Transmission of DS-TB and MDR-TB

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Outline

• Epidemiologic factors in transmission
• Ability of the transmitter to transmit
• Susceptibility of the exposed person
• Infectivity of the organism
• Preventive strategies
Epidemiologic factors in transmission

- Risk that the people an exposed person interacts with has infectious pulmonary TB disease
- Duration of time that the exposed person shares air with the source case
Risk of TB Infection and Closeness of Contact

Contact Investigations in 5 US Cities

TST+/total (%)

Close Contact 301/701 (42.9)*
Not Close 301/953 (31.6)

*p<.001
## Tuberculosis Infection in the U.S. - Incidence

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital workers</td>
<td>1-11/100 p-y</td>
</tr>
<tr>
<td>HIV Infection</td>
<td>6-10/100 p-y</td>
</tr>
<tr>
<td>Farm Workers</td>
<td>10/100 p-y</td>
</tr>
<tr>
<td>IVDU</td>
<td>3-13/100 p-y</td>
</tr>
<tr>
<td>Incarcerated persons</td>
<td>6.3/100 p-y</td>
</tr>
<tr>
<td>Nursing Home residents</td>
<td>0.7-1/100 p-y</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>Unknown</td>
</tr>
<tr>
<td>Foreign Born</td>
<td>Unknown</td>
</tr>
<tr>
<td>General population</td>
<td>.02-.08/100 p-y</td>
</tr>
</tbody>
</table>
Effect of Limited Air Circulation on Airborne Particle Density

Fig 5. Particle production as a function of respiration in a clinical TB patient. CO₂ concentration (solid line and left ordinate) and particle counts (dots and right ordinate) in the 1–2.5 μm size range for a TB patient.
Figure 1  Annual tuberculosis transmission risk at locations of public importance in Dar es Salaam, Tanzania. Annual tuberculosis transmission risk estimates based on varying environmental CO₂ levels (in parts per million, ppm) at higher risk (Panels A1 and B1) and lower risk locations (Panels A2 and B2, different scales), and under the assumption of the national TB prevalence (295
Ability of the transmitter to transmit

• Variability in number of organisms expressed
Tuberculous Infection Among Close Contacts (Children <15 yr)
by Bacteriologic Status of Index Case

Per cent infected

Bedfordshire
1948 - 1952
Rotterdam
1967 - 1969
Saskatchewan
1966 - 1971

Proportion of Contacts <15 Years with Tuberculous Infection, in Relation to Cough Frequency of Source

Per cent with infection

<table>
<thead>
<tr>
<th>Mean cough frequency</th>
<th>0</th>
<th>&lt;12.0</th>
<th>12.0-47.9</th>
<th>48.0+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per cent with infection</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cough and Respiratory Particle Production

FIG. 5. Particle size spectra versus respiratory mode for subject 5.
Variability Among Transmitters

B

CFU = 0
53 (55%)

CFU 1-9
18 (19%)

CFU ≥ 10
25 (26%)

Number of M. tuberculosis CFU in aerosol

AJRCCM 2013;187: 1007
High excretors infect more contacts

AJRCCM 2013;187:1007
Susceptibility of the Exposed Person

- HIV-infected persons: OR 6.1 (0.9-42)
- LTBI: OR 0.21 (0.14-0.30)
- BCG: OR 0.57 (0.34-0.98)

AJTMH 2006;75:58
Clin Infect Dis 2012;54:785
Clin Infect Dis 2016;63:10
Infectivity of the organism

- Virulence factors
M. tuberculosis Genetic Regions Associated with Transmission

Table 1. Significant Genes or Intergenic Regions by Phylogenetic Convergence Test

<table>
<thead>
<tr>
<th>Gene/Region (Rv number)</th>
<th>Original Dataset (n = 100)</th>
<th>Validation Dataset (n = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strains with Mutations, Deletions, and Insertions (n)</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>Clustering</td>
<td>Nonclustering</td>
</tr>
<tr>
<td>espE (Rv3864)</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>PE-PGRS56 (Rv3512)</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Unnamed (Rv0197)</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Unnamed (Rv2813–2814c)</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Unnamed (Rv2815–2816c)</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

AJRCCM 2017;195:1522
Transmissibility of MDR-TB

Fig 2. The incidence of second cases of tuberculosis disease in household contacts stratified by index case drug resistance.

In vitro Fitness of MDR-TB

**Fig. 2.** Relative competitive fitness of clinically derived rifampin-resistant mutants of *M. tuberculosis*. Four of the five mutants with the *rpoB* S531L mutation (light gray bars) had no fitness cost compared with their rifampin-susceptible ancestors. All mutants with other *rpoB* mutations (dark gray bars) had significant fitness defects (error bars indicate 95% confidence intervals).
Transmissibility of MDR-TB

**Figure 2.** The incidence of second cases of tuberculosis disease in household contacts stratified by index case drug resistance.
Trends in MDR-TB over time, Botswana

Figure 3  Trends in proportion (and 95% confidence intervals) of patients with MDR-TB by patient treatment category in Botswana’s national anti-tuberculosis drug resistance surveys, 1995–2008. MDR-TB = multidrug-resistant tuberculosis.
XDR-TB in KwaZulu Natal

Figure 3. Social Networks in Homes and Communities, Derived from Name-Based Person-to-Person Links.

MDR-TB Prevention

- Ensure that treatment of DS-TB is completed to prevent emergence of DR
- Find and promptly treat MDR-TB cases to reduce primary spread in the community
- Treatment of contacts with MDR-TB infection?
<table>
<thead>
<tr>
<th></th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHOENIx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>LVF (novel paediatric formulation) vs. placebo daily for 6 months</td>
<td>LVF vs. placebo daily for 6 months</td>
<td>DLM vs standard dose INH daily for 26 weeks</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Cluster randomized; superiority Community-based</td>
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<td>Cluster randomized; superiority Community-based</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>• 0-5 y regardless of TST or HIV status</td>
<td>• All ages</td>
<td>• HIV +</td>
</tr>
<tr>
<td></td>
<td>• Paediatric enrolment on hold</td>
<td>• Paediatric enrolment on hold</td>
<td>• Children 0-5 yrs</td>
</tr>
<tr>
<td></td>
<td>• TST +</td>
<td>• TST/IGRA + &gt; 5 yrs</td>
<td>• TST/IGRA + &gt; 5 yrs</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>LVF decreases TB incidence from 7 to 3.5% 80% power</td>
<td>LVF decreases TB incidence by 70% from 3% untreated 80% power</td>
<td>DLM decreases TB incidence by 50% from 5% to 2.5% 90% power</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>778 Households 1556 contacts</td>
<td>1326 Households 2785 contacts</td>
<td>1726 Households 3452 contacts</td>
</tr>
<tr>
<td><strong>Sites, funder</strong></td>
<td>South Africa BMRC/Wellcome Trust Hesseling/Seddon</td>
<td>Viet Nam Australian MRC Fox/Nguyen</td>
<td>ACTG &amp; IMPAACT sites DAIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Churchyard, Swindells, Gupta, Hesseling</td>
</tr>
<tr>
<td><strong>Timelines to open</strong></td>
<td>Open</td>
<td>Open</td>
<td>Q1 2018</td>
</tr>
</tbody>
</table>
Conclusions

- MDR-TB transmitters may be more likely to have cavities and thus be more infectious
- Exposure duration likely longer for contacts to MDR-TB
- MDR-TB isolates may be less likely to spread at first, but this property is likely not retained
- No clearly effective preventive treatment for those exposed to MDR-TB, but clinical trials now underway
To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Website

www.resisttb.org