“Tuberculosis: The Emerging Public Health Threat”

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Disclaimer

- Do not speak for the IHS or the USPHS
- No profits from TB

OBJECTIVES

- Current status of TB globally
- Recognize the “super-spreader” phenomenon
- Aware of clinical and management implications
- Why a grave public health threat?
Historic Failures against TB

- March 24, 1882, Dr. Robert Koch first announced the discovery of *Mycobacterium tuberculosis*
- TB killed one out of every seven people living in the United States and Europe.
Historic Failures against TB

- Effective TB medication in 1940s with streptomycin
- Resistance developed rapidly, leading to multiple drug regimen that is the gold standard today

“It is time to close the book on infectious diseases, and declare the war against pestilence won.”

Definitions

- Resistant TB-Any first line drug
  - INH, Rifampin, Ethambutol, Pyrazinamide, or Streptomycin
  - Led to principle of multi-agent regimen
- MDR TB-Multiple drug resistance TB
  - Resistance to INH and Rifampin

Development and Spread of Resistance

- Naturally occurring intrinsic resistance of organisms to one drug is 1 in 1 million to 100 million
- For two drugs, 1 in 100 trillion organisms
Definitions

- XDR - Extensively drug resistant TB
- INH and Rifampin AND additional resistance to
  - At least one Quinolone
  - One injectable-Amikacin, Kanamycin, or Capreomycin

Definitions

- TDR - Total drug resistance?
  - Difficult to define and currently no consensus
  - 93% of atypical XDR Beijing isolates had mutations that confer resistance to 10 anti-TB drugs.
How Bad is the Problem?

- About 2 billion people are infected with TB, about 1/3 of world population
- Peak in 2003
- 95% of TB cases occur in developing countries

Good news from Global TB Report 2015

- TB mortality has fallen 47% since 1990
- Saved an estimated 49 million lives between 2000 and 2015.
FIGURE 2.3
Estimated absolute numbers of TB cases and deaths (in millions per year), 1990–2014

TB incidence
- All TB cases
- HIV-positive TB cases

TB deaths
- TB deaths among HIV-negative people
- TB deaths among HIV-positive people

Associated deaths are classified as HIV deaths according to ICD-10.

FIGURE 2.9
Less welcoming news

- In 2015, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive).
- 10.4 million new TB cases
- 37% of new cases went undiagnosed or were not reported
Figure 1. Global Incidence of Tuberculosis.
Panel A shows global trends in the estimated incidence of tuberculosis from 1990 through 2011 among all patients, those with human immunodeficiency virus (HIV) coinfection, and without HIV coinfection. The shading around the data curves indicates uncertainty intervals on the basis of available data. Panel B shows the estimated global incidence of tuberculosis in 2011.
**Figure 2.6**

Estimated TB incidence rates, 2014

**Figure 2.** Global Numbers of Cases of Multidrug-Resistant Tuberculosis.

Shown are the estimated numbers of cases of multidrug-resistant disease (including extensively drug-resistant disease) among cases of pulmonary tuberculosis that were officially reported in 2011.
Figure 4.2
Percentage of new TB cases with MDR-TB

3 Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2000 not shown.
Timeline of Drug Resistance

- First MDR TB case in 1985 South Africa
- First XDR TB case 1997
- First TDR TB case 2003
Geographical Distributions of XDR-TB

- In Summer of 2010, only 45 countries or so.
- As of end of 2010, up to 68 countries
- A few years later, 84 countries, according to WHO

Worse news

- 117 countries by 2016.
- 9.7% of people with MDR-TB have XDR-TB.
- India, China and the Russian Federation accounted for 45% of the combined total of 580,000 cases.

- WHO TB Report 2015
## Percentage of XDR among patients with MDR TB

- Belarus (29.3% in 2014)
- Georgia (15.1% in 2014)
- Latvia (18.6% in 2014)
- Lithuania (24.7% in 2013)

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**Enrollment on MDR-TB Treatment**

A total of 125,000 patients were enrolled on MDR-TB treatment in 2015 (up from 111,000 cases in 2014). This however represents only about 22% of incident MDR/RR-TB cases in 2015. The gap between detected MDR/RR-TB cases and enrolments on treatment appears to have narrowed globally over time. Over 7000 XDR-TB patients were started on treatment in 2015.

Unthinkable news

- Specter of Totally Drug Resistant TB is indisputable
- Reported cases in Italy, Iran, Japan, South Africa, US?

Factors Leading to Development and Spread of Resistance

- Poor or erratic compliance
- HIV
- Nosocomial transmission
- Local drug availability
- WHO’s one size fits all approach
When to Suspect Resistance?

- Previous treatment for TB
- Contact with a pt with known resistance (TB Ward)
- HIV
- ETOH abuse

When to Suspect Resistance?

- Acquiring TB in certain geographical regions
- Failure to respond to standard first line TB regimens
- No clinical improvement or persistently positive sputum after two months of therapy.
Diagnosis of MDR

- History
- Sputum culture and sensitivity - 85%-90% in pulmonary TB
- Absence of conversion from positive smear to negative after treatment
- Extrapulmonary disease?
Diagnosis of MDR

- Rapid testing options:
  - Assay GeneXpert MTB/RIF-automated nucleic acid amplification test for M.TB and Rifampin resistance
  - 98% correct ID with smear Pos TB
  - 72% correct ID with Smear Neg TB
  - Very simple to perform-available result in two hours.
Diagnosis of MDR

- Rapid testing options:
  - Assay MTBDRplus—a molecular probe capable of detecting INH and Rifampin resistance mutations
  - 99% sensitivity and specificity for MDR
  - Available result in one to two days
  - Successful even when AFB smear was negative.

Diagnosis of MDR

- Rapid testing options:
  - Direct DNA sequencing analysis of sputum specimens
  - Results available in four days
Diagnosis of MDR

- Greatest limitations?
  - High cost
  - ID only INH and Rifampin resistance
  - Inability to ID which pts are “sputum smear positive” for infection control and treatment monitoring purposes.

Treatment Options

- First-line agents
  - INH
  - Rifampin
  - Pyrazinamide
  - Ethambutol
  - And injectable streptomycin
Treatment Options

- Second-line agents
  - Thionamides (ethionamide, prothionamide)
  - Serine Analogues (Cycloserine, terizidone, thiacetazone)
  - Fluoroquinolones

Treatment Options

- Second-line agents (continue)
  - Injectable-Aminoglycosides (amikacin, Kanamycin)
  - Capreomycin
Treatment Options

- Third-line agents - have lower overall potency and very limited efficacy data
  - Linezolid
  - Clofazimine
  - Augmentin
  - Clarithromycin
Figure 3. Sites and Mechanisms of Action of Antimycobacterial Agents. Shown are the known targets of various agents that have been used clinically in tuberculosis treatment. Many antimycobacterial agents target the M. tuberculosis cell envelope. The box is a high-resolution representation showing the agents that act on each of the three component polymers of the micromolecular outer cell envelope. Drugs such as aminosalicylic acid act like antimetabolites; they are incorporated into folate metabolism as substrates and inhibit downstream folate-dependent processes. The mode of action of pyrazinamide remains enigmatic, and the drug appears to act at least partially by acidifying the cytoplasm of the cell.
New Drugs?

- Bedaquiline (TMC 207)
- Delamanid (OPC 67683)
- PA 824
- Sutezolid
- AZD 5847
- SQ 109

What these drugs have in common?

- Bedaquiline (TMC 207)
- Delamanid (OPC 67683)
- Clofazimine
- Moxifloxacin
Cautionary Tale

- A 35 yo Tibetan male refugee
- 10 kg weight loss, night sweats, and cough X 5 months.
- Acid-fast bacilli (AFB)+
- CXR bilateral cavitary lesions
- Active hepatitis B, HIV negative
Early Drug Sensitivity Profiles

- The initial isolate was classified as pre-XDR
- Resistant to 7 drugs
  - isoniazid, rifampicin, pyrazinamide, streptomycin
  - ethionamide, linezolid and moxifloxacin,

Antituberculous therapy was initiated in March 2011

- Cycloserine, capreomycin, para-aminosalicylic acid (PAS), ethambutol and **Bedaquiline**
- Smear and culture negative after 6 months
- Cured clinically 24 months of RX
Events to follow five months later?

- Re-admitted with fever and cough.
- Sputum positive with AFB
- New resistance to clofazimine and bedaquiline-(9 drugs)

Additional resistance amplification

- New Regimen 2:
  - Ethambutol
  - cycloserine, capreomycin, inhaled amikacin, PAS
  - Meropenem and Augmentin
  - Four sputums remained smear positive and culture-positive.
- Newly acquired resistance to capreomycin(10 drugs)
Therapy in March 2014

- Regimen 3
  - Cycloserine, PAS, ethambutol, levofloxacin, Bactrim and delamanid
  - In June 2014, three consecutive sputum samples were smear-negative but remained culture-positive.
  - In July 2014, the sputum became smear positive
- Treatment failure

Discharged February 2015

- Delamanid resistance(11 drugs)
- Lobectomies bilaterally
- 7-drug regimen 4 consisting of
  - PAS, ethambutol, amikacin
  - Levofloxacin, meropenem, augmentin and clarithromycin
Why is it a public health catastrophe?
Imagine for a moment you have MDR TB 12/8/2015

- “You face two years of treatment, during which time you will see a health provider nearly every day and receive 250 injections and 15,000 pills.
- Treatment for XDR TB can reach almost a half a million in the US.
- Globally today, only about 1 in 5 people with MDR TB receive appropriate treatment, and only half of those are cured.
HIGH MORTALITY AMONG MDR TB AND XDR TB PATIENTS IN THE HIGH HIV PREVALENCE SETTING OF TUGELA FERRY, SOUTH AFRICA

At the end of one year, 71 percent of MDR TB patients and 83 percent of XDR TB patients died in large part due to late appearance for care, delay in diagnosis of TB and HIV and limitations of therapy for drug resistant TB. The majority of deaths occurred within the first 30 days after sputum collection. 40 percent of MDR TB patients and 51 percent of XDR TB patients died within the first 30 days, most before the results of their culture and drug-susceptibility tests were available.

HE LANCET
Respiratory Medicine

Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home discharged patients with programmatically incurable tuberculosis: a prospective cohort study

Prof Keeran Dheda, PhD, Jason D Limberis, BSc Hon, Elize Pietersen, MScSc, Jody Phelan, BSc, Aliasgar Ali, MD, Maia Lesosky, PhD, Kevin P Fennelly, MD, Julian de Rie, MMed, Barbara Mastrapa, MD, Elizabeth Mercer, PhD, Tania Dolby, BSc, Abdallah M Abdallah, PhD, Fathia Ben-Rached, PhD, John Simpson, MMed, Liezel Bell, PhD, Tawanda Gumbo, MD, Prof Paul van Helden, PhD, Frederick A Sirgel, PhD, Ruth McNerney, PhD, Grant Lyon, PhD, Arnab Pain, PhD, Prof Taine G Clark, PhD, Prof Robin M Warren, PhD
Transmission of Extensively Drug-Resistant Tuberculosis in South Africa


Extensive Transmission of *Mycobacterium tuberculosis* from a Child


Young children rarely transmit tuberculosis, in five recently published reports of school-based outbreaks, all source patients were adults or adolescents. Tuberculosis in young children is rarely infectious, because young children are less likely than adults to have a productive cough, to generate the force needed to aerosolize organisms into droplet nuclei, or to have cavitary lesions on chest radiography. In July 1998, infectious tuberculosis was identified in a nine-year-old child residing in North Dakota. The child was screened because extrapulmonary tuberculosis had been diagnosed in his female guardian. Bilateral cavitary tuberculosis was diagnosed in the child. Because the child was the only known possible source of his female guardian's tuberculosis, an investigation of the child's contacts was undertaken.
WHO described MDR TB as a “public health crisis”
Number of bacilli-by clinical extent of disease

<table>
<thead>
<tr>
<th>Extent</th>
<th>Quantity</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granuloma</td>
<td>10^3</td>
<td>LTBI</td>
</tr>
<tr>
<td>Infiltrates</td>
<td>10^6-10^7</td>
<td>AFB neg Cx+</td>
</tr>
<tr>
<td>Cavity</td>
<td>10^8-10^9</td>
<td>AFB +, ++</td>
</tr>
<tr>
<td>Many Cavities</td>
<td>10^{10}-10^{12}</td>
<td>AFB +++</td>
</tr>
<tr>
<td>Death</td>
<td>10^{13}</td>
<td>rigor mortis</td>
</tr>
</tbody>
</table>

Southeastern National TB Center, Dr. Dick Menzies

Why is it a public health catastrophe?

- Powerful driving forces:
  1. Poverty
  2. HIV
  3. Poor clinical practice
  4. Worse public health infrastructure
  5. Collapse in health care system
“It is difficult to think nobly when one thinks only of earning a living”

Jean-Jacques Rousseau
Terrible success rates

- In a 2011 cohort, treatment was successful for only 48% of patients with MDR TB and for 22% of those with XDR TB.

TB Remedies of Centuries Past

- Fresh air
- Milk
- Eating wolf livers
- Drinking elephant urine
- Voyages to Egypt and Libya
- Blood letting
Inappropriate Treatment

- 2010 survey of 106 private practitioners in Mumbai, India, found that only 6 prescribed appropriate TB treatment and that the group prescribed 63 different regimens (8).

Inappropriate Treatment

- 89.3% of private physicians (Philippines) usually treated TB with inappropriate regimens (9).

- In many areas, anti-TB medications are available over-the-counter with no input from physicians at all (11).
Morphological variations of TDR TB

- Bacilli were round (35%)
- Oval (15%) or even multiple branching forms.
- Thicker cell wall than MDR-TB isolates

“The totally drug resistant tuberculosis (TDR-TB)” by Ali Akbar Velayati,1 Parissa Farnia,1 and Mohammad Reza Masjedi2
"Super Spreader" Phenomenon
Early works on Super-spreader?

- **Riley et al. 1960s**
  - 4% pts produced 77% of infections
  - 13% pts for all transmissions

- **Van Geuns et al. 1975**
  - Only 28% of smear + pts are infectious

- David R. Park, M.D. "TB Transmission and Pathogenesis” Presentation from Curry TB Center UCSF
Who is superspreader?

- Increased strain virulence
- Higher pathogen shedding
- And differences in the host–pathogen relationship

**FIGURE 2.** Probable cases of severe acute respiratory syndrome, by reported source of infection* — Singapore, February 25–April 30, 2003

* Patient 1 represents Case 1; Patient 6, Case 2; Patient 35, Case 3; Patient 130, Case 4; and Patient 127, Case 5. Excludes 22 cases with either no or poorly defined direct contacts or who were cases translocated to Singapore and the seven contacts of one of these cases.

Anatomy of a MERS outbreak

In S.K. males and females experienced an outbreak of MERS-CoV respiratory syndrome, or MERS-CoV. Between March and April, 110 people contracted the MERS-CoV virus and eventually died. This diagram shows how quickly the virus spread from infected to uninfected individuals via a network of superspreading. **Note:** Labels may be inaccuracy due to the limited size of the image.
Important Question?

- What to do with MDR-TB LTBI?
- In MDR or XDR TB exposures, RIF/INH are not feasible.

Two options

- No treatment with CXR q 6 months for two years
- Treatment with Fluoroquinolones paired with Pyrazinamide for 6 months
An Obituary for Iulian, a Romanian XDR-TB Patient, Husband, Father, and my Friend

by JSTILLO on MAY 29, 2012 • 1 COMMENT

On May 5th 2012, Romania lost one of its most loving citizens at the young age of 42. This is an obituary for Iulian Ilie Dobre, one of the 1,500 Romanians who die of tuberculosis (TB) every year. When desperately poor people like him die, few people notice. Beyond his immediate family, I don't know how many will miss him. But Iulian's death matters. It matters to me and

© Jonathan Stillo. Iulian patiently sat while I photographed him. This is the first shot and my favorite because he looks so peaceful.
What is expected infection rate to contacts?

- An index case can infect up to 20%-30% of contacts with LTBI, and 1% with TB disease

Why is it a public health catastrophe?

- With 580,000 cases of MDR TB, we are looking at equal number of TB Contact Investigations
- At minimum, a few millions will be infected with LTBI-treatment?
- At least 1% of exposed will develop MDR TB disease
What about MDR TB Contacts?

- 6.5% for active tuberculosis
- 50.7% for LTBI
- >50% of secondary cases with DST results were concordant with those of the source case.
- Majority detected within 1 year

"Yield of Contact Investigations in Households of Patients With Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis" by N. Sarita Shah,1 Courtney M. Yuen,2 Moonseong Heo,1 Arielle W. Tolman,2 and Mercedes C. Becerra2,3, 1Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, and 2Harvard Medical School and 3Partners in Health, Boston, Massachusetts

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Alerts > Medscape Medical News

**Patient With XDR TB Sets Off Contacts Hunt**

By_LOWES

June 09, 2015

18 comments

**DRS’ RECOMMENDATIONS**

- One in Eight TB Cases in Children Is Isoniazid-Resistant
- Plan to Add More AIDS, TB Drugs to Essential Medicines List, Sources
- Tuberculosis and Superbug Strains 'Eating' Europe, WHO Warns

A search is on for individuals in at least three states who may have come in close contact with a woman from India now being treated for extensively drug-resistant tuberculosis (XDR TB) at the National Institutes of Health Clinical Center in Bethesda, Maryland.

The woman was transported on June 5 from a hospital in suburban Chicago, Illinois, to the National Institutes of Health facility, which has isolation rooms designed for patients with dangerous respiratory infections, according to the National Institutes of Health and the Centers for Disease Control and Prevention (CDC). The CDC today described her condition as stable.

The woman had previously been treated for TB in India, a
Federated States of Micronesia, 2007--2009

- 124 (60%) have LTBI.
- Among 21/205 confirmed and suspected MDR TB cases, 10 were <15 years old.
- A total of five persons have died of MDR TB.

Implications of Resistance

- Have to use less potent and more toxic agents
- Prolonged hospitalization
- May have to send pts to National TB Centers?
National TB Centers

- The Francis J. Curry National Tuberculosis Center
- Heartland National TB Center (HNTC)
- New Jersey Medical School Global Tuberculosis Institute
- Mayo Clinic Center For Tuberculosis
- Southeastern National Tuberculosis Center

Implications of Resistance

- Increased in morbidity and mortality
- Taxing health care system
- Up to 98% mortality in South Africa and about 60% in US
- For XDR, treatment up to 18 months after conversion.
Exacting Costs

- Prolonged isolation
- Disabling side effects
- Expensive medications
- Lost of employment
- Collapse of social support?

Three Central Strategies to TB Elimination

- Early detection and treatment of TB disease cases
- Preventive treatment of LTBI
- Limit hospital transmission
What about vaccines?

Nurse With Tuberculosis May Have Exposed Over 1,000, Including 350 Infants

By LIAM STACK  DEC. 13, 2015

Over 1,000 people, including 350 infants, may have been exposed to tuberculosis in the maternity wing of a hospital in California after an active case of the disease was diagnosed in a nurse, hospital officials said on Sunday.
INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY, JULY 2013, VOL. 34, NO. 7

CONCISE COMMUNICATION

Nosocomial Pulmonary Tuberculosis Contact Investigation in a Neonatal Intensive Care Unit

Kate E. Fisher, MPH, MBChB; Robert Guarro, FRACP; Jacqueline Stack, FRACP; Sheila Simpson, MPH; William Krause, DipAppSc, GradCertCrtCareN; Karen D. For, RN; Emilia Ryan, BBiomedSci; Stephen Connolly, FAAP HM, MPH, MBBS; Kirsty Hope, PhD; David Isaacs, MD; Paul Chay, FRACP; John Eastwood, PhD; Guy B. Marks, PhD

The diagnosis of smear-positive pulmonary tuberculosis in a medical officer working in a metropolitan Australian neonatal intensive care unit led to a contact investigation involving 125 neonates, 165 relatives, and 122 healthcare workers with varying degrees of exposure. There was no evidence of nosocomial tuberculosis transmission from the index case.

Infect Control Hosp Epidemiol 2013;34(7):754-756

Research letter

Neonatal exposure to active pulmonary tuberculosis in a health care professional

Mithu Sen, Daniel Gregson, James Lewis

Abstract

Nosocomial transmission of tuberculosis (TB) is a recognised risk. Although many outbreaks of TB in health care settings have been reported, there are few cases of nosocomial transmission to neonates. We report our experience in investigating and managing the exposure of 16 days of 124 neonates, 201 visitors, and 219 health care workers to a health care worker with active TB in a neonatal intensive care unit.

The Canadian Tuberculosis National Advisory Committee (NTAC) recommends the management of patients with pulmonary TB in health care settings. Our index case is ventilated by the common system. Air is recirculated mixed with 4–5 changes per hour.

Contact investigation. Three categories of neonates, their relatives, and healthcare workers were included. The expert panel overseeing the investigation is surveillance model, with all contacts as a precautionary approach.

Neonates classified as exposed were on the index case was on duty, were in the index case had written in the sputum diary by the index case in the period. Exposed neonates in the index case was clear, neonates were recommended prophylaxis (10 mg/kg/day) until they were at least 3 months corrected for the last contact, whichever was later. Pneumococcal and tuberculosis is unreliable at detecting TB. Relatives who visited exposed the index case was shared common shifts with the index case, potentially exposed and offered TB.

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Epidemiologic investigations and public health actions

We categorized visitors and neonates who might have been exposed to the index case as being at high risk (exposed without respiratory precautions to the index case during the 5-day period when he was contagious) or at low risk (exposed with respiratory precautions to the index case during the 5-day period when he was contagious).
Last month, one man single-handedly exposed the fact that the US public health system doesn’t always do its job. Infected with a deadly drug-resistant strain of tuberculosis, Andrew Speaker traveled to several countries, exposing more than 600 people on two flights, even though a scan of his passport brought up a warning to keep him in custody and contact health authorities.

One could argue that it’s the public health system’s fault that he developed extremely drug-resistant tuberculosis (XDR-TB) in the first place. TB becomes resistant to antibiotics when improperly treated, and XDR-TB is resistant to at least two main first-line drugs and at least three of the six second-line drugs. If we thoroughly treated TB in its less deadly form, the US Centers for Disease Control and Prevention wouldn’t have had to institute its first federal quarantine in nearly 45 years.

Summary

- We must prepare for the unknown and unseen
- We must screen providers that volunteer overseas aggressively
- Be mindful of a superspreader
- It is better to be proactive than reactive
“Behind every successful man stands a surprised mother-in-law”

Voltaire