THE MANY FACES OF PEDIATRIC TUBERCULOSIS

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INFECTIOUS DISEASES
ALASKA NATIVE TRIBAL HEALTH CONSORTIUM/
PRIVATE PRACTICE
ANCHORAGE, AK
Objectives

- Describe current epidemiology of *M. tuberculosis* and compare Alaska’s rates to those around the USA and the world
- Identify age-related risks of progression to active tuberculosis
- Recognize various manifestations of pediatric tuberculosis and their likelihoods based on age and timing of exposure
- Discuss current and evolving methods for diagnosis of active TB in children
Disclosures

- None
March 24, 1882

TB Trivia

- Robert Koch was born in 1843 in...
  a) Vienna, Austria
  b) Clausthal, Germany
  c) Schivelbein, Pomerania
  d) Dole, France
Which of the following individuals is NOT believed to have died of tuberculosis?

a) Emily Brontë  
b) John Keats  
c) Frédéric Chopin  
d) Paul Gauguin  
e) René Laennec
The three states with the highest incident TB rates include:

a) Alaska, District of Columbia, and Hawaii
b) Louisiana, Texas, and Alabama
c) California, Arizona, and Florida
d) New York, Massachusetts, and Illinois
TB Trivia (4)

- Dr. Westley was destined to love TB because...
  a) His birthday is March 24 (World TB Day)
  b) His home state has been strongly influenced by the struggle against TB
  c) His niece in Cambodia was recently diagnosed with abdominal TB
  d) TB is the coolest disease ever
  e) All of the above
“Rogue” Housestaff

Going Rogue
An American Life
Beautiful Bethel Beaches
Note

ISONIAZID PROPHYLAXIS AMONG ALASKAN ESKIMOS:
A Final Report of the Bethel Isoniazid Studies

Summary

As a result of numerous trials, isoniazid prophylaxis was shown to be effective in preventing tuberculosis in many different populations and under a variety of conditions. However, the duration of the protective effect has been of some concern. In a previous report, the protective effect of isoniazid prophylaxis among Alaskan Eskimos was shown to persist through the fifteenth year after its administration. In this final report, the protective effect is shown to persist for more than 19 years. The magnitude of the effect is related to the amount of isoniazid taken. The results of the study are consistent with the hypothesis that the decrease in risk of tuberculosis produced by isoniazid preventive therapy is lifelong.

the rate in the placebo group. On the other hand, if tubercle bacilli harbored by infected persons are killed or otherwise rendered incapable of causing disease by isoniazid, or are decreased sufficiently in numbers so that the bodily defenses of most persons can handle the surviving bacilli, the drug’s protective effect should be lifelong, assuming that “exogenous” reinfection does not occur.

In a previous publication we reported that the effectiveness of isoniazid prophylaxis among Alaskan Eskimos had persisted through the fifteenth year after its administration (2). This final report extends our observations to slightly longer than 19 years. It deals with 2 topics: (1) the duration of effectiveness if isoniazid prophylaxis, and (2) the relationship of subsequent tuberculosis case rates to the amount of isoniazid taken in 2 Alaskan chemo-prophylaxis programs.
The Bethel Isoniazid Studies

- In 1934, one-third of all Alaska Native deaths were due to tuberculosis\(^1\)
- TB incidence of 3,000/100,000 in 1950s\(^2\)
- In 1957, the US Public Health Service began studies of isoniazid prophylaxis vs. placebo
- INH expanded to all residents in the Bethel area in 1963
  - 4 – 8 mg/kg daily x 12 months
- Patients followed for 19 years

<table>
<thead>
<tr>
<th>Annual Dose of Isoniazid Taken in Second Program (%)</th>
<th>Placebo in First Program</th>
<th>Isoniazid in First Program</th>
<th>Significance of Difference between Placebo and Isoniazid Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population (no.) (%)</td>
<td>Population (no.) (%)</td>
<td></td>
</tr>
<tr>
<td>Took &lt; 40 per cent of annual dose in first program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–39</td>
<td>208 8 3.85</td>
<td>191 4 2.09</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>40–69</td>
<td>82 1 1.22</td>
<td>103 1 0.97</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>70+</td>
<td>97 3 3.09</td>
<td>88 2 2.27</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>387 12 3.10</td>
<td>382 7 1.83</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Took 40 to 69 per cent of annual dose in first program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–39</td>
<td>210 5 2.38</td>
<td>210 3 1.43</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>40–69</td>
<td>140 4 2.86</td>
<td>160 0 —</td>
<td>P &gt; 0.05</td>
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<tr>
<td>70+</td>
<td>131 4 3.05</td>
<td>136 1 0.74</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>481 13 2.70</td>
<td>506 4 0.79</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Took 70 per cent or more of annual dose in first program</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–39</td>
<td>513 28 5.46</td>
<td>572 10 1.75</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>40–69</td>
<td>420 10 2.38</td>
<td>425 4 0.94</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>70+</td>
<td>617 4 0.65</td>
<td>636 8 1.26</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>1,550 42 2.71</td>
<td>1,633 22 1.35</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Total for each medication group in first program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–39</td>
<td>931 41 4.40</td>
<td>973 17 1.75</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>40–69</td>
<td>642 15 2.34</td>
<td>688 5 0.73</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>70+</td>
<td>845 11 1.30</td>
<td>860 11 1.28</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>2,418 67 2.77</td>
<td>2,521 33 1.31</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>
The Bethel Isoniazid Studies

<table>
<thead>
<tr>
<th>Initial Tuberculosis Status</th>
<th>Placebo in First Program</th>
<th></th>
<th>Isoniazid in First Program</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Population</td>
<td>(no.)</td>
<td>(%)</td>
<td>Population</td>
</tr>
<tr>
<td>Previously treated</td>
<td>584</td>
<td>17</td>
<td>2.91</td>
<td>478</td>
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<tr>
<td>Inactive, untreated</td>
<td>629</td>
<td>29</td>
<td>4.61</td>
<td>731</td>
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<tr>
<td>No known disease</td>
<td>1,205</td>
<td>10</td>
<td>0.83</td>
<td>1,312</td>
</tr>
<tr>
<td>Total</td>
<td>2,418</td>
<td>67</td>
<td>2.77</td>
<td>2,521</td>
</tr>
</tbody>
</table>
TB Rates

![Graph showing TB rates from 1991 to 2011 for AK and U.S.](image)
Pediatric TB in Alaska, 2002-2011

<table>
<thead>
<tr>
<th>Year</th>
<th># cases</th>
<th>Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>2003</td>
<td>7</td>
<td>4.3</td>
</tr>
<tr>
<td>2004</td>
<td>6</td>
<td>3.7</td>
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<td>2005</td>
<td>7</td>
<td>4.4</td>
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<tr>
<td>2006</td>
<td>7</td>
<td>4.4</td>
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<td>2007</td>
<td>4</td>
<td>2.5</td>
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<tr>
<td>2008</td>
<td>4</td>
<td>2.5</td>
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<tr>
<td>2009</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>2010</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>2011</td>
<td>6</td>
<td>3.8</td>
</tr>
</tbody>
</table>
TB Cases, by Race, Alaska, 2001-2010

Alaska TB Cases
N=539

- AK Native 66%
- White 10%
- Black 2%
- Asian/PI 22%

All Alaska Residents
N=710,231

- White 67%
- Other Race 2%
- Asian/PI 6%
- AK Native 15%
- Black 3%
- ≥2 Races 7%
East Timor, 2005
“Another child with bronchopneumonia...”

- 4 month-old HIV-exposed female
- Presents to the OPD at Nelson Mandela Hospital, Mthatha, South Africa
- Cough, intermittent fever, increased work of breathing, and poor feeding for 10 days
- In the care of the grandmother
  - Mother died of a respiratory illness when the baby was three weeks old
- Exam reveals moderate respiratory distress, oral thrush, and hepatosplenomegaly
Questions raised:

- What is this child’s risk for active TB?
- What are the clinical manifestations of pulmonary TB in 4 month-old children?
- Are infants likely to develop cavitary disease? Pneumothorax?
- How shall sputum studies be obtained?
- The child has been coughing for less than 2 weeks… does this make TB less likely?
Overwhelming Global TB Burden

- 2 billion infected worldwide
- 8.8 million new cases in 2010
- 1.45 million deaths annually
- 1.3 million cases and 450,000 deaths in children under 15
- 9.7 million TB orphans worldwide

WHO 2011
FIGURE 2.3
Estimated TB incidence rates, 2010

Estimated new TB cases (all forms) per 100,000 population:
- 0–24
- 25–49
- 50–99
- 100–299
- ≥300
- No estimate
TB/HIV Co-Epidemic
TB in Children: Classic Teaching

- Immunologic responses vary by age
- Clinical manifestations are different than in adults
- Bacteriologic diagnosis is difficult to achieve
- Disease in childhood represents primary infection and contact with an index case
- Children under 8 are rarely infectious
Congenital Tuberculosis

- Very rare, ~300 cases reported
- Bacillemia in mother leads to placental infection
- Organisms reach fetus via umbilical vein
- Primary focus in the liver
- Diagnosed by demonstration of MTB on liver and endometrial biopsies

Congenital Tuberculosis

- Lesions present in first week of life
- Striking hepatosplenomegaly
- Pulmonary disease with miliary pattern can occur
- May present as sepsis-like syndrome or failure-to-thrive
Congenital Tuberculosis

http://www.scielo.br/img/revistas/bjid/v10n5/a14fig02.gif
Basics of TB Infection

- Bacilli inhaled, reach terminal airway
- Parenchymal (Ghon) focus develops
- Bacilli drain to regional nodes
  - Upper lobes to paratracheal nodes
  - Middle and lower lobes to hilar nodes
- Ghon complex = Focus plus adenopathy
- From regional nodes bacilli may enter systemic circulation and disseminate
5 phases of childhood infection

- Phase I: Hypersensitivity phase
  - Formation of primary complex
- Phase II: Disseminated phase
- Phase III: Progressive pulmonary disease
  - Pleural effusion or bronchial disease

5 phases of childhood infection

- **Phase IV: Calcification of the primary complex**
  - Adult-type cavitary disease
  - Osteoarticular infections
- **Phase V: Reactivation disease**
  - Very rare in childhood if immunocompetent
5 phases of childhood infection

Primary complex
Disseminated
Effusion, Bronchial
Osteoarticular, adult type
Reactivation

0 1 2 3 4 6 8 10 12 2 3 4
Infection Months Years

Time
Importance of the CXR

- Each phase of disease is correlated with hallmark radiographic features
- Children often have paucibacillary disease
- Sputum very difficult to obtain in infants
- Microbiologic diagnosis in only 40-50% \(^1\)
- Therefore accurate interpretation of CXR plays a critical role in clinical diagnosis

\(^1\) Marais, BJ. Clinical Infectious Diseases 2006; 42:e69–71
5 phases of childhood infection

- Phase 1: Hypersensitivity Phase
  - 3 – 8 weeks after primary infection
  - Fever
  - Erythema Nodosum
  - Formation of the Primary complex
  - Historically, PPD usually positive by the middle of phase I
5 phases of childhood infection

- Phase 2: Disseminated Disease
  - 1 - 3 months after primary infection
  - Miliary disease
  - Tuberculous meningitis
  - Usually in infants and children under 2 years of age
5 phases of childhood infection

- **Phase 3**
  - 3 – 7 months after primary infection
  - Pleural effusion (age >5)
  - Segmental bronchial disease (age <5)
A word on pneumothorax...

- Leading cause of spontaneous pneumothorax in the pre-chemotherapeutic era
- Found in 0.6 – 1.4% of PTB cases
- Mechanisms:
  - Complication of pleural disease with hydropneumothorax
  - Ball-valve effect from partial extra-bronchial compression leads to local hyperexpansion
  - May also complicate miliary-pattern disease

5 phases of childhood infection

- Phase 4: Calcification of primary complex
  - 1 – 3 years after primary infection
  - Osteoarticular disease (children <5)
  - Adult-type disease (adolescents)
  - Risk of progressive primary disease very low after calcification of primary complex complete
5 phases of childhood infection

- **Phase 5: Reactivation disease**
  - Occurs *after* calcification of complex
  - >3 years after initial infection
  - Pulmonary reactivation disease
  - Very rare during childhood in non-HIV
Age dependent risk of disease

- Infants > adolescents > school-aged
- Manifestations determined by vigor of immune response
- HIV-infected children *tend* to present similar to children under the age of 2 years¹
  - Disseminated disease more common
  - Frequent progressive primary disease with early cavitation

¹MARAIJS, BJ. INT J TUBERC LUNG DIS 2004; 8(4):392–402
## Risk of disease by age group

<table>
<thead>
<tr>
<th>Age at Primary Infection</th>
<th>Disease Type</th>
<th>Risk following primary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>No disease</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>30 – 40%</td>
</tr>
<tr>
<td></td>
<td>Ghon focus, nodal disease, or bronchial disease</td>
<td>10 – 20%</td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM</td>
<td></td>
</tr>
<tr>
<td>1 – 2 years</td>
<td>No disease</td>
<td>70 – 80%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>10 – 20%</td>
</tr>
<tr>
<td></td>
<td>Ghon focus, nodal disease, or bronchial disease</td>
<td>2 – 5%</td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM</td>
<td></td>
</tr>
<tr>
<td>2 – 5 years</td>
<td>No disease</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Ghon focus, nodal disease or bronchial disease</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM</td>
<td></td>
</tr>
</tbody>
</table>
## Risk of disease by age group

<table>
<thead>
<tr>
<th>Age at Primary Infection</th>
<th>Disease Type</th>
<th>Risk following primary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 10 years</td>
<td>No disease</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Nodal, bronchial disease, effusion, or adult-type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>No disease</td>
<td>80-90%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>10-20%</td>
</tr>
<tr>
<td></td>
<td>Effusion or adult-type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miliary or TBM</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>
Summary of risk by age

- Infants at extremely high risk of early dissemination\(^1\) and may cavitate
- Disease usually from progressive primary infection
- Adolescents tend to develop adult-pattern disease\(^2\)

\(^1\)MARAI$S$, BJ. INT J TUBERC LUNG DIS 2004; 8(4):392–402
Diagnostic Challenges in Pediatric TB: Classic Dogma

- Difficult to induce sputum in infants and toddlers
- Paucibacillary disease predominates
  - Relatively less likely to cavitate than adults
  - HIV+ patients more often smear negative than their immunocompetent counterparts
Diagnostic Challenges in Pediatric TB

- Culture often not sent in resource-limited settings
- Commonly reported sputum smear-positive rate 10 – 15%
- As many as 60% of patients treated in high-incidence settings may be culture negative

Marais, BJ. Clinical Infectious Diseases 2006; 42:e69–71
Clinical Diagnosis of Pediatric TB: “The TB Triad”

- Close contact with an infectious index case
  - High risk of progression to active disease if prolonged exposure to smear+ case
  - Difficult to document in high-incidence areas

- Positive Tuberculin Skin Test (TST)
  - Positive in less than 50% of HIV+ children with smear+ TB\(^1\) and may be >5mm after BCG vaccination

- Suggestive signs on CXR
  - Difficult to interpret without significant training, often not available in rural areas with resource-limitations

\(^1\)Marais, et. al. JID 2007; 196:S76–85
TB Symptom-based Diagnostic Tool

- 1024 children <13y referred for evaluation
- 428 children with >2 weeks cough were enrolled in study in Cape Town

Categorized by the following:

- Bacteriologically proven TB
- Radiologically certain TB
- Probable TB
  - Suggestive CXR
  - Weight gain >10% and Sx resolution 3m after Rx
- Not TB

Marais, et al. Pediatrics 2006;118;1350-1359
TB Symptom-based Diagnostic Tool

- Triad of *cough* >2 weeks, *FTT*, and *fatigue*
  - 82% sensitive, 90% specific for PTB in HIV-negative children >3y (PPV 82%)
- “Sx based approach offered little value in HIV-infected children.”

Marais, et al. *Pediatrics* 2006;118;1350-1359
Failure of Symptom-Based Tool in Children with HIV

- 15% of HIV+ children with TB had cough < 2 weeks
- 25% of HIV+ children without TB had cough > 2 weeks
- 11/12 (92%) of children with severe PTB who did not meet entry criteria of > 2 weeks cough were either < 3y old or HIV+

Marais, et al. *Pediatrics* 2006;118;1350-1359
The South Africa Pediatric Criteria for Initiating TB therapy

- Two of the following:
  1. Close contact with active TB or positive TST, \textit{and/or}
  2. Signs/symptoms consistent with active TB, \textit{and/or}
  3. CXR consistent with active TB

South Africa TB guidelines, 2010
Retrospective review from 6 centers in UK

333 children 2 months to 16 years of age

- 49 “Definite TB”
  - Culture confirmation

- 146 “Probable TB”
  - Compatible syndrome, CXR or CSF abnormality, Response to TB therapy, and history TB exposure

- TST + either TSPOT or Quantiferon Gold

Arch. Dis. Child, 2009
Results

- **TST Results:**
  - 108/172 (63%) >15mm overall
  - 37/45 (82%) in confirmed cases

- **T-SPOT.TB**
  - 47/103 (46%) positive overall
  - 18/27 (67%) in confirmed cases
  - 34/50 (68%) positive in those with TST >15mm

- **QuantiFERON Gold-In-Tube**
  - 101/170 (59%) positive overall
  - 36/46 (78%) in confirmed cases
  - 79/97 (81%) positive in those with TST >15mm
TST combined with IGRA

- “Definite” cases
  - TST >15mm OR positive TSPOT
    - 24/25 (96% sensitivity)
  - TST >15mm OR QuantiFERON Gold-In-Tube
    - 39/43 (91% sensitivity)

- “Definite” AND “Probable” cases
  - TST >15mm OR TSPOT
    - 61/91 (67% sensitivity)
  - TST >15mm OR QuantiFERON Gold-In-Tube
    - 114/158 (72% sensitivity)
Culture Positivity in South Africa

307 children <13y with radiographic evidence of pulmonary TB were reviewed.

- Specimens collected by GA, IS, NP, or pleural aspirate.
- Specimens collected from 196 of 307 (64%).
  - 122/196 (62%) AFB smear or culture positive.
  - 14/14 (100%) with adult-type disease.
  - 14/15 (93%) with miliary disease.
  - 24/69 (34%) with uncomplicated lymph-node disease.

Marais, BJ. Clinical Infectious Diseases 2006; 42:e69–71
Sputum collection in children

- **Gastric Aspirate**
  - Historical standard
  - At least 4h fasting overnight
  - Place NG prior to getting up from bed in AM
  - Aspirate gastric contents
    - If <20 mL obtained, insert 20 mL NS in tube, wait 2-3m, reaspirate
    - Repeat 5-10 mL lavages until 20 mL total gastric contents obtained
Sputum collection in children

- Induced sputum
  - Can be done in children as young as 1 month
  - 2-3h fasting
  - Pre-treat with inhaled albuterol by MDI
  - 5% hypertonic saline given by jet nebulizer for 15 minutes
  - Chest percussion then done
  - Coughed secretions present in posterior pharynx are NP suctioned with 6 or 7 Fr catheter
String test

- Novel approach
- Coiled nylon string inside gel capsule
- String unravels through hole in capsule after being swallowed
- Capsule then dissolves in stomach
- String extracted 1 - 4 hours later
  - Washed with NS, vortexed 30m, then centrifuged x 5m
- In adults, more sensitive than induced sputum

Indian J Med Microbiol 2006;24:249-51
Is Gastric Aspirate Really Better?

- Zar, et al. in Cape Town studied 250 children 1m to 5y admitted with suspected PTB*
  - All underwent serial gastric aspirate and induced sputum collections x3 days
    - Nebulized 5% saline followed by NP aspirate for induced sputum
  - 95/250 (38%) HIV+
  - 121/250 (48%) less than 1 year of age

*Cough >28 days *plus* household contact or FTT or PPD+ or abnormal CXR
Gastric Aspirate vs. Induced Sputum

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Culture positive</th>
<th>Smear positive</th>
<th>Culture or smear positive</th>
<th>Cumulative yield</th>
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</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>250</td>
<td>58 (23%)</td>
<td>29 (12%)</td>
<td>62 (25%)</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Induced sputum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>51 (20%)</td>
<td>25 (10%)</td>
<td>54 (22%)</td>
<td>87%</td>
</tr>
<tr>
<td>First specimen</td>
<td>250</td>
<td>37 (15%)</td>
<td>19 (8%)</td>
<td>41 (16%)</td>
<td>66%</td>
</tr>
<tr>
<td>Second specimen</td>
<td>244</td>
<td>27 (11%)</td>
<td>13 (5%)</td>
<td>30 (12%)</td>
<td>79%</td>
</tr>
<tr>
<td>Third specimen</td>
<td>227</td>
<td>29 (13%)</td>
<td>11 (5%)</td>
<td>31 (14%)</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Gastric lavage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>38 (15%)</td>
<td>17 (7%)</td>
<td>40 (16%)</td>
<td>64%</td>
</tr>
<tr>
<td>First specimen</td>
<td>250</td>
<td>19 (85%)</td>
<td>8 (3%)</td>
<td>20 (8%)</td>
<td>32%</td>
</tr>
<tr>
<td>Second specimen</td>
<td>244</td>
<td>22 (9%)</td>
<td>12 (5%)</td>
<td>26 (11%)</td>
<td>56%</td>
</tr>
<tr>
<td>Third specimen</td>
<td>234</td>
<td>18 (8%)</td>
<td>10 (4%)</td>
<td>22 (9%)</td>
<td>64%</td>
</tr>
</tbody>
</table>

Data are number or %.

Table: Cumulative yield of *M. tuberculosis* from repeated induced sputum or gastric lavage specimens

1Zar, et. al. Lancet 2005; 365: 130–34
Other studies of IS vs. GA

- **Hatherill et al, 2009, Cape Town, RSA**
  - 191 culture confirmed cases
  - 108 positive by IS, 127 by GA
  - Paired IS and GA on single day 67% yield

- **Qureshi et al, 2011, Jammu, India**
  - 65 children with cough >28d, median age 4y
  - 8 (13%) positive by IS, 5 (8%) by GA

- **Al-Aghbari et al, 2009, Yemen**
  - 213 children, 29 (14%) culture positive
  - Smear positivity among culture proven cases:
    - 35% by GA, 20% by IS
  - Culture positive rate: 9% by GA, 16% by IS
Other potential samples for microbiologic diagnosis

- Nasopharyngeal aspirate
  - Less technically challenging than IS or GA
  - Mixed data, probable lower yield
- Stool culture or PCR
  - AFB swallowed after coughing
  - Resistant to digestion
  - 9/192 healthy children at immunization clinic in Nigeria culture positive for M. tuberculosis or africanum
- Urine for culture or PCR

2 Cadmus 2010, Donnald 1996
The Future: GeneXpert MTB/RIF, Cepheid

Boehme CC et al, NEJM 2010
Xpert Performance

- 1730 patients in Peru, Azerbaijan, South Africa, and India
- In less than 2 hours from specimen collection, identified:
  - 551/561 (98.2%) of smear+ cases
  - 124/171 (72.5%) of smear- cases
  - Highly specific (99.2%)
  - Identified 200/205 (97.6%) with rifampin resistance

GeneXpert in Children

- Children 0 – 5y in South Africa
- Inclusion criteria (≥1 of the following):
  - Cough >2 weeks
  - FTT or severe acute malnutrition
  - Unexplained fever, fatigue, lethargy, or reduced playfulness
  - Documented TB contact in prior 12m
- Classified as “confirmed”, “probable”, “possible”, and “not” pulmonary TB
- Study is ongoing

Hesseling et al, Desmond Tutu TB Center, Stellenbosch University, South Africa
Conclusions

- Tuberculosis remains a leading cause of pediatric morbidity and mortality in the developing world.
- Children <2y or HIV-infected are at high risk of disseminated disease, and clinical prediction rules in these groups often fail.
- Microbiologic diagnosis in only ~50% of cases.
  - Induced sputum may be more efficacious in infants and children than previously realized.
- CXR critical piece of diagnostic information.
- The future is Molecular, and It is here!!