Determining Infectiousness of TB Patients

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TB Rates over the Last Century
Cape Town, New York, and London

Driven by transmission
Determining TB Infectiousness:
- Clinical – cough, cavitary CXR, smear pos.
  - *Mtb* strain infectiousness, environment.
- Public health – contact investigation.
  - Concentric circle approach
- Quantitative air sampling
  - Cannot culture *Mtb* from ward air
    - Can from artificial aerosols of BCG, e.g.
  - Human to guinea pig transmission
- CASS – cough aerosol sampling
- Molecular detection of *Mtb* DNA
- Viable particle counting.
- CO2 monitoring – rebreathed air fraction
Propagation of *Mycobacterium tuberculosis*
Wells’ Air Centrifuge, 1931

“On Airborne Infection, Study II.
Droplets and Droplet Nuclei”

*Instructor, Sanitary Service, HSPH

Wells developed his air centrifuge to sample bacteria from air in a New England textile mill. Richard Riley was his student.
Wells/Riley Experimental TB Ward


- Riley RL. What nobody needs to know about airborne infection. (How It Really Happened) AJRCCM 2001; 163:7-8.

Quantitative air sampling for TB
Wells/Riley Ward – Results (Exp 2)

- 2.6 GPs infected per month
  - strict criteria
- 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
Human to GP results

- *Mtb* is airborne
- Highly variable infectiousness
  - *Mtb* variability (Beijing, etc)
    - Drug resistance – fitness cost?
  - Source strength highly variable
    - $q = 1.25 \text{ vs } 13 \text{ vs } 60 \text{ vs } 250 \text{ qph}$
    - Effective treatment stops transmission quickly
Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis

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Rapid impact of effective chemotherapy on transmission of drug-resistant tuberculosis: pity the quinea pig

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F-A-S-T: a refocused, intensified, administrative tuberculosis transmission control strategy

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Witbank, Mpumalanga Province, SA

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Dedicated 2005,
Rededicated 2015
Airborne Transmission - Interventions

Aerobiology
- Environmental stresses: temperature, humidity, radiation

Pathogenesis
- Infection, disease
- Host resistance
- Source strength
- Organism
- Drug resistance, viability, number
- Virulence
- Treatment
- Isolation
- Immunization
- Resp Protection
- Dilution (ventilation)
- UVGI
- “F-A-S-T” (Admin. Controls)
- Treatment of latent infection

Source
- Strength
- Take off
- Landing
- Masks on patients

Treatment
- Drug resistance
- Number
- Viability

Isolation
- Temperature and humidity
- Landing

Dilution (ventilation)
- Filtration
- UVGI

Immunization
- Resp Protection

Resp Protection
- Masks on patients

Dose
- Host resistance

Pathogenesis
- Disease
- Infection

Treatment of latent infection
AIR, Experimental Plan

Guinea Pig Air Sampling

Odd days

Even days

UVGI or other intervention

3 patient rooms
Plus common areas

Pt. TB RFLP

Guinea Pig TB RFLP
Ventilation ducts in patient rooms

Paddle Fans Assure Good Air Mixing
# Results

<table>
<thead>
<tr>
<th>UV1</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<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>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>TST-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UV2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TST1</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>TST-2</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>TST3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15</td>
<td>48</td>
</tr>
</tbody>
</table>

* *p*<0.0005

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

**Note:** Equivalent of adding 24 ACH to the AIR facility wards

AJRCCM – available on line
# New UVGI Dosing Criteria:

<table>
<thead>
<tr>
<th>Study</th>
<th>Nominal UVGI dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riley study</td>
<td>30 W (nominal)</td>
<td>Per 200 sq ft floor area. Does not take lamp or fixture efficiency into account.</td>
</tr>
<tr>
<td>NIOSH study (primary)</td>
<td>30 – 50 µW/cm² avg. UV fluency rate (measured in a horizontal plane at the level of the lamp)</td>
<td>Hard to predict in advance. No standard measurement method.</td>
</tr>
<tr>
<td>NIOSH study</td>
<td>6.3 W total UVGI lamp wattage per cubic meter upper room volume</td>
<td>Does not take fixture efficiency into account.</td>
</tr>
<tr>
<td>AIR Facility study (primary)</td>
<td>6 µW/cm² avg. UV fluency rate (for the entire room)</td>
<td>Requires gonioradiometry of fixtures for input into Visual-UV CAD program (incorporates ray length).</td>
</tr>
<tr>
<td>AIR Facility study (practical)</td>
<td>15-20 mW total fixture UV output/m³ room volume (or approx 20 mW/m³)</td>
<td>Requires Total Fixture UV Output measurement (supplied by manufacturer). Must adjust for avg ray length in a given room.</td>
</tr>
</tbody>
</table>
How Effective are Surgical Masks on Patients?

For patients

For health care workers

Respirators
How Effective Are Surgical Masks on Patients?

<table>
<thead>
<tr>
<th>Guinea Pig Group</th>
<th>TST 0</th>
<th>TST 1</th>
<th>TST 2</th>
<th>TST 3</th>
<th>TST 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>4</td>
<td>15</td>
<td>39</td>
<td>11</td>
<td>69</td>
</tr>
</tbody>
</table>

Approx 53% Effective

Dharmadhikari AS, et. al.  

NIOSH funded
What is Infection?
Figure 1. Stages of tuberculosis: (1) primary TB in the lower left lung, resulting from the inhalation of infectious droplet nuclei, (2) primary TB usually resolves with or without treatment, but sometimes leaves scars, as evidenced in the left lower lung, (3) months to years later, reactivation of infectious foci, often in the upper lung, leads to the chronic form of the disease, with lung cavitation. It is the cavitary form of the disease that is most likely to be infectious to others.
Laboratory exposure 15 – 30 cfu
All animals clearly infected, all die

Our GPs were sacrificed at approximately 280 days

Observations from AIR Pilot Study

1. 53 guinea pigs reverted their skin test back to 0 mm.
2. No guinea pigs that reverted had signs of TB or pathology

33 guinea pigs reverted and had another episode of TST reactivity
Here Today—Gone Tomorrow: The Case for Transient Acute Tuberculosis Infection

Along with death and taxes, another widely known certainty of life (within medical circles at least) is that once infected with *Mycobacterium tuberculosis*, human hosts carry the organism in a latent state to the grave, with a relatively small and diminishing risk of reactivation along the way. So secure are we in this perceived wisdom that no further skin testing is done for tuberculin skin test (TST)-positive persons. Of course, skeptics have repeated skin tests, and for decades reports of TST reversions have appeared in the literature. Given the vagaries of the TST and our still incomplete understanding of the human immune response to this ancient pathogen, these reports have been con-

are thought to improve on the TST in terms of reproducibility and specificity (10). They may also focus attention on defenses mediated by T cells of the effector memory subset (TEM) (11). Both factors may contribute to the present observations. Some caveats are in order, however. Since both reports identified the subset of interest retrospectively based on their initial response, they may be susceptible to the statistical artifact of regression to the mean, as well as the other recognized shortcomings of subset analysis. In addition, prospective studies should reduce the small possibility that such artifacts are playing a role.

Differences in either innate or acquired host responses may
MODEL SYSTEMS

Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis

Ashwin S. Dharmadhikari a,*, Randall J. Basaraba b, Martie L. Van Der Walt c, Karin Weyer d, Matsie Mphahlele e, Kobus Venter e, Paul A. Jensen e, Melvin W. First f, Sydney Parsons g, h, David N. McMurray b, Ian M. Orme b, Edward A. Nardell a, e

Exposure – no infection (91, 25%)

Exposure – infection (271, 75%)

Exposure – infection – reversion (53, 15%)

Exposure – infection – reversion – reinfection (33, 9%)

Exposure – infection – (reinfection) – disease (54, 15%)
GP Evidence of Reinfection

Graphs showing the evidence of reinfection for GP 338 and GP 251 over time.
Endogenous Reactivation (Endog. Path.)

- CMI Response Activated
  - Primary complex is eventually sterilized
  - Bacillary population drops to dormant level

- 10^5 cfu

- 10^3 cfu

- Cavitary pulmonary tuberculosis

- Sputum positive for tubercle bacilli

- Transmission to contact

1st infection via airway
2nd infection via airway
3rd infection via airway
4th infection via airway
Nth infection via airway leads to apical implant

Immunoospressive event → CMI↓

Aerosol implants to mid-to-lower lung

Stead Theory

Don Smith Alternative Pathway to Cavitary TB

Hospitals as Drug Resistant TB Factories

Half of the 500,000 new MDR cases per year are transmitted.

Hospitalized drug susceptible TB patients in Tomsk, Siberia are more than 6 times more likely to develop MDR-TB.


Drug Susceptible TB or No TB at all

Health care workers and patients at great risk of infection and death.

HIV co-infected at greatest risk

Gila Kaplan, BMGF, “its all about transmission”
Hospitals as Causes of Human Suffering

Referring to the Hotel-Dieu in Paris which had a mortality rate of 1 in 4 patients

“A fragment of space closed on itself, a place of internment of men and disease, its ceremonious but inept architecture multiplying the ills of its interior without preventing their outward diffusion, the hospital is more of a centre of death (foyer de mort) for the cities where it is sited, than a therapeutic agent for the population as a whole”

Ref: Medicine and Magnificence – British Hospital and Asylum Architecture, 1660 – 1815, by Christine Stevenson, Yale University Press, 2000, page 155
Florence Nightingale 1820-1910
“Notes on Hospital Design 1859”

Key role of nurses in airborne Infection control research
Building Design and Engineering for Airborne Infection Control (2008-2016)

One week courses this summer in Lima, Peru; and Pretoria, South Africa
Two-week course Harvard Course, Boston, Aug 1-16, 2016
Butaro District Hospital, Rwanda (PIH, MASS Design Group)

Indus Hospital, MDR Clinic, Karachi, Pakistan

Alert Hospital, MDR Clinic, Addis Ababa, Ethiopia
How Do We Know These Building Designs Work – or Don’t?

• Hypothesis: Average personal shared air experience by workers in different hospitals reflects building design and use.

• Personal ambient CO2 monitoring represents the balance between production (40,000 ppm) by occupants, and reduction by ventilation (400 ppm outside)
  – An index of shared air – indicator of risk of TB infection if there is an infectious source
Ethiopia: St. Peter’s New Building

Very large interior space – glass!!

No ventilation
How do we know these designs work?

Current Assessment Tools

- Smoke tubes
- Flow meters
  - Vanometers
- Tracer gases
  - CO₂ decay

Generally reflect a moment in time
Risk of indoor airborne infection transmission estimated from carbon dioxide concentration

Abstract The Wells–Riley equation, which is used to model the risk of indoor airborne transmission of infectious diseases such as tuberculosis, is sometimes problematic because it assumes steady-state conditions and requires measurement of outdoor air supply rates, which are frequently difficult to measure and often vary with time. We derive an alternative equation that avoids these problems by determining the fraction of inhaled air that has been exhaled previously.
Concept

• Avg personal ambient CO$_2$ over 4 – 8 hrs reflects avg rebreathed air experience.
  – An index of airborne risk given a source of infection
• Reflects building ventilation AND its use, especially occupancy.
• Compare nurses doing the same job in two different hospital settings
Other Hospital Evaluations Planned in South Africa

- Tygerberg Hospital, Stellenbosch
- Kimberly Hospital
- New London Hospital
New Transmission Issues

• Global warming – need for AC
  – Split systems increasingly common – no ventilation
    • Windows closed in ambulatory center, Mumbai

• MDR/XDR surgery – how to do it safely
  – Backlog of cases in Peru – staff fearful
  – Major concern of Lion Hospital, Ethiopia
  – ORs normally positive pressure
  – Isolation rooms normally negative pressure
    • Role for GUV and PAPRs
Cough Aerosol Sampling
Kevin Fennelly, MD

Each patient performs 2 cough sampling sessions over 2 successive days
Instantaneous Viable Particle Detection System

A new potential tool to evaluating air disinfection

- Particle counter – sorts viable and non-viable
- Not Mtb specific – environmental organisms in facilities vs. Mtb under aerosol chamber conditions
- Instantaneous read out
- Can be used on occupied ward
- Detects NADH and riboflavin as viability biomarkers
Conclusions:

- **Determining TB Infectiousness:**
  - Clinical – cough, cavitary CXR, smear pos.
    - *Mtb* strain infectiousness, environment.
  - Public health – contact investigation.
    - Concentric circle approach
  - Quantitative air sampling
    - Cannot culture *Mtb* from ward air
      - Can from artificial aerosols of BCG, e.g.
    - Human to guinea pig transmission
    - CASS – cough aerosol sampling
    - Molecular detection of *Mtb* DNA
    - Viable particle counting.
  - CO2 monitoring – rebreathed air fraction