Therapeutic Considerations in TB

Plenary Symposium 5: Common Issues and Controversies in Childhood Tuberculosis

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23rd Annual Convention, PIDSP

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Gorilla
(Gorilla gorilla)
Bonobo
(Pan paniscus)
Orangutan
(Pongo pygmaeus)
Chimpanzee
(Pan troglodytes)

Case Scenario 1

- 13-month-old male infant
- Prolonged fever and cough
- TST 22 mm induration, 72 hrs
- Chest X-ray: probably normal (poor inspiration, vessel crowding)
- Grandmother lives with family

- Vulnerable age group
- Other S/S? Wt loss, weakness, poor appetite RR, auscultation findings,
- Infectious process, pulmo?

Rule out bacterial infection

- Significant reaction - TB infection
- Poor CXR procedure

  Given antimicrobials?
- Exposure? Status, other household members

Work – up OPD

- Gastric aspirates: all AFB smears negative
- Third aspirate, 2 wks: grew *Mycobacterium tuberculosis*
- Repeat CXR, 2 wks: left lower lobe infiltrate
- Treatment HRZE (strain sensitive to all agents)
- Child improved within a few days; clinically well & cured
- Treatment discontinued after 2 weeks
- Negative smear does not rule out TB; can do rapid test too (Xpert MTB/RIF)
- Ignore CXR & culture +?
- Source? What if Lola is smear positive?
- Smart to d/c treatment in spite of positive culture and lobar infiltrate, with clinical improvement?

WHO/HTM/TB/2006.371
WHO/FCH/CAH/2006.7

Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children

World Health Organization

RAPID ADVICE

Treatment of tuberculosis in children

World Health Organization

INTERNATIONAL STANDARDS FOR

Tuberculosis Care

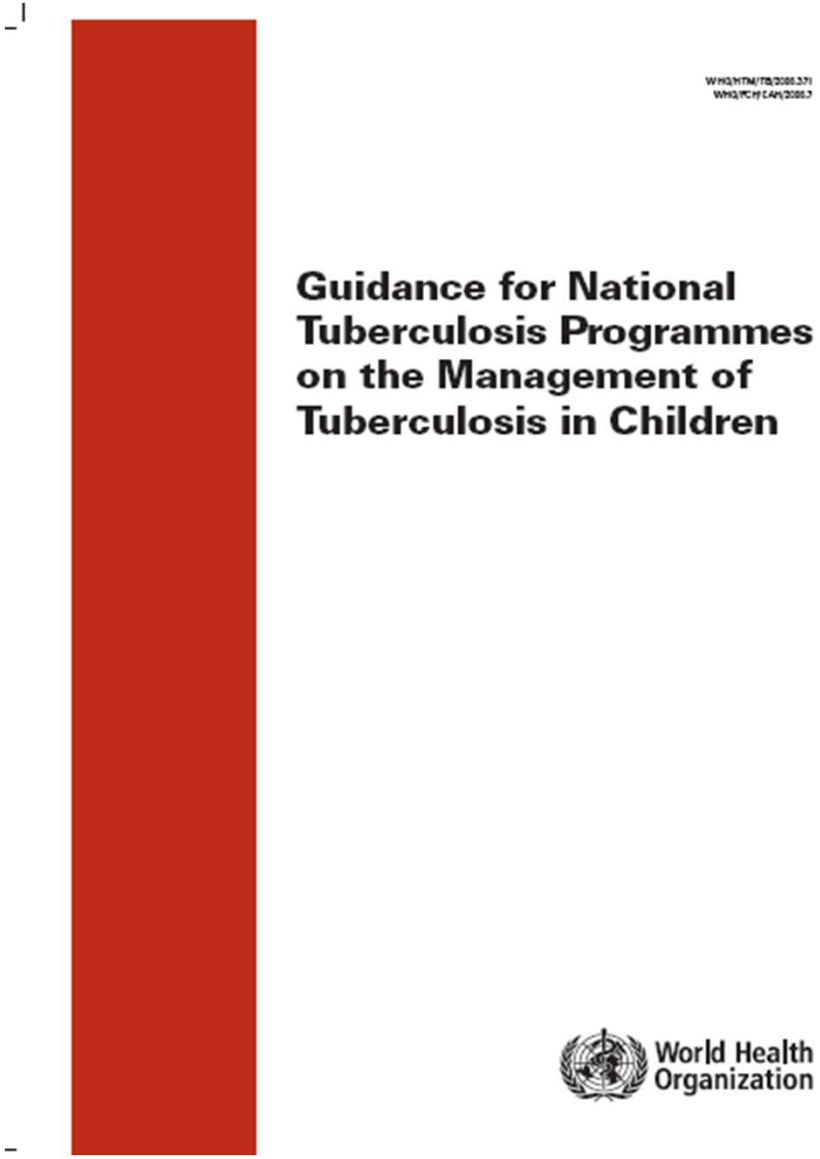
DIAGNOSIS TREATMENT PUBLIC HEALTH

National Tuberculosis Control Program

MANUAL OF PROCEDURES

5th Edition

28 Recommendations



- **On Diagnosis** Rec #1-7

  Xpert MTB/RIF, #1- 4

  IGRAs, #5

  Commercial serodx, #6

  Routine HIV testing, #7

- **On Treatment** Rec #8-14

- endemicity, HIV or TB setting, resistance MDR-/XDR-; contact investigation, IPT

- **Children living with HIV &/or TB** Rec #25-26

- **Mx of DR-TB in Ch** Rec #27

- **NTP imp & mx; integration** Rec #28

Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

Suspected pulmonary TB

Chest radiography is useful in the diagnosis of TB in children. In most cases, children with pulmonary TB have radiographic changes suggestive of TB; the commonest picture is one of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-negative children is highly suggestive of TB.

Good-quality chest radiographs (including lateral view, if and where possible) are essential for proper evaluation and should preferably be read by a radiologist or a health care worker trained in their reading. A practical guide for interpreting chest radiographs of children with suspected TB has been developed.

Use of Xpert MTB/RIF in children

- Recommendation 1

  Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

  (Strong recommendation, very low quality of evidence)

Use of Xpert MTB/RIF in children

- **Recommendation 2**

  Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

  (Conditional recommendation acknowledging resource implications, very low quality of evidence)

Box 1. Guidance on approach to diagnosis of TB in children

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin testing
- Chest X-ray (if available)
- Bacteriological confirmation whenever possible
- Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
- HIV testing

Box 2. Key risk factors for TB in children

- Household or other close contact with a case of pulmonary TB (especially smear-positive or culture-positive pulmonary TB)
- Age less than 5 years
- HIV infection
- Severe malnutrition

Figure 1. **Symptom-based screening approach to child contact management[a]**

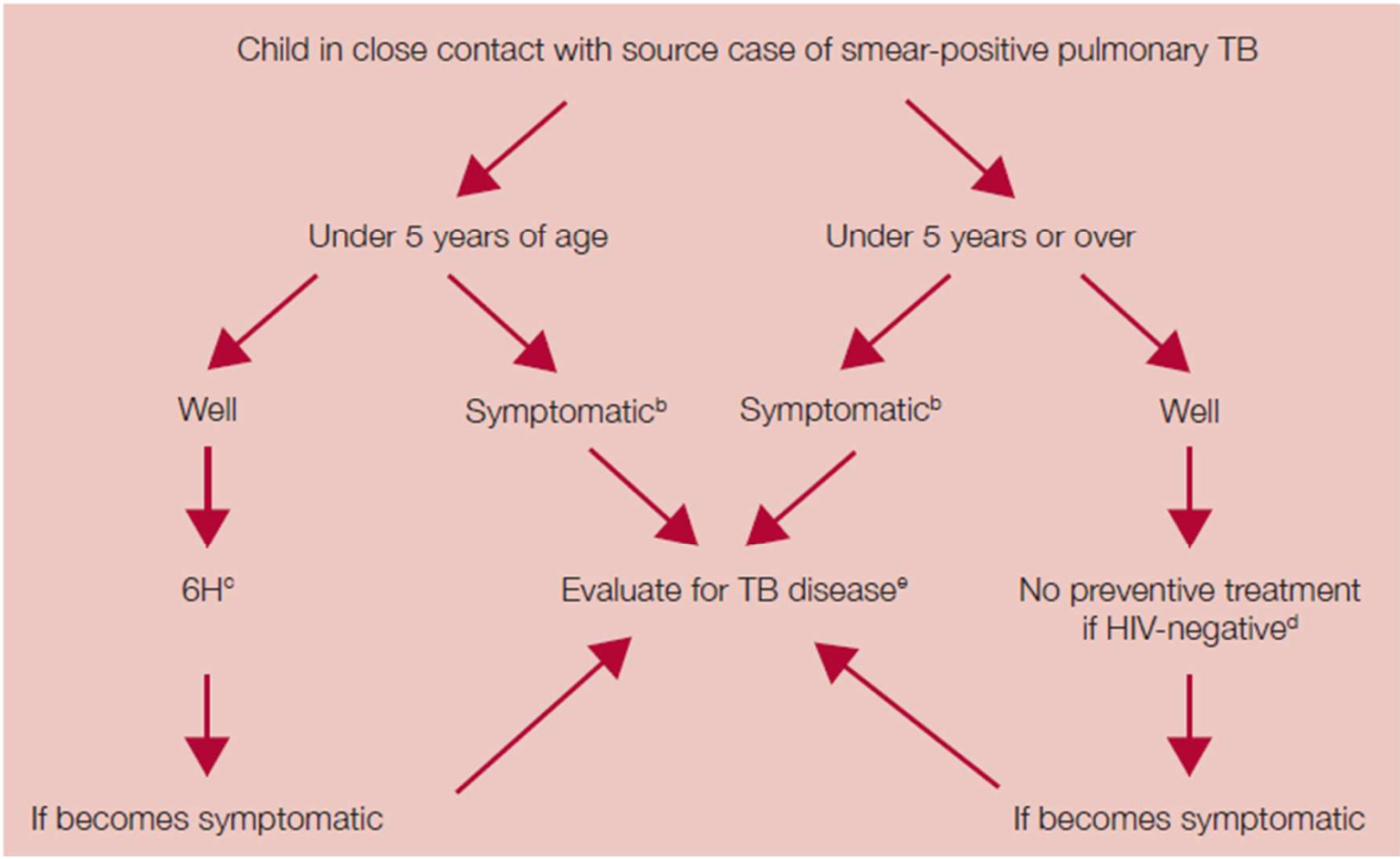


Table 3. **Recommended daily doses of first-line anti-TB drugs for children**

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose (mg)
Isoniazid	10 (7-15)[a]	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	–
Ethambutol	20 (15–25)	–

[a] The higher end of the range for isoniazid dose applies to younger children; as the children grow older the lower end of the dosing range becomes more appropriate.

Remark: As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations, as further discussed in Annex 5.

Recommendation 18 WHO ARE AT RISK?

Clinical evaluation of household and close contacts for active TB should be done on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts who are:

-children with symptoms suggestive of TB,

-children <5 years of age,

-children with known or suspected immunocompromising conditions (especially those living with HIV), and

-child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)

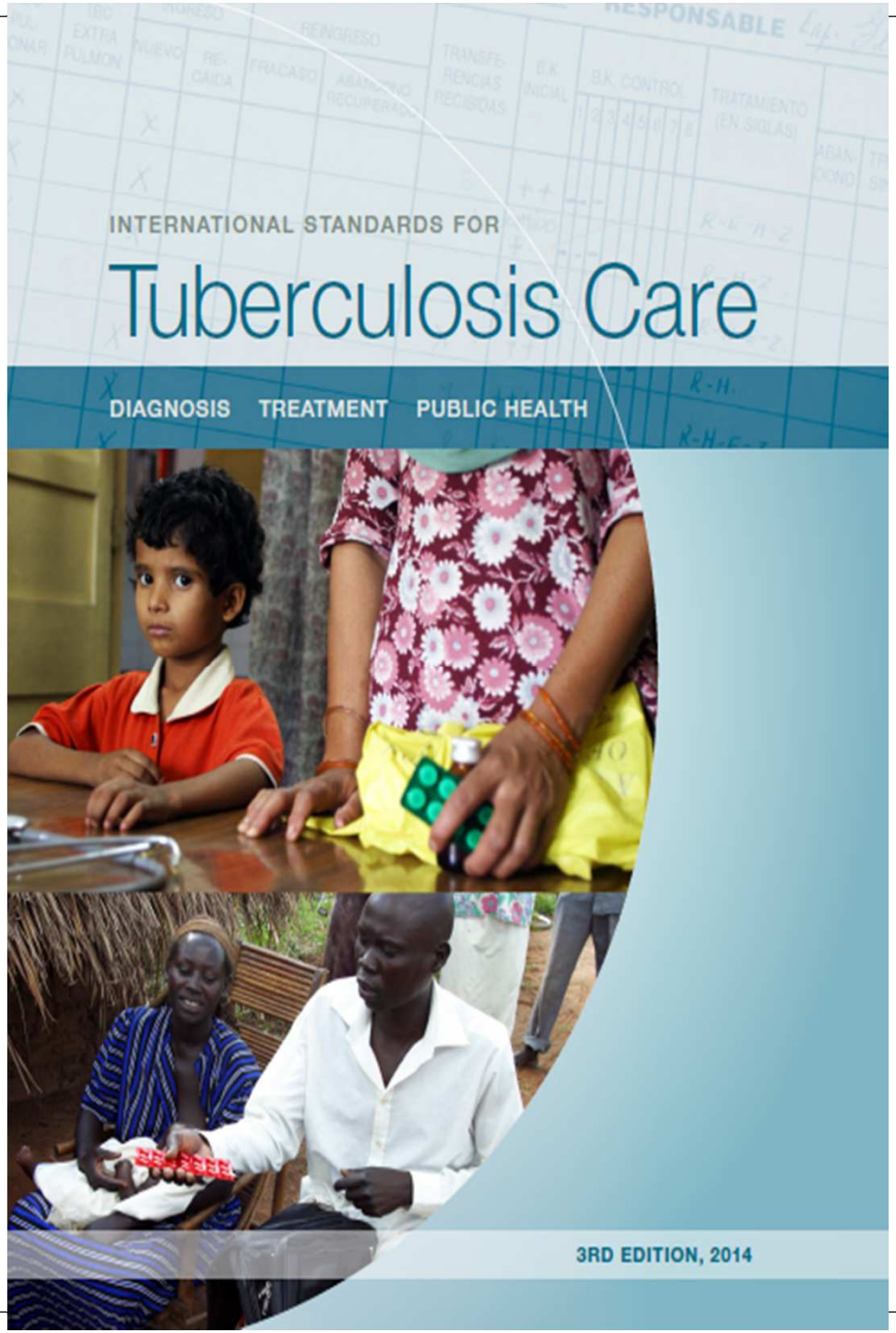
(Strong recommendation, very low quality of evidence)

Recommendation 19 *(new)*

It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- has sputum smear-positive pulmonary TB;
- has multidrug-resistant or extensively drug-resistant TB (proven or suspected);
- is a person living with HIV; or
- is a child <5 years of age

(Strong recommendation, very low quality of evidence)


INTERNATIONAL STANDARDS FOR
Tuberculosis Care
DIAGNOSIS TREATMENT PUBLIC HEALTH
3RD EDITION, 2014

21 STANDARDS

- **Standards for Dx,** #1-6

Early dx, #1

Cough, CXR, #2

Smear, Xpert, #3-6

- **Standards for Treatment,** #7-13
- **Standards for HIV,** co-morbids #14-17
- **Standards for Public Health & Prevention,** #18-21

ISTC Standard 1

- To ensure early diagnosis, providers must be aware of individual and group risk factors for tuberculosis and perform prompt clinical evaluations and appropriate diagnostic testing for persons with symptoms and findings consistent with tuberculosis.

- Patient diagnosed early
- Young age, risk factor
- Symptoms consistent with TB; other info needed (weight percentile? Poor activity or weakness?)
- TST done
- CXR done
- Gastric secretion study: AFB smear negative but positive culture 3rd +

ISTC 2

- All patients, including children, with unexplained cough lasting **two** or more weeks or with unexplained findings suggestive of tuberculosis on chest radiographs should be evaluated for tuberculosis.
- Duration of cough not mentioned - can also be less than two weeks, considering other clinical manifestations
- 2nd CXR on follow-up after 2 wks, left lower lobe infiltrate

ISTC 2

- In TB… "the cough is often accompanied by systemic symptoms such as **fever, night sweats, and weight loss**. In addition, findings such as **lymphadenopathy** consistent with concurrent extrapulmonary tuberculosis, may be noted.
- **However,** "10–25% of patients with bacteriologically-confirmed tuberculosis do not report cough…chronic cough with sputum production is not always present, even among persons having sputum smears showing acid-fast bacilli. Data from several tuberculosis prevalence surveys show that an important proportion of persons with active tuberculosis do not have cough of 2 or more weeks that conventionally has been used to define suspected tuberculosis.

Symptom Review (Symptom-based Screening)

- "evaluation for tuberculosis, using a symptom review that includes, in addition to **cough of 2 weeks or more, cough of any duration, fever, night sweats, or weight loss,** may be indicated in select risk groups, especially in areas where there is a **high prevalence** of the disease and in high risk populations and individuals with increased susceptibility, such as persons with HIV infection. Use of this broadened set of questions in a population of PLHIV was found to have a **negative predictive value** of 97.7% for tuberculosis. [Comment: pursue as research Q in pedia CPG]

ISTC 2

- "…in high prevalence countries, tuberculosis will be one of the leading diagnoses to consider, together with other conditions…Tuberculosis should also be considered in the differential diagnosis of **community acquired pneumonia,** especially if the pneumonia fails to resolve with appropriate antimicrobial treatment.

ISTC 2 …Sputum, rapid tests

- Although sputum (or other specimen) smear microscopy remains the most widely available test to establish a microbiological diagnosis, other more sensitive means of identifying *M. tuberculosis, particularly rapid molecular tests, are rapidly gaining acceptance as…*

ISTC 2 … Chest Xray

- In many settings … the initial test used for persons with cough (to consider conditions like TB).
- …may serve as the **entry point** for a TB diagnostic evaluation.
- Also… useful to evaluate persons who are suspected of having TB but have negative sputum smears and/or negative Xpert MTB/RIF.
- However, a diagnosis of tuberculosis **cannot be established by radiography alone.**

- CXR was done initially, with follow-up after 2 weeks (Also grew MTb on culture of 3rd gastric aspirate)
- Left lower lobe infiltrate – what was considered?
  - treatment options?

ISTC 3

…children, who are suspected of having pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert® MTB/RIF* testing in a quality-assured laboratory. **Patients at risk for drug resistance, who have HIV risks, or who are seriously ill**, should have Xpert MTB/RIF performed as the initial diagnostic test. Blood-based serologic tests and interferon-gamma release assays should not be used for diagnosis of active tuberculosis.

- Patient's data do not conform to any of the 3 conditions
- Sputum by gastric aspiration 3X, all negative AFB smear, but grew TB culture #3
- Candidate for Xpert? Maybe –

ISTC 3

- Currently, WHO recommends that the Xpert MTB/RIF assay should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults and children **suspected of having MDR TB or HIV-associated tuberculosis.**
- Data suggest that a combination of sputum smear microscopy and Xpert MTB/RIF can substantially increase the diagnostic yield. Xpert MTB/RIF as an add-on test following a negative smear microscopy result has a sensitivity of 68% and specificity of 99% compared with culture.
- WHO recommendations also indicate that Xpert MTB/RIF may be used as the initial test in all patients if resources are available.

ISTC 5

- In patients suspected of having pulmonary TB whose sputum smears are negative, Xpert MTB/RIF and/or sputum cultures should be performed.
- Among patients with sputum that is negative by smear and Xpert MTB/RIF who have clinical evidence strongly suggestive of tuberculosis, antituberculosis treatment should be initiated after collection of specimens for culture examination.

ISTC 6

- For all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of respiratory secretions (expectorated sputum, induced sputum, gastric lavage) for smear microscopy, an Xpert MTB/RIF test, and/or culture.

ISTC 6

- The diagnosis of TB in children relies on a thorough assessment of all the evidence derived from a careful history of exposure, clinical examination, and other relevant investigations.
- Although most children with TB have pulmonary involvement, they commonly have **paucibacillary** disease without evident lung cavitation but frequently with involvement of intrathoracic lymph nodes. Consequently, compared with adults, sputum smears from children are more likely to be **negative**.
- Although bacteriological confirmation of tuberculosis in children is not always feasible, it should be sought **whenever possible** by sputum (or other specimen) examination with Xpert MTB/RIF, smear microscopy, and culture. Because many children less than five years of age do not cough and produce sputum effectively, culture of **gastric lavage** obtained by naso-gastric tube or induced sputum has a higher yield than spontaneous sputum.

Guidance on approach to diagnose TB in children

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Chest X-ray if available
5. B acteriological confirmation whenever possible
6. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
7. HIV testing

FIND THE MISSING CHILDREN

WHO's Integrated Management of Childhood Illness (IMCI) program, which is widely used in first-level facilities in low- and middle-income countries states that tuberculosis should be considered in any child with:

- Unexplained weight loss or failure to grow normally;
- Unexplained fever, especially when it continues for more than 2 weeks;
- Chronic cough;
- Exposure to an adult with probable or definite pulmonary infectious tuberculosis.

2HRZE? or 2HRZ?

Quadruple? Or Triple?

Hmmmmmm, thinking about it...

2HRZE? or 2HRZ?

- **Evidence of isoniazid resistance will require quadruple therapy**

- **Primary TB involving hilar nodes, likely to be paucibacillary, for triple therapy. Besides, the drug sensitivity is for all four drugs, including isoniazid.**

- **Lobar TB disease, likely to be multibacillary, for quadruple therapy**

RAPID ADVICE

Treatment of tuberculosis in children

World Health Organization

Quadruple therapy in intensive phase when isoniazid resistance is high

WHO Recommendation 2

Children living in settings where the prevalence of the HIV is high, or **where resistance to isoniazid is high**, or both, with suspected or confirmed **pulmonary tuberculosis or peripheral lymphadenitis**; OR,

Children with **extensive pulmonary disease** living in settings of low HIV prevalence or low isoniazid resistance

Should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the following dosages:

Isoniazid (H) – 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day

Rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day

Pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)

Ethambutol (E) – 20 mg/kg (15-25 mg/kg)

(Strong recommendation, moderate-quality evidence)

PPS Position:

AGREE

CASE Scenario 2

- 15-year-old girl
- 9-day history of productive cough and fever
- unresponsive to amox
- CXR bilateral lower lobe infiltrates
- Sputum smear positive
- For TB culture, Xpert
- Dx: Pulmonary TB (r/o CAP resistant to amox; or worse, EPTB)
- Missing Information

  Other symptoms: wt loss

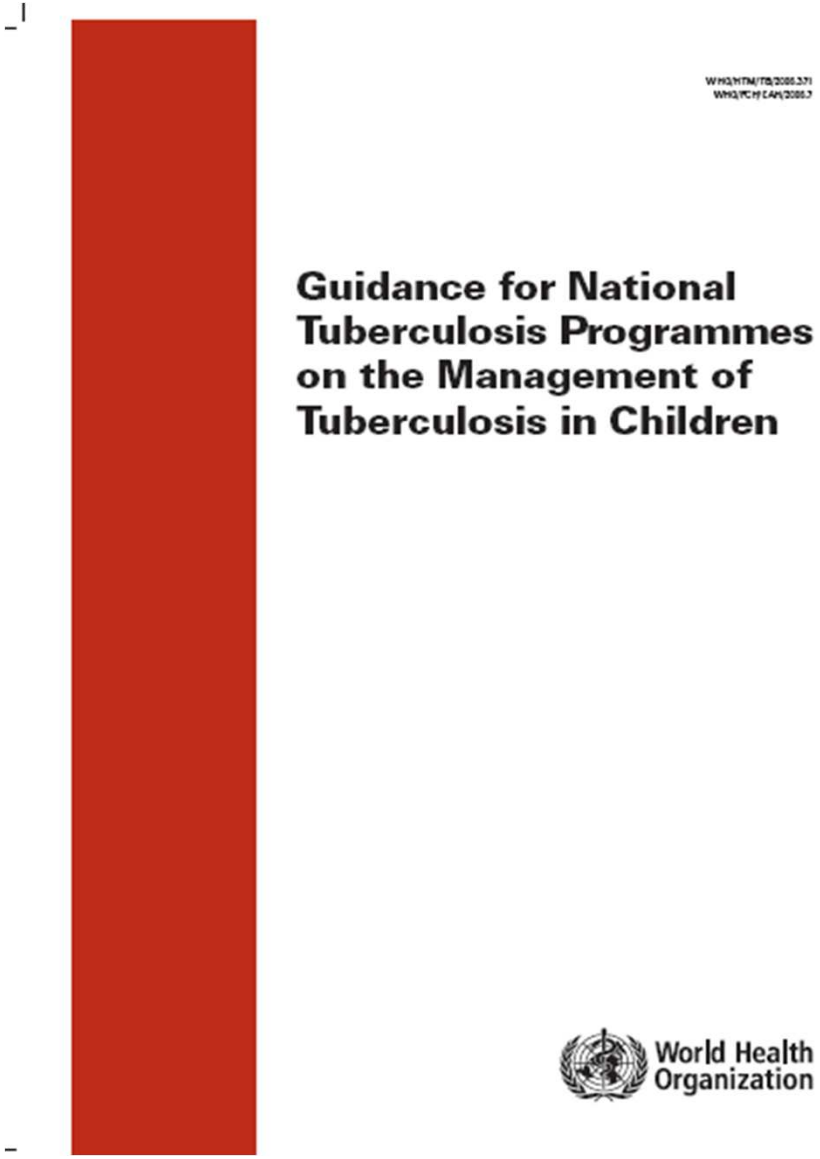
  BCG

  Past Medical Hx (TB)

  Family History (ie, TB)

  PE (sensorium, wt, chest, lymph nodes, neuro exam, organomegaly)
- Work-up: HIV test

28 Recommendations



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2014 WHO Guidance Recommendation 7

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB.
(Strong recommendation, low quality of evidence)

Adolescent patients with TB have radiographic changes similar to adult patients, with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease with hilar adenopathy and collapse lesions.

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Remark: As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations, as further discussed in Annex 5.

Progress Toward Appropriate Medicines for Childhood TB

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October 27, 2014

Childhood TB Subgroup Meeting

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

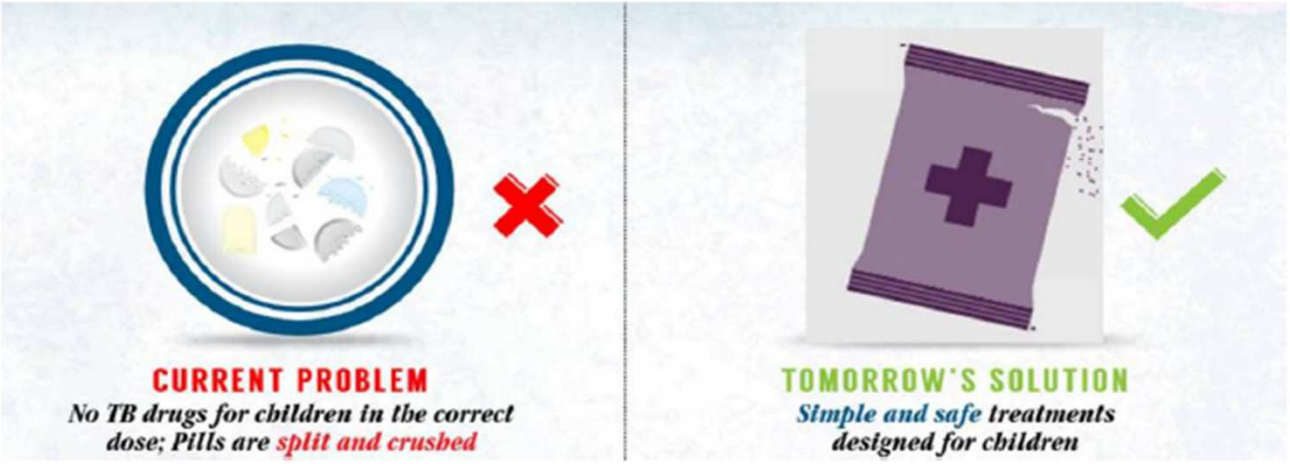
UNITAID

USAID
FROM THE AMERICAN PEOPLE

The Problem

Children with TB are the neglected of the neglected

- **The market for pediatric medicines is "broken" and needs repair and requires:**
  - Better estimates of how many children get TB and where they are located
  - Clarity on drug registration pathways
  - Consistency of treatment policies and practices
  - Prioritization by governments, donors, in-country stakeholders (i.e., NGOs, private sector) and drug companies



Overview

Speeding Treatments to End Pediatric TB (STEP)-TB

Unmet Medical Need

Not enough kids being treated – and not being treated appropriately

Goal

Increase access to correctly dosed, properly formulated, affordable, high quality pediatric TB medicines

Implementing Partner

World Health Organization

Key Product Information

- ❑ Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150 mg
- ❑ Rifampicin 75 mg + Isoniazid 50 mg

- Availability: mid to late 2015 through Expert Review Panel (ERP) and through Global Drug Facility (at least one manufacturer)
- Registration: submit for WHO Prequalification by early 2015 (at least two manufacturers); pursue local registrations in parallel
- Formulation: dispersible; flavors—mango, strawberry, raspberry
- Price: close to currently available pediatric products, dependent on anticipated volumes

- ❑ Ethambutol 100 mg
- ❑ Isoniazid 100 mg

- Availability/Registration: later timeline—6-12 months behind FDCs; one manufacturer committed
- Formulation: dispersible
- Price: close to currently available products, dependent on anticipated volumes

Video: Anatomy of Neglect

- Click the link below to view the video:
  - https://www.youtube.com/watch?v=o8zr5OMcuok

SMART OR SMARTER

SMART OR SMARTER

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