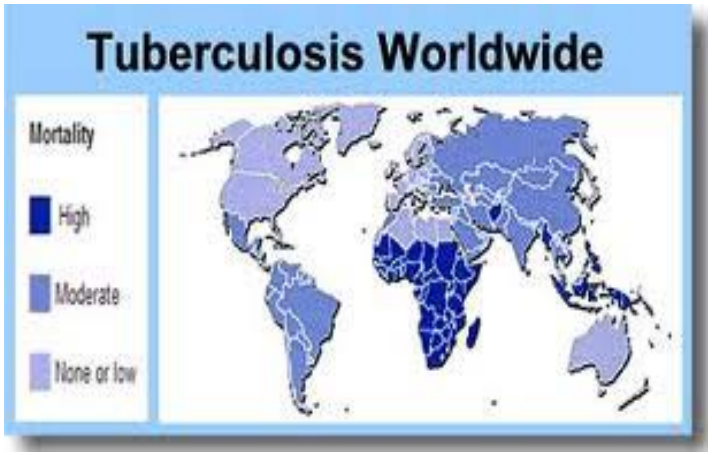
Childhood Tuberculosis: Diagnosis, Treatment and Prevention of TB in HIV-infected Children

Celia DC Christie-Samuels
Professor of Paediatrics
(Infectious Diseases, Epidemiology and Public Health)
University of the West Indies, Jamaica



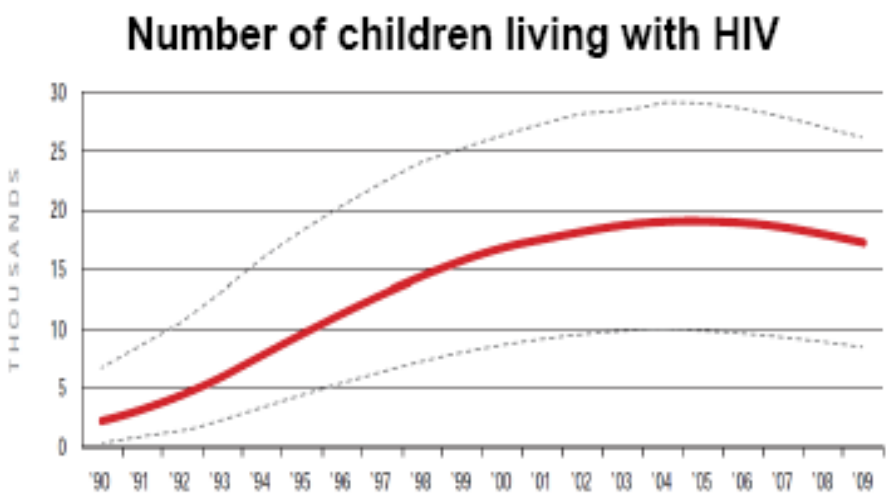
The Problem

- One million new TB cases in children < 15 years old annually (WHO)
  - 11% of annual burden of cases
- Frequency depends on local TB/HIV epidemic, age structure, diagnostic tools, Rxn, contact investigation
- Children present with TB at any age
- Transmission to a child, results from close infected adult or adolescent contact
- TB infection → Gohn focus → regional adenopathy
- CMI halts disease progression, not functioning in HIV+

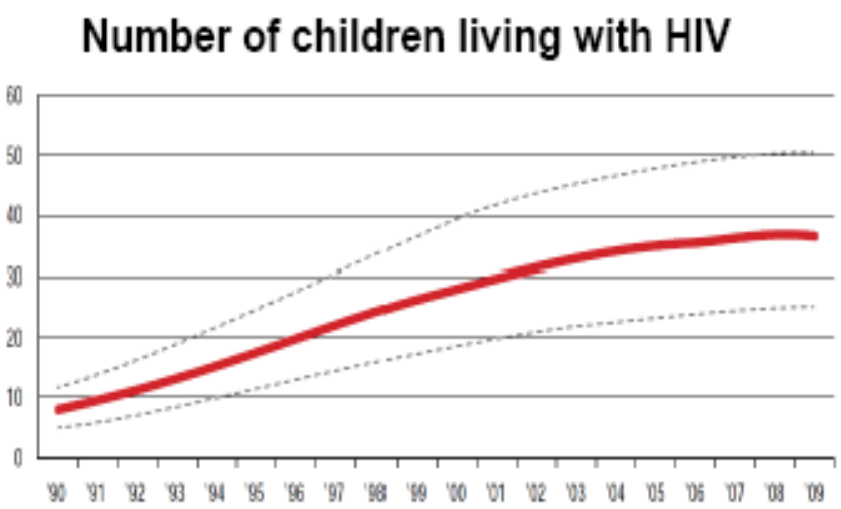
Children Living with HIV in Latin America and the Caribbean

Number of children living with HIV, 1990-2009

Caribbean



Central America



Fuente: UNAIDS. AIDS epidemic update 2010.

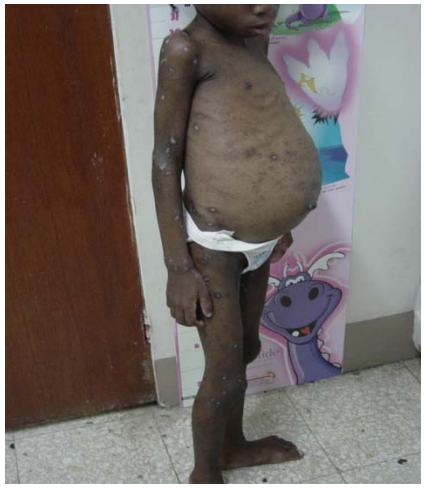
DIAGNOSIS

Clinical Presentations in Children

- Pulmonary TB
  - Mostly primary (not reactivation)
  - Uncomplicated
    - Unilateral adenopathy, cervical adenitis
    - Typical primary complex
      - Hilar, mediastinal adenopathy, lung opacity
  - Complicated
    - Lobar/ segmental adenopathy, bronchial compression
    - → atelectasis
    - Unilateral hyperinflation
    - Cavitation (rare)
    - TB bronchopneumonia
- Adenopathy, cervical adenitis
- Meningitis, tuberculomas
- Disseminated TB
- TB effusions
  - Pericarditis, pleuritis, peritonitis
- Spinal TB

Presentations of TB in Children with HIV

- Depends on stage of HIV
- Early HIV infection
  - TB presentation same as in HIV negative child
- Late HIV infection
  - Disseminated TB common, eg., meningitis, miliary, TB adenopathy
- Older children with TB/HIV
  - Same presentation as in HIV+ adults
- TB/HIV co-infection have longer hospital stays, malnutrition, higher mortality
- High index of suspicion for TB in HIV+ child
- Isolate *M. tuberculosis* from expectorated sputum, lymph node, CSF, effusions, tissue

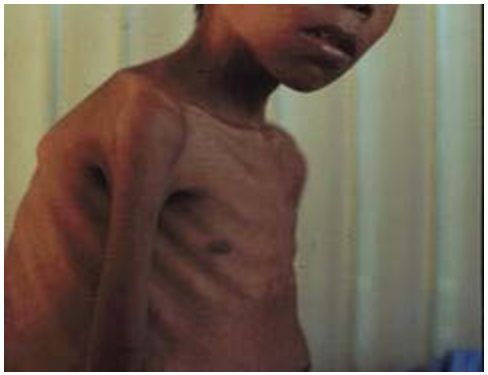


Diagnosis of TB in HIV-infected Children

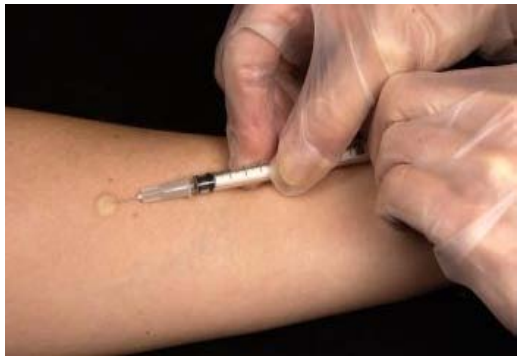
- Children do not produce sputum,
  - sputum, gastric washings usually M. tb-negative
- Careful history
  - Chronic cough > 2-3 weeks
  - Fever > 14 days, excluded common causes
  - Weight loss, failure to thrive
- Contact
  - Older household, caregiver with smear-positive TB
  - Especially HIV-infected adults

Clinical Examination

- Uncommon, highly suggestive
  - Gibbus, vertebral TB
  - Painless, cervical adenopathy with fistula formation



- Meningitis, not responding to antibiotics
- Pleuritis
- Pericarditis
- Ascites
- Painless adenopathy without fistula
- Painless joint enlargement
- Tuberculin hypersensitivity

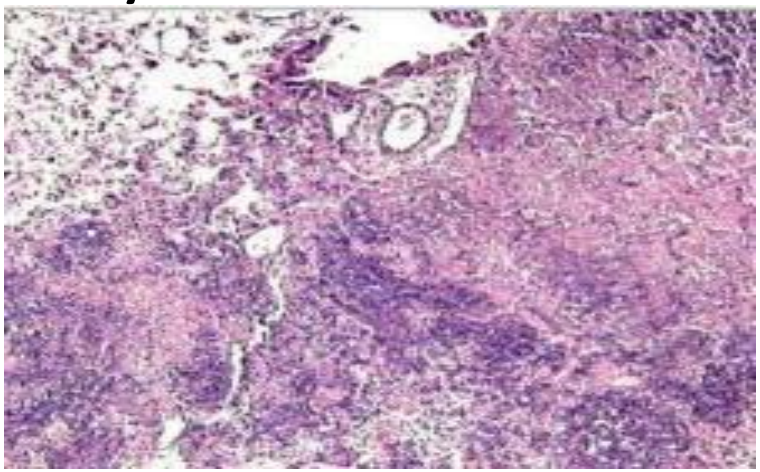


Mantoux Tuberculin Skin Test

- Mantoux is positive with TB infection
- Mantoux+ with suggestive clinical symptoms is diagnostic of tuberculosis disease
  - Usually, 5 tuberculin units of PPD, trained health care workers administer test
  - High risk cases: TST $\geq$ 5 mm
  - HIV+, close contacts to active TB, malnutrition, CXR suggestive of TB
  - All other children: TST $\geq$ 10 mm induration,
    - Without regard to BCG vaccination status
  - Negative Mantoux does not exclude active TB disease, especially in HIV-infected children

Bacteriologic Confirmation

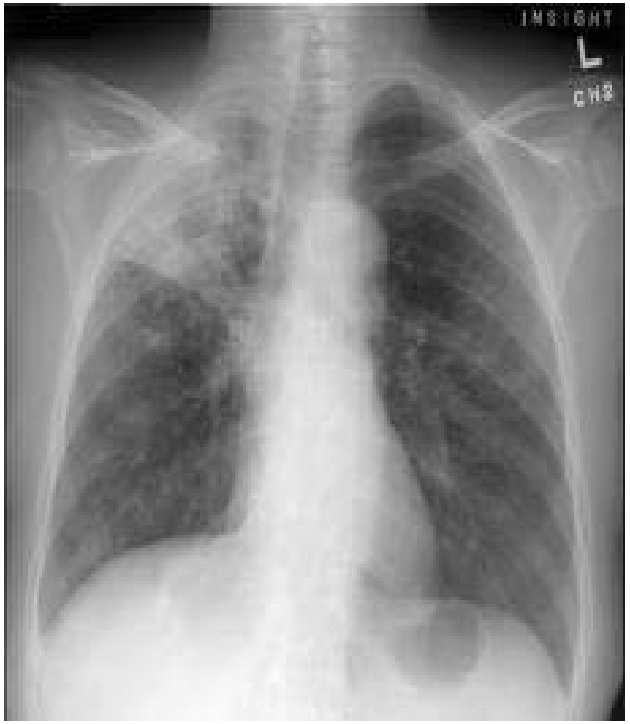
- Bacteriologic diagnosis preferable, using available specimens, especially for
  - Suspected drug resistance
  - HIV infection
  - Complicated/ severe cases
  - Uncertain diagnosis



- Sputum in children > 10 years
- Gastric aspirates
- MTB-RIF Xpert rapid dx also applies to children

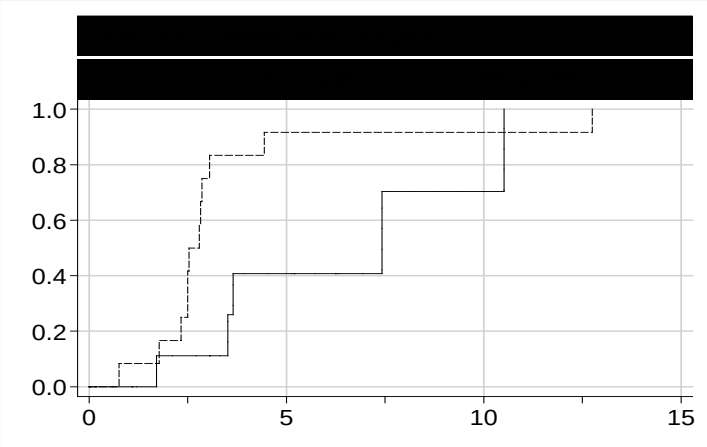
Investigations for Pulmonary and Extra Pulmonary TB

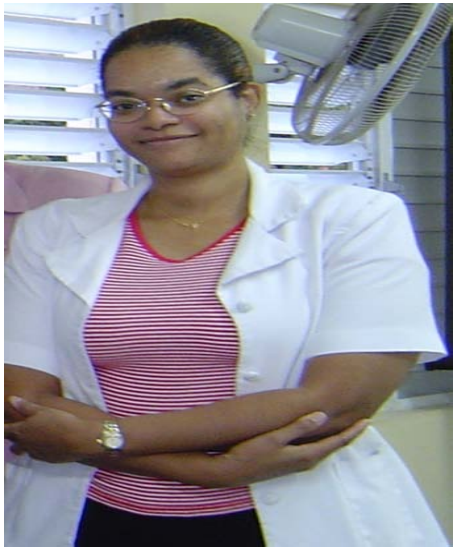
- CXR changes of TB
  - Persistent lung opacities
  - Collapse consolidation
  - Hilar/mediastinal adenopathy
  - Opacification does not improve after antibiotics
  - Pleural effusions
- Histology, other special investigations (EPTB), CSF for TB meningitis
- PCR, interferon gamma release assay (IGRA), need more research for TB diagnosis in children
- CT, MRI's, bronchoscopy not usually recommended in children



HIV and TB Co-infections in Jamaican Children

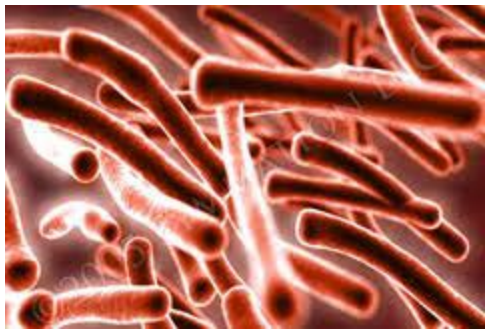
- Significant increase in TB and TB/HIV co-infections at UHWI over four years
- 24 TB cases; All had BCG vaccine
- HIV–infected statistically more likely to be
  - Older
  - Have failure to thrive
  - Digital clubbing
  - Hepatomegaly
  - Splenomegaly
  - Generalized adenopathy
  - Negative Mantoux skin tests
- Appropriate in house-anti-TB Rxn, > 2 mos
- Death more likely and hospital stay longer in HIV infected vs., non-infected
- Household family members with active TB in 12 cases





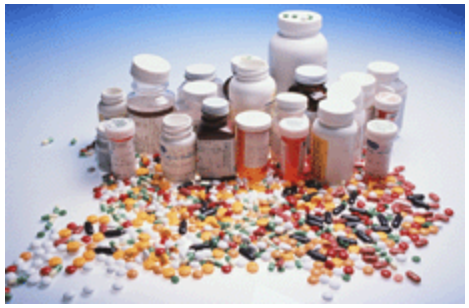
Geoghagen M, Farr JA, Hambleton I, Pierre R, Christie CDC. *WIMJ*, 2004:53;5:339-345.

TREATMENT



Treating Childhood TB/HIV

- New smear negative PTB and less severe EPTB
  - 2 mos INH, RIF PZA plus 4 mos INH, RIF
- New smear positive TB, new smear negative TB with extensive parenchymal involvement, Severe EPTB, or Severe concomitant HIV disease
  - 2 mos INH, RIF, PZA, ETH plus 4 mos INH, RIF
- Miliary TB and TB meningitis: use higher doses
  - 2 mos INH, RIF, PZA, STR plus 4 mos INH, RIF (WHO), or
  - 2 mos INH, RIF, PZA, STR (or ETH) plus 5-7 mos INH, RIF (AAP)
- Previously treated smear positive TB, with relapse, treatment after interruption, treatment failure
  - 2 mos INH, RIF, PZA, ETH, STR plus 5 mos INH, RIF, ETH
- MDR TB
  - Special regimens, after consultation

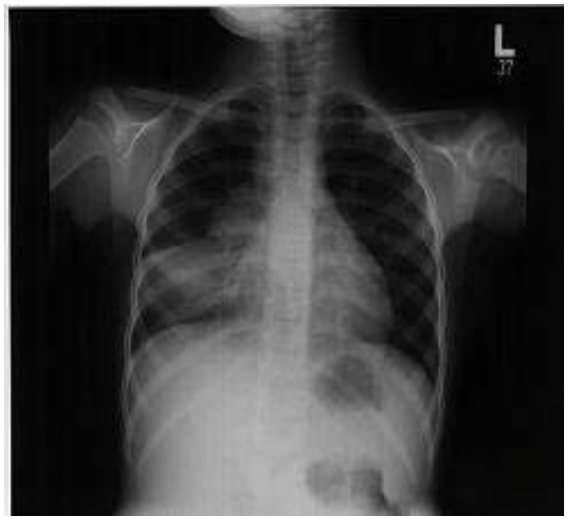


Management of HIV-related TB

- Cotrimoxazole prophylaxis
  - Daily, prolongs survival and reduces respiratory infections and hospitalizations
  - All HIV+ children with advanced immune-suppression should be placed on cotrimoxazole
- Antiretroviral therapy
  - In HIV+ child, priority is to commence anti-TB drugs
  - Many drug-drug interactions between ARV's and RIF
  - Similar adverse reactions in anti-TB drugs and ARV's
  - When to start, not optimally determined for children
  - Consider degree of immune-suppression and child's progress during anti-TB Rxn

Timing of ART after anti-TB Treatment with Rifampin-containing regimen

- Extra Pulmonary TB
  - Start ART 2-8 wks after anti-TB treatment
- Pulmonary TB and lymph node TB
  - If clinical Mnx:
    - Start ART 2-8 wks after anti-TB Rxn or
    - Delay ART until anti-TB Rxn completed
  - CD4 values available
    - Severe/advanced immune deficiency
      - Start ART 2-8 wks after anti-TB Rnx
    - Mild or no immune deficiency
      - Delay ART until anti-TB Rxn is completed



- ART's:
  - < 3 years -- Triple NRTI 1st line regimen d4T /AZT + 3TC+ ABC, or 2 NRTI's + NVP
  - > 3 years: triple NRTI 1st line d4T/ AZT + 3TC +ABC, or standard 1st line 2 NRTI's + EFV

Special Considerations

- Immune reconstitution
  - Exacerbation of symptoms, signs, CXR manifestations after anti-TB therapy
  - Self limited, consider steroids
- Steroids for TB meningitis, miliary TB, airway obstruction by TB lymph glands, pericarditis
  - Improves survival, reduces mortality
  - Taper the dose after 4 weeks

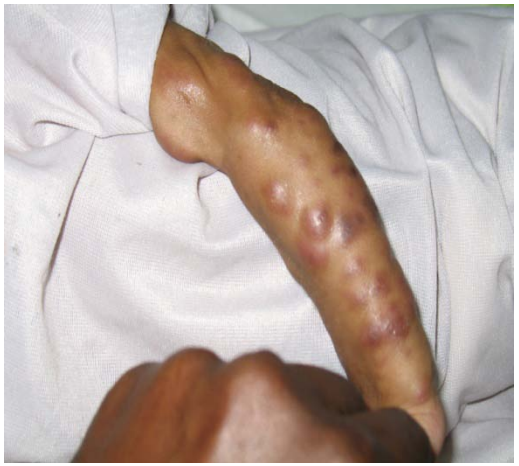
Adherence

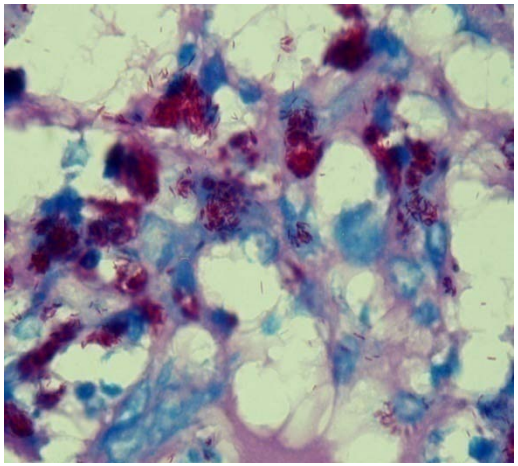
- Educate children and caregivers about TB and importance of completing therapy
- Support for care giver/family, record doses on Rxn card
- Treatment should be free, give fixed dose drugs
- Hospitalise children with severe TB for intensive management
  - Meningitis
    - Local vasculitis, tuberculoma, raised ICP and hydrocephalous
  - Miliary TB
  - Respiratory distress
  - Spinal TB
  - Severe adverse events, eg., hepatotoxicity
  - Adherence questionable

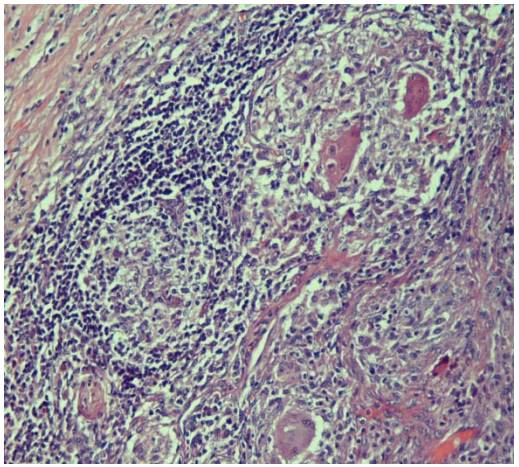
Monitoring During Treatment

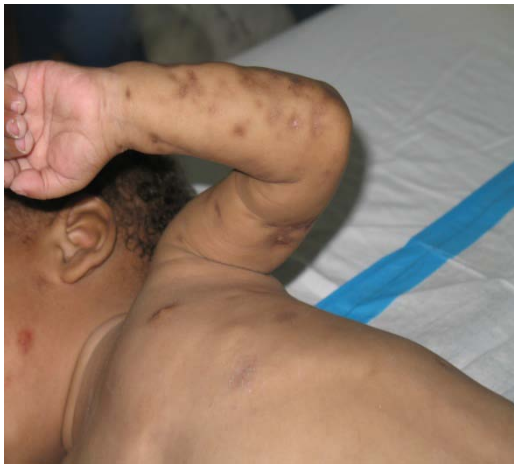
- Symptom assessment
- Adherence
- Adverse events, eg., LFT's, haematology, rashes, IRIS
- Weight and medication adjustment for wt. gain
- Adherence and reviewing treatment card
- Followup sputum for AFB smear microscopy (if +)
  - Followup CXR's not routine, slow recovery
  - Non-response → drug-resistance, complications, non-adherence, other?

Isoniazid-resistant Disseminated *M. tuberculosis* in a Jamaican Infant with HIV/AIDS









l **Singh-Minott**, RB Pierre, O Olugbuyi, J Dunkley-Thompson, D Haughton, CDC Christie. ***West Indian Med J*** 2008;57(3):298-302.

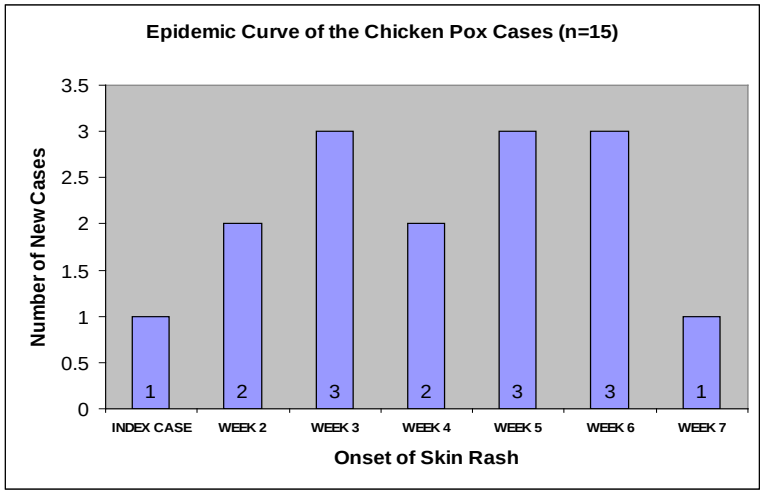
PREVENTION

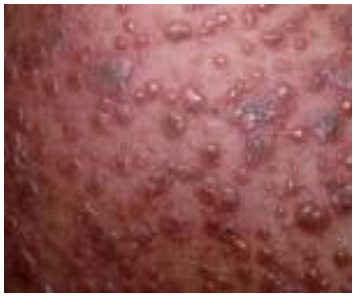
Child Contact

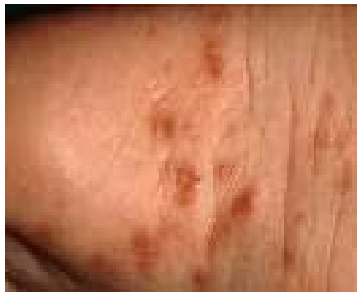
- Newly infected children with TB at high risk for miliary TB, meningitis if no preventive Rxn
- Close contact screening and management, adults family member, day-care contact with infectious TB
- Mantoux skin test-positive children:
  - If well (no symptoms, Normal CXR and growth), give INH preventive therapy x 6 months
  - If unwell, evaluate and treat for TB, if present
- Mantoux skin test negative children:
  - If well, IPT x 2 months, repeat Mantoux skin test
  - If positive at 2 months, continue IPT for 6-9 months
  - If negative at 2 months, discontinue IPT

Tuberculosis, Scabies and Chicken Pox Outbreaks in an Orphanage for Children with HIV/AIDS in Jamaica

- Concurrent outbreaks of tuberculosis (N=4), chicken pox (N=15), scabies (N=14) among 24 children residing in an AIDS orphanage
- Emphasizes need for:
  - Immunizations
  - Screening of staff and clients
  - Infection control
  - Education







Geoghagen M, Pierre R, Evans-Gilbert T, Rodriguez B, Christie CDC. ***WIMJ***, 2004:53;5:346-351.

Intensive Case Finding and Prevention in Children with HIV – TB Screening

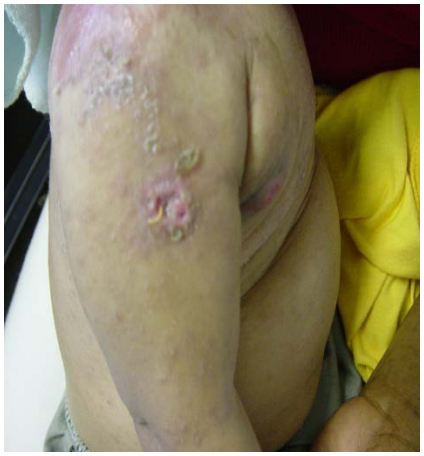
- Children living with HIV who do not have poor weight gain, fever, or current cough -- are unlikely to have active TB
- Children living with HIV who have poor weight gain, fever, or current cough, or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of age.
  - ***Strong Recommendation, low quality of evidence***

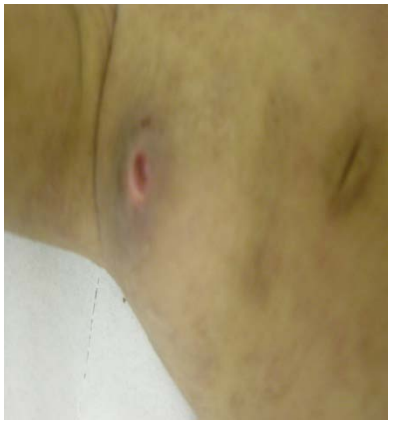
INH Regimen and Duration

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom screening and have no contact with a TB case should have 6 months of IPT (10 mg/kg/day)
- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB should receive 6 months of IPT, if the evaluation shows no TB disease
  - ***Strong recommendation, moderate evidence***
- All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional 6 months
  - ***Conditional recommendation, moderate evidence***

BCG lymphadenitis and Immune Reconstitution Syndrome in HIV-infected Children on Antiretroviral Therapy in Jamaica

- Three children with HIV infection developed BCG adenitis **after** initiation of highly active antiretroviral therapy (HAART)
- All “rapid progressors” with severe HIV/AIDS
- “Immune reconstitution syndrome”
- BCG vaccination should continue, per WHO policy





Dunkley-Thompson J, Pierre R, Steel-Duncan J, Palmer P, Davis D, Figueroa P, Christie CDC. ***West Indian Med J*** 2008;57(3):302-307.

BCG Vaccination in Children

- HIV-infected children who received BCG vaccine at risk for disseminated BCG disease
- Vaccinate:
  - HIV-uninfected children in high prevalence HIV+ populations
  - Infants born to women with unknown HIV status
  - HIV-exposed infants, asymptomatic, unknown HIV status
- Do not vaccinate:
  - Known HIV+ children, asymptomatic
  - Unknown HIV status in symptomatic children
  - Known HIV infected children, symptomatic


Are we going to see
THE END OF TB
in our lifetimes?
A call from the millennium children of the Eastern Mediterranean Region
Stop TB
STOP TB
BAHRAIN STOP TB
EGYPT STOP TB
JORDAN STOP TB
SAUDI ARABIA STOP TB
CYPRUS STOP TB
SOMALIA STOP TB
AFGHANISTAN STOP TB
PALESTINE STOP TB
OMAN
دحر السل
MOROCCO STOP TB
World Health Organization

Thank you