

Riley Re-visited: MDR-TB Transmission Dynamics

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Content

1. The challenges and insights in drug resistant TB control
2. Historical background on TB air sampling and aerobiology
3. New research on MDR-TB transmission in guinea pigs – preliminary data and research plans
4. Conclusions

Learning Objectives

- Review the past and current importance of transmission in the global spread of MDR-TB
- Understand the past, current, and future role of guinea pig air sampling in testing infection control interventions and unraveling the dynamics of MDR-TB transmission



Collaborators

Harvard

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Pine Street Inn 1984 TB Outbreak

INH & SM res

Shelter
Transmission

Exogenous
Reinfection



UVGI Air
Disinfection

Air Filtration

(Nardell, et al. NEJM 1986; 315:1570-5)



Number of MDR-TB patients to be treated per year under DOTS-Plus by region, 2006–2015



XDR-TB

Among 53 XDR TB
patients
n (%)

Characteristic

Prior TB Treatment History (n=47):

No prior TB treatment 26 (55%)

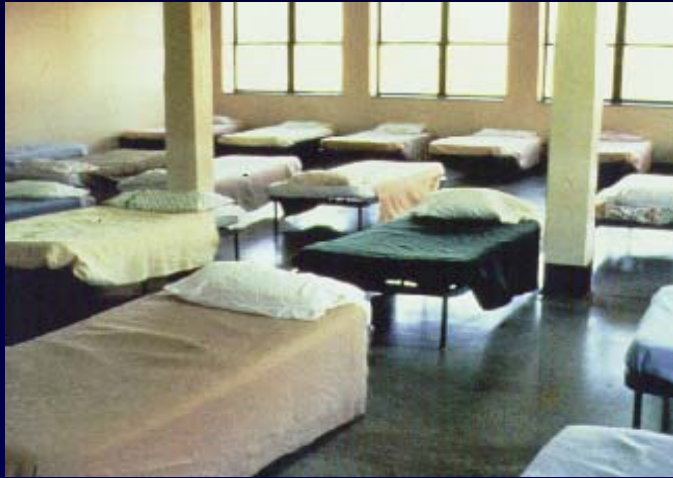
Cure or Completed treatment 14 (30%)

Default or Treatment Failure 7 (15%)

Prior Hospitalization (n=42): 28 (67%)

From Gandhi, NR et.al. Extensively Drug Resistant Tuberculosis As A Cause Of Death In Patients Co-Infected With Tuberculosis and HIV In A Rural Area Of South Africa. Lancet 2006; 368:1575-80.

Congregate Settings



Shelter in Boston



Prison in South Africa



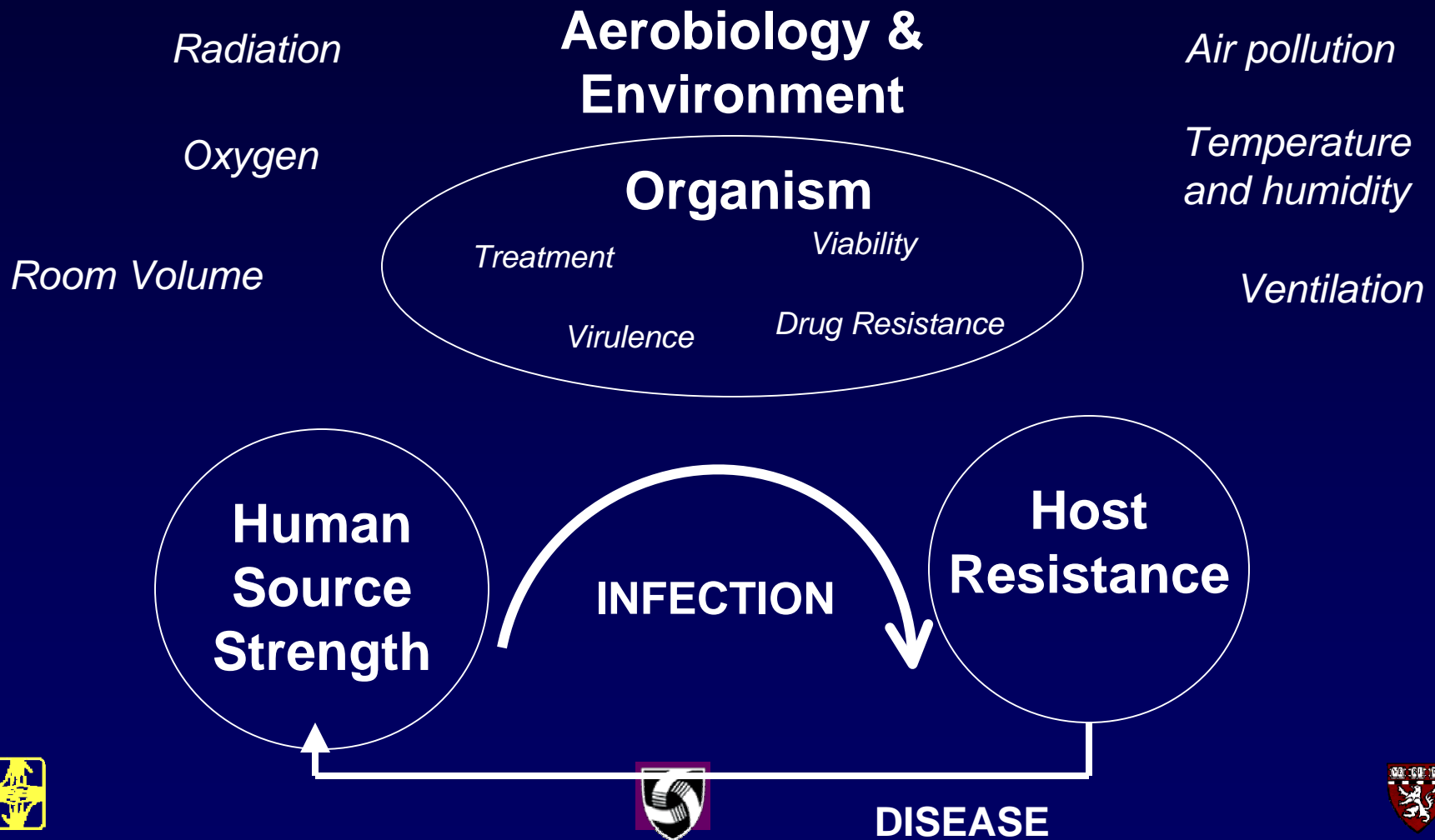
Hospital in Rwanda



What do we know about *Mtb* transmission, aerobiology and control of airborne infections?



Mycobacterium TB Transmission— Many Factors



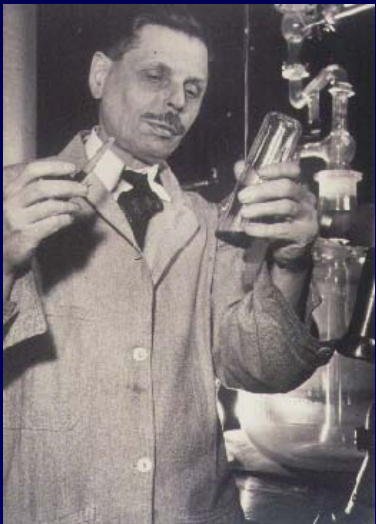
How to measure transmission?

- Epidemiological observations
 - Often confounded by variable source, organism, host, and environmental factors
- Air sampling from human sources
 - Ability to test interventions
 - Study basic aerobiology



Wells' Air Centrifuge, 1931

- “*On Airborne Infection, Study II. Droplets and Droplet Nuclei*”
 - W. F. Wells*. *Am J Hygiene*, 1934:20. 611-18.
 - *Instructor, Sanitary Service, HSPH



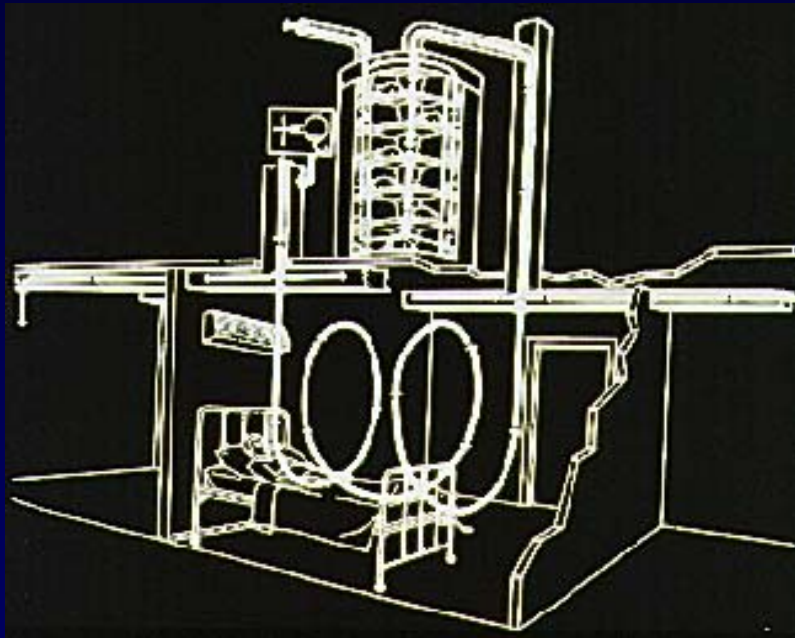
- In 1931 Wells developed his air centrifuge to sample bacteria from air



Richard L. Riley & William F. Wells



Wells/Riley Experimental TB Ward



- Riley RL, Mills C, Nyka W. Aerial dissemination of tuberculosis – a two year study of contagion on a tuberculosis ward. *Am J Hyg* 1959; 70:185-196.
(reprinted as “classic” in *Am J Epidemiol* 1995; 142:3-14)

Quantitative air sampling for TB



Wells/Riley Ward - Results

- 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



Wells/Riley Ward - Results

| TST reaction | # guinea pigs autopsied | confirmed TB | % confirmed TB |
|-------------------------|-------------------------|--------------|----------------|
| 0 – 5 mm | 39 | 0 | 0 |
| 6 – 13 mm - no necrosis | 24 | 6 | 25 |
| 6 – 13 mm – necrosis | 16 | 13 | 81 |
| 14+ mm – necrosis | 55 | 52 | 95 |



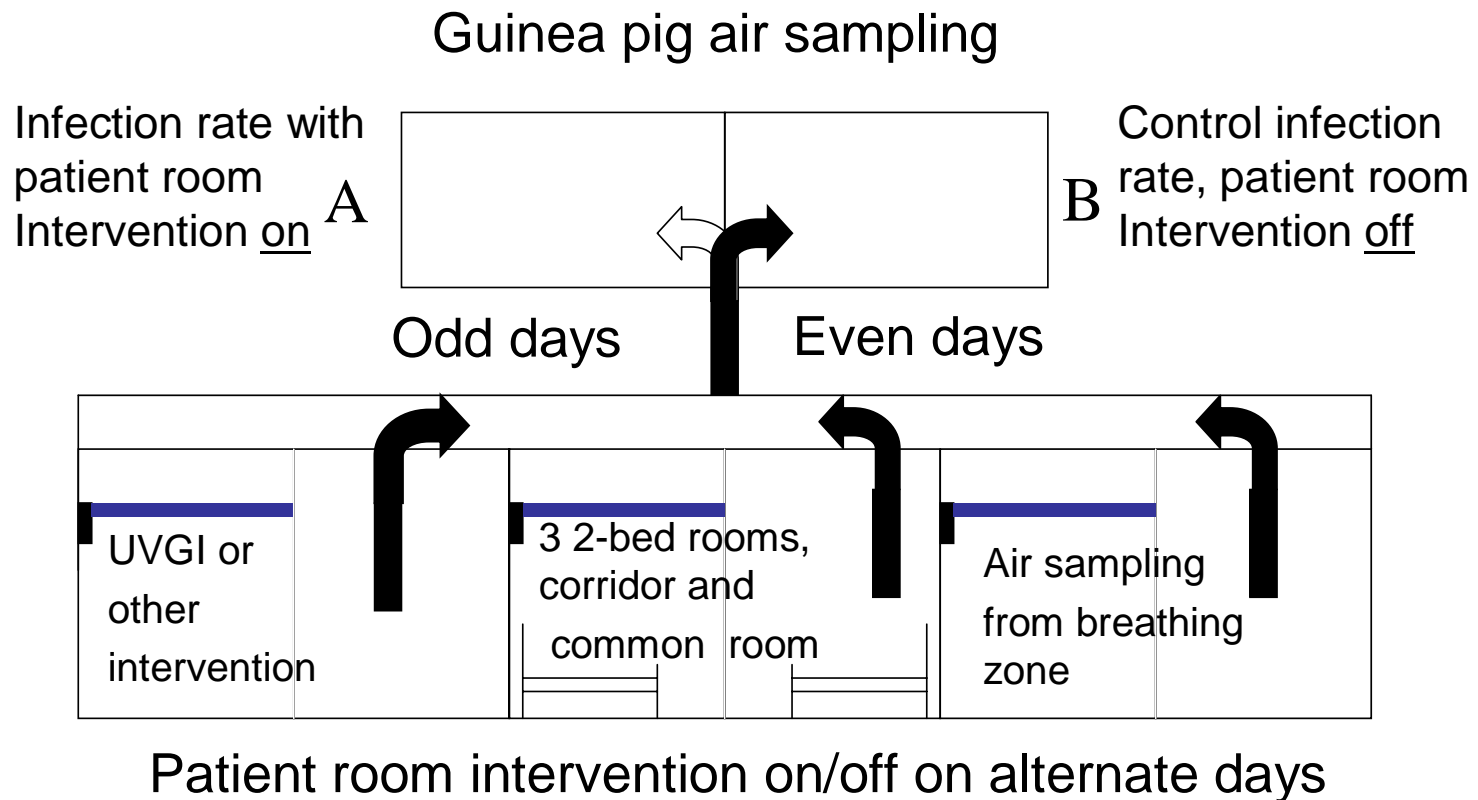
From Historic Ideas To Contemporary Applications



The AIR Facility



AIR Facility, Experimental Plan



Guinea Pig Skin Testing



AIR facility capabilities:

Test conventional & novel air infection control interventions

- a. Masks on patients
- b. Portable room air disinfection units
- c. Upper room UVGI
- d. Novel aerosolized TB drugs
- e. Agents to reduce droplet production



AIR facility capabilities:

Study basic TB aerobiology

- a. Human source factors
- b. Organism factors – the fitness issue
- c. Host responses (pathogenesis)
- d. Environmental factors (humidity)

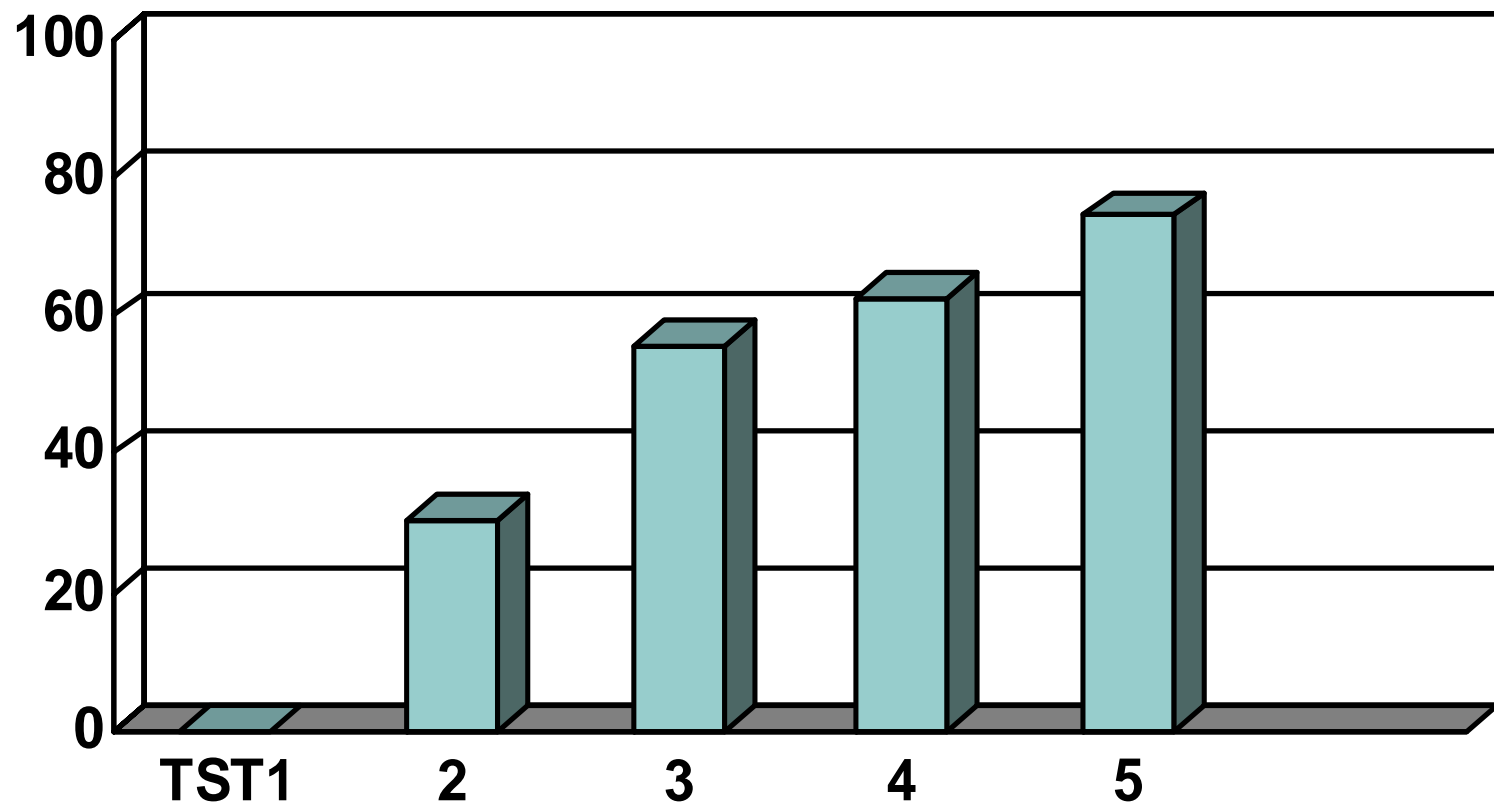


First Experiment at AIR:

- 4 months exposure of 360 GPs
- 28 different patients (~ 1/2 HIV positive)
- Most infectious MDR-TB patients selected
- All animals autopsied and cultured
- Isolates fingerprinted and matched human sources

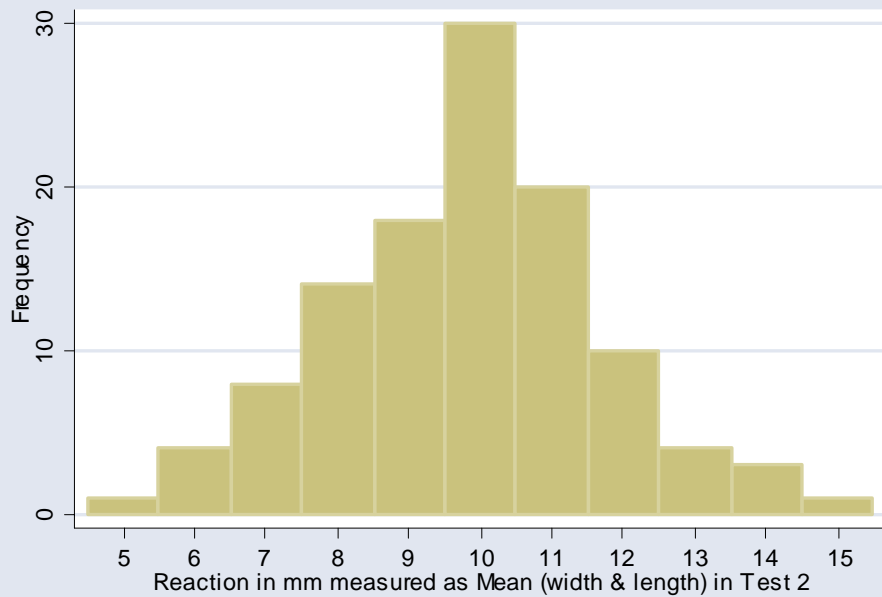


Using 6 mm as positive 75% of GPs infected

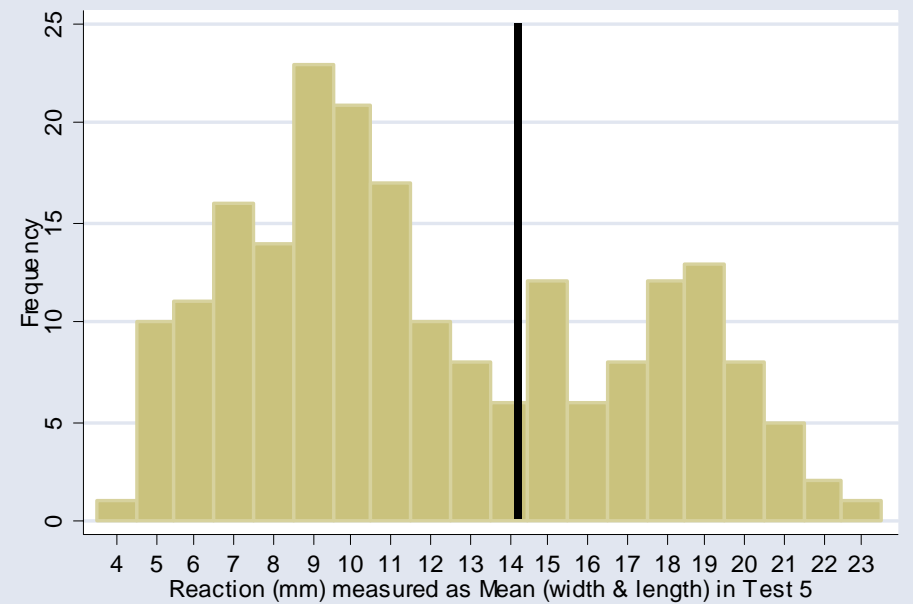


Skin Test Results

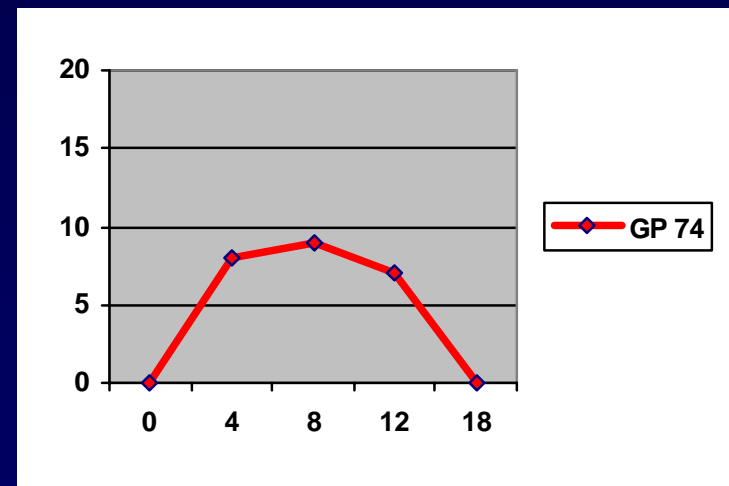
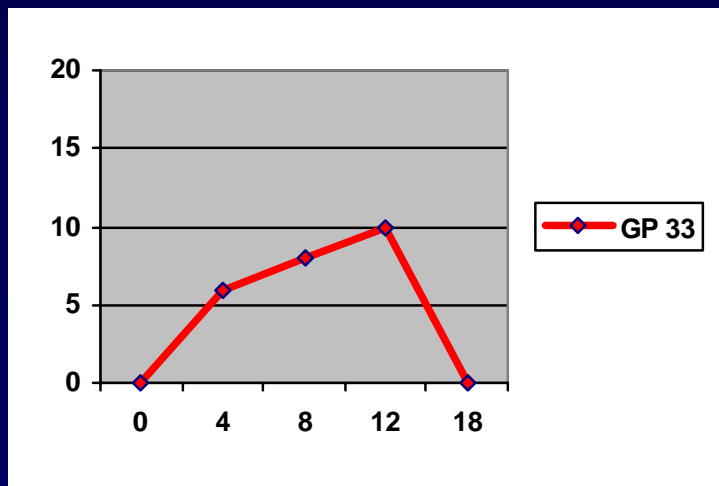
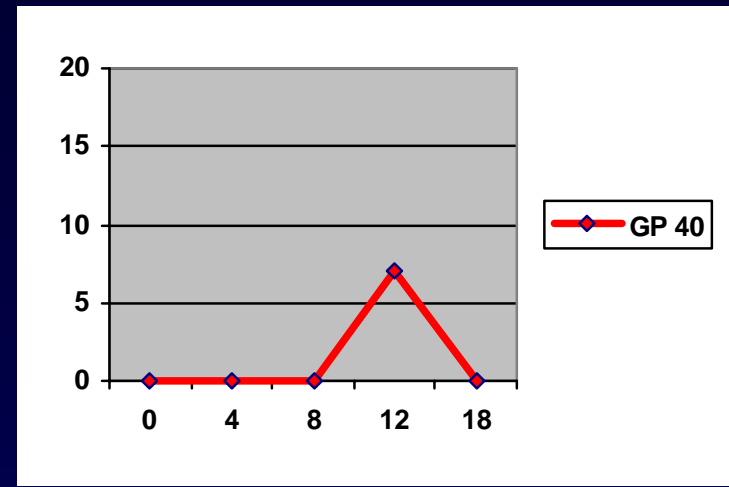
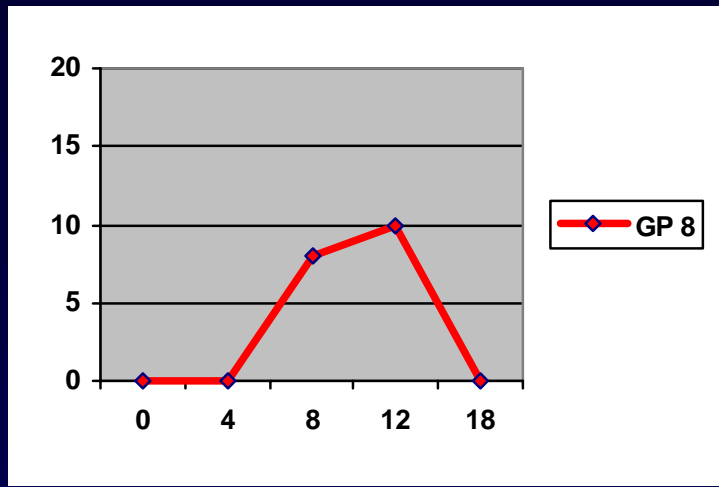
Distribution of Reaction Size in Test 2



Distribution of Reaction Size in Test 5



Did Infection Resolve?



TST reversion – aborted infections or self-cures?

- Riley also observed small, non-progressive GP reactions not consistently associated with disease on autopsy.
- Reversion of TSTs known to occur in humans after prompt treatment for LTBI and among the elderly without anergy
- With gamma interferon release assays, reversions being observed with repeated testing among contacts - with and without treatment.



Summary

- Transmission contributes importantly to MDR-*Mtb* infection rates
- Infection control is often neglected in resource-limited settings
- Novel interventions need to be developed and tested
- The AIR facility:
 1. Can quantify MDR-*Mtb* airborne infection
 2. Test infection control interventions
 3. Lead to a greater understanding of MDR-*Mtb* aerobiology and virulence

