XDR and MDR TB
Urgent Research Priorities

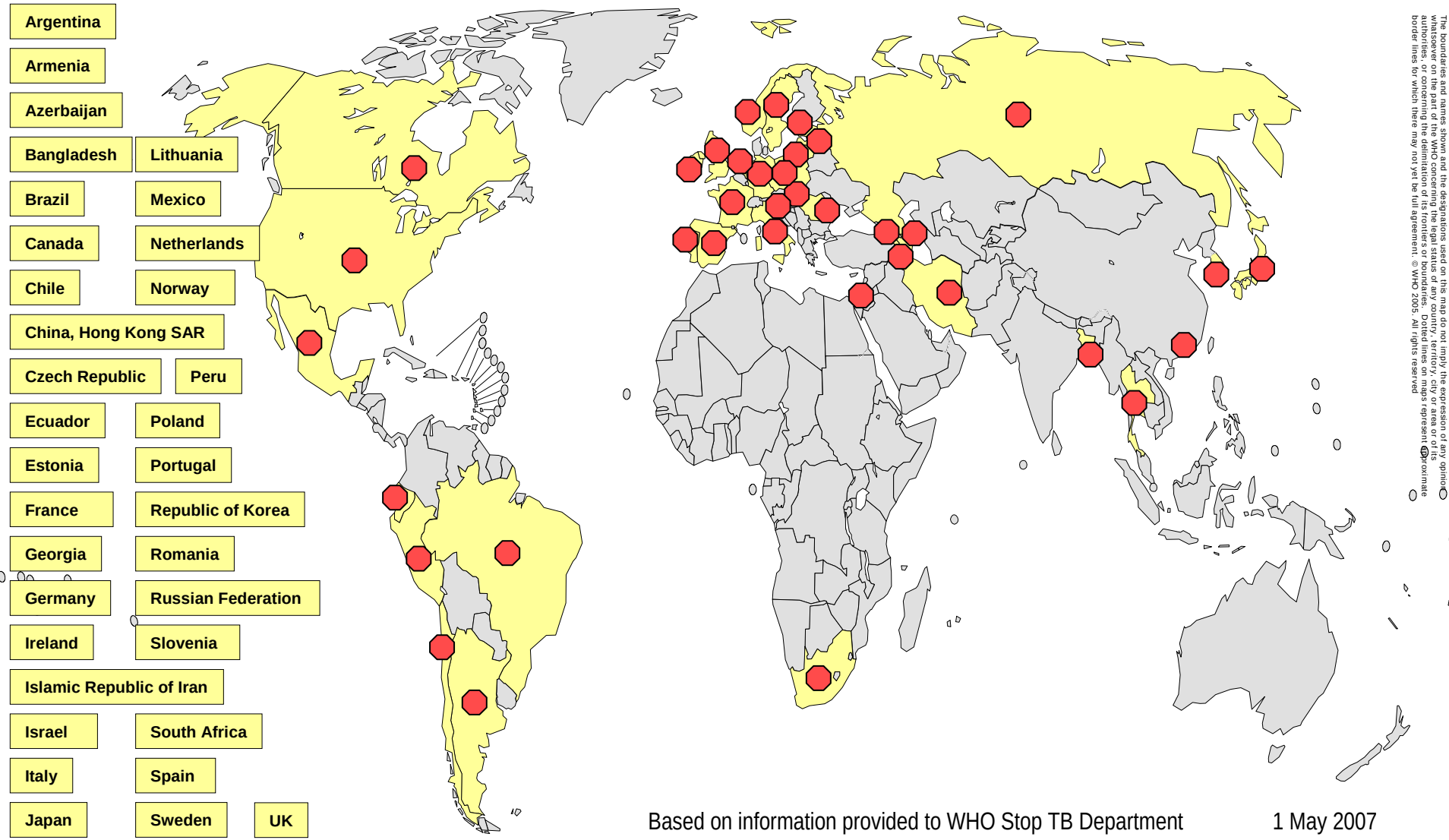
Gerald Friedland MD
Yale School of Medicine
Nelson R Mandela School of Medicine
TF CARES

The Year of MDR XDR TB

- **CDC, WHO report on global XDR TB**
  - XDR TB defined
  - Global distribution
  - Africa, India and Southeast Asia missing
  - HIV not recorded
- **Rural South Africa-Tugela Ferry epidemic**
  - Higher rates both of MDR and XDR TB
  - HIV associated
  - Nosocomial transmission
  - Extremely high mortality
- **Global burden estimates**
  - >400,000 MDR, >26,000 XDR TB
- **Expert meetings and recommendations**
  - WHO, CDC, NIH, Forum, national and international meetings
- **The ASPE-single patient airborne event**

Countries with XDR-TB Confirmed cases (May 2007)

WHO



Based on information provided to WHO Stop TB Department

1 May 2007

M/XDR TB is a wake up alarm call

- **MDR and XDR TB uncovers past and current deficiencies in TB knowledge, strategies and programs**
- **Illustrates global nature TB drug resistance**
- **For high TB and HIV prevalence areas, threatens success of both StopTB and historic ARV roll out**
- **For high TB and low HIV prevalence areas with high HIV incidence, alerts ominous danger**

MDR XDR TB Research Priorities

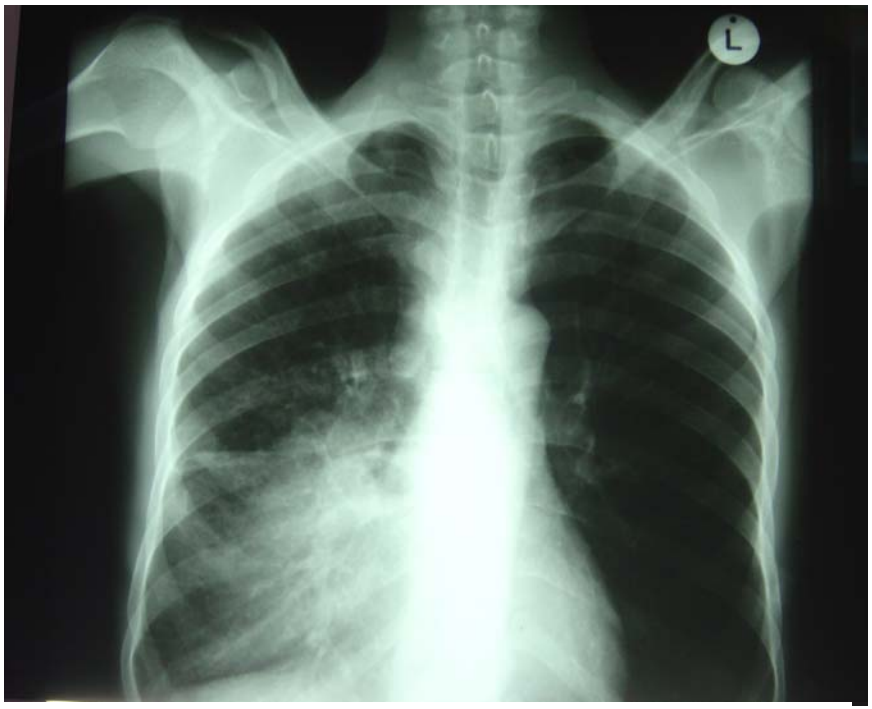
- Broad and complex areas of need
  - Epidemiology
  - Diagnosis
  - Treatment
- Urgency requires both short term and longer term goals, approaches, and solutions
- Operational research necessary
- New Resources critical

Two Case Studies MDR/XDR TB

both illustrate same challenges

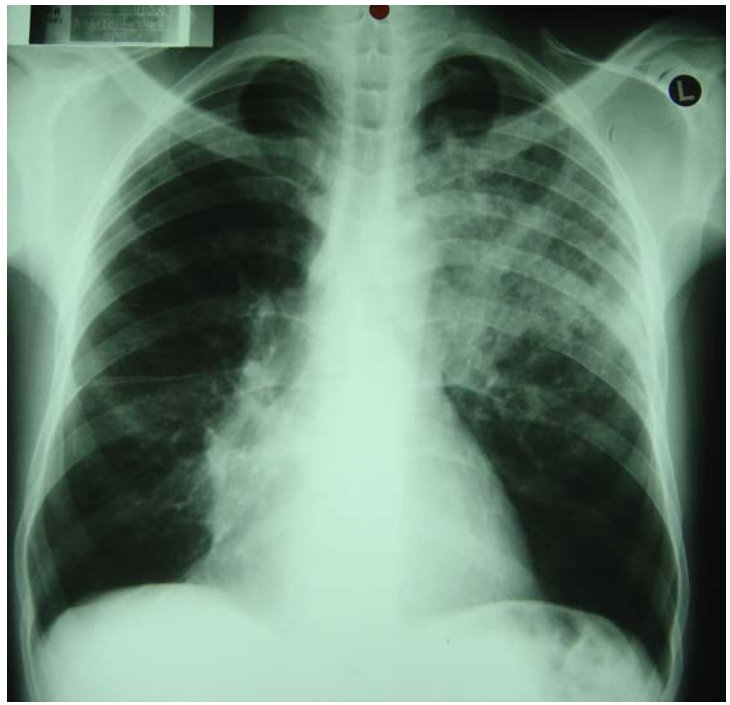
 Tugela Ferry	 ASPE
High TB/M/XDR TB and HIV Prevalence	Single case
Diagnostic limitations No microbiologic monitoring	Diagnostic limitations Delayed and discordant results
Standardized treatment	Standardized treatment
TB control program-poor success	?
HIV epidemic	
KZN strain	
Lack of attention to transmission	Puzzling attention to transmission
Absence of treatment options	Limited treatment options
Ethical dilemmas	Ethical dilemmas

Hospital acquired XDR-TB



12 January 2007

Drug susceptible TB



11 April 2007

XDR-TB

Epidemiology

- **Desperate need for epidemiologic characterization and interventions**
  - ***Short term***
    - What is the best way to quickly characterize the global extent of XDR and XDT TB?
      - What is best way to characterize “hot spots”?
      - How can information on drug resistance from highest TB burden countries be developed and assembled, particularly in areas with limited laboratory capacity?
    - How to define primary and acquired resistance and determine role of community and nosocomial transmission be determined?
    - What is role and best way to use molecular epidemiologic techniques?
    - **How can transmission be interrupted?**
  - ***Longer term***
    - How can long term sustainable surveillance data be acquired?
    - What is the relationship between resistance, virulence, specific strains?

Diagnostics

- **Desperate need for modern, rapid M.TB diagnosis and drug susceptibility testing (first and second line drugs, point of care)**
  - ***Short term***
    - Are there simple clinical and laboratory methods to predict drug resistance?
    - How to expand and make more widely available existing technologies?
      - Standard culture and DST
      - Expansion of SL DST in existing labs
      - Should these be leapfrogged by newer technologies?
    - Which rapid tests are most useful and practical in resource limited settings?
      - Mycobacterial culture and DST- MODS
      - Rapid rifampin based resistance
      - Which of available promising rapid tests (rifampin based resistance) best?
    - Expand rapid testing technologies be developed to include second line drugs?
  - ***Longer term***
    - How to make widely available best rapid diagnostic technologies and facilities?
    - Can diagnostic research be enhanced and respected?
    - How to train and retain laboratory personnel?

Therapeutics

- **Desperate need for new drugs and shorter regimens**
  - ***Short term***
    - How to best develop public-private partnerships for drug development?
    - How can drug evaluation and approval process be speeded up?
      - How to exploit new and more flexible designs for studies?
        - "Salvage therapy", OBT vs new drug? Shorter follow-up?
      - Can surrogate markers for clinical outcomes be developed and tested?
      - Is there a role for expanded access of new drugs before approval?
    - Are there important first and SLD TB and ARV pK and pD interactions and added toxicities?
    - How to develop and employ novel treatment delivery strategies for SLD-treatment?
      - Decentralized community based SLD treatment
  - ***Long term***
    - How to better support basic research in drug development?

Special HIV and TB Issues

- **Universal access to antiretroviral therapy**
  (decrease susceptible population)
  - ***Short term***
    - How to accelerate ARV roll out?
    - When to start?-will starting earlier reduce TB drug resistance incidence and prevalence?
- **Strengthening TB programs**
  - ***Short and long term***
    - How to promote treatment completion?
    - What parts of programs need most strengthening to avert drug resistance?
- **Programmatic collaboration and integration**
  - ***Short and long term***
    - How to best define and implement integration and collaboration?
    - What is effectiveness of these in reducing drug resistance?

Urgent need to interrupt transmission

Urgent need to interrupt transmission

- Primary nosocomial transmission critical- no or limited infection control

- ***Short term***
  - **focus on developing, implementing and monitoring site appropriate infection control strategies in health care facilities**
    - What is the best method to develop site specific administrative environmental, personal strategies?
    - How to implement and monitor existing strategies?
    - How to best protect health care workers?
    - How to study effectiveness and best demonstrate reduction in transmission of drug resistance-individually and in concert?
    - What is the role of enforced confinement?

- ***Long term***
  - **Vaccine**
  - **Alleviation of social and economic conditions and health disparities that breed both TB and HIV**

Future projections Tugela Ferry
Effect of infection control interventions

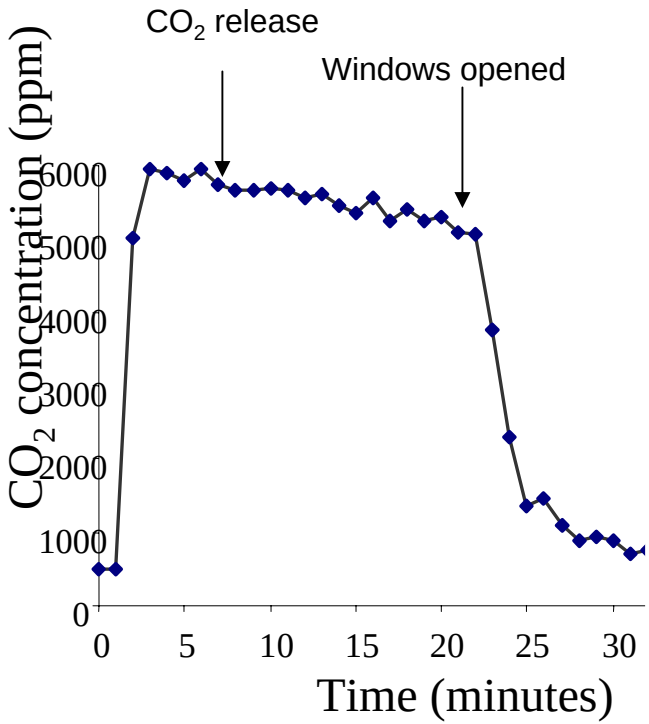
(2007-20012)

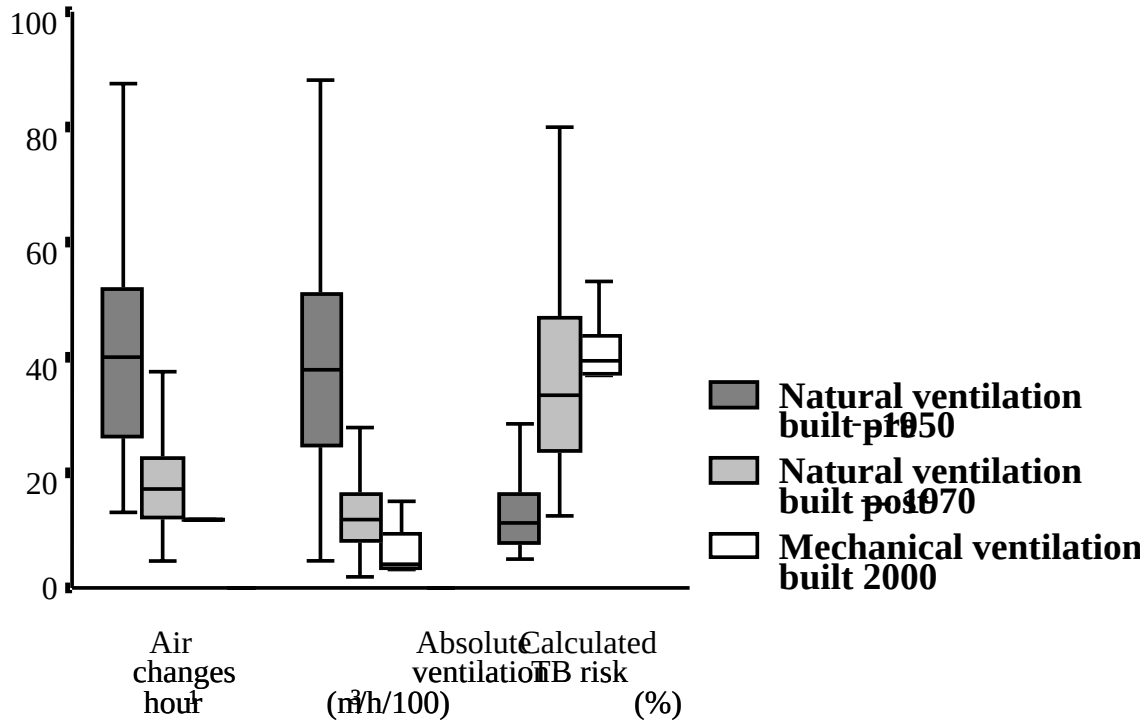
- If no new interventions are introduced, a total of ~1,300 cases of XDR tuberculosis predicted
  - Over half nosocomially transmitted.
- Implementing and testing effectiveness of recommended infection control strategies critical
- Combining available interventions could significantly avert new XDR TB infections
  - reduced hospitalization time, shift tooutpatient therapy, rapid drug resistance testing, HIV treatment
  - improved ventilation, reasonable tuberculosis isolation facilities
  - mask use

OPEN ACCESS Freely available online PLOS MEDICINE

Natural Ventilation for the Prevention of Airborne Contagion

A. Roderick Escombe[1,2,3*], Clarissa C. Oeser[3], Robert H. Gilman[3,4], Marcos Navincopa[5], Eduardo Ticona[5], William Pan[4], Carlos Martínez[5], Jesus Chacaltana[6], Richard Rodríguez[7], David A. J. Moore[1,2,3], Jon S. Friedland[1,2], Carlton A. Evans[1,2,3,4]





Slow CO_2 concentration decay with windows closed 0.5 ACH
Rapid decay with windows open 12 ACH

TF CARES
Tugela Ferry Care and Research Collaboration

Philanjalo

Tony Moll

Nelson Mandela School of Medicine

AW Sturm

Prashini Moodley

Umesh Lalloo

Yale School of Medicine

Gerald Friedland

Jason Andrews

Sanjay, Basu

Albert Einstein College of Medicine

Neel Gandhi

Sarita Shah

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