Tuberculosis Treatment

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Epidemiology

- TB remains a significant national health problem
- 14,093 cases of TB in the US in 2005
- Rate of 4.8/100,000 (lowest rate ever)
- 15,000,000 people infected in the US
- foreign born individuals
  - 7x increased rate
  - 76% of MDRTB
- Cases of TB 2004 –
  - New - 8.9 million
  - Existing – 14.6 million
  - 95% in developing countries (Africa & Asia)

Causative Agent of TB

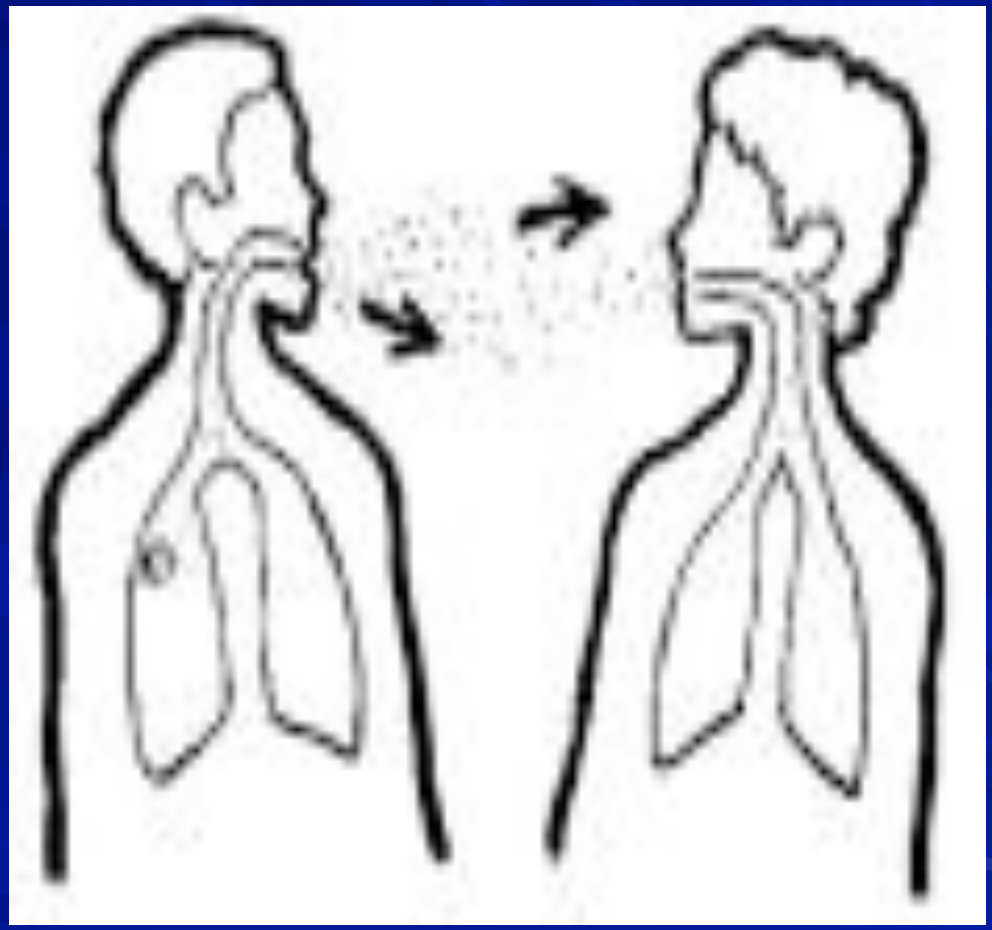
- MTB Complex
  - MTB
  - *Mycobacterium bovis*
  - *Mycobacterium Africanum*
  - *Mycobacterium microti*
  - *Mycobacterium canetti*

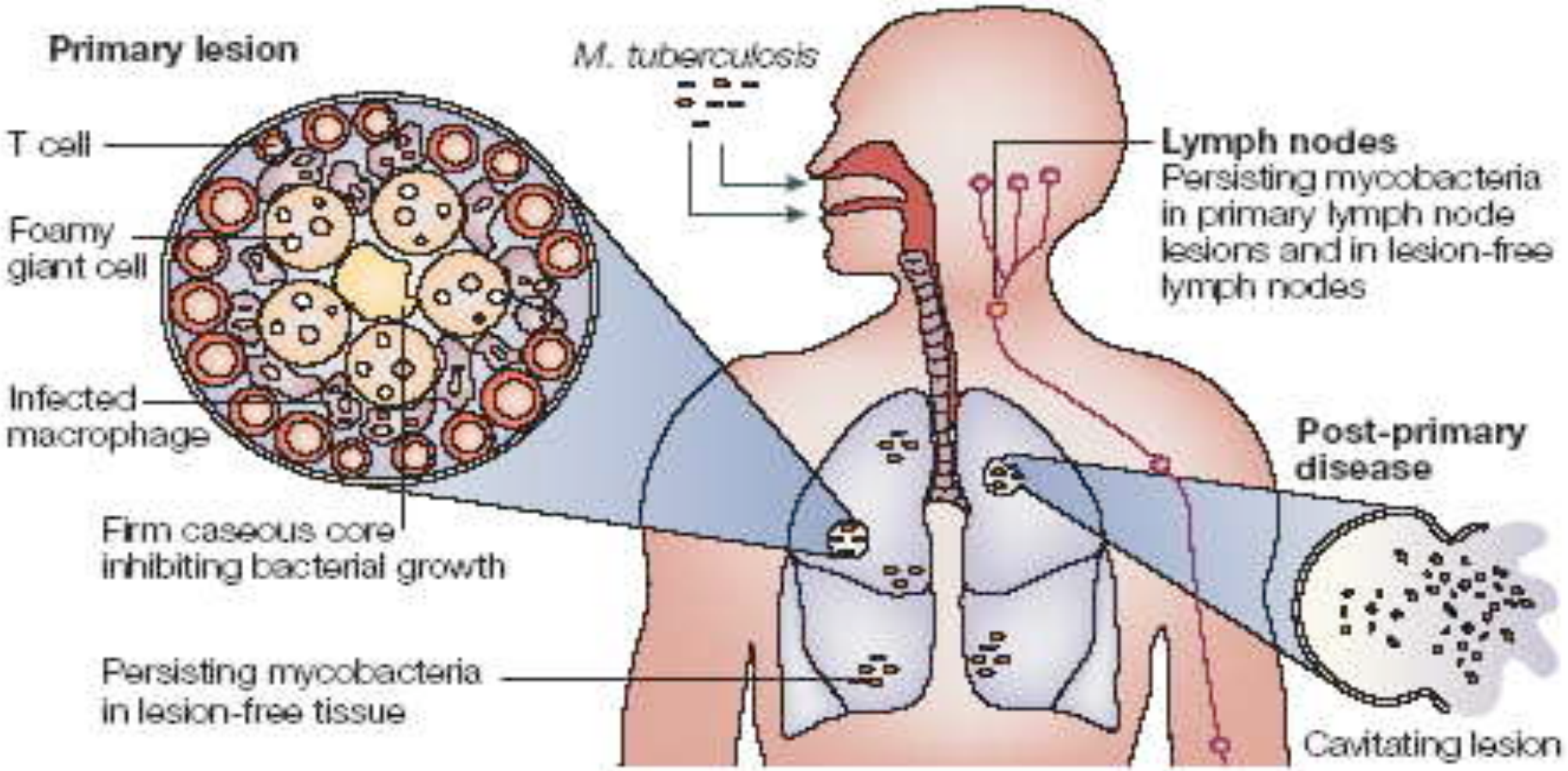
Transmission Risks

- Contact with a person with active TB
- Immigration from an endemic area (Africa, Asia, or Latin America)
- Exposure to persons with untreated cases of TB in congregate living facilities
- Age
- Residence in high incidence locations

Transmission

- Human to human through the air
- Droplet nucleic particles 1 to 5 μm in diameter
- 1/3 of exposed individuals become infected




Primary lesion
M. tuberculosis
T cell
Foamy giant cell
Infected macrophage
Firm caseous core inhibiting bacterial growth
Persisting mycobacteria in lesion-free tissue
Lymph nodes
Persisting mycobacteria in primary lymph node lesions and in lesion-free lymph nodes
Post-primary disease
Cavitating lesion

Diagnosis and Treatment of LTBI

- Tuberculin skin testing (TST)
- Positivity
  - ≥ 5mm induration
    - HIV
    - Recent TB Contact
    - Fibrotic changes on CXR consistent with old TB
    - Patients with organ transplant or immunosupressed patients (receiving the equivalent of ≥ 15mg/day of prednisone for ≥ 1 mo)
    - Pts. Who will be tx with TNF-α blockers

Diagnosis and Treatment of LTBI

- Positivity
  - ≥ 10mm induration
    - Recent arrivals (<5yrs) from high prevalence countries
    - Injection drug users
    - Residents and employees of high risks environments
      - Prisions
      - Nursing homes
      - Homeless shelters
      - Hospitals
    - Mycobacterial lab personnel
    - Clinical conditions that make pts high risk; Silicosis, DM, Chronic renal failure, leukemia, lymphoma, some malignancies (head, neck and lung), wt.loss ≥ 10% ibw, gastrectomy, jejunoileal bypass
    - Children < 4 yrs or infants and children exposed to adults in high risk

Diagnosis and Treatment of LTBI

- Positivity
  - ≥ 15mm induration
    - Persons with no risk factors for TB
- BCG
  - PPD reactivity wanes after 7-10 yrs
  - Usually < 15mm
  - Ignore BCG vaccination hx if positive PPD

Diagnosis and Treatment of LTBI

- Blood assays for MTB (MQuantiFERON-Gold)
  - Quantification of interferon-γ released from sensitized lymphocytes in whole blood incubated overnight with antigens that are specific for MTB
  - Reported to be more specific than TST
  - Advantages (just one visit to draw the specimen)
  - Disadvantages (specimen must reach lab within 12h of drawing the sample; needs better definition for immunosupressed persons and young children)

Approach to a Patient with LTBI

Clinical Evaluation –
Cough, chest pain, hemoptysis, fever, chills, night sweats, anorexia, weight loss, fatigue
Past Medical History – TB treatment or exposure
Social History -- Demographic factors increasing the risk of acquiring TB or resistant strains HIV status (voluntary testing and counseling should be offered routinely))
Chest Radiograph -- postero-anterior and lateral
Sputum (3 specimens) -- For: patients with symptoms (even if chest radiograph is normal), or patients with radiologic abnormalities (images compatible with old, fibrotic changes)

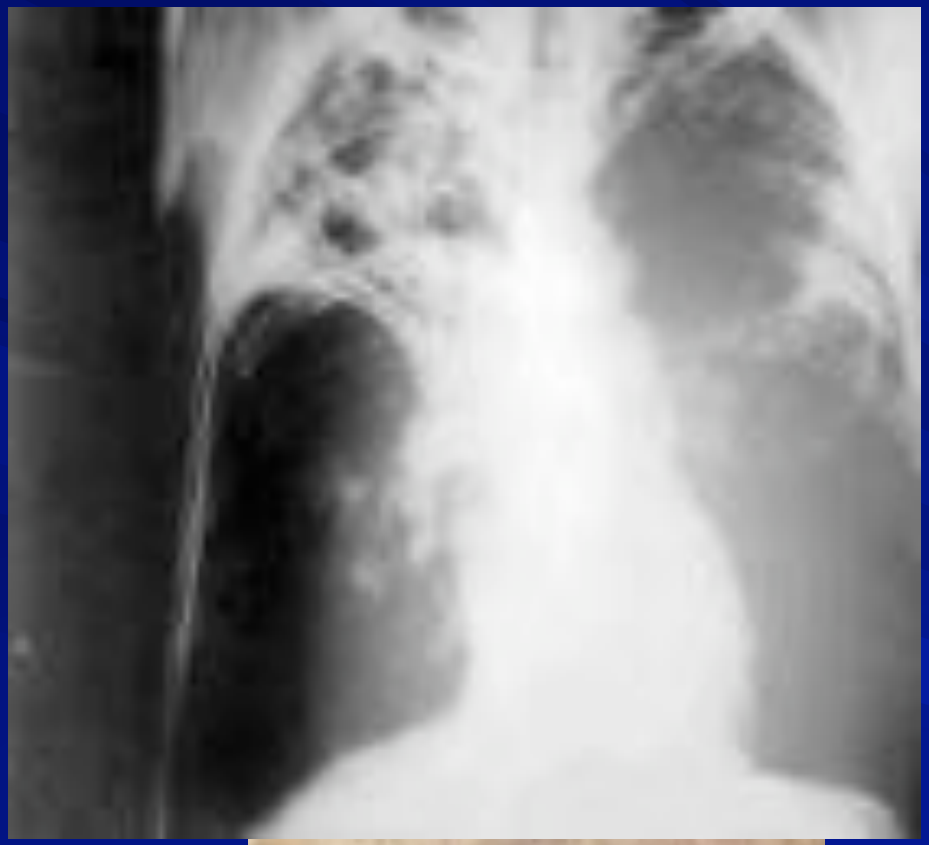
Obtain baseline laboratory testing (for: HIV-infected patients, pregnant and post-partum women, those with liver disease, and those who use alcohol regurlaly)

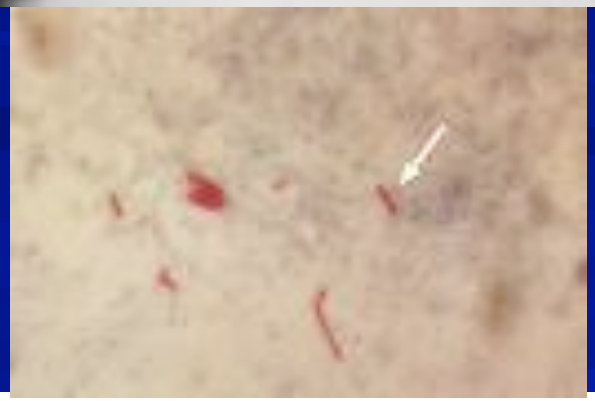
Those without clinical, radiologic, or microbiologic evidence of active disease: LTBI therapy (those with abnormal liver function tests at baseline require continuous monitoring)

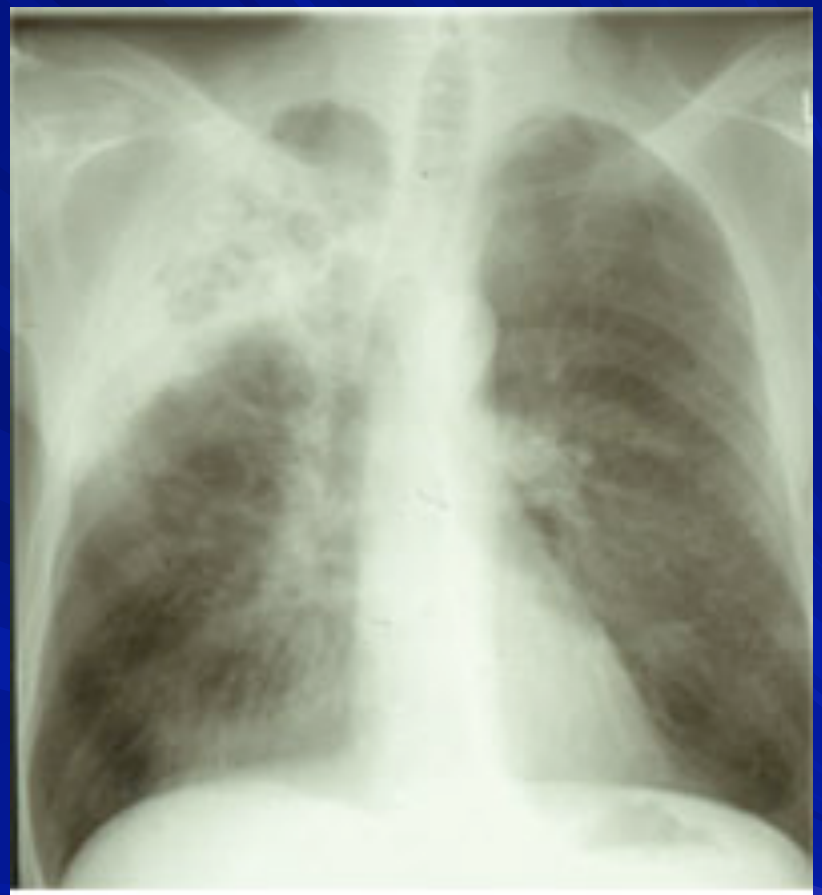
Treatment

- Isoniazid (INH) for 9 mos. for all individuals or
- Rifampin for 4 mo. or
- Rifampin + Pyrazinamide (PZA) daily for 2 mo. In HIV+ individuals (must monitor due to increased hepatotoxicity)

Active TB Disease







Chest X-ray of TB affecting the upper lobes of the lung

Fundamental Responsibility and Approach in TB Treatment

- Provider (or program) responsible for prescribing appropriate regimen AND ensuring successful completion of therapy
- Directly observed therapy (DOT) with patient-centered case management is preferred approach

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*
- Gatifloxacin*

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

Drug Abbreviations

Ethambutol	EMB
Isoniazid	INH
Pyrazinamide	PZA
Rifampin	RIF
Rifapentine	RPT
Streptomycin	SM

Role of New Drugs (1)

- **Rifabutin**: For patients receiving medications having unacceptable interactions with rifampin (e.g., persons with HIV/AIDS)
- **Rifapentine**: Used in once-weekly continuation phase for HIV-negative adults with drug-susceptible noncavitary TB and negative AFB smears at completion of initial phase of treatment

Role of New Drugs (2)

- **Fluoroquinolones (Levofloxacin, Moxifloxacin, Gatifloxacin)**: Used when

  -first-line drugs not tolerated;

  -strains resistant to RIF, INH, or EMB; or

  -evidence of other resistance patterns with fluoroquinolone susceptibility

Factors Guiding Treatment Initiation

- Epidemiologic information
- Clinical, pathological, chest x-ray findings
- Microscopic examination of acid-fast bacilli (AFB) in sputum smears
- Nucleic acid amplification test (when performed)

When to Consider Treatment Initiation

- Positive AFB smear
- Treatment should not be delayed because of negative AFB smears if high clinical suspicion:
  - History of cough and weight loss
  - Characteristic findings on chest x-ray
  - Emmigration from a high-incidence country

Baseline Diagnostic Examinations for TB

- Chest x-ray
- Sputum specimens (= 3 obtained 8-24 hours apart) for AFB microscopy and mycobacterial cultures
- Routine drug-susceptibility testing for INH, RIF, and EMB on initial positive culture

Other Examinations to Conduct When TB Treatment Is Initiated (1)

- Counseling and testing for HIV infection
- CD4+ T-lymphocyte count for HIV-positive persons
- Hepatitis B and C serologic tests, if risks present

Other Examinations to Conduct When TB Treatment Is Initiated (2)

- Measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, serum creatinine, and platelet count
- Visual acuity and color vision tests (when EMB used)

IDSA/USPHS* Rating System for Treatment Recommendations

Strength of the Recommendation

A. Preferred; should generally be offered

B. Alternative; acceptable to offer

C. Offer when preferred/ alternative regimens cannot be given

D. Should generally not be offered

E. Should never be offered

Quality of Supporting Evidence

I. At least one properly randomized trial with clinical endpoints

II. Clinical trials that either are not randomized or were conducted in other populations

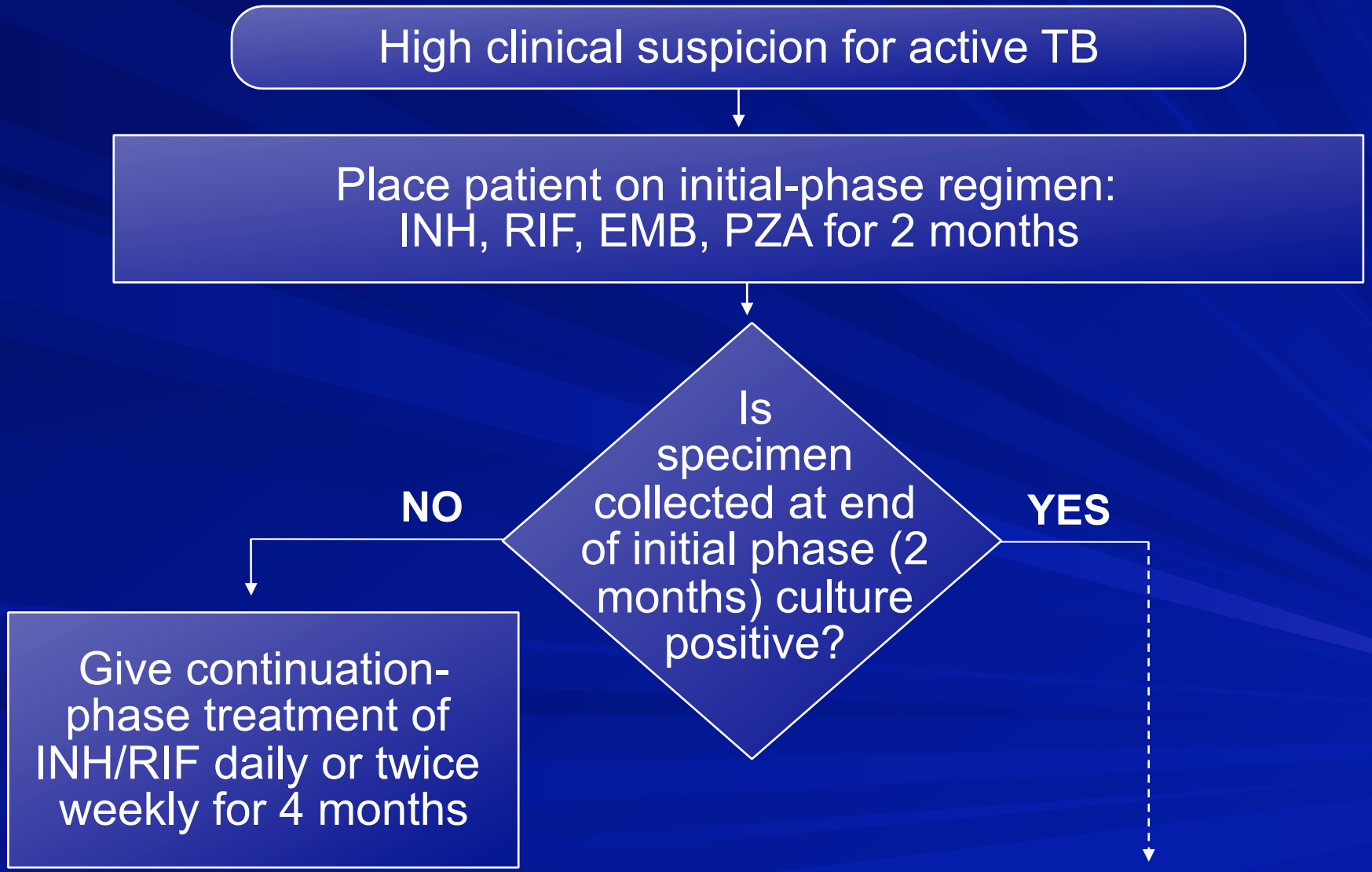
III. Expert opinion

*IDSA-Infectious Diseases Society of America; USPHS-U.S. Public Health Service

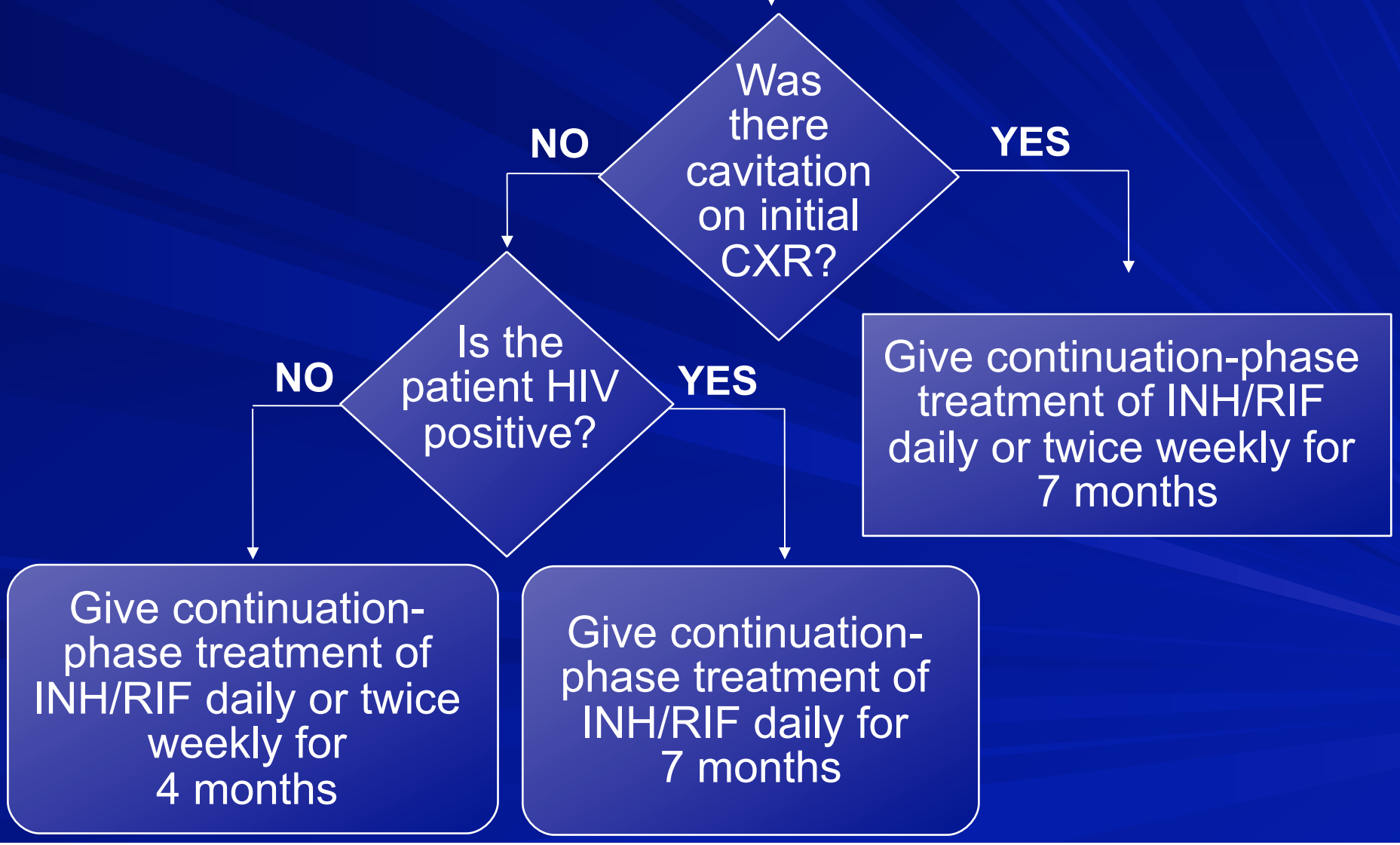
Treatment Regimens

- Four regimens recommended for treatment of culture-positive TB, with different options for dosing intervals in continuation phase
- Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months, (except one regimen that excludes PZA)
- Continuation phase: additional 4 months or (7 months for some patients)

Algorithm to Guide Duration of Continuation-Phase Treatment for Culture-Positive TB Patients



Algorithm to Guide Duration of Continuation-Phase Treatment for Culture-Positive TB Patients (Continued)



Treatment of Culture-Positive TB (1)

(Rated: AI in HIV-negative, AII in HIV-positive patients)

Initial Phase

2 months - INH, RIF, PZA, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF daily (126 doses, within 18 weeks)
2) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
3) 7 months - INH, RIF daily (217 doses, within 31 weeks)*
4) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

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* Continuation phase increased to 7 months if initial chest x-ray shows cavitation and specimen collected at end of initial phase (2 months) is culture positive

Treatment of Culture-Positive TB (2)

Twice-Weekly Options

(Rated: AII for HIV-negative, BII for HIV-positive patients*)

Initial Phase

0.5 months - INH, RIF, PZA, EMB daily (10-14 doses, within 2 weeks)

THEN

1.5 months - INH, RIF, PZA, EMB twice / week (12 doses, within 6 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF twice / week (36 doses, within 18 weeks)
2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)

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* Regimen rated BII for HIV-positive patients with CD4+ T-lymphocytes cell count >100/µl. Not recommended for those with CD4+ T-lymphocytes cell count < 100/µl

Treatment of Culture-Positive TB (3)

Thrice-Weekly Options

(Rated: BI for HIV-negative, BII for HIV-positive patients)

Initial Phase

2 months - INH, RIF, PZA, EMB 3 times / week (24 doses, within 8 weeks)

Continuation Phase

Options:

1) 4 months - INH, RIF 3 times / week (54 doses, within 18 weeks)
2) 7 months - INH, RIF 3 times / week (93 doses, within 31 weeks)

Treatment of Culture-Positive TB (4)

Regimens without Pyrazinamide

(Rated: CI for HIV-negative, CII for HIV-positive patients)

Initial Phase

2 months - INH, RIF, EMB daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 7 months - INH, RIF daily (217 doses, within 31 weeks)
2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*

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* Twice weekly dosing is not recommended for persons with CD4+ T-lymphocytes cell count < 100/µl

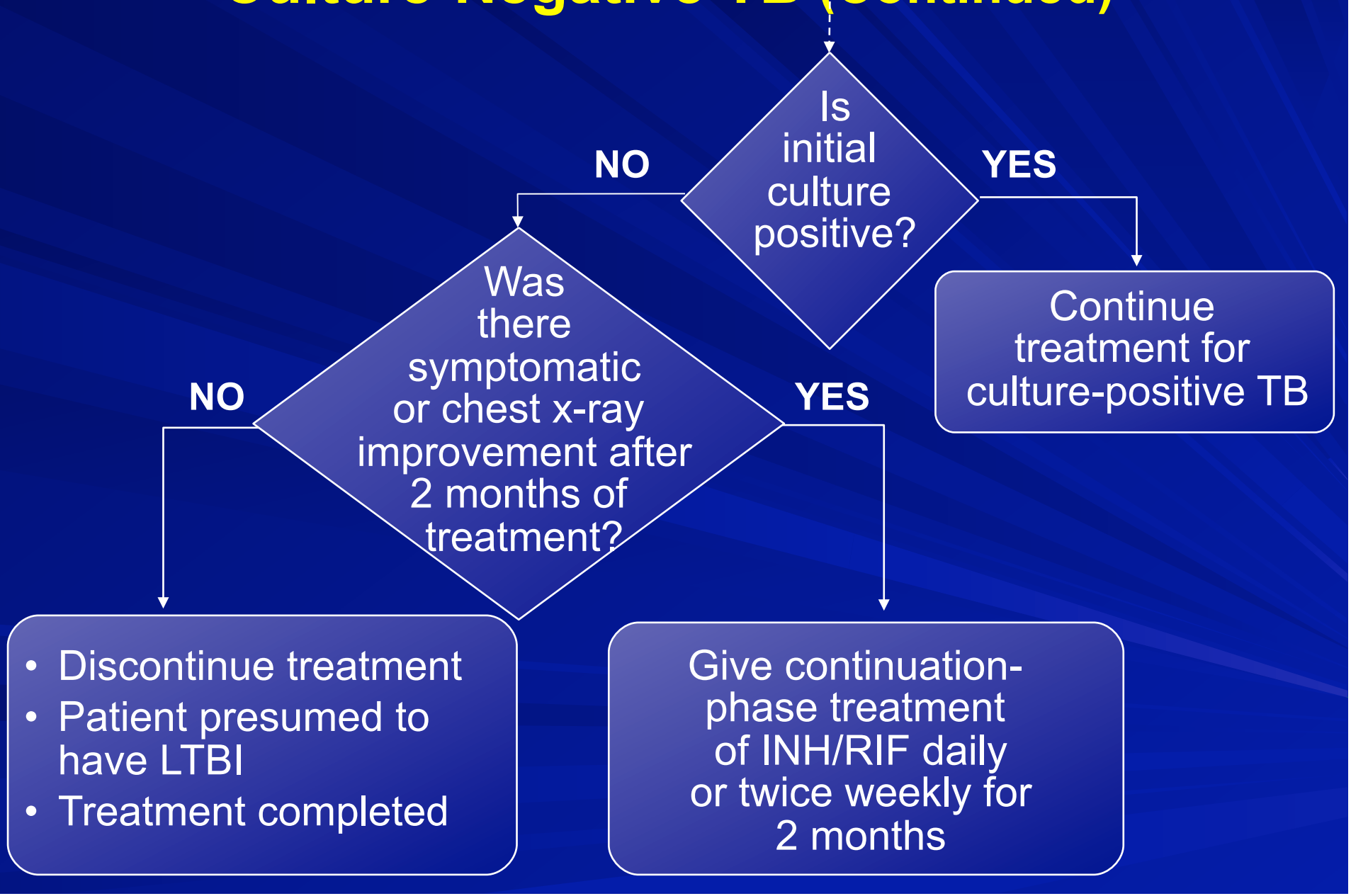
Algorithm to Guide Treatment of Culture-Negative TB

High clinical suspicion for active TB despite negative smears based on:

- Abnormal chest x-ray
- Clinical symptoms
- No other diagnosis
- Positive tuberculin skin test

Patient placed on initial phase regimen:
INH, RIF, EMB, PZA for 2 months

Algorithm to Guide Treatment of Culture-Negative TB (Continued)



Treatment of Culture-Negative TB*

Initial Phase

2 months - INH, RIF, EMB, PZA daily (56 doses, within 8 weeks)

Continuation Phase

Options:

1) 2 months - INH, RIF daily (56 doses, within 8 weeks)
2) 2 months - INH, RIF twice / week (16 doses, within 8 weeks)

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* All cultures are negative, but evaluation at 2 months reveals clinical and chest x-ray response to antituberculosis drug therapy

Treatment Monitoring (1)

- Monthly sputum for AFB smear and culture (until 2 consecutive cultures negative)
- Serial sputum smears every 2 weeks to assess early response
- Additional drug-susceptibility tests if culture-positive after 3 months of treatment

Treatment Monitoring (2)

- Periodic (minimum monthly) evaluation to assess adherence and identify adverse reactions
- Repeat chest x-ray:

  -At completion of initial treatment phase for patients with initial negative cultures

  -At end of treatment for patients with culture-negative TB

  -Generally not necessary for patients with culture positive TB

Treatment Monitoring (3)

- Renal function, AST, ALT, bilirubin, and platelet count if abnormalities at baseline
- Visual acuity and color vision monthly if EMB used > 2 months or doses > 15-20 mg/kg

Determining Drug Completion (1)

- Completion primarily defined by number of ingested doses within specified time frame
- Examples

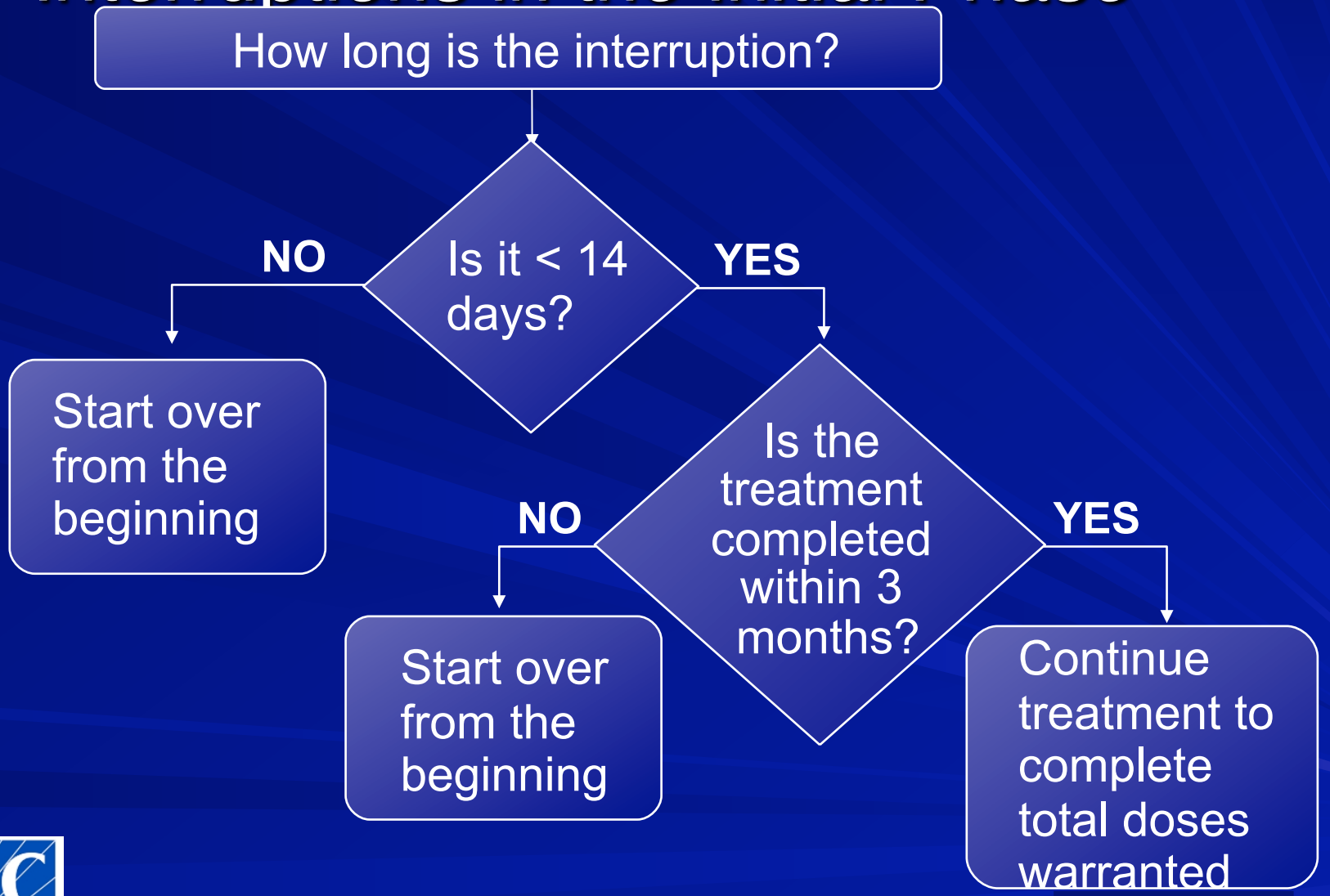
1) 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA

2) 6-month daily regimen (5 days/wk) = at least 130 doses

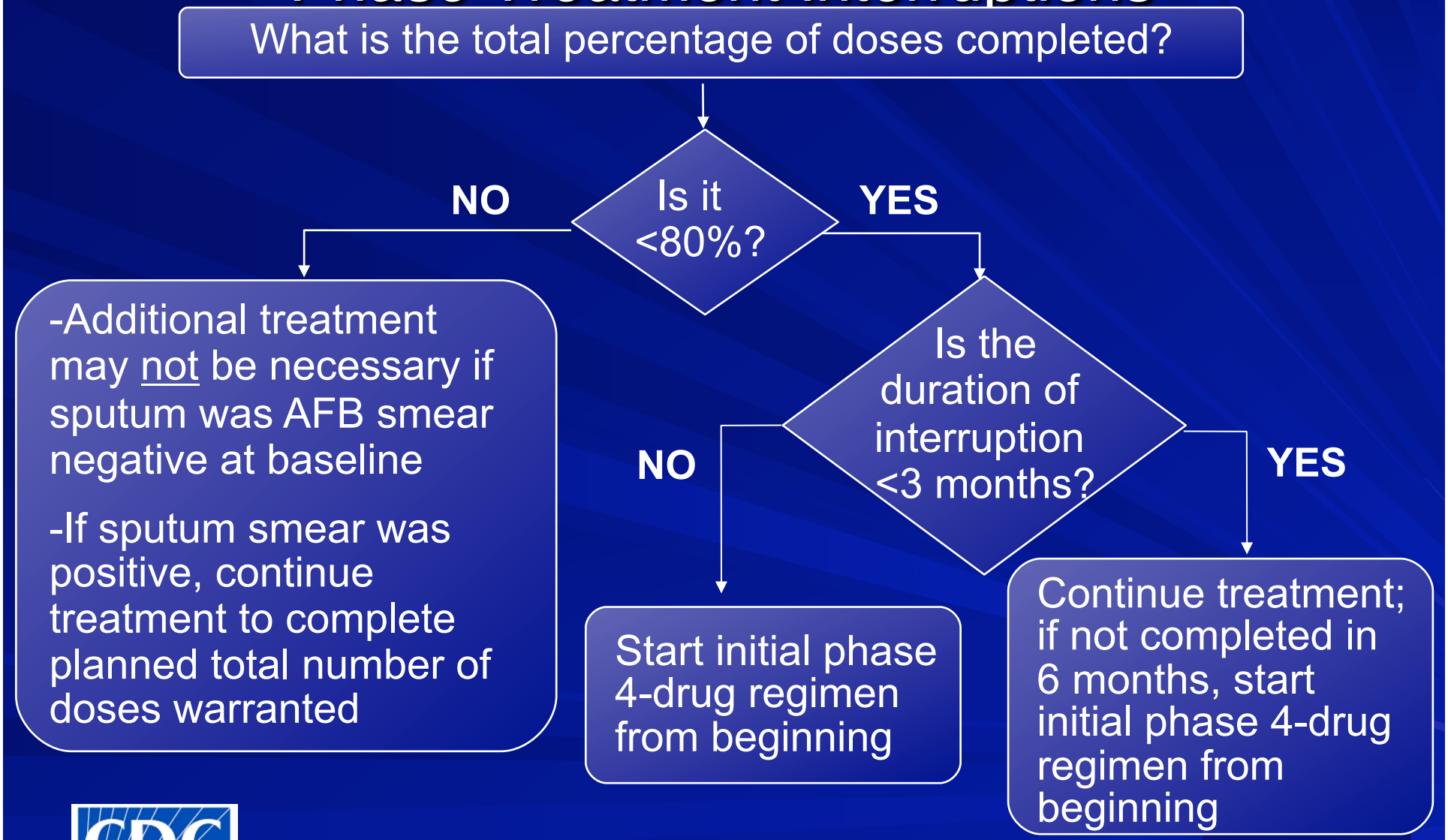
Determining Drug Completion (2)

- Specified doses must be administered
  1) Within 3 months for initial phase
  2) Within 6 months for 4-month continuation phase
- $ Consider therapy interrupted if target doses not met within specified time period

Algorithm for Management of Treatment Interruptions in the Initial Phase



Algorithm for Management of Continuation Phase Treatment Interruptions



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Common Adverse Reactions to Drug Treatment (1)

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergy	Skin rash
Ethambutol	Eye damage	Blurred or changed vision Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea Vomiting Yellowish skin or eyes Dark urine

Common Adverse Reactions to Drug Treatment (2)

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance	Upset stomach, vomiting, lack of appetite
	Arthralgia	Joint aches
	Arthritis	Gout (rare)
Streptomycin	Ear damage	Balance problems
		Hearing loss
		Ringing in the ears
	Kidney damage	Abnormal kidney function test results

Common Adverse Reactions to Drug Treatment (3)

Caused by	Adverse Reaction	Signs and Symptoms
Rifamycins • Rifabutin • Rifapentine • Rifampin	Thrombocytopenia	Easy bruising Slow blood clotting
	Gastrointestinal intolerance	Upset stomach
	Drug interactions	Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment

Treatment Failure

- positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured
- Single new drug should never be added to a failing regimen; it may lead to acquired resistance to the added drug
- Add at least three new drugs (e.g., fluoroquinolone, ethionamide, and an injectable drug: SM, amikacin, kanamycin, or capreomycin) to the existing regimen being cognizant of the possibility of drug resistance

Drug Resistance (1)

- Established only by drug-susceptibility testing
- Treatment of TB caused by drug-resistant organisms should be done in close consultation with an expert
- Patients not on DOT in the past or who had irregular treatment are at risk of drug resistance

Drug Resistance (2)

- Consider the following expanded regimen for drug resistance:
  - INH, RIF, PZA, EMB plus three additional agents based on probability of in vitro susceptibility (e.g., fluoroquinolone, ethionamide, or an injectable drug: SM, amikacin, kanamycin, or capreomycin)

Special Treatment Situations HIV/AIDS

- Treatment for HIV-positive patients same as for HIV-negative patients, except
  1) Once-weekly INH-rifapentine in continuation phase is contraindicated in HIV-positive patients
  2) Twice-weekly INH-RIF or INH-rifabutin should not be used in patients with CD4+ T-lymphocyte counts less than 100/:l
- Every effort should be made to use a rifamycin-based regimen for the entire course of therapy

Special Treatment Situations Extrapulmonary TB

- Similar treatment regimen for pulmonary TB*
- 6- to 9-month regimens that include INH and RIF are effective
- Corticosteroids used as adjunctive therapy for patients with TB meningitis and pericarditis
- If PZA cannot be used in the initial phase, continuation phase must be increased to 7 months

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* Except for central nervous system (CNS) TB, including meningitis; length of therapy is 9-12 months

Special Treatment Situations Pregnancy and Breastfeeding

- Untreated TB represents greater hazard to a woman and her child than tx of disease
- Tx of pregnant woman with suspected TB should be started if probability of TB is moderate to high
- Initial phase treatment regimen should consist of INH, RIF, and EMB
- SM should not be substituted for EMB because of teratogenic effects
- PZA not generally recommended for pregnant women

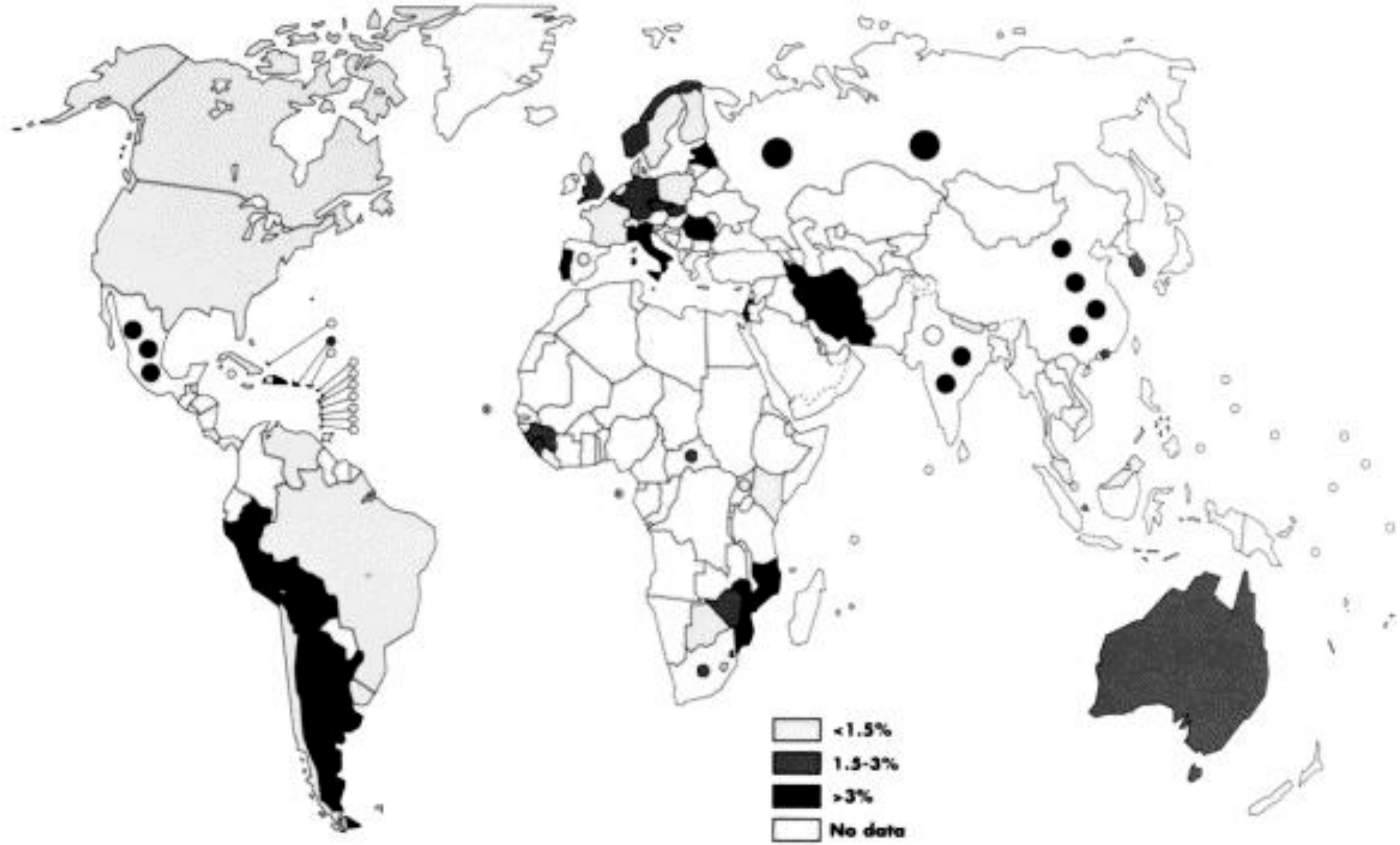
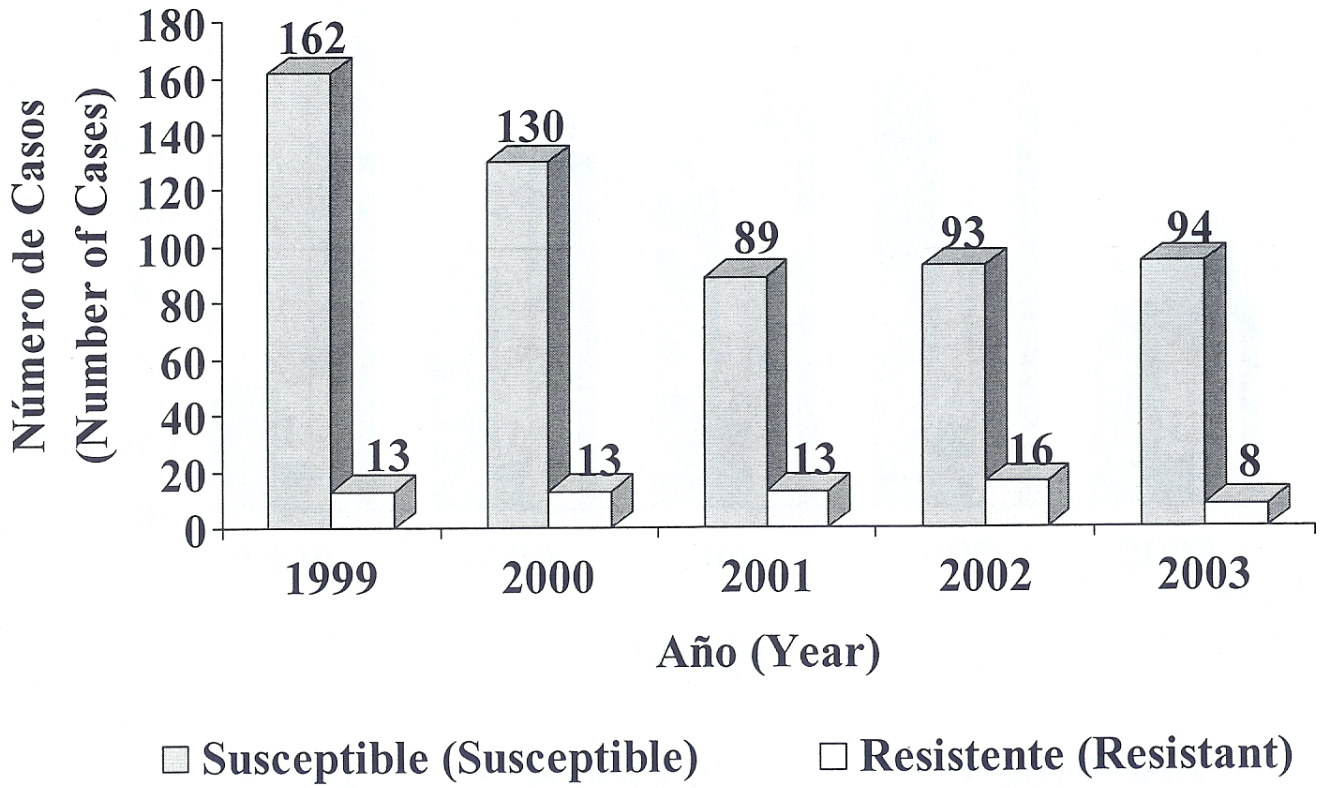


Figure 1. Prevalence of combined **multidrug-resistant tuberculosis** in countries and regions surveyed between 1994 and 1999

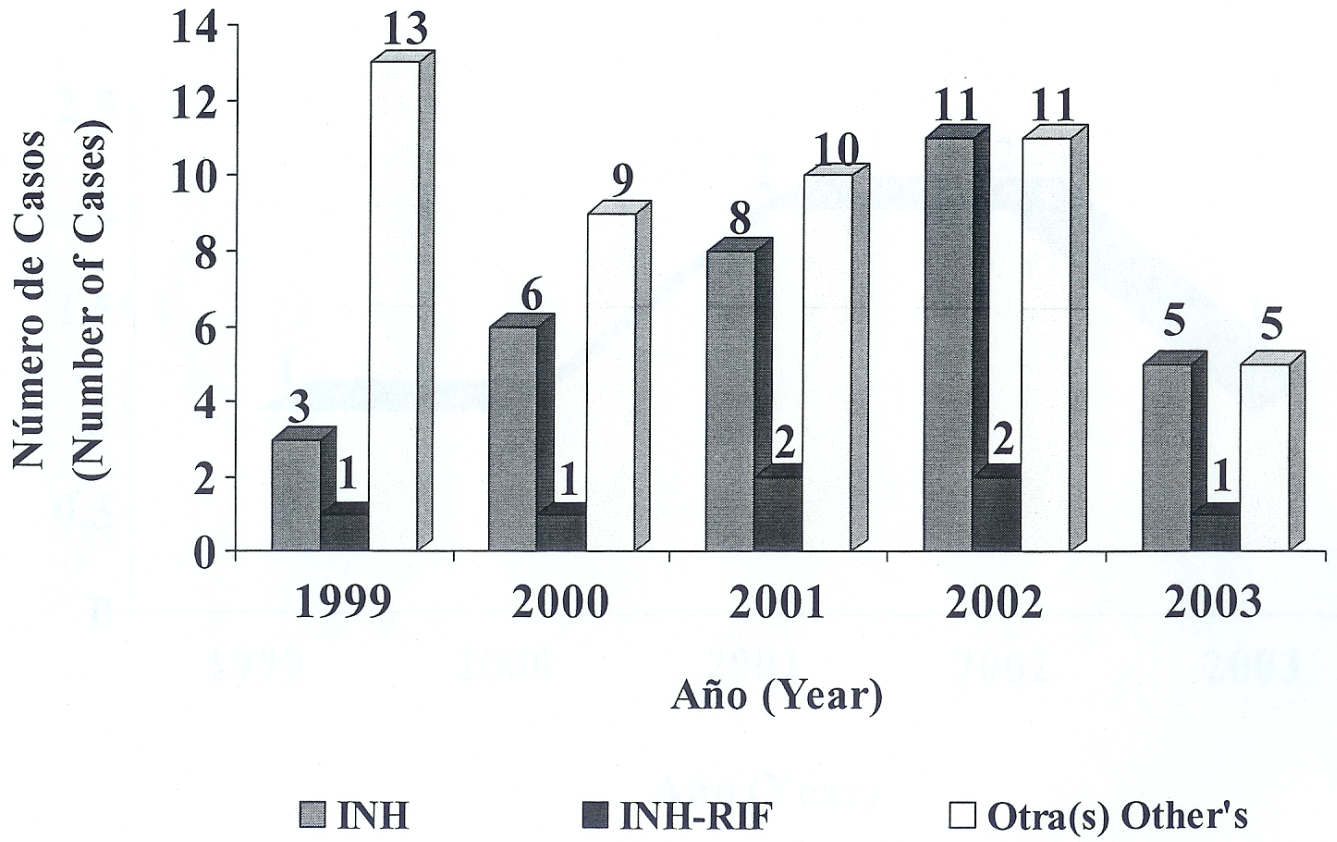
Infect Dis Clin N Am 2002, 16:1022-1025

Susceptibilidad de Casos de TB, Puerto Rico 1999-2003
(TB Cases Susceptibility, Puerto Rico 1999-2003)



Programa Control Tuberculosis
Departamento de Salud

Casos de TB Resistentes a una o más Drogas, Puerto Rico 1999-2003
(Resistant TB Cases, Puerto Rico 1999-2003)



Programa Control Tuberculosis
Departamento de Salud

Extensively drug-resistant tuberculosis (XDR TB)

- Rare type of multidrug-resistant tuberculosis (MDR TB). It is
- resistant to almost all drugs used to treat TB,
  - First line: isoniazid and rifampin
  - Is also resistant to the best second-line medications: fluoroquinolones
  - and at least one of three injectable drugs (i.e., amikacin, kanamycin, or capreomycin).
- In the United States, 49 cases of XDR TB have been reported between 1993 and 2006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Departamento de Salud
Sección para el Control de la Tuberculosis

Tel (787) 274-5553, Fax (787)274-5554

CDC:

Diagnostic Standards and Classification of Tuberculosis in Adults and Children

Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005 MMWR Vol. 54 / RR17;1-141.

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Treatment of Tuberculosis American Thoracic Society, CDC, and Infectious Diseases Society of America MMWR Recommendations and Reports 2003: 52, (RR11);1-77

Update: Adverse Event Data and Revised American Thoracic Society/ CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection---United States, 2003 MMWR 2003; 52 (No. 31)

Thank You