When Does Treatment Render TB Patients Non-infectious?

FAST: A re-focused, intensified, administrative approach to institutional TB transmission control

Edward A. Nardell, MD
Professor of Medicine
Brigham & Women's Hospital
Harvard Medical School
enardell@gmail.com

World TB Day

- US issues
  - How long should patients with pulmonary TB remain in hospital?
    - Over isolation due to antiquated rules
    - A case: pediatrician with hemoptysis
- Global issue
  - Reducing MDR-TB transmission

Where is the TB Risk in Hospitals?

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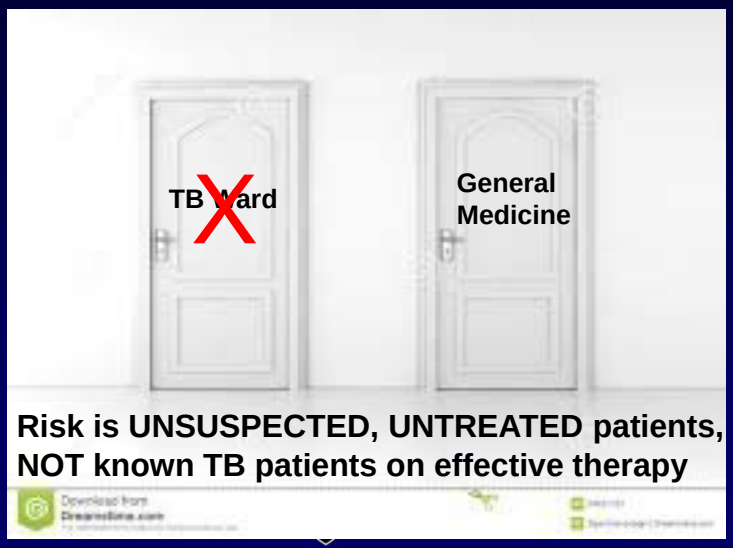


Risk is UNSUSPECTED, UNTREATED patients, NOT known TB patients on effective therapy

Importance of the Unsuspected TB Case

Arzobispo Loayza Hospital, Lima, Peru

Willingham, F. F., et al. Emerg Inf Dis 2001; 7:123-7

- 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

Transmission: Hospitals as MDR TB Factories

Tomsk, Siberia
Glemanova, et al., Bull WHO, 2007; 85:703-711.

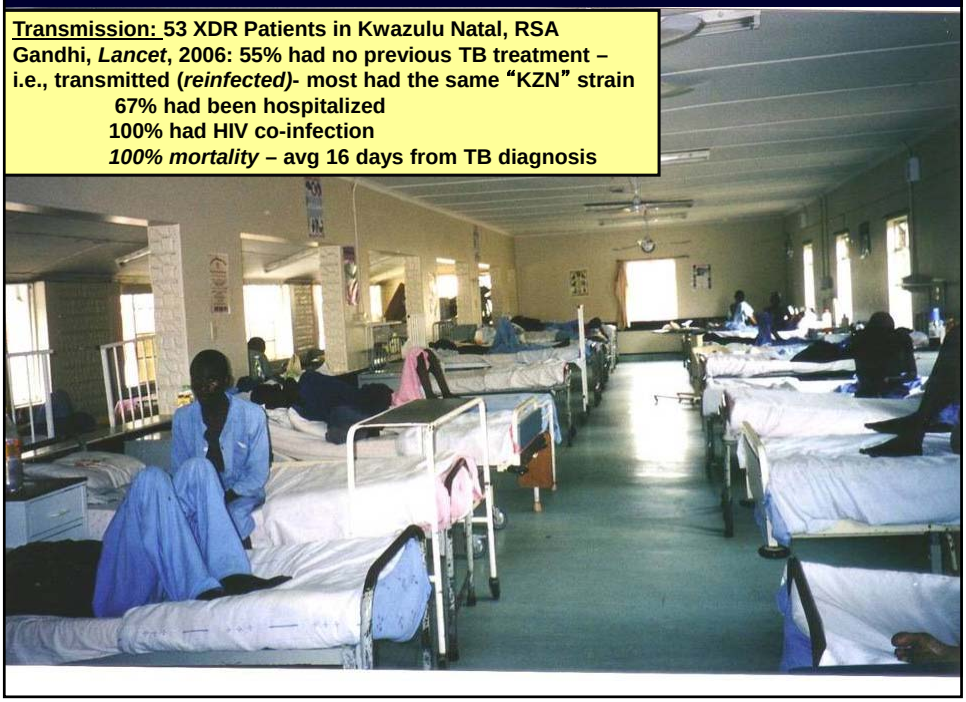
- Studied the role of non-adherence and default on the acquisition of multidrug resistance
- Substance abuse was NOT associated with MDR-TB
- MDR-TB occurred among *adherent* patients who had been *hospitalized*
  - Odds Ratio: 6.34 for hospitalized vs. patients treated as outpatients.

Patients admitted with drug susceptible TB
- *Re-infected* with MDR TB

Unsuspected Drug Resistance

- Patients admitted to the hospital with smear + TB – no isolation
- *Assumed* to have DS TB
- Treated with standard 4-drugs until treatment failure: 2-3 months
- Further 6 – 8 weeks for conventional DST
- Could be 5 months to detect drug resistance and start effective treatment – transmission!!!

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



How many days of effective treatment before TB patients are no longer infectious?

1. 2 days?
2. 2 weeks?
3. 2 months?

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 predict 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

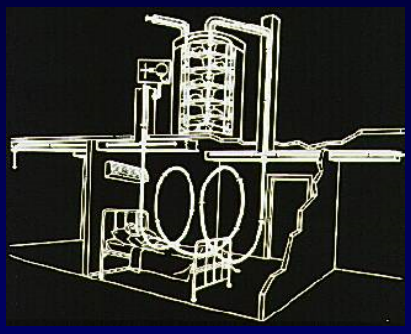
- Rouillon A, Perdrizet S, Parrot R. *Transmission of tubercle bacilli: The effects of chemotherapy*. Tubercle 1976; 57:279-299.
  - Sputum smear and culture positivity correlate with transmission before but **not** on therapy
  - **Evidence that smear and culture positive TB patients on *effective* 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 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" Am J Epidemiol 1995; 142:3-14)

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%**

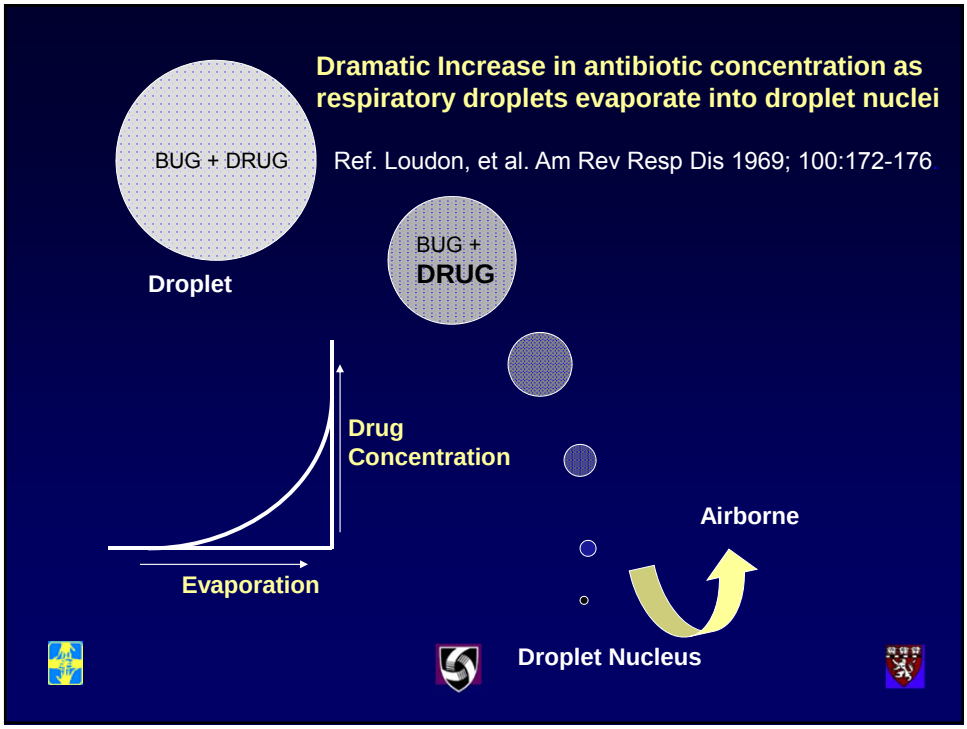
*all smear positive patients, relative to the amount of time on the ward

Riley's conclusions

ARRD 1962; 85:511-525

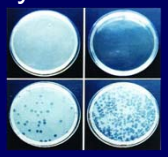
"The treated patients were admitted to the ward at the time treatment was initiated and were generally removed before the sputum became completely negative. Hence the decrease in infectiousness preceded the elimination of the organisms from the sputum, indicating that the effect was prompt as well as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



Why sputum smear/culture & infectiousness for GPs may differ

- Sputum culture
  - Promotes growth
  - No aerosol damage
  - No drug concentration
  - Does not include aerosol generation ability



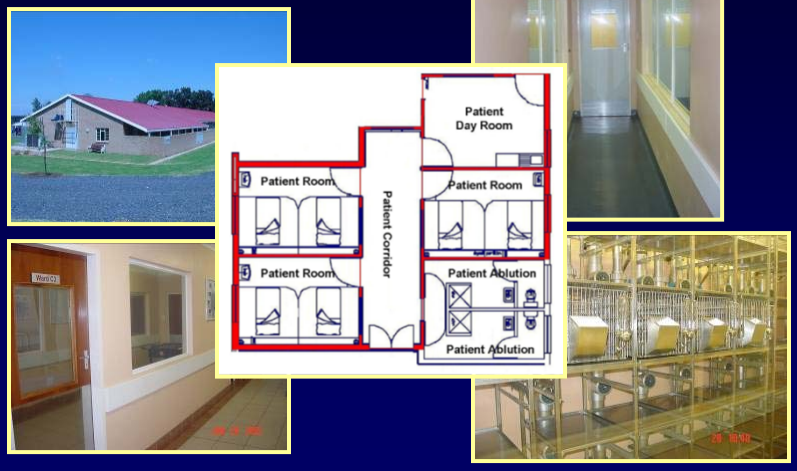
VS

- Guinea pig infection
  - Host defenses inhibit growth
  - Aerosol damage
  - Drug concentration
  - Includes aerosol generating ability

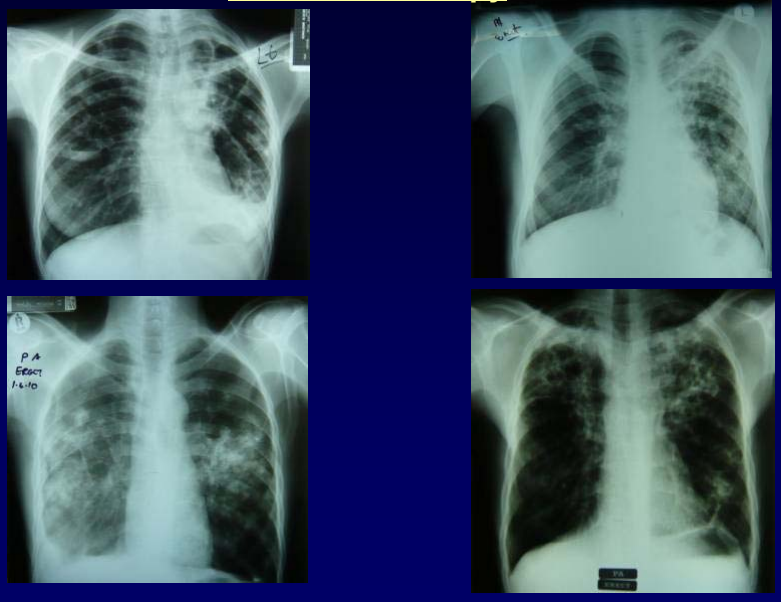
How effective is treatment in stopping MDR-TB transmission?

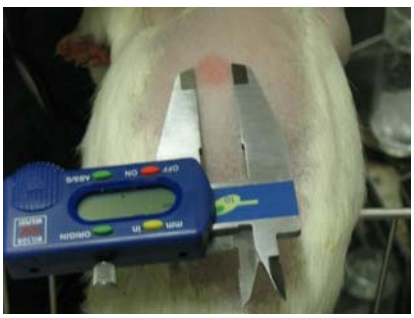
The AIR Facility

Witbank, Mpumalanga Provence, RSA



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





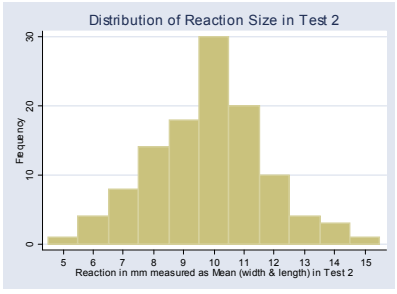
AIR Pilot Study:

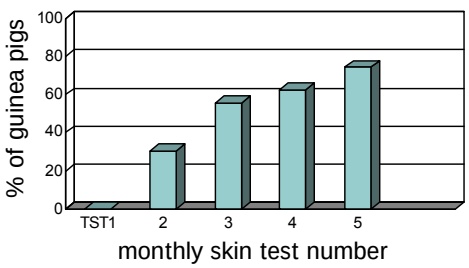
362 GPs exposed to

26 MDR-TB patients over 4 months

GP TST ≥ 6 mm

Ref: Dharmadhikari AS, Basaraba RJ, Van Der Walt ML, Weyer K, Mphahlele M, Venter K, Jensen PA, First MW, Parsons S, McMurray, DN, Orme IM, Nardell EA. **Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis. Tuberculosis**, 2011. **91**(4): p. 329-38.





Guinea Pig Transmission: South Africa

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

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

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

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Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis

A. S. Dharmadhikari,*† M. Mphahlele,‡ K. Venter,‡ A. Stoltz,§ R. Mathebula,‡ T. Masotla,‡ M. van der Walt,‡ M. Pagano,¶ P. Jensen,# E. Nardell*†

*Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, and †Division of Global Health Equity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ‡South African Medical Research Council, Pretoria, §University of Pretoria, Pretoria, South Africa; ¶Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, #Centers for Disease Control and Prevention, Atlanta, Georgia, USA

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PAUL E FARMER, MD PHD*†
MARIO C RAVIGLIONE, MD, FRCP (LONDON)‡
*Partners In Health
†Harvard Medical School
Boston, Massachusetts, USA
e-mail: paul_farmer@hms.harvard.edu
‡Director, Global Tuberculosis Programme
World Health Organization
Geneva, Switzerland
e-mail: raviglionem@who.int

EDITORIAL

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

Airborne Infections Research (AIR) Facility, Mpumalanga, South Africa

Impact of BDQ/LZD treatment
Human to Guinea Pig MDR/XDR-*M.tb* Transmission

5 hospitalized smear and culture positive MDR/XDR treatment failure patients being evaluated for BDQ/LZD treatment

Result: 24 of 90 guinea pigs infected
pre- treatment of patients

8 days exposure of 90 naïve guinea pigs pre-BDQ/LZD treatment of patients
Chamber A

72 hrs treatment

8 days exposure of 90 naïve guinea pigs patients on-BDQ/LZD treatment
Chamber B

Result: 25 of 90 guinea pigs infected
post-treatment

Interpretation: 11 days Bedaquiline/Linezolid had no impact on transmission

Summary: A refocused approach to institutional TB transmission control

1. Importance of unsuspected, untreated, or inadequately treated TB cases as sources of transmission
   NOT known patients on Rx – the focus of most TB IC
2. New appreciation of rapid impact of *effective* treatment on transmission
3. Focus on active case finding – cough surveillance
4. Development and rapid implementation of rapid molecular testing for TB and MDR – Xpert-TB

TB Triage – Rapid DR Diagnosis

Smear status may not be critical if on effective treatment

XDR by LPA

Individual Isolation

Effect of treatment unknown
Novel interventions

Gene Xpert: TB, DS or MDR

Community based – *on effective treatment – responding*

Complications

Hospitalized patients *on effective treatment - responding*

Re-focused Transmission Control Strategy: *"F-A-S-T"*

- **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** *temporarily to reduce exposure*
  - Building design and engineering
  - Cough hygiene and triage
- **Treat** *effectively, based on rapid DST*
  - Focus on rapid molecular DST – Xpert TB

USAID FROM THE AMERICAN PEOPLE

Not new, *but <u>focused</u>, <u>intensified</u> and more precisely <u>defined</u>*:

F-A-S-T Strategy

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

- **Implementation & Assessment**
  1. **<u>Process indicators</u>**

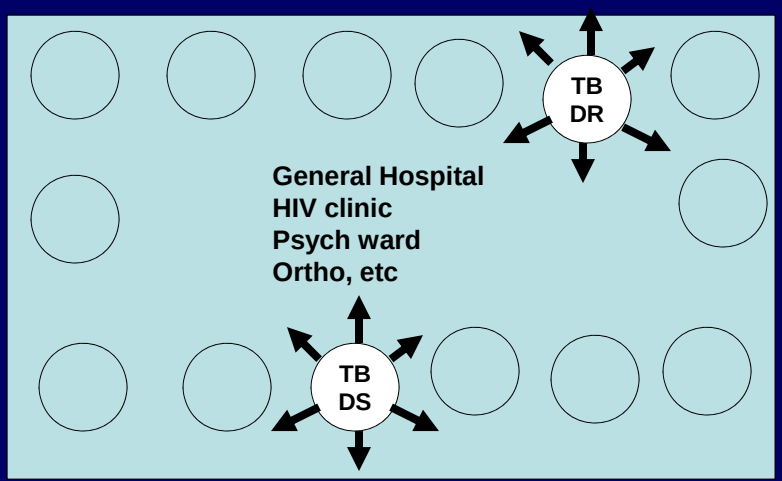
General medicine:
- Time from cough detection to sputum collection
- Time from sputum collection to lab
- Time from lab to result
- Time from result to notification
- Time from notification to treatment

TB Hospital
- TB: time from admission to DST result
- Time to effective treatment

2. **<u>Outcome indicators</u>**
- HCW infection or disease

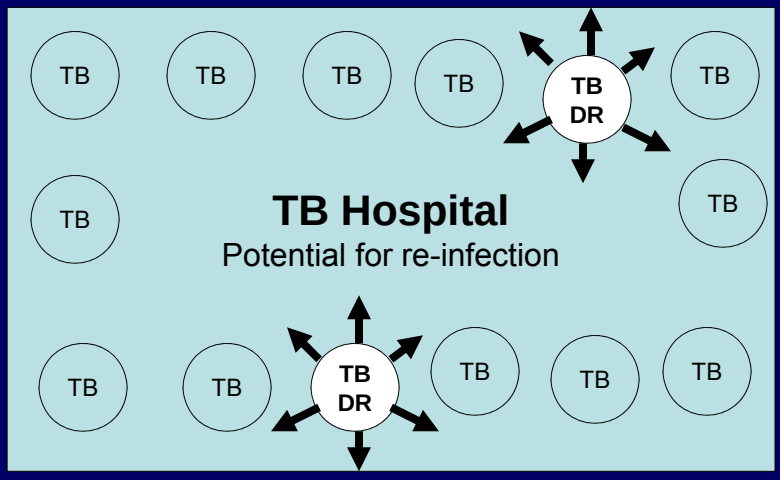
Unsuspected, untreated TB

Active case finding, Lima Hospital
13 of 40 TB cases (33%) detected/yr – UNSUSPECTED!
(Emerg Inf Dis 2001; 7:123-7)



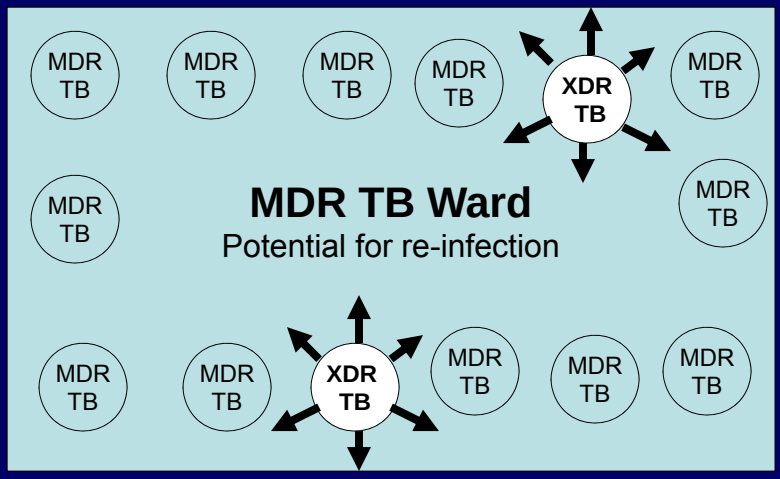
Unsuspected, untreated MDR/XDR TB

All other patients on effective treatment



Unsuspected, untreated XDR TB

All other patients on effective treatment



What FAST is NOT:

- NOT an educational campaign like hand washing
- NOT business as usual added on to the work of existing staff
- NOT implementable using volunteers
- NOT sustainable without added resources
  - Requires administrative buy-in
- NOT the same in all settings
  - General hospital vs chest hospital vs TB hospital

Early *FAST* Implementation Sites

- Zambia (TB Care 1)
- Nigeria (TB Care 1)
- Bangladesh (TB Care 2)
- Viet Nam (TB Care 2)
- Peru (Fogarty)*
- Russia (Lilly Foundation)
- Haiti (PIH)

Educational materials available through PIH

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PERSPECTIVE

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

E. Barrera,* V. Livchits,† E. Nardell‡

*Partners in Health, Boston, Massachusetts, USA; †Partners in Health, Russia; ‡Division of Global Health Equity, Brigham & Women's Hospital, Boston, Massachusetts, USA

Early FAST Results

National Institute of Diseases of the Chest, Dhaka, Bangladesh

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doi: 10.5588/ijtld.16.0794

Preliminary Results on the FAST Strategy at NIDCH*

Disease Category	Total Samples Tested	Number of Unsuspected TB Cases Identified (%)	Number of Unsuspected MDR-TB Cases Identified (%)
Current TB disease	42		3 (7.12)
Other respiratory disease with previous TB history	169	40 (23.66)	3 (1.77)
Other respiratory disease	850	80 (9.41)	6 (0.70)
Total	1062	120 (11.29)	12 (1.12)

*Data reflect 11 weeks of implementation, starting February 2014.

Impact of Prompt/Effective Treatment on MDR-TB Transmission – Russia (i.e., acquisition of MDR-TB)

- Tomsk, Siberia: Odds **6.32** for acquiring MDR TB treated in hospital vs. ambulatory – transmission!
  - Glemanova, et al., Bull WHO, 2007; 85:703-711.
- FAST implemented (Xpert – separation – effective treatment) compared to historical control rates (pre-FAST) – *accepted JID, Miller, et al*
  - Voronezh - 800 bed TB Hospital (Pre-FAST – 1/09 – 12/09)
  - Petrozavodsk - 120 bed TB Hospital (Pre-FAST – 1/10 - 12/11)
    - Weeks spent in hospital the same (20.7 vs 20.0)
  - Result: 709 pts HR sens on admission
    - Pre-FAST – 450 (63.5%) - **12.2%** acquired MDR within 12 mos of finishing treatment
      - Avg 76.5 days before separation and effective treatment started.
    - Post-FAST – 259 (36.5%) - **3.1%** acquired MDR within 12 mos of finishing.
    - FAST associated with a **78% odds reduction** in MDR acquisition
      - remained after adjustment for TB severity, time in hospital, BMI, marital status, or alcohol use.

Summary

1. Transmission is driving the TB epidemic – esp MDR TB
2. TB risk in hospitals is from unsuspected cases of TB and TB patients with unsuspected drug resistance
3. Effective TB treatment stops DS and MDR TB transmission quickly – much sooner than 2 weeks – days, maybe less…
4. Finding and treating unsuspected TB and unsuspecting drug resistance is number one priority of TB transmission control, that is, **FAST**
5. Not every case of TB or drug resistance can be quickly identified – need for air disinfection.
6. GUV is the safest and most effective method for air disinfection in some climates, but sustainable effective GUV requires attention to new application guidelines and maintenance.