Ending the Global TB Epidemic 2035: <100/million

Grand Medical Rounds
May 8, 2015
We will consider:

• Global TB incidence in SLOW decline- Anne
• How TB presents in Canada- Michael Hawkes
• Impact of global TB on Alberta- Ryan Cooper

Challenge to Elimination- Mario Raviglione, Director
Global TB Programme WHO

Is it possible?
And do we have the political will?
TB 101

• Bacterial infection
• Spread by cough
• 9/10 never symptomatic
• 10th progresses, half now, half late
• Reactivation with immunity HIV, transplant, age
• 80% lung: cough, fever, weight loss: 20% other sites
• Untreated >60% die over 5 years
• Treatment: 4 drugs X 2 months, 2 drugs X 4 months
• >85% cure if early, drug sensitive & compliant with treatment (cost$13 for drugs, $1-300 program)
• Prevention:
  – BCG Vaccine poor; new candidate trials slow
  – Treatment of latent TB protects 70-90%-NB in Elimination
• Impediments to elimination: Drug Resistance, HIV co-infection, social determinants, political will!
TB history

- 19th century- TB incidence declined as poverty .
- Sanatorium care and surgery had little impact.
- Drugs: Strep 1945; INH (H)1952; Rifampin (R) 1970.
- Standard regimen: 2HRZE/4HR
- 1990 World Bank judged this TB Rx system, most cost-effective for years of life saved
- 1993 global emergency, incidence rising: WHO marketed “DOTS”: five prong strategy to STOP TB
Evolution of the Global Program

• Management system - Directly observed Therapy, Short course
• Marketed as DOTS, to STOP TB
• Global STOP TB partnership to mobilize dollars and scientific input
  – DOTS expansion
  – HIV TB
  – MDR TB
  – Lab expansion
  – New tools

• Led by the Global Program at WHO
2015 Global TB Targets

Millennium Development goal #6 - by 2015:
Halt and reverse the rise in TB incidence
(rate peaked in 2002, 137, now 126 falling 2 %/yr)

STOP TB partnership goal - by 2015
Halve prevalence and deaths (c/w 1990)
  a) Half of 300/100k prevalence (169 in ‘13)
  b) Half of 30/100k deaths (13 in ‘13)

Target reached in 4 regions, not Afro, Euro
MDG Goal 6: 2013 Incidence, Prevalence, Mortality: global estimates; incidence 126, prevalence 169, MR 13

Target= reverse the rise 126/100,000, 2013

Target=147, will be met in 3 regions

shaded area = uncertainty band  

Courtesy M Raviglione, 2014 GTB Report
Global TB estimates & notification – 2013

- **Estimated number of cases**
  - All forms of TB: 9.0 million (126 per 100,000)
  - New Smear positive: 6.1 million (80 per 100,000)
  - HIV-associated TB: 1.1 million (13%)
  - Children: 0.55 million
  - Multidrug-resistant (MDR): 480,000* (3.5%)
  - XDR: 50,000
  - Deaths: 1.5 million (.36 mHIV, 0.51 women, 0.080 kids, 0.21 MDR)
  - Missing: 3.1 million

- **Cases reported DOTS**
  - New Smear positive: 2.6 million
  - HIV-associated TB: 97,000 treated
  - MDR: 486,000
Estimated TB incidence rates, 2013

- South-East Asia: 38%
- Western Pacific: 18%
- Africa: 29%
- E. Mediterranean: 8%
- Americas: 3%
- Europe: 4%

34% in India + China
23% in India
Impediments to reaching the goals

- HIV co-infection:
- Drug Resistant disease (MDR, resistance to H&R)
- Weak health systems, especially in poor and marginalized communities
- Inadequate funding for R&D for new tools
- DONOR FATIGUE- $2 Billion missing
**Vision:** A world free of TB

*Zero TB deaths, Zero TB disease, and Zero TB suffering*

**Goal:** End the Global TB epidemic (<10 cases per 100,000 population)

<table>
<thead>
<tr>
<th>INDICATORS</th>
<th>TARGETS</th>
<th>SDG 2030</th>
<th>End TB 2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in number of TB deaths compared with 2015 (%)</td>
<td>90%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Reduction in TB incidence rate compared with 2015 (%)</td>
<td>80% (&lt;20/100 000)</td>
<td>90% (&lt;10/100 000)</td>
<td></td>
</tr>
<tr>
<td>TB-affected families facing catastrophic costs due to TB (%)</td>
<td>Zero</td>
<td>Zero</td>
<td></td>
</tr>
</tbody>
</table>
Ten countries account for 2.4 million missing

- 75% in Asia and Africa
- Need access to Dx, Rx for poor & marginalized
- Improve childhood TB diagnosis to 0.20 million missing
78% of TB HIV in Africa
41% of all TB cases were HIV +

- Only half co-infected found
- Test all HIV+ for TB and treat or prophylaxis
- Test all TB for HIV, but < 50% currently
- Of the HIV+ found 70% started on ARV, 85% on CPT
- Infection control to protect HCW
Highest MDR in former USSR

- 60% of MDR in China, Russia, India, Pakistan, Ukraine
- Globally 3.5% of new, 20.5% of retreatments have MDR; 9% is XDR!
- Need:
  - Better first treatment - DOTS
  - Drug sensitivity testing for all
  - Prompt effective treatment
  - Reduce cost, $9350/case
What will it take to move the curve down? Dye et al, 2013 Ann Rev PH
Could we demonstrate Elimination in Canada:

Omitting South Africa 838/100,000
The Case

Michael Hawkes
Consult to Peds ID service:

- 3 mo old female (premature, 30 wk GA)
- Respiratory failure, difficulty weaning ventilatory support
- Nodular lesions on CT chest
History:

• Birth:
  – Twin gestation (IVF), PROM
  – Emergency c-section at 30 weeks GA, AGA

• NICU course:
  – CPAP x 24 hours, empiric amp+gent x 48h
  – Bilateral sub-ependymal hemorrhages
  – Apnea of prematurity
  – Feeding difficulty and GE reflux, Rx: lansoprazole
  – Discharged home @ 5 weeks of age

• Returned 2X to ER for cough, ↑ WOB (GERD)
Current admission:

- At 10 weeks of age, presented to hospital (Fort McMurray) with a 5 day history of:
  - Cough, nasal congestion
  - Poor feeding
  - Increased work of breathing
- **Physical exam:**
  - RR 64, HR 160, SpO₂ 93% on RA
  - Chest indrawing
  - Normal cardiac examination
- **Working Diagnosis:** Aspiration Pneumonia
- **Treatment:** Ampicillin & Cefotaxime
Current admission:

• Transferred to the U of A:
  – increasing respiratory distress
  – positive blood culture: *Neisseria mucosa*

• Course on Peds ward @ U of A:
  – Continued IV antibiotics, followed by po amoxicillin-clavulanate
  – Deterioration on day 10 hospitalization: respiratory distress
  – Transferred to PICU
Current admission:

• Course in PICU:
  – Intubated; conventional ventilatory support → high frequency oscillation → ECMO
  – ECMO x 5 days, then weaned off
  – Unable to wean ventilator, prompting CT chest
  – Antibiotics: pip-tazo

• Microbiology:
  – Blood cultures repeatedly negative
  – ETT culture *S. aureus* (MSSA) on one occasion
Differential diagnosis:

- S. aureus necrotizing pneumonia
- Septic emboli
- Congenital immunodeficiency (e.g., CGD)
- Fungal, mycobacteria, Nocardia, actinomyces
Tuberculosis contact?

- Parents immigrated from Pakistan
  - Father: 7 years ago
  - Mother: 2.5 years ago
  - Immigration screen for TB: CXR normal, Mantoux positive for both parents
  - No cough, weight loss
  - No travel to Pakistan, no visiting relatives

- Share a house with couple from Philippines
  - Also no cough, no TB symptoms
A DIAGNOSTIC TEST WAS OBTAINED...
DIRECT SMEAR FOR ACID-FAST BACILLI

*** Acid-fast bacilli WERE SEEN.

The smear was examined by fluorescent microscopy (Auramine Rhodamine stain)

<< Reported to Health Agency >>

MYCOBACTERIAL CULTURE

**Mycobacterium tuberculosis** ISOLATED using the automated system BACTEC MGIT after 6 day(s) incubation.
<table>
<thead>
<tr>
<th>Date</th>
<th>Sample Type</th>
<th>AFB Culture</th>
<th>Days to Positive Culture</th>
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<tr>
<td>1 Sept</td>
<td>ETT</td>
<td>3+ AFB</td>
<td>+ 6d</td>
</tr>
<tr>
<td></td>
<td>ETT</td>
<td>3+ AFB</td>
<td>+ 6d</td>
</tr>
<tr>
<td></td>
<td>gastric asp.</td>
<td>?AFB</td>
<td>+ 20d</td>
</tr>
<tr>
<td>2 Sept</td>
<td>BAL(mod)</td>
<td>3+ AFB</td>
<td>+ 9d</td>
</tr>
<tr>
<td></td>
<td>sputum</td>
<td>3+ AFB</td>
<td>+ 6d</td>
</tr>
<tr>
<td></td>
<td>gastric asp.</td>
<td>1+ AFB</td>
<td>culture –</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>no AFB</td>
<td>culture –</td>
</tr>
<tr>
<td>3 Sept</td>
<td>ETT</td>
<td>3+ AFB</td>
<td>+ 8d</td>
</tr>
<tr>
<td></td>
<td>gastric asp.</td>
<td>1+ AFB</td>
<td>+ 26d</td>
</tr>
<tr>
<td></td>
<td>blood</td>
<td></td>
<td>culture -</td>
</tr>
<tr>
<td>11 Sept</td>
<td>ETT</td>
<td>2+ AFB</td>
<td>+ 11d</td>
</tr>
<tr>
<td>19 Sept</td>
<td>ETT</td>
<td>no AFB</td>
<td>+ 41d</td>
</tr>
<tr>
<td>27 Sept</td>
<td>gastric asp.</td>
<td>no AFB</td>
<td>culture inconclusive</td>
</tr>
<tr>
<td>28 Sept</td>
<td>gastric asp.</td>
<td>no AFB</td>
<td>culture -</td>
</tr>
</tbody>
</table>
How did this infant contract TB?

- Mother was investigated for **primary infertility**
- 2011: Laparoscopy suggested **chronic PID**, bilateral hydrosalpinx, adhesions of ovaries and adnexa.
- Bilateral **obstructed fallopian tubes**
- Endometrial biopsy – Multiple small epithelioid **granulomas** with occasional multinucleated cells, few containing central necrosis but no caseation. Special stains for AFB and fungus were negative.
Endometrial curettings with Granulomatous Endometritis
Granulomata
Granulomata with giant cells (*)
IVF

- She traveled to Pakistan to enquire about IVF but could not find satisfactory access
- Referred to Fertility Clinic in Calgary Jan 2012
- IVF over summer and fall 2012
- No available records

*embryos were implanted at the very locus of mycobacterial replication...*
PERINATAL/NEONATAL CASE PRESENTATION

Infertility, *in vitro* fertilization and congenital tuberculosis

JF Flibotte¹, GE Lee², GL Buser², KN Feja³, BN Kreiswirth⁴, GD McSherry⁵, SM Nolan², RW Tolan Jr³ and H Zhang¹

Congenital tuberculosis (CTB) due to maternal genitourinary (GU) TB infection is a rare occurrence, as infection of the genital tract in women generally leads to infertility. Increasing availability of assisted reproductive technology creates the potential for CTB to emerge as a significant problem. We describe five infants (two sets of twins and a singleton birth) conceived by *in vitro* fertilization who developed CTB. All five infants were born to mothers who had immigrated to the United States from India and none had GU TB diagnosed before the birth of their infected infants.


**Keywords:** *in vitro* fertilization; tuberculosis; TB; congenital tuberculosis; genitourinary TB

- 5 cases- 2 sets of **twins** & 1 singleton
- All **IVF**
- All **premature**
- All had “**chorioamnionitis**” & PROM
- All from **Indian sub-continent**
- One died, 4 recovered
Course and Outcome

- Ruled out CNS TB
- 4 drugs initially: INH, RIF, PZA, and moxifloxacin
- Total duration – 10 mo (cavitary, complicated course)
- Growth and development: delayed, but progressing

- **Her twin:**
  - Respiratory disease, suspicious CXR
  - Treated for TB, no microbiologic confirmation
- **Her mother:**
  - Endometrial biopsy confirmed TB
  - Treated
- **Her hospital contacts:**
  - 22/26 tested with follow-up: no skin test conversions
Take-home points

• **Old world disease meets new world technology:**
  – GU TB causes infertility
  – IVF circumvented obstructed GU tract, but led to congenital TB
  – ECMO kept baby alive to diagnosis and treatment

• **Recognize genital and congenital TB**
  – Pakistan & India: largest immigrant group to Canada
  – TB incidence: India 128/100,000 vs Canada 5/100,000
  – Not *yet* time to close the chapter on TB…
TB in Alberta:
TB Incidence Rate Alberta 1986-2014
Number of TB Cases Alberta, by Demographic Group, 2000-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>FB</th>
<th>CBNA</th>
<th>CBA</th>
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<td>2000</td>
<td>133</td>
<td>86</td>
<td>20</td>
<td>27</td>
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<tr>
<td>2001</td>
<td>116</td>
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<td>2002</td>
<td>128</td>
<td>93</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>2003</td>
<td>110</td>
<td>73</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>2004</td>
<td>109</td>
<td>88</td>
<td>9</td>
<td>12</td>
</tr>
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<td>2005</td>
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<td>2006</td>
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<td>2012</td>
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<td>156</td>
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<td>18</td>
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<tr>
<td>2013</td>
<td>187</td>
<td>159</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>2014</td>
<td>211</td>
<td>184</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>
Provincial TB Cases by Demographic Group, 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion FB</th>
</tr>
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<tbody>
<tr>
<td>1986</td>
<td>35%</td>
</tr>
<tr>
<td>2000</td>
<td>60%</td>
</tr>
<tr>
<td>2014</td>
<td>87%</td>
</tr>
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</table>
Local TB Transmission in Alberta occurs but less often than reactivation of imported infection

<table>
<thead>
<tr>
<th>TB Cases in Alberta 2014, Pediatric*</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>211</td>
<td>98.5%</td>
</tr>
<tr>
<td>Pediatric</td>
<td>3</td>
<td>1.5%</td>
</tr>
<tr>
<td>Total</td>
<td>214</td>
<td></td>
</tr>
</tbody>
</table>

*Age < 5 years

Proportion of Culture Positive TB cases with unique DNA fingerprint, Alberta 2006-2013*

*24-loci MIRU fingerprinting
Treating LTBI in Immigrants to Alberta
Number of International Immigrants to Alberta, by Year

Philippines, India, and China are top 5 source countries – accounting for more than ½ of our immigrants

Alison Scott, AH 2015
# Screening Immigrants for LTBI in Alberta, 2013

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Immigrants To Province receiving IME</td>
<td>64631</td>
</tr>
<tr>
<td>Number Referred to TB Program for Post-Landing Surveillance</td>
<td>1858</td>
</tr>
<tr>
<td>Number Offered LTBI treatment</td>
<td>309</td>
</tr>
<tr>
<td>Number Completed treatment</td>
<td>173</td>
</tr>
</tbody>
</table>

*Average Completion Rates for immigrants past 5 years ~65%*
How can we better target our efforts? Which immigrants highest risk of TB?

![Table 1: Development of active TB amongst permanent residents within five years of landing in Ontario](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referred for Medical Surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>10.18</td>
<td>8.51 12.17</td>
</tr>
<tr>
<td>TB Incidence Rate in Birth Country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 50 per hundred thousand</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50-100 per hundred thousand</td>
<td>6.19</td>
<td>3.68 10.41</td>
</tr>
<tr>
<td>100-200 per hundred thousand</td>
<td>10.93</td>
<td>6.69 17.87</td>
</tr>
<tr>
<td>200 or more per hundred thousand</td>
<td>15.20</td>
<td>9.30 24.85</td>
</tr>
<tr>
<td>Immigration Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Refugee or Caregiver</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Refugee</td>
<td>2.63</td>
<td>1.89 3.65</td>
</tr>
<tr>
<td>Caregiver</td>
<td>3.77</td>
<td>3.12 4.55</td>
</tr>
<tr>
<td>Immunosuppression (HIV, Chronic Renal Failure, Diabetes)</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>1.65</td>
<td>1.14 2.37</td>
</tr>
</tbody>
</table>

Courtesy Khan
2015 Submitted
LTBI in Refugees – Enhanced Screening Program at the Edmonton NCC

Findings:
- Screened almost 350 refugees per year in Edmonton
- High retention in care during screening process
- Reasonably high completion rates given population

Figure 1. Care Cascade 2011-2013
New “Efficiencies” in LTBI

• Shorter Treatment Regimens
  – Three months of INH and Rifampin similar efficacy as 9 months INH\(^1\)
  – 12 weekly doses of Rifapentine and INH\(^2\) non-inferior

• Better Diagnostic Tools
  – IGRA more specific than TST, probably similar sensitivity\(^3\)
  – Reduces the number of positive results → less people to treat, focus resources, increase cost-effectiveness\(^4\)

1. Ena CID 2005
2. Sterling NEJM 2011
4. Campbell Mol Diag Ther 2015
Summary

• TB incidence in Alberta is not declining – we aren’t on target to elimination

• Immigrants account for an increasing proportion:
  – Unique challenges: Lack of health insurance, employment/visa status fears, language barrier, itinerant, stigma

• To eliminate TB in Alberta must better address reservoir of latent infection in foreign-born
TB rates in Canada, Alberta, and America, 1997-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Canada</th>
<th>Alberta</th>
<th>USA</th>
</tr>
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<tbody>
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<td>1997</td>
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<td>1998</td>
<td>5.9</td>
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