LA TUBERCOLOSI: UNA PATOLOGIA RI-EMERGENTE?

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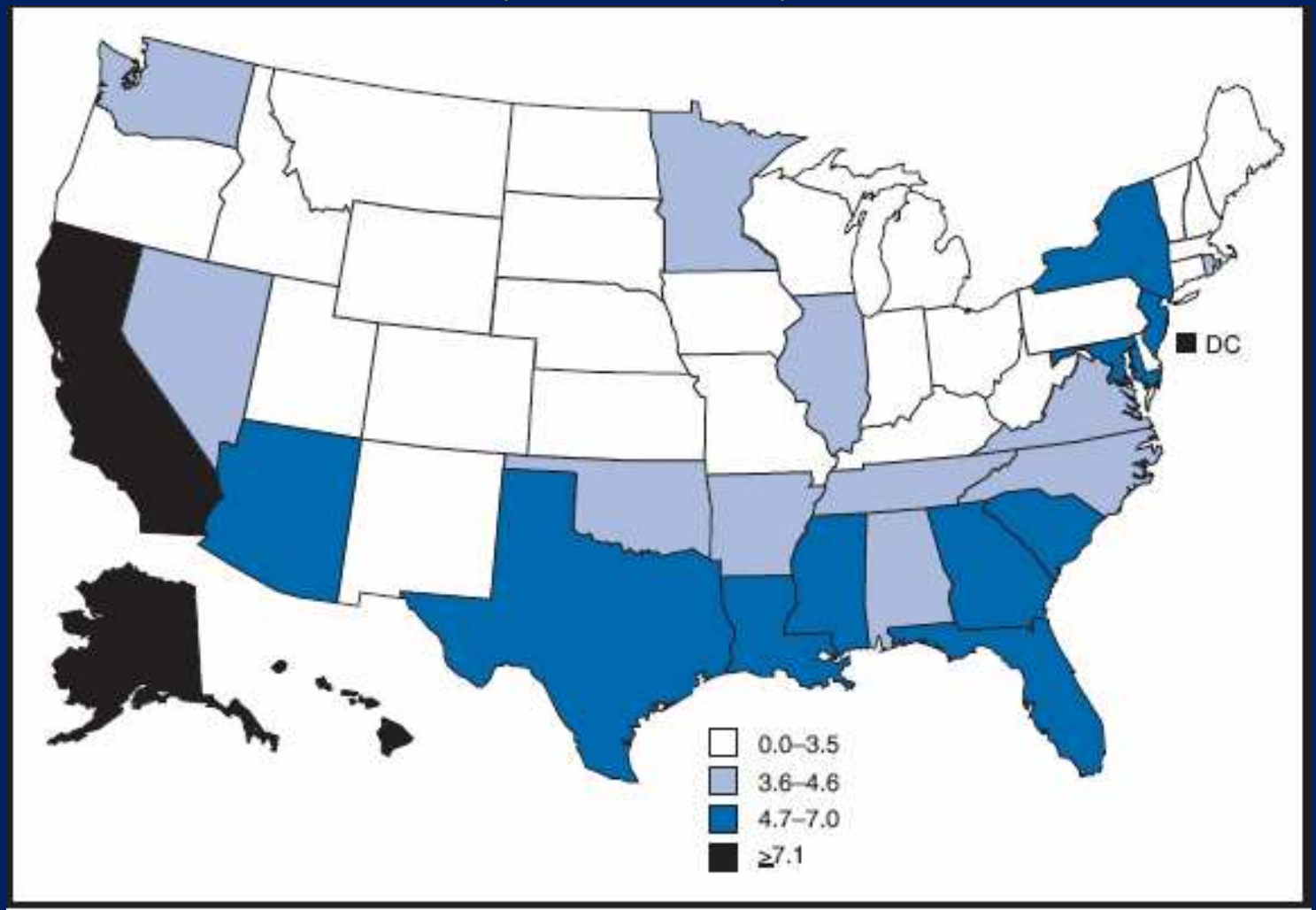
RATE OF TB CASES BY STATE (U.S.A. 2007)

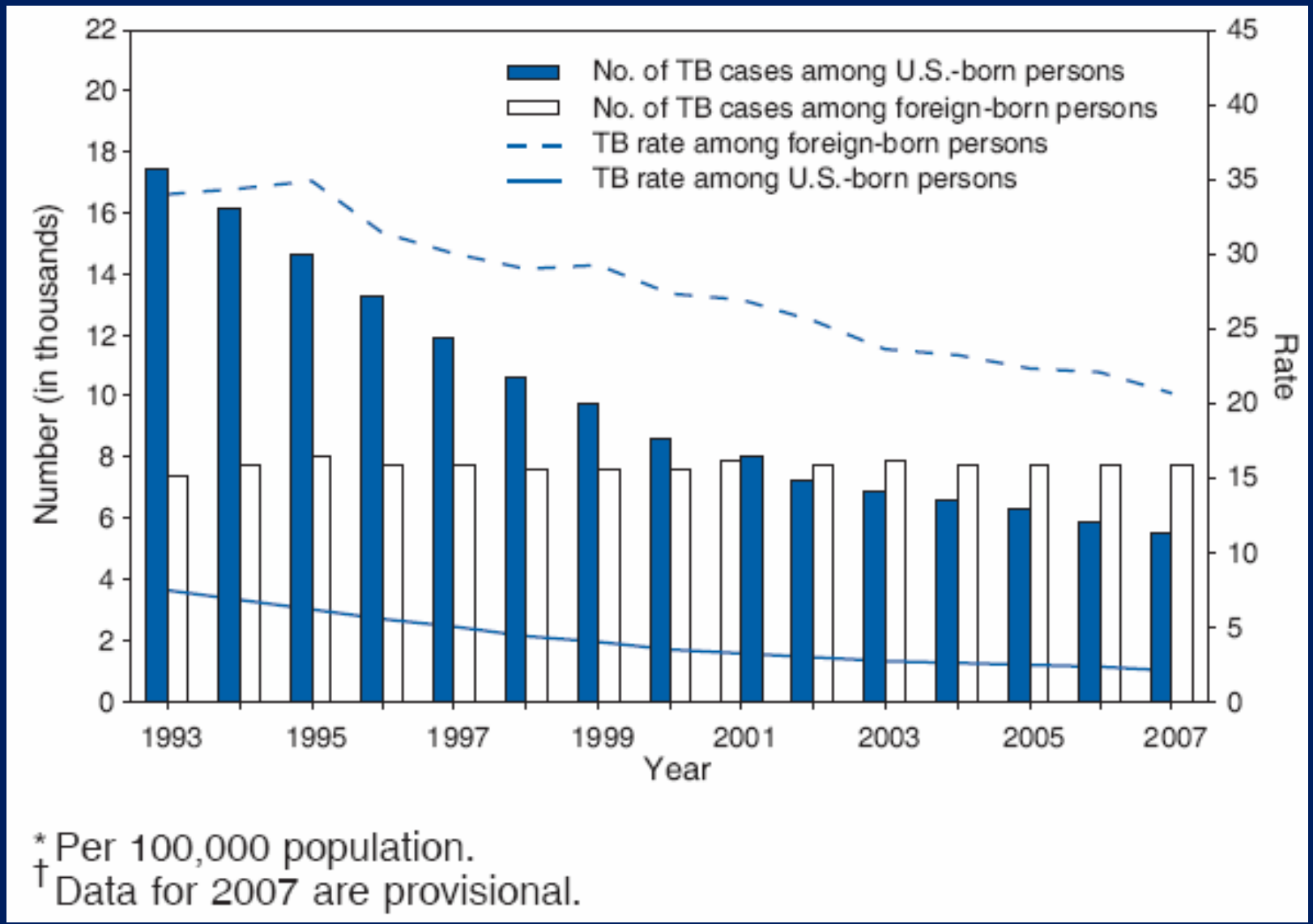
(MMWR,2007)



* Per 100,000 population.
† Data are provisional.

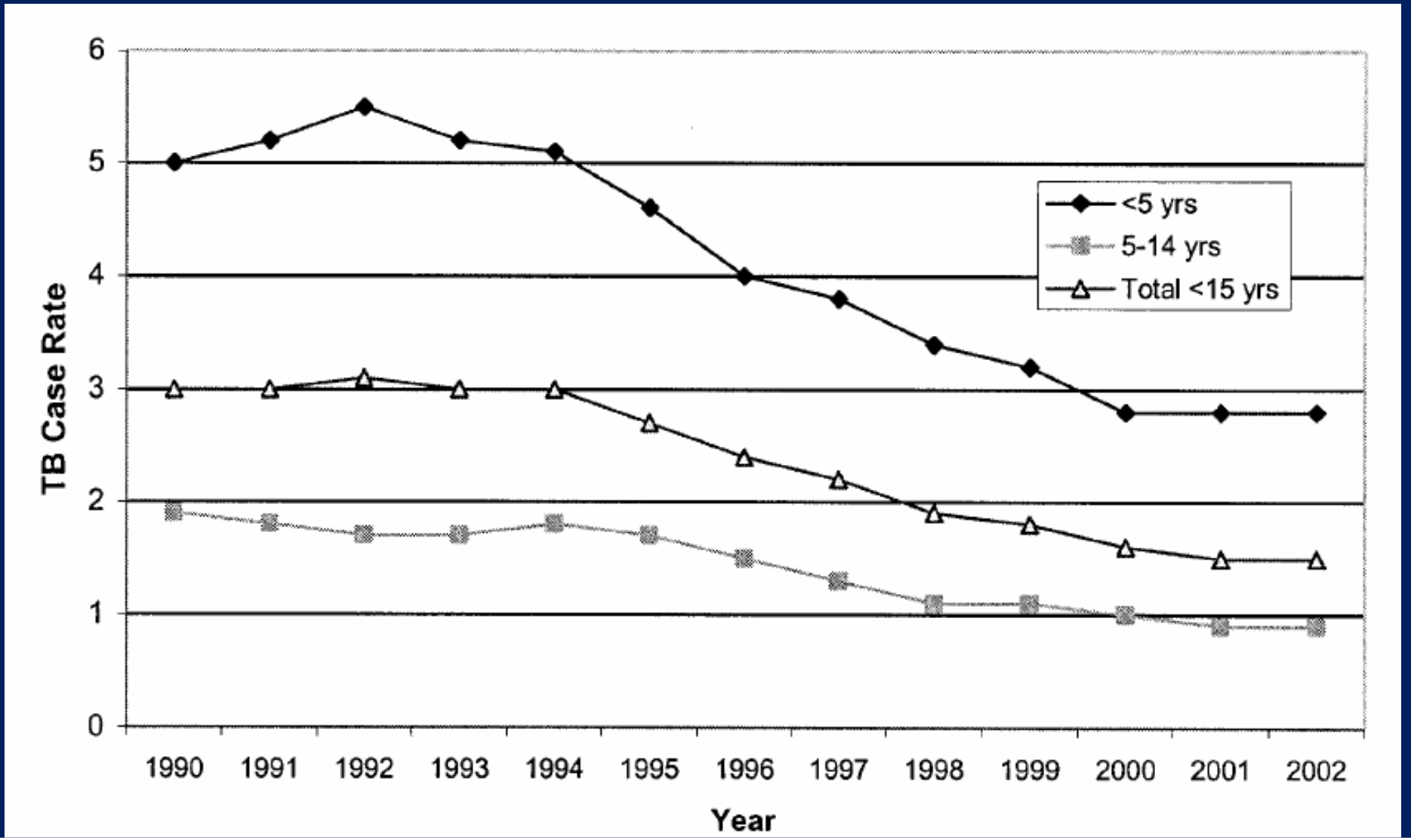
NUMBER AND RATE OF TB CASES AMONG US AND FOREING-BORN PERSONS BY YEAR (U.S.A. 1993-2007)

(MMWR 2007)

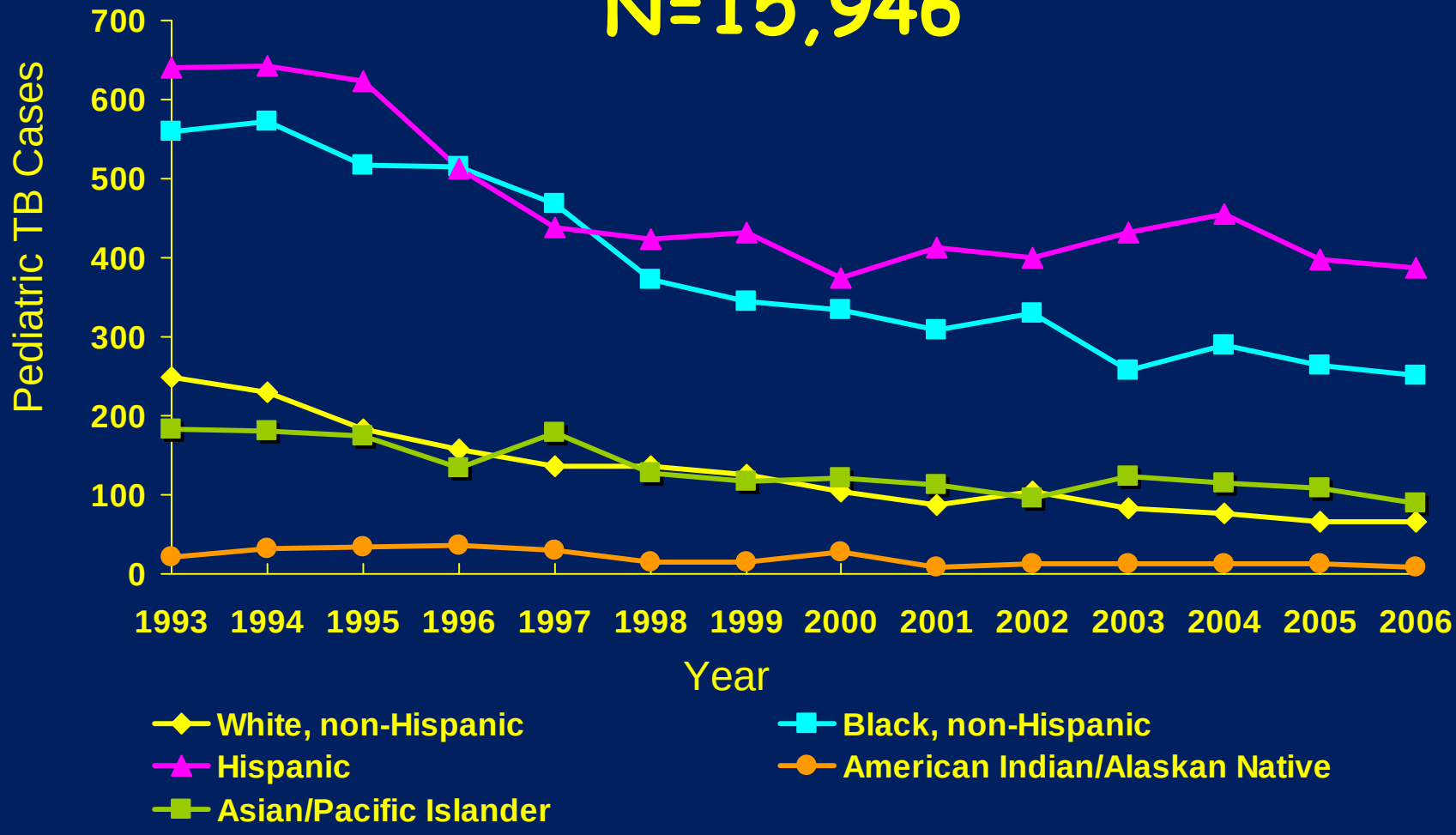


PEDIATRIC TB CASE RATES IN THE U.S.A. PER 100,000 POPULATION BY AGE GROUPS

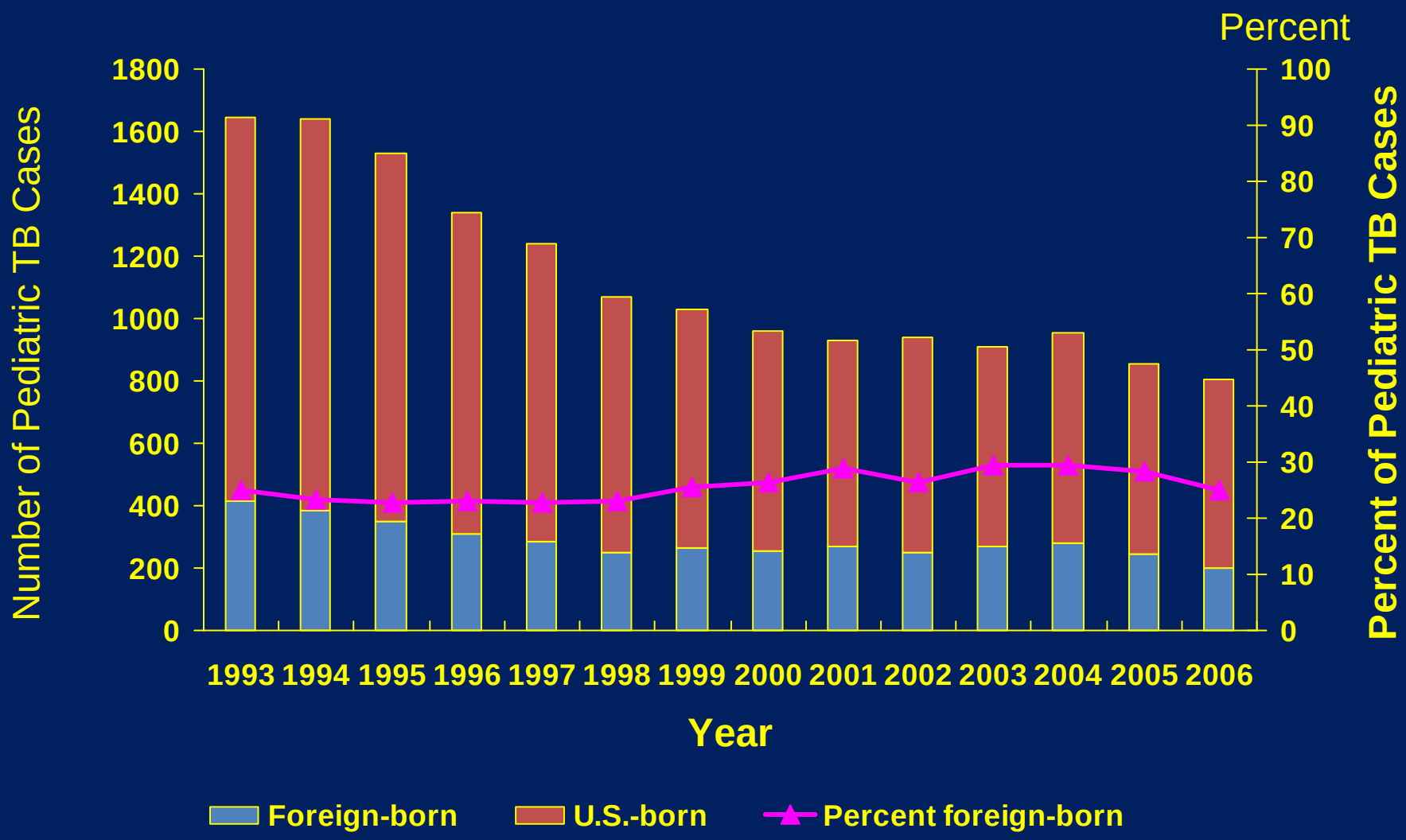
(From Pediatric Tuberculosis Collaborative Group, Pediatrics 2004)

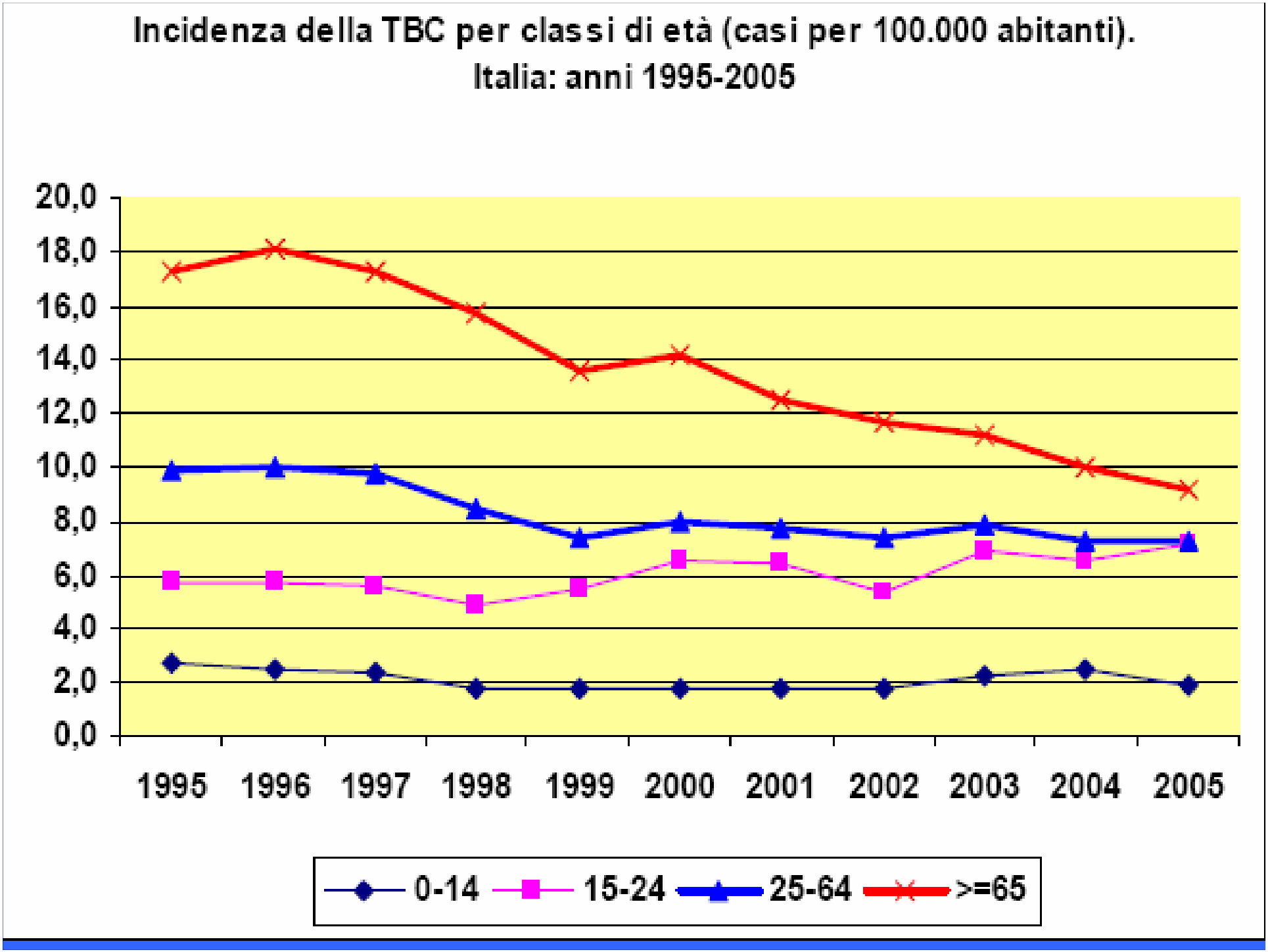


Pediatric TB Cases by Race/Ethnicity 1993–2006 N=15,946

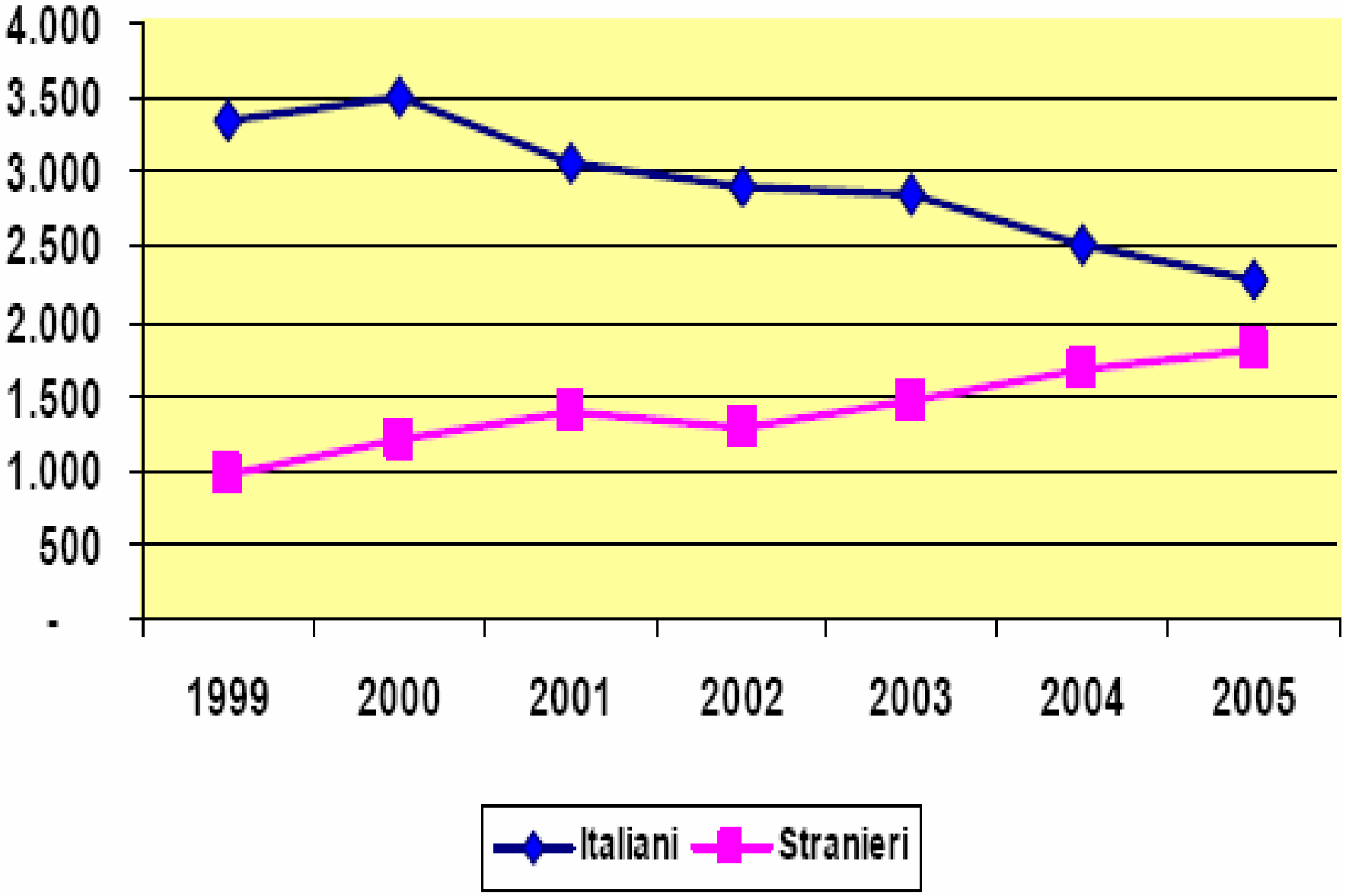


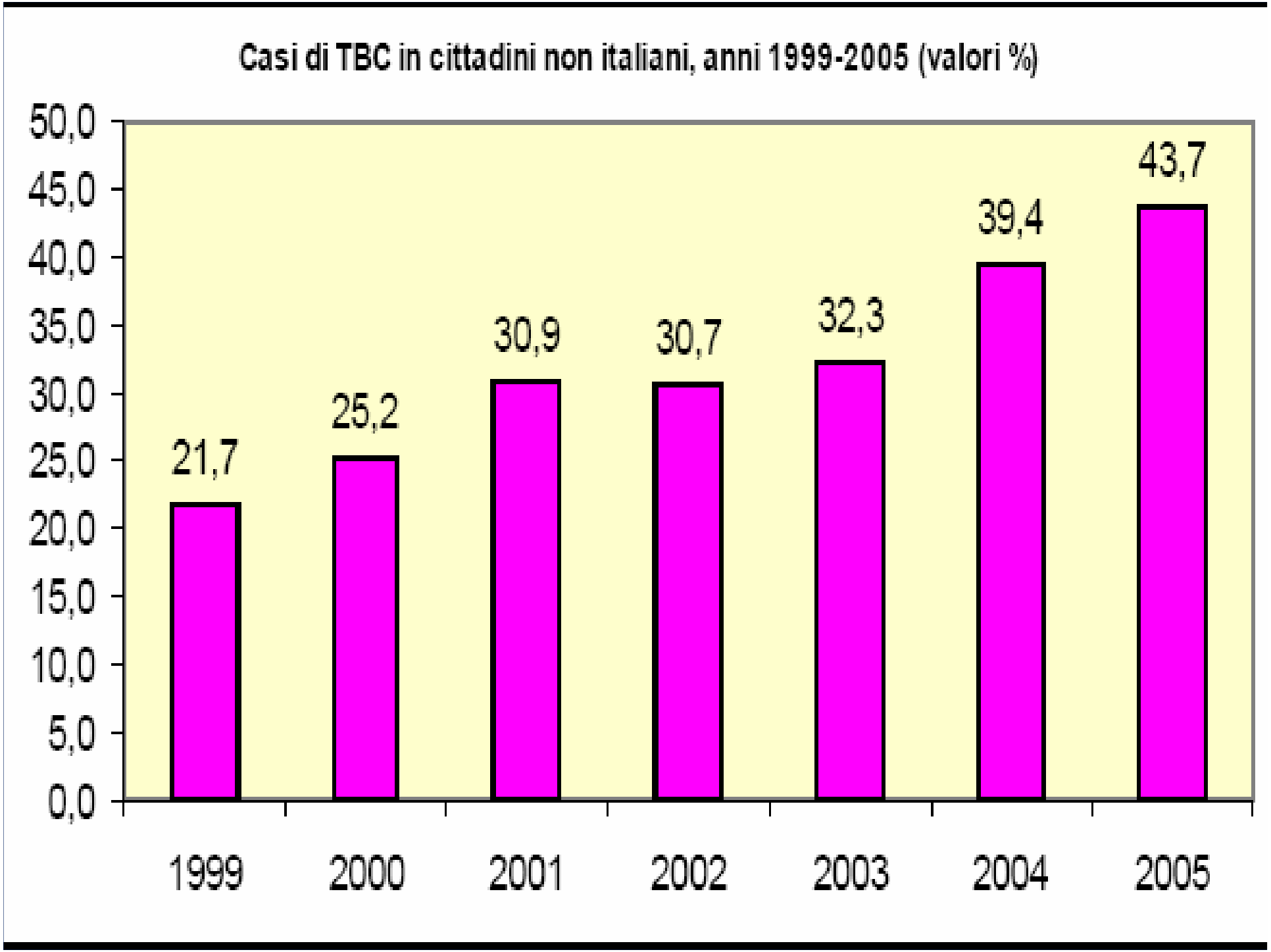
Number and Percent Foreign-born Pediatric TB Cases, 1993–2006




Incidenza della TBC per classi di età (casi per 100.000 abitanti).
Italia: anni 1995-2005
20,0
18,0
16,0
14,0
12,0
10,0
8,0
6,0
4,0
2,0
0,0
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
0-14
15-24
25-64
>=65

Casi di TBC in Italia, per nazioanlità. Anni 1999-2005




Casi di TBC in cittadini non italiani, anni 1999-2005 (valori %)
50,0
45,0
40,0
35,0
30,0
25,0
20,0
15,0
10,0
5,0
0,0
21,7
25,2
30,9
30,7
32,3
39,4
43,7
1999
2000
2001
2002
2003
2004
2005

Terminology

- "Treatment of latent TB infection" replaces the terms "preventive therapy" and "chemoprophylaxis" to promote greater understanding of the concept for both patients and providers.
- Targeted tuberculin testing is used to focus program activities and provider practices on groups at the highest risk for TB.

LTBI vs. Pulmonary TB Disease

Latent TB Infection

- TST* or QFT† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

Pulmonary TB Disease

- TST or QFT usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

*tuberculin skin test

†QFT (QuantiFERON-TB and QuantiFERON-Gold) is a blood test to detect *M. tuberculosis* infection.

DEFINITIONS OF POSITIVE TST RESULTS IN CHILDREN AND ADOLESCENTS USING 3 CUTOFF LEVELS (I)

(From Pediatric Tunerculosis Collaborative Group, Pediatrics 2004)

Induration ≥5 mm

- Children or adolescents in close contact with a known or suspected infectious case of TB
- Children or adolescents with suspected TB disease:
  - Finding on chest radiograph consistent with active or previously active TB
  - Clinical evidence of TB disease
- Children or adolescents who are immunosuppressed (eg, receiving immunosuppressive therapy or with immunosuppressive conditions [eg, HIV infection])

DEFINITIONS OF POSITIVE TST RESULTS IN CHILDREN AND ADOLESCENTS USING 3 CUTOFF LEVELS (II)

(From Pediatric Tunerculosis Collaborative Group, Pediatrics 2004)

Induration ≥10 mm

- Children or adolescents at increased risk of disseminated disease:
  - Those <4 y old
  - Those with concomitant medical conditions (eg, Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition)
- Children or adolescents with increased risk of exposure to cases of TB disease:
  - Those born in a country with a high prevalence of TB cases
  - Those who travel to a country with a high prevalence of TB cases
  - Those with parents born in a country with a high prevalence of TB cases
  - Those frequently exposed to adults with risk factors for TB disease (eg, adults who are HIV-infected or homeless, users of illicit drugs, those who are incarcerated, or migrant farm workers)

DEFINITIONS OF POSITIVE TST RESULTS IN CHILDREN AND ADOLESCENTS USING 3 CUTOFF LEVELS (III)

(From Pediatric Tunerculosis Collaborative Group, Pediatrics 2004)

Induration ≥15 mm

Children ≥4 y old with no known risk factors

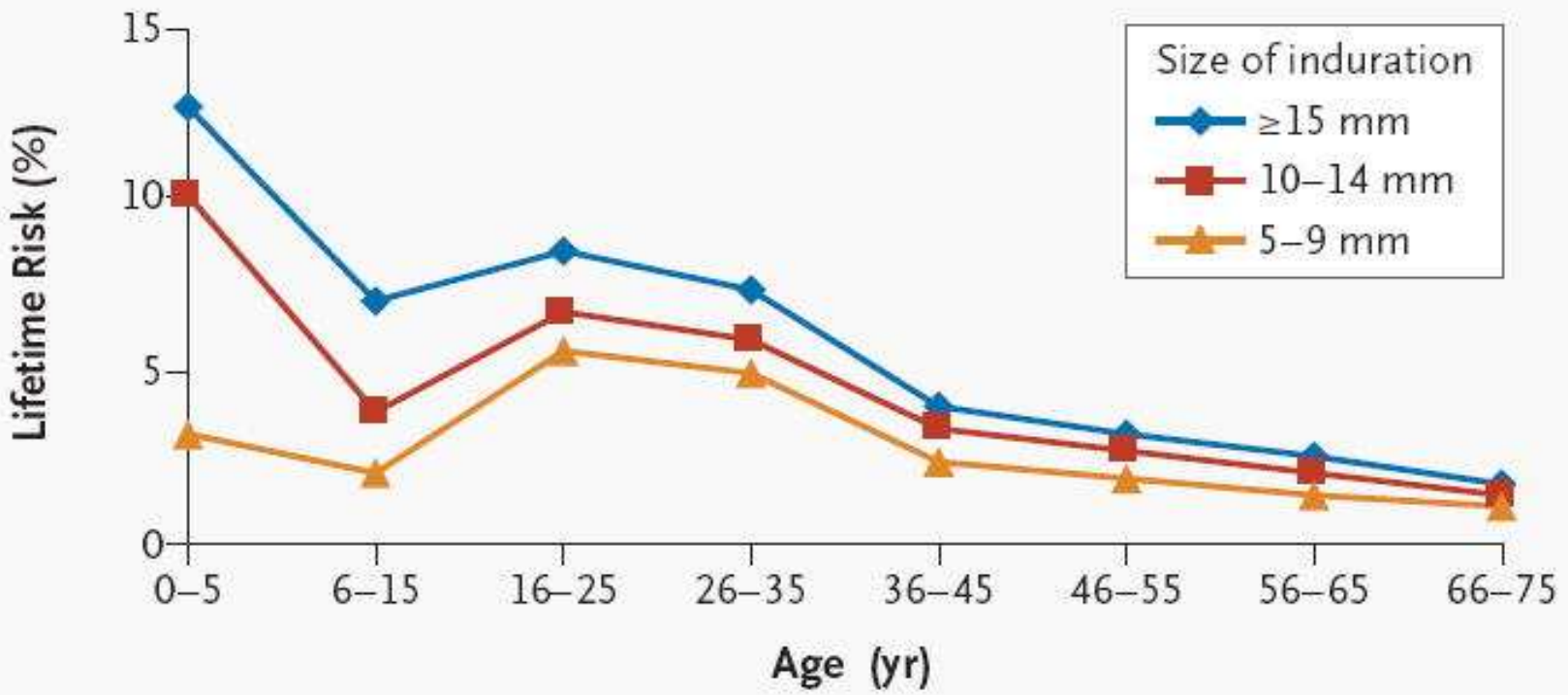


Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Non-conversion Positive Tuberculin Skin Test.

Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.

Da Horsburg R. N Engl J Med 2004

FACTORS ASSOCIATED WITH FALSE/NEGATIVE OR FALSE/POSITIVE TST REACTIONS

(From Pediatric Tunerculosis Collaborative Group, Pediatrics 2004)

Factors	False-Negative Reactions	False-Positive Reactions
Infections	Viral illnesses (HIV, measles, varicella) Bacterial (typhoid fever, brucellosis, typhus, leprosy) Early TB infection (<12 wk) TB disease (meningitis, miliary, pleural) Fungal (*Blastomycosis*)	Exposure to NTM (eg, *M marinum, M kansasi*
Live virus vaccines	Measles Polio Smallpox	BCG vaccine
Concomitant medical conditions	Metabolic abnormalities (chronic renal failure) Malignancies (Hodgkin's disease, lymphoma, leukemia) Sarcoidosis Poor nutrition	Transfusion with whole blood from donors with known positive TST[152]
Drugs and technical factors	Corticosteroids, chemotherapy Newborns and <2 y of age Material: poor quality; inadequate dose (1 TU); improper storage (exposure to heat/light); expired Administration: not injected intradermally; too long in syringe Reading: inexperienced or biased reader; recording error; read too early/late	Inexperienced or biased reader
Interpretative	Decreasing mm of induration	Increasing mm induration

EFFECT OF BCG IMMUNIZATION ON TST REACTIVITY

(From Pediatric Tunerculosis Collaborative Group, Pediatrics 2004)

Country*	Subjects, *n*	BCG Immunization, age	TST Placed	TST ≥ 10 mm, %	Comment
Sri Lanka[81]	112	<1 mo	3 mo	~12	Values approximated from figures
	106	<1 mo	18 mo	~18	
	285	<1 mo	5 to 7 y	~7	
	237	<1 mo	9 to 11 y	~6	
United States (Navajo Indian)[83]	250	Birth	3 mo	31	
		Birth	9 mo to 4 y	0	
		Birth	5 y	2	
		Birth	6 y	4	
Saudi Arabia[85]	1522	Birth	5 to 11 y	6–13	Comparable to age-matched unvaccinated controls
	224	Birth	12 y	20	4% (3 of 77) among unvaccinated controls† ($P < .001$)
	199	Birth	13 y	16	4% (3 of 73) among unvaccinated controls† ($P = .006$)
Israel[82]	512	Birth	7 to 24 mo	2.5	
Chile[86]	40	Birth	6 y	10	Repeat TST in 2 wk: 45% ≥ 10 mm
Uganda[77]	151	Birth	≤5 y	15	53% (75 of 142) known TB exposure‡
South Africa[84]	85	Birth	6 mo to 6 y	13	
Canada[87]	463	Birth	11 y	5	
	198	Birth	16 y	8	
Brazil[76]	60	Birth	0 to 5 y	0	45% (18 of 40) known TB exposure‡
Botswana[78]	781	Birth	3 mo to 5 y	6–8	
Israel[82]	135	13 y	14 y	36	
Denmark[90]	601	7 y	8 to 10 wk later	~38–99	Values approximated from figures; dependent on vaccine type
			12 y	~39–97	
Canada[87]	306	2–8 y	11 y	13	
			16 y	17	
			18 to 25 y	26	
United States (Alabama)[91]	63	> 5 y	18 to 21 y (8–15 y later)	16	
Brazil[76]	233	Birth and school age	5 to 9 y	2	44% (22 of 50) known TB exposure‡
			≥10 y	6	53% (27 of 51) known TB exposure‡
South Africa[84]	42	Birth and school age	6 to 14 y	33	
Israel[82]	96	Birth and age 13 y	14 y	62	
Sri Lanka[81]	61	Birth and age 10 y	3 mo after 2nd BCG	53	

PUBLISHED STUDIES ON DIAGNOSTIC PERFORMANCE OF THE NEW BLOOD TESTS FOR SENSITIVITY IN LATENT TUBERCULOSIS INFECTION

(From Lalvani et al., Chest 2007)

ELISpot (T-SPOT.*TB*)†			ELISA (QuantiFERON-Gold)‡		
Study Design	Subjects, No.	Correlation With Tuberculosis Exposure	Study Design	Subjects, No.	Correlation With Tuberculosis Exposure
Contact tracing[16]	535		Contact tracing[20]	125	Same as TST
Contact tracing[18]	413		Case control[14]	48	Higher than TST
Contact tracing[19]	91		Total	173	
Contact tracing[17]	88	Higher than TST§			
Contact tracing[7]	50				
Total	1,136				

*In the absence of a "gold standard" for LTBI, these studies used degree of exposure to infectious index cases as a surrogate reference standard.
†ELISpot correlates with tuberculosis exposure better than TST.
‡ELISA has similar correlation with tuberculosis exposure as TST.
§Statistically significant ($p = 0.03$ and $p = 0.007$) difference between ELISpot and TST in Ewer et al.[16]

PUBLISHED STUDIES ON DIAGNOSTIC PERFORMANCE OF THE NEW BLOOD TESTS FOR SPECIFITY IN BCG-VACCINATED UNEXPOSED CONTROL SUBJECTS

(From Lalvani et al., Chest 2007)

ELISpot (T-SPOT.*TB*)*			ELISA (QuantiFERON-Gold)†		
Study Design	Subjects, No.	Specificity, %	Study Design	Subjects, No.	Specificity, %
Case control[10]	28	100	Case control[9]	216	98
Case control[23]	40	100	Case control[14]	99	96
Case control[5]	33	100	Total	315	
Case control[4]	26	100			
Total	127				

*ELISpot more specific than TST.
†ELISA more specific than TST.

RECOMMENDED DOSAGES FOR THE TREATMENT OF LTBI IN CHILDREN AND ADOLESCENTS

(From Pediatric Tuberculosis Collaborative Group, Pediatrics 2004)

Dosage	INH
Daily dose	10–15 mg/kg
Maximum dose	300 mg
Daily dose by weight categories	
3–5 kg	50 mg
6–7.5 kg	75 mg
7.5–10 kg	100 mg
10–15 kg	150 mg
15–20 kg	200 mg
>20 kg	300 mg
Weekly dose	
2 times per wk	20–30 mg/kg
Maximum dose	900 mg
3 times per wk	20–30 mg/kg
Maximum dose	900 mg

Rifampin is occasionally used for LTBI treatment for children at 10 to 20 mg/kg per dose up to a maximum of 600 mg.

Rifampin Regimens (1)

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

Laboratory Monitoring (1)

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with the following risk factors:

- HIV infection
- History of liver disease
- Alcoholism
- Pregnancy or in early postpartum period

Laboratory Monitoring (2)

Repeat laboratory monitoring if patient has

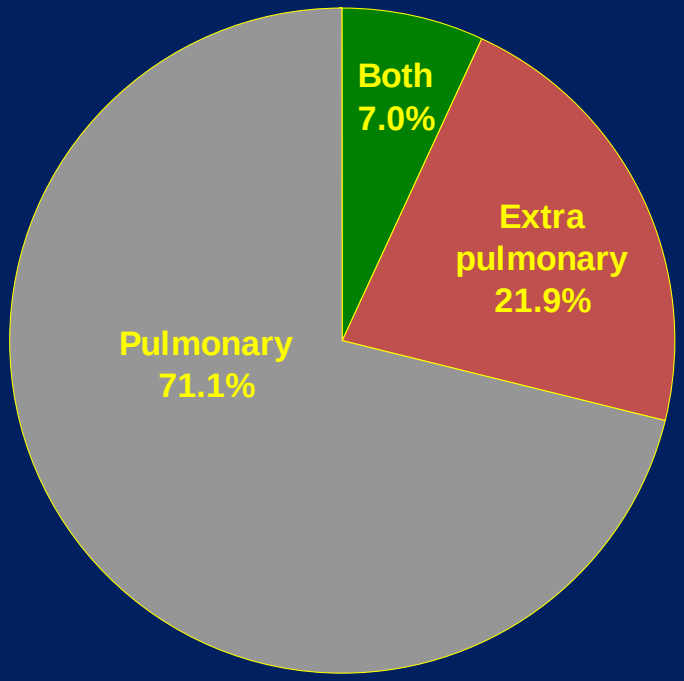
- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination

Laboratory Monitoring (3)

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of treatment
- Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic[7]

[7]MMWR June 9, 2000; 49(No. RR-6): 39

Pediatric TB Cases by Site of Disease, 1993–2006



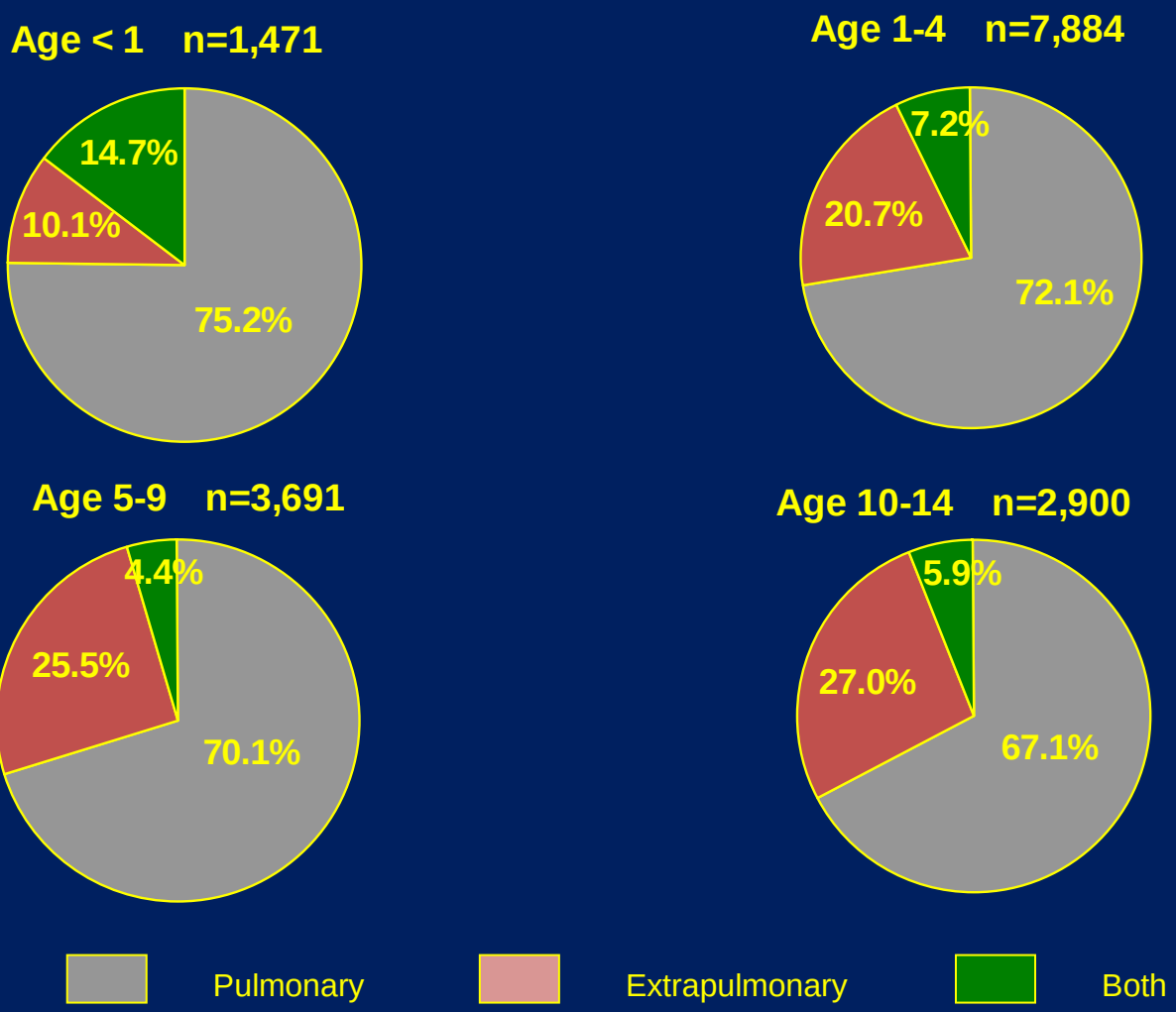
Any extrapulmonary involvement*
(totaling 28.9%)

Lymphatic	18.9%
Meningeal	3.1%
Miliary	1.5%
Bone & Joint	1.5%
Other	3.9%

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both

Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

Percent of Pediatric TB Cases by Site of Disease*, 1993–2006 N=15,946



Pediatric TB Cases by HIV Status, 1993–2005*
N=14,990

- **Information on HIV result is not available for the majority of pediatric TB cases (80.7%)**
- **Percent of pediatric TB cases with HIV-positive test results, minimum estimate** (1.0%)**
- **Percent of pediatric cases with HIV-positive test results of those patients with known results (5.1%)**

*California HIV data through 2004 only
**Pediatric TB cases with positive HIV test results divided by all pediatric TB cases .
California only reports positive HIV test results based on TB and AIDS registry matching; all other California TB cases are classified as “Unknown.”

SYMPTOMS OF PULMONARY TB

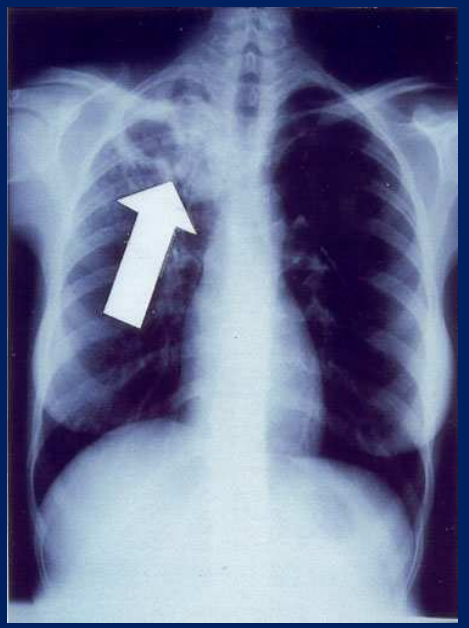
- Productive, prolonged cough (duration of >3 weeks)
- Chest pain
- Hemoptysis

SYSTEMIC SYMPTOMS OF TB

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability

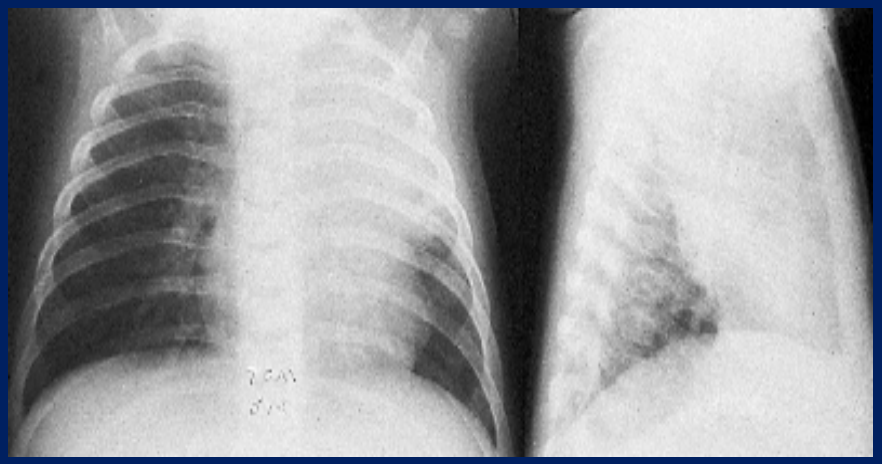
CHEST RADIOGRAPH

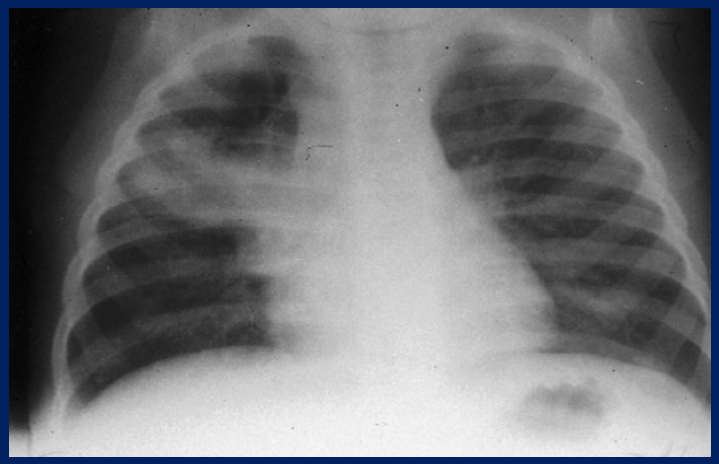
- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe
- May have unusual appearance in HIV-positive persons
- Cannot confirm diagnosis of TB

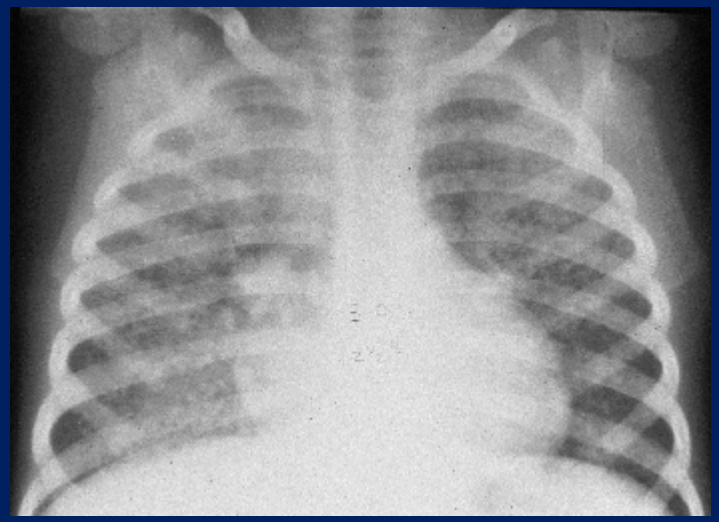


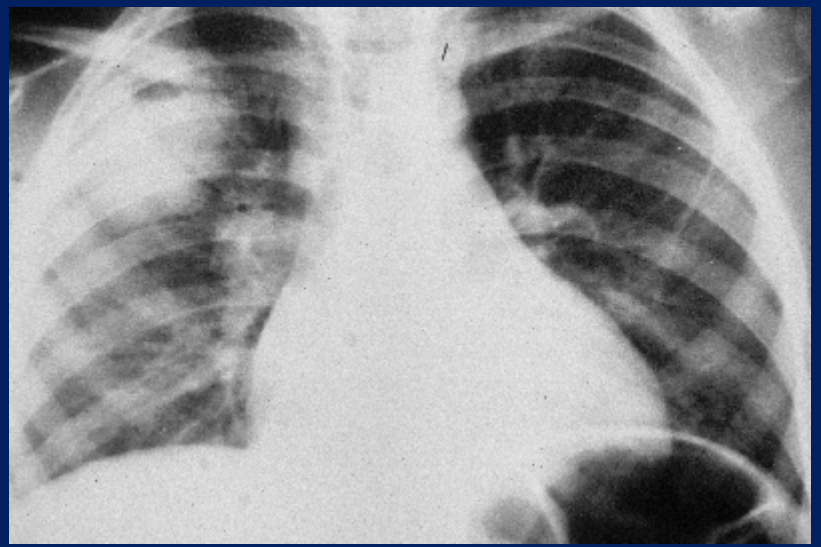
Arrow points to cavity in patient's right upper lobe

TUBERCOLOSI IN ETA' PEDIATRICA

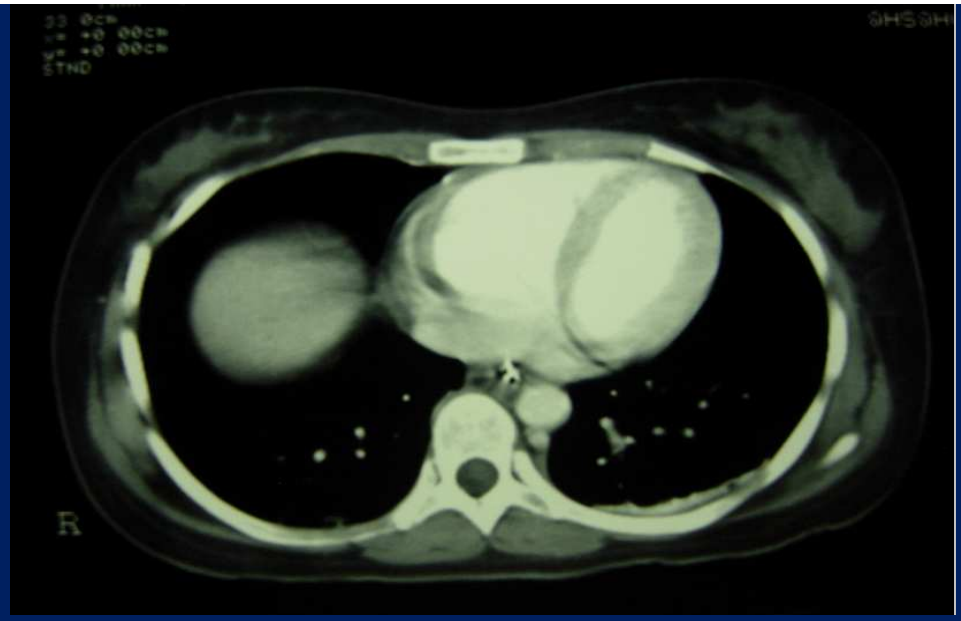


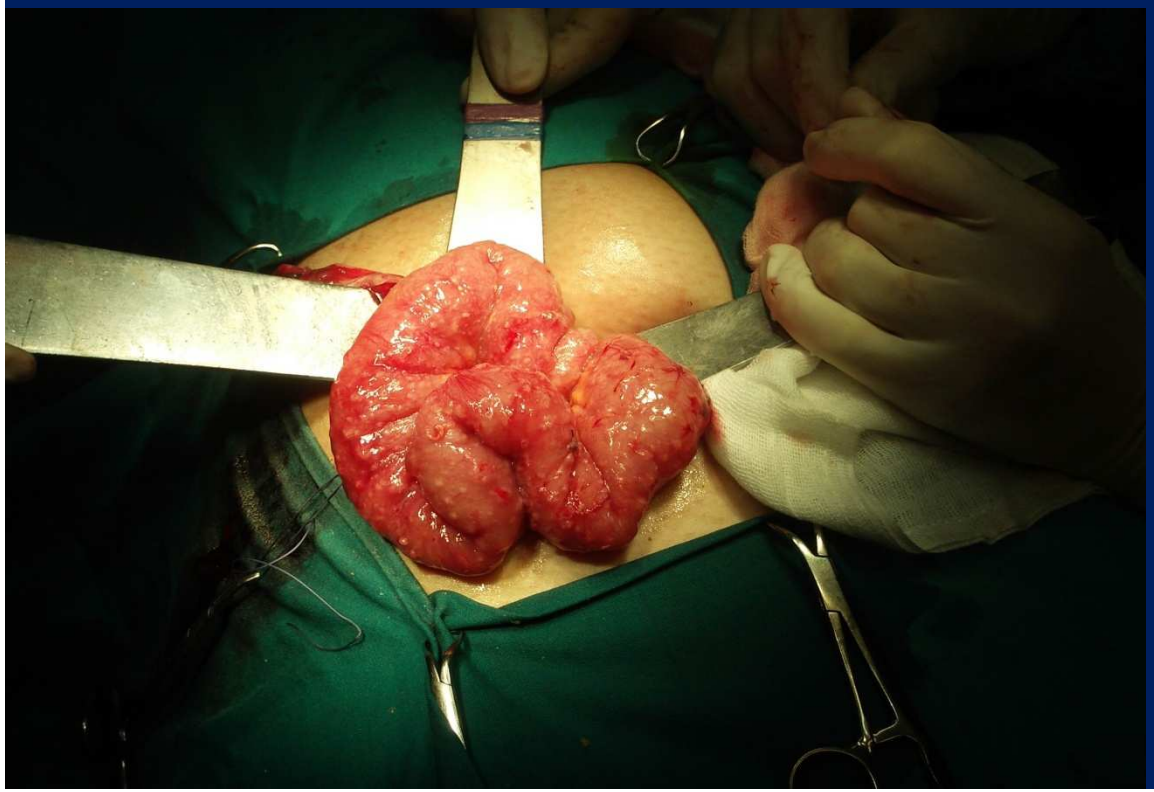






LINFOADENITE TUBERCOLARE





PERITONITE TUBERCOLARE

TB Case Definition and Verification

- Incident case of disease
- Case verification categories:
  1) Laboratory confirmed cases-"Gold Standard"
     - Positive culture, DNA probe, or nucleic acid amplification test
     - Positive AFB smear when culture not attainable
  2) Clinical case definition
     - Positive tuberculin skin test
     - Signs and symptoms of TB disease
     - Current treatment for TB disease
  3) Provider diagnosis:
     - Diagnosed by health care provider
     - Does not fulfill all criteria necessary to meet laboratory or clinical case definitions

SPECIMEN COLLECTION

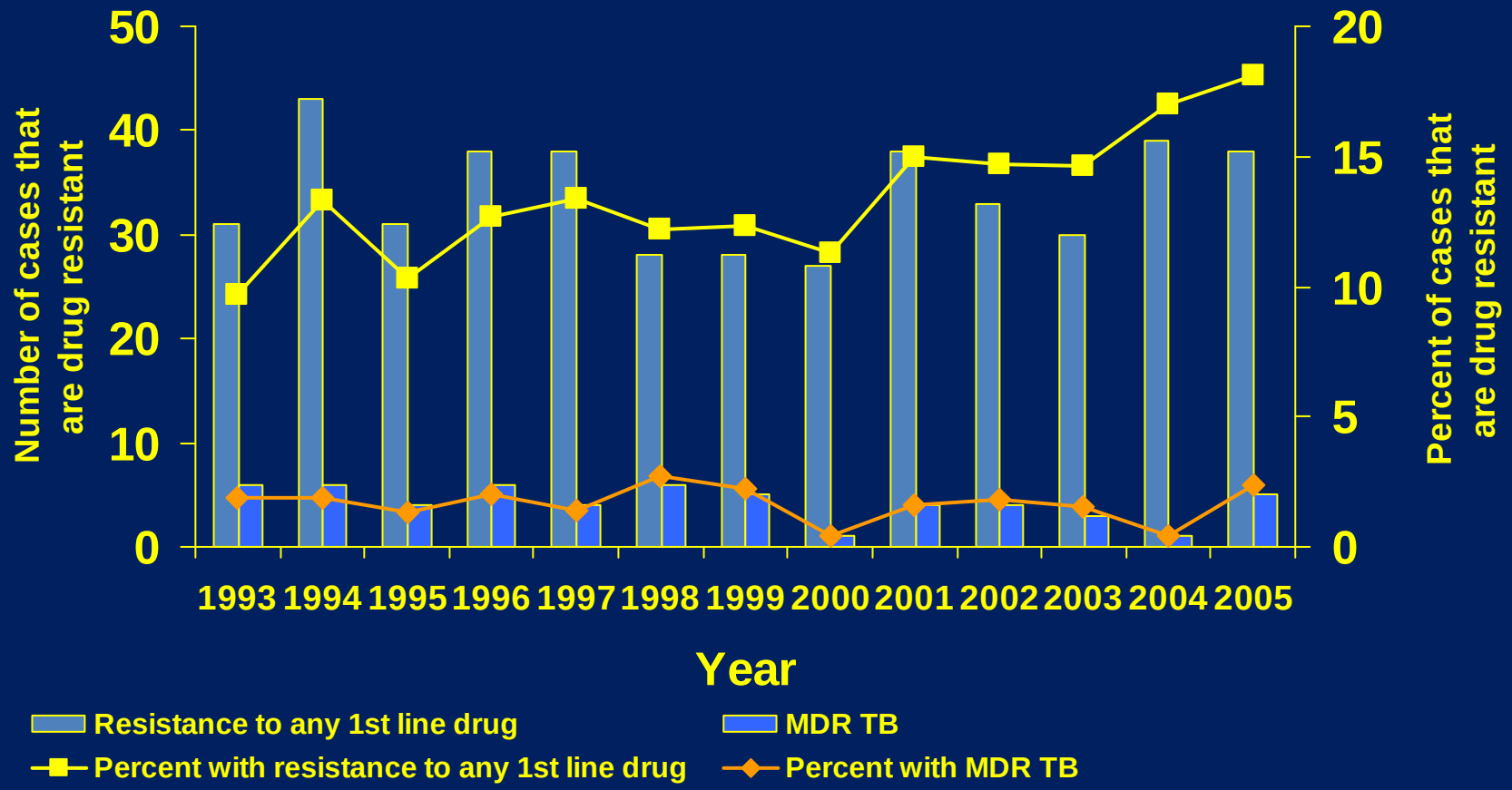
- Obtain 3 sputum specimens for smear examination and culture
- Persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspiration
- Follow infection control precautions during specimen collection

DEATHS OCCURRING AMONG PEDIATRIC TB CASES, BY AGE GROUP, 1993–2004
N=14,282

Age Group of Cases	Cases	Deaths**	%
Age < 1	1298	26	2.0
Age 1-4	7094	46	0.6
Age 5-9	3334	20	0.6
Age 10-14	2556	20	0.8

Note: Cause of death not recorded in TB case reports
**Death includes died during therapy or dead at TB diagnosis

Number and Percent of Culture-confirmed Pediatric TB Cases with Drug Resistance, 1993–2005

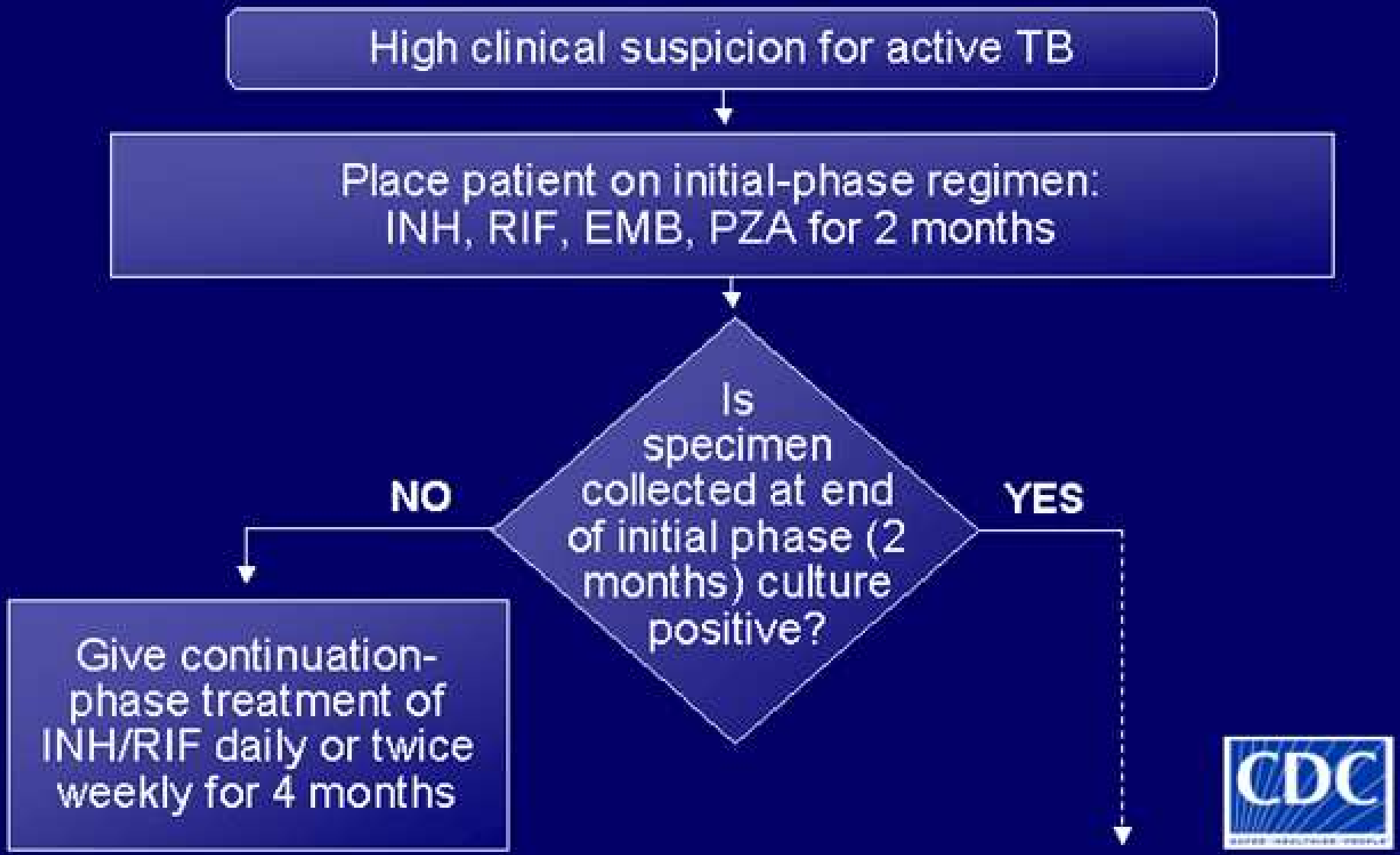


First line drugs are Isoniazid, Rifampin, Pyrazinamide and Ethambutol
MDR TB = resistance to at least Isoniazid and Rifampin

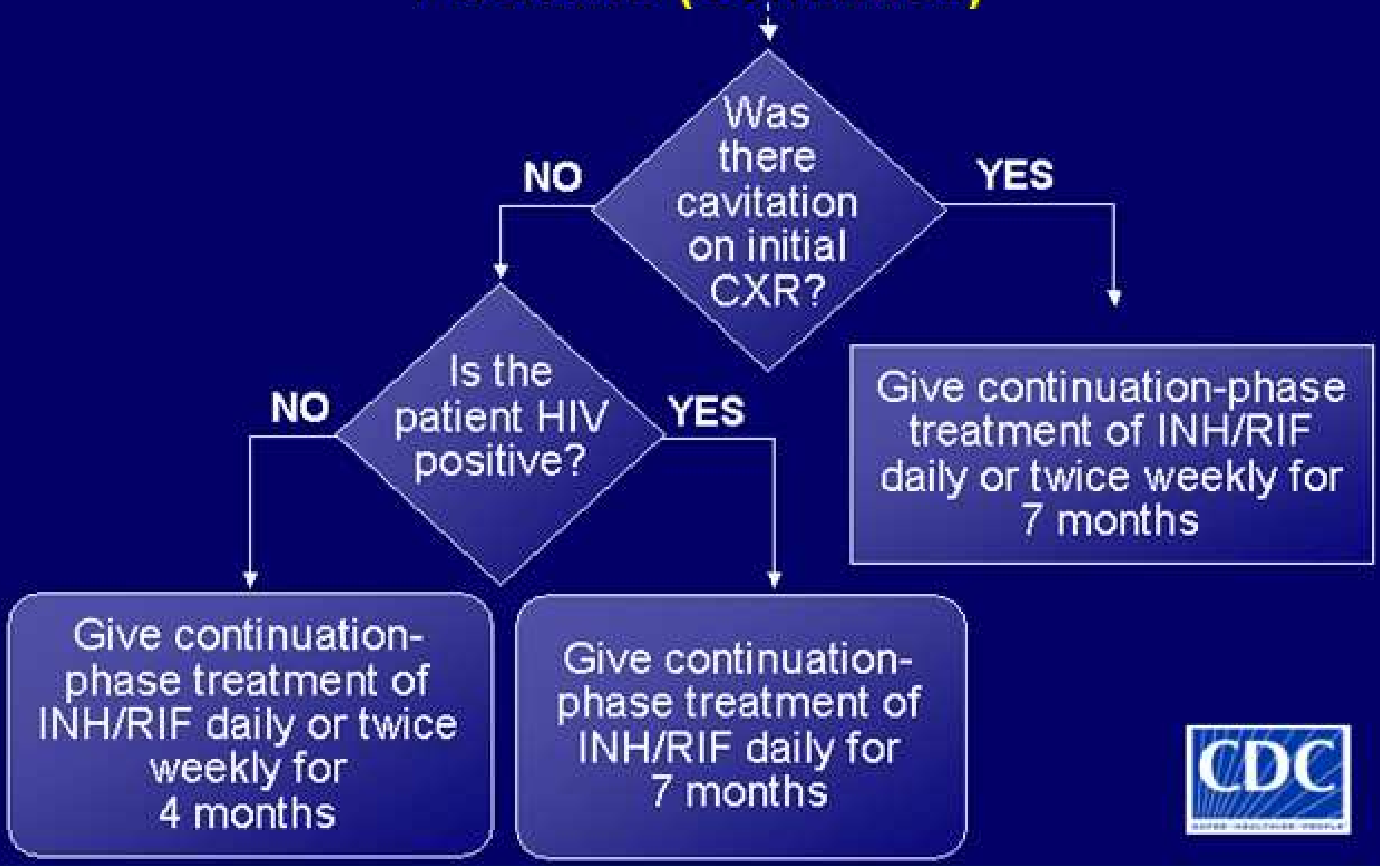
When to Consider Treatment Initiation

- 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

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)



Special Treatment Situations (Children and Adolescents)* (1)

- Use DOT
- Treat young children (<5 years old) with three (rather than four) drugs in initial phase (i.e., INH, RIF, and PZA)
- EMB not recommended unless increased likelihood of INH resistance or diagnosis of adult-like TB**

* Defined as persons <15 years old
** Defined as upper-lobe infiltration and cavitation associated with sputum production

CDC

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