MDR TB
How Much of a Risk to Texas

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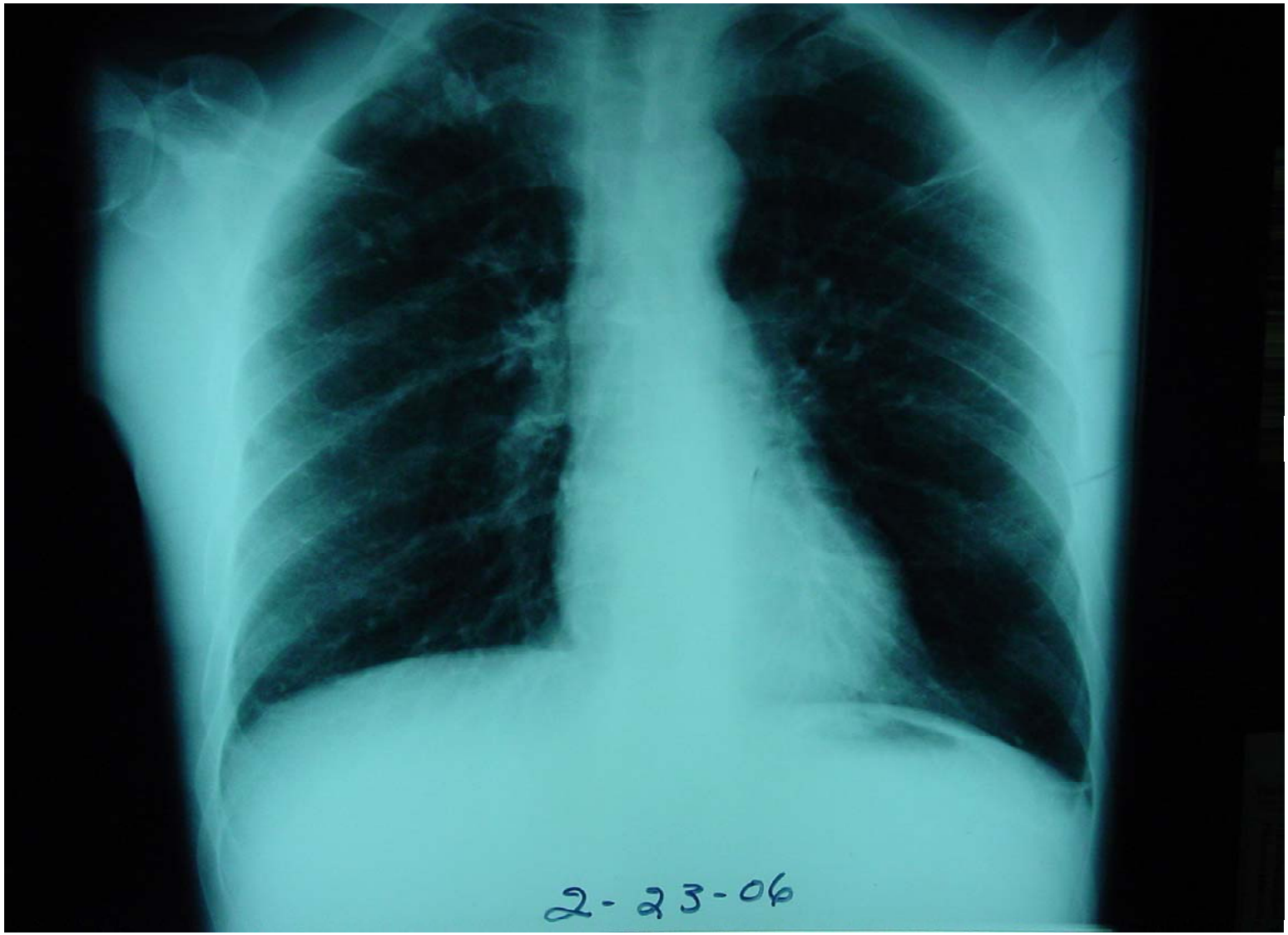
Can This Patient Be Treated?

- 56 yr old male, TST positive, abnormal CXR
- Cough, fever, sweats, weight loss x 4 months
  - Culture positive M TB Resistant to:
    - INH,
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Levofloxacin
    - Ethionamide



Primary MDR TB DOB:10-10-52, Date of film: 2-23-06

What Situations Contribute to Drug Resistant TB in Texas?

- Inadequate management in past leading to acquired MDR TB
  - Extensive drug resistant chronic patients
  - Untreatable patients
  - Transmission leading to primary MDR TB
- Missed opportunities for treatment of contacts of MDR TB
- Binational TB
- Foreign Born TB in immigrants and refugees

Inadequate Management from Past

Can This Patient Be Treated?

- 56 male, TST+ **contact to father who died with MDR TB in 1994**
  - Cough, fever, sweats, weight loss x 4 months
  - Culture positive M TB Resistant to:
    - INH,
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Levofloxacin
    - Ethionamide
- Father was drug susceptible at first diagnosis!
- Chronic, untreatable disease with transmission created by inadequate therapy, non-compliance and public health decisions

What Situations Contribute to Drug Resistant TB in Texas?

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Pathogenesis of Drug Resistant Tuberculosis

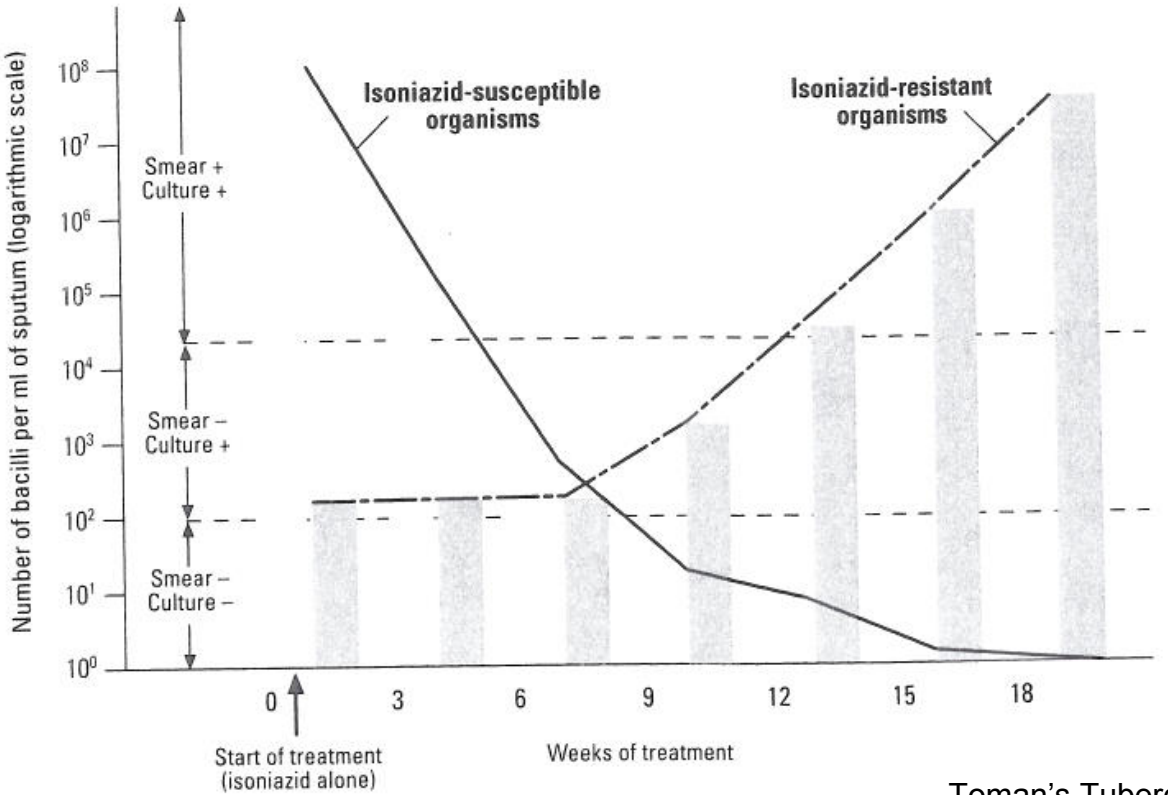
- Genetic mutations occur spontaneously that confer resistant to an anti-tuberculosis drug
  - Are present in wild type M tuberculosis isolates.
  - Occur by chance alone
  - Do not depend on prior drug exposure
  - Not linked
  - Occur in frequency specific for each drug
    - INH: 1 in $10^{6,}$ rifampin: 1 in 10^{8}
    - INH and rifampin: 1 in 10^{14}
      - Individual risk of each drug multiplied together

Pathogenesis of Drug Resistant Tuberculosis

- Because of the natural occurrence of spontaneous mutations, if treatment is given with only one drug (or one effective drug) resistance will ultimately develop in the whole population of mycobacteria.
- Treatment should always include two drugs
  - which the population of M Tb is susceptible to
  - which have activity at the site.
    - PZA is not active in cavitary lesions or lesions with actively dividing mycobacteria,

“Fall and Rise” phenomenon

Figure 16
The “fall and rise” phenomenon[a]

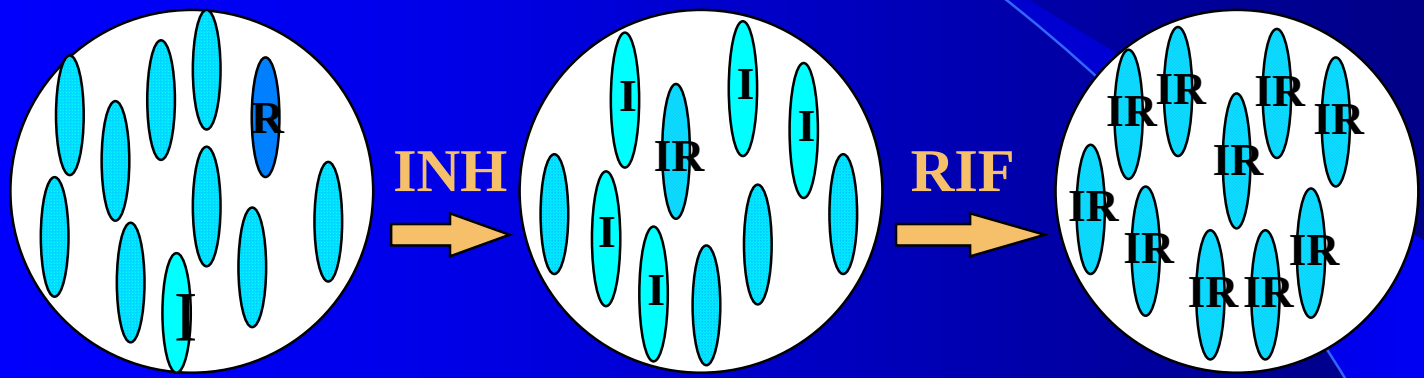


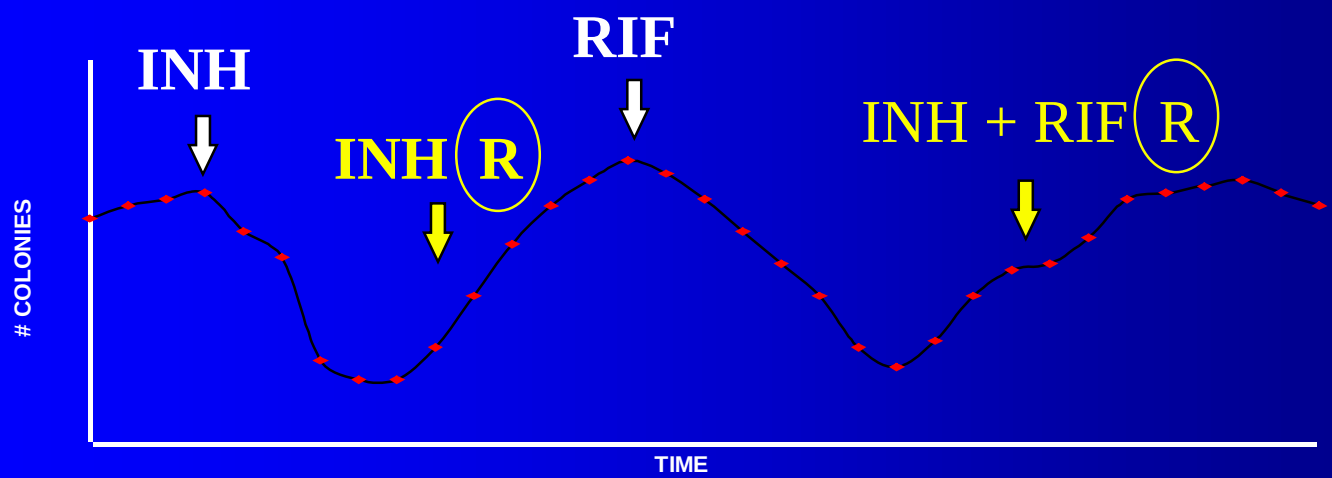
Toman’s Tuberculosis 2nd Ed.

Amplification of Drug Resistance

- Development of additional drug resistance during treatment of TB.
  - Acquired Drug Resistance

DEVELOPMENT OF DRUG RESISTANCE





Protecting Rifampin

Preventing Amplification of Drug Resistance:

- Initial RX: INH, Rifampin, EMB, & PZA.
  - If INH resistance is present:
    - EMB will protect rifampin during initial phase of treatment

Amplification Can Develop During Initial Therapy with INH, Rifampin, & PZA if INH resistance is present:

- PZA is not active in cavities and rapidly growing lesions so it does not protect rifampin

- Continuation phase: INH & Rifampin
  - If there is INH resistance which is not detected:
    - Rifampin is only active drug

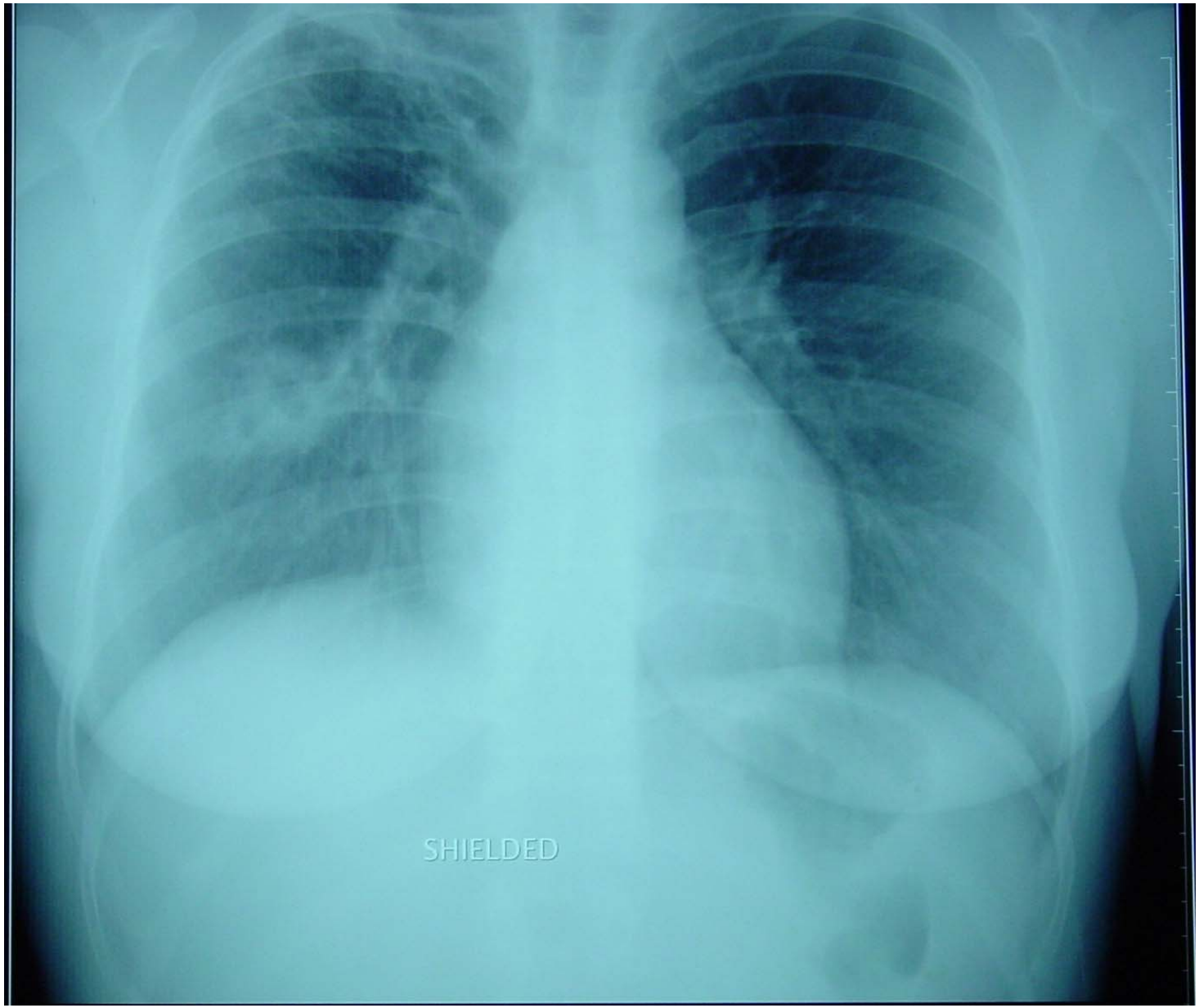
Fluoroquinolone resistance

- Mice infected with *M.tb complex* and treated with four concentrations of moxifloxacin (0.125, 0.25, 0.5, 1.0%).
- Selection of fluoroquinolone resistant mutants occurred in all surviving mice
- Conclusion: Fluoroquinolone resistance in tuberculosis may rapidly emerge

GinsburgAS, Sun R, Calamita H, Scott CP, Bishai WR, Grosset JH. *Antimicrob Agents Chemother* 2005 Sep;49(9):3977-9

Is Our Detection and Management of LTBI Good? But What About Undetected Drug Resistance?

- 55 year old female; 3 mo history of cough, fever, weight loss, TST negative
  - Rheumatoid Arthritis
    - Prednisone 20 mg twice daily
    - Adalimumab (Humira) stopped three months ago
    - Immigrated from Honduras 10 years ago
    - Worked in egg processing plant
- After 7 weeks of therapy report of resistance to INH, ethambutol, & PAS



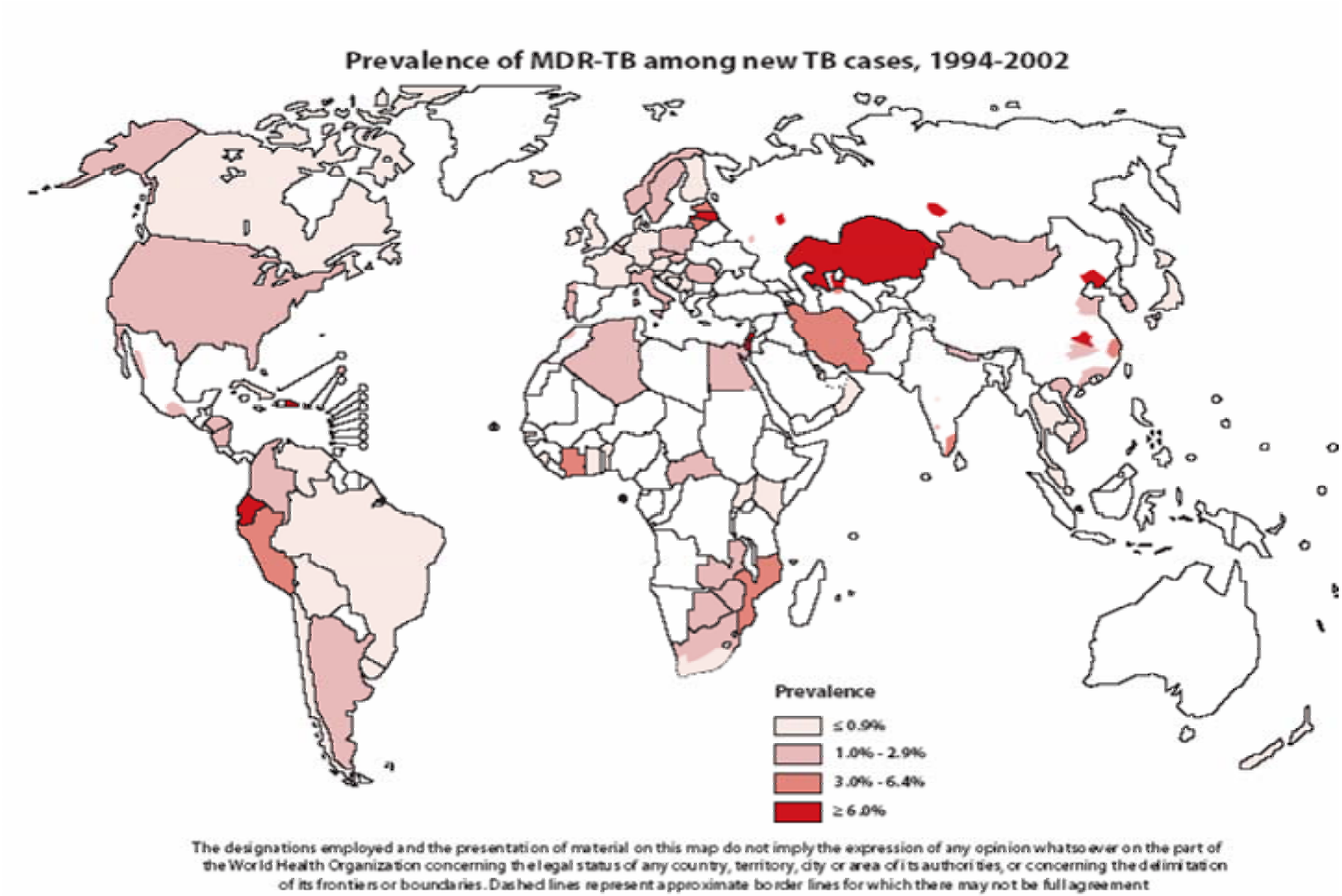
Nov 22, 2005: 30 yr old refugee from Uzbekistan

How Aggressive is Our Management of Contacts of MDR TB?

- Use 2 drugs to which the infecting organism has demonstrated susceptibility
  (Ethambutol, levofloxacin, Moxifloxin and PZA)
- Treat for 6 months or observe without treatment
  (HIV-negative)

- Treat HIV-positive persons for 12 months
  - **Follow for 2 years regardless of treatment**
  - **CXR and clinical evaluation**

Anti-tuberculosis drug resistance in the world report no. 3 **WHO/HTM/TB/2004.343**



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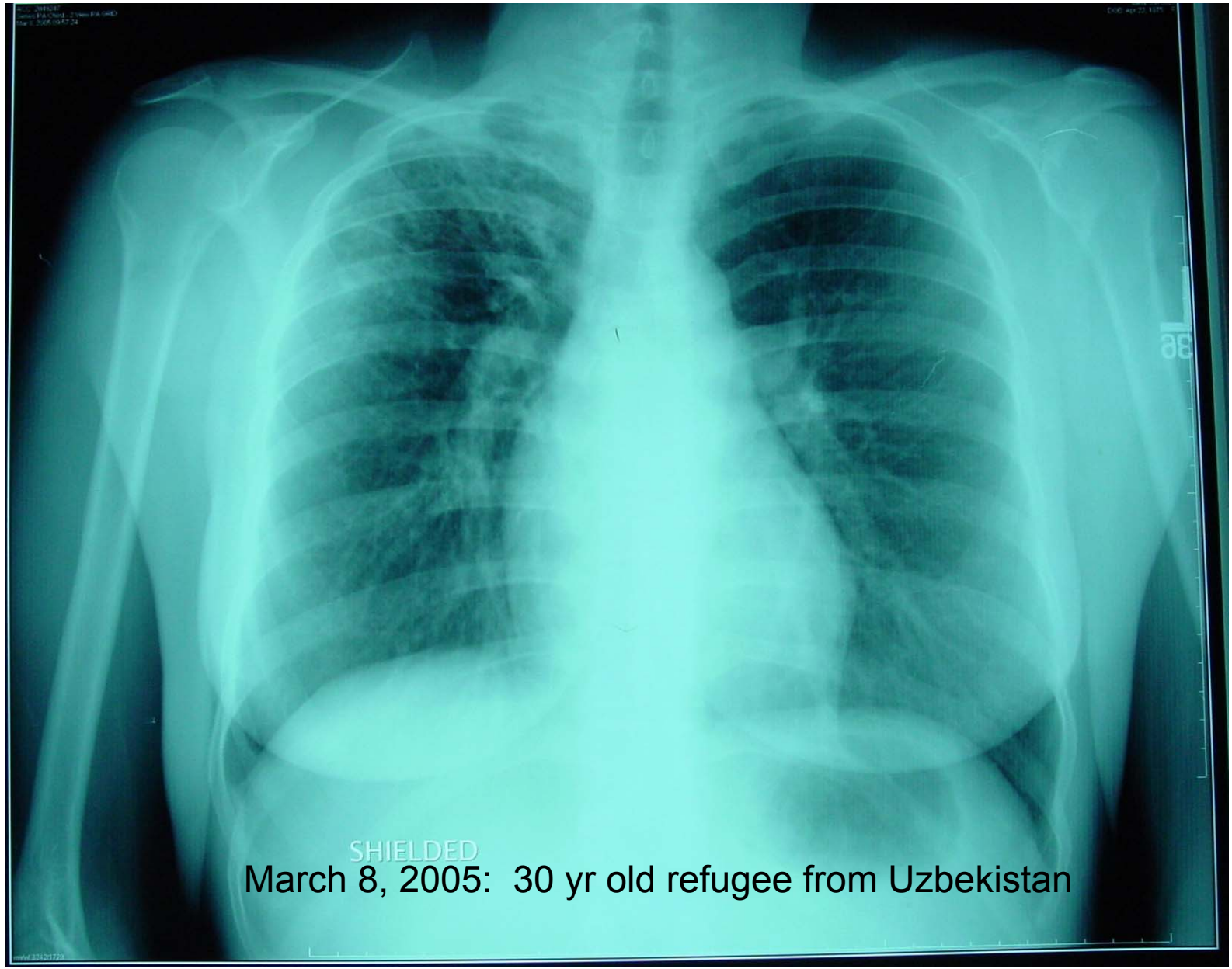
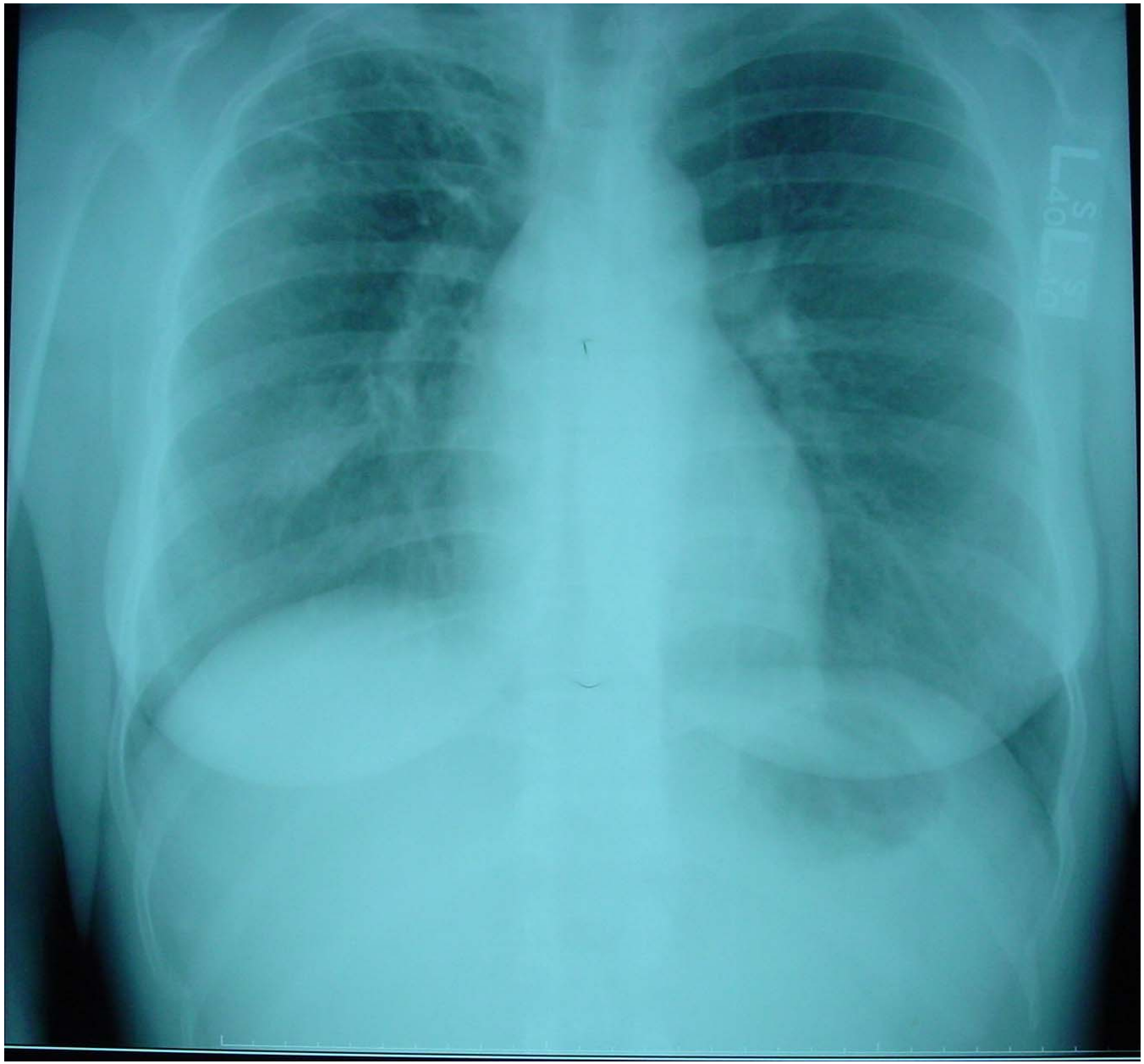
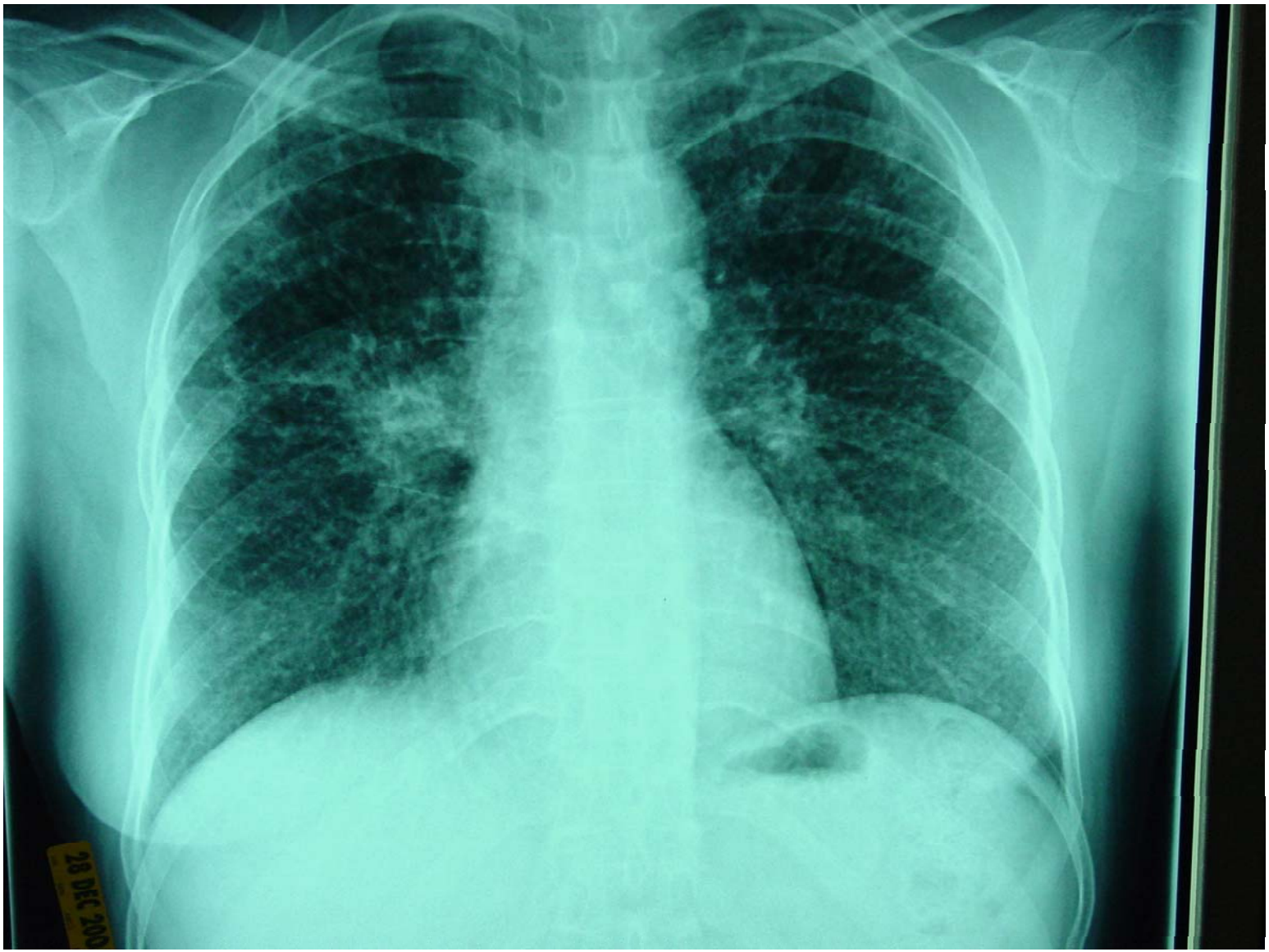


March 8, 2005: 30 yr old refugee from Uzbekistan

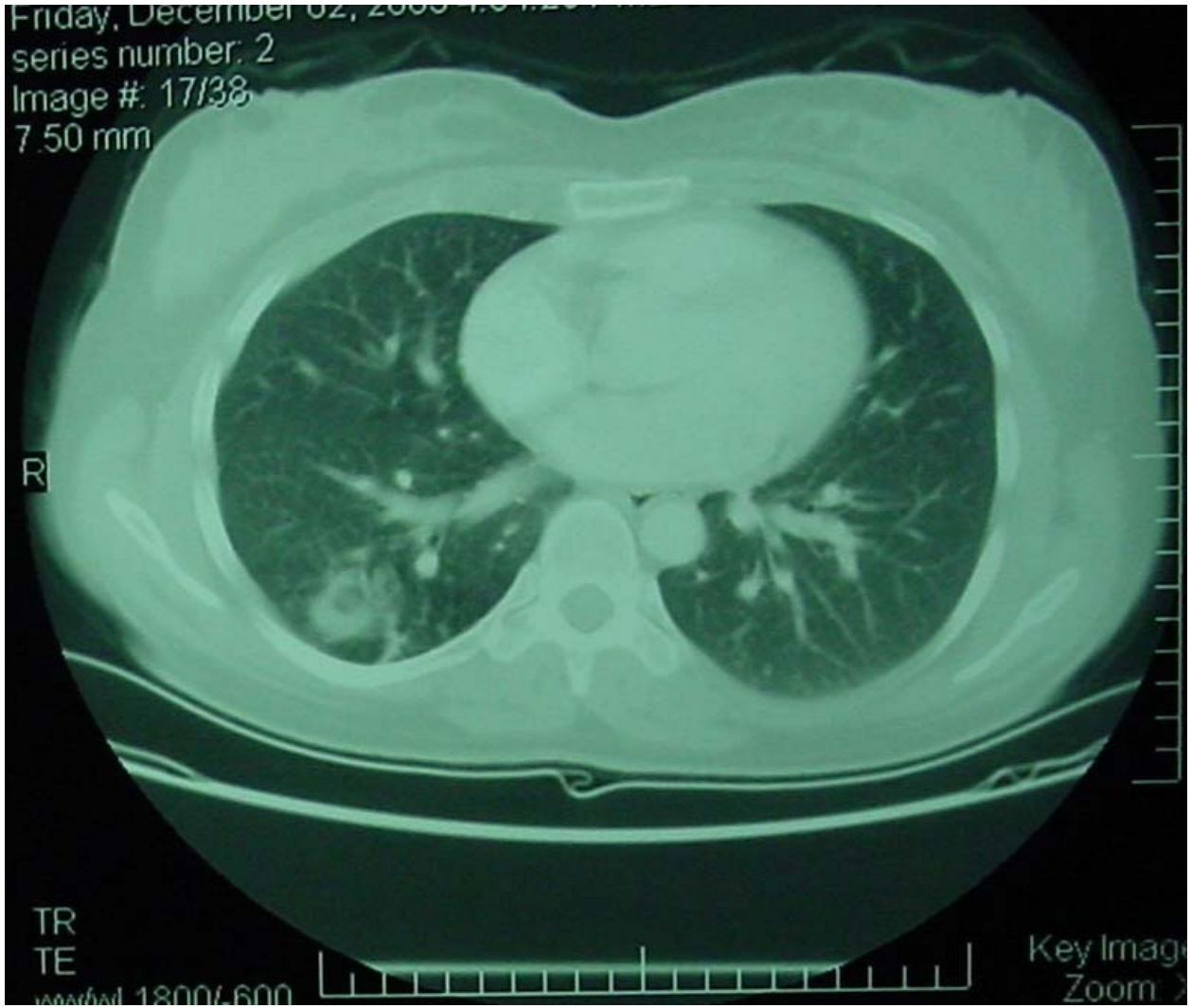
How Good is Our Management of Refugees?



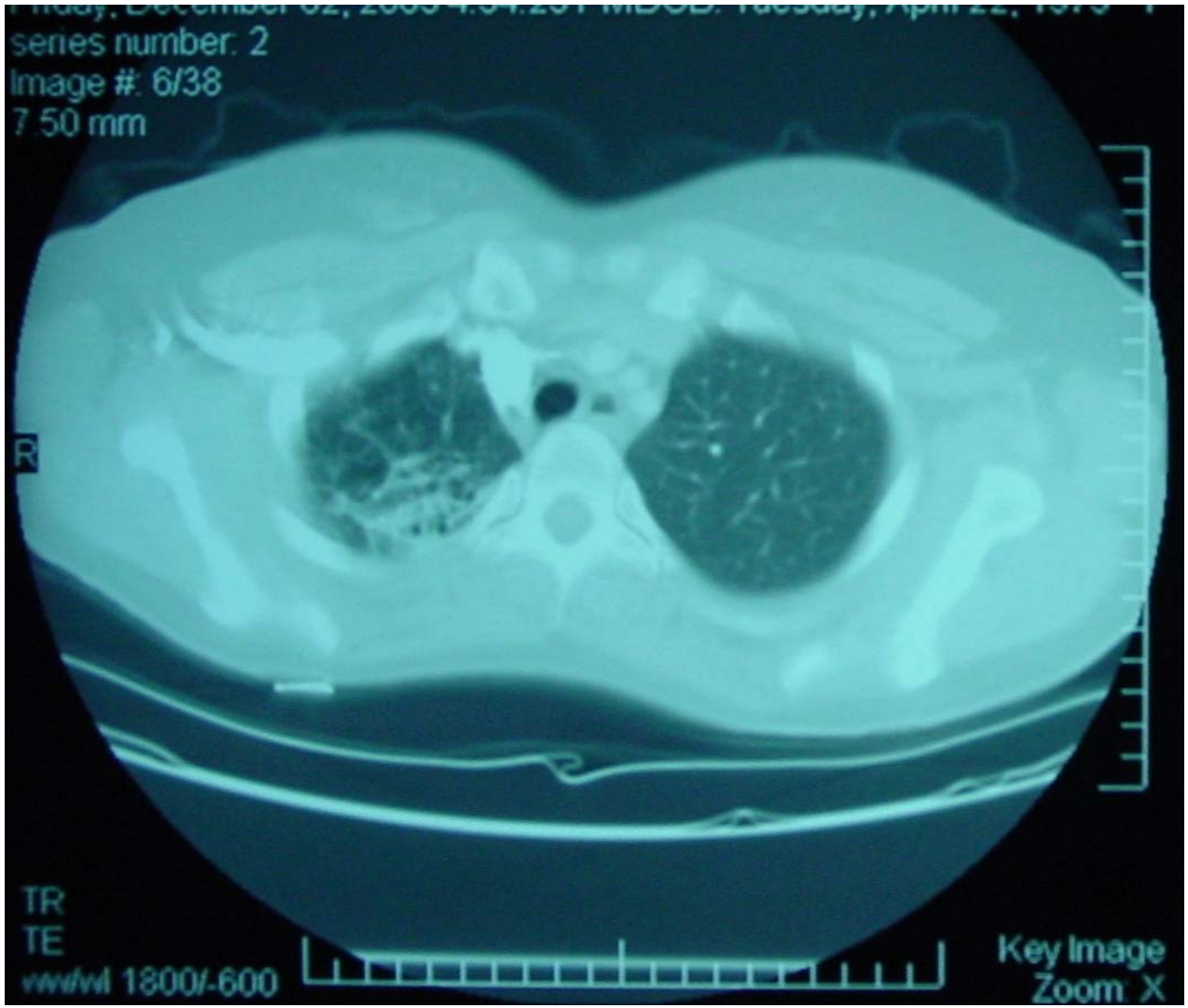
Sept 1, 2005: 30 yr old refugee from Uzbekistan



, DOB: 12.08.1950, Date of film: 12-28-2005



December 2005



December 2005

MMWR
Morbidity and Mortality Weekly Report

March 24, 2006 / Vol. 55 / No. 11

Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs — Worldwide, 2000–2004

Extensive MDR TB (XDR TB)

- TB resistant to INH and rifampin and at least 3 additional classes of drugs
  - Aminoglycosides: Amikacin, Kanamycin
  - Polypeptides: Capreomycin
  - Fluroquinolones: Ciprofloxin, Ofloxacin
  - Thioamides: Ethionomide Prothionamide
  - Cycloserine
  - PAS
- No mention of ethambutol or PZA

XDR TB

- CDC/WHO survey of 25 Supranational TB reference labs on 6 continents: 2000-2004
  - 20% MDR TB
  - 2% XDR TB (10% of all MDR isolates)
- Identified in all regions but most common
  - South Korea 15% of all MDR
  - Eastern Europe/western Asia 14% of all MDR
- Increasing incidence 5% (2000), 7% (2004)

XDR TB

- Increasing incidence:
  - Eastern Europe/western Asia
    - Latvia
      - 30/204 (15%) cases 2000
      - 39/186 (21%) cases 2002
  - Industrialized countries
    - (UK, US, Australia, Belgium, Canada, France, Germany, Ireland, Japan, Portugal, & Spain)
    - United States
      - 37/944 (3.9%) cases 1993-96
      - 17/381 (4.5%) cases 2001-04

Treatment Outcomes of XDR TB

TABLE 2. Tuberculosis treatment outcomes among patients with extensively drug-resistant tuberculosis (XDR TB) and multidrug-resistant tuberculosis (MDR TB) — Latvia, 2000–2002, and United States, 1993–2002*

Outcome	XDR TB No. (%)	MDR TB No. (%)	Relative risk (95% CI†)	p-value
Latvia§¶				
Total	**115**	**490**		
Cure/Completion	70 (61)	339 (69)	Referent	
Death/Failure	30 (26)	83 (17)	1.5 (1.1–2.2)	0.02
Death	3 (3)	35 (7)		
Failure	27 (23)	48 (10)		
United States¶**				
Total	**64**	**1,513**		
Completion	20 (31)	828 (55)	Referent	
Death	21 (33)	375 (25)	1.6 (1.2–2.2)	0.01

* Inclusion in this cohort was truncated at December 2002 to allow time for MDR TB treatment completion and reporting.
† Confidence interval.
§ Outcome definitions used are based on international standards (*5*).
¶ Excludes 83 patients (15 with XDR TB and 68 with MDR TB) from Latvia and 333 patients from the United States (23 with XDR TB and 310 with MDR TB) for whom treatment outcome was unknown.
** Among persons who were alive at time of TB diagnosis and who initiated therapy with more than one anti-TB drug.

MMWR March 24, 2006

Very Resistant MDR TB

- Texas Morbidity and Non-morbidity
  - Average # drugs resistant to is 4.8
  - 9/17(53%) resistant ≥ 3 drug + INH & rifampin
    - Counts drugs such as ethambutol and PZA
  - At least one is XDR (5.9%)
  - 1/17 (5.9%) simple MDR TB

- Nuevo Laredo Binational Project
  - Average # drugs resistant to is 5
  - 2/25(8%) XDR-TB
  - 8/25 (32%) resistant 2 classes +/- PZA, EMB

Drug Resistance in Nuevo Laredo Binational Project

- 25 patients
  - 6 Resistant to RIPE
  - 5 Resistant to Rifampin, INH and Ethambutol
  - 3 Resistant to Rifampin, INH and PZA
- Only 3 Resistant to Rifampin, INH and Rifabutin

- ALSO
  - 9 Resistant to Ethionamide
  - 4 Resistant to Ofloxacin
  - 2 Resistant to all Injectables

Individualized Treatment for MDR TB Nuevo Laredo – 25 Patients

- Culture and Susceptibility
- Case Management and DOT
- Toxicity Assessment and intervention
- Outcomes
  - 12 Completed therapy as cured
    - 8 well at F/U 12+ mo, 1 at 6 mo
  - 8 in treatment
    - 5 culture negative by 3 mo, 3 Rx < 3 months
  - 1 Failed (Resistant RIPE, ethionamide, all injectables)
  - 3 Lost (all converted culture prior to loss)

MDR Treatment Outcomes: WHO Standard Retreatment Regimen

Cure: Negative smear at 5 and 8 months

- 2SHRZE / 1HRZE / 5HRE
  - 5HRE given three times/week
- 42 MDR patients*
  - 14 (33%) smear negative at end of therapy

*Cases were relapse or treatment failure from Vietnam

- Historical controls 1947
  - 26% smear negative at 4 years of follow-up

Springett Tubercle 1971

Lan. Int J Tuberc. Lung Dis 2001

Retreatment Strategies After Failure of Standard Category 1 Treatment - Peru

- Strategy A: (Standard Category 2 Rx)
  - 3SHREZ/5HRE(2x/wk)
    - If failure then -
  - Standard Rx MDR TB
    - 3 KM CPX ETH EMB PZA/15 CPX ETH EMB PZA
  - No drug susceptibility
  - 28/73 (38%) cured

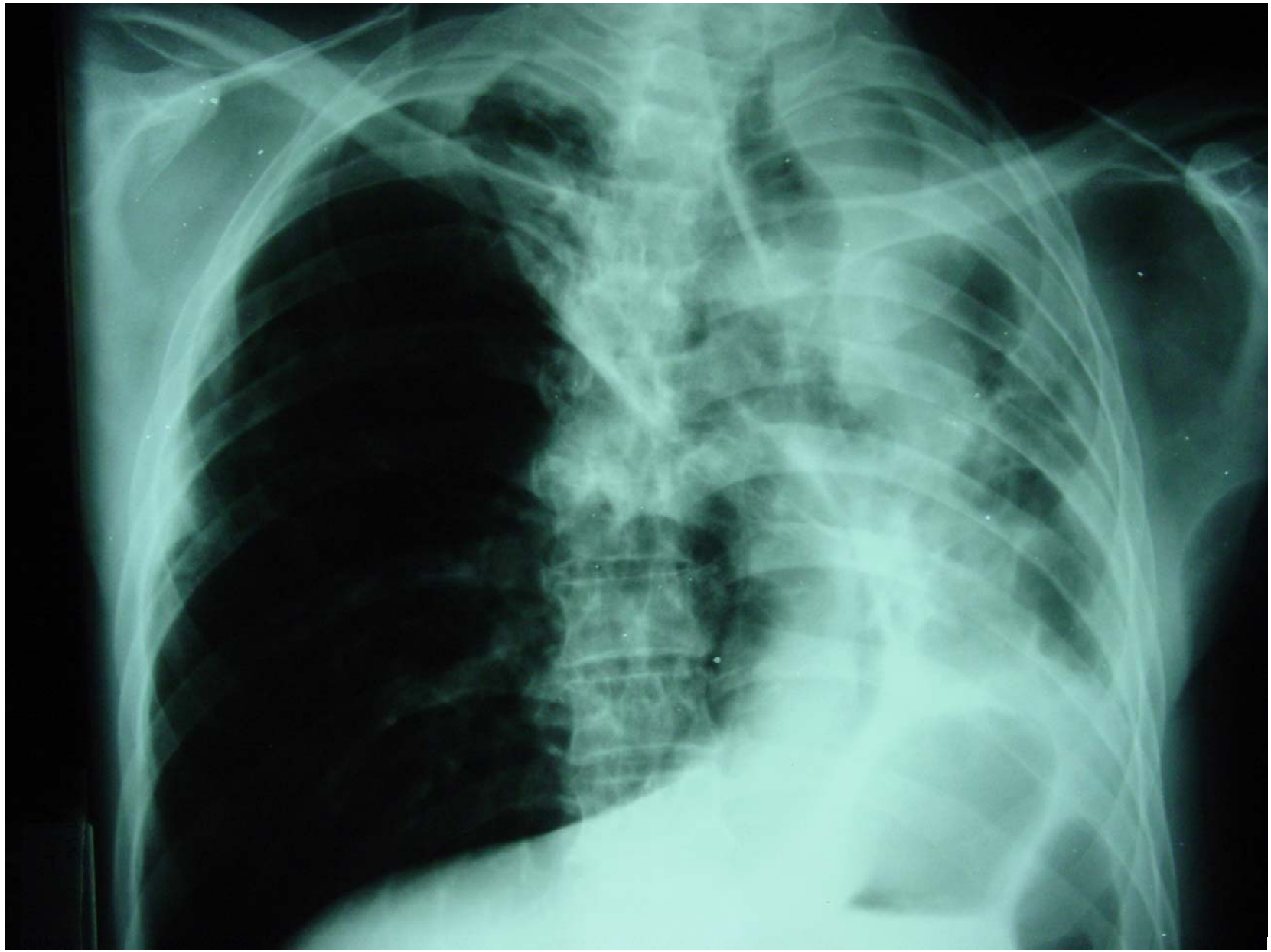
Stragegy B:

  - Culture and susceptibility
  - Empiric therapy MDR TB
    - Pending susceptibility
    - Same as standard
  - Individualized Therapy for DST
    - 18-24 mo, 5 or > drugs
  - 41/52 (79%) cured

- Saravia. Int J Tuber Lung Dis 9:421, 2005

Chronic MDR TB
Extensive Drug Resistance

- 56 y.o. male, treated age 37, relapsed 2002
  - Positive smear after 5 months of Rifater
    - Ciprofloxacin 2 ½ months led to negative smears
- Relapsed 2003, smear remained + after Rifater, EMB and Ciprofloxacin for 6 months
- All treatment was in private sector
- 2005: Cough, SOB, wt loss, destroyed lung
  - Referred to Binational Project



Extensive MDR TB, Nuevo Laredo, Date of film: 02-13-06

Chronic MDR TB
Extensive Drug Resistance

- 2005: Referred to Binational Project
  - Resistance: INH, Rifampin, Rifabutin, Strep, PZA, EMB, Ethionamide, Levofloxacin and Imipenem
  - Susceptible: Amikacin, Capreo, Cycloserine, PAS, Linezolid
  - Intermediate: Moxifloxacin 1.0 microgram/ml
- Treatment: Amikacin, Capreo, Moxifloxin 800mg, PAS and Linezolid 600mg
  - Culture conversion at 3 months
  - A long way still to go

THEY ALWAYS COME BACK

Do It Right The First Time!

Regional Training and Medical Consultation Centers (RTMCCs) Areas of Coverage