Treating MDR and XDR TB: Cases, Contacts and Complex Decisions

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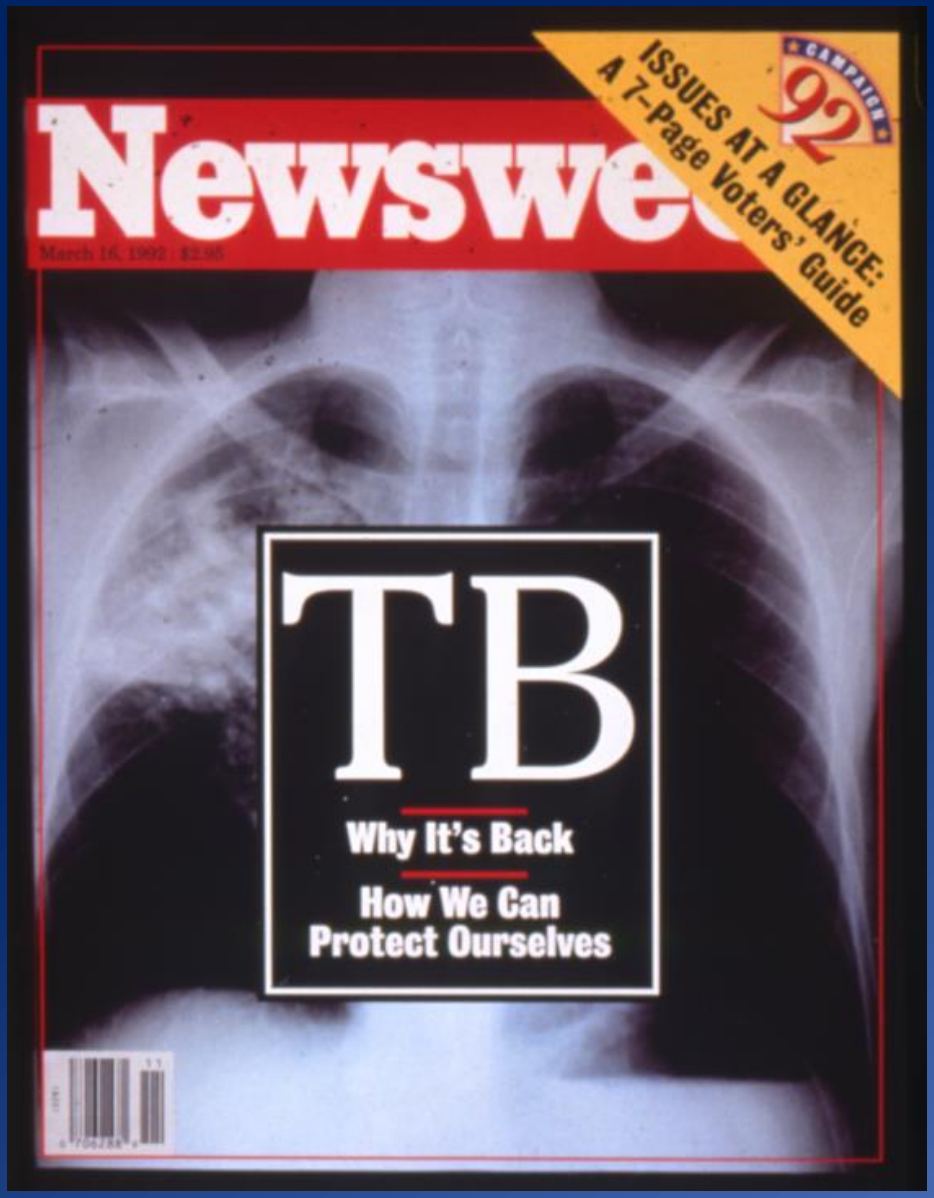
Objectives

- Definitions
- Discuss the epidemiology and pathogenesis of MDR TB
- Discuss MDR TB treatment principles and new drugs
- Review special situations (HIV, Pregnancy, Surgery)
- Present case(s)

1992: Multidrug-resistant (MDR) TB



Definition of Drug Resistant TB

- MDR TB
  - A specimen of *M. tuberculosis* isolate that is resistant to at least INH and RIF
  - Can be resistant to other drugs as well
- ODR TB
  - Resistant to INH, sensitive to RIF, with or without resistance to other first or second-line drugs
  - Resistant to RIF, sensitive to INH, with or without resistance to other drugs
  - Resistance to any (1 or more) first-line drugs (EMB, PZA, SMN) other than INH or RIF

2005: Extensively drug-resistant (XDR) TB

THE SUNDAY INDEPENDENT

SEPTEMBER 10 2006 | R9,50 (INC VAT) | ANNUAL SUBSCRIBERS: R7,67 — BUSINESS REPORT — PUBLISHED IN SOUTH AFRICA — iol

The Zuma saga — Page 5

9/11 FIVE YEARS ON — *Special Report* — Pages 13 to 15

End of a dynasty — Page 12

Killer TB tightens fatal grip

Despite indications that SA is in the forefront of infection, health minister tries to put a clamp on news and snubs global conference

BY CHRIS MAKHAYE AND CHARLENE SMITH

Buzubani Phungula died in the Church of Scotland Hospital, Tugela Ferry, in the early hours of Thursday. He was the latest victim of extreme drug-resistant tuberculosis (XDR-TB) – a deadly strain of the disease that kills almost everyone who contracts it and is almost impossible to cure.

It was announced at an emergency international conference in Johannesburg this week that XDR-TB is being recorded across South Africa, Lesotho, Mozambique and Swaziland. Yet, while it appears to be a huge problem in South Africa, nobody from the health department attended the seminar, having been reportedly ordered by Manto Tshabalala-Msimang, the health minister, to stay away.

Tuberculosis is airborne and stays in the air for four hours after an infected person has left a room. Research completed this month in Mpumalanga by the Medical Research Council shows that multi-drug-resistant tuberculosis (MDR-TB, the parent of XDR-TB) is significantly more infectious than was first believed.

South Africa has the world's second worst rate of MDR-TB, with 6 000 cases a year. It emerges when TB treatment is not administered effectively.

Yet, while scores and experts flew in from World Health Organisation offices in Europe, the Centres for Disease Control in the United States and all the ...

Zanele Madonsela sits next to her daughter in the female ward at the Church of Scotland hospital in Tugela Ferry, KwaZulu-Natal

TB infected patients and warned them not to speak to the media or allow jour- ... 31 patients in the ward, with three more waiting to be admitted. The hospi- ... At Church of Scotland Hospital the first cases of XDR-TB were recorded in ... medical manager and acting hospital manager, said some hospital staff had ...

Prospect of an epidemic sets medics trembling

BY CHARLENE SMITH AND LIZ CLARKE

At just one small hospital in Tugela Ferry a sixth of the world's known XDR-TB cases have been found.

Dr Tony Moll of Church of Scotland Hospital at Tugela Ferry said: "We have seen HIV move in and create havoc in our community. We tremble in our boots with XDR-TB. Up to 80 percent of new cases are TB co-infected with HIV."

A large proportion of deaths were attributed to Aids, but a recent study from January 2005 to March 2006 shows that 71 percent of those receiving antiretrovirals who died had MDR-TB.

"Worldwide, there are 347 cases of XDR-TB. We picked up 53 cases in our small hospital alone; 51 percent had no prior TB, 38 percent had prior treatment and 14 percent were newly infected with drug-resistant strains. We lost two health workers to XDR-TB."

He said "52 of the 53 died within 16 days of sputum collection; many died before sputum results came out. We have two to five new patients with XDR-TB each month."

A South African scientist who has supervised the clinical research said this week that "the options for patients with this extreme strain" were not running out – they had already run out.

There were no alternative drugs available, warned Professor Umesh Lalloo of the University of KwaZulu-Natal's Nelson Mandela School of Medicine in Durban, the leader of MDR-TB research at Tugela Ferry.

"Several drugs are under investigation but still far from clinical use. That is why this is such a tragedy. It shows more than ever the urgent need to fast-track TB drug development ... epidemic," said Lalloo.

All those in contact with the extreme form of TB were at risk of developing it, including health personnel: "That is the calamity."

Patients diagnosed with MDR-TB should be hospitalised to ensure adherence and efficacy, he said. "The support and tracking of such patients is central to any programme to manage and prevent the spread of MDR-TB."

While all the resources needed were in place, having freely available drugs was a serious problem if they were not issued as part of a well-defined programme: "We are the most resourced country on the continent in respect of TB, yet we have one of the worst cure rates for TB."

Fifty-two of the 53 patients diagnosed with MDR-TB have already died at Tugela Ferry and continuing research points to the strain having spread to other regions of the country.

The extent of this virtually untreatable strain is not known, however, as mass screening is expensive and difficult to monitor. Many patients are dying without having been diagnosed. All 53 patients studied so far had XDR-TB.

And the place where you are most likely to catch a lethal strain of TB? In a South African hospital, because of inadequate infection controls there.

Dr Karin Weyer, who heads the Medical Research Council's TB programme, said: "South Africa is the epicentre of HIV and TB. HIV has the capacity to fast-track MDR into an uncontrollable epidemic. If the epidemic gets out of control the impact ... could be severe."

Professor Rob Warren of Stellenbosch University has been genotyping XDR-TB. He said it had been found in KwaZulu-Natal, Limpopo, Western ...

Definition of XDR TB

- Resistance to at least INH and RIF from among the 1st -line anti-TB drugs (MDR TB)
- Plus resistance to any fluoroquinolone
- And to at least one of 3 injectable 2nd-line anti-TB drugs used in TB treatment
  - Capreomycin
  - Kanamycin
  - Amikacin

2012: Totally drug-resistant TB?

WHO meets in Geneva; Central TB Unit sending team

Panic and chill in the air as TDR-TB claims 3 of 12 lives

- India only the third country where the deadliest form of tuberculosis has struck
- People the 12 patients came in contact with to be identified and tested for TB

DEEPAK TURBHEKAR

Anita Davare with the photograph of her daughter Supriya who succumbed to Totally Drug Resistent Tuberculosis on Jan 5. The 20 year old had been under treatment for three years but with no relief

Lata Mishra and Jyoti Shelar
mirrorfeedback@indiatimes.com

Less than a week after top chest physician Dr Zarir F Udwadia broke the news of presence of totally drug resistant tuberculosis (TDR-TB) cases in the city, it was revealed on Friday that three of the 12 patients he studied have died in the past two weeks.

Nobody would have known of these deaths if the Directorate of Health Services and BMC's health officers, completely taken aback by Dr Udwadia's research, had not launched a drive to visit the 12 patients to collect sputum samples of their family members.

While the identities and addresses of the 12 patients are not available, Mumbai Mirror traced one of the dead patient's family to its Patilwadi, Ranade Road, Dadar (west) home.

Supriya Daware, 20, died on January 5 after three years of being treated for TB across four hospitals. She was first diagnosed with TB when she was in class 12.

Ashok Daware, her distraught father, said she was last taken to the TB Hospital in Sewri on December 28. "They told her she was in the last stage. My daughter shrunk from 42 kg to 18 kg in the three years she was being treated."

TURN TO PAGE 2 »

CHEST

Original Research

TUBERCULOSIS

Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

Super Extensively Drug-Resistant Tuberculosis or Totally Drug-Resistant Strains in Iran

Ali Akbar Velayati, MD; Mohammad Reza Masjedi, MD; Parissa Farnia, PhD; Payam Tabarsi, MD; Jalladein Ghanavi, MD; Abol Hassan ZiaZarifi, PhD; and Sven Eric Hoffner, MD

Background: **The study documented the emergence of new forms of resistant bacilli (totally drug-resistant [TDR] or super extensively drug-resistant [XDR] tuberculosis [TB] strains) among patients with multidrug-resistant TB (MDR-TB).**

Methods: **Susceptibility testing against first- and second-line drugs was performed on isolated *Mycobacterium tuberculosis* strains. Subsequently, the strains identified as XDR or TDR *M tuberculosis* were subjected to spoligotyping and variable numbers of tandem repeats (VNTR).**

Results: **Of 146 MDR-TB strains, 8 XDR isolates (5.4%) and 15 TDR isolates (10.3%) were identified. The remaining strains were either susceptible (67%) or had other resistant patterns (20%). Overall, the median of treatments and drugs previously received by MDR-TB patients was two courses of therapy of 15 months' duration with five drugs (isoniazid [INH], rifampicin [RF], streptomycin, ethambutol, and pyrazinamide). The median of *in vitro* drug resistance for all studied cases was INH and RF. The XDR or TDR strains were collected from both immigrants (Afghan, 30.4%; Azerbaijani, 8.6%; Iraqi, 4.3%) and Iranian (56.5%) MDR-TB cases. In such cases, the smear and cultures remained positive after 18 months of medium treatment with second-line drugs (ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, and ciprofloxacin). Spoligotyping revealed Haarlem (39.1%), Beijing (21.7%), EAI (21.7%), and CAS (17.3%) superfamilies of *M tuberculosis*. These superfamilies had different VNTR profiles, which eliminated the recent transmission among MDR-TB cases.**

Conclusions: **The isolation of TDR strains from MDR-TB patients from different regional countries is alarming and underlines the possible dissemination of such strains in Asian countries. Now the next question is how one should control and treat such cases.**

(CHEST 2009; 136:420–425)

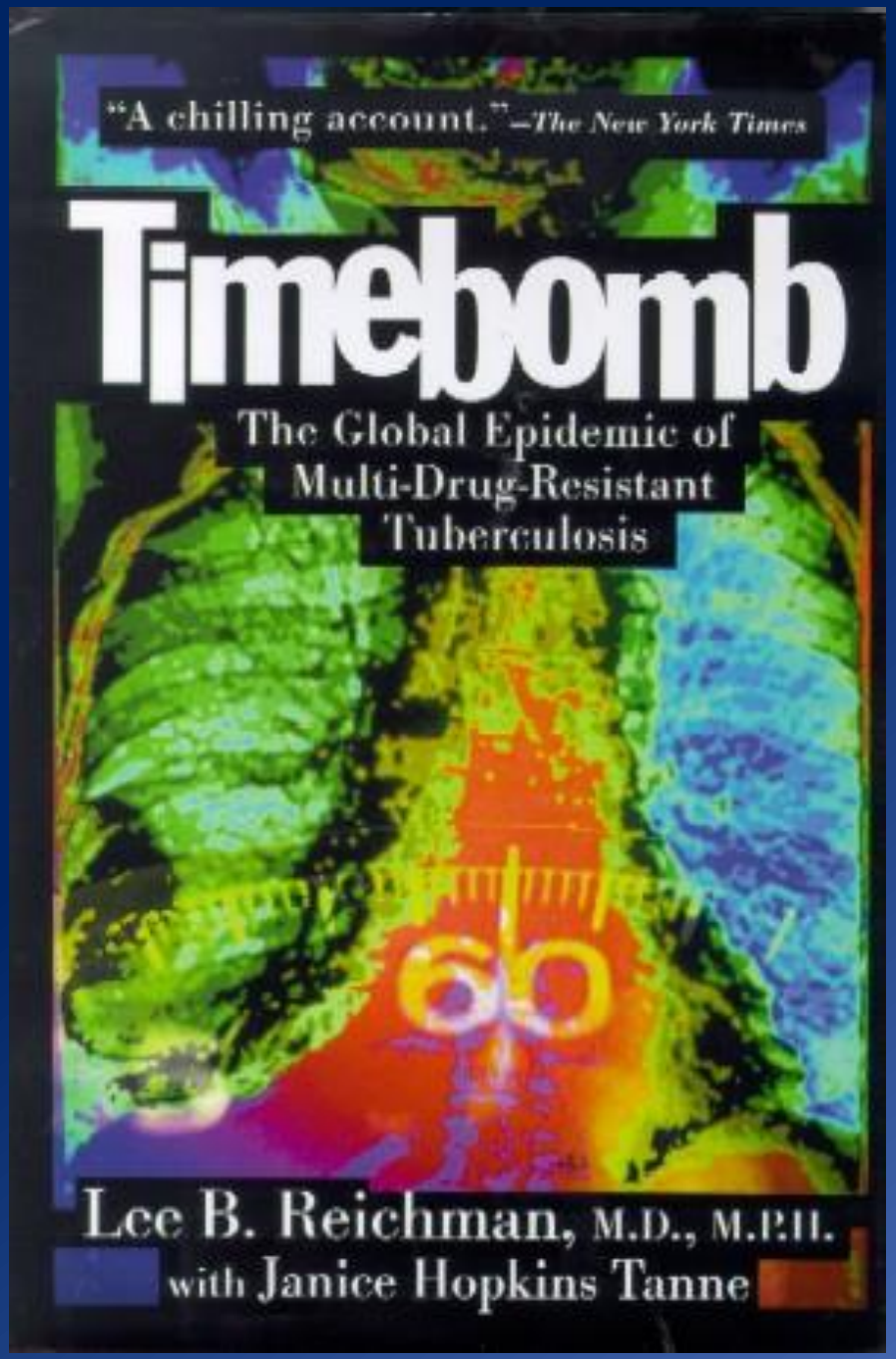
Emergence of Totally Drug Resistant (TDR) TB

- XDR TB plus cycloserine, PAS, all injectables
- 15 TDR isolates; 56% Iranian, 30% Afghani
- Cases + smear/culture after 18 months Rx
- 95% XDR/TDR had history of prior TB treatment
- 10 % had resistance to all second line drugs (Iranian)
  - Believed due to exposure to aminoglycosides and FQ for treatment of other respiratory diseases
- Recent transmission was not the reason for emergence of TDR

Chest 2009; 136:420-425

Definitions (3)

- MDR or XDR-TB
  - Primary Resistance: person is exposed to TB which is already drug-resistant and develops disease
  - Secondary (acquired) Resistance: drug resistance develops during the course of treatment


"A chilling account." —The New York Times
Timebomb
The Global Epidemic of Multi-Drug-Resistant Tuberculosis
Lee B. Reichman, M.D., M.P.H.
with Janice Hopkins Tanne

Impact of MDRTB

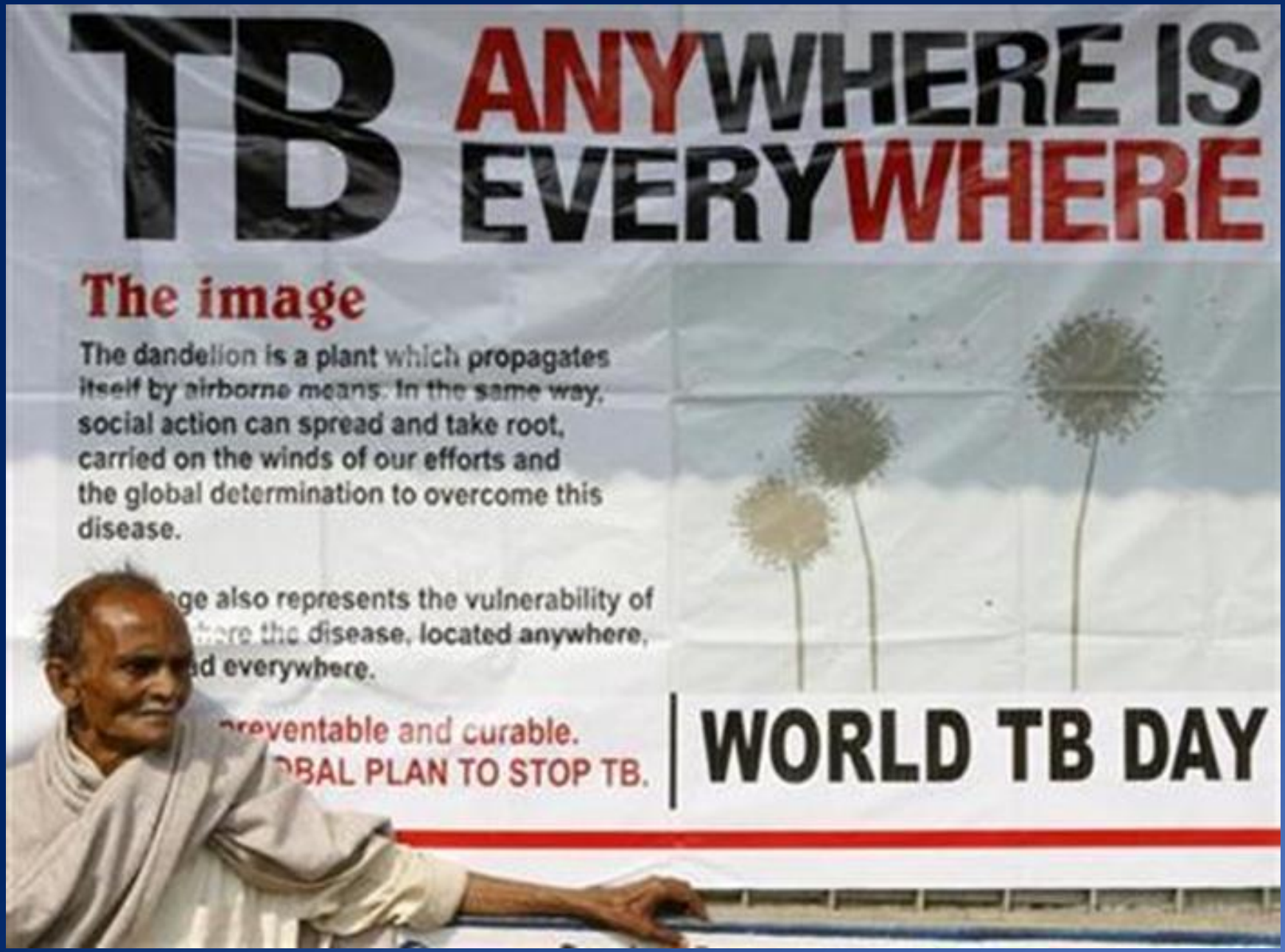
- Enormous resource sink
- Prolonged treatment/monitoring required
- Large cost incurred (drugs, hospitalization, DOT, lab testing)
- Major impact to individual health
- Prolonged isolation, inability to work
- Pool of clinical experts diminishing
- Increasingly complex healthcare systems to navigate
- No proven therapy for contacts

Treatment Costs

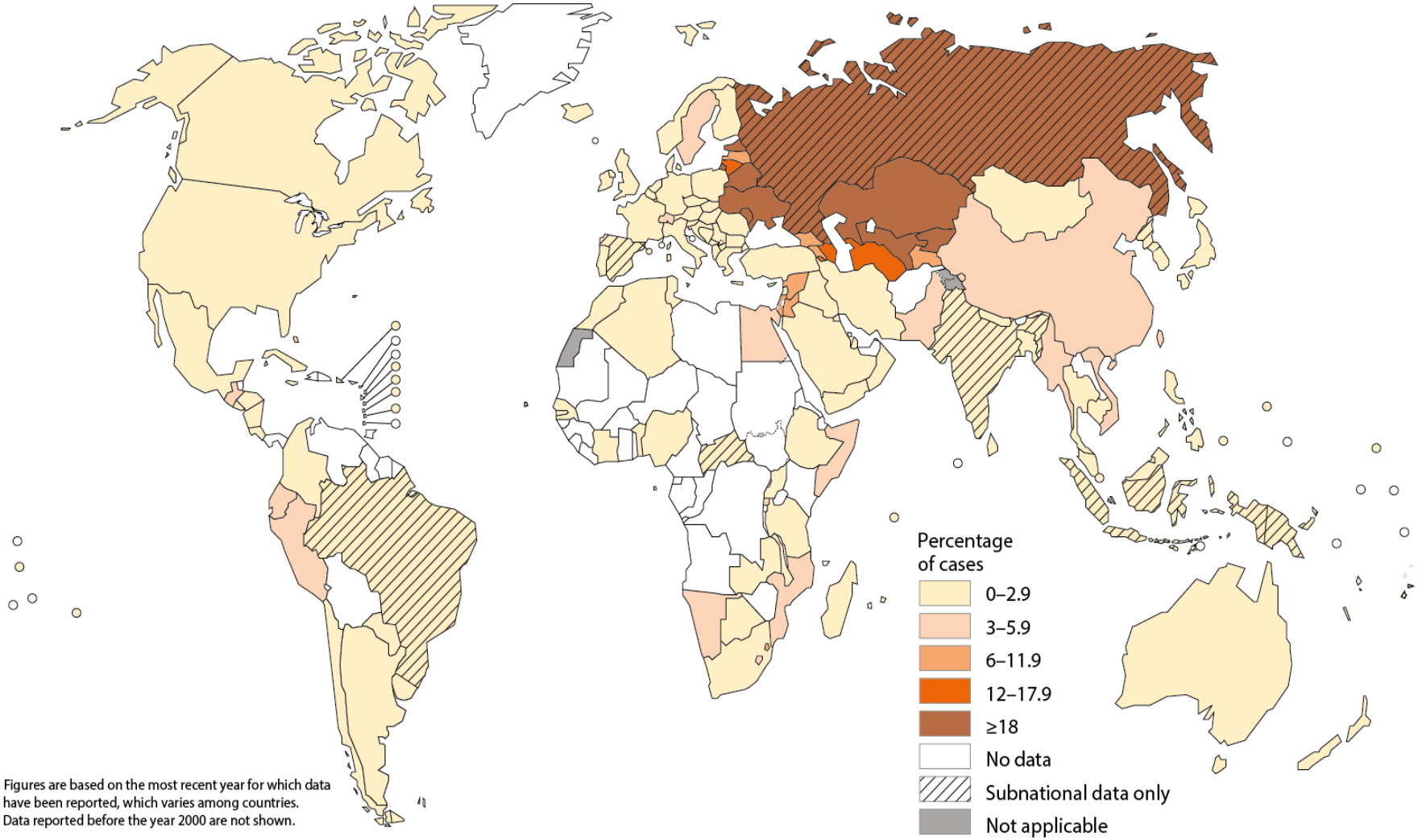
- Direct costs, mostly covered by the public sector
- $134,000 per MDR TB patient (average)
- $430,000 per XDR TB patient (average)
- $17,000 per non-MDR TB patient

Marks SM, et al. *EID* 2014;20(5):812-21

Epidemiology


TB ANYWHERE IS EVERYWHERE
The image
The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.
ge also represents the vulnerability of
re the disease, located anywhere,
d everywhere.
reventable and curable.
BAL PLAN TO STOP TB.
WORLD TB DAY

Percentage of new TB cases with multidrug-resistant tuberculosis[a]

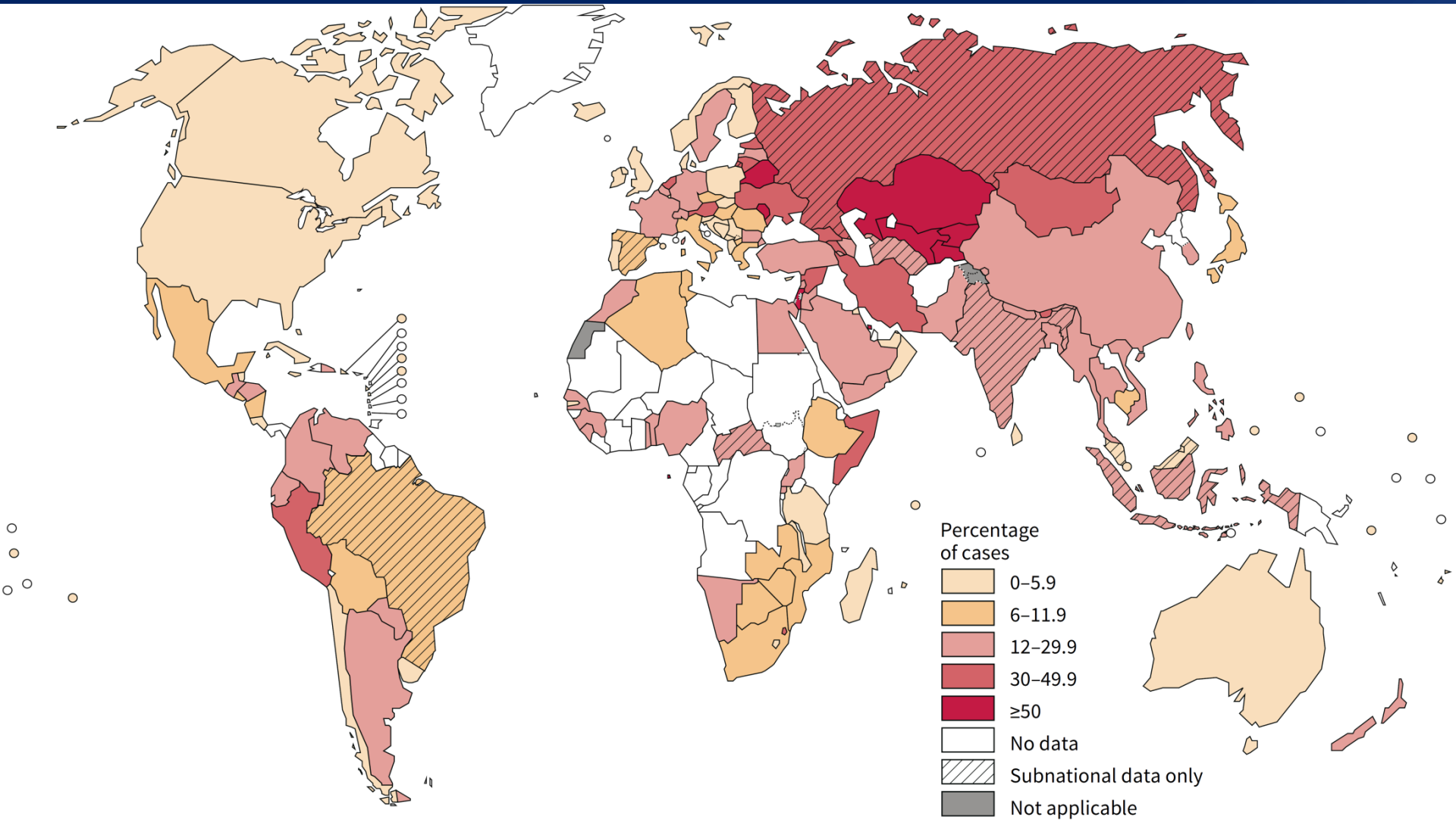


a Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2000 are not shown.

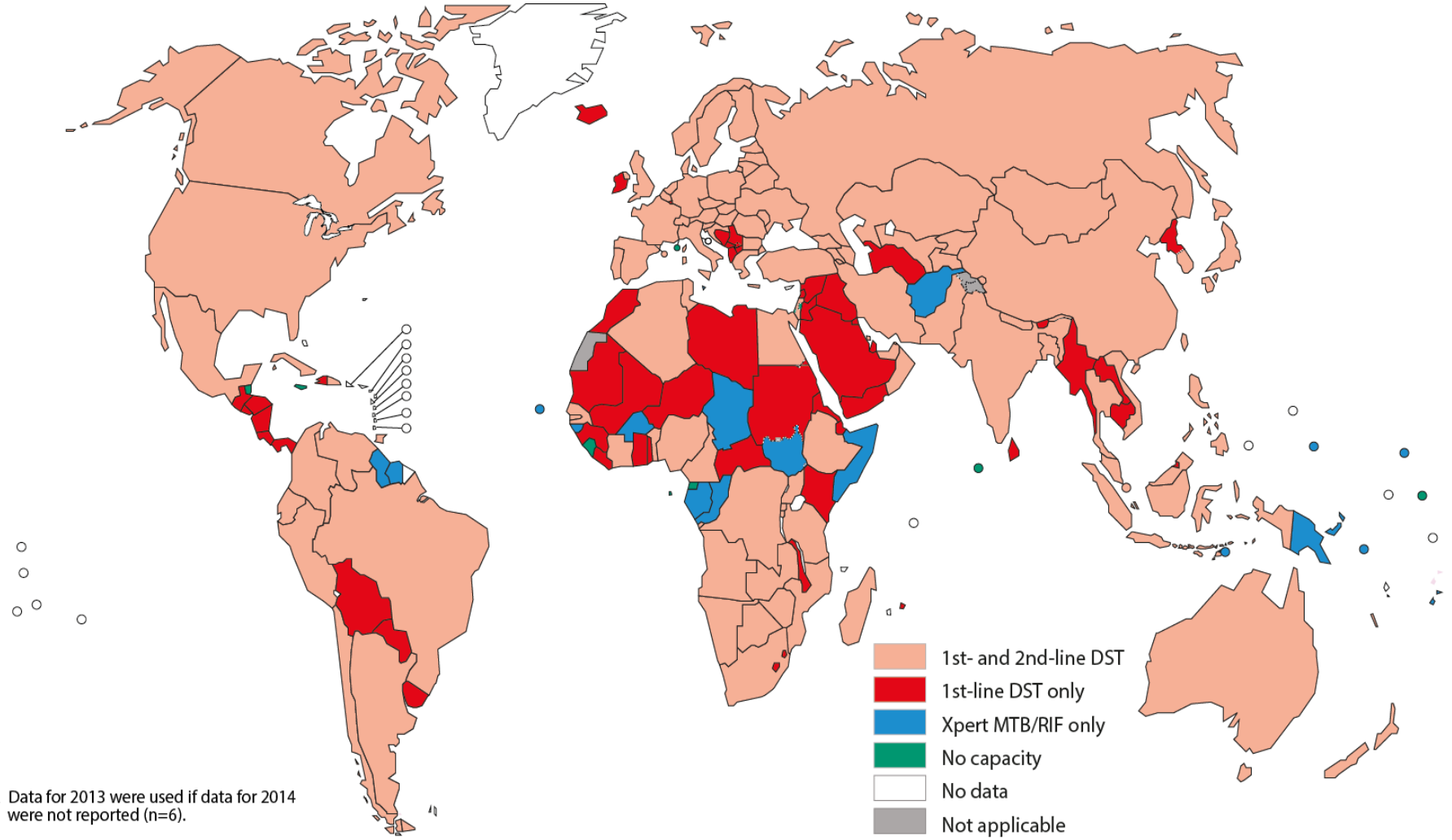
Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Percentage of Previously Treated TB Cases with MDR-TB



Global capacity for drug-susceptibility testing (DST), 2014[a]

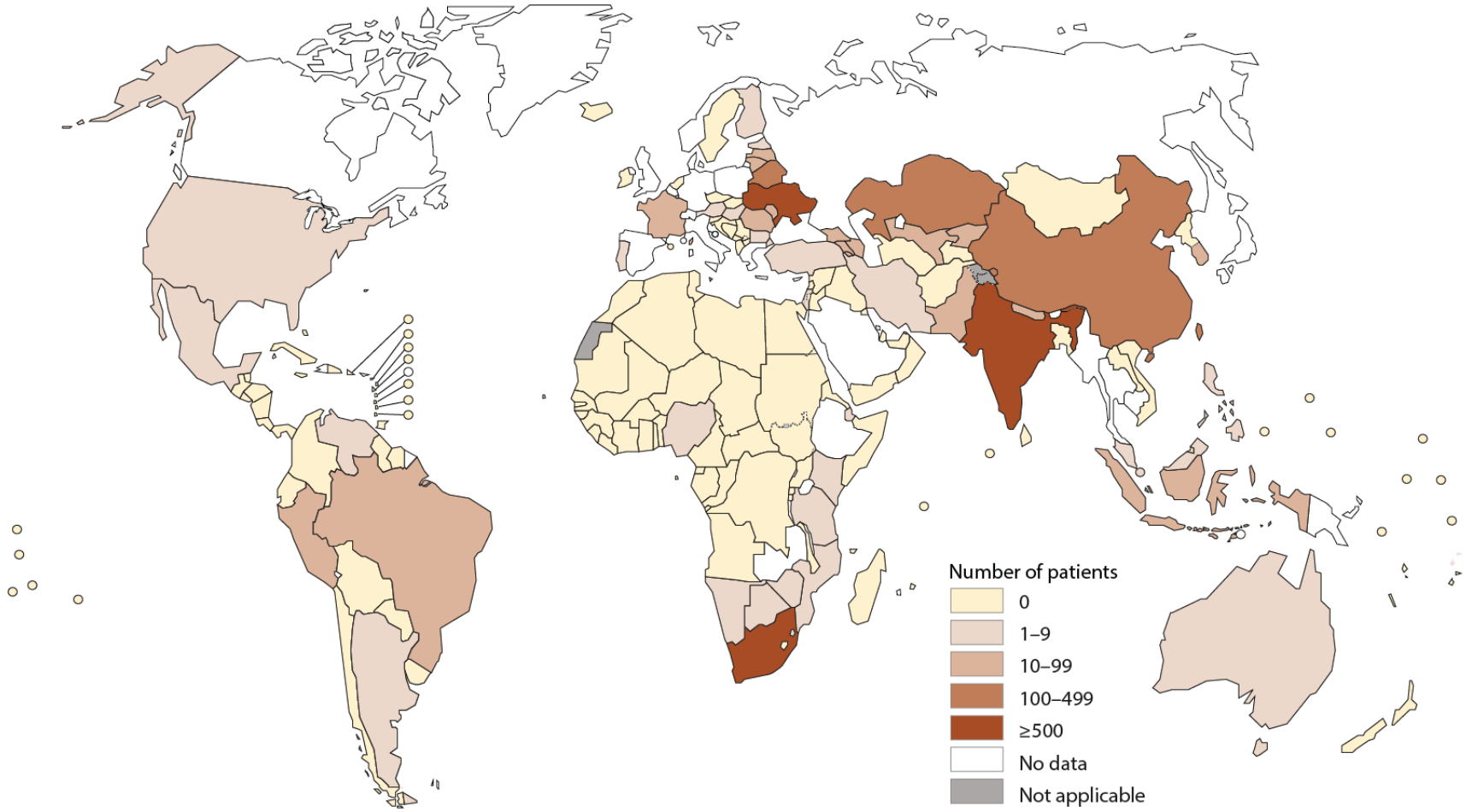


a Data for 2013 were used if data for 2014 were not reported (n=6).

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Number of patients with laboratory–confirmed XDR–TB started on treatment in 2014



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

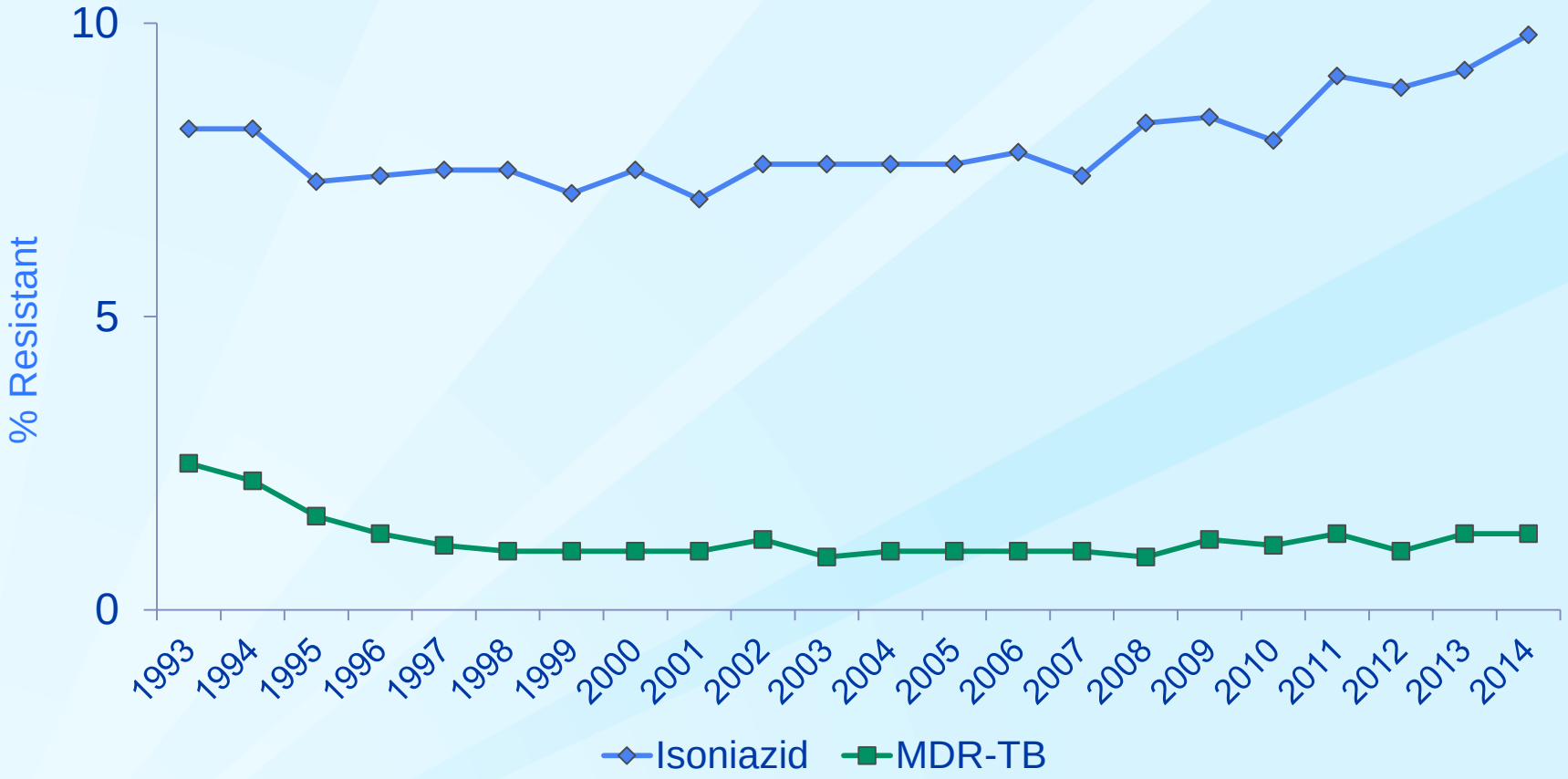
XDR TB

- XDR TB had been reported by 92 countries by the end of 2012
  - 13 countries had >10 XDR TB cases
  - On average, 9.6% of MDR TB cases have XDR TB

- Highest in:
  - Azerbaijan (Baku city: 12.8%)
  - Belarus (11.9%)
  - Lithuania (24.8%)
  - Tajikistan (Dushanbe city and Rudaki district: 21%)

Global Tuberculosis Report 2013. World Health Organization.
http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1 Accessed March 21st, 2014.

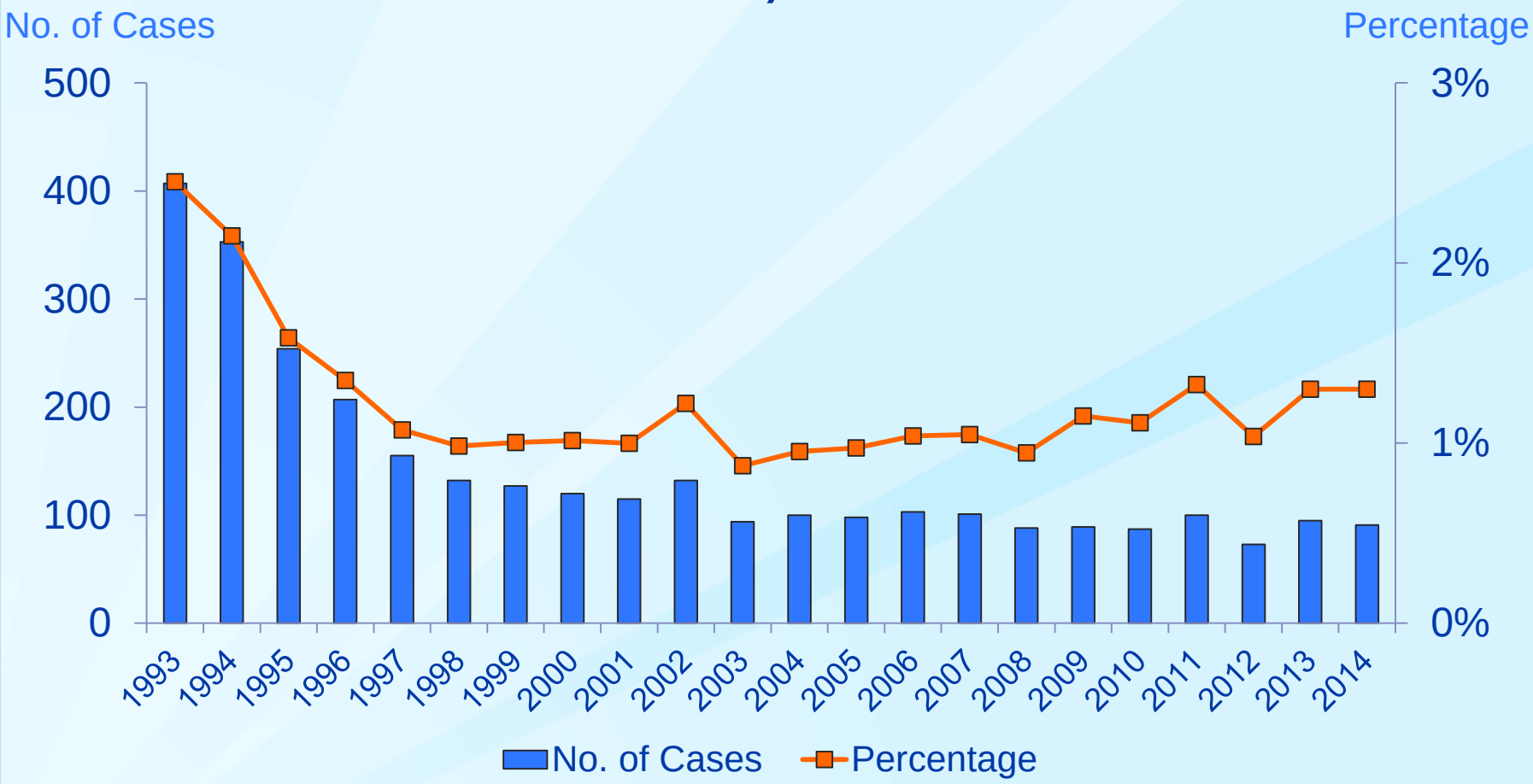
Primary Anti-TB Drug Resistance, United States, 1993 – 2014*



*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.

Primary MDR TB, United States, 1993 – 2014*



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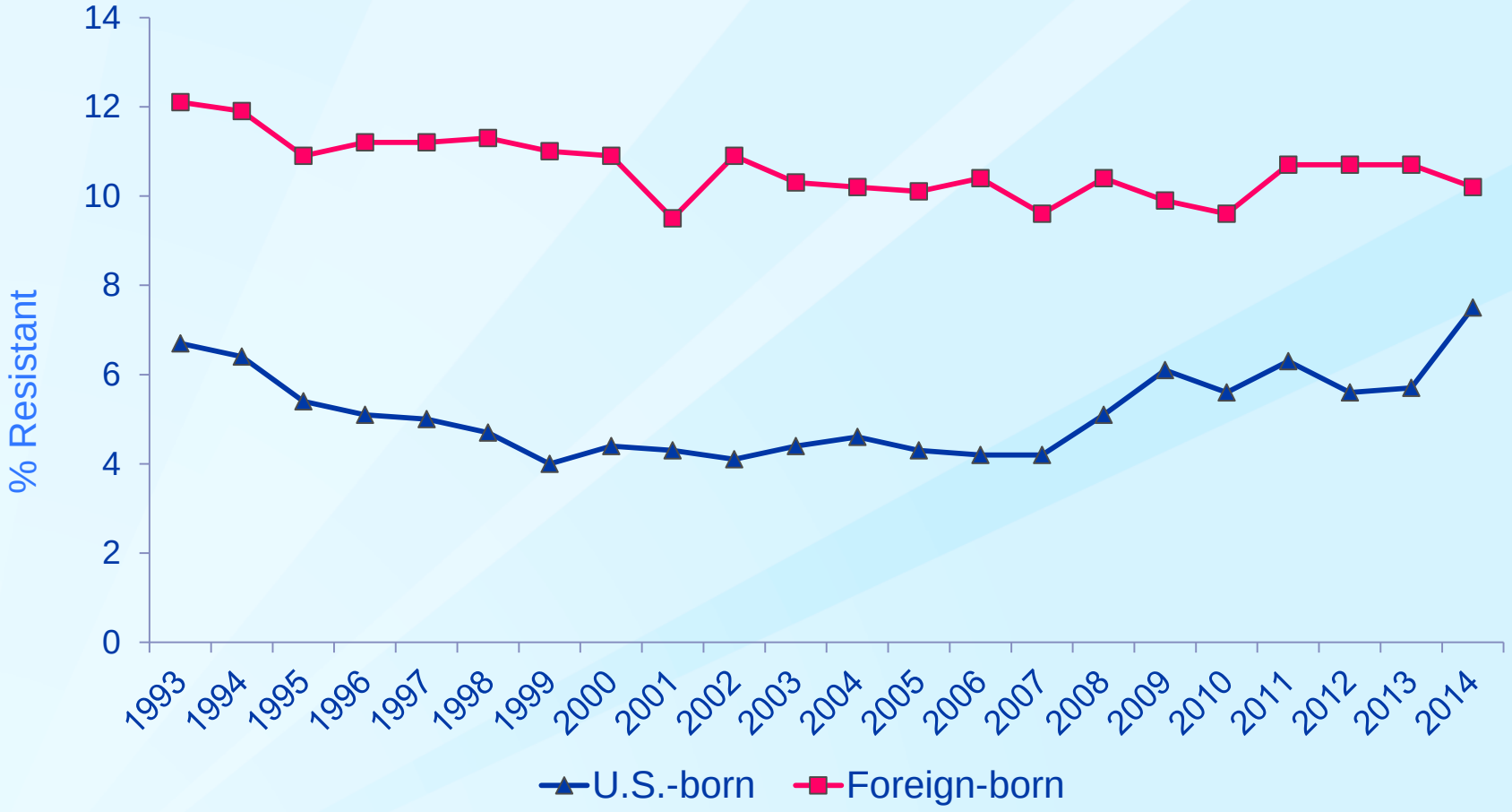
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

Primary Isoniazid Resistance in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2014*



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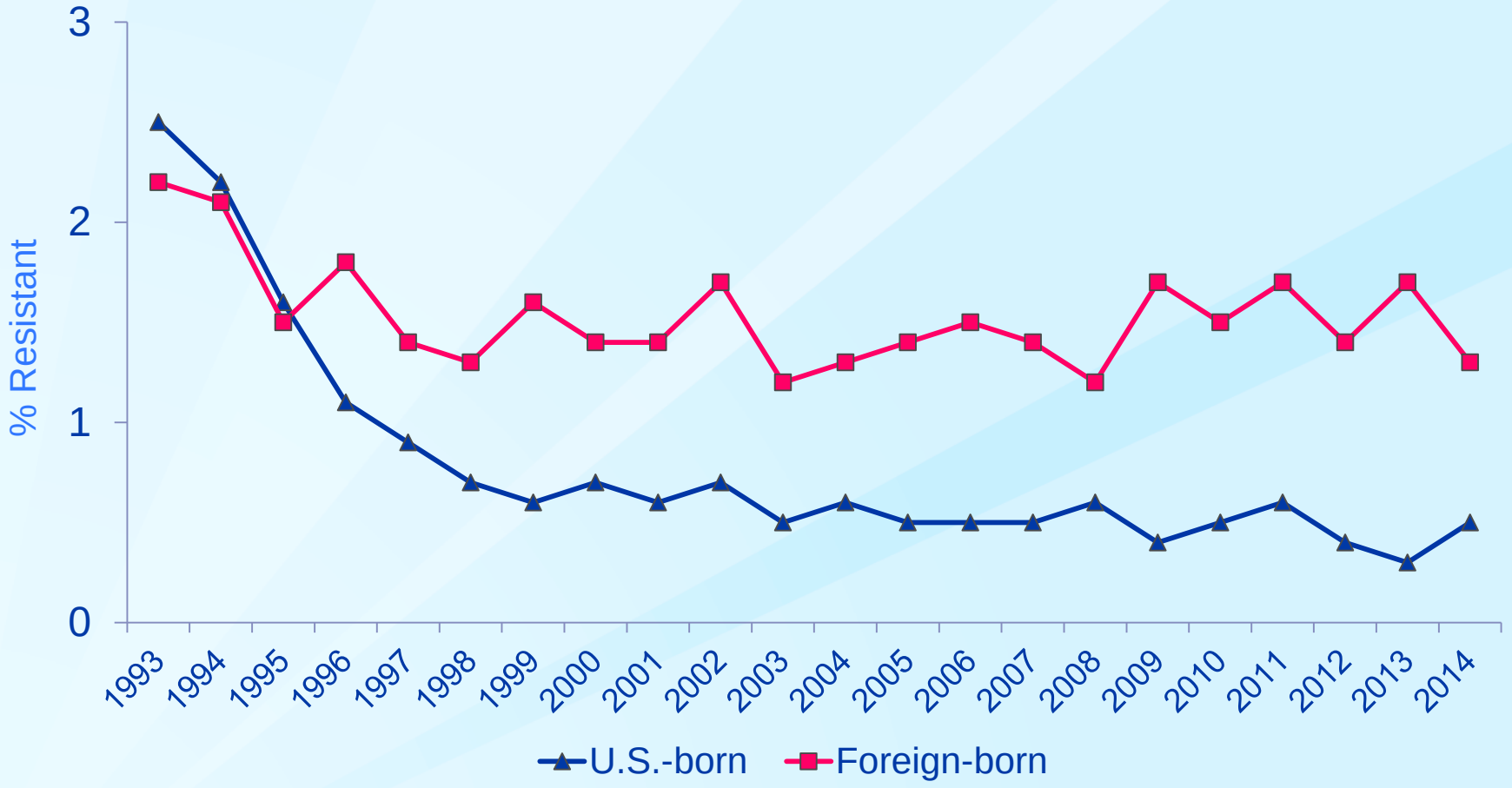
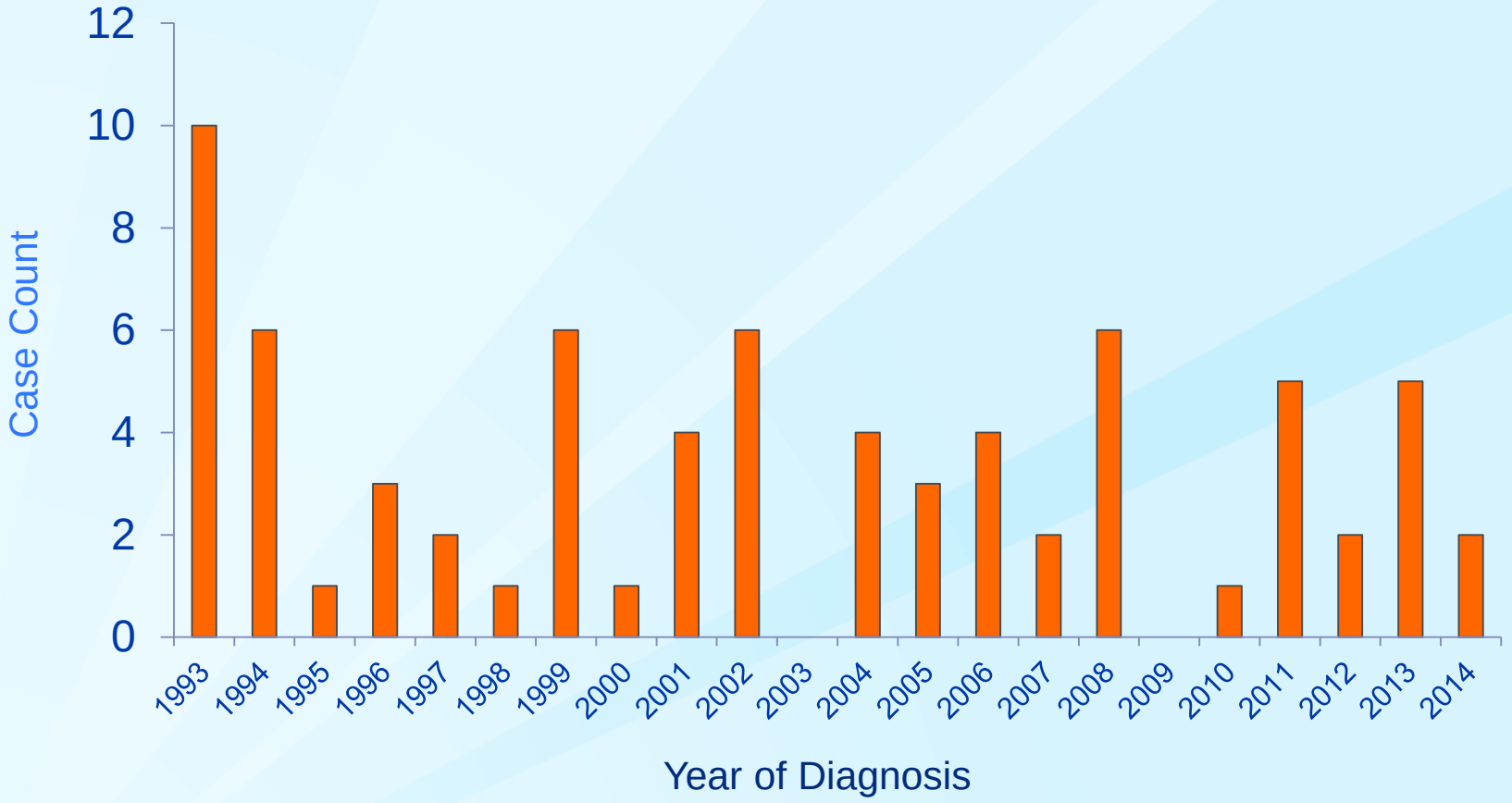
Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2014*



*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

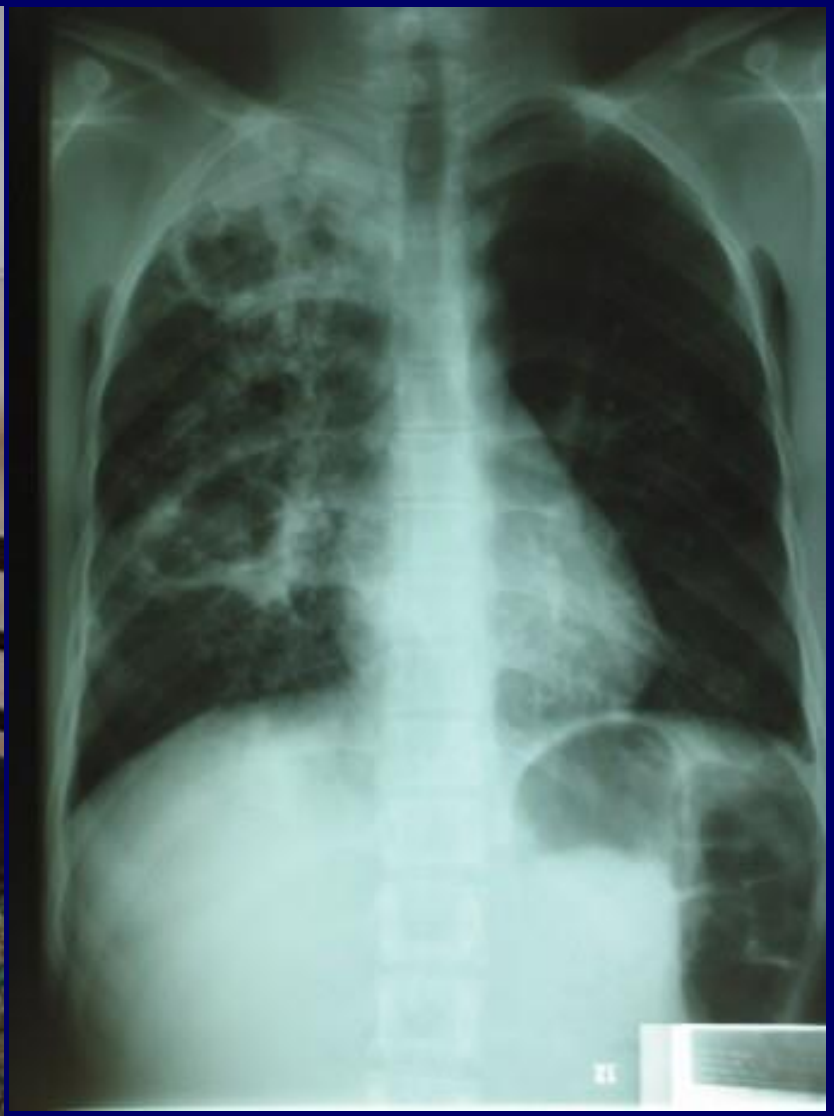
XDR TB Case Count Defined on Initial DST* by Year, 1993 – 2014**



* Drug susceptibility test.

** Updated as of June 5, 2015.

Note: Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.



Which Patients are at Risk of Drug Resistant TB?

- Birth/ residence in country with high incidence of drug resistant TB
- U.S. residents who travel to high risk areas
- Exposure to patient with relapse or failure

- Prior treatment for TB
- Treatment failure
- Relapse in a patient not on DOT
- Poor adherence
- Clinical deterioration during 4 drug therapy

Why Do We Have Drug Resistance?

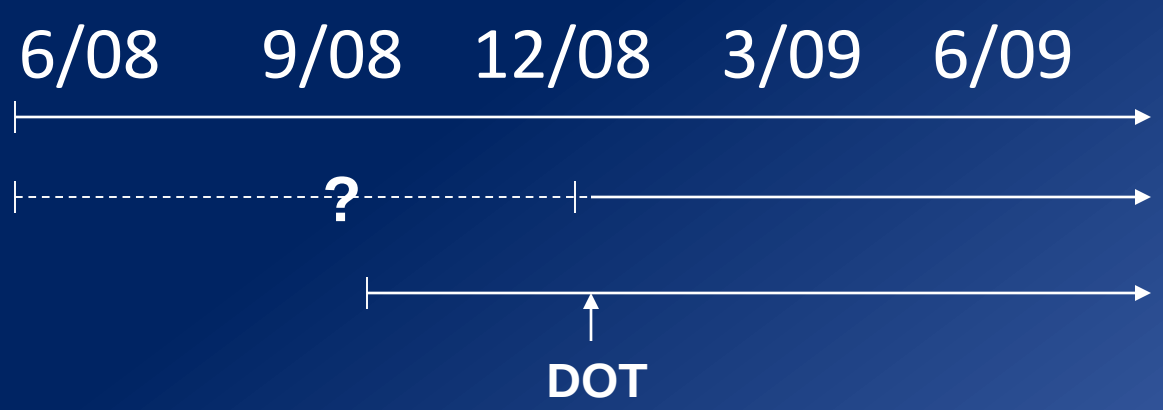
- Inadequate treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence

Transmission of Drug-Resistant TB

- Transmitted same way as drug-susceptible TB
- Drug resistance is divided into two types
  - Primary resistance develops in persons initially infected with resistant organisms
    - Healthcare-associated transmission
    - Community transmission
  - Secondary resistance (acquired resistance) develops during TB therapy
    - Nonadherence to therapy
    - Inappropriate therapy

Emergence of Resistance
(Inappropriate Therapy)

Emergence of Resistance
(Nonadherence and Inappropriate Therapy)



	6/08	9/08	12/08	3/09	6/09
Smear	+	+	+	-	+
Culture	+	+	+	+	+
Susceptibility					
Isoniazid	S	R	R	R	
Rifampin	S	S	S	R	
Ethambutol	S	S	R	R	

Drug Resistant Mutants Selected by:

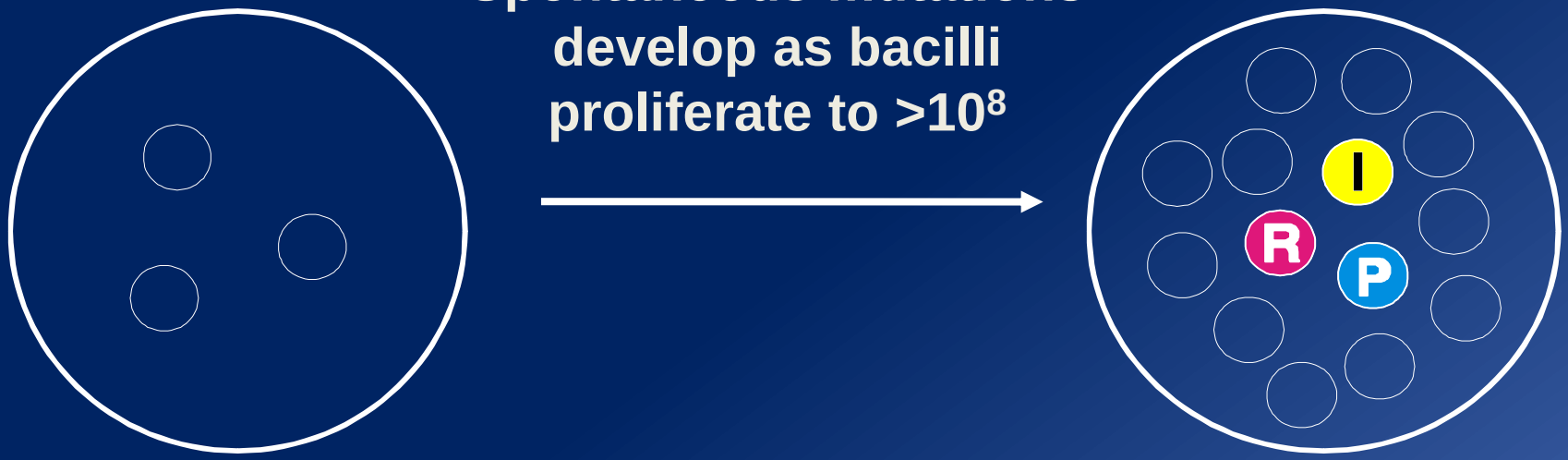
- Non-adherence
- Malabsorption
- Inadequate drug regimen

Rates of Natural Resistance in *M. tuberculosis*

- Isoniazid 1 in 10^6
- Rifampin 1 in 10^8
- Ethambutol 1 in 10^6
- Streptomycin 1 in 10^5
- INH & RIF 1 in 10^{14}

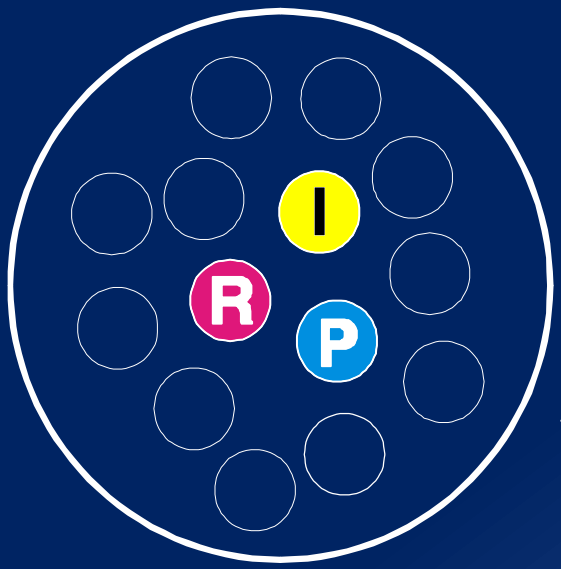
Number of organisms in a TB cavity = 10^9-10^{11}

Pathogenesis of Drug Resistance



Drug	Mutation Rate
Rifampin	10^{-8}
Isoniazid	10^{-6}
Pyrazinamide	10^{-6}

Drug-resistant mutants in large bacterial population

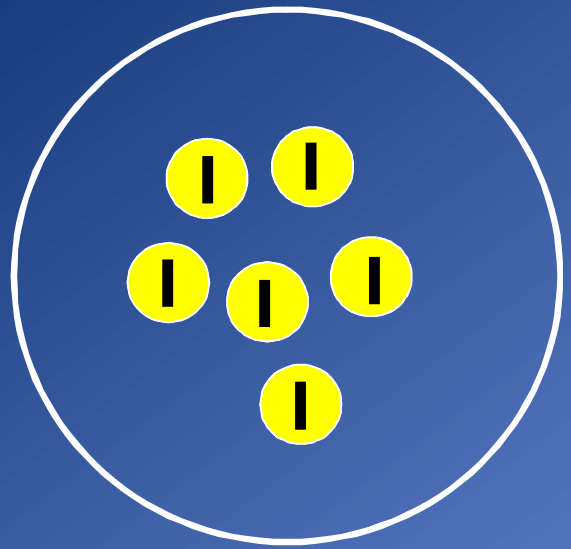


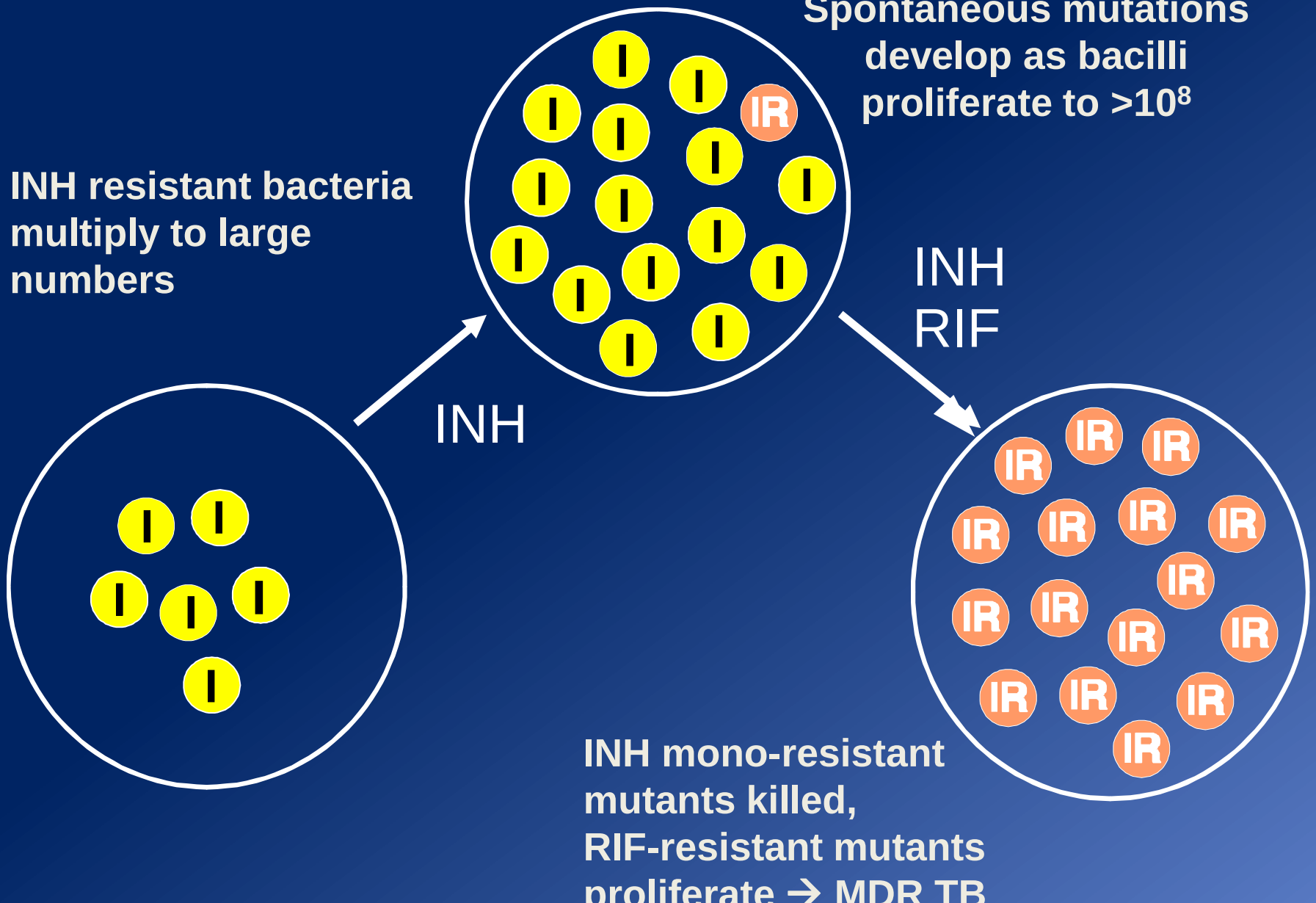
INH
RIF
PZA

Multidrug therapy:
No bacteria resistant to all 3 drugs

INH

Monotherapy:
INH-resistant bacteria proliferate




Spontaneous mutations develop as bacilli proliferate to >10^8
INH resistant bacteria multiply to large numbers
INH
INH
RIF
IR
INH mono-resistant mutants killed, RIF-resistant mutants proliferate → MDR TB

What Do Patients with MDRTB Need?

- Patients with MDR TB need to have
  - Accurate and prompt identification
  - Notification to the field staff and provider(s)
  - Appropriate case management
  - Appropriate treatment based on drug susceptibility test results
  - Appropriate infection control measures instituted

Treatment Strategies

Standardized treatment	Regimen is designed based on Drug Resistance Surveillance (DRS) data from a representative patient population
Empirical treatment	Regimen is individually designed based on patient's previous history of TB treatment and DRS data as above
Individualized treatment	Regimen is designed based on the patient's previous history of TB treatment and individual DST results

Antituberculosis Drugs

First-Line Drugs

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

Second-Line Drugs

- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*/Moxifloxacin*

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* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB

Drug Activity Against TB
Bactericidal vs. Bacteriostatic

Bactericidal

- INH
- Rifampin
- Streptomycin
- Capreomycin
- Kanamycin/Amikacin
- Moxifloxacin

Bacteriostatic

- PZA
- Ethambutol
- Levofloxacin *(may be bactericidal)*
- Ethionamide
- PAS
- Cycloserine

Third-Line Drugs Used in MDR TB Treatment

- Linezolid
  - Used since 2000 in selected cases
    - More recently a 2nd or 3rd line drug
  - Adverse effects of pancytopenia and peripheral/optic neuritis
    - May or may not be reversible
    - May or may not be ameliorated by vitamin B_6
    - Consider using 600 mg daily (300mg/day being studied)
  - Use with caution with selective serotonin reuptake inhibitors (SSRIs)
  - Lactic acidosis
  - Expensive

Third-Line Drugs Used in MDR TB Treatment -2

- Clofazimine
  - More commonly used in patients with leprosy
  - Used in selected cases
  - Needs Investigational New Device (IND) from FDA

- Bedaquiline
  - 1st new class of TB medication approved since RIF
  - New class of antibiotics, diarylquinolones
  - Given as part of MDR combination therapy
  - New mechanism of action: inhibits ATP synthase

Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available

PLUS

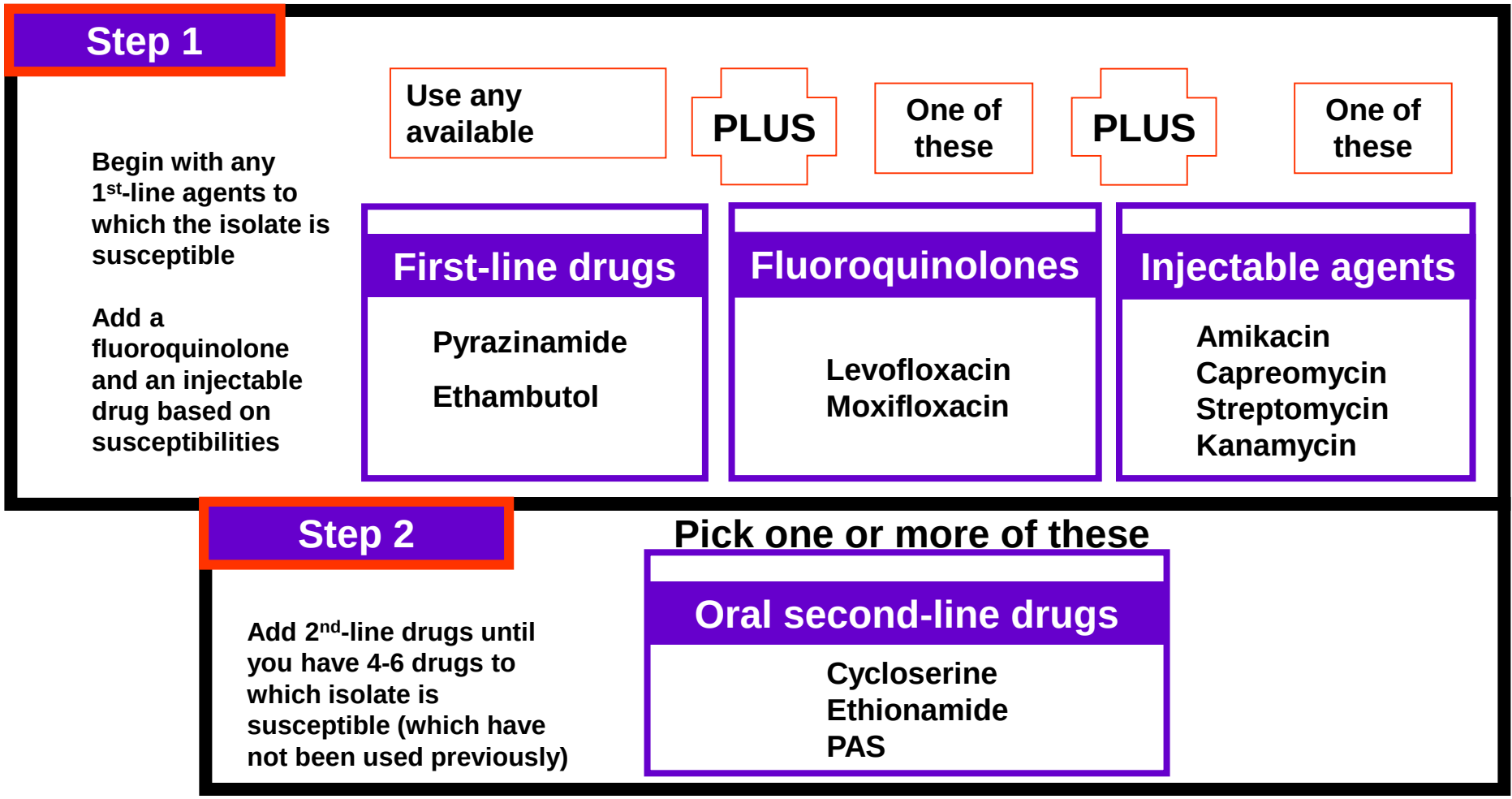
One of these

PLUS

One of these

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide Ethambutol	Levofloxacin Moxifloxacin	Amikacin Capreomycin Streptomycin Kanamycin

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center



Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center

Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs

Pyrazinamide

Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin

Injectable agents

Amikacin
Capreomycin
Streptomycin
Kanamycin

Step 2

Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second-line drugs

Cycloserine
Ethionamide
PAS

Step 3

If there are not 4-6 drugs available consider 3rd-line in consult with MDRTB experts

Consider use of these

Third-line drugs

Linezolid Clofazimine Bedaquiline
High-dose isoniziad Macrolides
Imipenem Amoxicillin/Clavulanate

Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center

Principles for Managing MDR TB

- MDR TB should never be treated without expert consultation of a specialist in MDR TB treatment
- Patients must be treated with a regimen of at least 3-5 anti-TB medications to which the strain is likely to be susceptible (4-6 or better)

Principles for Managing MDR TB - 2

- A single new drug should never be added to a failing regimen
- When initiating or revising therapy, always attempt to use at least 3 previously unused drugs to which there is *in vitro* susceptibility
  - One agent should be an injectable agent
  - A good response does not justify continuation of an inadequate regimen

Principles for Managing MDR TB - 3

- Injectable agents can be given 5 days/wk initially
  - After culture conversion, dosing can be 2-3x/wk
- With extensive disease or slow conversion of sputum cultures, the injectable should be used for longer periods after culture conversion
- Capreomycin is the initial injectable agent of choice
- Surgery should be considered if a patient's cultures fail to convert to negative after 4 months of appropriate treatment

Principles for Managing MDR TB - 4

- Some experts use EMB at a dose of 25 mg/kg daily when used as treatment of patients with MDR TB
  - If this higher dose is used, monthly visual monitoring is recommended
- Fluoroquinolones:
  - Oral agents, well tolerated
  - One of the two most important agents in MDR treatment

Specific Drug Resistances

- If isolates show resistance to INH only at a low concentration, INH 900 BIW (high intermittent dose) can be used
  - Do not rely on its effectiveness as a main agent
- There is cross-resistance between amikacin and kanamycin
- Determination of resistance to PZA is problematic, but is uncommon in the absence of resistance to other 1st-line drugs
  - If monoresistance to PZA is found, consider the specimen may be *M. bovis*, not *M. tb*

Rifampin Resistance

- Resistance to RIF is generally associated with cross-resistance to rifabutin and rifapentine
  - When RIF resistance is present but *in vitro* sensitivity to rifabutin is reported, treatment should still be the same as if RIF-resistant
- For all with RIF-resistance (mono-RIF or MDR TB), consider extended therapy (up to 24 months)if:
  - There is cavitary or extensive disease
  - The patient is HIV-positive or has risk factors for HIV infection
  - The patient is immunosuppressed
  - Time to culture conversion is prolonged

Treatment of HIV-related MDR-TB

- Rapid diagnosis of drug resistance
- Important to treat with the most active anti-TB regimen available
- Initiate antiretroviral therapy based on CD_4 count and other individual patient variables
- Use therapeutic drug monitoring when drug interactions are possible or malabsorption is suspected

MDR TB in Pregnancy

- Most medications used to treat MDR TB are known to cause fetal abnormalities or have not been studied adequately regarding their safety in pregnancy
- PZA can be used as a main agent and is recommended by WHO & ATS
  - WHO recommends its use in pregnancy even for drug-susceptible TB patients
  - In the U.S., it is considered a category C agent

Monitoring Serum Drug Levels

- Serum drug level monitoring can be used in patients with the following medical conditions:
  - HIV positive/AIDS
  - Diabetes
  - Malabsorption syndromes
  - Renal failure
  - Failure to improve on treatment/relapse
  - MDR TB

Drug Intolerance

- In general, length of treatment for patients with drug intolerance is the same as for those who have drug resistance

DOT for MDR TB

- Essential that MDR TB patients be treated with Directly Observed Therapy (DOT)
  - Improved overall cure rates
  - Reduction in community prevalence of MDR
- Intermittent regimens should not be used
- All 2nd-line agents must be administered daily
- Twice/day DOT should be used when feasible, and more frequent dosing than twice daily should be avoided
- All doses must be observed

DOT: Effect on Resistance and Relapse

	Self-RX N=407 (pre 1987)	**DOT** N=581 (1987 +)
Primary R	13%	6.7%
Secondary R	10.3%	1.4%
Relapse	20.9%	5.5%
MDR relapse	6.1%	0.9%

*** P < 0.001**

Source: Weis, NEJM 1994; 330, 1179

New Treatments for MDR TB

- Bedaquiline (Janssen)
- OPC-67683: Delamanid (Otsuka)
- PA 824 (nitroimidazol-oxazine)
- Linezolid
  - NIH and TBTC studies in progress
  - Already in wide use globally

Linezolid for TB

- Used as second and third line treatment for MDRTB
- Has adverse effects:
  - affects the bone marrow
  - peripheral neuropathy
  - optic neuropathy
  - hepatic dysfunction
  - muscle injury

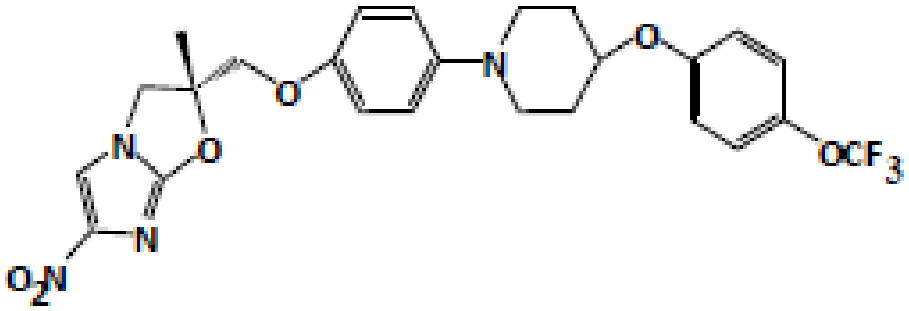
Pts had improved survival with the lower dose of 300mg/day instead of 600mg/day

Bedaquiline (SIRTURO™)
TMC207

- First new TB drug since RIF (1970)
- New class of potent anti-TB drugs: diarylquinolones
  - Accumulates in the body by binding to phospholipids
- Used as part of combination therapy for pulmonary MDR TB in adults (>18 yrs)
- Administered under DOT
- New mechanism of action: inhibits mycobacterial adenosine triphosphate (ATP)-synthase
  - BDQ binds to ATP-synthase, the main energy source for *M. tb* growth
  - Prevents it from supplying energy for the cell, therefore killing the bacterium

Chemical Structure of OPC-67683

Delaminid



OPC-67683 : (*R*)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy) piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole

Delamanid (OPC-67683)

- New mechanism: inhibits cell wall of TB but exact mode of action unclear
- Given along with background MDR regimen
  - Both regimens had sputum culture conversion at 2 months
- Mild adverse effects
- Had prolongation of the QT intervals
- Nov. 2013: European Medicines Agency (EMA) recommended conditional approval
  - Likely effective in treating drug resistant TB over 6 months as it had in the 2 month study
  - Additional studies required for data on long-term benefits and safety - Phase III trials currently underway with data expected within next 3 years

Standard MDR-TB regimens currently recommended by WHO

- Intensive phase of 8 months treatment using at least 4 second line drugs with proven effectiveness plus PZA
  - Total treatment of 20 months
  - Recommendation on duration of treatment is subject to adaptation based on patient response to treatment

http://www.who.int/tb/challenges/mdr/short_regimen_use/en/

Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update. (WHO/HTM/TB/2011.6). Geneva, World Health Organization. 2011.

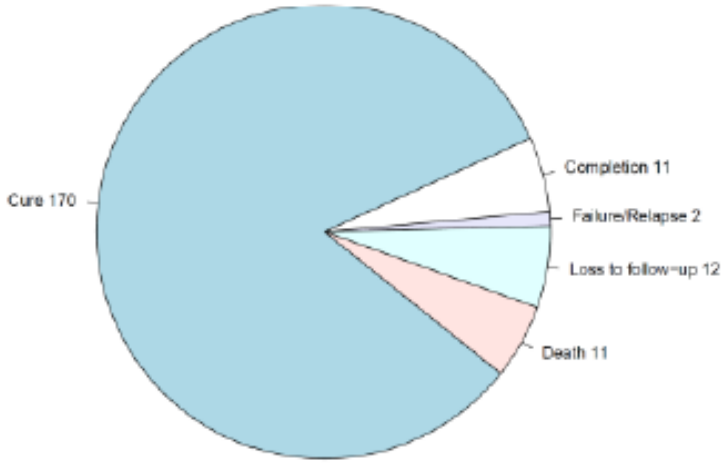
Shorter Regimens for MDR TB

- Shorter regimens for MDR TB:
  - Typically last 9-12 months (differs from standard WHO recommended 20 month MDR TB regimen)
  - Less costly and likely to be better tolerated by patients
  - Evidence on their use reported in Bangladesh with success rates comparable to those for treatment of drug-susceptible TB
  - Being introduced by National TB Programs in African countries (Benin, Cameroon, Central African Republic, Cote d'Ivoire, DR Congo, Niger, Swaziland)

Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

Completion 5.3%
Cure 82.5%
Death 5.35
Default 5.8%
Failure 0.5%
Relapse 0.5%



Km=kanamycin; Cfz=clofazimine; Gfx=gatifloxacin; E=ethambutol; H=high-dose isoniazid; Z=pyrazinamide; Pto=prothionamide

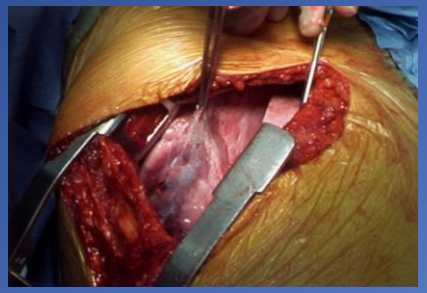
Source: van Deun A et al (2010); Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 182(5):684–92.

STREAM: standardized treatment regimen of Anti-TB drugs for patients with MDR TB

- Trial is currently taking place in Ethiopia, South Africa and Vietnam, India
- Plan to recruit at least 400 patients with MDR-TB
- High dose Fluoroquinolones and clofazimine with a 7 drug regimen for 9 months:
  - Moxi, colfazimine, ethambutol and PZA for 9 months, with supplemental prothionamide, kanamycin and INH during the 4 month intensive phase
- The trial is expected to run for 2 years, with results available in 2016

Indications for Surgery - 1

- Adequate 1st and 2nd -line regimens of anti-TB medications have failed to cure or cause *M. tb* cultures to convert to negative within 4 to 6 months
- Sufficient medications are available to treat the patient postoperatively
- Disease is sufficiently localized to allow lobectomy or pneumonectomy
- Remaining lung tissue is relatively free of disease
- Acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection



Indications for Surgery - 2

- Additional possible indications for surgery:
  - ✓Major bronchial obstruction
  - ✓Severe hemoptysis
  - ✓Bronchopleural fistula (BPF)

Surgery for MDR TB Patients

- Even after lung resection, the patient must complete a full course of treatment (i.e., 18-24 months after culture conversion) with medications to which the *M.tb* strain is susceptible
- If patient is culture negative after surgery, then surgery is considered the conversion episode

Follow-up of MDR TB Patients after Treatment Completion

- Patients with TB resistant to INH and RIF or treated without RIF/RBT
  - Medical evaluation every 4 months during the 1st year after treatment completion
  - Then every 6 months during the 2nd year
- Months: 4, 8, 12, 18, 24 post treatment
- Educate about relapse and to return if they develop symptoms

Treatment of Contacts to Drug Resistant TB

- Persons exposed to INH-resistant TB:
  - Rifampin:
    - 4 months adults
    - 6 months children
- Persons likely infected with MDR TB:
  - 6-12 months PZA and EMB, or PZA and FQ (i.e., ≥ 2 drugs to which organism is susceptible)
    - Limited experience with FQ as single agent

Principles of Treatment in MDR TB Contacts

- Always exclude active TB disease before considering LTBI treatment
  - *Evaluate all exposed contacts to identify all active cases and prevent further transmission*
- Estimate likelihood of infection with an MDR TB strain
- Consider the risk of progression to active TB disease
  - HIV testing and counseling

Principles of Treatment in MDR TB Contacts

- Tailor LTBI treatment to individual case
  - Regimen should contain 1 to 2 drugs to which source case isolate is susceptible
  - Immunosuppressed individuals should not be treated with monotherapy
- Remember:
  - Efficacy of the regimen largely dependent on adherence and completion of therapy
  - Education of patients is important – adverse effects and importance of adherence

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Reprinted from
MORBIDITY AND MORTALITY WEEKLY REPORT
Recommendations and Reports
June 19, 1992 / Vol. 41 / No. RR-11

CDC
CENTERS FOR DISEASE CONTROL

Management of Persons Exposed to Multidrug-Resistant Tuberculosis

Potential Drug Regimens: Drug-Resistant Tuberculosis

Resistance Pattern	LTBI Treatment Options
INH	Adults: RIF 4 months; Children: RIF 6 months
INH, RIF	PZA/EMB or Fluoroquinolone +/- EMB or PZA
INH, RIF, EMB	Fluoroquinolone +/- PZA
INH, RIF, PZA	Fluoroquinolone +/- EMB
INH, RIF, PZA, EMB	Fluoroquinolone +/- Ethionamide*
INH, RIF, PZA, EMB, injectable	Fluoroquinolone +/- Ethionamide*
INH, RIF, PZA, EMB, injectable, ethionamide	Fluoroquinolone +/- Cycloserine
INH, RIF, PZA, EMB, fluoroquinolone	Cycloserine/PAS or PAS/Ethionamide or Ethionamide/Cycloserine

*Better tolerated in children than in adults.

**Taken from Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Second Edition*

Resources

- **CureTB**: Binational TB Referral Program for TB patients and their contacts who travel between the United States and Mexico
  http://www.curetb.org/
- **TBNet**: A multi-national TB patient tracking and referral project designed to work with mobile, underserved populations
  http://www.migrantclinician.org/network/tbnet
- **National Jewish Medical Center**
  http://www.njc.org/disease-info/diseases/tb/index.aspx

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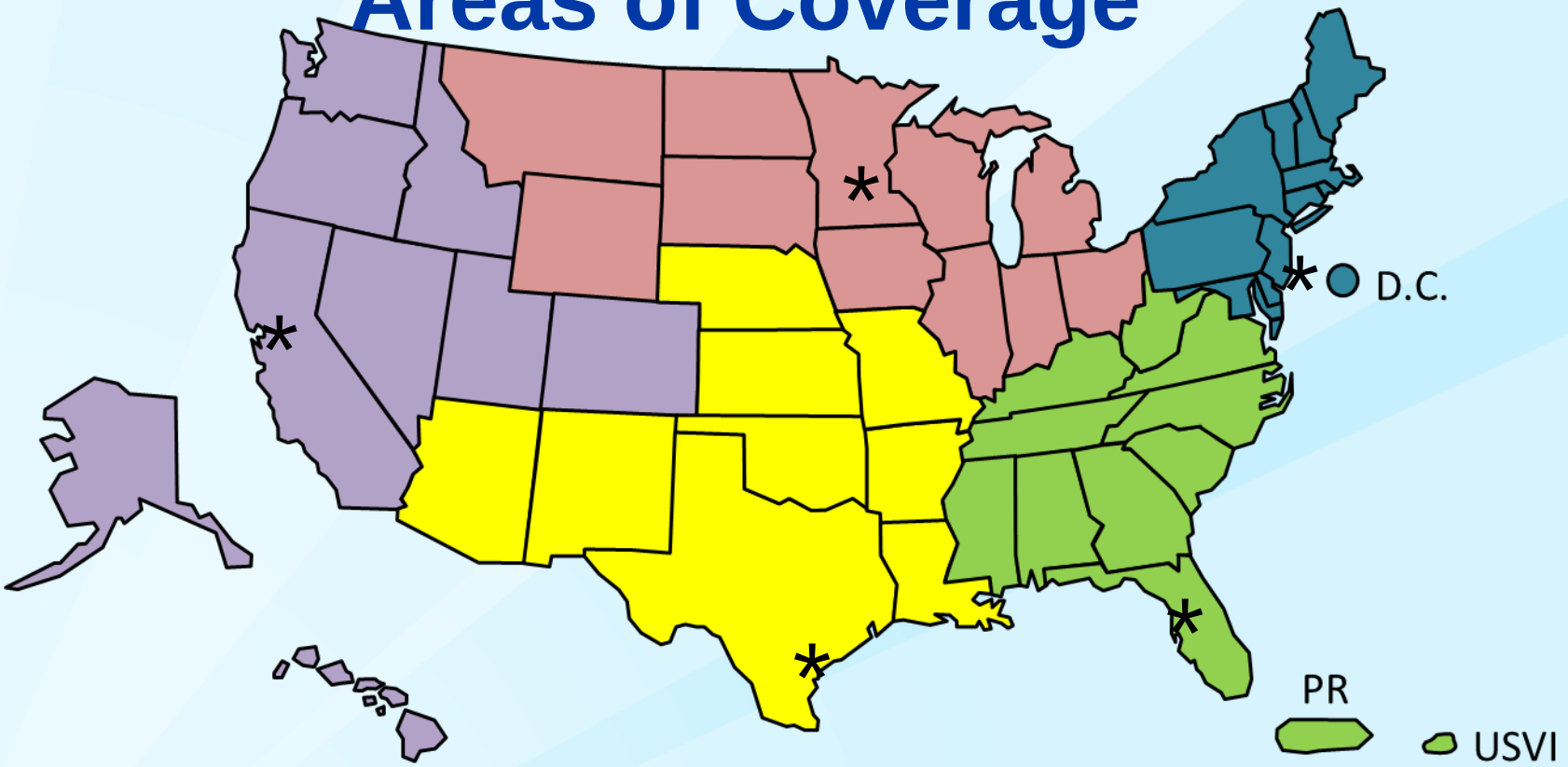
TB RTMCCs, 2013-2017
Areas of Coverage



Curry International Tuberculosis Center

Heartland National Tuberculosis Center

Mayo Clinic Center for Tuberculosis

Southeastern National Tuberculosis Center

New Jersey Medical School Global Tuberculosis Institute

* Center Location

Resources

- MDR-TB Service
  - Provides clinical consultation, case management, CI assistance
- CA Microbial Diseases Lab
  - Provides MBs for drug resistance; phenotypic DST for first-line drugs and Amikacin, Levofloxacin, Capreomycin, and Ethionamide; genotyping

Acknowledgements

- CDC
- MDR TB experts at the Regional Training and Medical Consultation Centers
- WHO


MDR/XDR

Case # 1

- 35-year-old male with chronic cough x 6 months
- Diagnosed with TB in Mexico and treated with a standard four drug treatment regimen 1/97-7/97, but continued to be smear-positive in 1998
- Extensive TB treatment history and history of non-compliance with medications between 10/98-3/00
- Instituto Nacional de Enfermedades Respiratorias (INER) in Mexico City was consulted 3/00 and patient was placed on ethionamide, dapsone, RIF, PZA, and kanamycin from 3/3/00 to 2/01

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Case # 1

- 10/00 the patient had a positive smear and culture and susceptibility testing reported 2/01 showed resistance to INH, PZA, and EMB
- Treatment regimen was changed to RIF 600 mg po qd, ethionamide 500 mg po qd, clofazimine 100 mg po qd, streptomycin 1 gram IM QD, erythromycin 300 mg po qd
- Had a positive smear 5/15/03 and was treated with INH/EMB (75mg/400mg) po TID, erythromycin 300 mg po TID, (tionitrozona) thiocetazone 150 mg po qd, PZA 500 mg po TID
- Returned 9/19/03 and was found to be 5 + smear-positive; emigrated to the U.S. 11/03

Case # 1

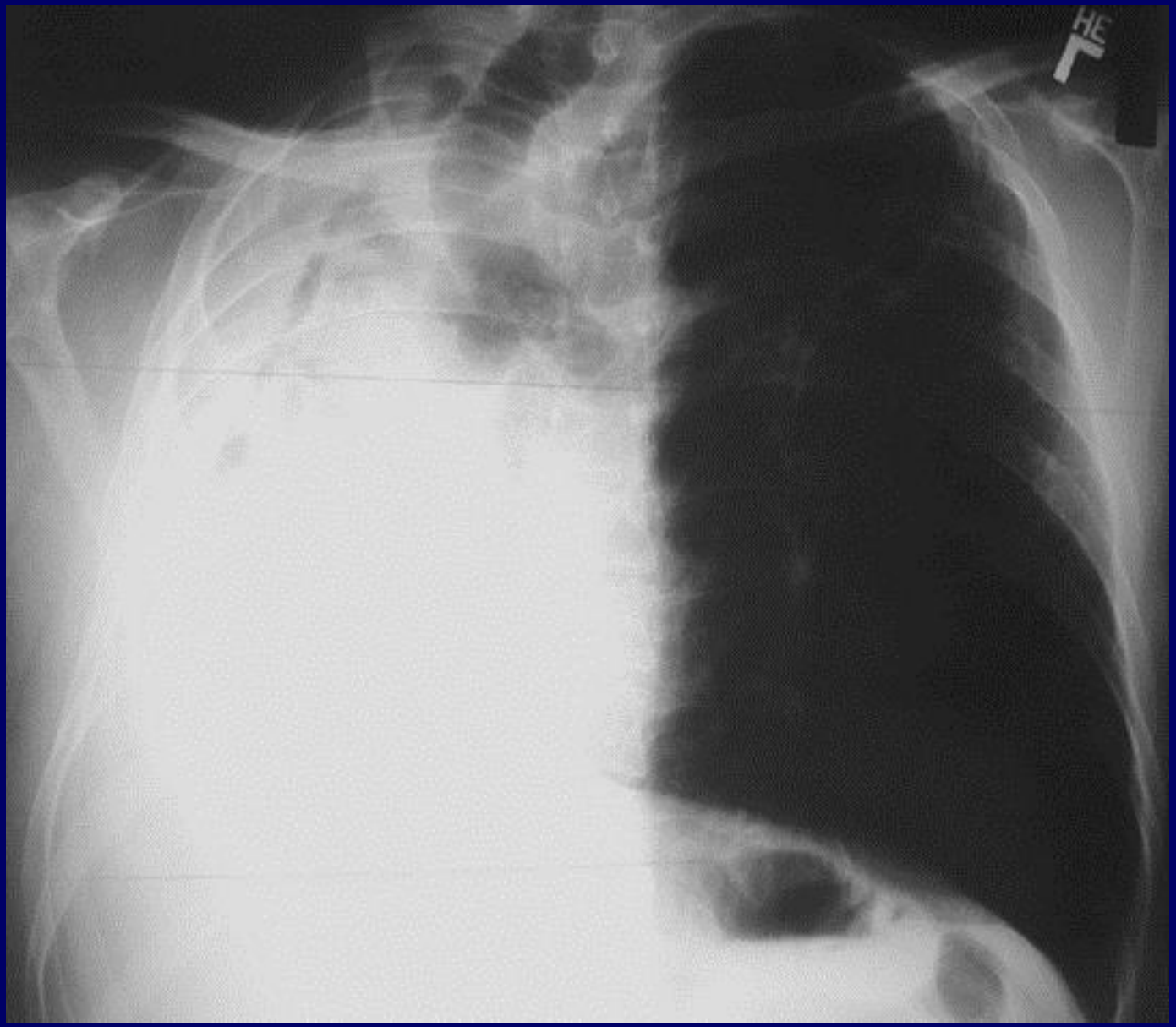
- Found to be TST negative at a clinic in the U.S. 12/03 and he discontinued the last TB regimen which was prescribed in Mexico

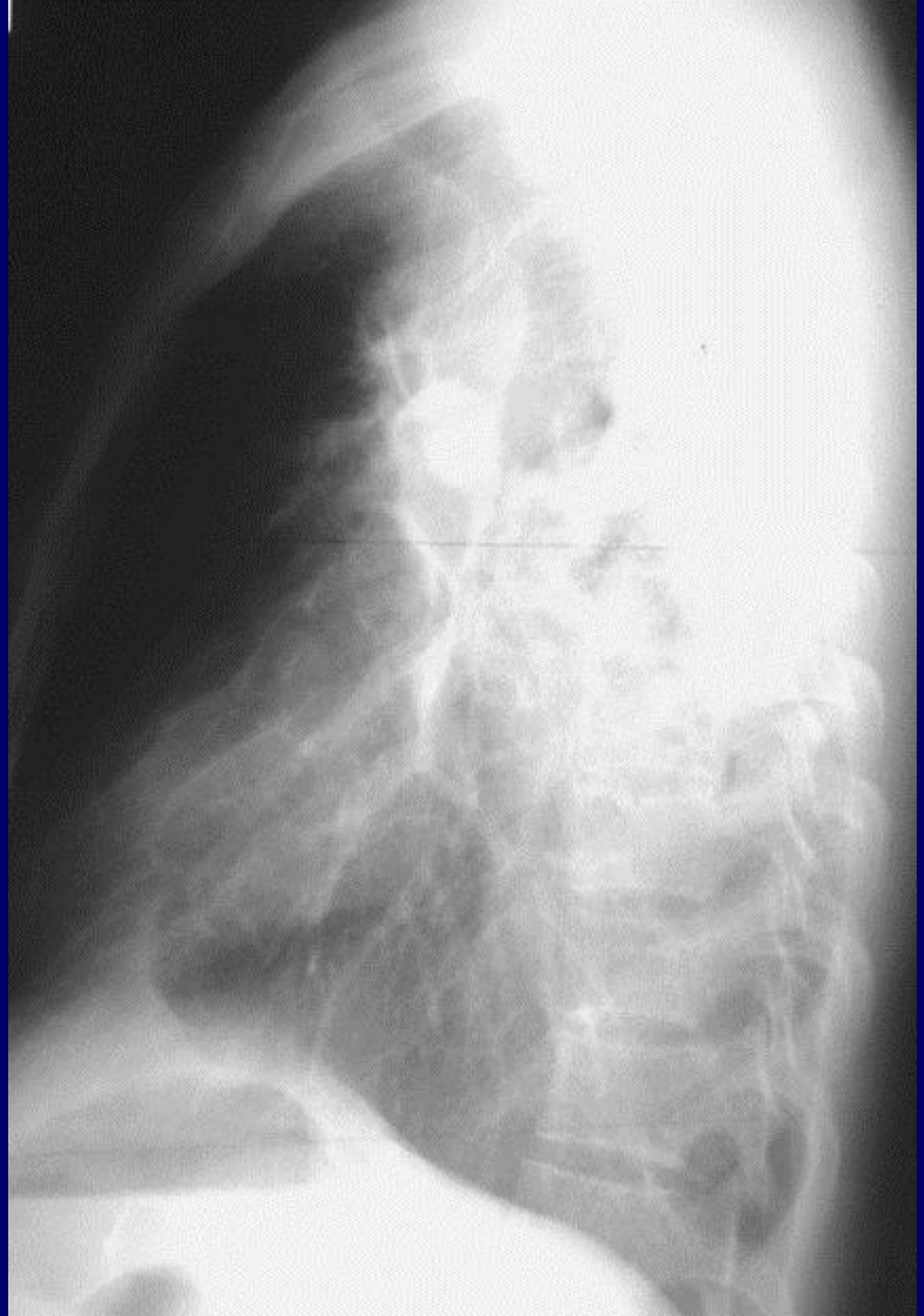
Next steps

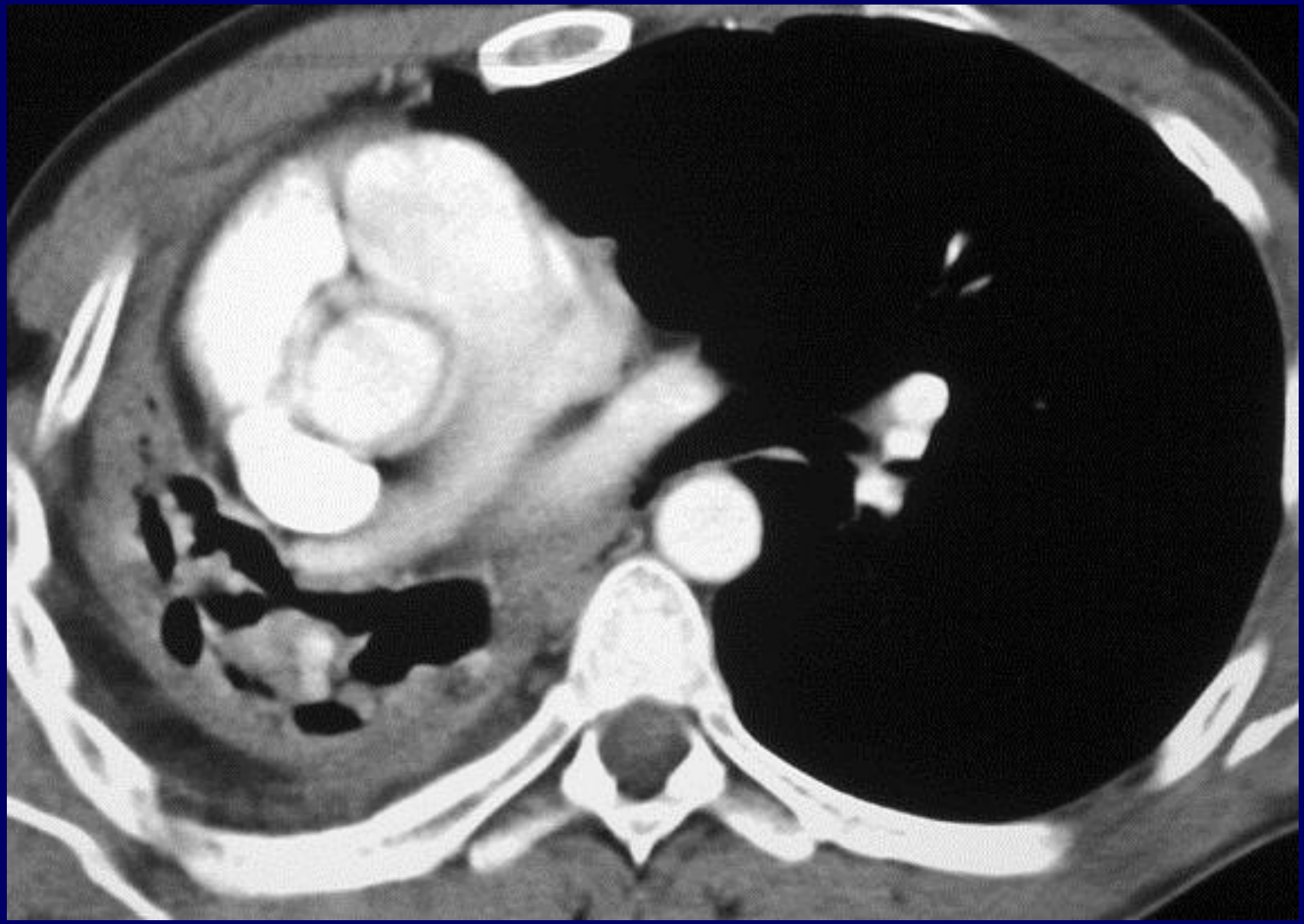
- Tell patient that he does not have TB
- Obtain QFT
- Take a good history, perform symptom review, CXR
- Take a good history, perform symptom review, CXR and obtain sputa for AFB smear and cx x 3

Case # 1

- Evaluated for chronic cough in LHD clinic in 3/04
- CXR obtained







Case # 1

- Found to have 4+ smear-positive, cavitary TB, hospitalized and placed in isolation
- Started initially on INH 300 mg po qd, RIF 600 mg po qd, EMB 1200 mg po qd, PZA 1000 mg po qd, and ethionamide 750 mg po qd on 3/4/04
- MDR-TB service consultation 4/01/04 because patient was on surgery schedule for right pneumonectomy

Recommendations?

- Advise immediate pneumonectomy
- Advise OR staff to wear N95 respirators and proceed with immediate pneumonectomy
- Advise a delay in surgery
- Wait until smear conversion and then proceed with pneumonectomy
- Wait until smear and culture conversion and then proceed with pneumonectomy

Case # 1

- Surgery delayed
- Patient placed empirically (based on treatment history) on moxifloxacin 400 mg po qd, PAS 4 grams bid, capreomycin 750 mg IM qd, cycloserine 250 mg po bid, and linezolid 600 mg po qd on 4/06/04

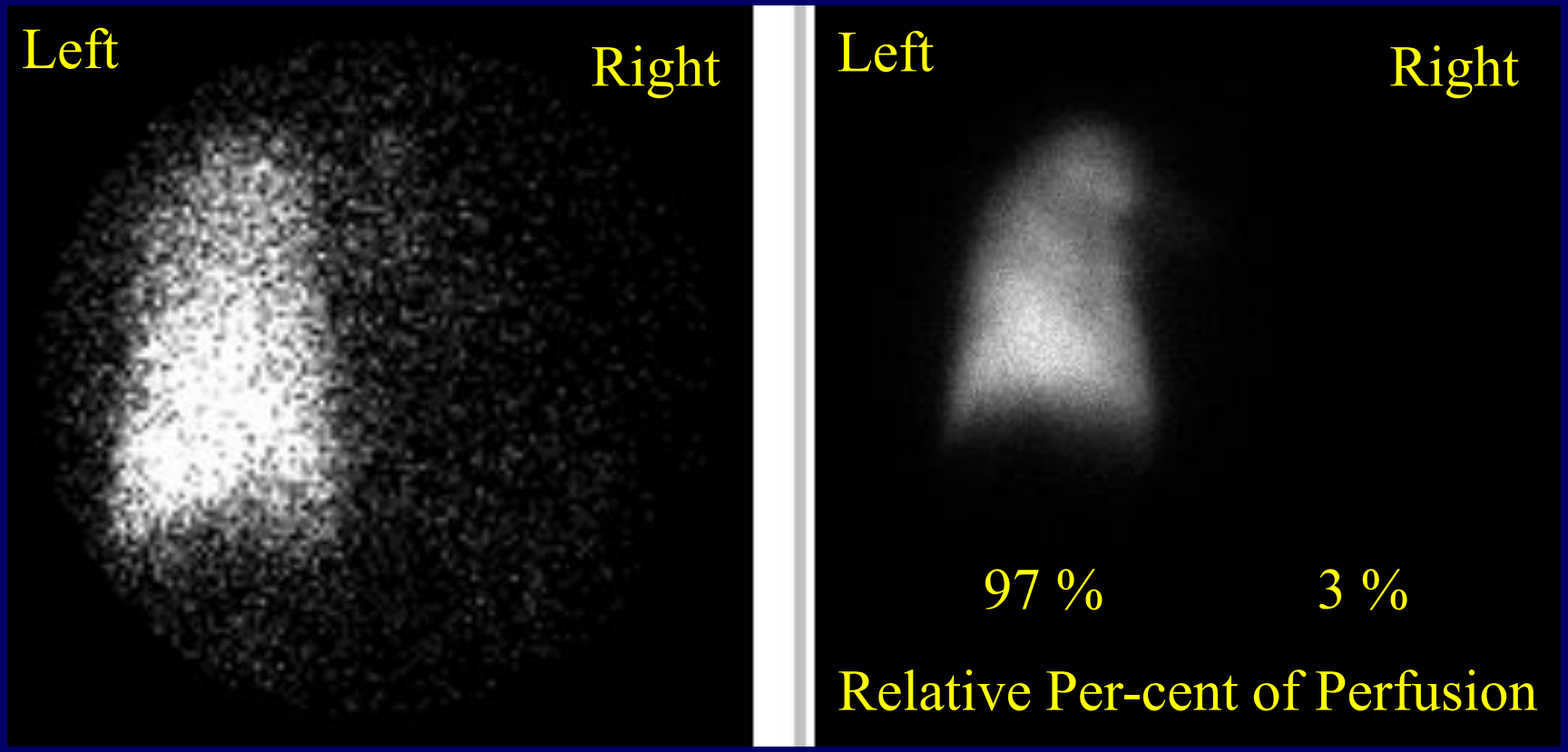
Case # 1

- Patient culture converted on 4/18/04
- Isolate found to be resistant to all first-line drugs, SM, augmentin, imipenem, clarithromycin, and clofazimine
- Smear negative 5/04
- Presented at San Francisco General Hospital (SFGH) TB case conference and felt to be a good candidate for surgery
- Transferred to SFGH Medical Center for right pneumonectomy on 7/15/04

Case # 1

- Pt feeling “better” since starting TB Rx’s in 4/04. On Directly Observed Therapy. No F/C/cough. Initially gained 12 kg 3/04 – 6/04
- Decreased bilateral hearing prior to starting TB medications (last audiogram 5/04)
- Physical Exam only notable for minimal breath sounds right base
- HIV negative. Capreomycin serum level = 48.3, cycloserine serum level = 35.6
- V/Q: near-complete absence of V&Q to R lung, 97% total to L lung. Right pneumonectomy 7/26

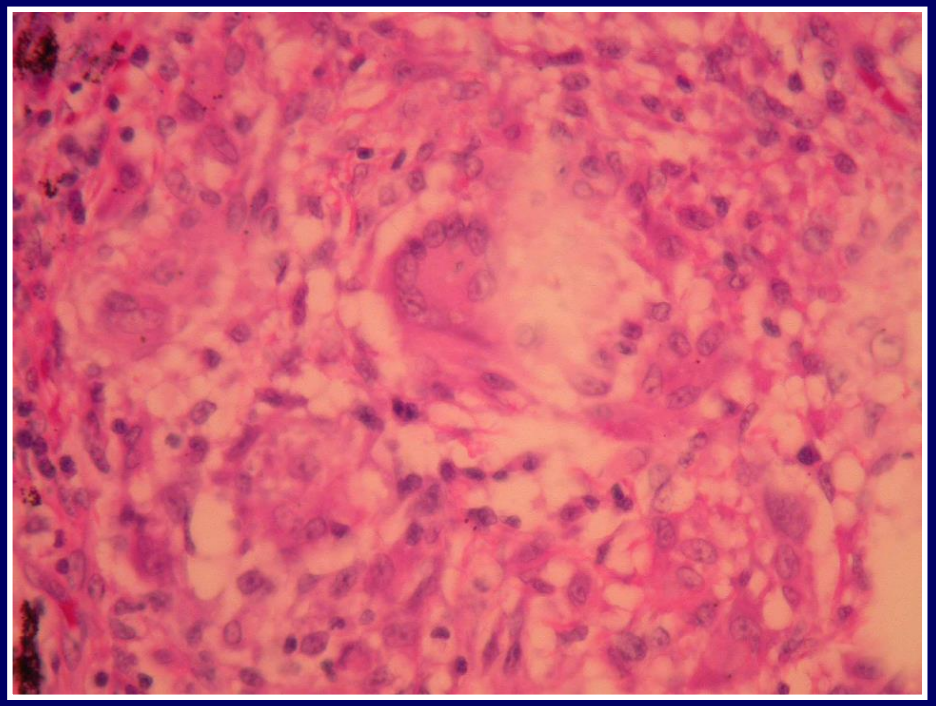
LUNG V/Q SCAN IMAGES - Posterior View

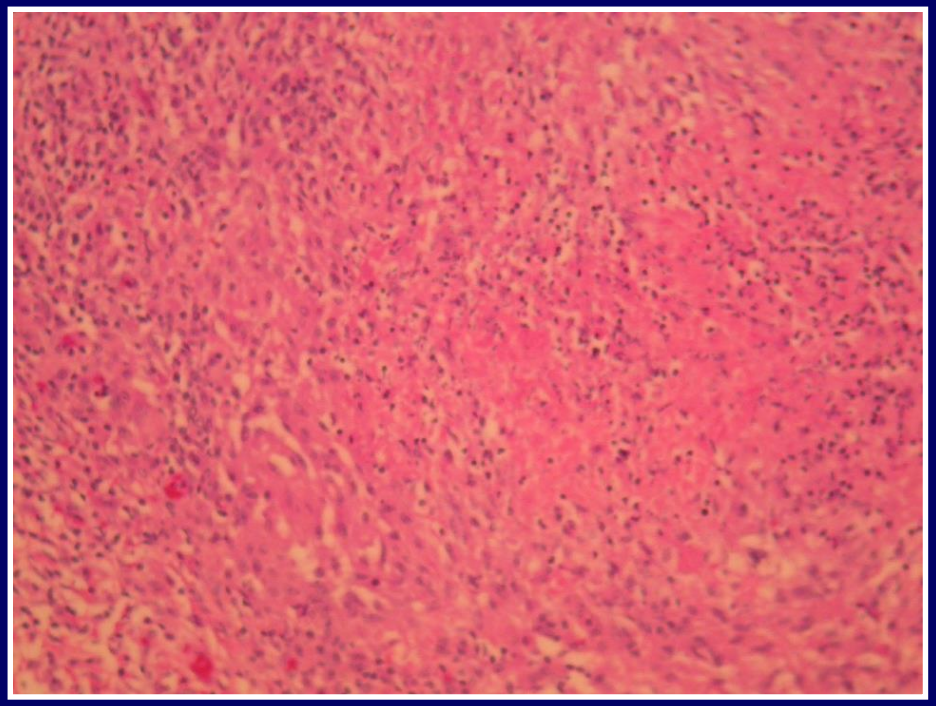


Xe-133 Ventilation Image

Tc-99m MAA Perfusion

Case # 1



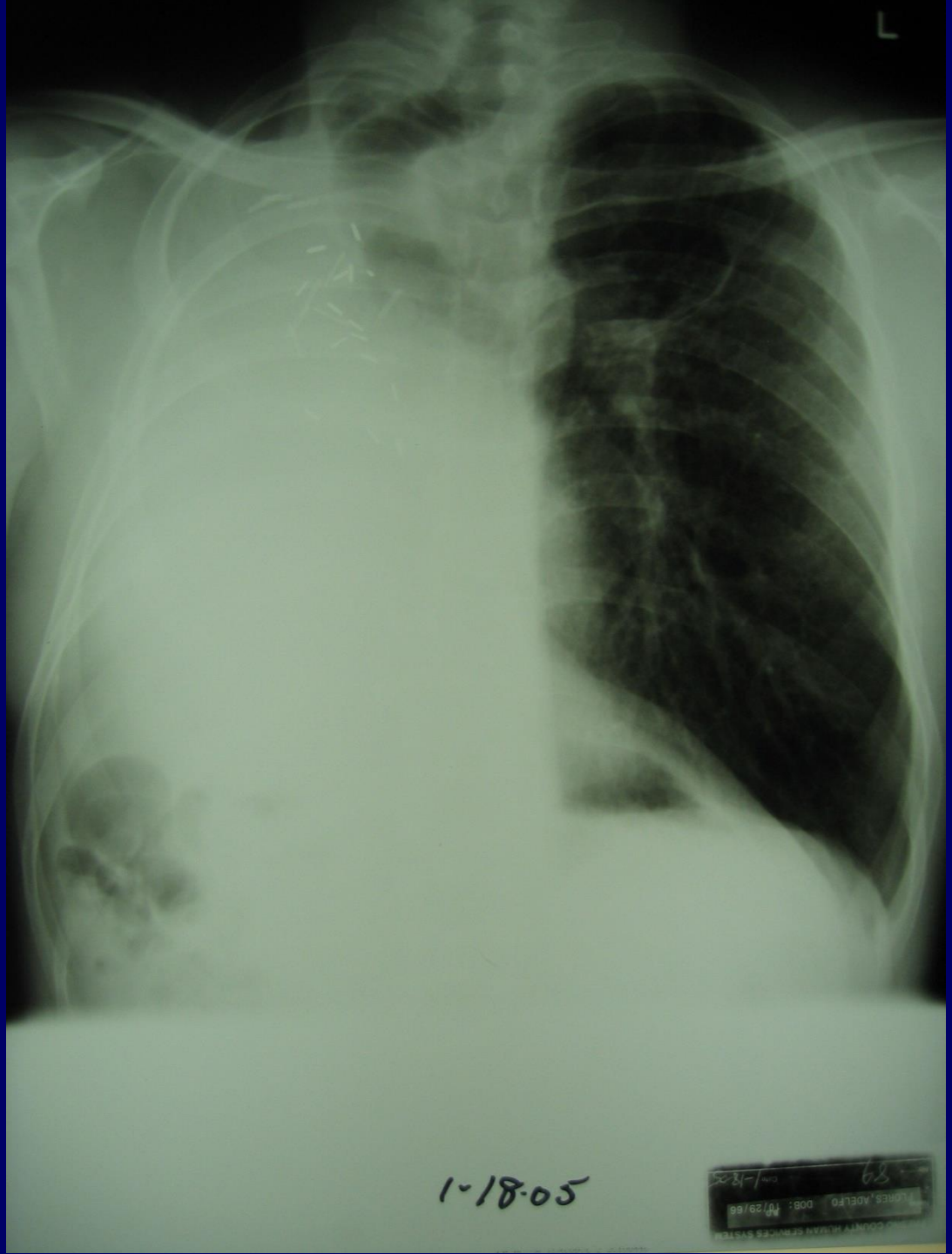


Case # 1

- The patient did very well post-operatively, ambulating with minimal pain medications
- Chest tube removed within 1 week
- Discharged to home within 2 weeks of surgery
- Doing well clinically with some weight loss post surgery (5kg)
- Continued on moxifloxacin 400 mg po qd, PAS 4 grams bid, capreomycin 750 mg IM qd, cycloserine 250 mg po bid, and linezolid 600 mg po qd on 4/06/04 all by DOT

Case # 1

- Patient is doing well with weight gain, reported to be asymptomatic, AFB smear, and culture-negative
- Capreomycin discontinued 3/29/05
- No further toxicities to medications
- Completed treatment in 2007
- Recent CXRs from 1/18/05 and 4/18/05


L
1-18-05

Preventing Acquired Drug Resistance, Case # 2

- 48 year old U.S.-born ♀, recent onset NIDDM
- Diagnosis 1/5/06 with cough, sputum, 40 lb. weight loss in another state
- 4 (+) AFB sputum, extensive bilateral disease with cavitation
- Treatment: 3 weeks “daily” IRZE given DOT M-F
  - No weekend doses

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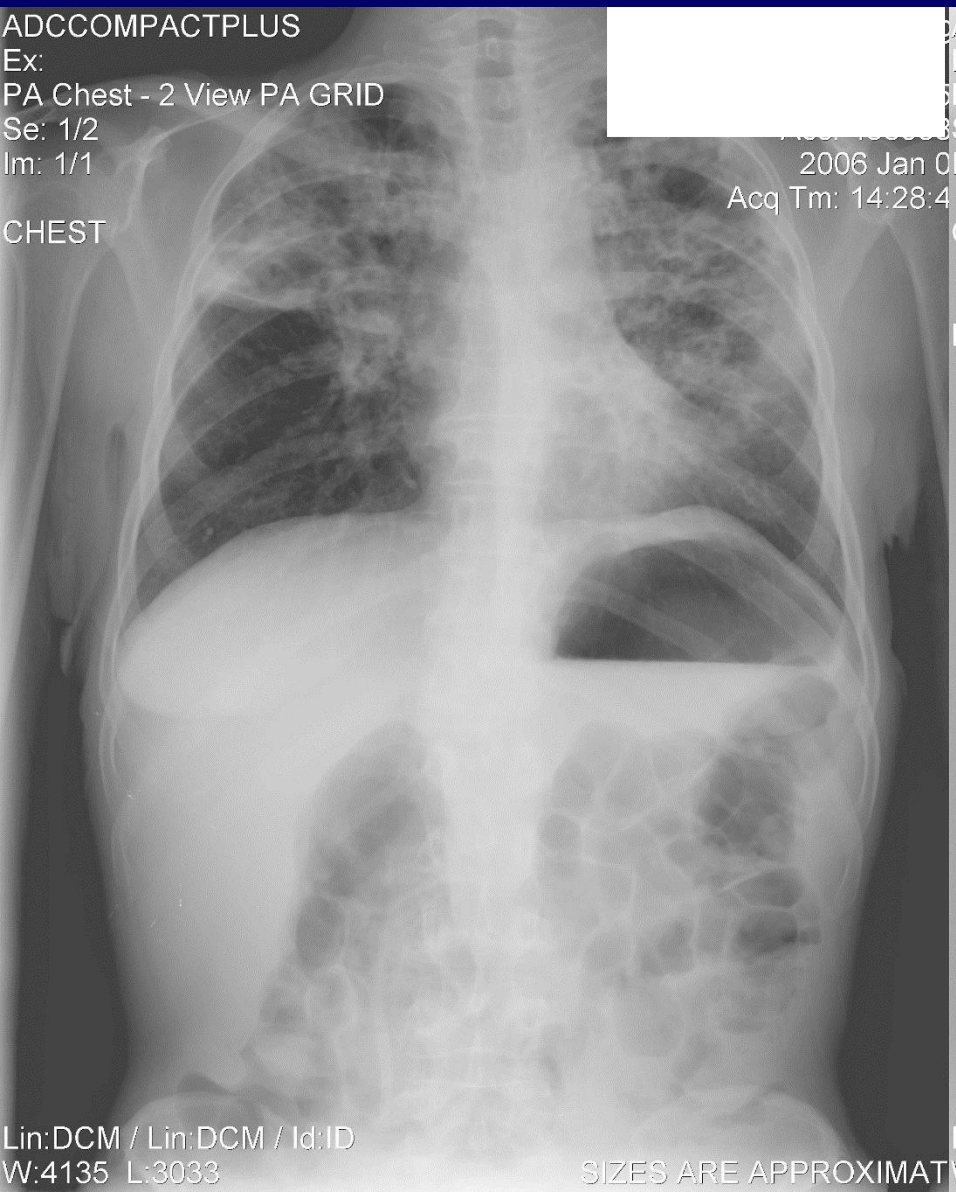
Case # 2


ADCCOMPACTPLUS
Ex:
PA Chest - 2 View PA GRID
Se: 1/2
Im: 1/1
2006 Jan 0
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CHEST
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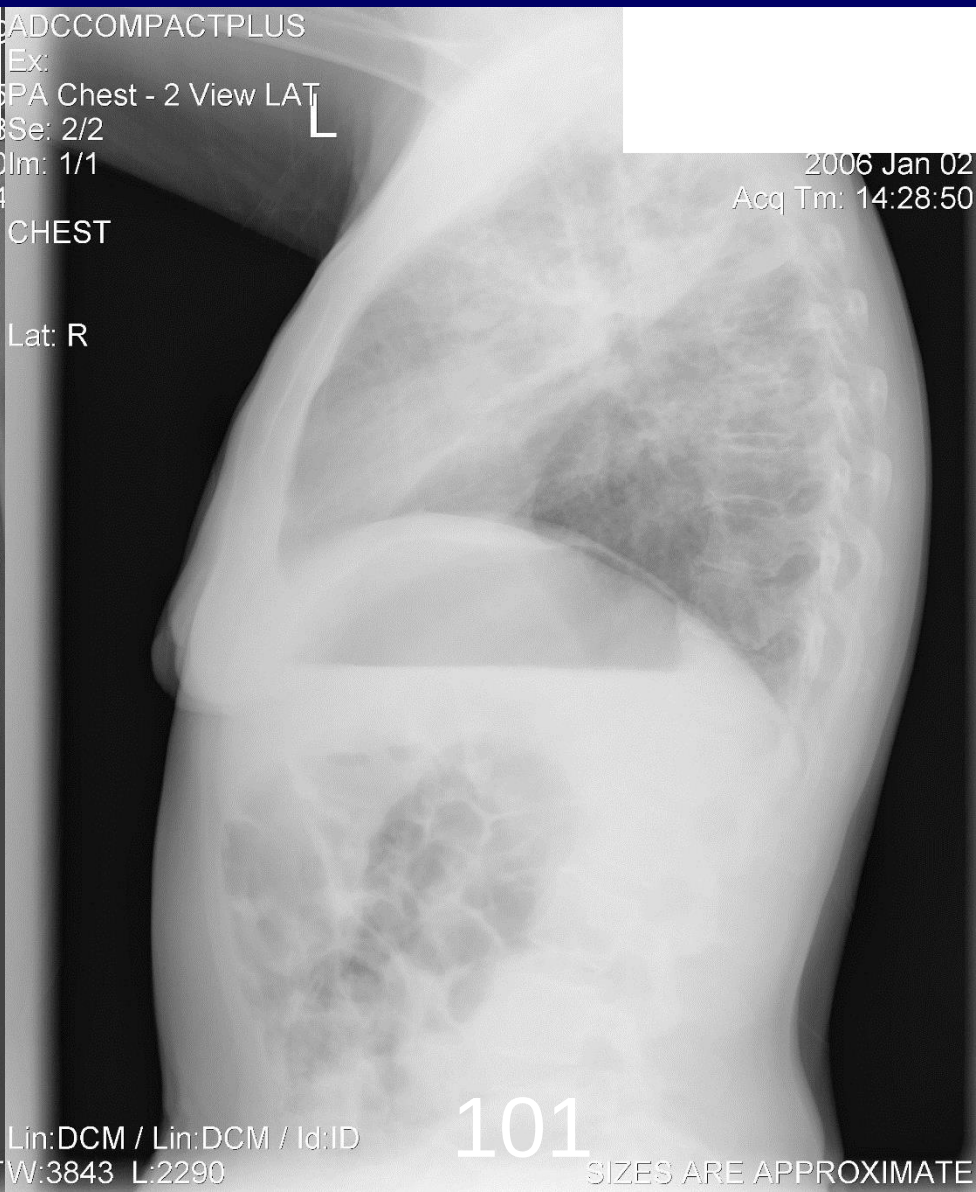
SIZES ARE APPROXIMAT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PA Chest - 2 View LAT
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CHEST
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W:3843 L:2290
SIZES ARE APPROXIMATE

Case # 2

- After 3 weeks, changed to t.i.w. DOT
- At start of week 4, DST = INH resistant

Treatment regimen?

- Continue HREZ tiw, five days a week
- Stop INH and continue REZ tiw, five days a week
- Change regimen to REZ daily by DOT five days a week
- Change regimen to REZ daily by DOT with weekend doses
- Change regimen to Moxi, REZ daily by DOT with weekend doses

Case # 2

- INH d/c'ed, but t.i.w. treatment continued

Case # 2

- Appropriate regimen
- Inappropriate regimen

Case # 2

- Culture still (+) June, 2006, now resistant to INH and Rifampin!
- Why did this patient acquire MDR-TB?

Case # 2

- Why did this patient acquire MDR-TB?

Case # 2

- Patient factors:
  - Extensive cavitary disease
  - 4 (+) AFB on smear
  - DM, with resultant immunocompromise
  - Debilitated state at diagnosis

Case # 2

- Programmatic factors:
  - Policy to give only 3 weeks daily therapy consisting of 15 doses (no option for patient to take weekend doses)
  - Continuing intermittent induction phase despite INH resistance

Case # 2

- DOT for all smear (+) and/or cavitary TB
- Daily therapy throughout induction phase if initial isolate is INH-resistant, or if patient is HIV (+)
- Reminder: CDC and ATS recommend intermittent therapy for drug susceptible TB, there is no recommendation to use intermittent therapy when resistance present

MDR-TB

Preventable!

Treatable!

Curable!

FDA Approval of BDQ

- MDR TB is orphan disease in USA: 98 pts in 2011
- Approved as an orphan drug 12/31/12
- Endpoint: sputum culture conversion
  - Mean culture conversion was 83 days compared to 125 days (79% of patients at 24 weeks)
- Found the drug efficacious
- Concerns about safety – Black Box Warning
  - ↑risk of QT interval prolongation-can cause arrhythmia
  - ↑number of deaths: 11.4% (9/79) compared to 2.5% (2/81)

QT Prolongation

- Drugs used to treat TB or NTMs
  - Fluoroquinolones
  - Clofazimine
  - Delaminid
  - PA-824 (nitroimidazol-oxazine)
  - Macrolides
- Electrolyte abnormalities: ↓K, Ca, Mg
- Other drugs that prolong QT interval
- History of Torsade de Pointes
- History of congenital prolonged QT syndrome
- History of hypothyroidism, bradyarrhythmias, uncompensated heart failure
- This effect can be additive

Other Clinically Relevant Information

- EKG at baseline and at least 2, 12, and 24 weeks after starting Bedaquiline
- Serum electrolytes, Ca and Mg
- Monitor LFTs
  - Avoid alcohol and hepatotoxic drugs
- Metabolized by CYP3A4-therapeutic effect may be reduced with inducers of CYP3A4
  - Rifamycins
  - Limited data on HIV/MDR TB co-infected patients

Dosage and Administration

- Given for 24 weeks with an individualized MDR background regimen
  - At least 3 drugs to which isolate susceptible
  - Must be given under DOT
- Should be taken with food
- Oral tablets 100 mg each
  - Weeks 1-2: 400 mg once a day (4 tablets)
  - Weeks 3-24: 200 mg (2 tablets together) 3x/wk
    - At least 48 hours between doses
    - Total dose of 600 mg/week