatment support should be available to those prescribed intermittent regimens or where adherence issues are a concern, given the commonly encountered practical difficulties, including (but not limited to) spitting out medicines, parental anxiety and taste issues with liquid suspension or crushed tablets. Routine baseline lab investigations are not required in otherwise healthy children who do not have any underlying conditions predisposing them to hepatotoxicity. Regular follow-up visits, either by public health staff or clinicians, should focus both on adherence to treatment and adverse event monitoring. Questions should focus on the early warning signs of drug-induced hepatitis: persistent nausea, vomiting, fatigue, anorexia or abdominal pain. Jaundice and scleral icterus are late signs of severe liver injury. If any of these symptoms are observed by the caregivers, they should be told to stop treatment immediately and report this to their health care team, followed by prompt assessment for hepatotoxicity.

Children with both TB infection and HIV should begin TB preventive treatment as soon as possible, which may happen concurrently with initiation of antiretroviral therapy. The preferred regimen in young children with HIV who cannot swallow pills is INH for 9 months, as it can be used with any antiretroviral therapy regimen without need for dose adjustment.[110,111] While shorter-course regimens with rifamycins may be considered, their practical use is limited by numerous drug-drug interactions and overlapping toxicities that may compromise their effectiveness in young children.[112,113]

If a child is exposed to, and/or confirmed to have, TB infection following a contact with an INH mono-resistant source case, then RMP is the treatment of choice. When TB preventive treatment is being considered for contacts of a confirmed multidrug-resistant (ie, resistant to INH and RMP) source case, then consultation with a local expert is recommended. The choice should always be guided by the susceptibility results of the source case and should never be empiric. If the source case has a fluoroquinolone-susceptible isolate, there are several case series showing that preventive therapy with a fluoroquinolone is effective.[114,115] Currently there are 2 randomized controlled trials in progress that are evaluating the efficacy of levofloxacin compared to placebo that are enrolling pediatric participants.

Recommendations

- **We strongly recommend that, in children ≥2 years old, TB infection be treated with either 12 weeks of once-weekly isoniazid and rifapentine (3HP, where available) or 4 months of daily rifampin** (*good evidence*).
- **We strongly recommend that, in children <2 years old, 9 months of daily isoniazid be an acceptable alternative given its historical use** (*good evidence*).
- **We conditionally recommend that, in children <2 years old, 4 months of daily rifampin (4R) be prescribed for TB preventive therapy** (*poor evidence*).

9. Management of pediatric contacts (window-period prophylaxis)

The most efficient way to prevent pediatric TB is the prompt evaluation and treatment of children exposed to an infectious adult source case. All close contacts should have a symptom inquiry and TST or IGRA. A chest x-ray and physical exam should be included for all children <5 years old, children with TB symptoms and children older than 5 years of age with a positive TST or IGRA. Children less than 5 years of age with a negative TST or IGRA and no evidence of TB disease by examination or radiology should be given a "window" of preventive therapy to prevent the development of TB disease. This is because it may take up to 8 weeks after infection for the TST or IGRA to convert to positive.[116] During this time, untreated infection may progress quickly to severe disease in young children. For children presumed to have been exposed to a drug-susceptible isolate, INH has traditionally been used but RMP may also be used, in accordance with the TB preventive therapy section, detailed previously. Preventive therapy may be discontinued if, after a period of 8 weeks following the last contact, the repeat TST or IGRA is negative, the child remains asymptomatic and is immunocompetent and more than 6 months of age.

In the exposed child, if the initial TST (≥5 mm) or IGRA is positive and there is no clinical or radiographic evidence of disease, then a full course of treatment for TB infection is recommended. When a child <5 years old is diagnosed with TB disease as the index case, reverse contact tracing should be undertaken to identify the infectious source case. Although most source cases are found among adolescent or adult household contacts of the child, other source cases may be found among adolescent or adult non-household contacts, such as babysitters and other caregivers either in or outside the household. Molecular characterization of *M. tuberculosis* isolates by genotyping can lead to identification of previously unrecognized source cases.[117] If the child is hospitalized, it is advisable to screen adolescent or adult visitors for evidence of TB disease.[118]

The optimal treatment of children in contact with patients with MDR-TB is not well-established. Consultation with a TB specialist is recommended (see Chapter 8: Drug-resistant Tuberculosis for more details).

10. Perinatal TB: Background and management

The literature on this subject is very limited and most of the evidence comes from a handful of retrospective studies of small cohorts of pregnant women.[116–123] There has been one systematic review and meta-analysis that has examined the pregnancy outcomes of TB patients, both maternal and neonatal, and the results show a significant association with

poorer outcomes in both the mother and fetus/newborn compared to their TB-unaffected counterparts.[124] The majority of congenital TB cases reported in the literature occurred between the time Bietzke published the initial proposed diagnostic criteria in 1935 (see the following section) and prior to the introduction of INH in the 1950s.[125]

In 2 different literature reviews, congenital TB occurred more frequently in women diagnosed with miliary, meningeal or genitourinary TB.[126,127] This is likely due to the route of transmission, either hematogenously through the umbilical cord or aspiration of infected fluids at the time of delivery.[23,128,129] In one review, almost three quarters of women were diagnosed with TB postpartum.[130] In both reviews, ≥50% of women were diagnosed with TB after their infant was diagnosed with congenital TB.[131,125]

The initial criteria for diagnosis of congenital TB were outlined by Bietzke in 1935 and updated by Cantwell in 1994.[126,127] Historically, to fulfill the diagnostic criteria for congenital TB, the infant must have "tuberculous lesions and at least one of the following: (1) lesions in the first week of life; (2) a primary hepatic complex or caseating hepatic granulomas; (3) tuberculous infection of the placenta or the maternal genital tract; or (4) exclusion of the possibility of postnatal transmission by a thorough investigation of contacts"[128]

However, many children who have congenital TB do not fulfill these criteria based on more recent literature reviews. The clinical features reported are nonspecific and overlap with neonatal sepsis. The most common symptoms reported include respiratory distress, fever, hepatomegaly (and/or splenomegaly), poor feeding, lethargy, irritability, lymphadenopathy, abdominal distension, ear discharge, pustular skin lesions and cyanosis.[118,129,130] The median age of presentation of congenital TB is between 2 to 4 weeks of life.[117,126]

Management of the newborn (adapted with permission):[132]

1. Maternal TB disease associated with hematogenous spread or genitourinary TB disease:
   - Send placenta for histopathology, AFB microscopy, culture and PCR.
   - Ensure mother has up-to-date HIV test (including third trimester).
   - Perform TST on newborn (note: a negative TST in a newborn does not rule out TB infection or disease).
   - Conduct physical exam of the newborn for signs and symptoms of congenital TB.
   - Carry out diagnostic investigations: chest x-ray, abdominal ultrasound, lumbar puncture for AFB microscopy and culture and PCR, gastric aspirates for AFB microscopy and culture.
   - Start empiric TB treatment immediately if any of the above are concerning for TB disease.
   - If no clinical or diagnostic evidence of TB disease then at a minimum prescribe preventive therapy with either isoniazid or rifampin if the source case is known to have drug-susceptible TB; if the drug susceptibilities are not yet known, then both isoniazid and rifampin preventive therapy should be considered.
   - Schedule follow-up appointment between 2 to 4 weeks of age with repeat CXR; continue routine follow-up until 6 months old.
   - If isoniazid is used as preventive therapy, then repeat TST at 6 months old; if negative it can be discontinued, if positive continue, repeat at 9 months.
2. Maternal pulmonary TB considered infectious by her treating physicians:
   - Send placenta for histopathology, AFB microscopy, culture and PCR.
   - Ensure mother has up-to-date HIV test (including third trimester).
   - Perform physical exam of the infant for signs and symptoms of congenital TB.
   - Consider more limited diagnostic evaluation: chest x-ray, abdominal ultrasound.
   - Perform TST on infant (note: a negative TST in a newborn does not rule out TB infection or disease).
   - Start preventive therapy if no evidence of congenital TB (same drug strategy as scenario 1).
   - Schedule follow-up at 4 weeks old with repeat CXR, with routine follow-up until 6 months old.
   - If isoniazid is used as preventive therapy, then repeat TST at 6 months old; if negative it can be discontinued, if positive, repeat at 9 months.
3. Maternal pulmonary TB considered noninfectious by her treating physicians:
   - Send placenta for histopathology, AFB microscopy, culture and PCR.
   - Ensure mother has up-to-date HIV test (including third trimester).
   - Conduct physical exam of the infant for signs and symptoms of congenital TB.
   - No routine diagnostic testing is necessary in healthy infant.
   - Schedule routine follow-up until 6 months old.
4. Mother completed TB treatment prior to pregnancy:
   - No specific actions required.
5. Household family member treated for TB:
   - If the family member is still infectious, there should be no household contact with the infant until they are deemed noninfectious.
   - If the family member is noninfectious and adherent to treatment, no specific action is required.
6. Neonate diagnosed with congenital TB:
   - The mother should be immediately investigated for TB disease, appropriate to the site of suspected disease.
   - Strong consideration should also be given to investigating other caregivers if the mother's evaluation is negative and the onset of symptoms is compatible with postnatal acquisition.

- These infants usually have large bacterial burdens: if they are intubated or have aerosol-generating procedures, then airborne precautions should be followed.

If the infant is diagnosed with congenital or neonatal TB disease, the same treatment regimens are used as in older children (as noted previously). In the absence of positive culture results from the infant, the treatment regimen chosen should be guided by source case's mycobacterial culture susceptibility results.

Separation of the infant and mother is recommended only if the mother is very ill, is still considered infectious or is suspected/confirmed of having drug-resistant TB. If these have been excluded, or the infant has been started on effective therapy for TB infection or disease, then it is safe for the infant to room in with the mother and breastfeed while the mother is on effective TB therapy. Discharge of the mother and infant should only occur if all other household members have been evaluated for TB disease and are on appropriate therapy.

In those children who qualify for the BCG vaccine, based on provincial or territorial guidelines, it should not be given to infants who: (1) are treated for suspected TB disease; (2) have a positive TST; (3) are on TB preventive therapy; or (4) are born to a mother with HIV (until HIV transmission has been ruled out). For those infants treated for perinatal TB infection or disease and who qualify for BCG, their BCG dose can be administered after the appropriate duration of treatment for infection or disease is completed.

Good practice statement

- **Investigation for congenital TB should be considered in a neonate born to a mother with epidemiologic risk factors for TB and who has features of sepsis, non-resolving pneumonia or failure to thrive.**

11. BCG vaccination

Bacille Calmette-Guérin (BCG) is the only vaccine currently in use against TB, and is the collective term applied to a family of attenuated strains of *Mycobacterium bovis,* initially developed by Albert Calmette and Camille Guérin (hence the name) at the Pasteur Institute in Paris between 1908 and 1921. Subsequent strains have undergone further development through repeated subculturing in many laboratories around the world. While there are data showing that these different BCG strains have different immunogenicity in humans,[133] it remains unknown whether they offer comparable protection against TB. Three parent strains of the BCG collective, Danish, Tokyo and Pasteur, now account for more than 90% of the TB vaccines used. The Pasteur strain of BCG serves as the reference strain of the vaccine and its complete genome sequence has been determined.[134–136]

According to the WHO/UNICEF Joint Reporting data from 2016, 155 of 194 member states recommended universal BCG vaccination at birth or within the first week of life, 25 countries recommended selective BCG vaccinations and 21 countries did not recommend routine vaccination.[137] The BCG World Atlas provides detailed information on current and past BCG policies and practices.[138]

Beginning in 1926 in Quebec and 1933 in Saskatchewan, the National Research Council sponsored controlled trials of the safety and efficacy of BCG. Thereafter, BCG vaccination, either universal or selective, was promoted throughout Canada. As anti-TB drugs became available and incidence rates fell, BCG was discontinued in most populations. In recent years, its use has been limited to the First Nations and Inuit populations, where it has been part of a TB-elimination strategy. In these populations, BCG vaccination, as well as TB infection screening and treatment programs, have been associated with significant decreases in TB incidence.[139,140] A summary of the usage of BCG in Canada over time is available on-line.[141]

11.1. Efficacy of BCG

The efficacy of BCG has been debated for many years, even though more than 3 billion doses of the vaccine have been administered. One systematic review estimated that there is a protective efficacy of 19% against infection after exposure, and 58% protection against progression to disease, among BCG vaccinated children compared with unvaccinated.[142] In a second review, the protection against meningeal and miliary TB for infants and young children was estimated to be 85-92%, and the protection against pulmonary disease in children was 74%.[143] The efficacy of BCG in adults is uncertain but is thought to be lower than in children. The duration of the protective effect of BCG against pulmonary and extra-pulmonary TB is at least 10 years, with evidence that longer-term efficacy declines with time.[144] There is good evidence from randomized trials that revaccination does not confer added protection.[145,146] There is also evidence that TST reactions do not correlate with protective immunity.[147,148]

11.2. BCG vaccine administration and adverse events

For information on vaccine administration, storage requirements, co-administration with other vaccines and vaccine safety and adverse events, see the Canadian Immunization Guide chapter on BCG.[149] In premature and low birthweight infants who require BCG vaccination, the use of the vaccine early is safe and immunogenic.[150]

Common local complications include injection site abscesses and regional lymphadenitis that may be suppurative.[151] Local disease is self-limited but often chronic, and optimal management is uncertain: observation alone with aspiration of abscesses just before rupture were suggested in a Cochrane review but the evidence was poor.[152] Local osteitis may occur in the absence of immune deficiency and requires drug therapy.[153] Disseminated BCG disease occurs in children with primary immune deficiencies, including severe combined immunodeficiency (SCID), mendelian susceptibility to mycobacterial diseases[154,154] and some cases of HIV infection.[155]

11.3. BCG and severe combined immunodeficiency

In patients with higher risk for SCID and who would qualify for vaccination with BCG, there are rare but significant risks of disseminated BCG disease.[139,153,154,155–161] As of 2021, newborn screening for SCID has been implemented in Alberta, Ontario, Manitoba, Prince Edward Island, Nova Scotia, New Brunswick and the Northwest Territories, with the rest of the provinces and territories in the process of implementation or evaluation (Dr. P. Chakraborty personal communication). The assay for T-cell receptor excision circle (TREC) identifies infants with most forms of SCID. Some programs have added other tests that target specific types of SCID. The positive predictive value of the screen is 37.5% (Newborn Screening Ontario 2020 annual report). In the absence of national guidelines, some jurisdictions (Nunavut and Northern Manitoba) have implemented delayed administration of BCG until the results of the SCID Newborn Screen are available, to prevent potential disseminated BCG disease. Programmatic evaluation is needed to ensure that this policy change has not diminished BCG vaccine uptake among those who would qualify. In populations receiving BCG vaccination at birth, without prior SCID newborn screening, one must have a high index of suspicion for disseminated BCG disease.

11.4. BCG recommendations from Canada's National Advisory Committee on immunization

We agree with the recommendation of the National Advisory Committee on Immunization (NACI)[162] that BCG vaccination should not be given routinely to all Canadians.

We also agree with the NACI recommendation[21] that BCG vaccination should be given to newborns in First Nations and Inuit communities, or other communities where:

i. the average annual rate of smear-positive pulmonary TB was >15/100,000 population or the average annual rate of culture-positive pulmonary TB was >30/100,000 during the previous 3 years; or,
ii. the annual risk of TB infection is >0.1%, or,
iii. early identification and treatment of latent TB infection (LTBI) are not available.

The annual risk of TB infection of 0.1%, is the threshold suggested by the International Union Against Tuberculosis and Lung Disease; below that threshold they have recommended selective discontinuation of BCG vaccination programs.[159] If BCG vaccination is currently offered to all infants in a community that does not meet one of the criteria described, the vaccination program should be discontinued as soon as a program of early detection and treatment of LTBI can be implemented.

For an infant to receive BCG, the child's mother should be HIV negative, and there should be no evidence or known risk factors for immunodeficiency in the child.

We agree with the NACI recommendation[163] that if BCG vaccination is delayed more than 6 months after birth, a TST test is recommended, and the vaccine should be given only to TST-negative infants. For infants aged between 2 months and 6 months, an individual assessment of the risks and benefits of TST prior to BCG vaccination is indicated.

Recommendations

- **In populations receiving BCG vaccination in infancy, we conditionally recommend that all newborns should be screened for severe combined immunodeficiency** (*poor evidence*).
- **We strongly recommend against revaccination with BCG** (*good evidence*).

Good practice statement

- **In jurisdictions with newborn severe combined immunodeficiency screening, BCG vaccination should be delayed until the results of the screen are available.**
- **Given that the BCG vaccine does not provide a high degree of protection, TB disease should still be considered in any BCG-vaccinated infant or child with a clinical presentation suggestive of TB.**

12. Conclusion

TB continues to be an important disease in Canadian children, especially Indigenous Canadian-born children, who have a disproportionately high burden of disease. Foreign-born children and the children of foreign-born parents are also at risk. Treatment of pediatric TB requires a team approach and easily accessible and culturally appropriate healthcare services. Public health programs should prioritize finding and screening TB-exposed children to prevent avoidable morbidity and mortality as well as reduce the reservoir of future TB cases.

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Appendix 1

A. Gastric aspirates: Some tips

This is a useful sputum collection procedure in young children. It attempts to collect children's swallowed mucous, which may contain tuberculosis (TB) bacteria, while it still sits in the stomach. These are some useful tips for carrying out the procedure:

- Patients should not eat for 6 hours prior to the procedure, or be exposed to food, in order to prevent the stomach from emptying. Ideally this is done just after the child wakes from sleep before the stomach has emptied.
- If the child cannot be admitted as an inpatient, then they should arrive at clinic first thing in the morning prior to eating or drinking.
- The child should be supine for the procedure, and may also need to be swaddled, depending on age.
- Measure the expected distance of nasogastric (NG) insertion from nose to stomach.
- Do not use bacteriostatic lubricant to moisten the NG tube.
- Insert NG tube and aspirate the stomach contents first and discard.
- If <10 cc of mucous is aspirated, then instill no more than 20-30 cc of sterile water (not normal saline) into the NG tube. Withdraw the aspirate quickly and place contents into a buffered specimen container or regular specimen container. (Note: Review local lab guidelines as to specimen collection containers available.)
- If a buffered container is not available, ensure the lab is open to immediately receive and neutralize specimen.

With thanks to Ann Loeffler, Oregon Health Sciences University. See also[63] where a video and many other resources are available.

B. Sputum induction: Sample protocol

Equipment

- Hypertonic saline: 3% Sodium Chloride, prefilled syringe
- Nebulizer with appropriately sized mouthpiece and facemask
- Personal protective equipment (PPE): gloves, gown, N95 respirator and eye protection
- Sputum sample cup, patient label and biohazard bag
- Ventolin: either metered dose inhaler with age appropriate aerochamber or liquid nebule with aerosol mask set-up (including oxygen)
- Suction setup, including appropriate size catheter and suction tip
- 100% oxygen setup and resuscitation equipment within close proximity

Protocol

1. Appropriately trained personnel will review patient record to ensure no medical contraindications exist.
   a. Medical contraindications: severe asthma, severe chronic lung disease, severe hemoptysis, hemodynamic instability, new acute respiratory illness or fasting <2 hours
   b. Note: for details around appropriate rooms to perform this procedure in refer to Chapter 14: Prevention and Control of Tuberculosis Transmission in Healthcare Settings
2. Identify patient and explain procedure to patient and family.
3. Perform hand hygiene.
4. Don PPE.
5. Perform pre-induction assessment: vital signs, history of asthma and intercurrent illness
6. Administer bronchodilator.
7. Assemble nebulizer with hypertonic saline and attach appropriately sized mouthpiece and facemask.
8. Initiate treatment with patient in sitting position.
9. Inform either the caregiver or patient (when appropriate) that coughing can occur and instruct them to attempt to breathe normally.
10. Instruct the patient to cough into the sputum container and/or suction contents from nasopharynx.
11. Label specimen container and place into biohazard bag.
12. Dispose of equipment and remove PPE (only remove N95 respirator after exiting from room).
13. Perform hand hygiene.
14. Document procedure in patient record.

Sample video of sputum induction procedure: FIND The Global Alliance for Diagnostics.[164]
*Adapted from "Sputum Induction Procedure" developed by the Respiratory Therapy Services at the Children's Hospital of Eastern Ontario, version date: May 2017.

C. Tips for improving adherence and completion rates for TB therapy

Adherence to and completion of therapy can be challenging for everyone, but especially among children. These tips can help improve adherence and completion rates:

- Use tablets crushed into semisoft vehicles, such as sugar-free pudding, to avoid stomach upset from the liquid preparation. Emphasize which medications are to be taken with meals (ethambutol and pyrazinamide) and which are to be taken on an empty stomach (isoniazid and rifampin).
- Warn the family that the first couple of weeks of therapy will be challenging.
- See patients monthly and supply only 1 month of medication at a time. Provide some extra doses to allow for spillage, or for when patients cannot make it to the follow-up appointment on time.
- Provide written education regarding reasons for therapy, benefits of therapy, symptoms of TB and potential side effects/toxicity.
- Develop a small, dedicated and enthusiastic team of staff providers, nurses and interpreters.
- Develop systems to encourage adherence. We encourage caregivers to consider the best time in their child's routine for them to take their TB medications. Establishing reward systems for children is also helpful.
- Have convenient clinic hours and short waiting times.
- Develop a system of immediately following up on patients who have missed appointments.
- Praise the family and child for good adherence and clinic attendance.

D. Practical tips for preparation of TB medications for children*

- Isoniazid, pyrazinamide and ethambutol pills may be crushed and reduced into powder format to facilitate administration. When possible, pyrazinamide and ethambutol should be given with meals, isoniazid on an empty stomach.
- Rifampin capsules may be opened and sprinkled on or mixed into food.
- To mask the taste of medications, crushed pills or powder can be mixed in a small quantity (1-2 teaspoons) of food that will mask the taste; popular examples include fruit purees, chocolate pudding and nut butters.
- Never mix the medications (liquid or powder form) with any of the child's essential foods (eg, milk, cereal).
- Never add the medications directly to an infant's bottle.
- Do not administer medications after a meal or feeding, to minimize risk of vomiting.
- If vomiting occurs within 10 minutes of administration, the medication should be re-administered.

*Adapted by Denis Blais from: The Practical Guide to Applying DOT.[165]

E. Practical tips for drug administration according to age*

Different strategies can be used for different age groups, as noted here.

Infants (0-1 year):
- Medications typically taken without difficulty prior to a feed.
- Always use small quantities and ensure amount has been fully swallowed before administering next amount.
- Monitor the baby for at least 30 minutes after administration because of risk of vomiting.

Toddlers (1-4 years):
- This is the most difficult age for administering TB drugs; multiple attempts may be needed to find the optimal format (i.e., suspension vs crushed powder) and food for mixing.
- It is important to identify nonessential foods that are palatable to the child, given the duration of treatment and tendency toward rapid aversion to certain foods.
- Support may be needed to guide caregivers administering these medications; this includes the approach (calm, firm), attitude (no negotiation, positive reinforcement) and how to properly hold a child who categorically refuses to take their medication to administer it.

School aged (5-12 years):
- Generally administered without difficulty.
- Choice of suspension vs pills depends on the child; ability to swallow pills varies by individual and may not be related to age.

Adolescents (12-18 years):
- Generally administered without difficulty in pill format.
- Adherence in this age group is a particular challenge; parents or caregivers need to be responsible for reinforcing adherence.

*Adapted by Denis Blais from: The Practical Guide to Applying DOT.[165]