In the name of GOD

Challenges of Diagnosis and Treatment of Mycobacteria

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Mycobacterium

- Mycobacteria are Gram-positive, catalase positive, non-motile, non-spore forming rod-shaped bacteria (0.2–0.6 μm wide and 1.0–10 μm long)

Acid-fast stains such as Ziehl–Neelsen, or fluorescent stains such as auramine are used to identify M. tuberculosis

WIKIPEDIA Mycobacterium : https://en.wikipedia.org/wiki/Mycobacterium

Species: Over 190 species

Slowly growing:

- M. tuberculosis complex
- M. avium complex
- M. gordonae clade
- M. kansasii clade
- M. terrae clade
- M. simiae clade
- Ungrouped

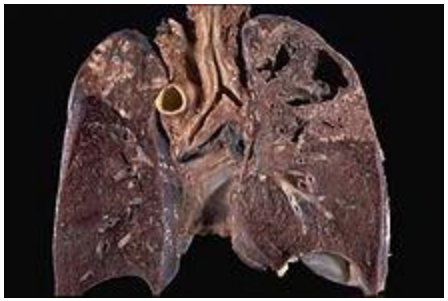
Rapidly growing:

- M. abscessus clade
- M. chelonae clade
- M. fortuitum clade
- M. mucogenicum clade
- M. parafortuitum clade
- M. vaccae clade
- Ungrouped

-

WIKIPEDIA Mycobacterium : https://en.wikipedia.org/wiki/Mycobacterium

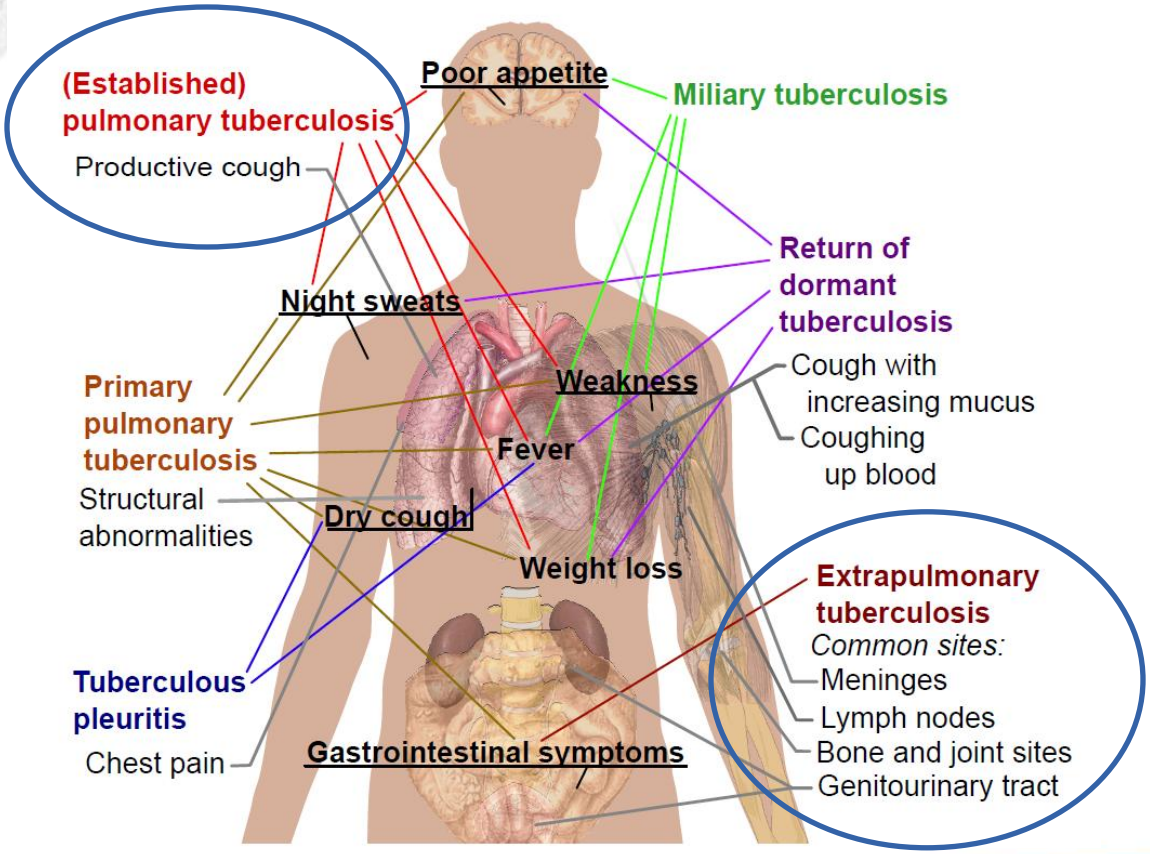
Clinical chapters/importance



- TB (M. tuberculosis)
- Leprosy (Mycobacterium leprae)
- Mycobacterium avium complex (MAC)
- Non-tuberculous Mycobacteria, NTM (other than MAC)

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition, 2020

Clinical manifestations/diseases



https://upload.wikimedia.org/wikipedia/commons/2/2f/Tuberculosis_symptoms.svg

History

- The oldest detected M. tuberculosis complex (MTBC) gives evidence of the disease in the remains of bison in Wyoming dated to around 17,000 years ago

https://en.wikipedia.org/wiki/Tuberculosis

History

Egyptian mummy in the British Museum – tubercular decay has been found in the spine.

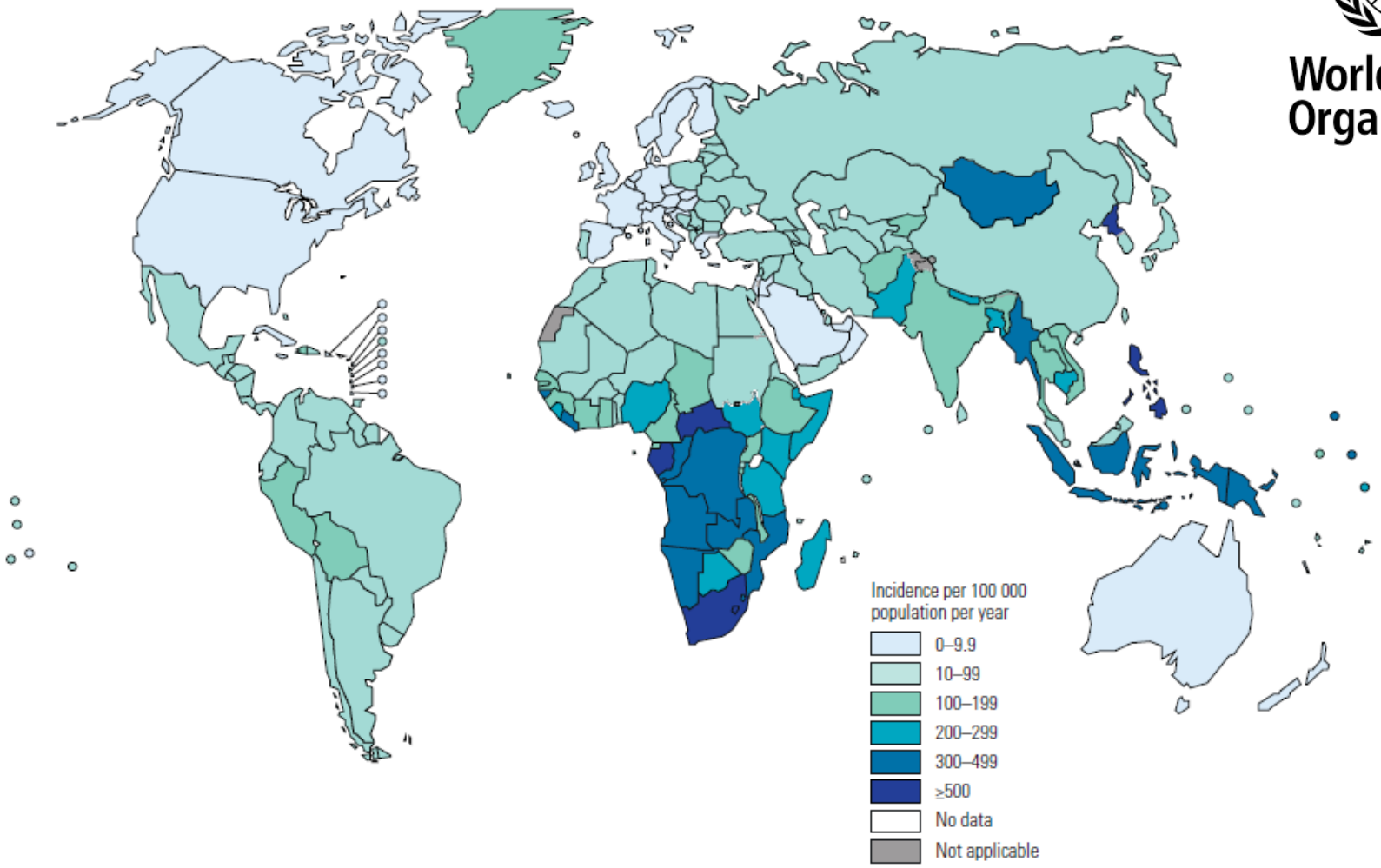
(3000 to 2400 BC)

History

- Robert Koch identified and described the bacillus causing tuberculosis, M. tuberculosis, on 24 March 1882. He received the Nobel Prize in Physiology or Medicine in 1905 for this discovery.

https://en.wikipedia.org/wiki/Tuberculosis#/media/File:RobertKoch.jpg

Estimated TB incidence rates, 2019

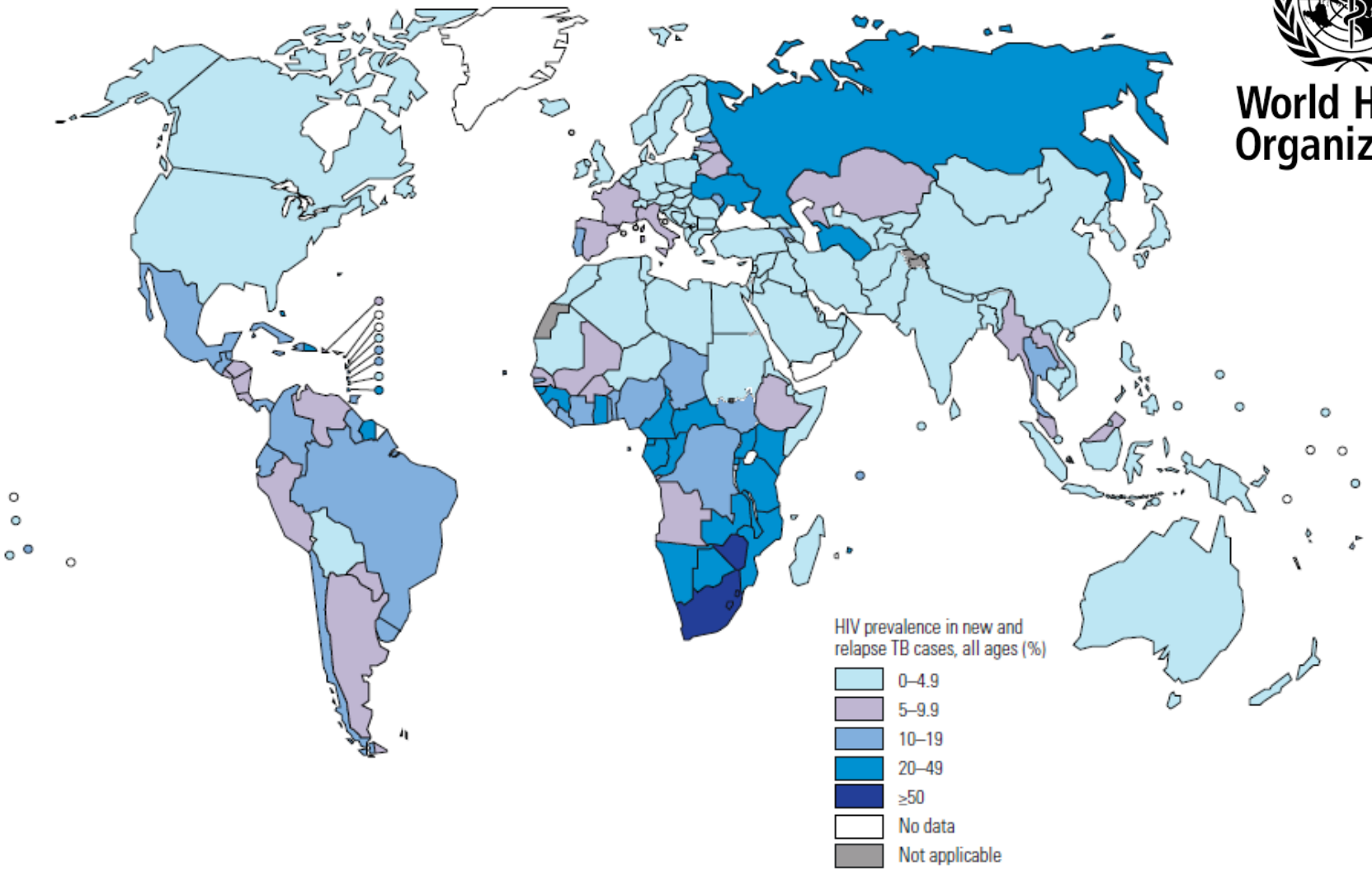


World Health Organization

WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

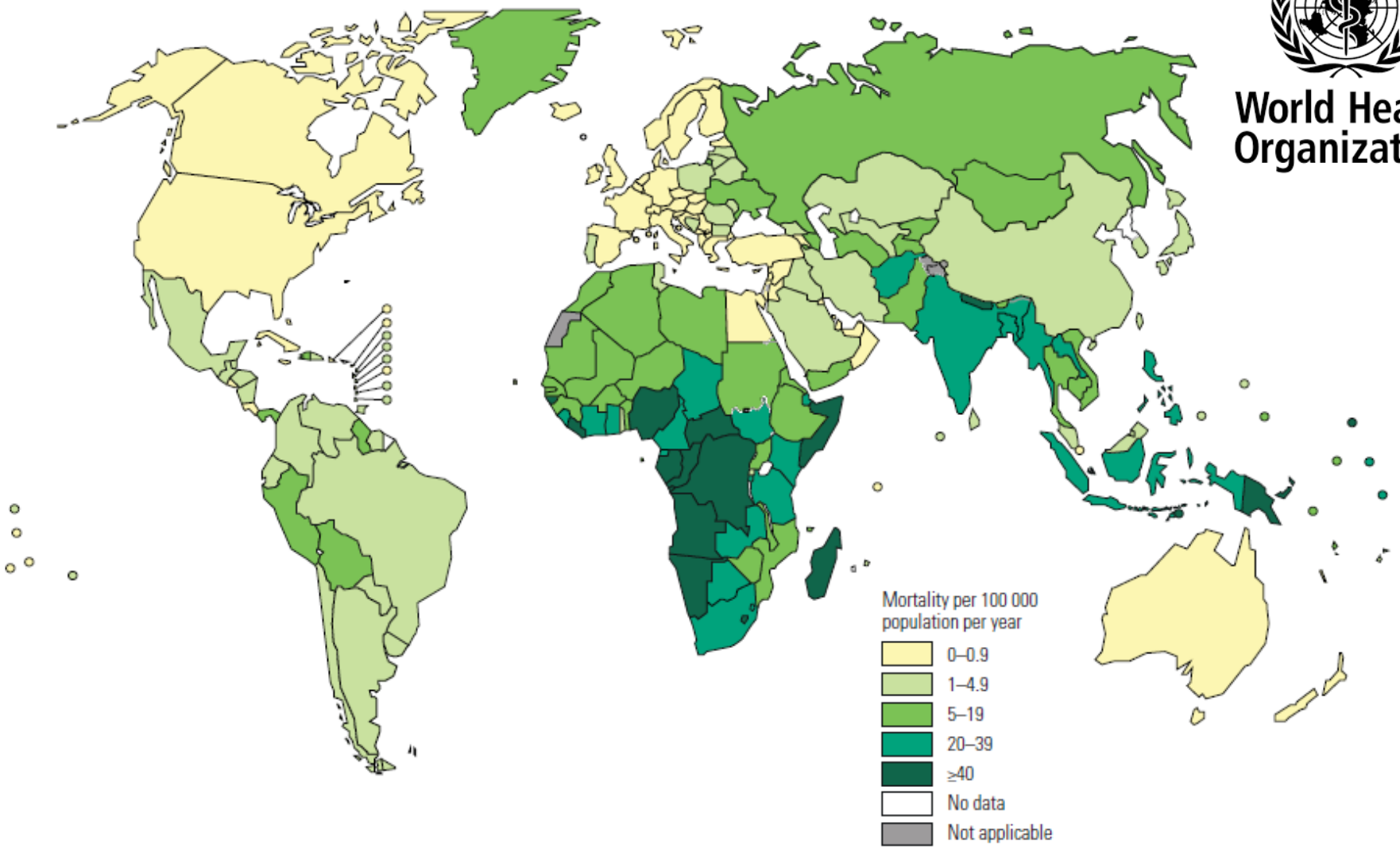
Estimated HIV prevalence in new and relapse TB cases, 2019

World Health Organization



WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

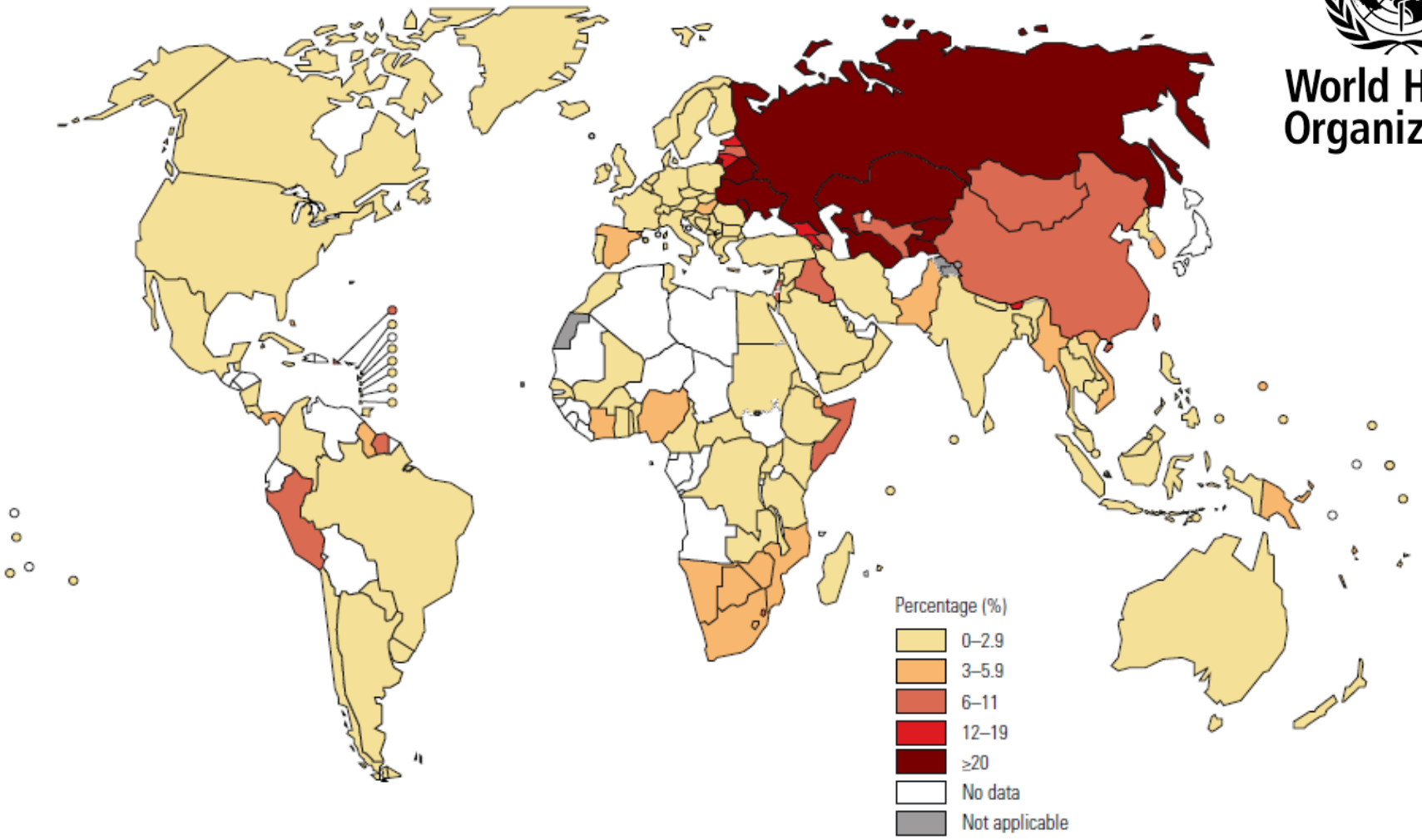
Estimated TB mortality rates in HIV-negative people, 2019



World Health Organization

WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

Percentage of new TB cases with MDR/RR-TB[a]

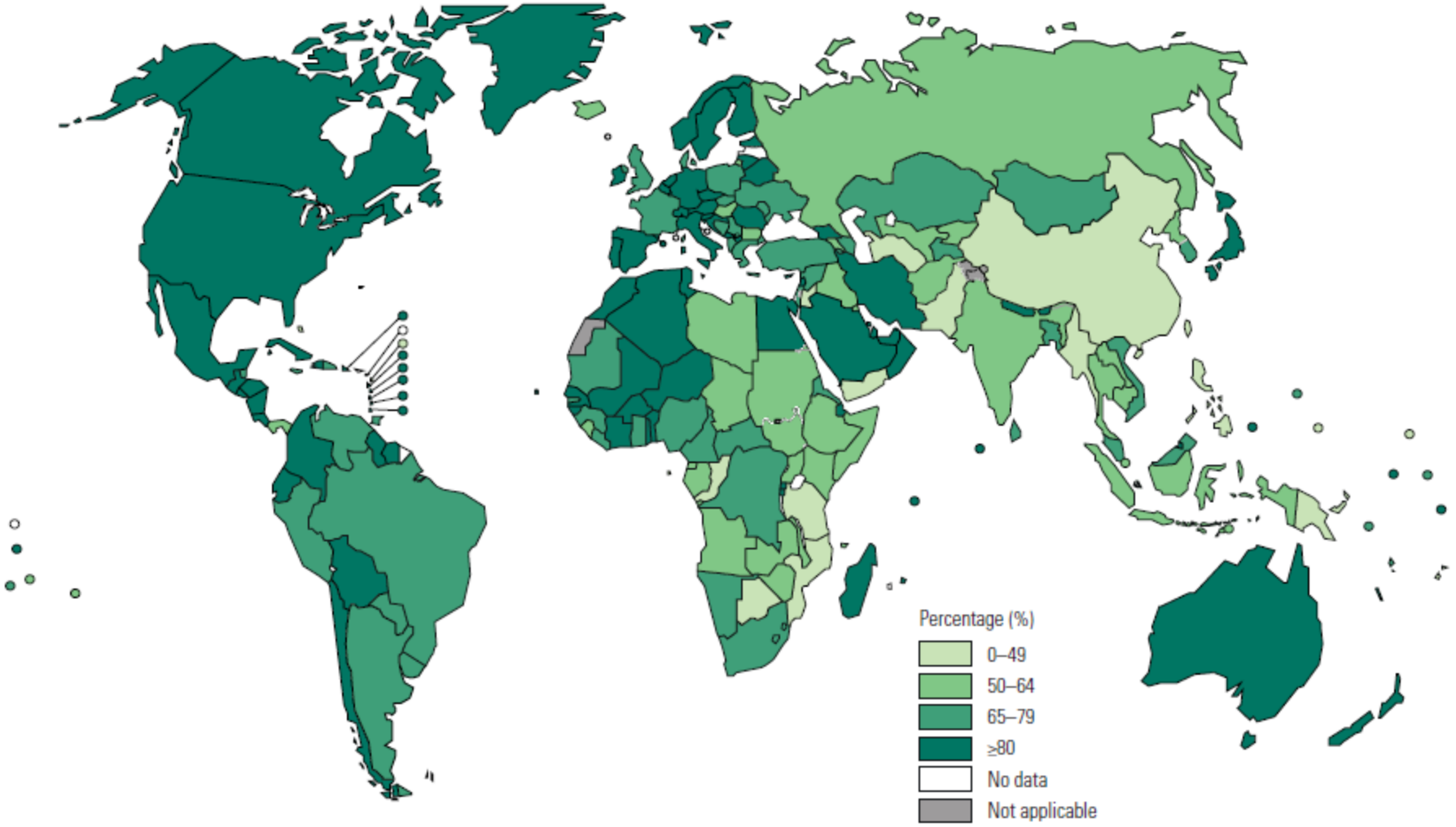


World Health Organization

[a] Percentages are based on the most recent data point for countries with representative data from 2005 to 2020. Model-based estimates for countries without data are not shown. MDR-TB is a subset of RR-TB.

WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

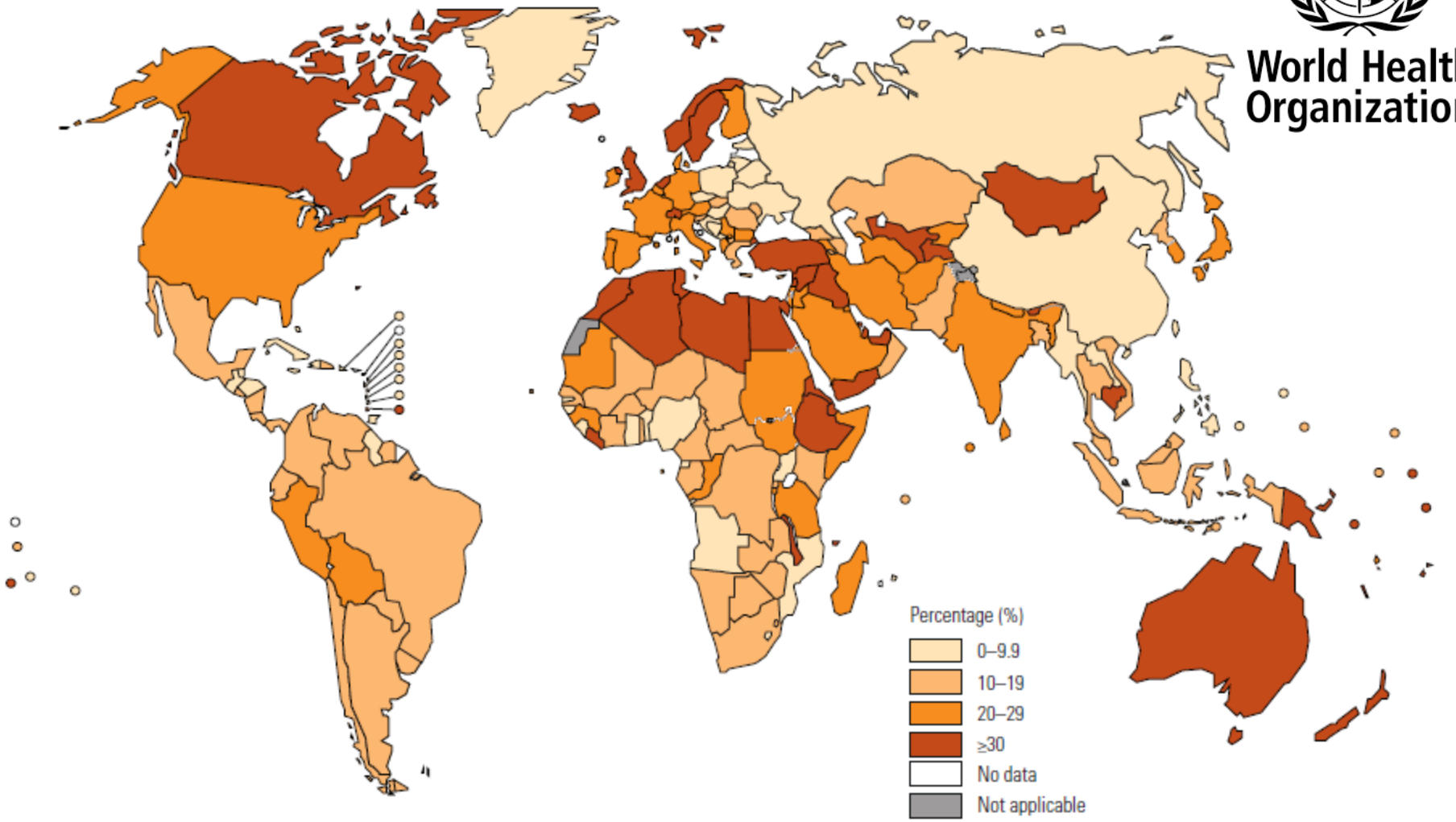
Percentage of new and relapse pulmonary TB cases with bacteriological confirmation, 2019



WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

Percentage of extrapulmonary cases among new and relapse TB cases, 2019

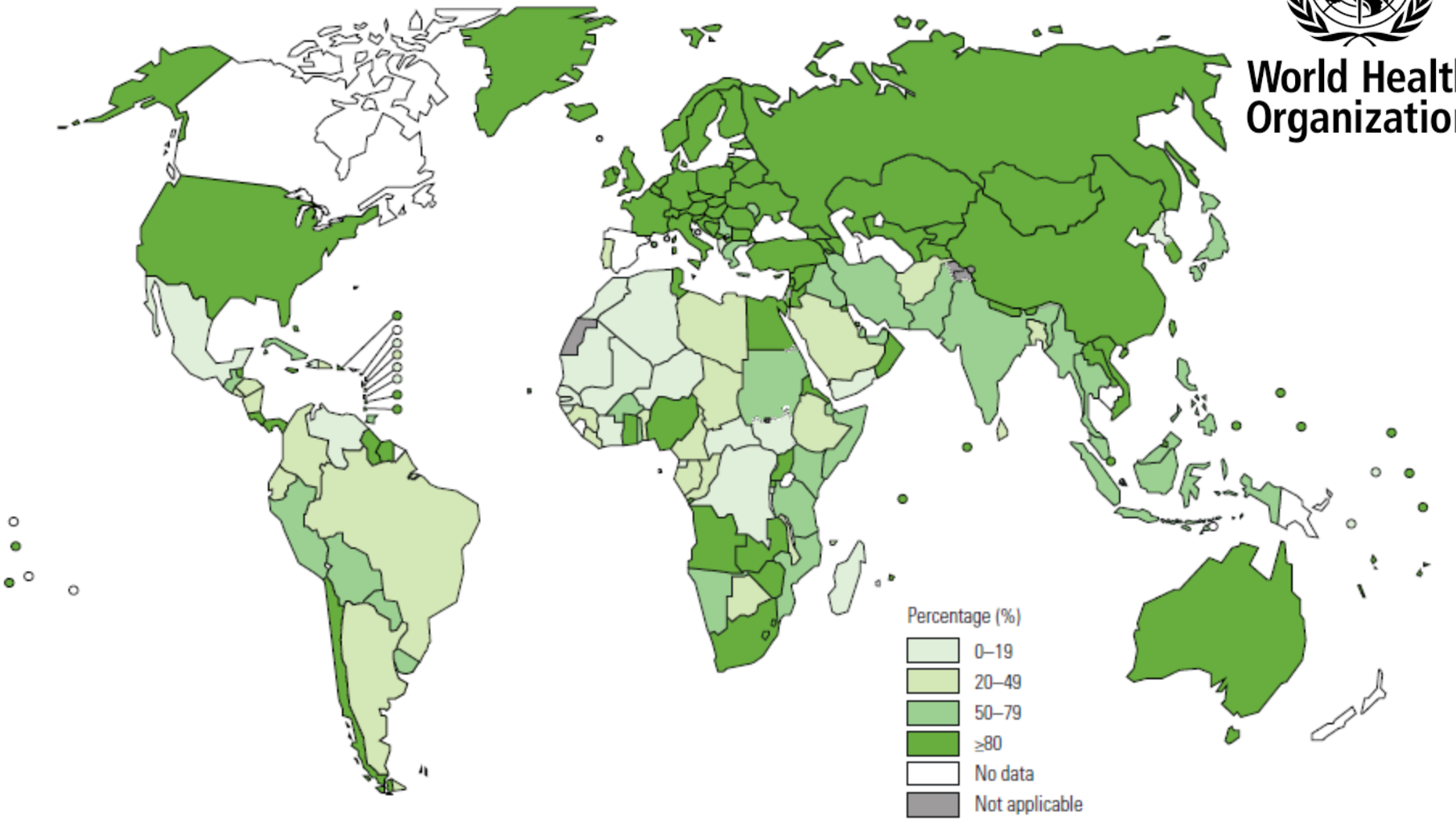
World Health Organization



WHO: GLOBAL TUBERCULOSIS REPORT 2020
https://static1.squarespace.com/static/5952880320099e4af548b918/t/605b6ea40253f160b4a2637b/1616604839692/GlobalTBReport_9789240013131-eng_2021-03-22.pdf

Percentage of bacteriologically confirmed TB cases tested for RR-TB, 2019[a]

World Health Organization



WHO: GLOBAL TUBERCULOSIS REPORT 2020
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Risk for Drug-Resistant TB

TABLE 249.4 Epidemiologic Circumstances in Which an Exposed Person Is at Increased Risk for Infection With Drug-Resistant *Mycobacterium tuberculosis*

- Exposure to a person who has known drug-resistant tuberculosis
- Exposure to a person with active tuberculosis who has had prior treatment for tuberculosis (treatment failure or relapse) and whose susceptibility test results are not known
- Exposure to persons with active tuberculosis from areas in which there is a high prevalence of drug resistance
- Exposure to persons who continue to have positive sputum smears after 2 months of combination chemotherapy
- Travel in an area of high prevalence of drug resistance

[a]This information is to be used in deciding whether to add a fourth drug (usually ethambutol) for children with active tuberculosis, not to infer the empirical need for a second-line treatment regimen.

From Centers for Disease Control and Prevention. Treatment of tuberculosis. American Thoracic Society, CDC and Infectious Diseases Society of America. MMWR Recomm Rep. *2003;52(RR–11):1–88.*

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition, 2020

TB in Early/Late HIV

TABLE 249.6 Clinical Manifestations of Active Tuberculosis in Early Versus Late HIV Infection

	EARLY HIV INFECTION	LATE HIV INFECTION
Tuberculin test result	Usually positive	Usually negative
Adenopathy	Common	Unusual
Pulmonary distribution	Upper lobe	Lower and middle lobe
Cavitation	Often present	Typically absent
Extrapulmonary disease	10%–15% of cases	50% of cases

[a]For practical purposes, "early" and "late" may be defined as $CD4^+$ cell counts greater than 300 cells/mm^3 and less than 200 cells/mm^3, respectively.
HIV, Human immunodeficiency virus.

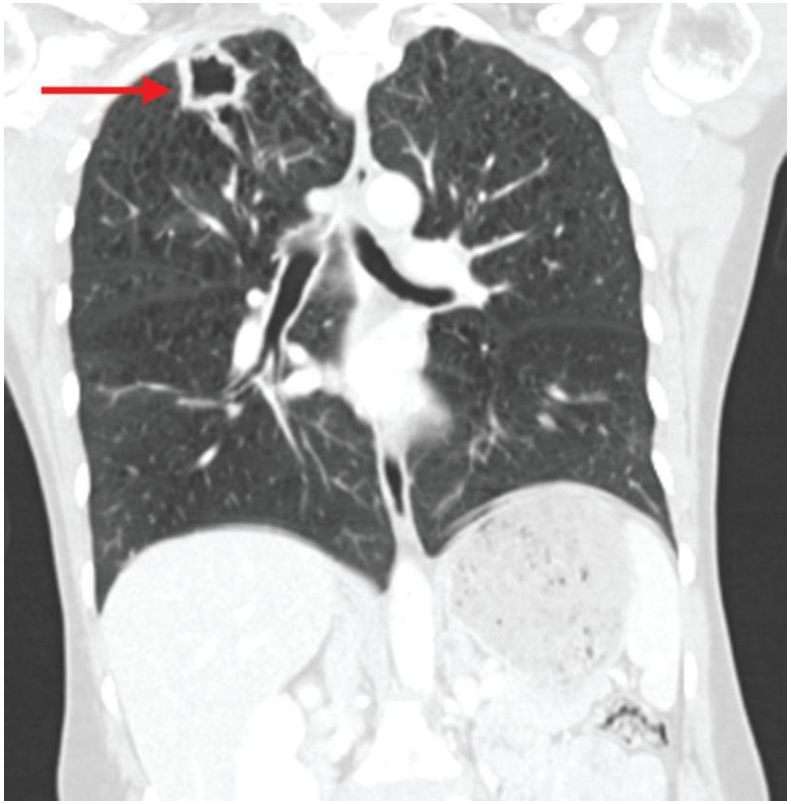
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition, 2020

Diagnosis

- Culture is the gold standard
  - takes 3 to 8 weeks on solid media,
  - 10 days (smear-positive) 20 days (smear-negative) liquid media.
- Sputum smear positivity
  - estimated 10,000 organisms per milliliter are required
- Nucleic acid amplification testing (NAAT)
  - sensitivities and specificities that approach those of culture
- Incomplete necrosis produces cheesy, acellular material (i.e., caseous necrosis)
- Radiograph: infiltrate in the lung apices is highly suggestive, especially if the infiltrate is cavitary

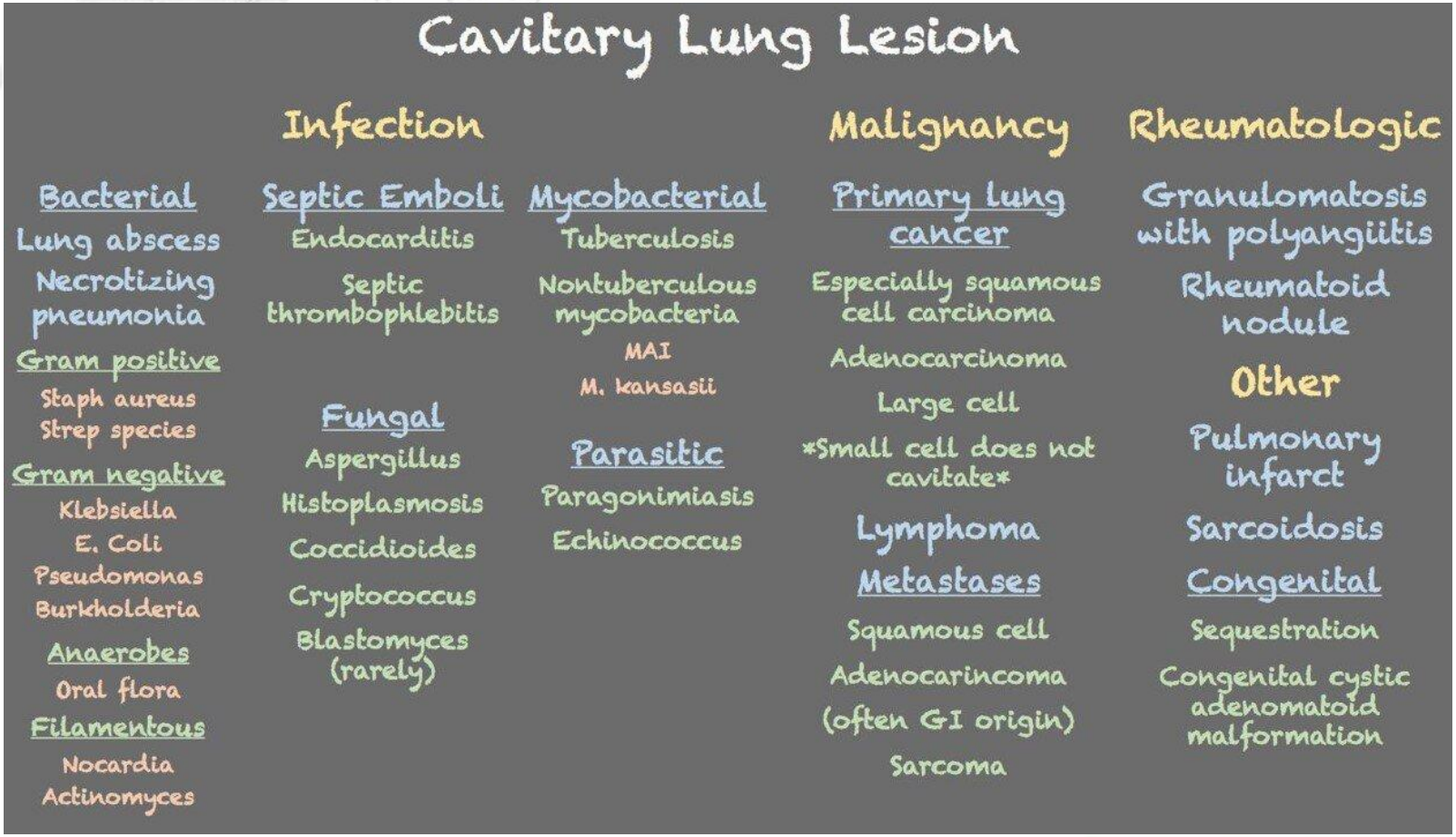
Challenges of Diagnosis

Initial coronal computed tomography scan showing right upper lobe cavitary lesion (arrow)



Viral K Doshi et al. Respir Care 2015;60:e56-e58

Differential Diagnosis (DDx)



http://www.imrespdx.com/blog/2020/7/24/cavitary-lung-lesion

28 Y woman: abdominal pain, low-grade fever, icterus

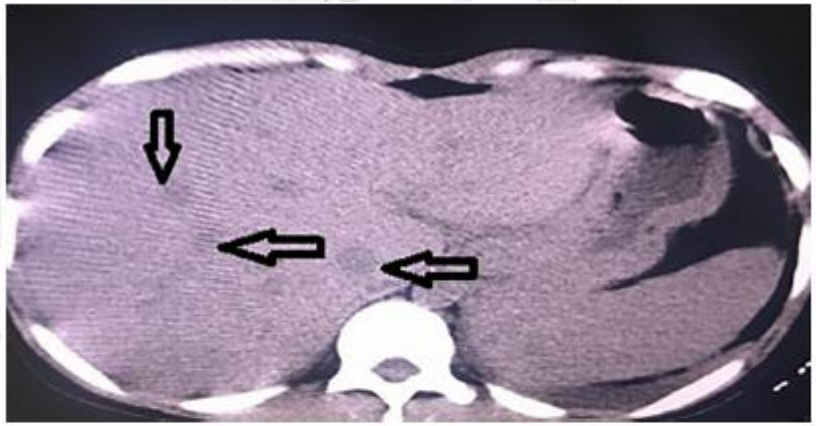
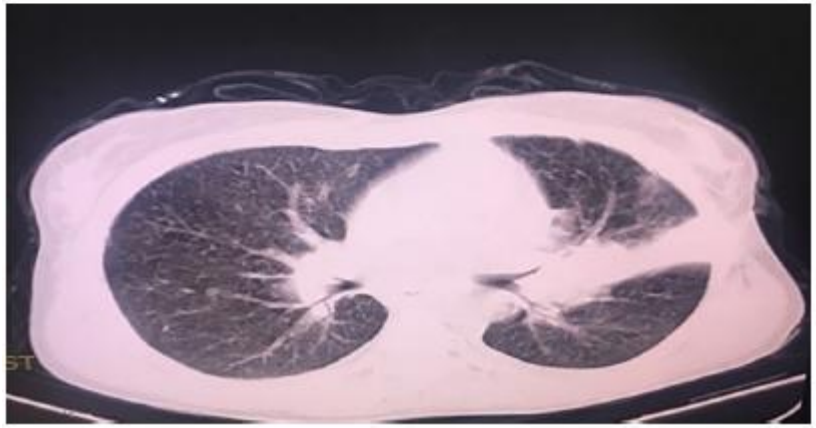


Figure 1. Multiple hypoechoic lesions in the liver



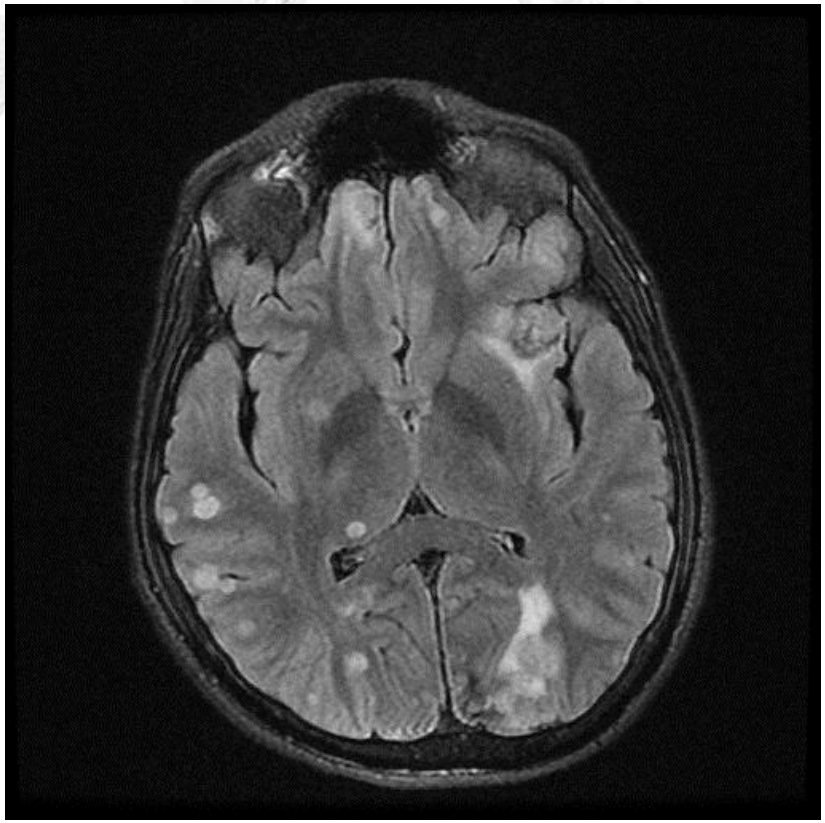
Box 1. Characteristics of focal liver lesions.

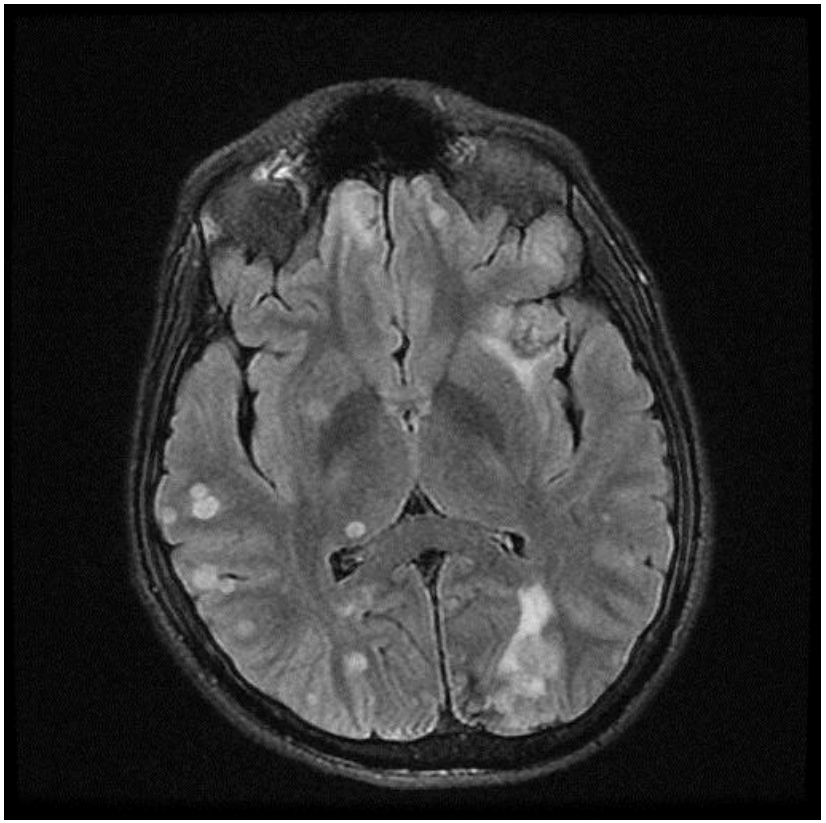
- Benign FLL
  - Serous cyst
  - Biliary hamartoma
  - Hemangioma (cavernous and capillary)
  - Focal nodular hyperplasia
  - Nodular regenerative hyperplasia
  - Hepatocellular adenoma
  - Inflammatory lesions (abscess, cholangitis)
- Malignant FLL
  - Fibrolamellar hepatocarcinoma
  - Cholangiocarcinoma
  - Metastases
- FLL of the cirrhotic liver
  - Regenerative nodule
  - Dysplastic nodule
  - Hepatocellular carcinoma

FLL: Focal liver lesion.

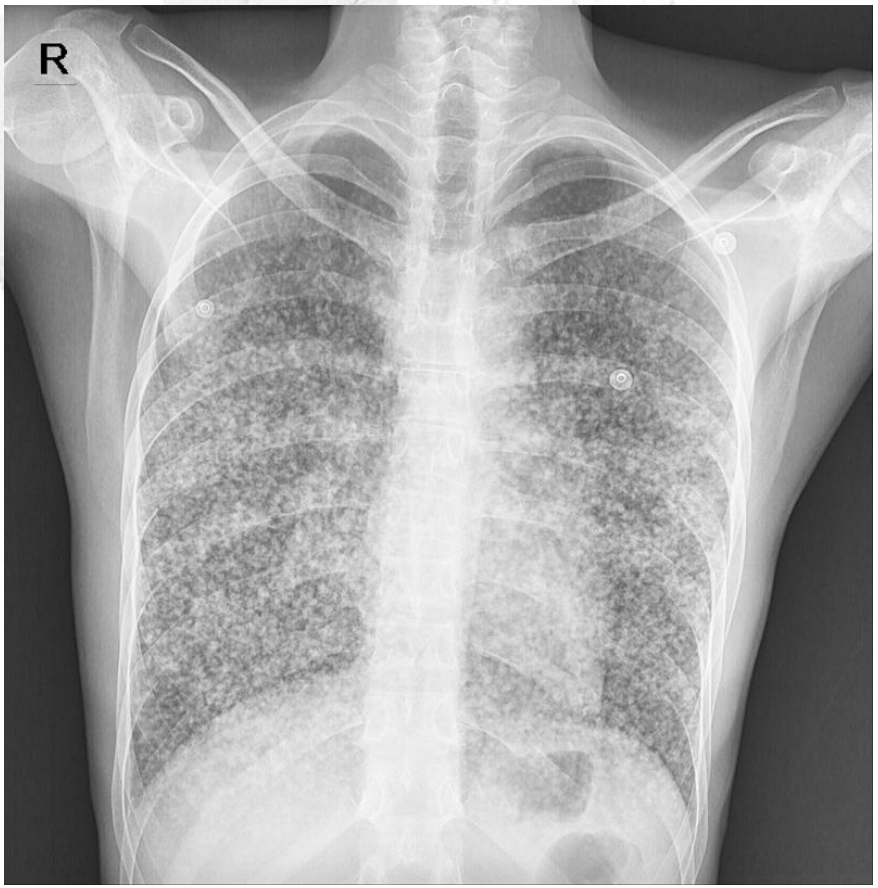
* Barazandeh F, et al. A Case of Primary Biliary Tuberculosis with Subsequent Pulmonary Presentation. Arch Clin Infect Dis. 2018; 13(6):e74374
* Morana G, et al. Optimal imaging of focal liver lesions. Imaging Med. (2010) 2(5), 497–518

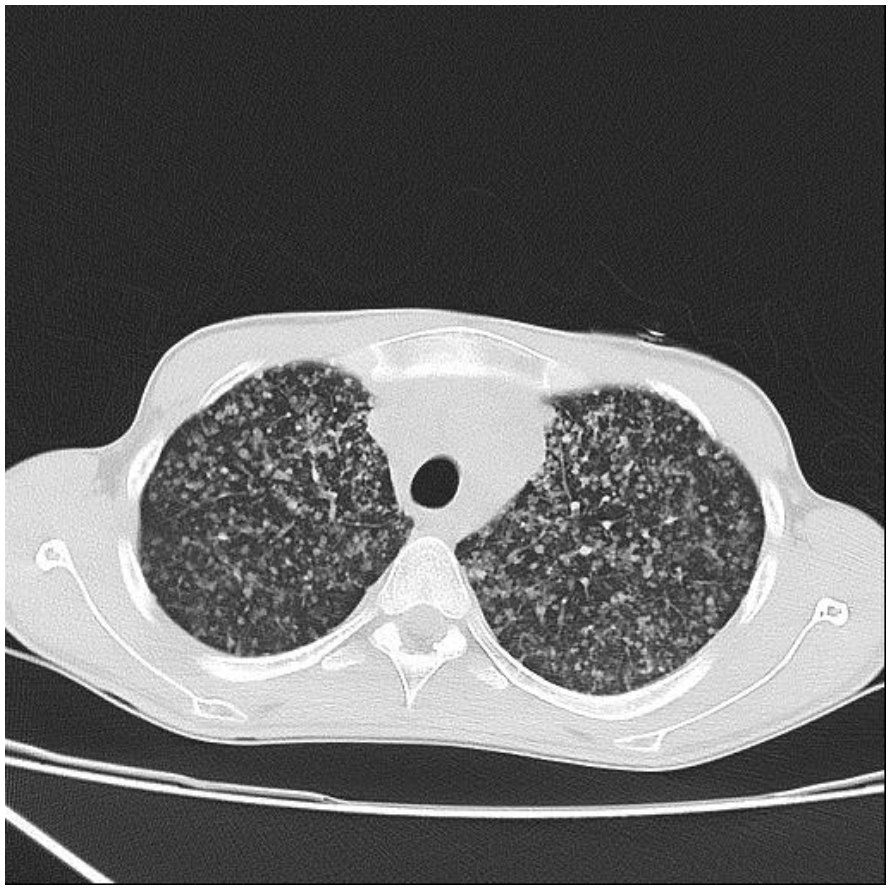
21 Y man: disorientation/ L.O.C.





21 Y man: HIV negative, R/O CGD





Sputum smear & MTB-PCR: Negative

NEXT DIAGNOSTIC STEP?

Non-tuberculous Mycobacteria (NTM)

Mycobacterium avium complex

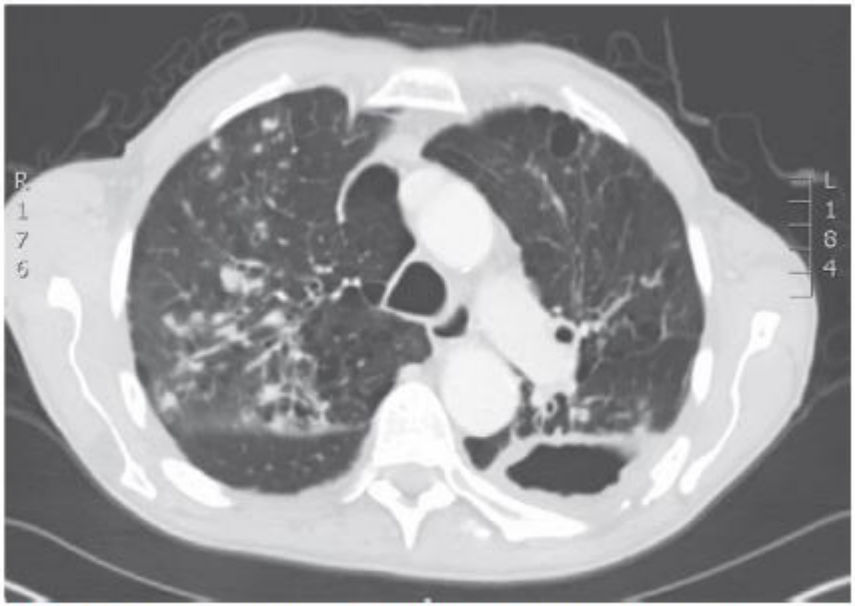
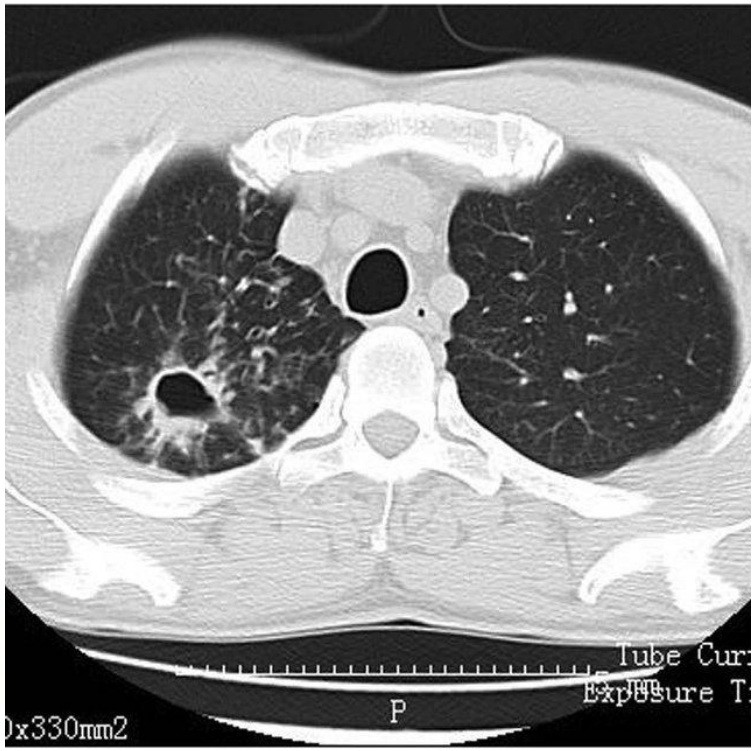


FIG. 251.2 Fibrocavitary pulmonary *Mycobacterium avium* complex in a male patient with a smoking history predisposing to underlying emphysema and bronchiectasis. Pleural thickening, nodular tree-in-bud opacities, and bullous changes of emphysema are also present.

Mycobacterium kansasii



Duan H, et al. Clinical Significance of Nontuberculous Mycobacteria Isolated From Respiratory Speci mens in a Chinese Tuberculosis Tertiary Care Center. Sci Rep 2016 Nov 3;6:36299

Treatment: Drug-Susceptible TB

راهنمای کشوری مبارزه با سل؛ ویرایش دوم

جدول (۳)- رژیم درمانی بیماران بر اساس سابقه درمان ضد سل قبلی (با نمایش کد استاندارد)[1]

بیماران تحت درمان	مرحله حمله ای	مرحله نگهدارنده
بیماران جدید	**2 HRZE**	**4 HR** (۳۲)
بیماران درمان مجدد (شامل شکست درمان، عود، غیبت از درمان و سایر)	**3 HRZE**	**5 HRE**

Treatment: Drug-Susceptible TB

TABLE 249.7 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			
REGIMEN[a,b,c]	DRUGS[d]	INTERVAL AND DOSES[e] (MINIMAL DURATION)	REGIMEN	DRUGS[d]	INTERVAL AND DOSES[e,f] (MINIMAL DURATION)	RANGE OF TOTAL DOSES (MINIMAL DURATION)
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)[g]	1	INH/RIF	7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)[g]	182–130 (26 wk)
2	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk), or 5 days/wk for 40 doses (8 wk)[g]	2	INH/RIF	3 times/wk for 54 doses (18 wk)	110–94 (26 wk)
3	INH RIF PZA EMB	3 times/wk for 24 doses (8 wk)	3	INH/RIF	3 times/wk for 54 doses (18 wk)	78 (26 wk)
4	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk), then 2 times/wk for 12 doses (6 wk)	4	INH/RIF	2 times/wk for 36 doses (18 wk)	62 (26 wk)

[a]Regimen effectiveness is greatest for Regimen 1 to least for Regimen 4. Regimen 1 is preferred for newly diagnosed pulmonary tuberculosis. Regimen 2 is a preferred alternative regimen when more frequent DOT during the continuation phase is difficult to achieve. Regimen 3 should be used with caution in patients with HIV and/or cavitary disease; missed doses can lead to treatment failure, relapse, and acquired drug resistance. Regarding Regimen 4, twice-weekly regimens should be avoided in HIV-positive patients and patients with smear-positive and/or cavitary disease; if doses are missed, therapy is equivalent to once weekly, which is inferior.
[b]If the patient's isolate is susceptible to both INH and RIF, EMB is not necessary, and the intensive phase can consist of INH, RIF, and PZA only.
[c]Variations of the preferred regimen may be acceptable in certain clinical and/or public health situations, as described elsewhere.[239]
[d]Pyridoxine (vitamin B_6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.
[e]When directly observed therapy is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
[f]Patients with cavitation on an initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.
[g]Five-day-a-week administration is always given by DOT.
DOT, Directly observed therapy; *EMB,* ethambutol; *HIV,* human immunodeficiency virus; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin.
Modified from Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. *2016; 63:e147–e195.*

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition, 2020

Treatment: Mycobacterium avium Complex

TABLE 251.2 Initial Regimens for Pulmonary *Mycobacterium avium* Complex

MILD TO MODERATE NODULAR/ BRONCHIECTATIC DISEASE	CAVITARY OR ADVANCED/SEVERE DISEASE
Azithromycin 250 mg PO daily or 500 mg PO three times weekly[b]	Azithromycin 250 mg PO daily[c]
Ethambutol 15 mg/kg PO daily or 25 mg/kg PO three times weekly	Ethambutol 15 mg/kg PO daily
Rifampin 10 mg/kg (600 mg max.) PO daily or three times weekly[d]	Rifampin 10 mg/kg (600 mg max.) PO daily[e] Amikacin 10–15 mg/kg IV three times weekly[f]

[a]See text for full dosing recommendations.
[b]Alternative: clarithromycin 500 mg PO twice daily or 500 mg three times weekly.
[c]Alternative: clarithromycin 500 mg PO twice daily.
[d]Alternative: rifabutin 300 mg PO daily or 300 mg PO three times weekly.
[e]Alternative: rifabutin 300 mg PO daily.
[f]Alternative: Streptomycin 10–15 mg/kg IV or IM three times weekly.
Modified from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. *2007;175:367–416.*

TABLE 251.4 Antibiotic Regimens for Disseminated *Mycobacterium avium* Complex

PREFERRED REGIMEN	ALTERNATIVE REGIMEN OR OPTION
Azithromycin 500 mg PO daily *plus*	Clarithromycin 500 mg PO twice daily *plus*
Ethambutol 15 mg/kg PO daily *plus*	Ethambutol 15 mg/kg PO daily *with or without a rifamycin*[b]
Rifampin 10 mg/kg (600 mg max.) PO daily *consider adding*	Rifabutin 300 mg PO daily
Amikacin 10–15 mg/kg IV three times weekly *for the first 4–12 wk*	

[a]See text for full dosing recommendations.
[b]Alterative acceptable regimen: macrolide (azithromycin/clarithromycin) + only ethambutol.
Modified from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. *2007;175:367–416.*

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition, 2020

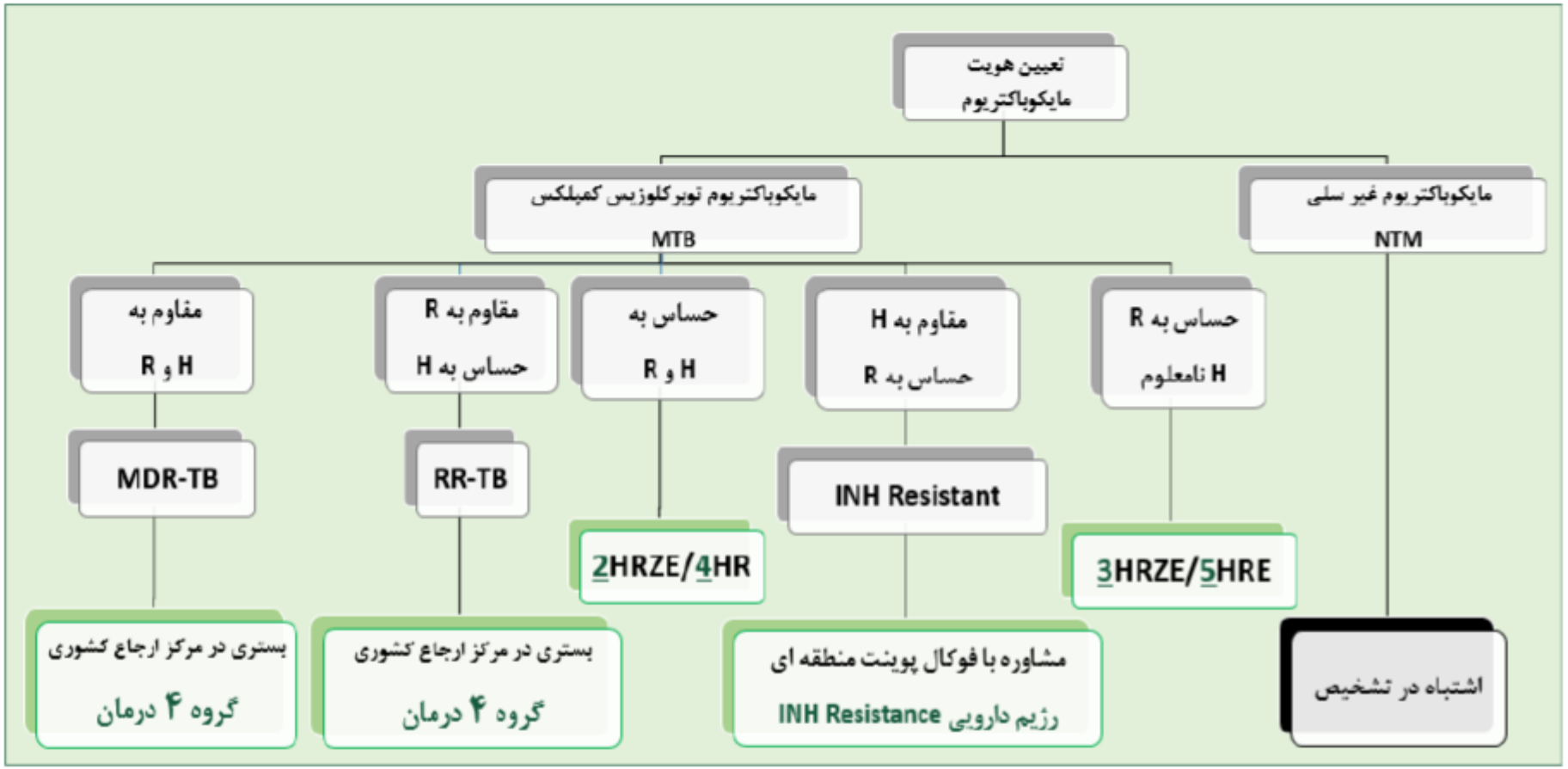
TABLE 252.4 Frequently Used Treatment Regimens for Common Nontuberculous Mycobacterial Pathogens Other Than *Mycobacterium avium* Complex

SPECIES	DISEASE[a]	DRUG	DAILY ADULT DOSES[b]	THREE TIMES WEEKLY ADULT DOSE	DURATION
M. kansasii	Pulmonary				
	(United States)	Isoniazid *or*	300 mg	—	Culture negative at least 12 mo
		Clarithromycin *plus*	500 mg bid	500 mg bid	
		Rifampin *plus*	600 mg	600 mg	
		Ethambutol	15 mg/kg	25 mg/kg	
	(United Kingdom)	Rifampin *plus*	600 mg	600 mg	9–12 mo
		Ethambutol	15 mg/kg	15 mg/kg	
	Disseminated	Same as pulmonary			
	HIV-positive	Same as pulmonary (United States) but replace rifampin (rifampin inactivates HIV drugs) with rifabutin *or*	150 mg		Same as pulmonary (United States)
		Clarithromycin[c]	500 mg bid		
M. abscessus subsp. *abscessus* (80% of isolates harbor functional *erm* gene)	Pulmonary (adults)	Amikacin IV (peaks in low 20s μg/mL)	7.5–10 mg/kg single dose daily[d]	NA	2 wk (designed to improve, not cure)
			500 mg daily inhaled amikacin or ALIS		ALIS: not determined
M. abscessus subsp. *massiliense* (no functional *erm* gene)		*Plus* imipenem IV *or*	1 g bid		
		Cefoxitin IV *or*	8–12 g/day (divided into 2–3 doses)		2 wk
		Tigecycline 25–50 mg IV once daily			
		Plus clarithromycin[e]	500 mg bid		6 mo
	Cutaneous localized	Clarithromycin	500 mg bid[f]		6 mo
	Disseminated or extensive cutaneous	Same three drugs as above[g]		NA	Not established
M. marinum	Cutaneous	Clarithromycin *or*	500 mg bid	NA	3 mo minimum for all regimens
		Minocycline *or*	100 mg bid		
		Rifampin *plus*	600 mg		
		Ethambutol	15 mg/kg		

[a]HIV-negative host unless otherwise stated.
[b]Drugs by mouth unless otherwise stated.
[c]Patients on HIV medicines inactivated by rifampin.
[d]Based on age, weight, and renal status (American Thoracic Society).
[e]If a functional *erm* gene is present, treatment with clarithromycin may not be warranted.
[f]Patients with complicated lesions may require surgical débridement and amikacin plus cefoxitin or imipenem.
[g]Amikacin plus clarithromycin plus imipenem or cefoxitin or tigecycline.
ALIS, Amikacin liposome inhalation suspension; *bid,* twice daily; *HIV,* human immunodeficiency virus; *IV,* intravenous; *NA,* not applicable.

Treatment: Drug Resistant TB

تصویر (۱)- تعیین رژیم دارویی در سل در یک نگاه
بر اساس جواب آزمایشات تعیین هویت و آنتی بیوگرام



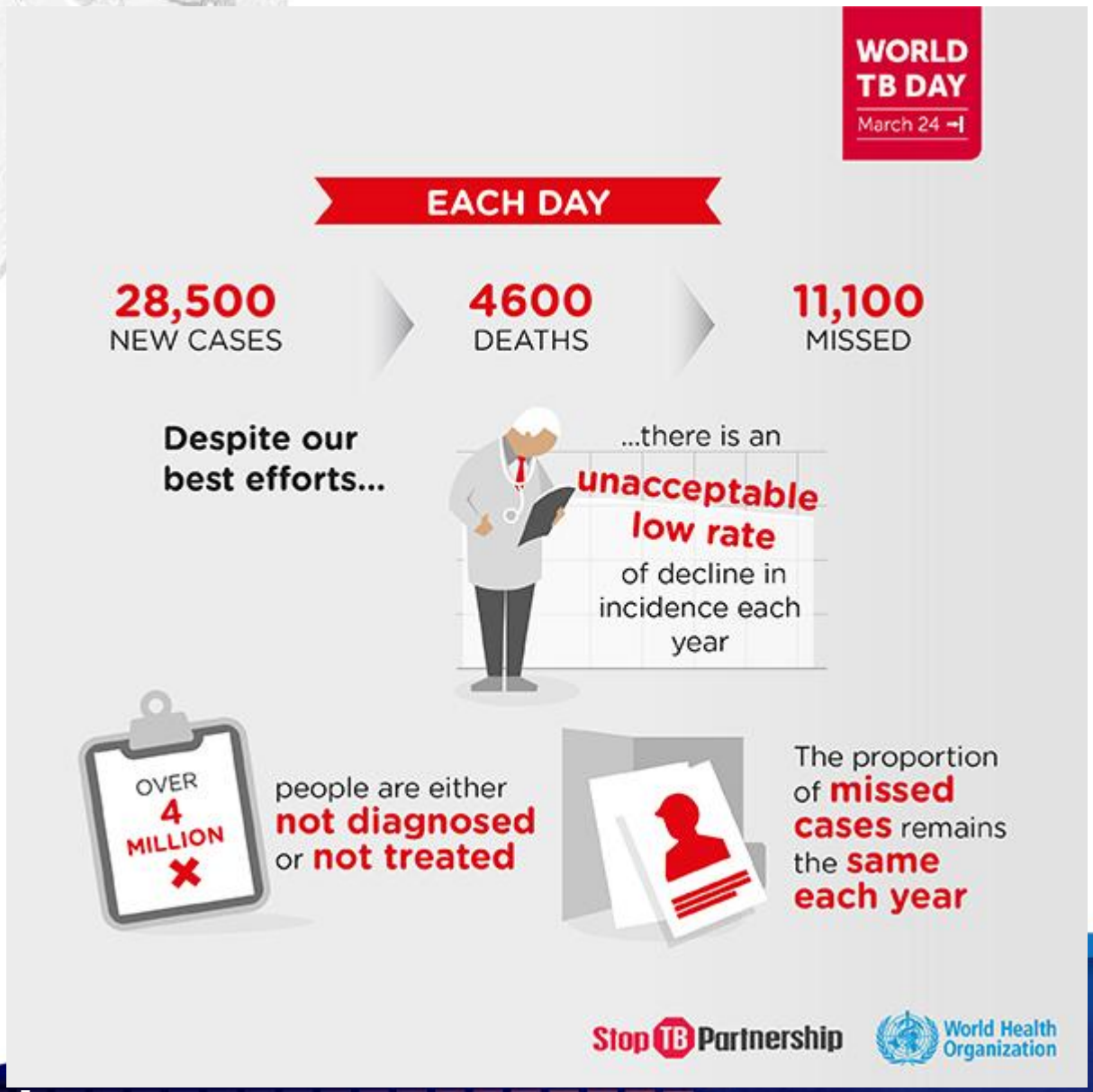
Treatment of Multidrug-Resistant TB

- Resistant to RIF/INH
- Sputum culture, susceptibility testing
- RIF resistance: >50% lack of conversion or relapse
- “aggressive” regimen of at least five likely effective drugs was associated with a decreased risk of death
- Treatment individualized based on susceptibility test
- **Fluoroquinolone** (levofloxacin, gatifloxacin), **ETM**, PZA (?), high-dose INH, **clofazimine**, prothionamide, Aminoglycoside (STM, **amikacin**, kanamycin), **bedaquiline**, capreomycin, ethionamide, **cycloserine**

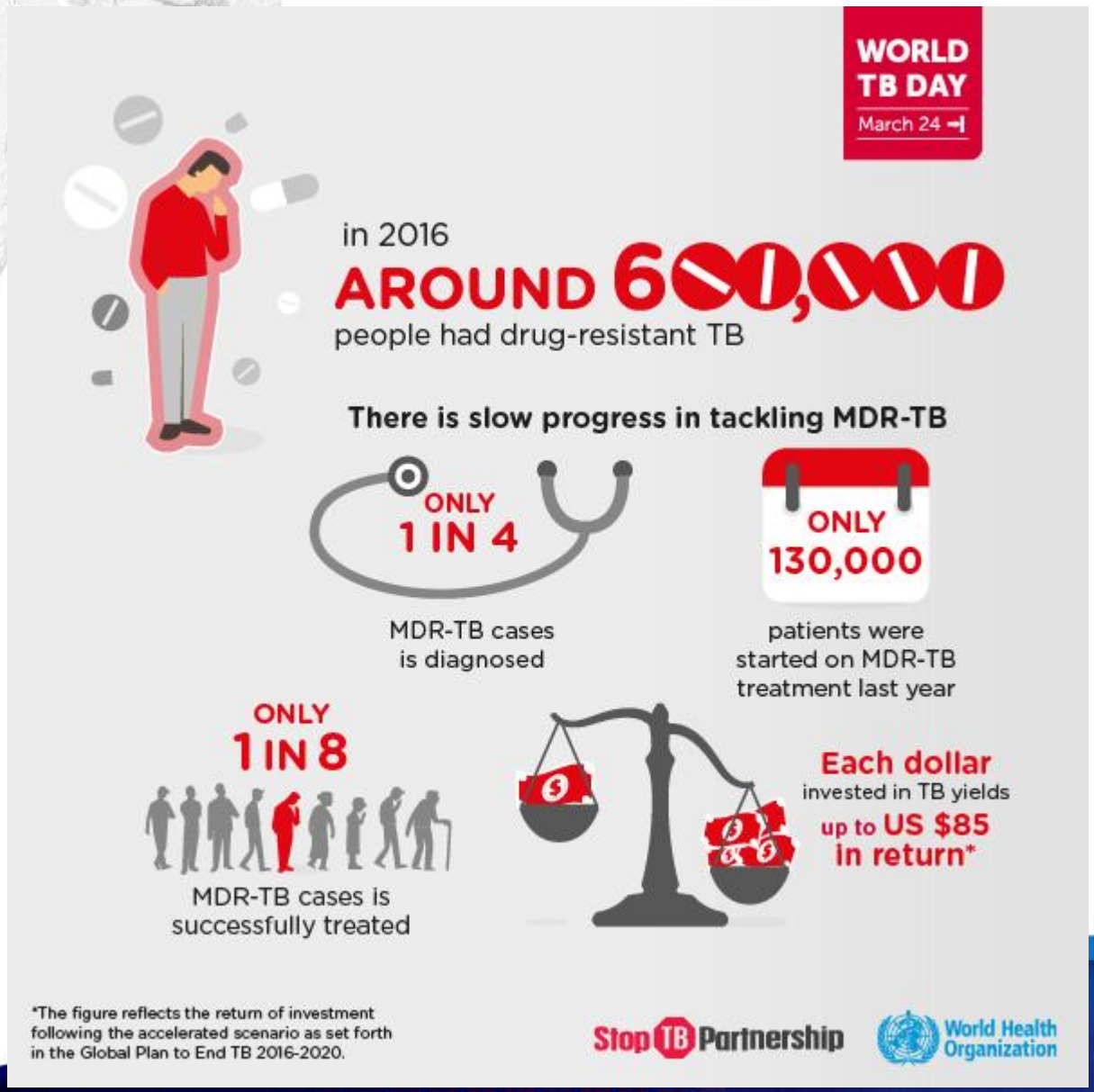
Therapy for Extensively Drug-Resistant TB

- resistance to, INH RIF, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin)
- African studies: low cure rate, only 5-10 %
- at least five/six drugs the organism is susceptible
- Chinese studies: adding Linezolid: better outcome, severe adverse effects

World Health Organization



World Health Organization



Thanks for your attention