TB Infection Control Reconsidered
(Redesign of Health Care Facilities, Administrative Controls and the Rapid Impact of Effective Treatment on Transmission)

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Brigham & Women’s Hospital
Harvard Medical School
Harvard School of Public Health
Partners In Health
The elephant in the room is the force of *transmission and re-infection*

- Strain typing is difficult and imperfect
- Underestimate transmission and reinfection
  - Previously treated patients said to have acquired MDR, but many represent re-infection
  - Can be re-infected with same strain in same community
- Impact on TB IC priorities
- Impact on LTBI initiatives
- Impact on vaccine development
Don Smith Alternative Pathway to Cavitary TB

Transmission: 53 XDR Patients in Kwazulu Natal, RSA
Gandhi, *Lancet*, 2006: 55% had no previous TB treatment –
i.e., transmitted (*reinfected*) - most had the same “KZN” strain
67% had been hospitalized
100% had HIV co-infection
100% mortality – avg 16 days from TB diagnosis
Transmission: Hospitals as MDR TB Factories
Tomsk, Siberia

- Studied the role of non-adherence and default on the acquisition of multidrug resistance

- Substance abuse was NOT associated with MDR-TB

- MDR-TB occurred among adherent patients who had been hospitalized,
  - Odds Ratio: 6.34 for hospitalized vs. patients treated as outpatients.

Patients admitted with drug susceptible TB
- Reinected with MDR TB
Evidence of ongoing Exogenous Reinfection

Proven by genetic fingerprinting:

- High HIV setting - South African (Sonnenberg et. al.)
  - 52% of recurrent cases due to reinfection
- Low HIV setting Shanghai, China (Gao et. al.)
  - 62% of recurrent cases due to reinfection
Importance of the Unsuspected TB Case
Arzobispo Loayza Hospital, Lima, Peru


- 250 of 349 pts admitted to on female ward in 1997 were screened for TB
  - sputum
  - CXR
  - history
  - physical exam
Importance of the Unsuspected TB Case - 2
Arzobispo Loayza Hospital
(Emerg Inf Dis 2001; 7:123-7)

• 40 pts (16%) had positive cultures
  – 26/40 (65%) smear positive
  – 13/40 (33%) unsuspected
  – 8/40 (20%) had MDR
    • Incl. 6/8 MDR unsuspected
      – 3/6 were smear positive
Physical Environment: Building configuration and usage - often neglected
Annual Risk of Infection Among Medical Students of Universidad Peruana Cayetano Heredia in Lima, Peru

- 488 students
- Pos. PPD increased from 3.5% to 45.9% over 7 years
- 6%/yr. avg.
Comparing Infection Rates: Hospital Cayetano and Hospital Loayza


![Bar chart comparing PPD and internal medicine rates between Hospital Loayza and Hospital Cayetano Heredia. The rate for Hospital Loayza is 12.7% and for Hospital Cayetano Heredia is 25.5%. The p-value is 0.006.]
Room Volume Per Bed:
Hospital Cayetano and Hospital Loayza

[Diagram showing room volumes per bed for Hospital Cayetano and Hospital Loayza]

- Room volume per bed: Yes
- Room volume per bed: No
Harvard Summer Course: “Building Design and Engineering Approaches to Airborne Infection Control”

Primarily for Architects and Engineers
also public health professionals/administrators

Summer post-graduate course (6th course)
August 5-16, 2013
Applications on line by Feb 11, 2013
PROPOSED TUBERCLOSIS CLINIC AT INDUS HOSPITAL
Limits of Natural Ventilation: Other approaches to air disinfection

• Germicidal UV (upper room)
  – Highly effective
  – Highly cost-effective
  – Few guidelines exist
  – Poor implementation and maintenance

• Other approaches
  – Air filtration and other room air cleaners – not recommended
  – UV in ducts – not recommended
  – Direct UVGI – not recommended
Ventilation ducts in patient rooms

Paddle Fans Assure Good Air Mixing

Upper room UVGI
AIR, Experimental Plan

Guinea Pig Air Sampling

Odd days
A

UVGI or other intervention

3 patient rooms
Plus common areas

Even days
B

Guinea Pig
TB RFLP

Pt. TB RFLP

Intervention on/off on alternative days
UVGI Results

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>TST-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TST-2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TST-3</td>
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<td>5</td>
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<tr>
<td>TST-4</td>
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<td>TOTAL</td>
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<table>
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<tr>
<td>TST-1</td>
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<tr>
<td>TST-2</td>
<td>12</td>
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<tr>
<td>TST-3</td>
<td>0</td>
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<td>TOTAL*</td>
<td>15</td>
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</table>

*p<0.0005

Combined hazard ratio 4.9 (CI.95: 2.8, 8.6) or about 80% effective.

Note: 6 ACH (mechanical). Doubling to 12 EqACH would reduce risk by about 50%; Doubling to 24 EqACH would reduce risk by about 75%; so UVGI added about 24-6 (mechanical) = about 18 EqACH to the AIR facility wards
Arguments for Community Based MDR Treatment

1. MDR treatment scale-up: bed availability
2. Cost effectiveness of community based vs. hospital care
3. Lower transmission risk with community-based treatment
   - Both staff and other patients
## Cost Effectiveness Argument


Compared 4 different MDR Treatment Sites:

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>Cost per DALY</th>
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<tr>
<td><strong>Hospital based:</strong></td>
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<tr>
<td>Tomsk, RF*</td>
<td>$14,657</td>
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<td>Estonia*</td>
<td>$10,880</td>
<td>$598</td>
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<td><strong>Community based:</strong></td>
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<tr>
<td>Philippines**</td>
<td>$3,613</td>
<td>$143</td>
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<tr>
<td>Peru**</td>
<td>$2,423</td>
<td>$163</td>
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</table>
Community Based Treatment

- Highly effective & cost effective
  - e.g., Peru, Lesotho, Cambodia, KZN, Ethiopia, and others
- Less opportunity for institutional transmission

But, what about community transmission?
Developing Guidelines for Discontinuation of Isolation for Patients with Multidrug-Resistant Tuberculosis

Sundari Mase MD, MPH
Barbara Seaworth MD
Edward Nardell MD
Jennifer Flood MD, MPH
Julian Thomas
<table>
<thead>
<tr>
<th>Organization</th>
<th>Title</th>
<th>Smear /Culture</th>
<th>Min Days Tx</th>
<th>Lab Results</th>
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<td>The Interdepartmental Working Group on Tuberculosis: The prevention and control of tuberculosis in the United Kingdom: Department of Health – Publications</td>
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<tr>
<td>Public Health Agency Canada</td>
<td>Canadian Tuberculosis Standards 6th Ed.</td>
<td>neg /pos</td>
<td>14</td>
<td>3 neg smears</td>
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<tr>
<td></td>
<td></td>
<td>pos/pos</td>
<td>14</td>
<td>none needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pos /neg</td>
<td>Not mentioned</td>
<td>3 neg cultures</td>
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<td>Smear/Culture</td>
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<td>Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC</td>
<td>all</td>
<td>Not mentioned</td>
<td>neg culture</td>
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Where does the 14 day rule come from? (for drug susceptible TB)

- Andrews RH. Bull WHO. 1960 (Madras, India)
- Crofton J. Bull IUAT. 1962 (Edinburg, Scotland)
- Brooks S. Am Rev Resp Dis. 1973 (Ohio)
- Riley R. Am Rev Resp Dis. 1974 (Baltimore)
- Gunnels J. Am Rev Resp Dis. 1974 (Arkansas)
- Rouillon A. Tubercle. 1976 (Review):
  - Evidence that smear and culture positive TB patients on therapy do not infect skin test negative close contacts.
  - Smear and culture correlate with infectivity only in untreated cases
- Menzies R. Effect of treatment on contagiousness of patients with active pulmonary tuberculosis. Infect Control Hops Epidemiol 1997; 18:582-586
Effects of Chemotherapy on Transmission

- Gunnels et al (ARRD 1974):
  - studied contacts of 155 patients sent home after 1 month of treatment in hospital
  - 69 Culture neg.
  - 86 Culture pos
    - 52 Smear and culture positive.

- No difference in infection rate among 284 contacts of culture pos cases versus 216 contacts of culture negative contacts
Effects of Chemotherapy on Transmission

  - Sputum smear and culture positivity correlate with transmission before but **not** on therapy
  - **Evidence that smear and culture positive TB patients on effective therapy do not infect close contacts.**
Effects of Chemotherapy on Transmission (Rouillon)

• “There is an ever-increasing amount of evidence in support of the idea that abolition of the patient’s infectiousness – a different matter from ‘cure,’ which takes months, and from negative results of bacteriological examinations, direct and culture, which may take weeks – is very probably obtained after less than 2 weeks of treatment”.

• “These facts seem to indicate very rapid and powerful action by the drugs on infectivity…”
Exactly How Much Treatment is Needed?
Wells/Riley Experimental TB Ward, 1956-62

Quantitative air sampling for TB

Riley Ward – 2\textsuperscript{nd} 2-year study
- included untreated patients

Relative infectivity of patients*:

– Susceptible TB
  • 61 Untreated \hspace{3cm} (29 GPs) \hspace{3cm} 100\%
  • 29 Treated \hspace{3cm} (1 GP) \hspace{3cm} 2\%

– Drug-resistant TB
  • 6 Untreated \hspace{3cm} (14 GPs) \hspace{3cm} 28\%
  • 11 Treated \hspace{3cm} (6 GPs) \hspace{3cm} 5\%

*all smear positive patients, relative to the amount of time on the ward
Riley’s conclusions
ARRD 1962; 85:511-525

“The treated patients were admitted to the ward at the time treatment was initiated and were generally removed before the sputum became completely negative. Hence the decrease in infectiousness preceded the elimination of the organisms from the sputum, indicating that the effect was prompt as well as striking.”

“Drug therapy appeared to be effective in reducing the infectivity of patients with drug resistant (H, SM, PAS only) organisms, but the data do not permit detailed analysis of the problem.”
Dramatic Increase in antibiotic concentration as respiratory droplets evaporate into droplet nuclei

How effective is treatment in stopping MDR-TB transmission?
The AIR Facility
Witbank, Mpumalanga Province, RSA
Collaborators:

• **MRC**
  – Martie van der Walt
  – Matsie Mphahlele
  – Kobus Venter
  – Anton Stoltz
  – Willem Lubbe
  – Thabiso Masotla
  – Karin Weyer
  – Bernard Fourie
  – Lourens Robberts
  – Daan Goosen, Veterinarian

• **CSIR**
  – Sidney Parsons*, engineer
  – Peta DeJegar and staff

• **CDC**
  – Paul Jensen, engineer
  – Charles Wells
  – Paul Arguin

• **Mpumalanga Provence Health Dept & Specialized MDR TB Referral Center**
  – Patients
  – Nurses
  – Administration
  – Doctors

• **Harvard University**
  Brigham & Women’s Hospital
  – Edward Nardell, PI
  – Melvin First
  – Ashwin Dharmadhikari

• **Other collaborators**
  – Dave McMurray – Texas A & M
  – Ian Orme – Colorado State
  – Randall Basaraba – Colorado State
  – Paul Van Helden, Rob Warren, Elizabeth Streicher - Centre for Molecular and Cellular Biology, Stellenbosch U.

• **Funding**
  – USAID/CDC
  – MRC
  – Brigham & Women’s Hospital
  – U. Pretoria
  – Harvard CFAR (NIH) – two awards
  – NIOSH (NIH) RO1
  – NIH K23 (A. Dharmadhikari, PI)
  – Fogarty International
  – Bill and Melinda Gates Foundation
125 patients: smear +, cavitary, coughing, recently started on therapy
AIR Pilot Study:
362 GPs exposed to 26 MDR-TB patients over 4 months
GP TST ≥ 6 mm

### Guinea Pig Transmission: South Africa

109 patients: smear +, cavitary, coughing, recently started on therapy

<table>
<thead>
<tr>
<th></th>
<th># Patients/ Exp. Duration</th>
<th>% guinea pigs infected (# exposed)</th>
<th>Patients # XDR (MGIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pilot</strong></td>
<td>26* / 4 mos</td>
<td>74% (360)</td>
<td>3/11</td>
</tr>
<tr>
<td><strong>Exp 1</strong></td>
<td>24 / 3 mos</td>
<td>10% (90)</td>
<td>5/10</td>
</tr>
<tr>
<td><strong>Exp 2</strong></td>
<td>15 / 2 mos</td>
<td>53% (90)</td>
<td>2/11</td>
</tr>
<tr>
<td><strong>Exp 3</strong></td>
<td>27 / 3 mos</td>
<td>1% (90)</td>
<td>0/21 0/27 (LPA)</td>
</tr>
<tr>
<td><strong>Exp 4</strong></td>
<td>17 / 3 mos</td>
<td>77% (90)</td>
<td>2/10</td>
</tr>
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</table>

* 8 different spoligotypes, but only 2 transmitted to GPs – both XDR-associated
Unsuspected, untreated TB

General Medical Ward
Orthopedic Ward
Obstetrics Ward
Psychiatric Ward
Unsuspected, untreated MDR/XDR TB
All other patients on effective treatment

TB Hospital
Potential for re-infection
TB transmission only from untreated patients – Peru

Escombe 2008 Plos Medicine; 5:e188

– 97 HIV+ pulmonary TB patients exposed 292 guinea pigs over 505 days
  • 66 cult +, 35 smear +

– 122/125 GP infections (98%) were due to 9 MDR patients
  • all inadequately or delayed treatment
    » 108/125 infections (86%) due to 1 MDR patient
  • 3 drug susceptible patients infected 1 guinea pig each
    » 2 had delayed treatment
    » 1 had treatment stopped
Unsuspected, untreated XDR TB
All other patients on effective treatment

MDR TB Ward
Potential for re-infection

XDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
MDR TB
TB Triage – Rapid DR Diagnosis

Gene Xpert: TB, DS or MDR

Community based – on effective treatment – responding

Complications

Hospitalized patients on effective treatment - responding

Individual Isolation

Effect of treatment unknown

Novel interventions

Smear status may not be critical if on effective treatment

XDR by LPA

- **Find** TB cases - rapid diagnosis
  - Focus on rapid molecular diagnosis – Xpert TB
  - Sputum smear – can also be rapid, but more limited

- **Active** case finding
  - Focus on cough surveillance at all entrance points

- **Separate** safely and reduce exposure
  - Building design and engineering
  - Cough hygiene and triage

- **Treat** effectively, based on rapid DST
  - Focus on rapid molecular DST – Xpert TB
Not new, but never prioritized:

**Traditional TB IC**
- Facility assessment
- Develop a TB IC plan
- Political will and resources
- TB IC committee
- WHO TB IC Policy
  - Administrative
  - Environmental
  - Respiratory protection
- Assessment
  - Process indicators
  - HCW cases

**F-A-S-T Strategy**
- Risk of undiagnosed TB and undiagnosed DR TB
- Approach: F-A-S-T
- Political will and resources
- Focus on certain administrative components
  - Rapid diagnosis
  - Active case finding
  - Exposure reduction
  - Effective treatment
- Assessment
  - Process indicators
  - HCW cases
Ndola Central District Hospital

Lab: Xpert TB (2 hr dx TB and RMP resistance)
RX – effective treatment -> no transmission

Process indicators:
1. Time from cough onset to detection
2. Time from cough detection to sputum smear or Xpert TB test
3. Time from sputum receipt to result
4. Time from result to effective treatment.

Ndola Central District Hospital

USAID F-A-S-T Implementation Project
Ndola District, Zambia
Summary:

1. Not enough hospital beds globally for inpatient treatment of MDR-TB
2. More expensive and not necessary
3. Transmission risk in community, clinic, and hospital can be profoundly reduced by the FAST approach:
   - active case finding followed by DST-guided effective therapy.