

Prevention & Infection Control of Drug-Resistant TB

“Reaching the Unreached”

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Kevin P. Fennelly, MD, MPH

Interim Director

Division of Pulmonary & Critical Care Medicine
Center for Emerging & Re-emerging Pathogens

UMDNJ-New Jersey Medical School

fennelkp@umdnj.edu

Objectives

1. To briefly review best methods to prevent drug-resistant TB.
2. To evaluate the level of evidence supporting current TB infection control measures.
3. To discuss limitations and deficiencies in our current approach to TB infection control.
 - Need to screen & treat HCWs for HIV.
4. To propose new methods and concepts that have potential to improve TB infection control and control of TB.
 - Need for a diagnostic test of infectiousness.

Disclosures

- Collaborations using outcome of cough aerosols of *M. tuberculosis* to assess effects of
 - inhaled kanamycin
 - Edward Nardell (Harvard-Partners in Health)
 - Inhaled PUR 003
 - Pulmatrix, Inc. (Lexington, MA)
- My research focuses on assessing infectiousness
- Impatience

Preventing Drug Resistant TB

- Do it right the first time: DOTS.
 - But need to detect poor response sooner to detect primary MDR
 - Make treatment simpler for both patients & systems
 - Address poverty and HIV.
- If not, do it right the second time: DOTS-Plus.
 - NEVER add a single drug to a failing regimen!
 - Need DSTs: culture vs. molecular?
 - Hospital- or community- based?
 - Need more lab and clinical expertise.
- XDR-TB or failing MDR-TB: Regional center of excellence.
 - All of above plus surgical expertise.

Amplification of Drug Resistance with WHO Re-treatment Regimen

- 410 re-treatment cases in Kampala, Uganda
- MDR-TB: 12.7%
- INH mono-resistance: 24.7%
- Resistant to one or more drug: 28.1%
- Among 250 followed over treatment, 5% developed additional resistance.
- Amplification assoc'd with DR at baseline ($p < 0.01$) and delayed culture conversion ($p < 0.01$)

Is TB an Occupational Disease of HCWs?

	Low- & middle-income countries	High-income countries
LTBI (prevalence)	63% (33-79%)	24% (4-46%)
TB disease (annual incidence)	5.8% (0-11%)	1.1% (0.2-12%)
TB mortality (inpt) (PMR) (outpt)	??	1.18 (1.04-1.35) 3.04 (1.62-5.19)

- Menzies D et al. IJTLD 2007; 11:593

'Fitness' of DR *M. tuberculosis*

- SF: Production of secondary cases
 - MDR-TB: none.
 - INH-resistant cases < DS.
 - RIF-resistant cases > DS
 - » Burgos M et al. JID 2003; 188:1878
- Fitness 'costs' of drug resistance are highly heterogeneous.
 - » Basu and Galvani. Epidemiol Infect 2008; 136:1585
- Compensatory mutations conferring increased fitness have been identified.
 - » Sherman D et al. Science 1996; 272: 1641

Evidence-based TB Infection Control

Type of Studies

Grade of Evidence

RCTs

4+

Before/after

3+

Retrospective observ.

2+

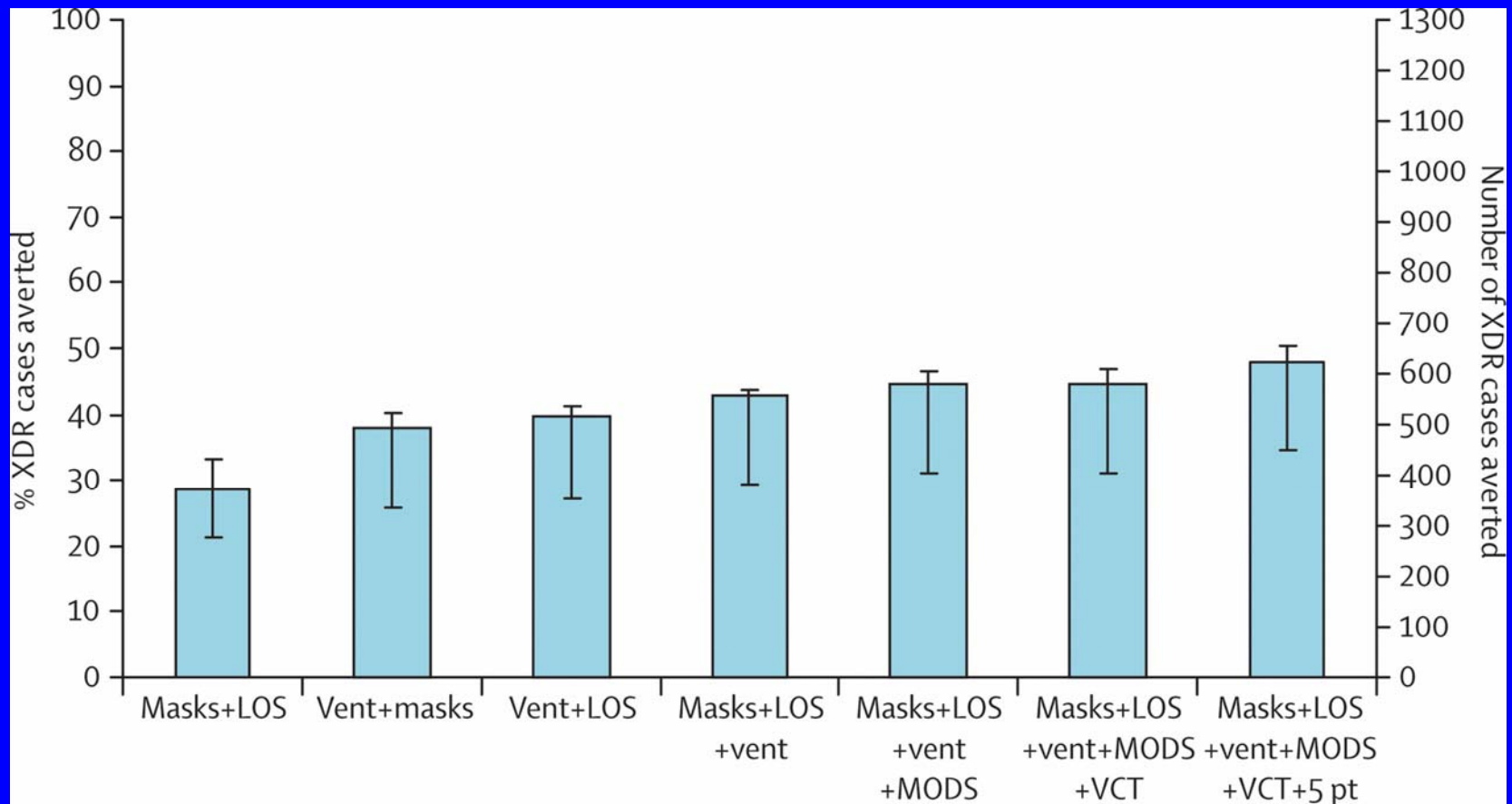
Modeling

1+

Efficacy of 'Package' of Combined Administrative, Engineering and PRP TB-IC 3-4+

- Multiple before and after studies of hospitals associated with outbreaks showed decreased TSTs among HCWs and decreased transmission to patients
 - Generally not possible to discriminate which individual control measures accounted for benefit

Combining Control Measures Predicted to Prevent XDR-TB Cases



- Basu S et al. Lancet 2007; 370: 1500

Efficacy of Administrative Controls

TB-IC 3+

- 6-month TST conversion rates decreased from 3.3% (to 0.4% ($P < 0.001$) after introduction of all 3 measures, but limited engineering and PRP
 - Blumberg HM et al. *Ann Intern Med* 1995;122:658
- Before simple TB-IC, 26 of 90 (28.9%) developed MDR-TB, and after 0 of 44 in spite of continued infectious cases
 - Moro ML et al. *Int J Tuberc Lung Dis.* 2000;4:61

Efficacy of Ventilation

TB-IC 2-3+

- Annual risk of TST conversion in lab or pathology workers associated with lower hourly air exchange rates (16.7 versus 32.5 with no conversion, $p < 0.001$).
 - Menzies D. Am J Respir Crit Care Med 2003 167:599
- TST conversions associated with ventilation of general or non-isolation patient rooms of less than 2 air exchanges per hour (adjusted hazard ratio, 3.4 [95% CI, 2.1 to 5.8])
 - But NOT with ventilation of isolation rooms!
 - Menzies D et al. Ann Intern Med. 2000;133:779.

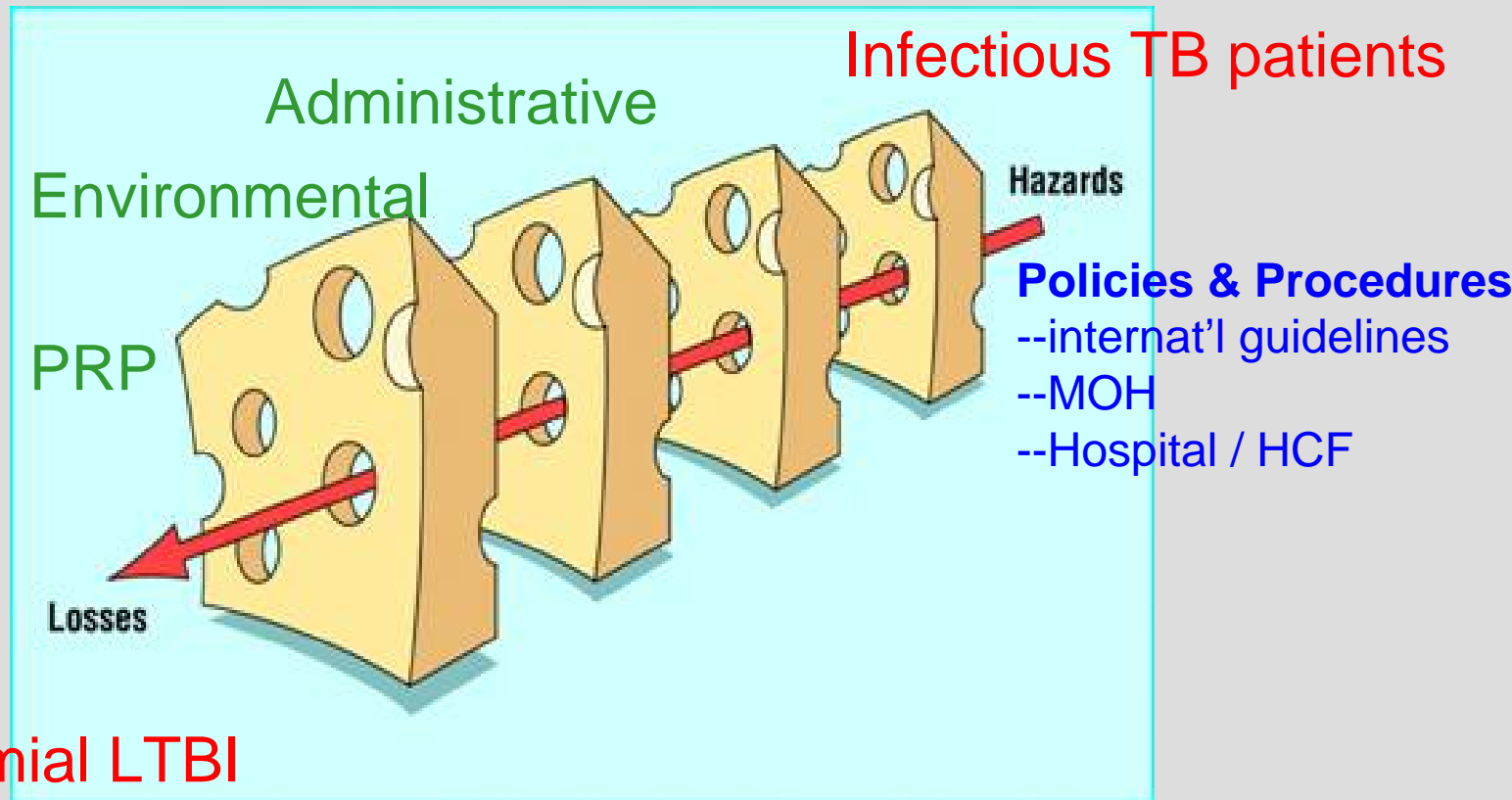
Efficacy of Personal Respiratory Protection (PRP) TB-IC 1+

- Based only on theoretical grounds and mathematical modeling studies, not on any outcome studies
 - Fennelly KP and Nardell EA. Infect Control Hosp Epidemiol 1998;19:754
 - Nicas M. Am J Ind Med. 1995;27:317
 - Gammaitoni L, Nucci MC. Emerg Infect Dis.1997;3:335

Summary of Evidence for TB Infection Control

Control Measure	Grade of Evidence
Package of all 3	3-4+
Administrative	3+
Ventilation	2-3+
PRP, UVGI	1+

Reason's Swiss Cheese Model of System Failure



Nosocomial LTBI

Nosocomial Disease

Nosocomial Death

HCW Deaths due to Nosocomial Transmission of DR-TB

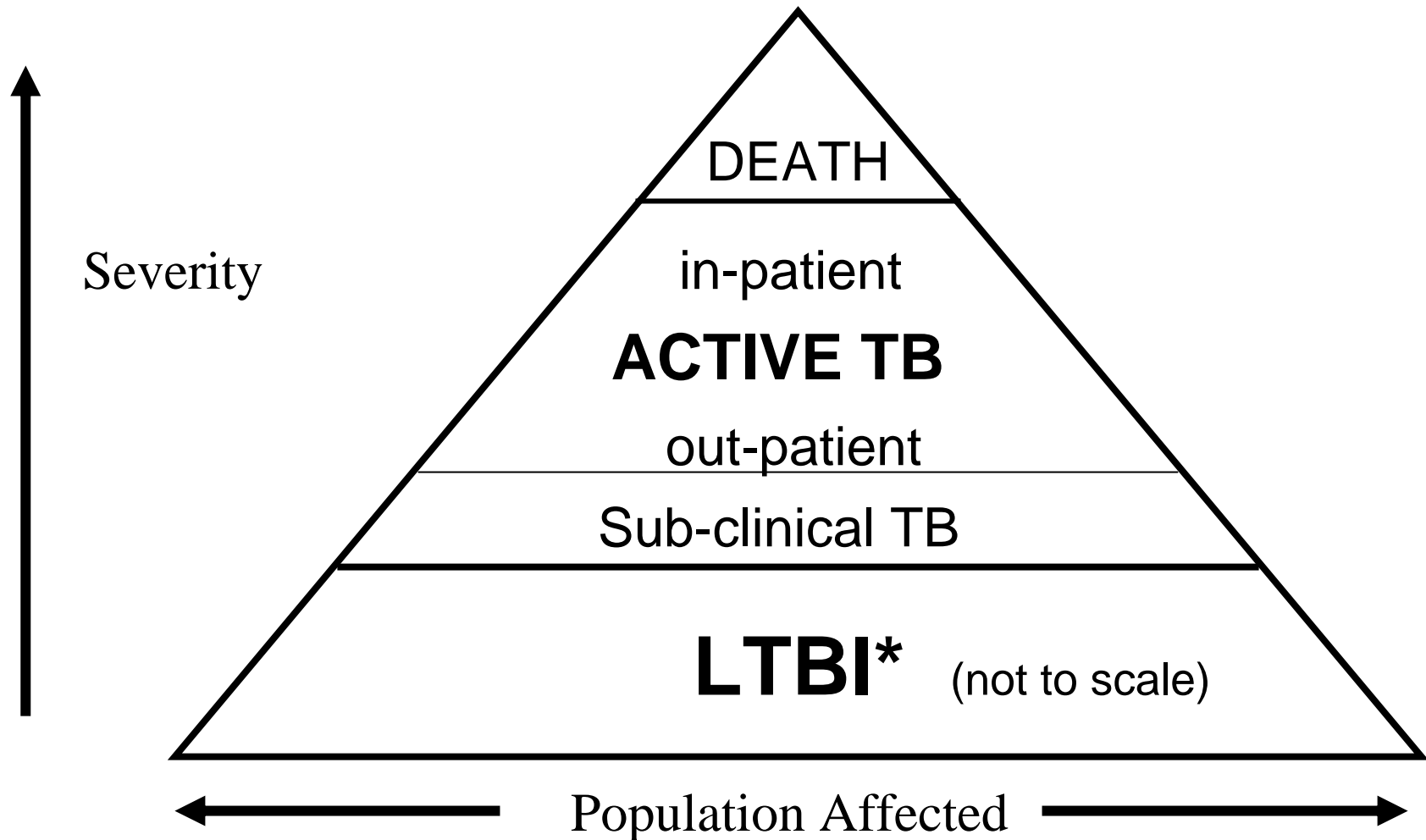
- MDR outbreaks U.S. 1980s-1990s
 - 90% of patients infected were HIV+
 - 9 HCWs
 - All immunocompromised, 8 with HIV
 - [Sepkowitz KA, EID 2005](#)
- XDR-TB outbreak, So Africa, 2006
 - 52/53 died of unrecognized XDR-TB
 - 44/44 tested were HIV+
 - Median survival from sputa collection=16 days
 - 2 HCWs died; 4 others sought care elsewhere
 - [Gandhi N, Lancet 2006](#)
 - Occurred AFTER publication of guidelines and consultations

Occupational TB in Sub-Saharan Africa

- Malawi
 - 25% mortality
 - Harries AD, Tran R Soc Trop Med Hyg 1999; 93: 32
- Ethiopia
- South Africa
- Nigeria
 - 32 of 2,173 HCWs
 - **15 (47%) as HIV-TB**
 - Salami AK, Nigerian J Clin Prac 2008; 11: 32

Spectrum of Biological Response to Mtb Infection

(adapted from ATS Guidelines as to What Constitutes an Adverse Respiratory Health Effect, ARRD, 1985; 131:666)



'Holes' in Administrative Controls

- TB mortality not prioritized & no surveillance
- HIV = major risk factor for TB disease & death
 - HAART now feasible in much of world
 - HIV screening advocated for inpatients in US
 - Guidelines recommend testing HCWs for HIV but observation suggests not being done
- Suspicion of TB relies on individual clinicians with varying degrees of expertise

HIV Testing & Treatment of HCWs Exposed to TB

- ‘HIV infection is the greatest risk factor for progression from LTBI to TB disease’
- ‘Therefore, voluntary HIV counseling, testing, and referral should be routinely offered to all persons at risk for LTBI.’
 - **CDC** Guidelines 2005; **54(RR17);1-141**
- ‘...HIV counseling and testing for staff with adequate access to treatment.’
 - Addendum to **WHO** Guidelines, 2006

'KISS' = Keep It Simple, System

- Whenever HCWs have TST or IGRA for workplace surveillance for TB, they should be offered HIV testing, counselling & referral.
 - Routine, opt-out.
- HCWs are a scarce resource.
 - Especially in areas with high rates of HIV
- May help destigmatize both TB and HIV by modeling positive behavior.

Variability of Infectiousness in TB: Epidemiology

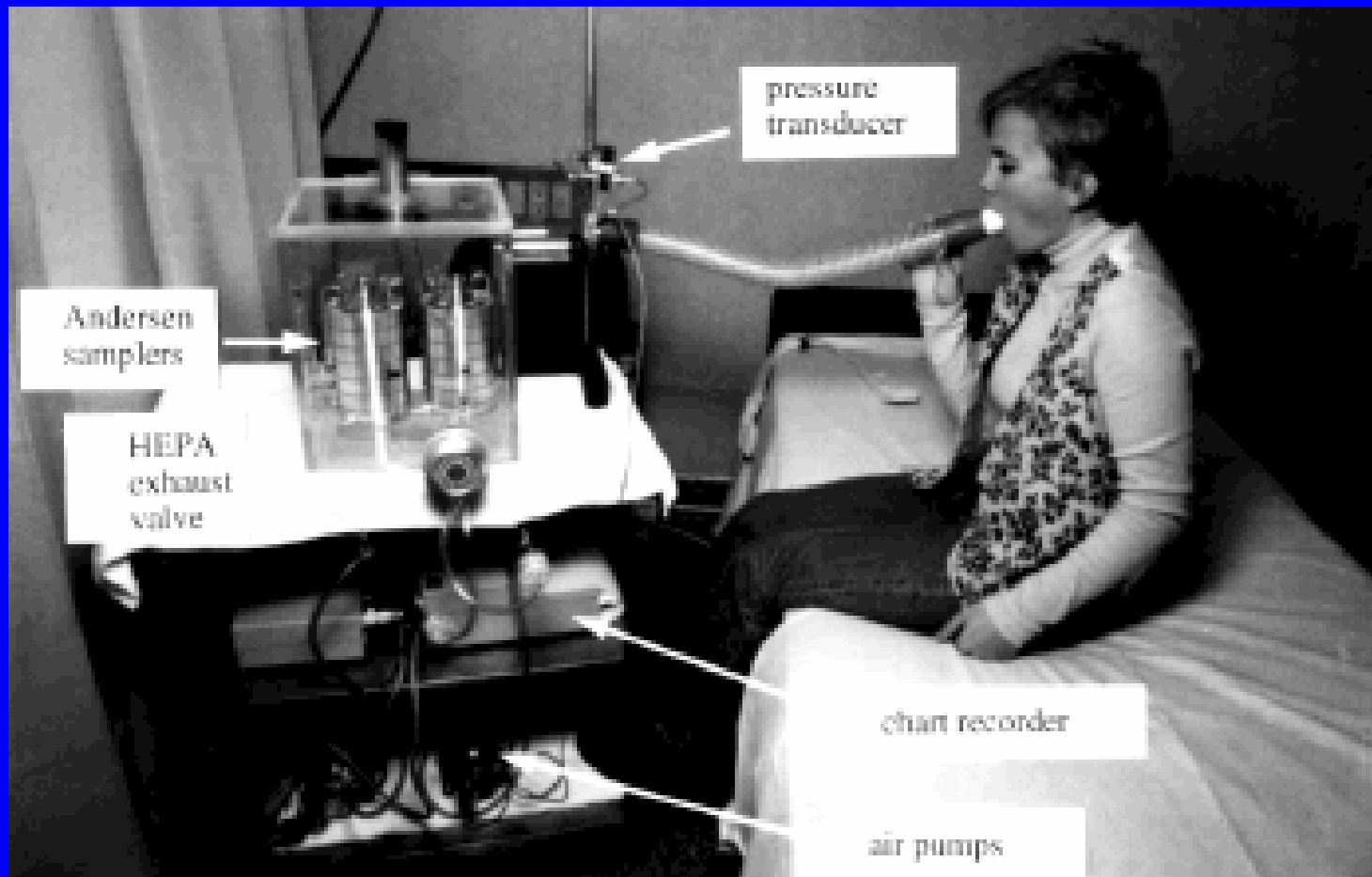
- Rotterdam, 1967–69: Only 28% of smear positive patients transmitted infections.
 - Van Geuns et al. Bull Int Union Tuberc 1975; 50:107
- Case control study 796 U.S. TB cases
 - Index cases tended to infect **most (or all) or few (or none)** of their contacts
 - Snider DE et al. Am Rev Respir Dis 1985; 132:125
- Ability to publish outbreaks suggests that they are episodic.

Variability of Infectiousness in TB: Experimental

- 3 (4%) of 77 patients produced > 73% of the infections in the guinea pigs.
 - Sultan L. *Am Rev Respir Dis* 1967; 95:435.
- All infections attributed to 8 of 61 (13%) patients. 50% of infections due to one patient with TB laryngitis.
 - Riley RL et al. *Am Rev Respir Dis* 1962; 85:511.
- Recent replication of this model in Peru
 - 118 hospital admissions of 97 HIV–TB coinfecting patients
 - 8.5% caused 98% of secondary GP infections
 - 90% due to inadequately treated MDR–TB
 - Escombe AR et al. *PLoS Medicine* 2008; 5:e188

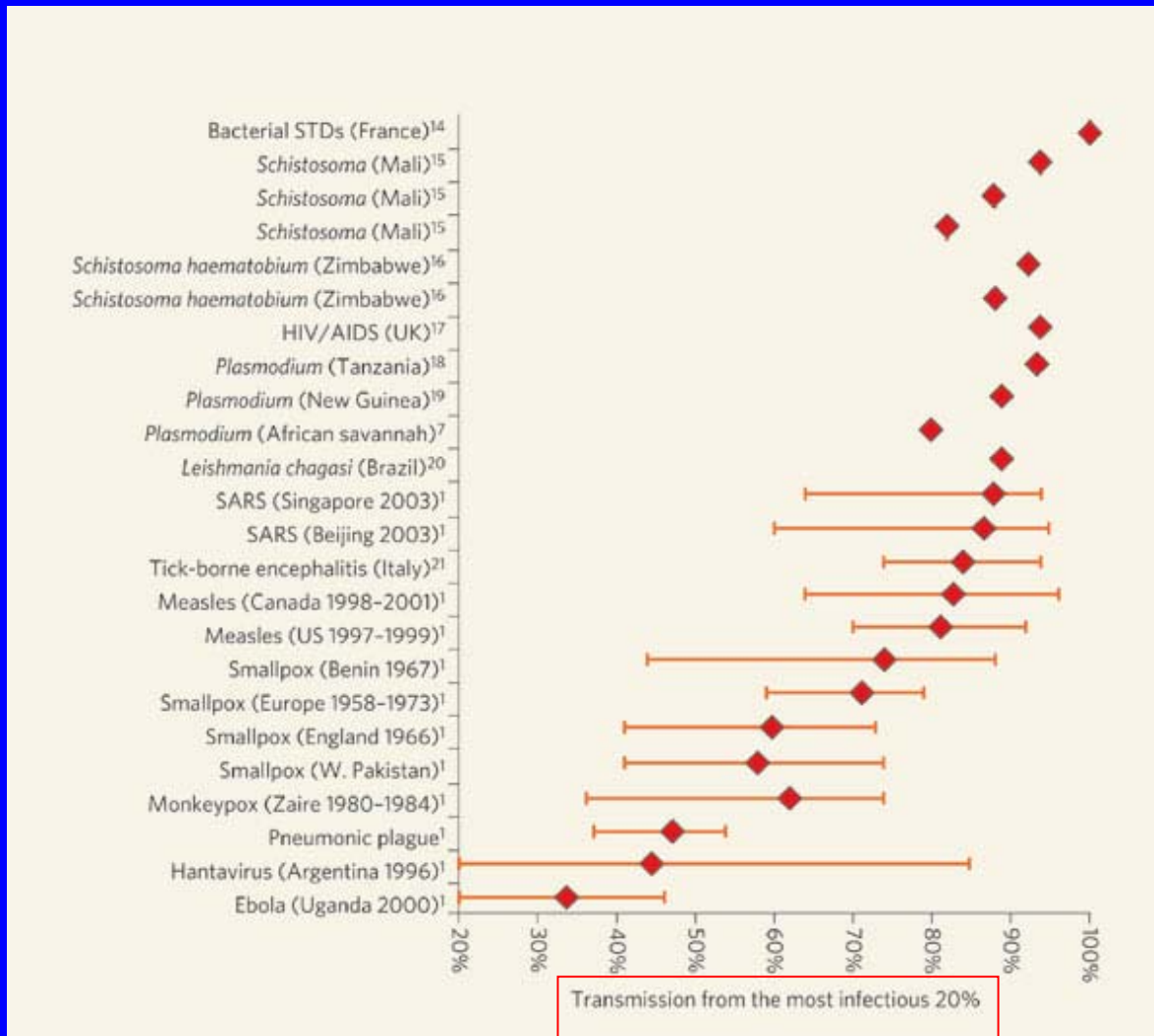
Cough Aerosol Sampling System

4 of 16 (25%) of sm+ subjects



- Fennelly KP et al. Am J Resp Crit Care Med 2004; 169; 604-9

Heterogeneity of Infectiousness in Various Diseases: the '20/80 rule'

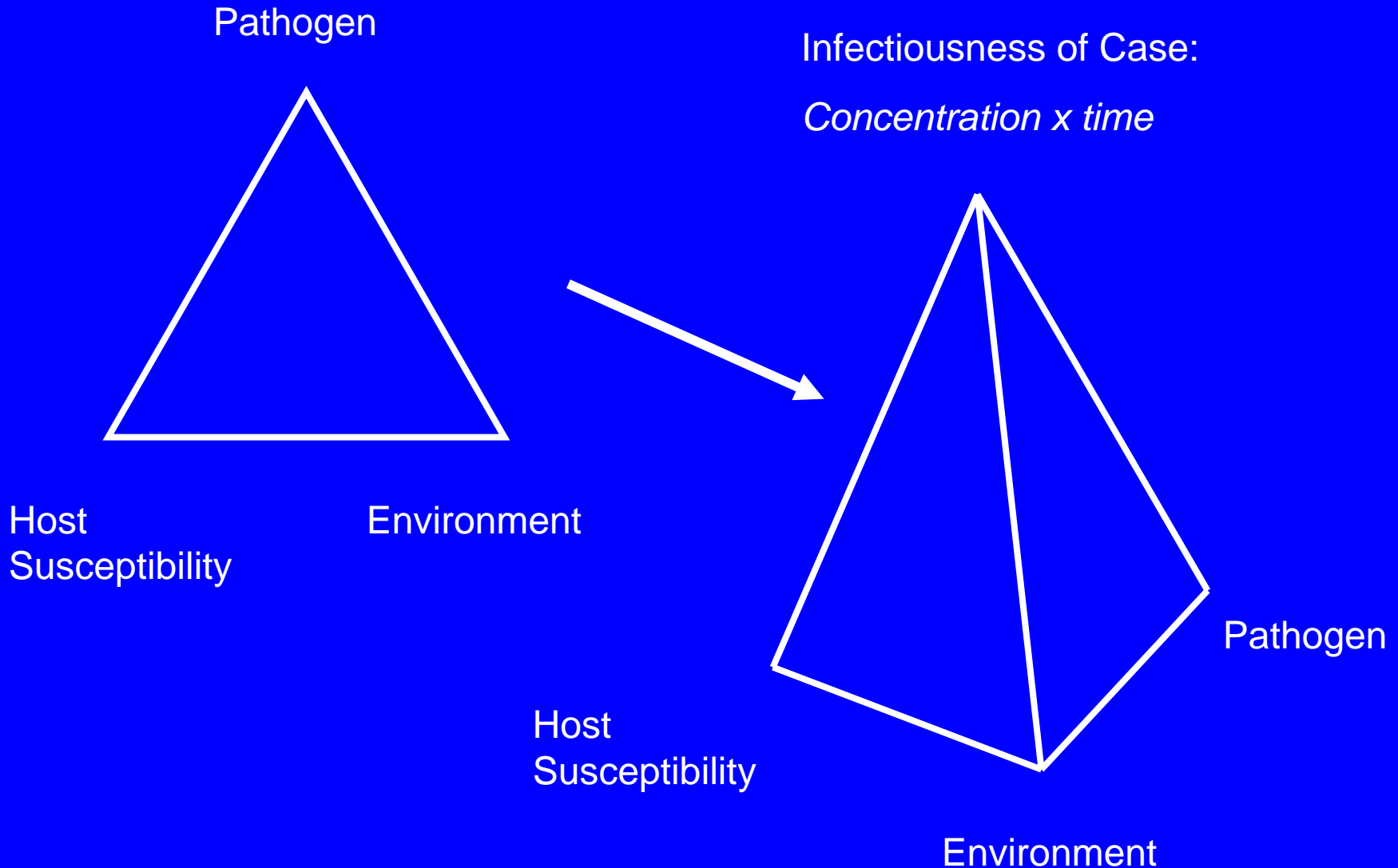


-- Galvani AP and May RM. Nature 2005;438:293

Heterogeneity in Transmission: Implications for Control

- In cattle, about 20% are supershedders who transmit 80% of *E. coli* O157
- Preventing infection in the 5% of most infectious would control spread
 - Matthews L et al. PNAS 2006; 103; 547
- If the cost of identifying and treating the core 20% (supershedders) < cost of treating entire population, then targeting efforts are preferred
 - Woolhouse MEJ et al. PNAS 1997; 94; 338

Re-assessing Our Conceptual Model of Infection



Implications of Heterogeneity of Infectiousness for TB Control

- Prioritize infection control resources.
- Target case-finding and treatment of LTBI around most infectious cases.
- Must be careful to avoid creating a new stigma.

Transmission in Smear-negative TB

- Sm-neg, cx-pos TB accounted for
 - 17% of transmission in SF
 - Behr M et al, Lancet 1999; 353:444
 - 17-22% of transmission in Vancouver, B.C.
 - Hernandez-Garduno E et al, Thorax 2004; 59:286

Estimating the Sensitivity & Specificity of AFB Smear for Infectiousness, not Disease

Conservative assumptions:

- 40% of AFB sm + transmit
- 17% of transmission from AFB sm –
- 65% of TB patients are AFB sm +
- 35% of TB patients are AFB sm –

Sensitivity & Specificity of AFB Smear for Infectiousness

		Infectious		
		+	-	
AFB smear	+	260	390	650
	-	53	297	350
		313	687	1000
		All infectious	All non-infectious	

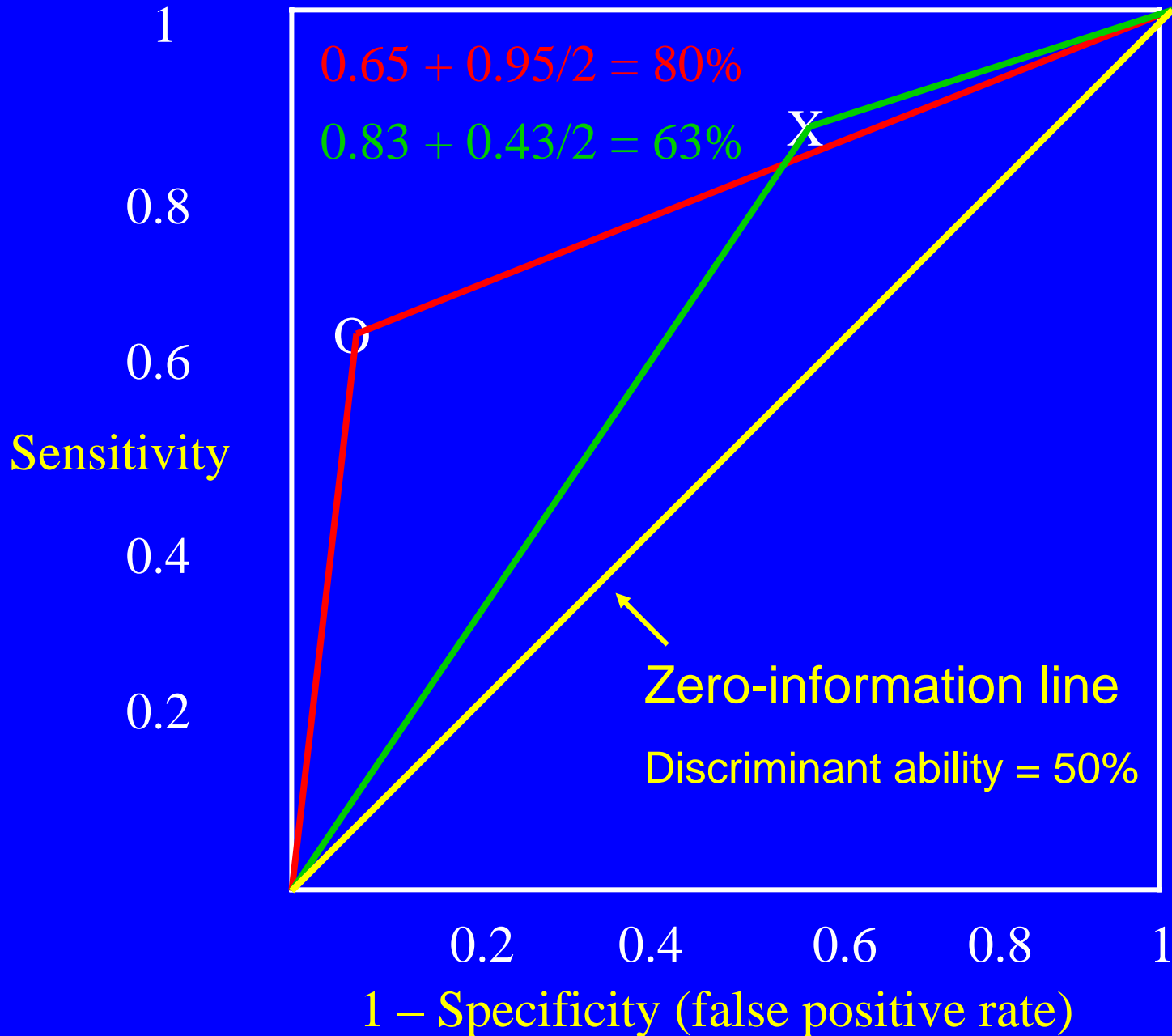
$260/650 = 40\%$

$53/313 = 17\%$

$Sens = 260/313 = 83\%$

$Spec = 297/687 = 43\%$

Discriminant Ability of AFB Smear Worse for Infectiousness



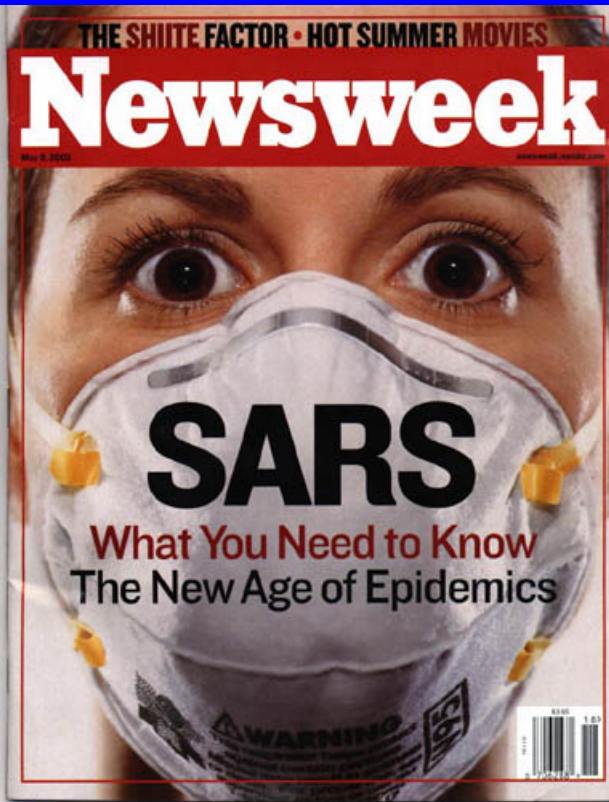
Future Candidates as Diagnostic Tests of Infectiousness

- Cough aerosol collections (point-of-service) ?
- Exhaled gas analysis with 'electronic nose' ?
- Combined clinical scores of cough and viable AFB vs. MODS
- Others?

Other Research Opportunities

- Agents to decrease infectiousness
 - Inhaled kanamycin or capreomycin
 - Inhaled ionic solutions
 - Simple anti-tussive treatment, e.g., codeine
- Effectiveness of UVGI in field?
- Natural vs. mechanical vs. both/back-up ventilation?
- Operational research
 - Is there less transmission of DR-TB with community-based versus hospital-based treatment?
 - Effect of routine HIV testing & treatment of HCWs?
 - Impact of test of infectiousness?

Universal Airborne Precautions from Advances in Studies of TB ?



Summary: TB-IC

- Most important: SEPARATE & VENTILATE
- KISS: 'Opt-out' HIV testing & treatment of all HCWs exposed to TB should at least be evaluated if not implemented
- Diagnostic test for infectiousness would allow for more effective targeting of resources
- Need to develop most cost-effective measures
- Guidelines are not enough.

Prevention of TB

- “ An ounce of prevention

is a ton of work.”

- Paul S. Frame, MD

(U.S. Preventive Services Task Force)