Impact of Treatment on MDR-TB Transmission

Preliminary Results from the Airborne Infections Research (AIR) Facility

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Harvard Medical School
Harvard School of Public Health
Partners In Health

Institutes of Medicine, New Delhi, April 18-19
Global MDR-TB Treatment Scale Up

• Estimated 500,000 new MDR-TB cases per year
  – More than half result from transmission
  – 2008 - 29,423 cases reported
    • 7% of estimated cases
    • 1% treated with quality assured drugs

• Most are treated in hospitals for first 6 months – until sputum smear or culture conversion

Source: Multidrug and extensively drug-resistant TB (M/XDR-TB)
2010 GLOBAL REPORT ON SURVEILLANCE AND RESPONSE
Community Based Treatment

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

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

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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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<tr>
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<td>UK Department of Health</td>
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<td>pos /pos</td>
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<td>3 neg cultures</td>
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**Discontinuation of Airborne Infection Isolation: Drug-Susceptible TB**
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</table>
Effects of Chemotherapy on Transmission – Early Papers

- Andrews RH. Bull WHO. 1960 (Madras, India)
- Crofton J. Bull IUAT. 1962 (Edinburgh, 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):
  - Smear and culture correlate with infectivity only in untreated cases
    - Discordance between effect of treatment on culture and smear
  - **Evidence that smear and culture positive TB patients on therapy do not infect skin test negative close contacts.**

- Menzies R. Effect of treatment on contagiousness of patients with active pulmonary tuberculosis. Infect Control Hops Epidemiol 1997; 18:582-586
The Madras Experience
(Bull WHO 1966; 34:517-32)

- The first clinical trials of ambulatory TB treatment demonstrated no more household conversions after the start of treatment
  - Most household contacts had been exposed for months before diagnosis and treatment
  - Susceptible contacts already infected
  - Patients no longer infectious
Effects of Chemotherapy on Transmission

• Brooks et al (ARRD 1973):
  – 107 TST-negative subjects living with 21 patients with positive sputum.
  – After up to 23 days hospitalization, 19 smear positive patients were sent home (they did not all become negative on culture until after 5 mos)
  – No TST negative subjects in contact after the beginning of treatment converted their skin test.
Effects of Chemotherapy on Transmission

• Riley and Moodie (ARRD, 1974):
  – studied 70 household contacts of 65 new TB cases on domiciliary treatment (non-RIF regimen)
    – never hospitalized.
  – A series of 6 TST results showed no transmission among 25 TST negative contacts after the start of treatment.
  – Most household contacts were infected in the month or two before diagnosis and treatment.
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
    - Discordance between effect of treatment on culture and smear
  - Evidence that smear and culture positive TB patients on 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…”
CDC/ATS Policy on Treatment in general hospitals, communities, and discharge

- 1969 ATS – Guidelines for the general hospital for the admission and care of tuberculosis patients.
- 1970 ATS – Bacteriologic standards for discharge of patients
- 1973 ATS – Guidelines for work for patients with tuberculosis
- 1974 CDC – Recommendation for health department supervision of tuberculosis patients
Another point of view

  - Assumes smear/culture pos. = infectious
  - But, no reported outbreaks from source case on therapy
  - Dismisses Madras due to high rates from the community
  - US studies were not randomized – Riley may have selected less infectious patients for home treatment.
  - Found faults with all epi studies - uninfected household contacts less vulnerable
  - Compared to early studies, most household contacts (in N. America) are uninfected and more vulnerable.
  - Concluded that smear + treated patients should still be considered infectious AFTER 2wks

  - Drug susceptible TB took median of 37 days to convert, 10% cult pos at 60 days
Riley Experimental TB Ward, 1956-60
(reprinted as “classic” Am J Epidemiol 1995; 142:3-14)

Hundreds of sentinel guinea pigs sampled the air from a 6-bed TB ward in Baltimore
TB transmission only from untreated patients - 1

- Patients selected:
  - strongly smear positive
  - cavitary TB
- 3 of 77 patients produced 35 of 48 (73%) of GP infections that were cultured
  - all drug resistant M. tuberculosis on inadequate therapy
  - 4 month period of no infections when drug susceptible patients were admitted to the ward and started on treatment the same day
Riley Ward – 2nd 2-year study
- included untreated patients

Relative infectivity of patients*:
- Susceptible TB
  • 61 Untreated (29 GPs) 100%
  • 29 Treated (1 GP) 2%
- Drug-resistant TB
  • 6 Untreated (14 GPs) 28%
  • 11 Treated (6 GPs) 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

Sputum culture vs. GP Infection

- Sputum sample
  - no evaporation
  - no aerosol damage
- No host defenses
- Growth support optimized

Smear and culture positive

- Droplet nucleus
  - evaporation with rising drug concentration
  - aerosol damage
- Host defenses
- Innate immunity

No guinea pig 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
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

- **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
  - Harvard CFAR (NIH) – two awards
  - NIOSH (NIH) RO1
  - NIH K23 (A. Dharmadhikari, PI)
109 patients: smear +, cavitary, coughing, recently started on therapy
Guinea Pig Transmission: South Africa

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

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<tr>
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<th># Patients/ Exp. Duration</th>
<th>% guinea pigs infected (# exposed)</th>
<th># XDR Patients (data incomplete)</th>
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<tr>
<td><strong>Pilot</strong></td>
<td>26* / 4 mos</td>
<td>74% (360)</td>
<td>3/11 (MGIT) No LPA</td>
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<tr>
<td><strong>Exp 1</strong></td>
<td>24 / 3 mos</td>
<td>10% (90)</td>
<td>5/10 (MGIT) 0/16 (LPA)</td>
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<tr>
<td><strong>Exp 2</strong></td>
<td>15 / 2 mos</td>
<td>53% (90)</td>
<td>2/11 (MGIT) 4/15 (LPA)</td>
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<tr>
<td><strong>Exp 3</strong></td>
<td>27 / 3 mos</td>
<td>1% (90)</td>
<td>0/21 (MGIT) 0/27 (LPA)</td>
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<tr>
<td><strong>Exp 4</strong></td>
<td>17/ 3 mos</td>
<td>77% (90)</td>
<td>2/10 (MGIT) 0/14 (LPA)</td>
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* 8 different spoligotypes, but only 2 transmitted to GPs – both XDR-associated
How much treatment on admission?

- Patients usually started on Standard South African MDR regimen on the day of admission or the next day.
- Exp 2: 10% infection rate
  - 24 patients had, on average, 0.46 days treatment on admission.
- Overall: 70% of patients had < 24 hrs treatment on entering the AIR facility
Unsuspected, untreated TB

General Medical Ward
Orthopedic Ward
Obstetrics Ward
Psychiatric Ward

TB
DR

TB
DS
Unsuspected, untreated MDR/XDR TB
All other patients on effective treatment

TB Hospital
Potential for re-infection
Unsuspected, untreated XDR TB
All other patients on effective treatment

MDR TB Ward
Potential for re-infection
TB Triage – Rapid DR Diagnosis

Smear status may **not** be critical if on effective treatment

**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*
New TB CARE Transmission Control Campaign:

Find Actively, Separate, & Treat “FAST”

- **Find TB cases Actively**
  - Active case finding based on **cough**
  - Rapid specific diagnosis by **Gene Xpert**

- **Separate** *safely*
  - Awaiting diagnosis and treatment
  - R/O XDR
  - Includes building design and engineering

- **Treat** *effectively, based on rapid DST*
  - Supervised treatment based on **DST (Gene Xpert)**
  - Secure supply, quality-assured drugs
Conclusions

• Airborne transmission may be the weak link in TB propagation
  – Only about 1/3 of pulmonary TB patients infect close contacts

• Very little effective treatment may tip the balance against transmission

• Strong rationale for prompt diagnosis of drug resistance and prompt therapy
  – can be in the community.