Improving Access to Lab-based Diagnosis for Pediatric TB: Key Practical Considerations for Planning and Budgeting Purposes

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Introduction

The purpose of this document is to provide general practical guidance on bacteriologic diagnosis of TB in children and to review key programmatic considerations regarding the implementation of sample collection procedures.

The document accompanies the Budgeting Tool for Sample Collection Procedures and provides basic programmatic and practical information that may be useful to better understand the tool and support its appropriate use.

This document is meant to provide not detailed technical guidance on the implementation of sample collection procedures but rather a summary overview of the key elements that are needed for successful introduction and roll-out of the procedures.

The target audience for this document includes National TB Programme managers and partners who are supporting development of National TB Strategic Plans and funding applications.

Role of Laboratory-Based Diagnosis in the Management of Pediatric TB and Importance of Improved Access to Laboratory Diagnostics for Children

Diagnosis of TB in children must rely on thorough assessment of all the evidence derived from a careful history of TB exposure, medical history, clinical examination, and relevant diagnostic investigations.

Most young children with TB disease do not have a positive result on bacteriologic tests due to the paucibacillary nature of the disease. Therefore, clinical diagnosis of TB with provision of TB treatment is necessary to decrease illness and death in children. However, it is important to seek bacteriologic confirmation of TB in children because this provides diagnostic reassurance.

International guidance clearly emphasizes that bacteriologic confirmation of TB disease in children should be sought whenever possible,[1] and since 2011 children have been included as one of the priority populations that should receive Xpert MTB/RIF (Xpert) as the initial diagnostic test.[2]

Obtaining bacteriologic confirmation can indeed streamline and accelerate the diagnostic work-up, especially if rapid molecular diagnostic tests are implemented initially. In addition, in the context of high multidrug-resistant tuberculosis (MDR-TB) prevalence, laboratory-based diagnosis will provide information about the drug resistance profile and allow for the design of the most appropriate and effective treatment regimen.

A recent meta-analysis of 15 studies, including more than 3,500 children as participants, showed that Xpert sensitivity for pediatric TB diagnosis is 62% when using expectorated or induced sputum and 66% when using samples from gastric lavage, compared with mycobacterial culture.[3] Although this represented a 36%–44% higher sensitivity when compared to smear microscopy, sensitivity remains poor when compared to an adult

population (for which a recent Cochrane meta-analysis reported a pooled sensitivity of 89% for Xpert performed on sputum samples[4]).

Obtaining bacteriologic confirmation in children is challenging mainly due to the following:

1. The paucibacillary nature of pediatric TB disease and hence the low bacterial load that characterizes pediatric TB samples (Compared to adult populations, currently available bacteriologic tests have low sensitivity to diagnose TB, and Xpert has lower sensitivity relative to culture.)
2. The difficulty of collecting respiratory samples from younger children (who cannot spontaneously expectorate)
3. The considerable proportion of children affected by extrapulmonary TB, with lymphadenitis' being the most common form of extrapulmonary TB (see below for more details)

The challenge of the lower sensitivity of Xpert relative to culture is partially addressed by a second-generation cartridge launched by Cepheid in 2017 called Xpert MTB/RIF Ultra (Ultra) and characterized by an improved sensitivity. Two studies have evaluated the performance of Ultra on frozen pediatric TB samples and similarly showed an about 10% increase in sensitivity using Ultra compared to Xpert.[5,6]

Because young children cannot produce sputum samples spontaneously, alternative respiratory specimens are needed for bacteriologic testing in children. Extrapulmonary specimens can aid in diagnosis of TB that is exclusively extrapulmonary or that is both pulmonary and extrapulmonary. Specimens used for diagnosis of TB in children include, for example, bronchoalveolar lavage, gastric aspirate, induced sputum, nasopharyngeal aspirate, stool, lymph node fine needle aspirate, pleural fluids, and cerebrospinal fluids (please see Annex 3 for more details). This document will focus on sample collection procedures that can be performed and implemented in lower-level facilities and on sample types that have been recommended for use with Xpert.[7,8]

Gastric aspirate: The bacteria that cause TB disease can be found in stomach fluid; this is thought to result from coughing up bacteria from the lungs and then swallowing them. Stomach fluid for bacteriologic diagnosis can be obtained by gastric aspiration. In this technique, the child refrains from eating or drinking (fasts) for a period of time in advance of the procedure to avoid breathing stomach contents into the lungs during the procedure. Typically, children are hospitalized so that they may fast overnight and specimens can be collected in the early morning; gastric aspiration also can be performed as an outpatient procedure if the child fasts beforehand (e.g., by coming to a health facility in the morning after fasting through the night). To obtain gastric fluid, the child is immobilized in a lying position (e.g., by being wrapped in a blanket or specialized wrapping device). A thin tube is inserted into one nostril, down the throat, and into the stomach; fluid from the stomach is then suctioned back through the tube using a syringe. A medicated nasal spray or gel may be used to decrease discomfort from insertion of the tube into the nose to the stomach.

Induced sputum: Young children are not able to cough up sputum from their lungs on their own; however, sputum can be forced from the lungs. To collect a respiratory specimen by sputum induction, the child is first immobilized in a lying position. Several puffs of

medication (e.g., salbutamol) are given to the child to breathe through a face mask; this helps prevent respiratory difficulty during the procedure. The child then breathes in a mist of salty water through the face mask for about 15 minutes. The salty water mist will cause the child to cough up secretions from the lung. If the child is able to produce sputum through the induced cough, the procedure terminates at this stage. If the child is not able to produce sputum through the induced cough (this is usually the case for younger children), nasopharyngeal aspiration must be performed to obtain a sample. Nasopharyngeal aspiration requires the availability of an electronic suction device and of mucus extractors. One end of a thin tube is connected to an electronic suction device, and the other end is inserted into the child's nose to suction out the secretions that are coughed up from the back of the nose and mouth. The secretions are collected into a mucus trap. A medicated nasal spray can be used to decrease discomfort from insertion of the tube into the nose. This procedure is performed after a period of fasting, though a shorter period than is typical for gastric aspiration. Sputum induction may be performed in an outpatient or inpatient setting.

Nasopharyngeal aspiration: Fluid can be collected from the back of the nose and mouth using nasopharyngeal aspiration. In this procedure, a few drops of water (or normal saline) are placed in each nostril. The child is immobilized in a lying position. A thin tube is attached to a suction machine on one end, and the other end is inserted into one nostril; fluid is suctioned out from the back of the nose and mouth. A medicated nasal spray can be used to decrease discomfort from insertion of the tube into the nose. It is not necessary for a child to fast before this procedure, and it can be performed in an outpatient or inpatient setting.

Lymph node fine needle aspiration: Material can be sampled from enlarged lymph nodes (typically lymph nodes in the neck) using fine needle aspiration. In this procedure, the child is immobilized. A medicated cream (i.e., lidocaine) can be applied to the skin over the enlarged lymph node to decrease discomfort from the procedure. The skin over the enlarged lymph node is cleaned to avoid introduction of germs into the skin during the procedure. A sterile bevel tip needle is attached to a syringe and inserted into the enlarged lymph node. Once the needle is in the node, the syringe plunger is pulled back to create suction; very small bits of lymph node material are pulled back through the needle and into the syringe because of the suction. A small amount of material from the lymph node is stained and viewed under a microscope to ensure that adequate material was collected during the procedure. The remaining material then can be tested in the laboratory for the bacteria that cause TB using Xpert or culture.

Stool: Mycobacterium tuberculosis–containing sputum may be swallowed, particularly during sleep, and acid-fast bacilli have been shown to survive digestion and are detectable in stool.[9,10] Stool can therefore provide a more acceptable and feasible alternative to conventional specimens for the evaluation of children with presumptive pulmonary TB, especially considering that this type of sample is relatively easy to obtain.

Addressing the challenge of collecting specimens for TB diagnosis in children requires investing resources in the implementation of sample collection procedures for respiratory and nonrespiratory specimens from children. Despite their effectiveness for TB diagnosis

when combined with Xpert testing, these methods have been poorly implemented so far due to operational challenges. However, several operational research projects in low- and medium-income countries have shown that this is feasible.[11,12,13,14,15] A recent pilot project implementing a comprehensive intervention that included intense training for health care providers as well as establishment of Xpert testing sites and an efficient sample transportation network was able to bacteriologically confirm 8% of the more than 42,000 presumptive TB children enrolled. Important to note, 8.83% of the children diagnosed with TB were infected by rifampicin-resistant strains.[13]

It is critical to emphasize that *a negative bacteriologic test result, including Xpert, does not rule out active TB disease in children* due to the limited sensitivity of bacterial tests for diagnosing TB disease in children. Therefore, while it is important to seek a bacteriologic-confirmed diagnosis of TB disease in children, in practice, bacteriologic confirmation will be achieved in only a minority of children with TB disease. Therefore, clinical diagnosis will continue to play a pivotal role in the management of pediatric TB, and it is critical to train frontline health care workers and empower them to diagnose pediatric TB on clinical grounds. Clinical diagnosis of TB in children is made by consideration of relevant information including suggestive symptoms, tests for TB infection such as Tuberculin skin test or Interferon-Gamma Release Assays (although it is important to emphasize that those tests cannot confirm active TB disease), chest X-ray, and history of known TB contact. Relevant signs and symptoms contribute to a diagnosis of TB, but no combination of signs or symptoms clearly defines or refutes a clinical diagnosis of TB.

In past decades several "scoring systems" have been developed to support the diagnosis of pediatric TB, mainly based on clinical assessment and nonbacteriologic investigations such as Tuberculin skin test and chest X-ray. Most of those diagnostic systems have not been thoroughly validated, and their performance remains unfortunately highly variable and suboptimal.[16,17] For those reasons, the scoring systems have not been recommended by WHO.[1]

In conclusion, please note the following:

- Bacteriological confirmation in children should be sought whenever possible, using rapid molecular diagnostics (i.e., Xpert or Ultra) as the initial test, as this can accelerate and streamline the diagnostic process for those who have positive test results and can provide critical information about drug resistance.
- Improving access to laboratory-based diagnosis for children is feasible and can have a significant impact on the management of pediatric TB, especially in high MDR-TB settings, but it requires well-planned resources and programming.
- *A negative bacteriologic test, including Xpert, does not rule out active TB disease* due to the limited sensitivity of bacteriologic tests for diagnosing TB disease in children. Clinical diagnosis remains the mainstay of pediatric TB management.[18]

Specimen Collection Considerations

The choice of specimen type depends on the suspected site of disease (pulmonary or extrapulmonary) and needs to be guided by a thorough clinical examination. Comprehensive guidance about the different types of samples to be considered is provided by the "Desk-guide for Diagnosis and Management of TB in Children" published by the Union, and it is summarized in Annex 3 .

In this document, we will limit our considerations to the types of samples that have been recommended for use with Xpert[8] and that have been evaluated for the diagnosis of the most common forms of TB disease observed in the pediatric population (please see Table 1):

- Pulmonary TB (note that pulmonary TB represents approximately 70%–80% of the pediatric TB burden[19,20])
- TB lymphadenitis (which represents the most common form of extrapulmonary TB)[21]

Table 1. Xpert Performance on Pediatric Respiratory Samples and Lymph Node Fine Needle Aspirates

Form of TB	Sample type	Xpert sensitivity (reference standard: culture)	Xpert specificity (reference standard: culture)
Pulmonary TB	Expectorated sputum	62%[3,a]	98%
	Induced sputum	62%[3,a]	98%
	Gastric aspirate	66%[3]	98%
	Nasopharyngeal aspirate	Not included in Detjen et al. systematic review. 46% sensitivity based on recent systematic review commissioned for guidelines update[7]	Not included in Detjen et al. systematic review. Specificity ranges 98%–100% based on recent systematic review commissioned for guidelines update[7]
	Stool	61% sensitivity based on recent systematic review commissioned for guidelines update	Not included in Detjen et al. systematic review. Specificity ranges 98%–100% based on recent systematic review commissioned for guidelines update
TB lymphadenitis	Fine needle aspiration	Sensitivity in published studies ranges 80%–93.5%[22,23,24]	Sensitivity in published studies

			ranges 69.2%–93.8%[22,23,24]

a. Detjen et al. systematic review did not assess separately the sensitivity of expectorated and induced sputum.

When considering which sample collection procedures to implement in different levels of the health care system, it is important to take into consideration the following key elements (see Table 2):

1. Infection control measures that need to be put in place in order to safely implement sample collection procedures (see Annex 1)
2. Number of commodities required
3. Safety considerations (e.g., induced sputum's being contraindicated for children with respiratory distress [cyanosis or low oxygen saturation] compared to gastric aspirate)
4. Patient preparation requirements (e.g., fasting overnight or for several hours—these have implications for use in inpatient versus outpatient settings or for use at initial or subsequent clinical encounters)

Table 2. Relative Comparison of Key Practical Elements That Have Planning and Programmatic Impact When Implementing Sample Collection Procedures

Sample collection procedures	Biosafety and infection control—risk assessment	Number of commodities required	Patient safety concerns
Pulmonary TB			
Gastric aspirate	Low	Very low	Very low
Induced sputum	Moderate	Moderate	Moderate (e.g., contraindicated for children with respiratory distress)
Nasopharyngeal aspirate	Low	Low	Very low
Stool	Very low	Very low[a]	No safety concerns
Extrapulmonary TB			
Lymph node fine needle aspiration	Low	Very low	Very low

a. The number of commodities required for sample collection procedure is minimal. The number of commodities required for sample processing depends on the stool processing procedure implemented. Studies are currently ongoing to compare different stool processing procedures. In the sample processing procedures under evaluation, the number of commodities needed varies from none to few.

Key Considerations for Implementation and Placement

To successfully implement sample collection procedures and to ensure that this activity has a meaningful impact on the management of pediatric TB, it is critical to ensure this is planned and rolled out as part of a more comprehensive implementation package. The key elements that this package should include are the following:

1. **Training on sample collection procedures targeting frontline health care workers (e.g., clinicians and nurses) as well as laboratory personnel**
   Once the facilities where sample collection procedures will be implemented have been selected, it is important to identify the staff who will be best placed to perform sample

collection (based on cadre and skill set) and ensure training on sample collection procedures (inclusive of practical sessions) will be delivered. It is therefore essential to include in the budget the development of training material and standard operating procedures for sample collection as well as the delivery of trainings (district-level trainings). *The attached budgeting tool has been built to support estimation of costs related to the delivery of training on sample collection procedures. If training materials are not readily available in the country, additional costs need to be factored in for this activity.*

2. Procurement of commodities needed to perform sample collection procedures

Performance of sample collection requires the procurement of a defined set of devices, accessories, and consumables, which are specific to the different types of sample collection procedures. Some of the commodities are needed to perform the sample collection procedure, and others are required for infection control measures (e.g., autoclave) or to ensure the safety of the procedure (e.g., oxygen concentrator, salbutamol for induced sputum). *The attached budgeting tool has been built to support estimation of costs related to the procurement of devices and commodities needed for sample collection procedures.*

3. Infrastructure upgrades needed to meet infection control measures (please refer to the table in Annex 1)

To safely implement sample collection procedures, it is critical to ensure that the key infection control requirements are met. This might require some infrastructure upgrade, depending on the facility and on the sample collection procedures that will be selected for implementation. While a detailed budget for infrastructure upgrades can be developed only after facilities have been identified and infection control assessments have been performed, it is recommended that a ballpark figure be considered and included for infrastructure upgrades that will vary depending on the number of sites where sample collection procedures will be implemented.

4. Sample storage and sample transportation network (please refer to the table in Annex 2)

It is essential to ensure that the facilities where sample collection procedures are implemented are served by a sample transportation network if rapid molecular testing (Xpert) is not available on-site. Unfortunately, the evidence on the storage and transport conditions for pediatric TB samples is limited and based mostly on research studies. Given the invasive procedures that are required to obtain those samples, it is strongly recommended that samples be handled under the best possible conditions to preserve their quality and integrity (see Annex 3 for details) and to protect the safety of the handler and the environment.

Sample storage: It is ideal to have the sample transported to the testing site for testing immediately after collection, but if samples are not picked up on the day of collection, refrigerators or cooler boxes are required for storage at 4°C.

Sample transportation: If a sample transportation network is already in place for TB and HIV samples, timely pickup can be achieved by slightly adjusting the frequency

of sample pickup (e.g., from one or two days a week to three days a week or on demand). If a sample transportation network is not in place, it is critical to ensure that this is implemented and budgeted for. Specific requirements for pediatric TB sample transportation (e.g., pickup schedule, transport conditions) can be built into the designing and planning phase.

5. **Procurement of Xpert cartridges**
   When sample collection procedures are implemented, it is critical that the quantity of Xpert cartridges to be procured takes into account the number of pediatric TB samples.

It is critical to make sure all the essential elements reviewed above are adequately planned and budgeted for to implement sample collection procedures.

Introduction to the Sample Collection Budgeting Tool

This tool was developed to assist the national TB program in estimating the costs related to the procurement of devices and consumables that are needed for collection of the following sample types in the pediatric population:

- Induced sputum
- Gastric aspirate
- Nasopharyngeal aspirate
- Stool
- Lymph-node fine needle aspiration

These sample types have been selected and prioritized because, as highlighted above, they represent the types of samples that are required for the diagnosis of pulmonary TB (the most common form of pediatric TB among all forms) and TB lymphadenitis (the most common form of extrapulmonary TB in children).

Stool has been included as a sample type for pediatric TB diagnosis in accordance with the latest guidance released by WHO in January 2020.[25] However, while the costs related to the collection of stool could be accurately estimated, information currently available does not allow for precise estimation of costs related to the processing of stool samples for Xpert testing. Indeed, different sample processing methods for stool samples are currently under evaluation, and final study results are expected by the end of 2021. As an interim measure, the budgeting tool for sample collection procedures includes an estimated cost of US$1 for the processing of a stool sample, but this will have to be revised and adapted once methodology(ies) for stool sample processing are finalized.

The list of consumables has been built considering that samples will be tested with Xpert. Additional reagents and consumables that may be needed for culture are not included. The main reasons for this choice are the following:

1. Xpert should be the initial diagnostic test for children per WHO recommendations.
2. Availability of TB culture is limited to national and regional labs in most TB-endemic countries, and therefore accessibility may be challenging.

If a national algorithm recommends that a child with a negative test result by Xpert be systematically referred for culture, the additional costs related to consumables required for culture should be considered.

In addition, the tool focuses on only the following elements:

- The costs related to the procurement of commodities
- The costs related to delivery of training on sample collection procedures

Specifically, the tool does not include costs for diagnostic tests (e.g., Xpert), specimen transport, and development of training material; however, these key supplies and activities need to be planned and budgeted for to ensure successful collection and diagnostic testing of pediatric specimens. These supplies and activities have not been included in this tool because of potential overlap with other planning and budgeting that might be undertaken as part of the development of the National TB Strategic Plan budget. For instance, a budget for a sample transportation network might be developed and included under TB laboratory strengthening activities.

We therefore have decided to avoid building parallel budgeting tools for those important activities and rather have highlighted here they key elements related to pediatric TB sample collection that need to be considered and included in the planning and budgeting exercise.

The development of this budgeting tools was led by Angela Kairu (independent consultant). We acknowledge the World Health Organization and the University of Sheffield for their collaboration and active contribution to the development of the budgeting tool.

ANNEX 1: Biosafety and Infection Control Considerations for Areas Dedicated to Sample Collection Procedures

Sample collection procedure	Risk assessment	Personal protective equipment	Infrastructure	
		If staff needs to assist patients during sputum collection procudures, they shoud always wear	Minimal requirements to be met	Optimal requirements to be met
Expectorated sputum	Moderate/high risk[26]	• N95 mask or similar • Gloves • Disposable apron	• Cough booth outside of the health facility, in open-air space and away from patient waiting areas and walk path to access the facility • If sputum is collected indoors, a dedicated room must be available with a unidirectional airflow with 6–12 ACH[27]	
Gastric aspirate	Low risk[1]	• N95 mask or similar • Gloves • Glasses for eye protection • Disposable apron	• Dedicated cough room with unidirectional airflow with 6–12 ACH • For gastric aspirate collection procedures, natural ventilation should be sufficient • *Air must flow away from the technician and across the work area along with potentially infectious materials, then away from occupied areas*	• Dedicated cough room with unidirectional airflow with 6–12 ACH • Ensure 6–12 ACH through mechanical ventilation • Mechanical fans can be installed in *windows* or *on walls,* or installed in ducts that expel air from the laboratory • *Ceiling fans are not adequate to ensure*

			of the room and outside the laboratory • In order to have directional control of contaminants in the air, air should move at least 0.5 m/s • 30–40 minutes should be allowed between patients if using natural ventilation	*unidirectional ventilation* • Mechanical ventilation systems are considered to be reliable in delivering the desired rate of airflow regardless of the impact of variable winds and ambient temperature • Mechanical ventilation can be used with an air-conditioning system to control temperature and humidity • Mechanical ventilation also can be achieved by using a ventilated work station
Nasopharyngeal aspirate[28]	Low risk	• N95 mask or similar • Gloves • Glasses for eye protection • Disposable apron	• Dedicated cough room with unidirectional airflow with 6–12 ACH • For nasopharyngeal aspirate collection procedures, natural	• Dedicated cough room with unidirectional airflow with 6–12 ACH • Ensure 6–12 ACH through mechanical ventilation

			ventilation should be sufficient • *Air must flow away from the technician and across the work area along with potentially infectious materials, then away from occupied areas of the room and outside the laboratory* • In order to have directional control of contaminants in the air, air should move at least 0.5 m/s • 30–40 minutes should be allowed between patients if using natural ventilation	• Mechanical fans can be installed in *windows* or *on walls,* or installed in ducts that expel air from the laboratory • *Ceiling fans are not adequate to ensure unidirectional ventilation* • Mechanical ventilation systems are considered to be reliable in delivering the desired rate of airflow regardless of the impact of variable winds and ambient temperature • Mechanical ventilation can be used with an air-conditioning system to control temperature and humidity • Mechanical ventilation also can be achieved by using a ventilated work station

Induced sputum	Moderate risk	• N95 mask or similar • Gloves • Glasses for eye protection • Disposable apron	• Dedicated cough room with unidirectional airflow with 6–12 ACH • Ensure 6–12 ACH through mechanical ventilation Mechanical fans can be installed in *windows* or *on walls,* or installed in ducts that expel air from the laboratory • *Ceiling fans are not adequate to ensure unidirectional ventilation* • Mechanical ventilation systems are considered to be reliable in delivering the desired rate of airflow regardless of the impact of variable winds and ambient temperature • Mechanical ventilation can be used with an air-conditioning system to control temperature and humidity • Mechanical ventilation also can be achieved by using a ventilated work station
Lymph node fine needle aspiration[29]	Low risk	• N95 mask or similar • Gloves • Glasses for eye protection • Disposable apron	• No environmental infection control measures required • Ensure sharps containers are available • Staff must wear personal protective equipment • Staff must handle specimen carefully and and make sure to avoid aerosol formation when transferring aspirates to the transport medium

ACH = air exchanges per hour; m/s = [???].

ANNEX 2: Storage and transport conditions for respiratory and nonrespiratory pediatric TB samples for Xpert testing

Gastric aspirates	Conditions
Storage	❖ Store at 2–8°C
Transport	❖ Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection. Samples ideally should be tested within the same day. ❖ Packaging of gastric aspirate samples must be of good quality and be strong enough to withstand leakage of contents, shocks, pressure changes, humidity, vibration, and manual or mechanical handling considered incident to ordinary transportation. It should follow the standard triple packaging system. ❖ Transport in a cool box at 2–8°C and out of direct sunlight.

Induced sputum and nasopharyngeal aspirates	Conditions
Storage	❖ Store at 2–8°C
Transport	❖ Transport in a cool box at 2–8 °C and out of direct sunlight. ❖ Packaging of sputum and nasopharyngeal aspirate samples must be of good quality and be strong enough to withstand leakage of contents, shocks, pressure changes, humidity, vibration, and manual or mechanical handling considered incident to ordinary transportation. It should follow the standard triple packaging system**.** ❖ Ideally, samples should arrive in the testing laboratory on the day of collection and be tested as soon as possible. If immediate testing is not possible, samples should be stored at 2–8°C for a maximum of 72 hours.

Fine needle aspiration biopsy (FNAB) of lymph nodes[29]	Xpert and Ultra
Storage	❖ Please refer to national standard operating procedures for instructions on the medium to use for FNAB sample storage and transportation. ❖ Store at room temperature.
Transport	❖ Samples should arrive in the testing laboratory within one day of collection, preferably on the day of collection. ❖ Packaging of FNAB samples must be of good quality and be strong enough to withstand leakage of contents, shocks, pressure changes, humidity, vibration, and manual or mechanical handling considered incident to ordinary transportation. It should follow the standard triple packaging system**.**

ANNEX 3: Common forms of extrapulmonary TB in children and diagnostic approaches[1]

Site of disease	**Practical approach to diagnosis**
Peripheral lymph node (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g., disseminated)	Chest radiograph and lumbar puncture (to test for meningitis)
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g., peritoneal)	Abdominal ultrasound (3) and ascitic tap
Osteoarticular TB	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap
Tuberculous meningitis	Lumbar puncture (and imaging where available)

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