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Treatment of Tuberculosis

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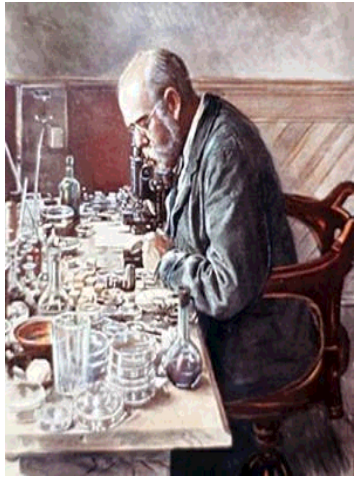
To cure sometimes,
To relieve often,
To comfort always.

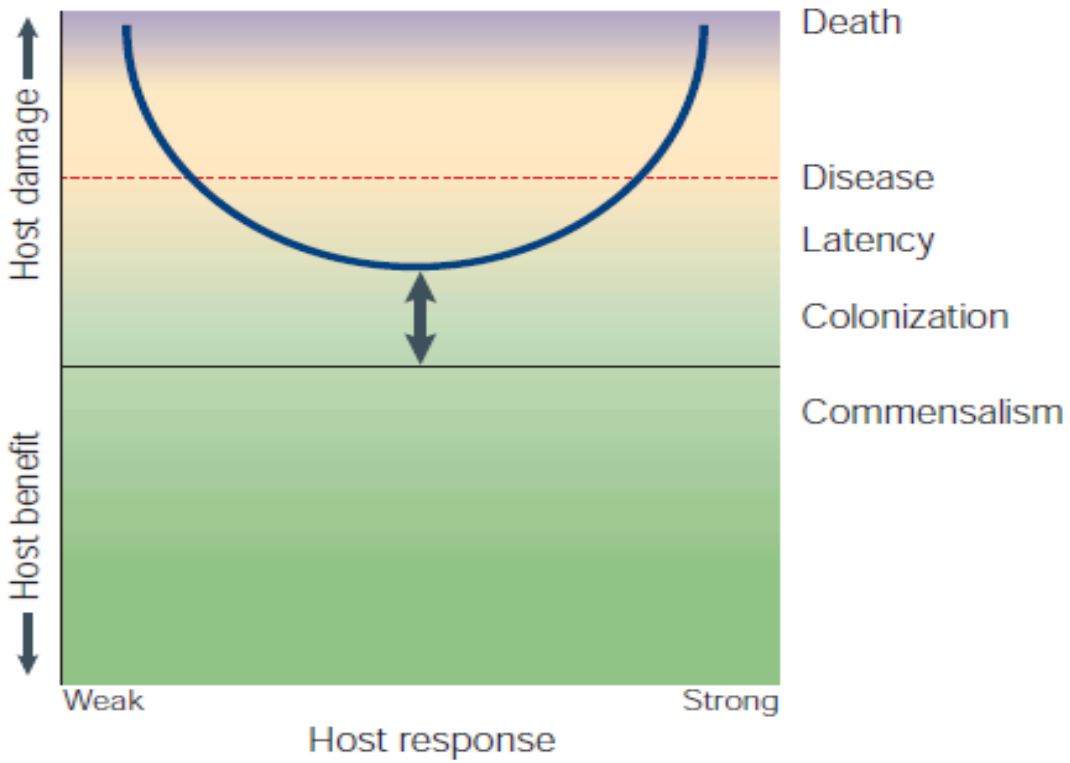
—— *E. L. Trudeau*

3/24/1882



1882年3月24日,罗伯特.科霍在德国柏林生理学会上宣布了结核菌是导致结核病的病原菌

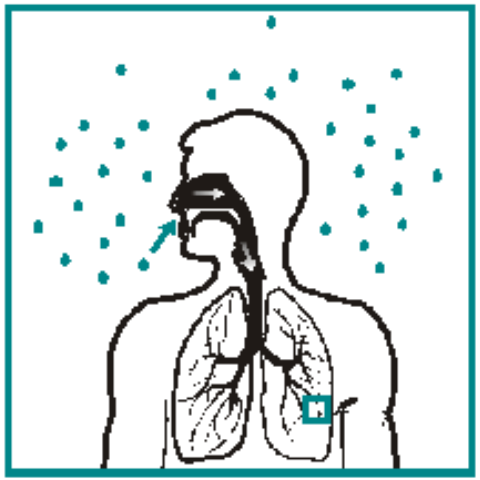
M.Tb and Host



Arturo Casadevall and Liise-anne Pirofski NATURE REVIEWS | MICROBIOLOGY 2003

TB Pathogenesis (1)

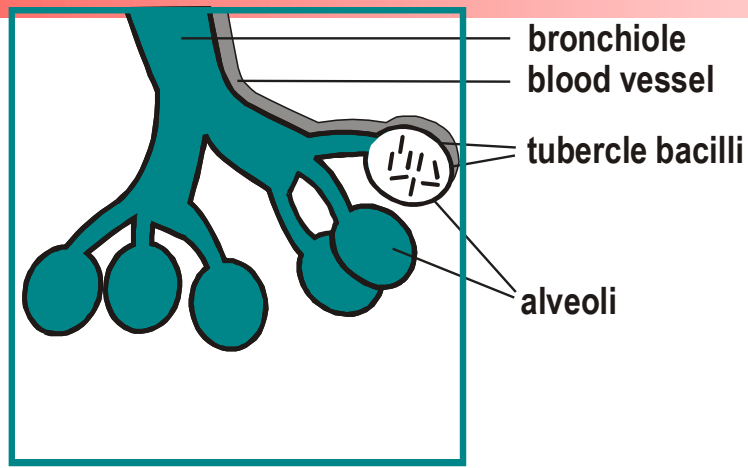
1



Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to small air sacs (alveoli)

TB Pathogenesis (2)

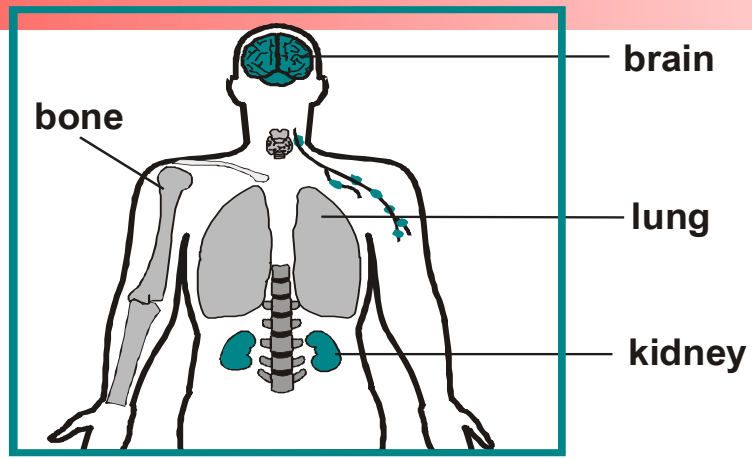
2



Tubercle bacilli multiply in alveoli, where infection begins

TB Pathogenesis (3)

3

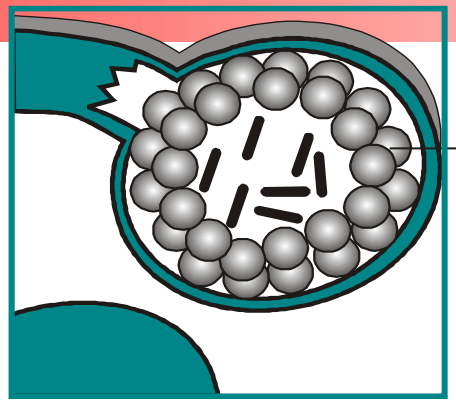


A small number of tubercle bacilli enter bloodstream and spread throughout body

TB Pathogenesis (4)

LTBI

4

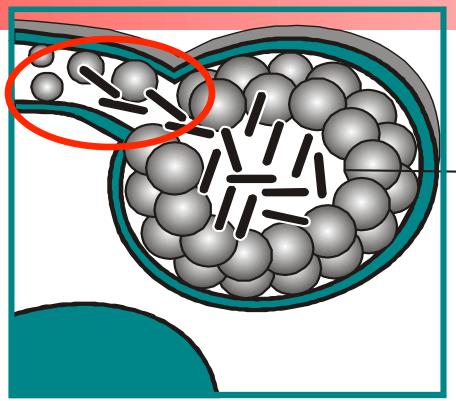


- **Within 2 to 8 weeks the immune system produces special immune cells called macrophages that surround the tubercle bacilli**
- **These cells form a barrier shell that keeps the bacilli contained and under control (LTBI)**

TB Pathogenesis (5)

TB Disease

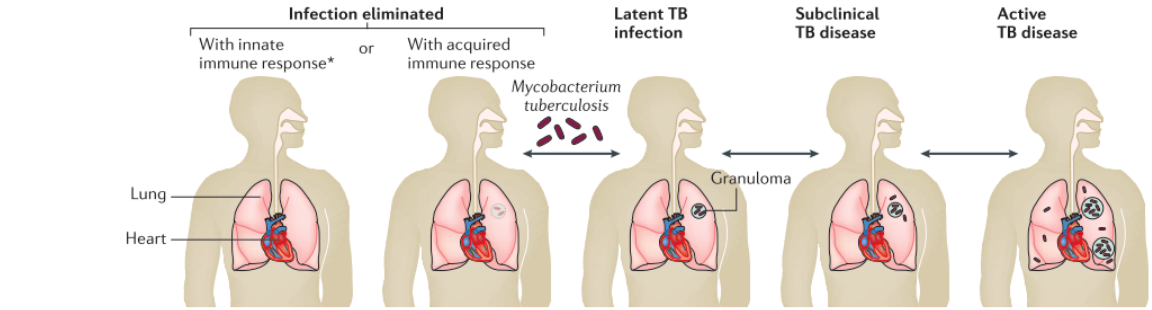
5



shell breaks down and tubercle bacilli escape and multiply (in this example, TB disease develops in the lungs)

- **If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease**
- **This process can occur in different places in the body**

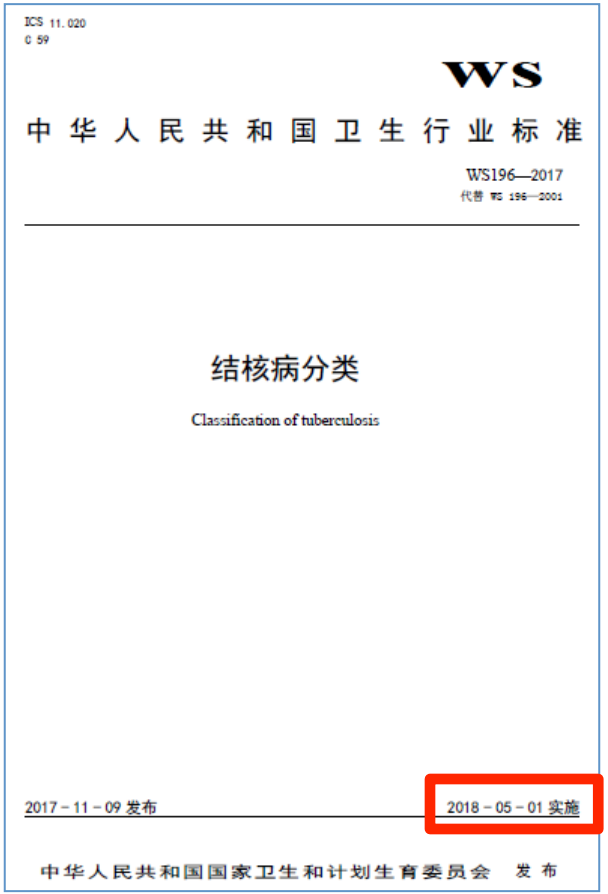
结核的疾病谱：从潜伏感染到活动性结核



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Tuberculosis. NATURE REVIEWS | DISEASE PRIMERS.2016

Classification of tuberculosis



ICS 11.020
C 59

WS

中华人民共和国卫生行业标准

WS196—2017
代替 WS 196—2001

结核病分类

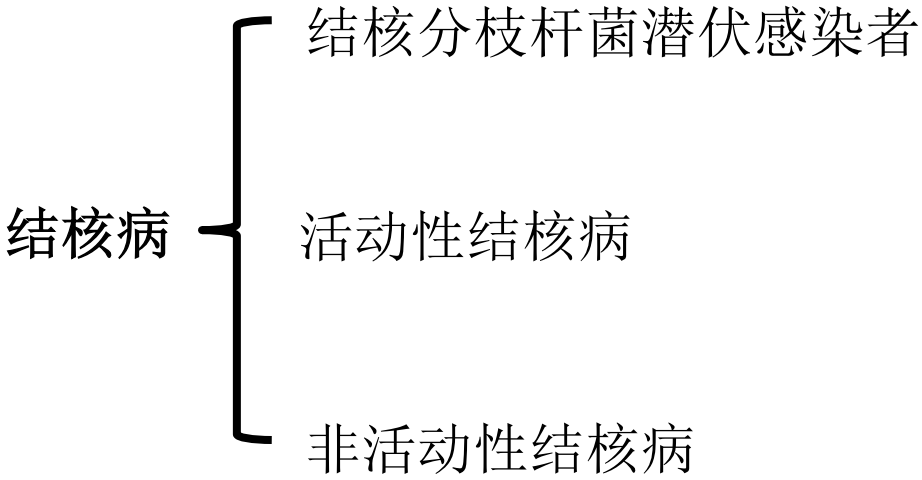
Classification of tuberculosis

2017－11－09 发布

2018－05－01 实施

中华人民共和国国家卫生和计划生育委员会 发布

Classification of tuberculosis

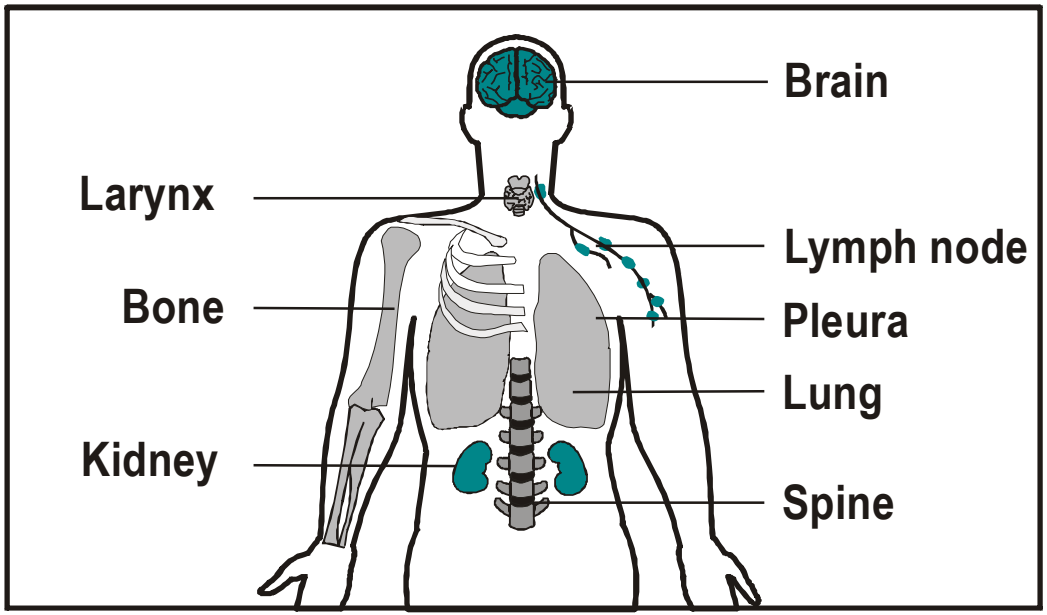


Classification of TB infection

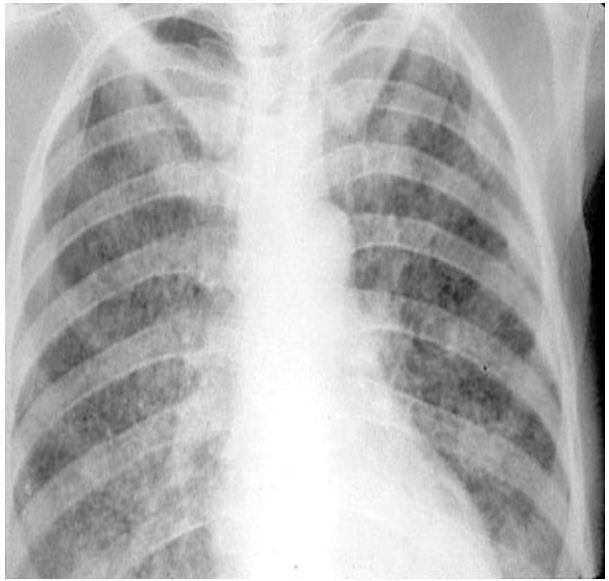
Latent TB (LTBI)	Active TB (in the lungs)
Inactive, contained tubercle bacilli in the body	**Active**, multiplying tubercle bacilli in the body
TST or blood test results usually positive	TST or blood test results usually positive
Chest x-ray usually **normal**	Chest x-ray usually **abnormal**
Sputum smears and cultures **negative**	Sputum smears and cultures may be **positive**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

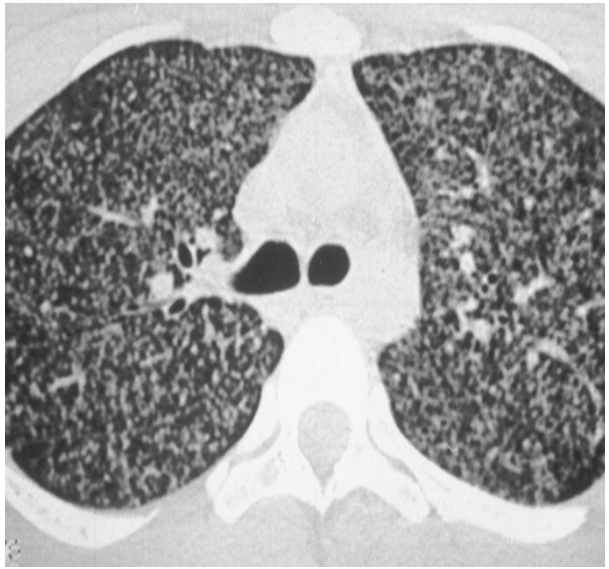
Sites of TB Disease (1)

Bacilli may reach any part of the body, but common sites include:

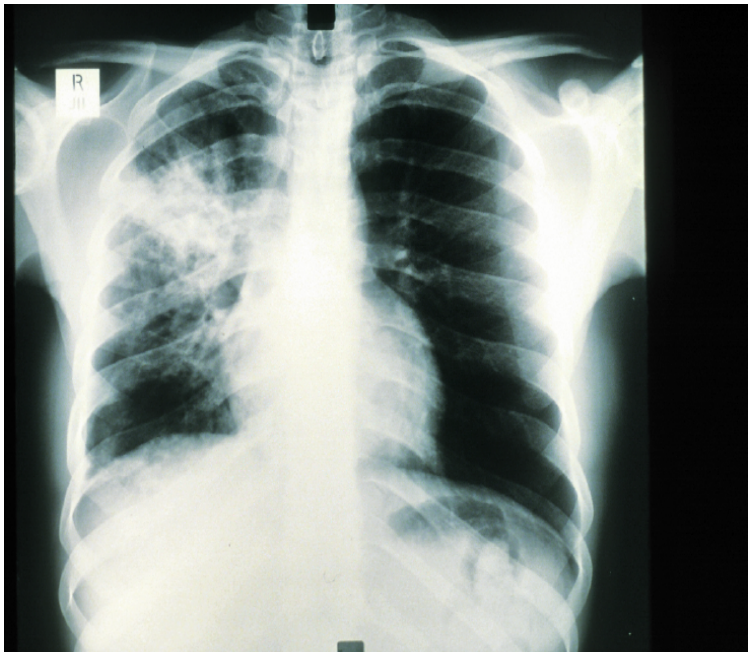


miliary tuberculosis

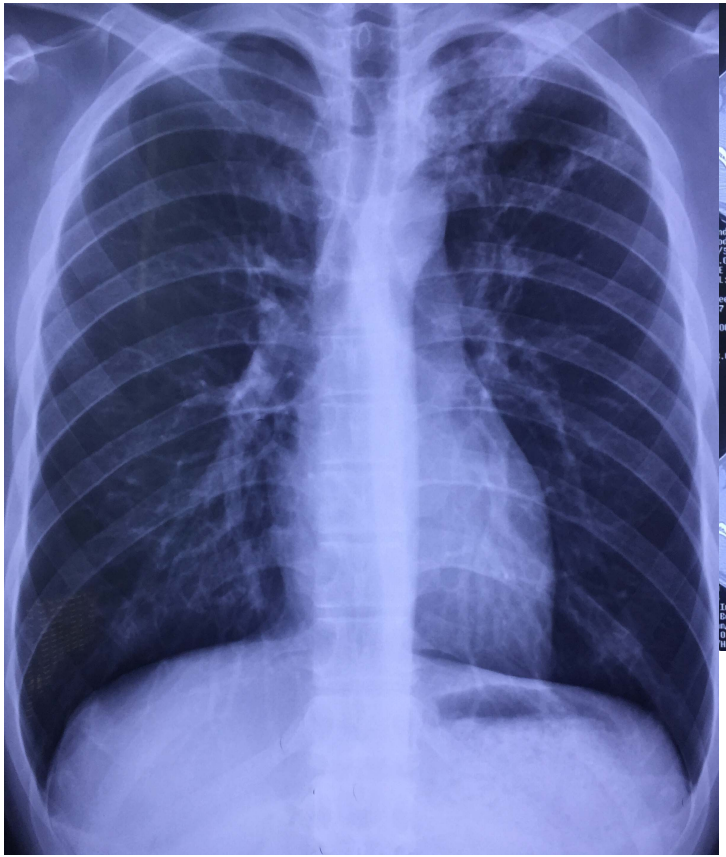


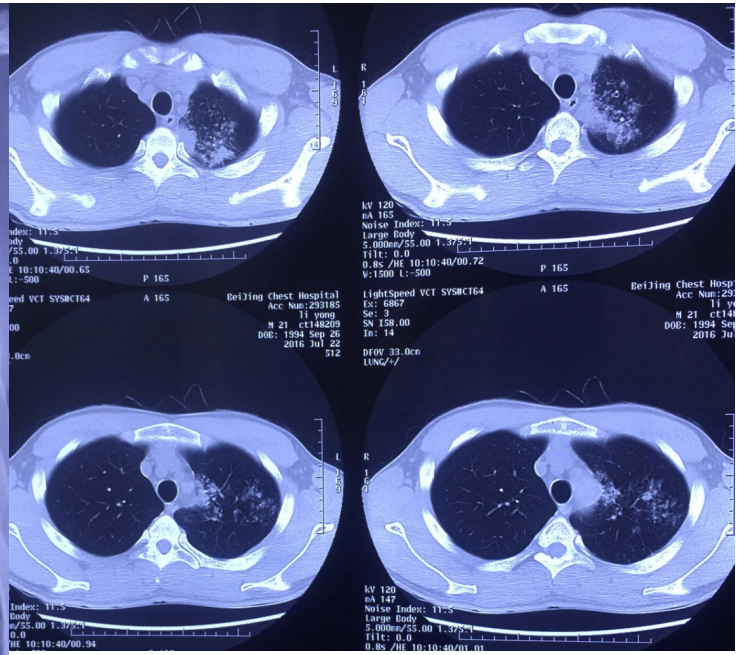


Pulmonary TB typically affects the upper zones of the lung



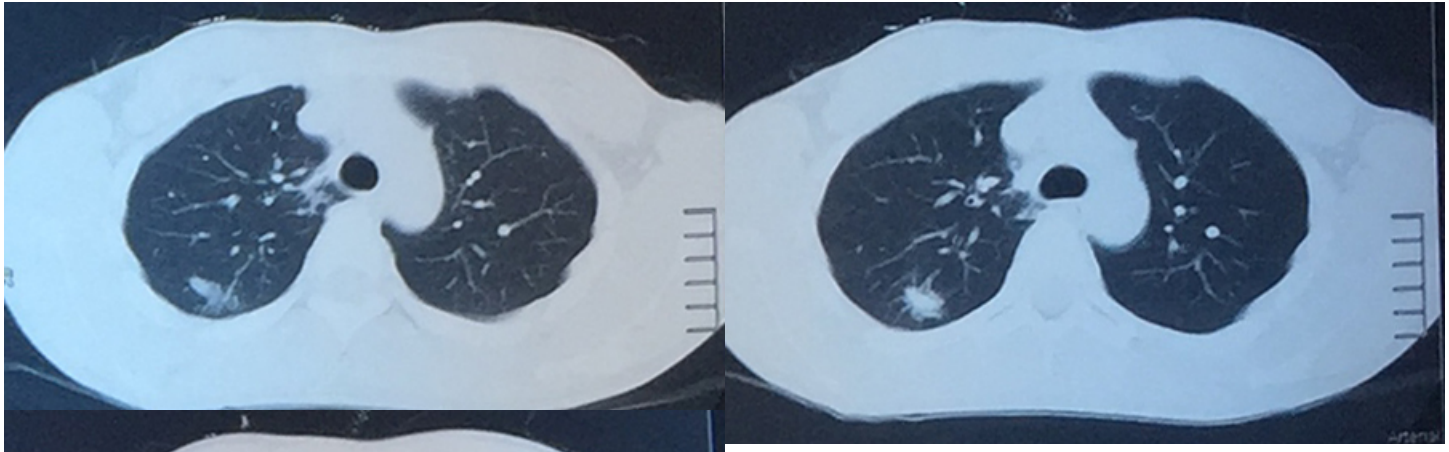
典型肺结核影像

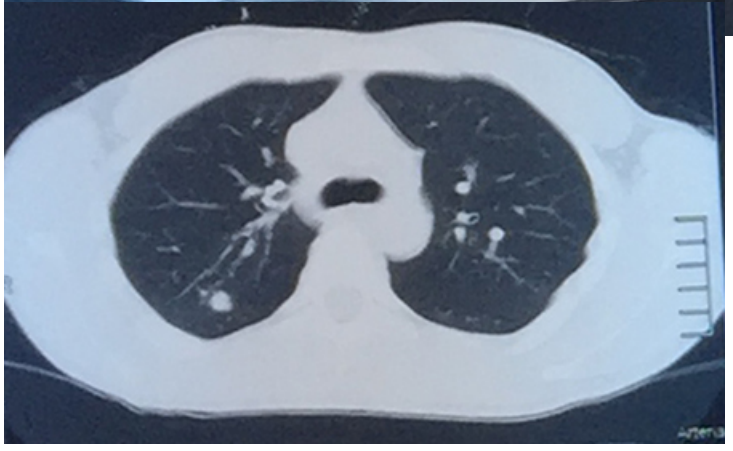




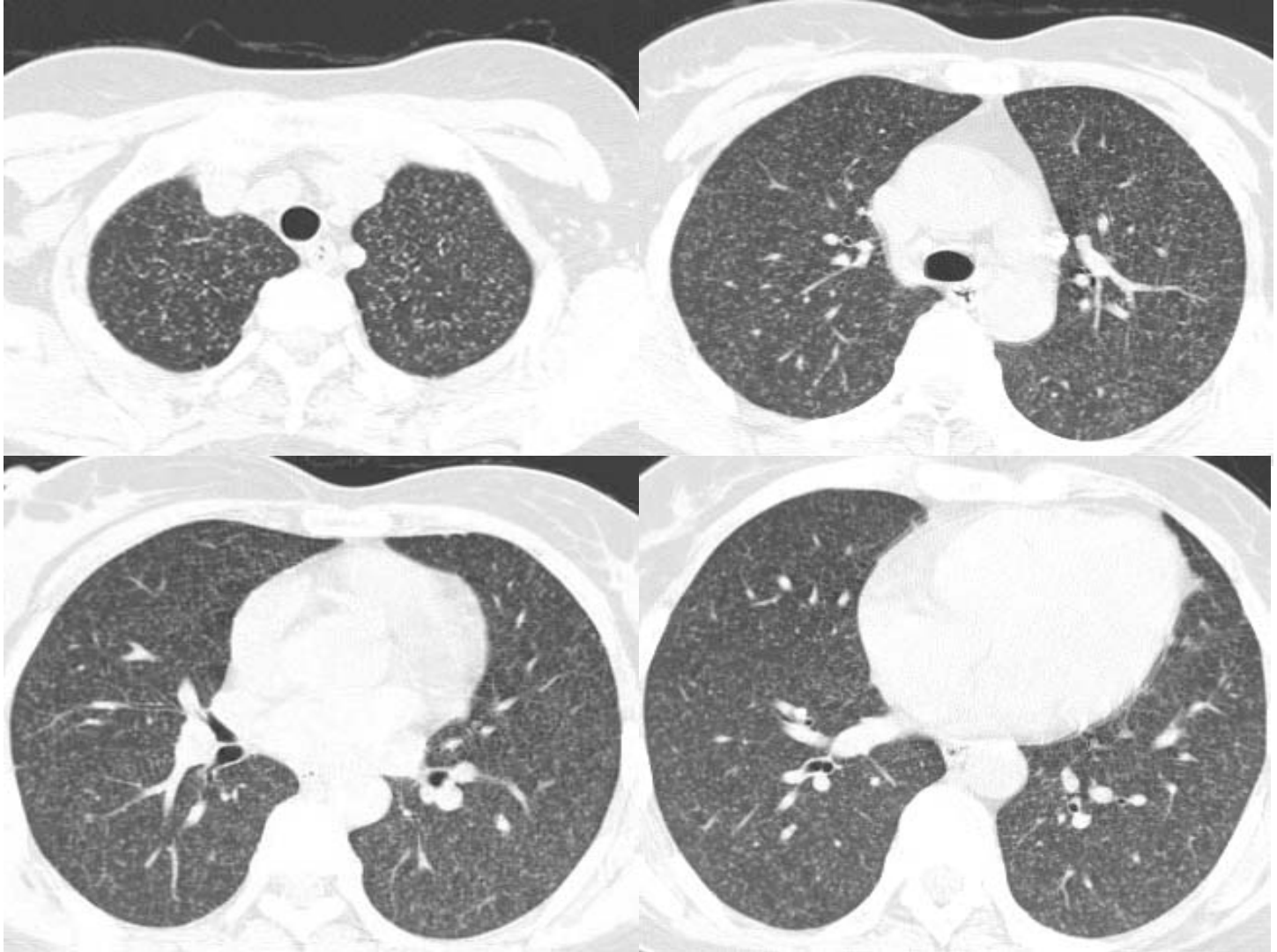
男性，22岁，学生，咳嗽1年

典型肺结核影像

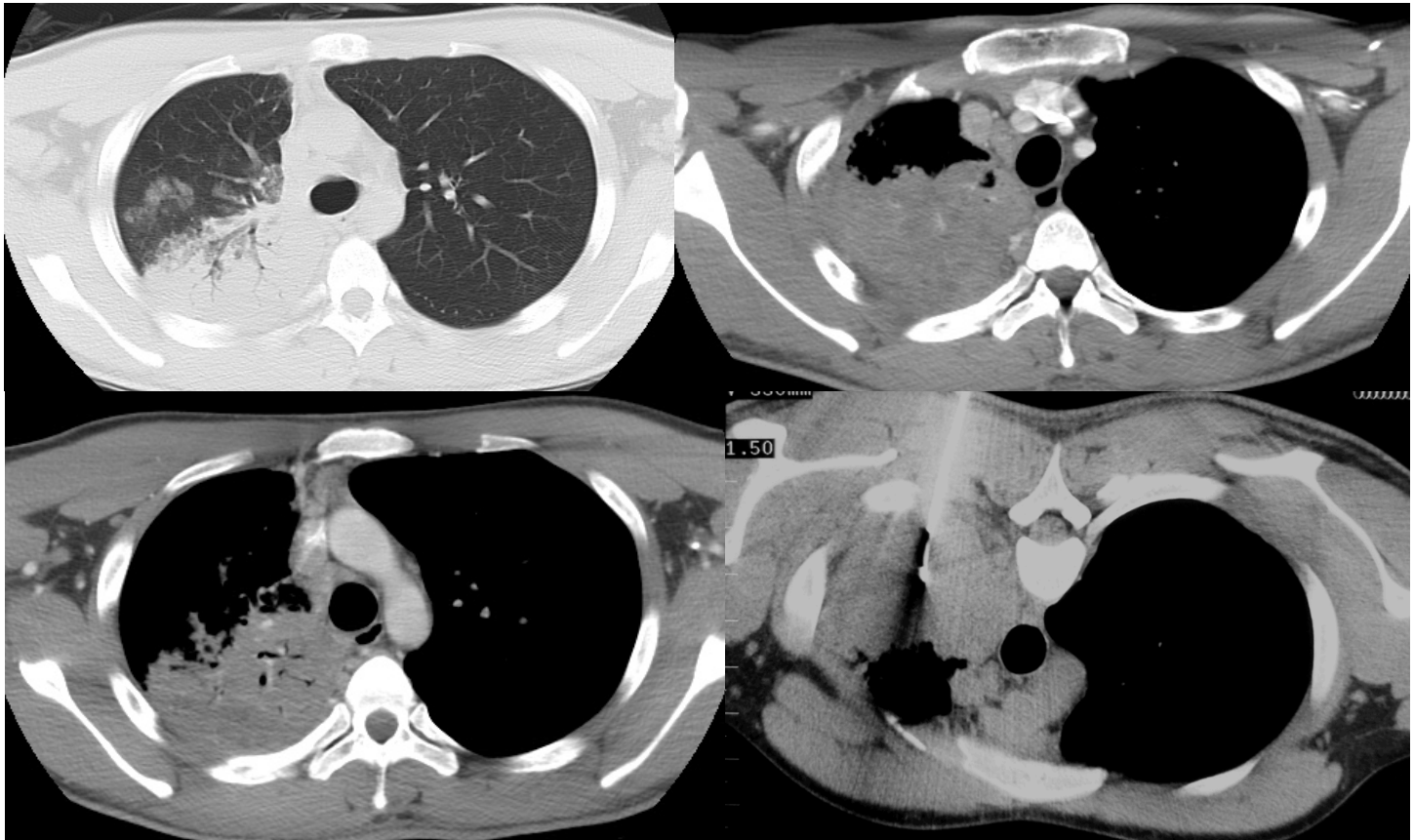




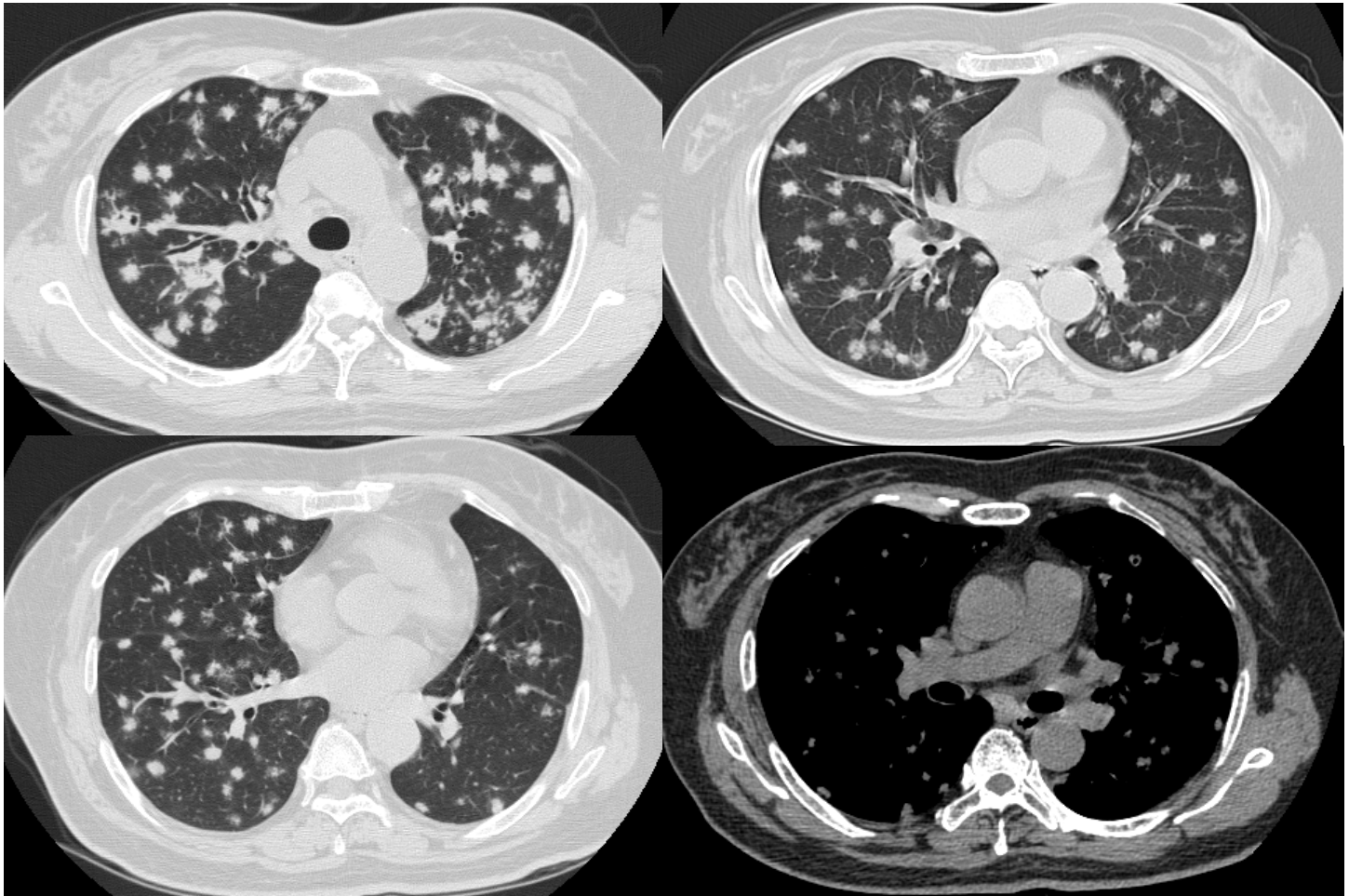
右上叶后段结节病灶，周围可见卫星病灶



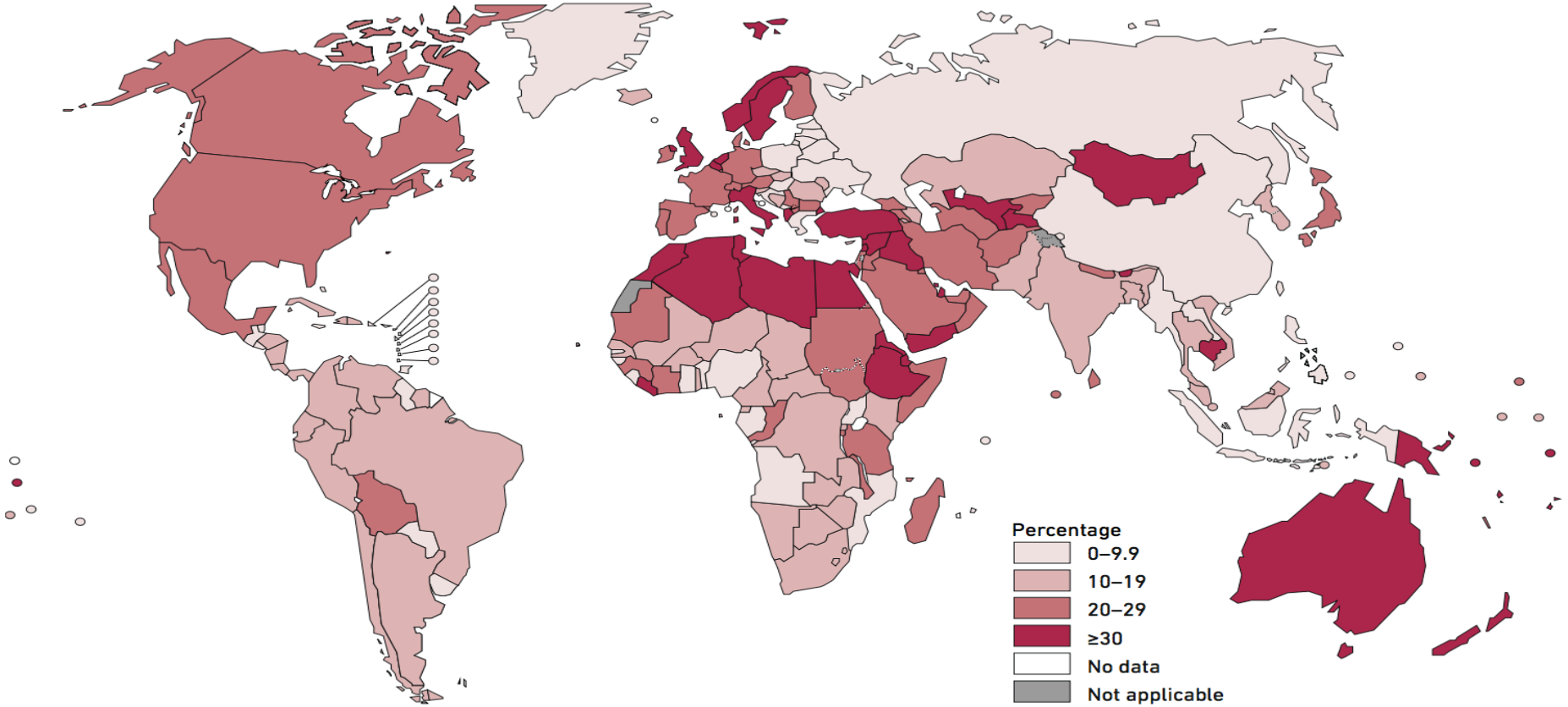
不典型肺结核影像



不典型肺结核影像

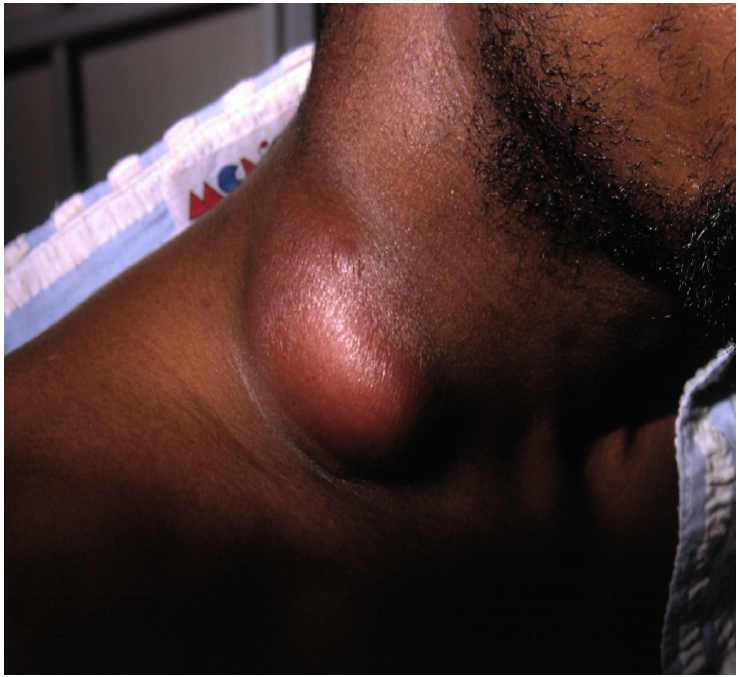


Percentage of extrapulmonary cases among new and relapse TB cases, 2017[a]

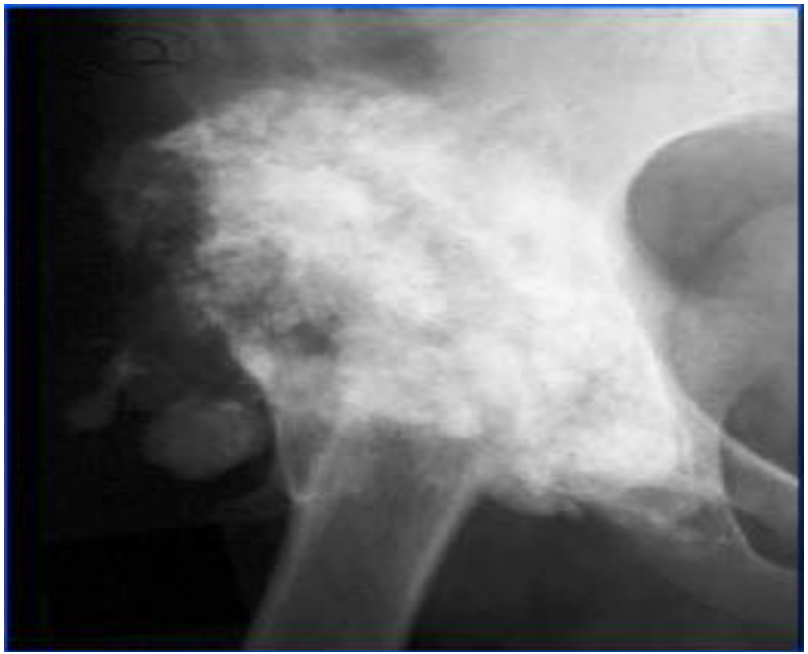


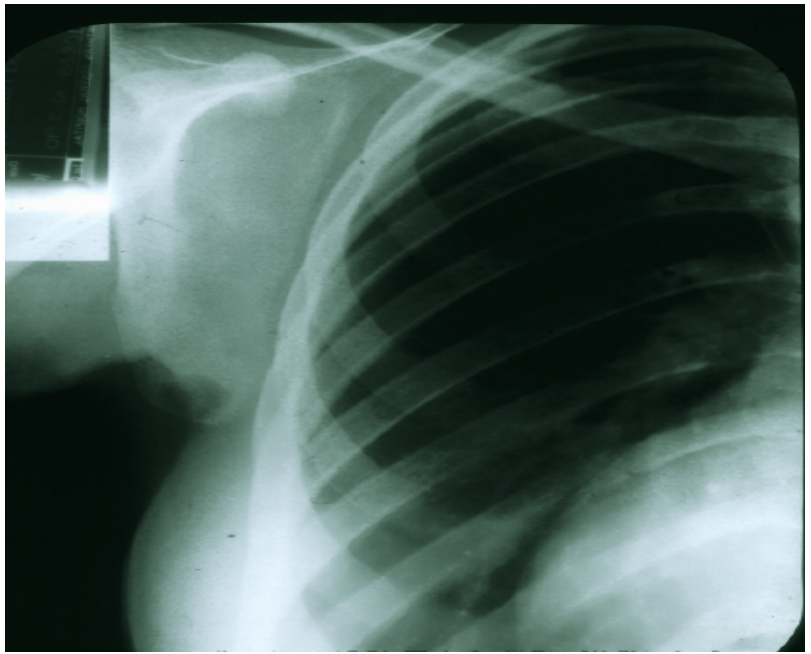
[a] 2016 data were used for 18 countries.

25 male African. Expanding non painful lesion in neck - Cervical lymph node TB progressing to abscess (beware deep extension - collar stud abscess)

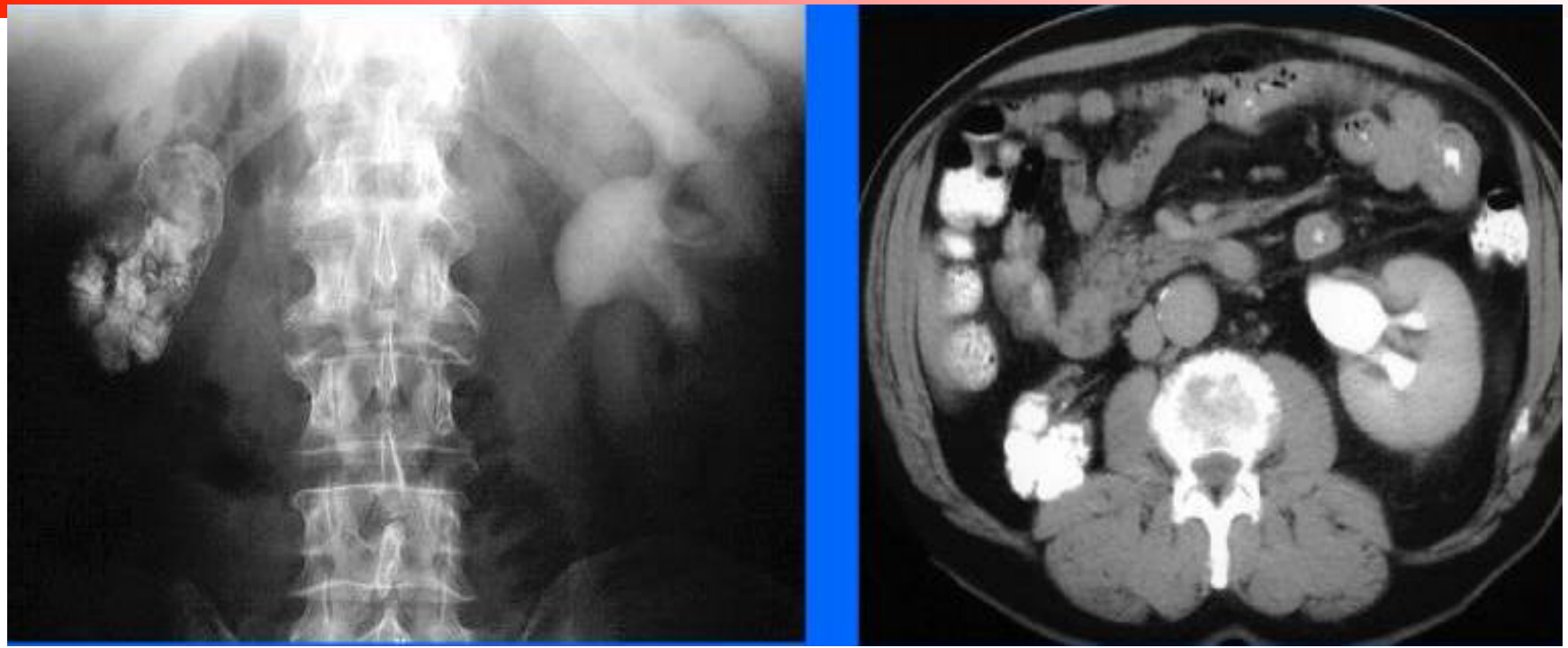


Often associated with delay in diagnosis – **any** chronic discharging lesion must be considered possibly TB





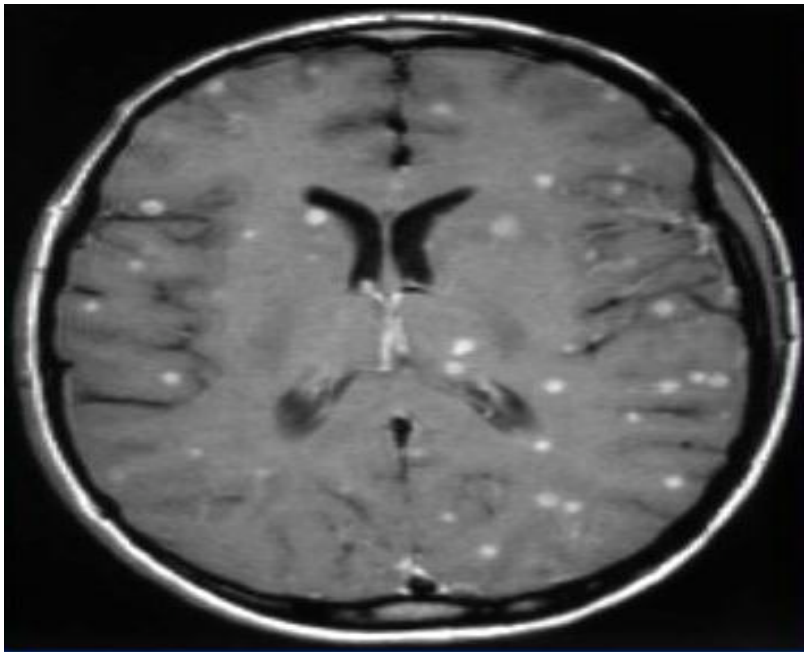
Renal tuberculosis (may have few or no symptoms) leading to autonephrectomy

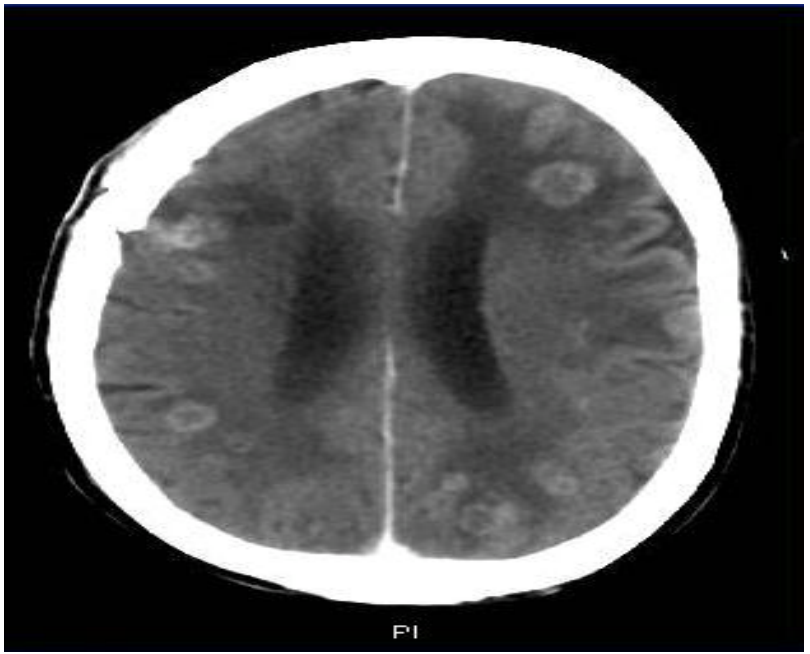


meningitis - diagnosis usually made on clinical grounds

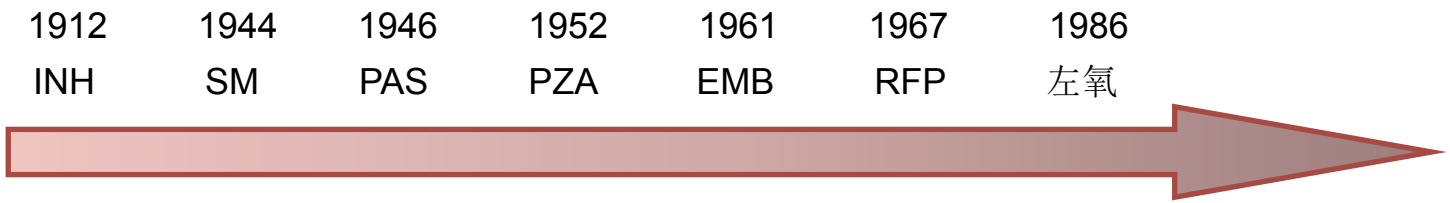
- Clinical
  - Acute or subacute
  - Prognosis related to severity of disease at onset of treatment
  - Commonly delay between presentation and diagnosis
  - Common in children
  - c100 cases per year in England
- **CSF**
  - **Cell count 50-500 (50% lymphs, 50% polys)**
  - **High protein ++**
  - **Low glucose**
  - Micro often negative (PCR/culture important)

miliary TB on MRI scan
tuberclomas on CT scan

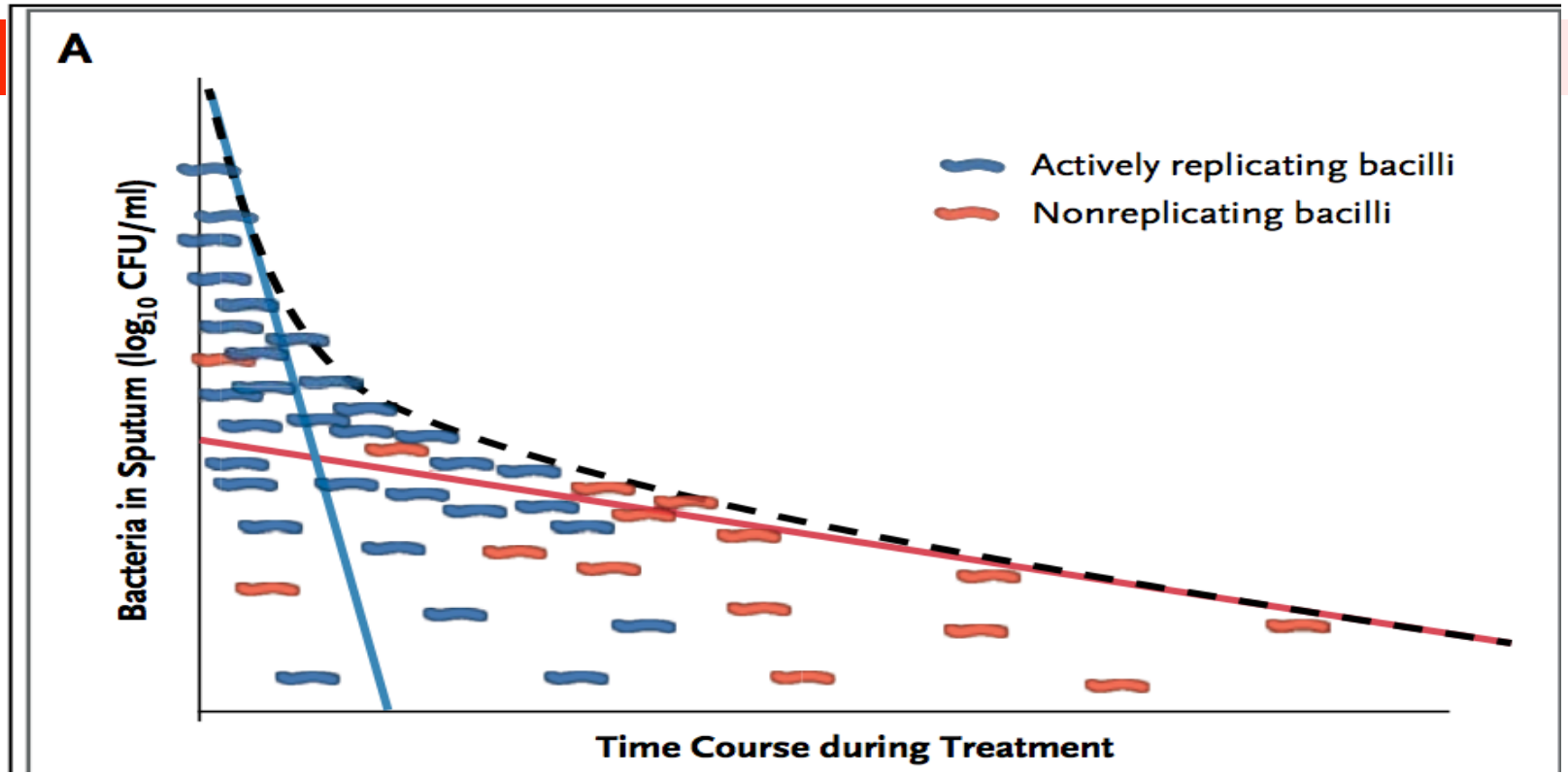




Discovery of antitubercular agents

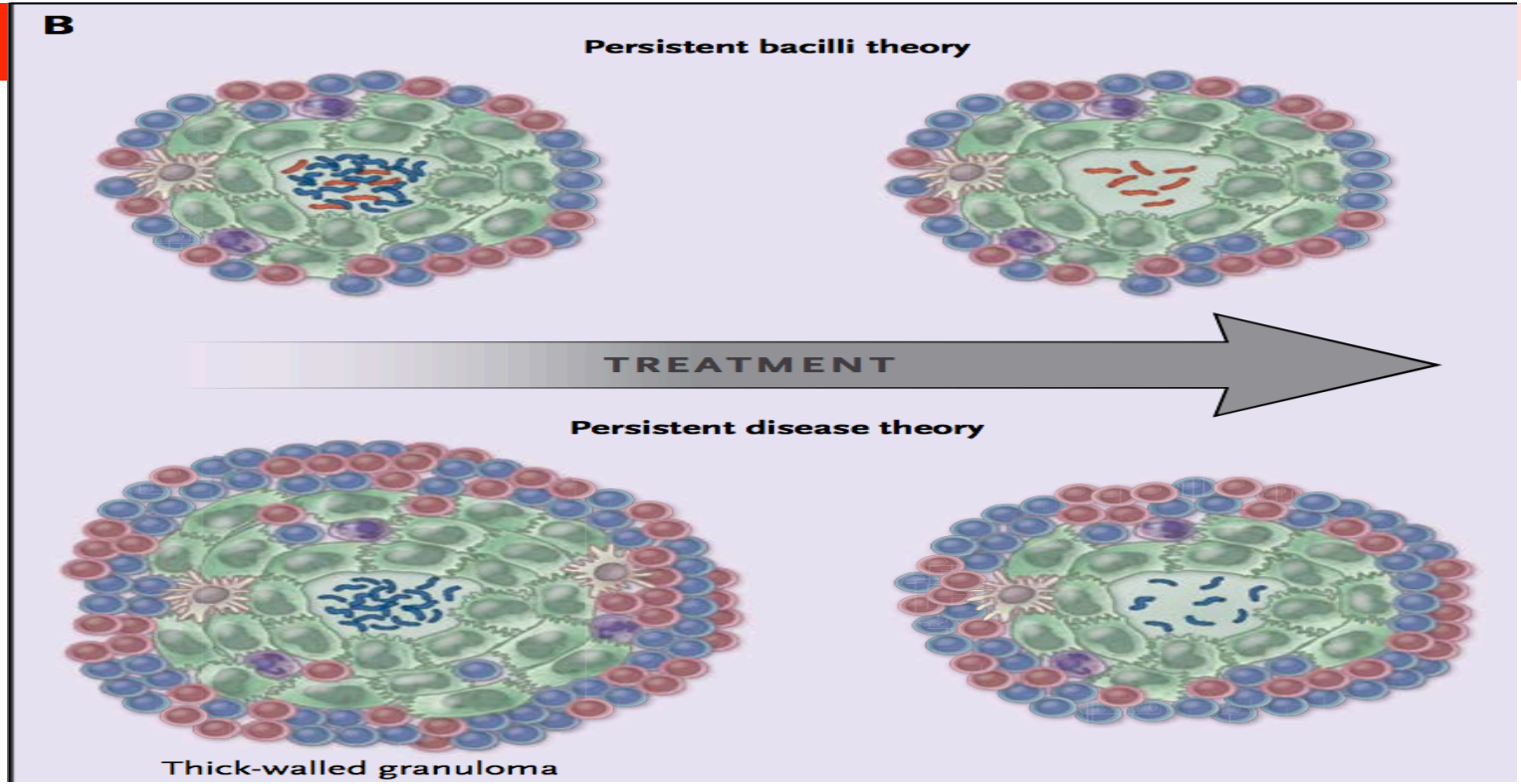


Biphasic Decline in Viable Bacteria during Treatment for Tuberculosis



N Engl J Med 2013;368:745-55.

Biphasic Decline in Viable Bacteria during Treatment for Tuberculosis



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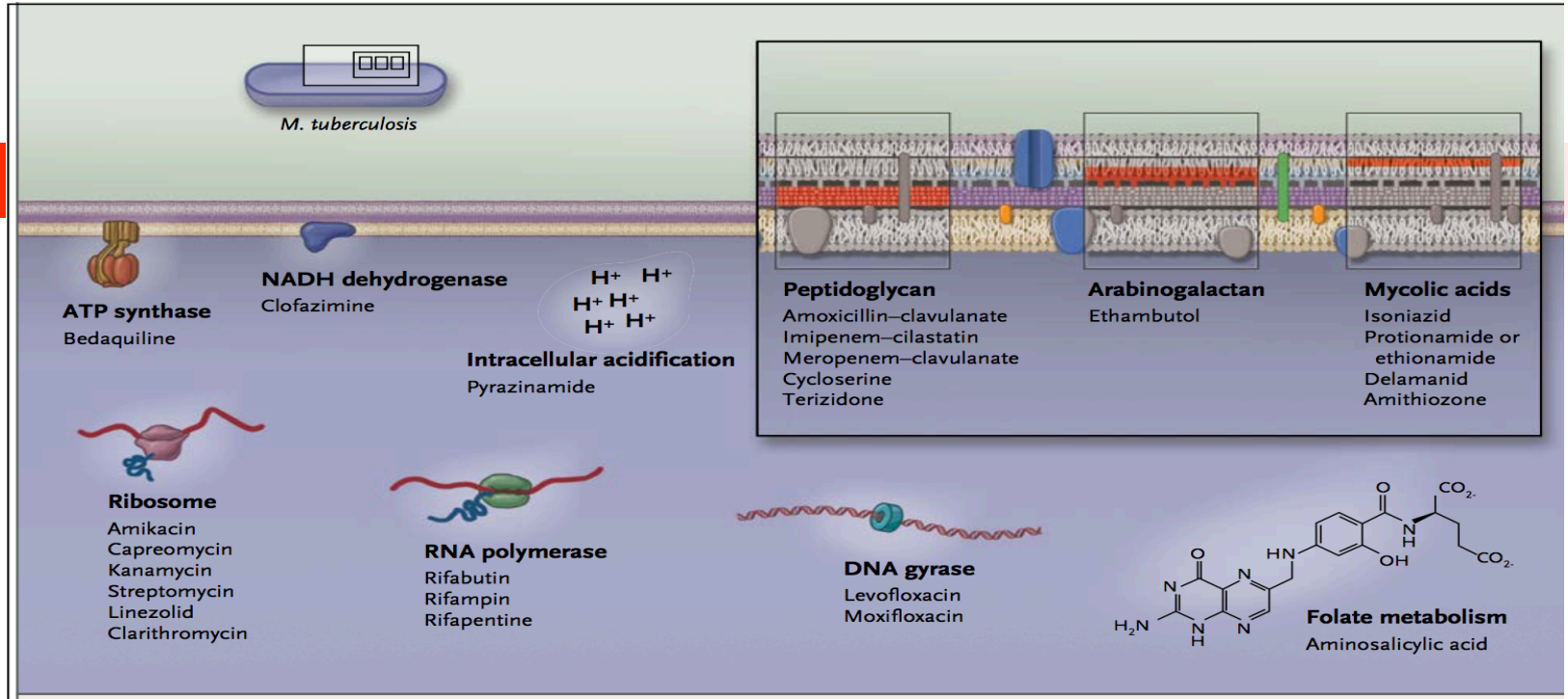


Figure 3. Sites and Mechanisms of Action of Antimycobacterial Agents.

Shown are the known targets of various agents that have been used clinically in tuberculosis treatment. Many antituberculosis agents target the *M. tuberculosis* cell envelope. The box is a high-resolution representation showing the agents that act on each of the three component polymers of the macromolecular outer cell envelope. Drugs such as aminosalicylic acid act like antimetabolites; they are incorporated into folate metabolism as substrates and inhibit downstream folate-dependent processes. The mode of action of pyrazinamide remains enigmatic, and the drug appears to act at least partially by acidifying the cytoplasm of the cell.

N Engl J Med 2013;368:745-55.

Table 1. Tuberculosis Drugs, Recommended Dosages, and Common Adverse Events.*

Drug	Route	Dose in Adults	Comments
Rifamycins			
Rifampin	Oral, IV	10 mg/kg daily (higher doses may be more effective)	A higher dose (13 mg/kg IV in the first 2 wk) improves treatment outcome in TB meningitis (low CSF penetration); monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Alternative rifamycins			
Rifabutin	Oral	5 mg/kg daily (doses up to 450 mg daily sometimes used)	Less likely than rifampin to interact with antiretroviral agents and may be useful in patients with HIV infection; monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Rifapentine	Oral	Not recommended in the U.S. for induction phase; consolidation phase: 600–1200 mg once weekly	Has a very long half-life and can be administered weekly in the consolidation phase; monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Isoniazid and later-generation fluoroquinolones			
Isoniazid	Oral, IV	5 mg/kg daily (higher dose recommended for MDR-TB)	MDR-TB: in the absence of a *katG* S315T mutation, *inhA* promoter mutations (8A/C, 15T, 16G) confer low-level isoniazid resistance (MIC, <1 mg/liter), and a dose of 16–20 mg/kg should be considered; monitor for hepatotoxicity; give with pyridoxine
Levofloxacin	Oral, IV	10–15 mg/kg daily	May potentiate QTc-interval prolongation when given with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval
Moxifloxacin	Oral, IV	400 mg daily	May potentiate QTc-interval prolongation when given with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with bedaquiline or delamanid not recommended
New drugs with documented efficacy			
Bedaquiline	Oral	400 mg daily for 2 wk, followed by 200 mg 3 times/wk for 22 wk (take with food)	Approved by the FDA and EMA as part of an appropriate combination regimen for MDR-TB when an effective treatment regimen is unavailable because of resistance to or unacceptable adverse effects of other medications; may potentiate QTc-interval prolongation when used with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with delamanid or moxifloxacin not recommended
Delamanid	Oral	100 mg twice a day for 24 wk	Approved by the EMA for use as part of an appropriate combination regimen for MDR-TB when an effective treatment regimen is unavailable because of resistance to or unacceptable adverse effects of other medications; may potentiate QTc-interval prolongation when used with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with bedaquiline or moxifloxacin not recommended
Injectable agents with sufficient efficacy data			
Amikacin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent

N Engl J Med 2013;368:745-55.

Table 1. (Continued.)

Drug	Route	Dose in Adults	Comments
Capreomycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; electrolyte abnormalities can be severe and life-threatening and should be monitored carefully; also monitor electrolytes and hearing; hearing loss can be substantial before becoming clinically apparent
Kanamycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent
Streptomycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent; many MDR-TB strains are resistant to streptomycin
Oral drugs with sufficient efficacy data†			
Ethambutol	Oral, IV	15–25 mg/kg daily	Companion drug in the WHO first-line regimen but with less sterilizing activity than rifampin and isoniazid; may induce visual disturbance that can be rapid in onset and can begin with loss of red–green discrimination; monitor visual acuity
Linezolid	Oral, IV	600 mg daily	Severe adverse events are common with long-term therapy; close monitoring of blood count and awareness of peripheral neuropathy is mandatory; give with pyridoxine
Aminosalicylic acid	Oral, IV	Oral: 4 g 3 times/day; intravenous: 12 g daily	Often not tolerated in combination with protionamide or ethionamide; IV dosing (available in Europe) by central venous catheter only
Protionamide or ethionamide	Oral	15–20 mg/kg (usually 750 mg as a single daily dose or in 2–3 divided doses)	Often not tolerated in combination with aminosalicylic acid; monitor liver and thyroid function; give with pyridoxine
Terizidone or cycloserine	Oral	10–15 mg/kg (usually 750 mg as a single daily dose or in 2–3 divided doses)	Terizidone, the fusion product of two molecules of cycloserine and one molecule of terephthalaldehyde, is less toxic than cycloserine; monitor mental status; give with pyridoxine
Pyrazinamide	Oral	Daily dosing (preferred): 25–35 mg/kg daily (maximum dose, 2000 mg); intermittent dosing: up to 50 mg/kg daily 3 days/wk	Companion drug in induction phase of the WHO first-line regimen; if hepatotoxicity develops, reexposure is not suggested if reexposure to isoniazid and rifampin is tolerated; if not part of a standard regimen in the induction phase, treatment should be prolonged; monitor for hepatotoxicity
Companion drugs with limited efficacy data			
Amoxicillin–clavulanate	Oral, IV	Amoxicillin component: 40 mg/kg 2 or 3 times/day (maximum dose, 3000 mg/day)	Administer with meropenem if clavulanic acid is not available as a single drug

N Engl J Med 2013;368:745-55.

Clarithromycin	Oral	500 mg twice a day	Monitor QTc interval
Clofazimine	Oral	100–200 mg daily	In cases of severe skin discoloration, reduce dose to 5 times/wk; monitor QTc interval
Imipenem–cilastatin	IV	Imipenem component: 1000 mg 2 or 3 times/day	Long-term IV access recommended; administer with clavulanic acid (available as amoxicillin–clavulanate) at a dose of 125 mg 2 or 3 times/day; very limited data on use for MDR-TB
Meropenem	IV	1000 mg 2 or 3 times/day	Long-term IV access recommended; administer 1000–2000 mg 2 or 3 times/day with clavulanic acid (available as amoxicillin–clavulanate)
Amithiozone	Oral	150 mg daily	Cross-resistance with protionamide, ethionamide, and isoniazid; contraindicated in patients with HIV infection; give with pyridoxine

* An expanded table that includes doses in children and adverse events is in the Supplementary Appendix, available at NEJM.org. ART denotes antiretroviral therapy, CSF cerebrospinal fluid, EMA European Medicines Agency, FDA Food and Drug Administration, HIV human immunodeficiency virus, IM intramuscular, IV intravenous, MDR-TB multidrug-resistant tuberculosis, MIC minimal inhibitory concentration, QTc corrected QT, and WHO World Health Organization.
† Some drugs in the oral drugs category may have injectable formulations but are almost always given orally for tuberculosis treatment.

N Engl J Med 2013;368:745-55.

DOTS strategy----early '90s

A survey conducted in 1989 -1990 revealed *1.7* thousand million people(one-third of the world‘s population) have been or are infected with Mycobacterium tuberculosis . Fewer than 15 countries have a built-in monitoring system .

TABLE 1. ESTIMATED GLOBAL TUBERCULOSIS SITUATION, 1990

Region	People infected (in millions)	New cases	Deaths
Africa	171	1 400 000	660 000
Americas[a]	117	560 000	220 000
South-East Asia	426	2 480 000	940 000
Europe and other industrialized countries[b]	382	410 000	40 000
Eastern Mediterranean	52	594 000	160 000
Western Pacific[c]	574	2 560 000	890 000
Total	1 722	8 004 000	2 910 000

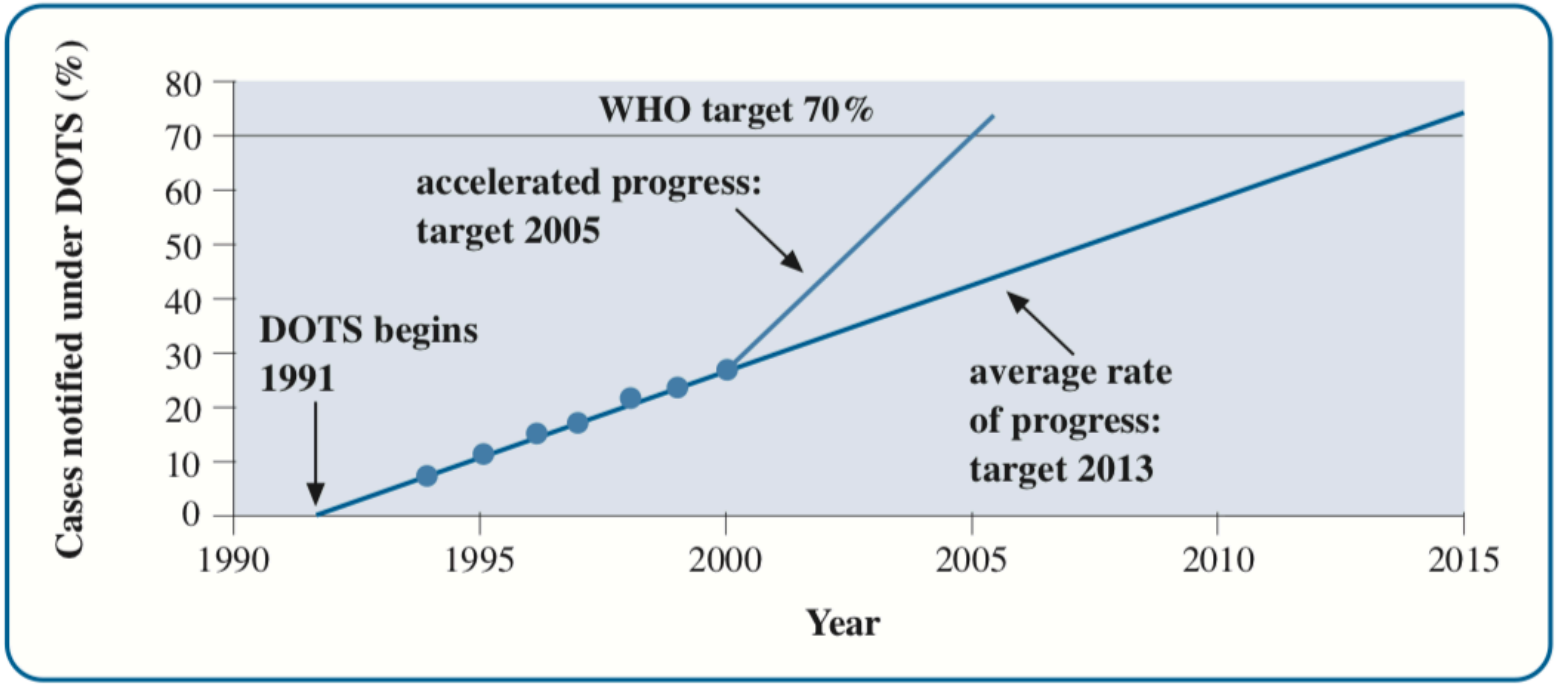
Report of the Ad Hoc Committee on the Tuberculosis Epidemic, London, 17-19 March 1998. Geneva, World Health Organization, 1998 (document WHO/TB/98.245).
World Health Organization. Forty-fourth World Health Assembly .Geneva,1991.

The **44th World Health Assembly (1991)** recognized the growing importance of TB as a public health problem

The forty-fourth World Health Assembly (1991)
Proposed global target : By the year 2000, 85% cure of all sputum-positive cases under treatment and 70% case detection.

World Health Organization. Forty-fourth World Health Assembly .Geneva,1991.

Progress towards the target of 70% case definition, for 22 high TB burden countries, given the current and accelerated rate of progress.



World Health Organization. Treatment of tuberculosis: guidelines for national programs. Geneva:World Health Organization, 2003.

Reassessment of tuberculosis

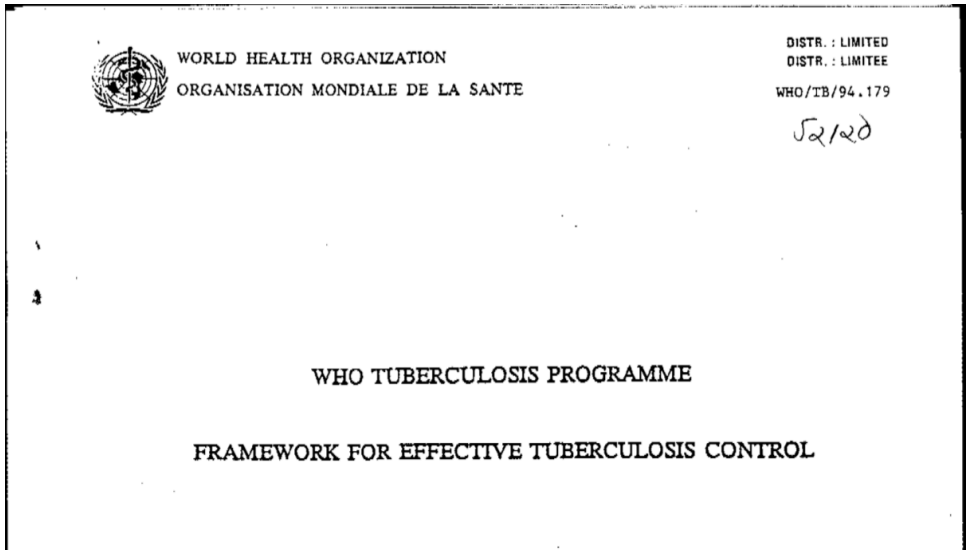
- failure to ensure accessible diagnosis and treatment services
- inadequate treatment regimens and failure to use standardized treatment regimens;
- lack of supervision and an information management system for the rigorous evaluation of treatment outcomes of TB patients;
- misguided policies for health sector reform, with cuts in health care budgets and resultant reduction in financial support to peripheral health services.

World Health Organization. Forty-fourth World Health Assembly .Geneva,1991.

In 1994

World Health Organization

Framework for effective tuberculosis control.



WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

DISTR. : LIMITED
DISTR. : LIMITEE
WHO/TB/94.179

WHO TUBERCULOSIS PROGRAMME

FRAMEWORK FOR EFFECTIVE TUBERCULOSIS CONTROL

World Health Organization. Framework for effective tuberculosis control. WHO/TB/94.179. 1994.

Core DOTs strategy regimen

Initial phase : 2(HRZE)

Continuation phase : 4 $(HR)_3$

DOTs strategy outcome

1995 JAMA

Eleven years of community-based directly observed therapy in Baltimore:

Completion rates : 90.1%

1998 JAMA

A summary pf published studies on DOTs in a consensus statement :
Treatment completion rates for pulmonary tuberculosis are most likely to exceed 90%。
An average of 86% completion for patients treated by DOT.

2004 Am J Respir Crit Care Med

monary tuberculosis (n = 372) in San Francisco County, California from 1998 through 2000. Patients treated by directly observed therapy at the start of therapy (n = 149) had a significantly higher cure rate compared with patients treated by self-administered therapy (n = 223) (the sum of bacteriologic cure and completion of treatment, 97.8% versus 88.6%, p < 0.002), and decreased tubercu-

Cure rate :97.8%

JAMA. 1995 Sep 27;274(12):945-51.
JAMA, 1998, 279(12):943-8.
Am J Respir Crit Care Med, 2004; 170: 561–566

Problems of TB therapy

- Toxicity e.g. liver
- Multiple therapy
- Prolonged treatment
- Drug interactions e.g. anti HIV drugs

END-TB strategy in US

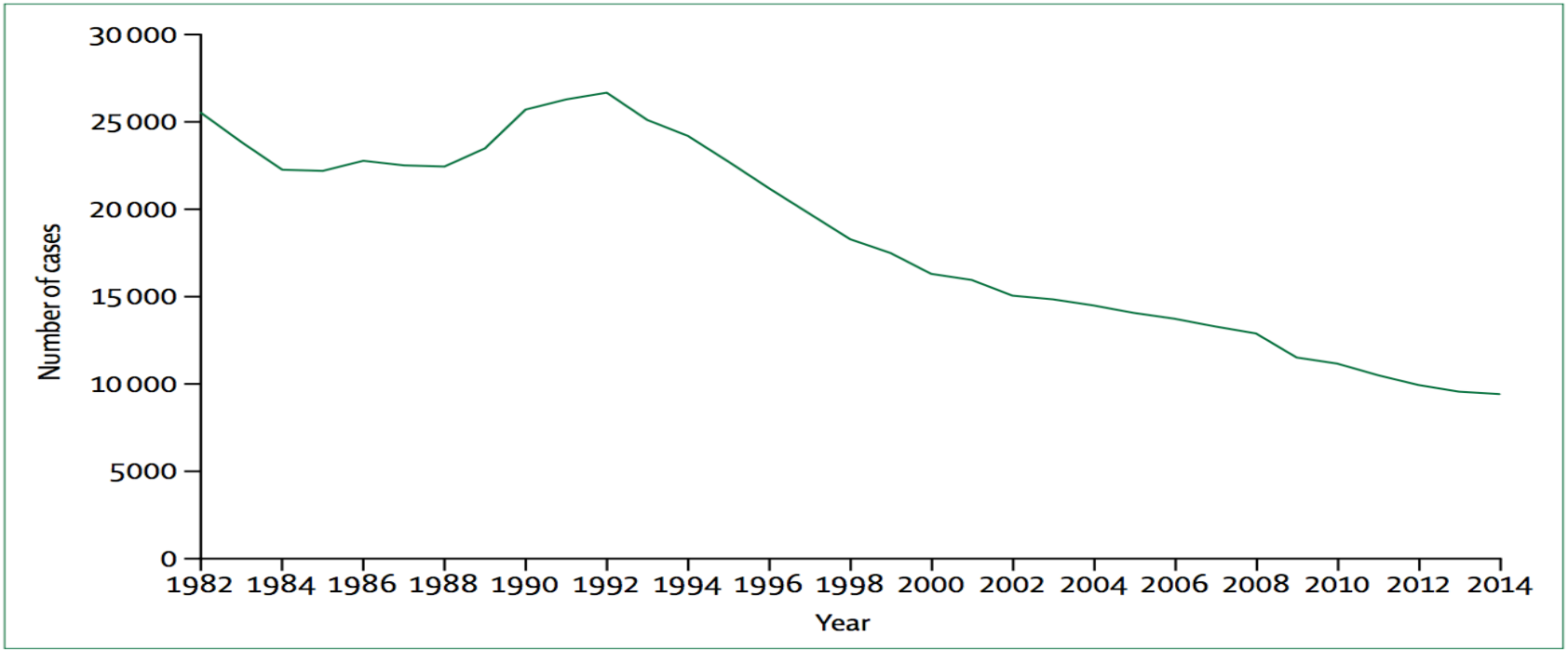


Figure 1: **Reported tuberculosis cases in the USA, 1982–2014**
Data from US Centers for Disease Control and Prevention.[6]

LoBue PA, Mermin JH. Lancet Infect Dis. 2017 Oct;17(10):e327-e333.

结核病治疗当前面临的问题

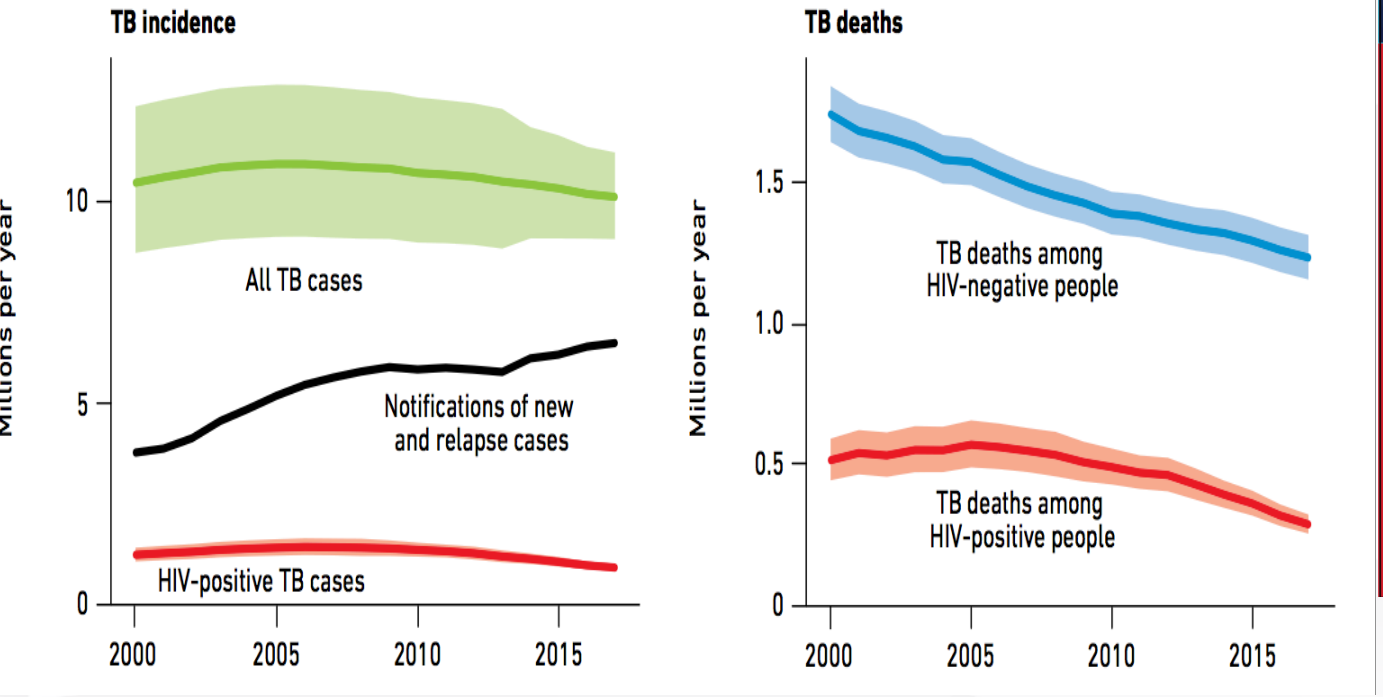
1.病人的发现率

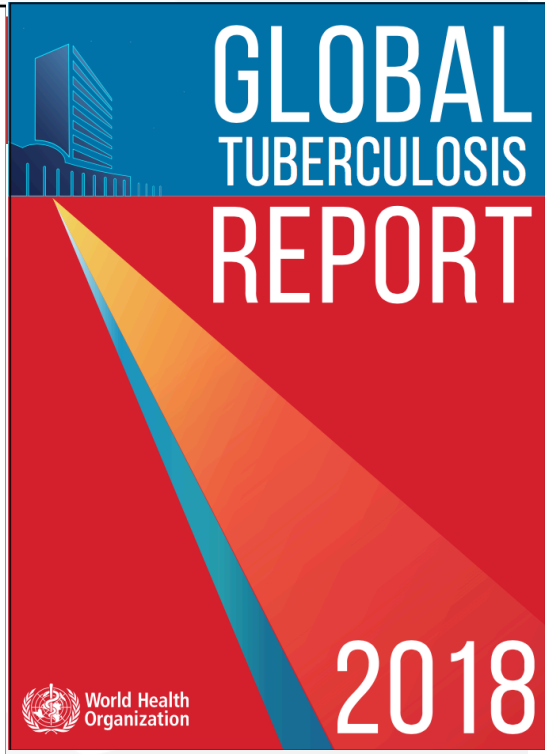
2.治疗的依从性

3.初治耐药

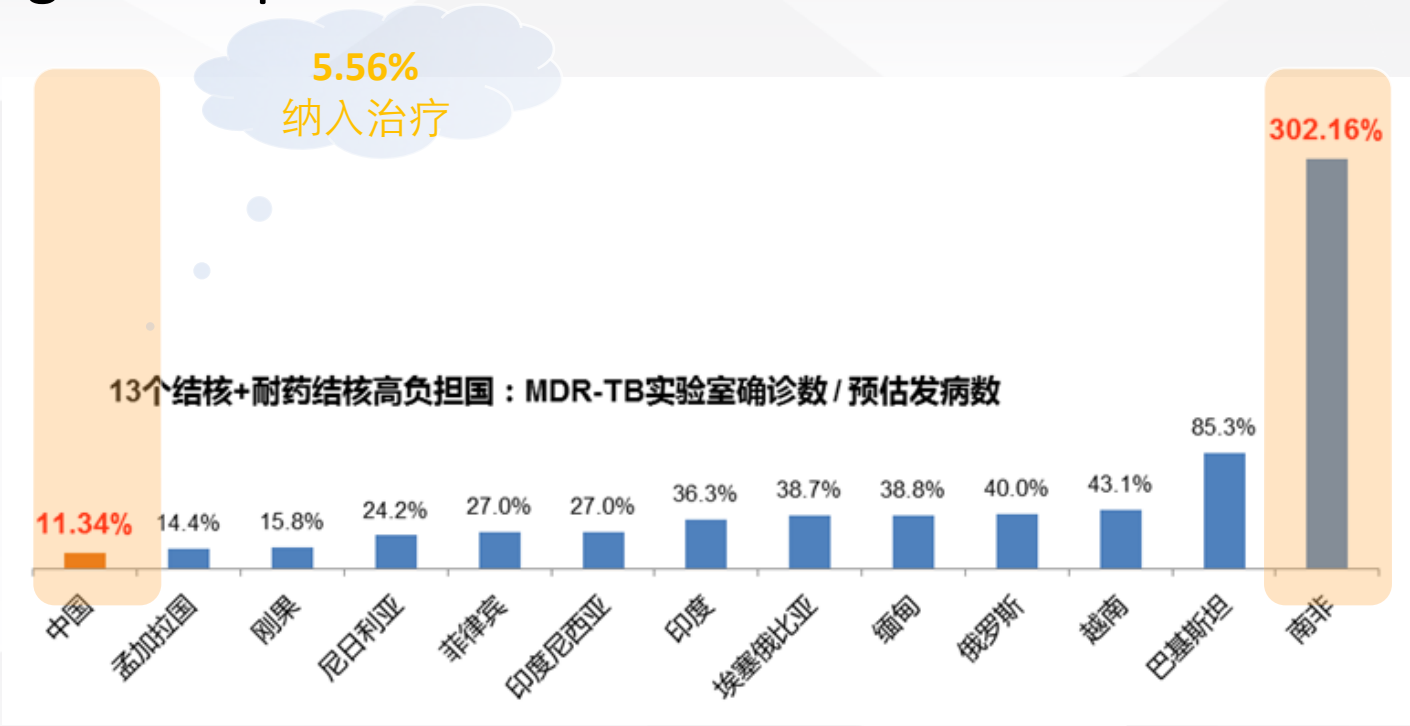
4.潜伏感染活动对新病人数量的贡献

Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2017. Shaded areas represent uncertainty intervals.

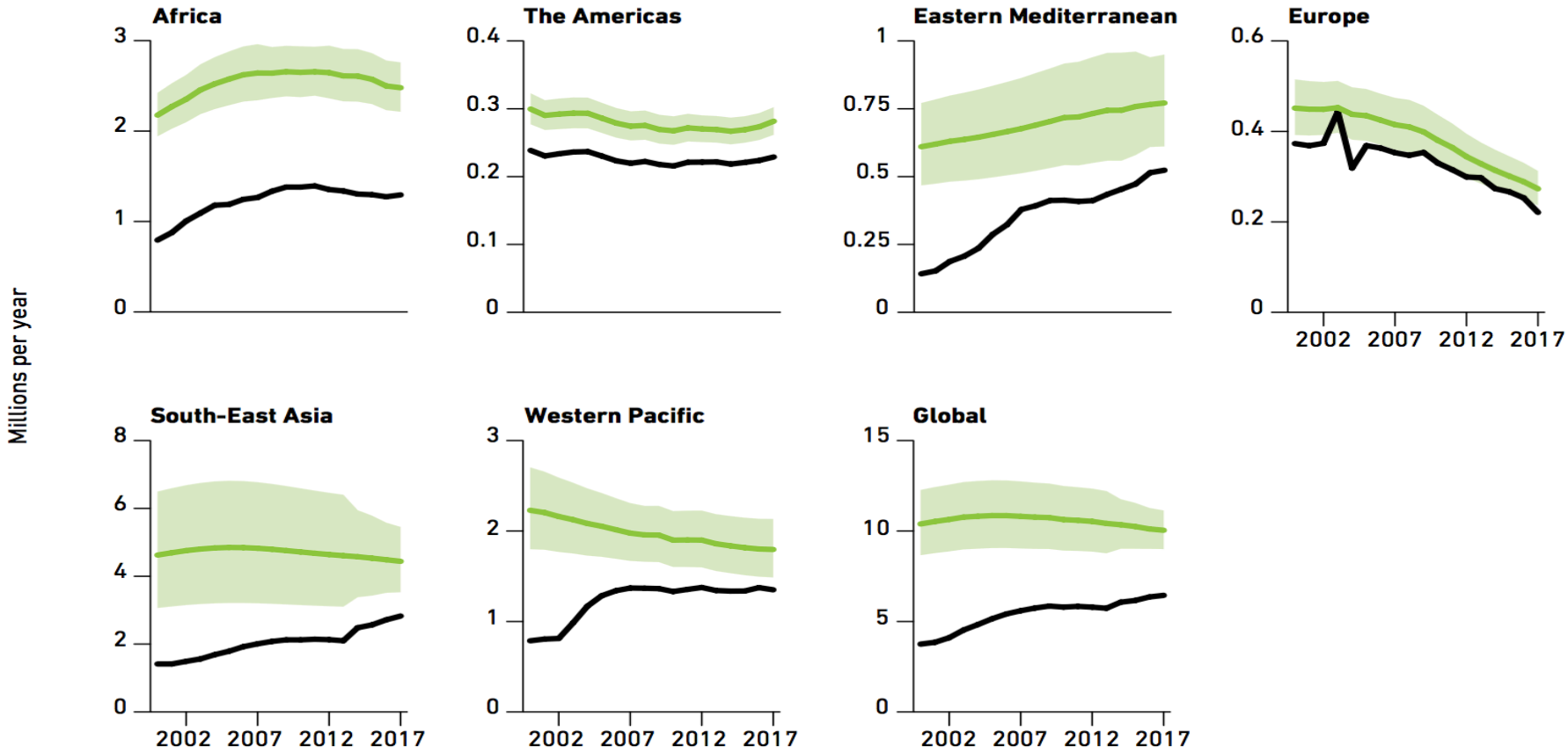




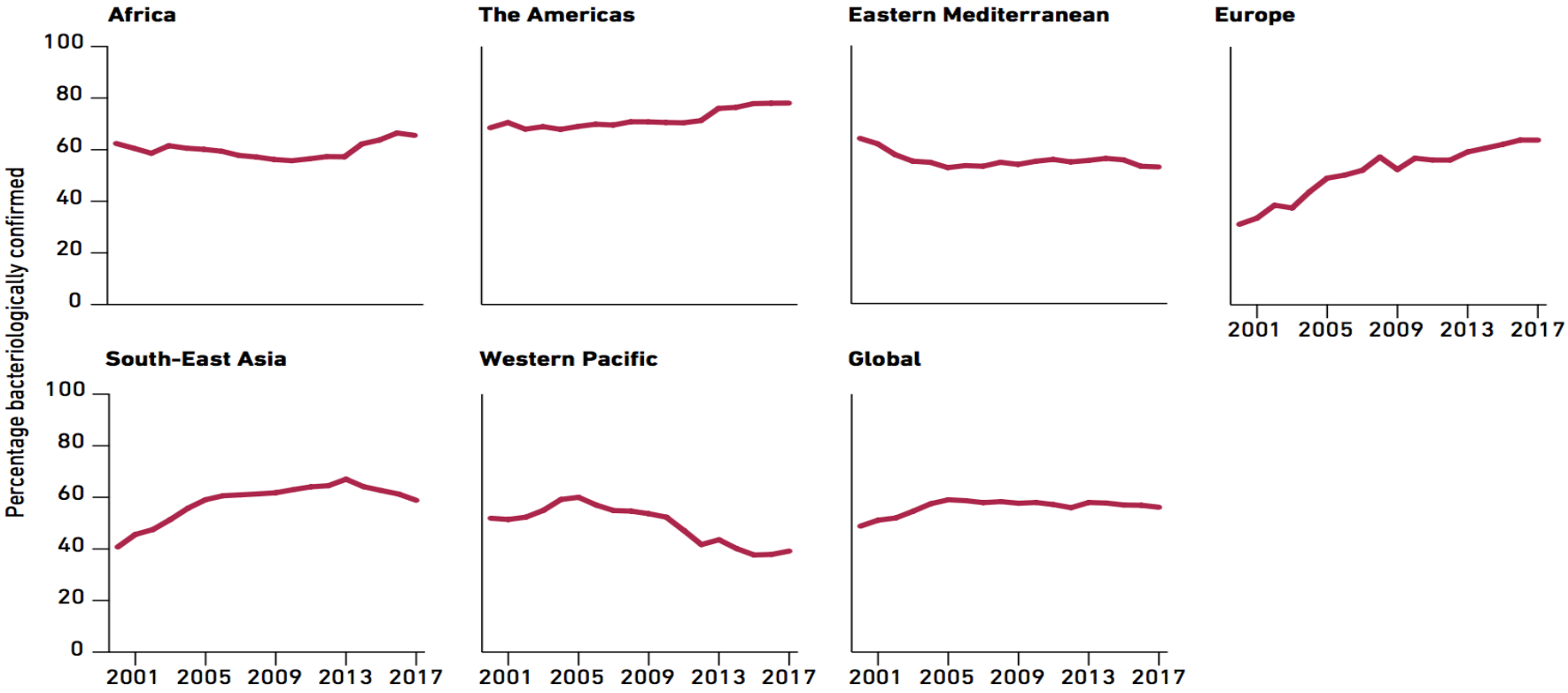
Hiding active patients



Notifications of TB cases (new and relapse cases, all forms) (black) compared with estimated TB incident cases (green), 2000–2017, globally and for WHO regions. Shaded areas represent uncertainty bands.

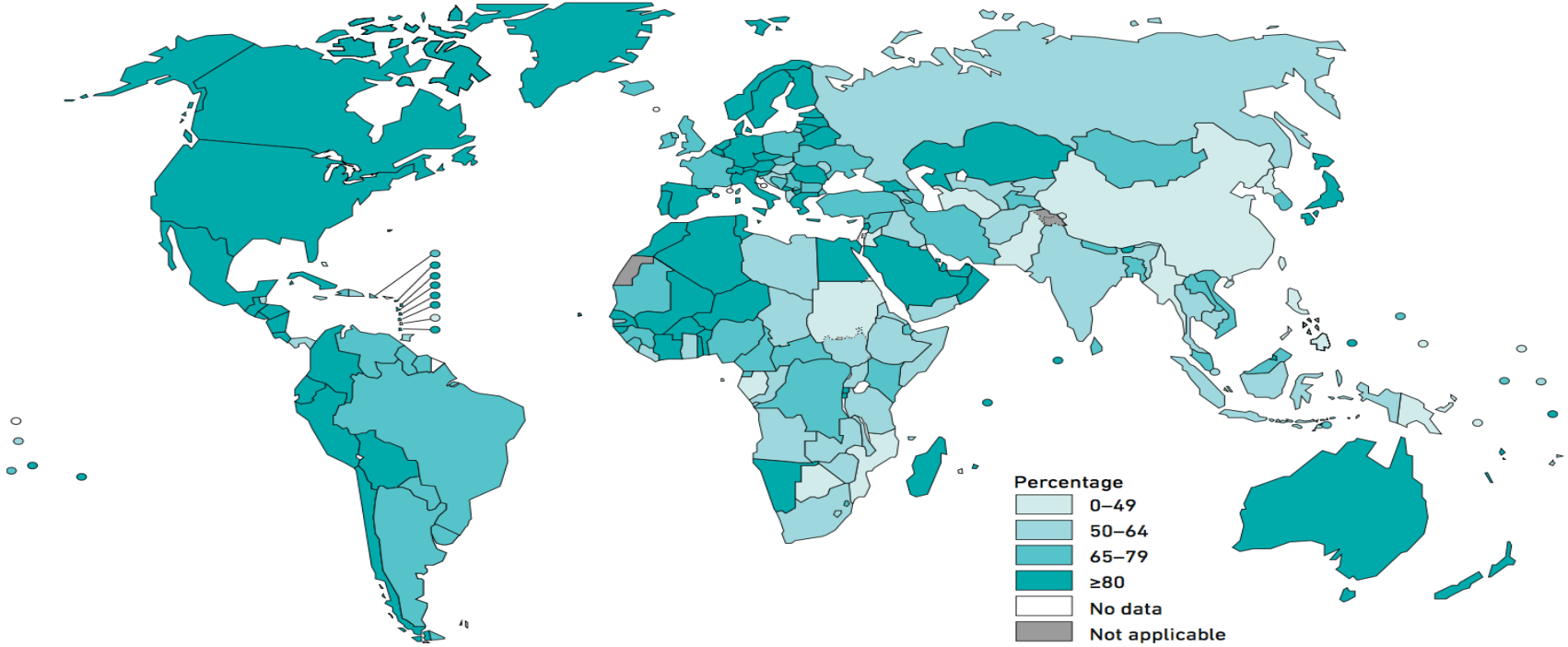


Percentage of new and relapse[a] pulmonary TB cases with bacteriological confirmation, globally and for WHO regions, 2000–2017



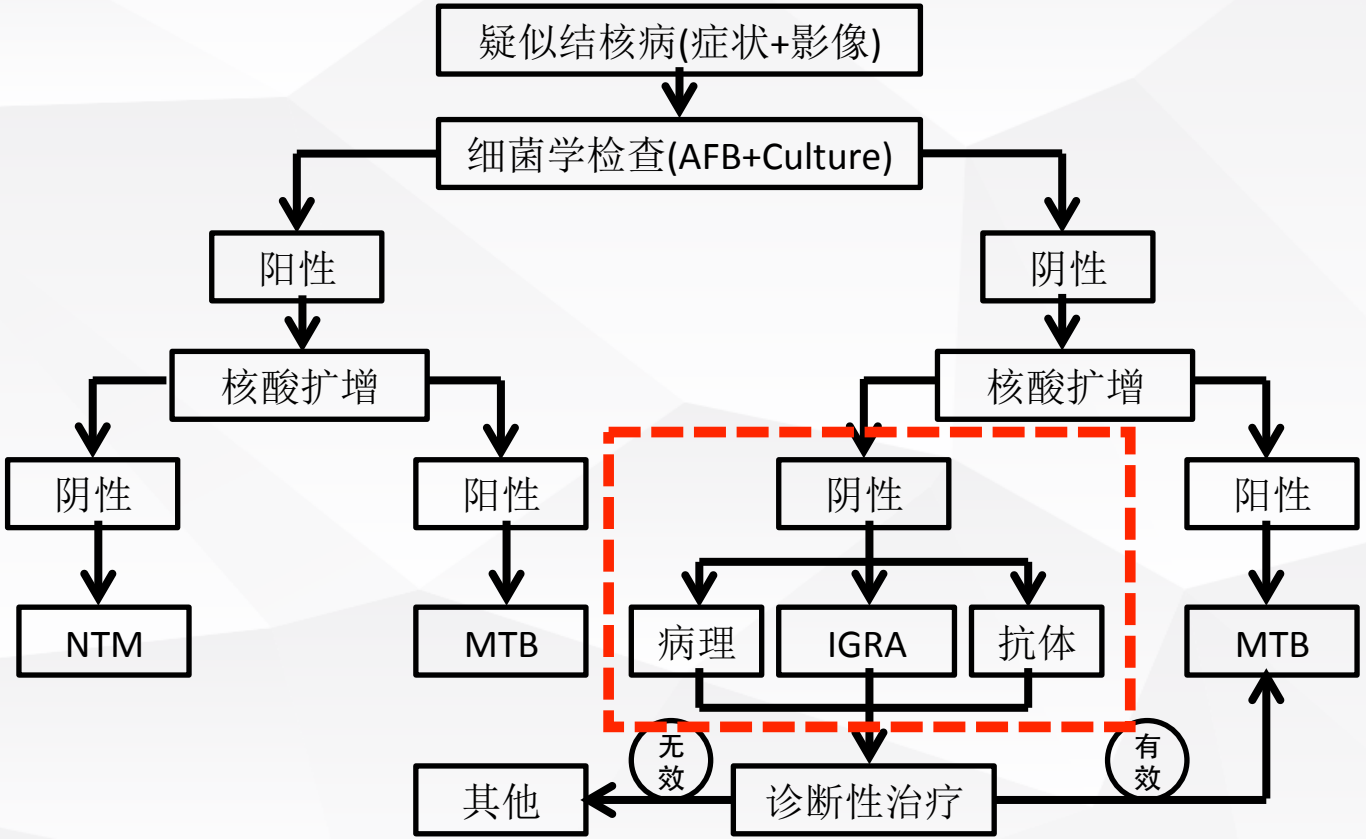
[a] The calculation is for new pulmonary cases in years prior to 2013 based on smear results, except for the European Region where data on confirmation by culture was also available for the period 2002–2012.

Percentage of new and relapse pulmonary TB cases with bacteriological confirmation, 2017

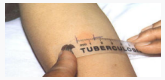


[a] 2016 data were used for 18 countries.

Diagnosis of bacteriological negative TB

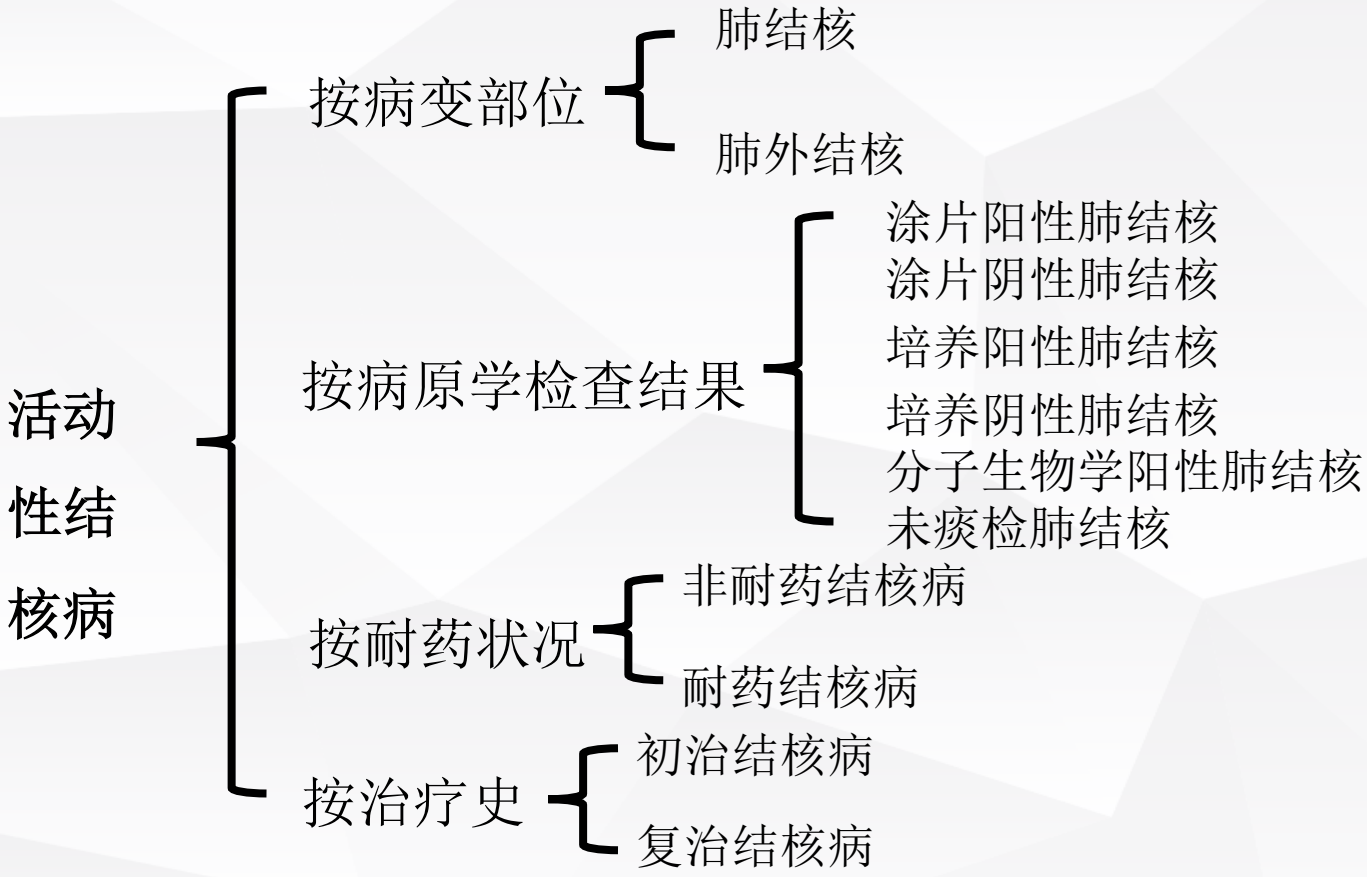


Molecular diagnosis

传统技术				现代技术	
					
影像学	涂片镜检	培养	皮肤菌素试验	IGRA	分子诊断
✓	✓	✓			✓

✓	用于**诊断**活动期结核感染
	用于**筛查**潜伏期结核感染（或既往暴露）

Increase the percentage of new and relapse pulmonary TB cases with bacteriological confirmation



不充分的病人治疗

Inappropriate Tuberculosis Treatment Regimens in Chinese Tuberculosis Hospitals

This investigation of tuberculosis (TB) treatment regimens in 6 TB hospitals in China showed that only 18% of patients with new cases and 9% of patients with retreatment cases were prescribed standard TB treatment regimens. Adherence to treatment guidelines needs to be improved in TB hospitals to control multidrug-resistant TB in China.

抽样调查显示中国**仅18%和初治结核患者与9%的复治结核患者**接受了标准的抗结核治疗

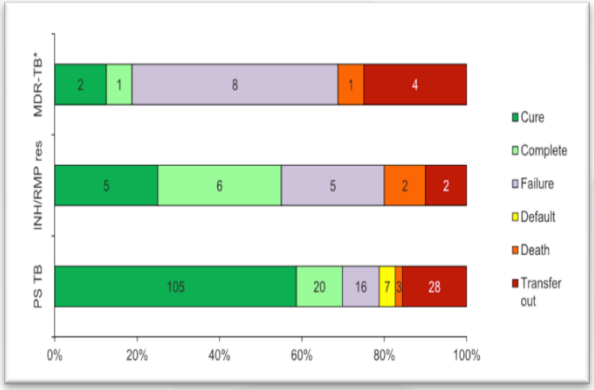
Table 1. Overview of the Different Treatment Regimens for New and Retreatment Tuberculosis (TB) Cases in TB Hospitals in China

Treatment regimen		New cases, % (*n*=541)	Retreatment cases, % (*n*=287)	Total cases, % (*n*=828)
Regimen with FLD only				
	NTP/WHO treatment regimens	17.6	9.1	14.6
	At least isoniazid plus rifampicin, but not NTP/WHO regimen	5.9	5.2	5.7
	Other regimen	0.7	1.7	1.1

He G X, van den Hof S, van der Werf M J, et al. Inappropriate tuberculosis treatment regimens in Chinese tuberculosis hospitals[J]. Clinical Infectious Diseases, 2011, 52(7): e153-e156.

MTBDR*plus* results correlate with treatment outcome in previously treated tuberculosis patients

F-L. Huang,* J-L. Jin,* S. Chen,* Z. Zhou,† N. Diao,* H-Q. Huang,† W. Liu,* Q. Wang,† X-H. Weng,* R. E. Chaisson,‡ Y. Zhang,*§ W-H. Zhang*¶‖



F-L. Huang, J-L

- MDRTBplus与预后
  - MDRTB预后最差
  - 异烟肼单耐患者其次
  - 敏感患者预后佳
- 目前复治方案会加重/扩大耐药情况，特别是耐药的复治患者中。

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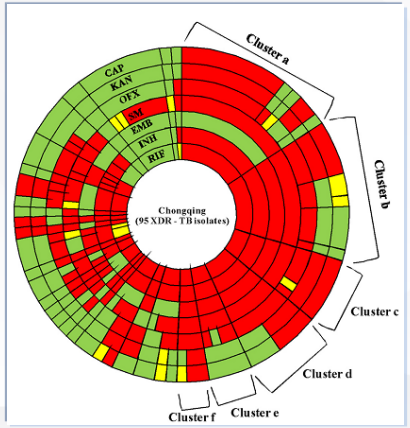
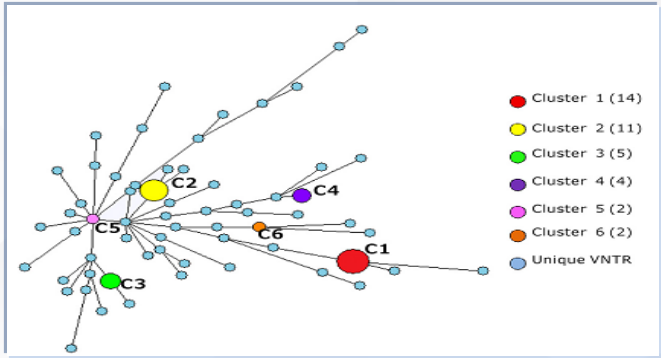
Evolution and Transmission Patterns of Extensively Drug-Resistant Tuberculosis in China

Feifei Wang,[a,b] Lingyun Shao,[a] Xiaoping Fan,[a] Yaojie Shen,[a] Ni Diao,[a] Jialin Jin,[a] Feng Sun,[a] Jing Wu,[a] Jiazhen Chen,[a] Xinhua Weng,[a] Xunjia Cheng,[b] Ying Zhang,[a,c] Wenhong Zhang[a,d]





回顾性分析检测了重庆地区95株广泛耐药结核病（XDR-TB）的分离株，对7种常用抗结核药物的8种耐药基因进行筛选，*katG*315和*inhA*启动子、*rpoB*、*gyrA*、rpsL、*rrs*、*embB*306、*pncA*与重庆地区广泛耐药结核病中INH、RFP、OFLX、SM、KM、EMB、PZA耐药相关

Feifei Wang et al. **Zhang WH.** Antimicrob Agents Chemother. 2015 ;59(2):818-25

From sensitive TB to extensive resistant TB

结核耐药性检测与药物选择

一线口服药物

注射类药物

喹诺酮类

二线口服抑菌药物

疗效不确切药物

Group	Drugs (abbreviations)
Group 1: First-line oral agents	• pyrazinamide (Z) • ethambutol (E) • rifabutin (Rfb)
Group 2: Injectable agents	• kanamycin (Km) • amikacin (Am) • capreomycin (Cm) • streptomycin (S)
Group 3: Fluoroquinolones	• levofloxacin (Lfx) • moxifloxacin (Mfx) • ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• para-aminosalicylic acid (PAS) • cycloserine (Cs) • terizidone (Trd) • ethionamide (Eto) • protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• clofazimine (Cfz) • linezolid (Lzd) • amoxicillin/clavulanate (Amx/Clv) • thioacetazone (Thz) • imipenem/cilastatin (Ipm/Cln) • high-dose isoniazid (high-dose H)[b] • clarithromycin (Clr)

重大变化1：药物重新分组，重新排序

药物分组		药物名称
A.氟喹诺酮类药物		莫西沙星（Mfx）； 左氧氟沙星（Lfx）； 加替沙星（Gfx）
B.二线注射类药物		阿米卡星（Am）； 卡那霉素（Km）； 卷曲霉素（Cm）； 链霉素（S）
C.其他核心二线药物		丙硫异烟胺（Pto）； 环丝氨酸（CS）； 利奈唑胺（LZD）； 氯法齐明（CFZ）
D.追加药物	D1	吡嗪酰胺（Z）； 高剂量异烟肼（H）； 乙胺丁醇（E）
	D2	贝达喹啉（Bdq）；德拉马尼（Dlm）
	D3	对氨基水杨酸、亚胺培南西司他丁、美罗培南、阿莫西林克拉维酸、（氨硫脲）

WHO 2016年更新耐多药结核病治疗药物种类

组别	药物	缩写
A组： 应包含所有3种药物 （除非不能使用）	左氧氟沙星或 莫西沙星	Lfx Mfx
	贝达喹啉[1,4] ↑ 利奈唑胺[2] ↑	Bdq Lzd
B组： 同时添加2种药物 （除非不能使用）	氯法齐明	Cfz
	环丝氨酸或 特立齐酮	Cs Trd
C组： 当A组和B组药物不能使用时添加本组药物组成方案	乙胺丁醇	E
	德拉马尼[3,4]	Dlm
	吡嗪酰胺[5]	Z
	亚胺培南-西司他丁或 美罗培南[5]	Ipm-Cln Mpm
	阿米卡星 （或链霉素）[7] ↓	Am (S)
	乙硫异烟胺 或 丙硫异烟胺	Eto Pto
	对氨基水杨酸	PAS

WHO 2018年推荐耐多药结核病治疗药物种类

重大变化1：药物重新分组，重新排序

组别	药物	缩写
A组： 应包含所有3种药物 （除非不能使用）	左氧氟沙星或	Lfx
	莫西沙星	Mfx
	贝达喹啉[1,4] ↑	Bdq
	利奈唑胺[2] ↑	Lzd
B组： 同时添加2种药物 （除非不能使用）	氯法齐明	Cfz
	环丝氨酸或	Cs
	特立齐酮	Trd
C组： 当A组和B组药物不能使用时添加本组药物组成方案	乙胺丁醇	E
	德拉马尼[3,4]	Dlm
	吡嗪酰胺[5]	Z
	亚胺培南-西司他丁或	Ipm-Cln
	美罗培南[5]	Mpm
	阿米卡星 ↓	Am
	（或链霉素）[7]	(S)
	乙硫异烟胺 或	Eto
	丙硫异烟胺	Pto
	对氨基水杨酸	PAS

WHO 2018年推荐耐多药结核病治疗药物种类

1、口服药物优先于注射剂：弃用卡那霉素和卷曲霉素，降低注射类药物的地位

- 卡那霉素和卷曲霉素在长程MDR-TB方案中的使用增加了治疗失败和复发的风险而不再推荐使用
- 阿米卡星没有显示出类似的关联，然而对其安全性的担忧与其他注射剂药物相同

2、贝达喹啉和利奈唑胺的地位明显提高，强烈推荐，除非不能使用

- 贝达喹啉和利奈唑胺的最佳疗程未定
- 贝达喹啉使用超过6个月的安全性和有效性证据不足
- 利奈唑胺使用至少6个月是非常有效的，尽管毒副作用可能会限制它的使用

基因测序技术逐渐应用于抗结核药物敏感性分析

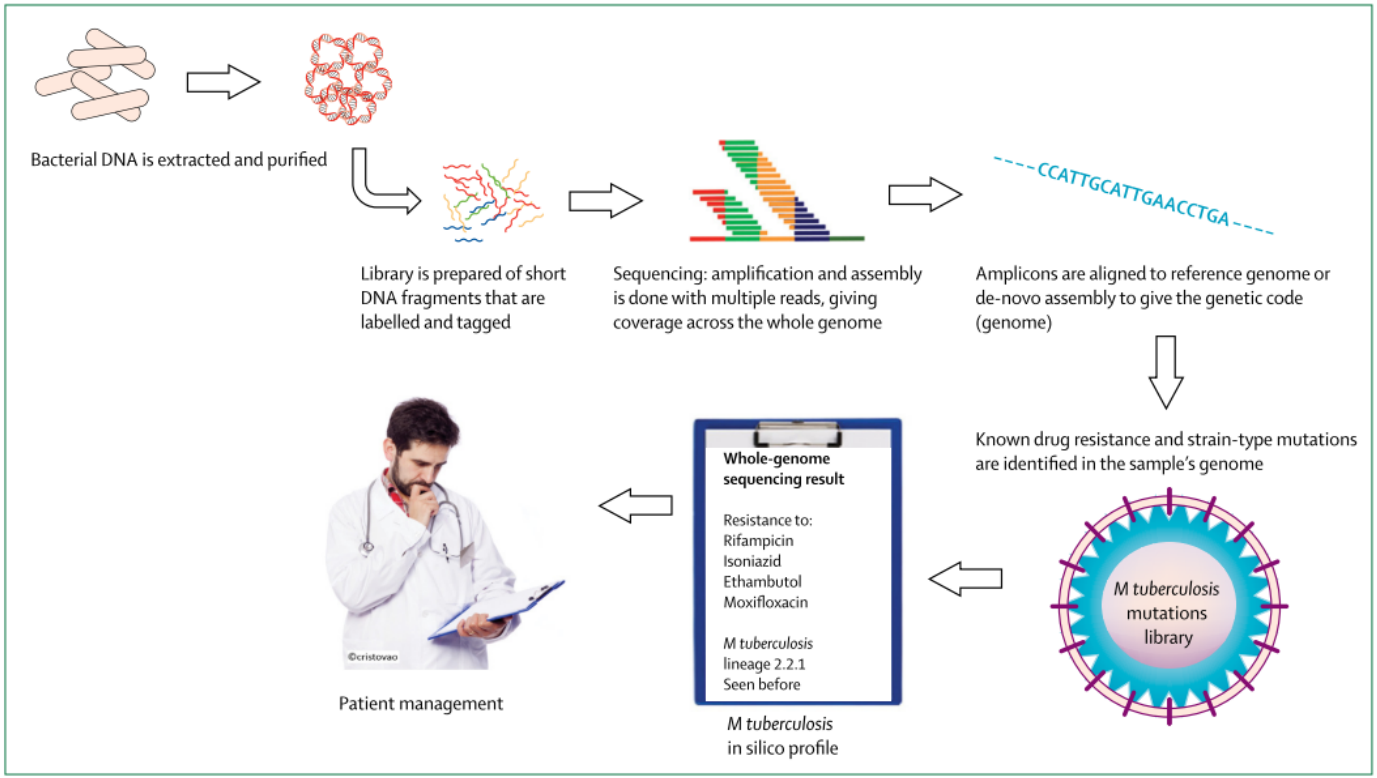


Figure 7: **Process of next-generation sequencing**

Lancet Respir Med 2017; 5: 291–360 http://dx.doi.org/10.1016/ S2213-2600(17)30079-

基因测序技术逐渐应用于抗结核药物敏感性分析

	Phenotypic tests	Xpert MTB/RIF	Line probe assays	Whole-genome sequencing
Time to result	Slow (weeks or months)	Less than 2 h	Rapid (hours or days) when done directly from samples	Rapid (hours or days) if done directly from samples
Sensitivity for detecting resistance	High	High for rifampicin; no other drugs included	Sensitivity limited by the number of loci incorporated in test; high for rifampicin	Dependent on knowledge of polymorphisms; high for rifampicin
Resistance levels	Ability to determine MICs	Does not assess MIC	Does not assess MICs; some tests provide knowledge of mutations that can be used to predict levels of resistance but have poor clinical validity	Does not assess MICs; ability to predict extent of resistance for some drugs from knowledge of mutations, but not yet validated for clinical use
Safety	High risk, requiring sophisticated microbiological protection	Low risk	Moderate microbiological risk when testing clinical samples. High risk if bacterial cultures are used	Moderate risk when testing clinical samples. High risk if bacterial cultures are used
Quality assessment	Quality assurance via WHO and International Union Against Tuberculosis and Lung Disease reference laboratory network	Test-specific quality assurance schemes not widespread	Test-specific quality assurance schemes not widespread	Quality assurance schemes not available
Efficiency	Separate tests for each drug	Detects resistance to one drug only	Two or three drugs per test	Single analysis for all drugs

MIC=minimum inhibitory concentration.

Table 5: **Comparison of test characteristics of whole-genome sequencing with current drug-resistance tests**

Lancet Respir Med 2017; 5: 291–360 http://dx.doi.org/10.1016/

基因测序技术逐渐应用于抗结核药物敏感性分析

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 11, 2018 VOL. 379 NO. 15

Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project

RESULTS

A total of 10,209 isolates were analyzed. The largest proportion of phenotypes was predicted for rifampin (9660 [95.4%] of 10,130) and the smallest was predicted for ethambutol (8794 [89.8%] of 9794). Resistance to isoniazid, rifampin, ethambutol, and pyrazinamide was correctly predicted with 97.1%, 97.5%, 94.6%, and 91.3% sensitivity, respectively, and susceptibility to these drugs was correctly predicted with 99.0%, 98.8%, 93.6%, and 96.8% specificity. Of the 7516 isolates with complete phenotypic drug-susceptibility profiles, 5865 (78.0%) had complete genotypic predictions, among which 5250 profiles (89.5%) were correctly predicted. Among the 4037 phenotypic profiles that were predicted to be pansusceptible, 3952 (97.9%) were correctly predicted.

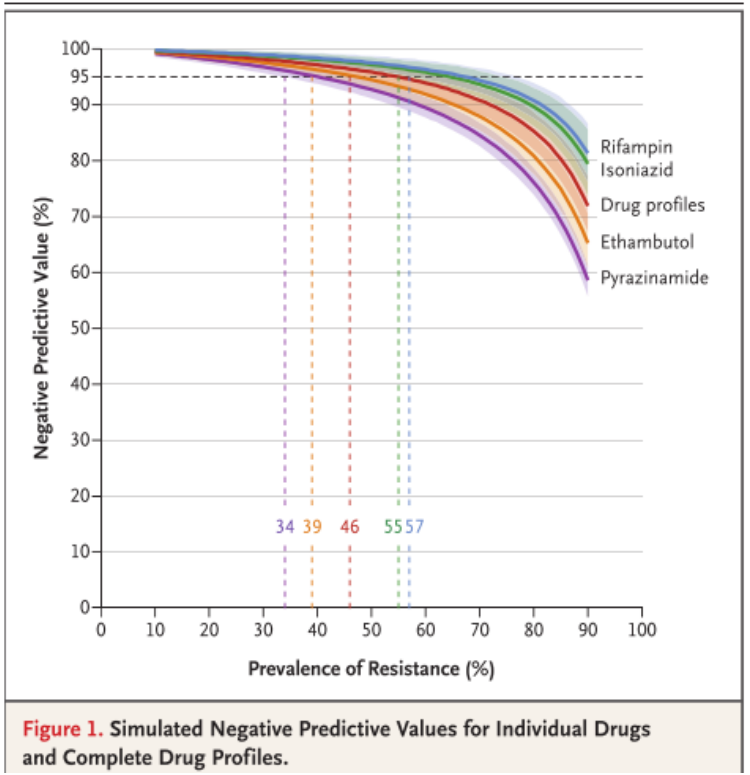


Figure 1. Simulated Negative Predictive Values for Individual Drugs and Complete Drug Profiles.

基因测序技术逐渐应用于抗结核药物敏感性分析

ORIGINAL ARTICLE

Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis

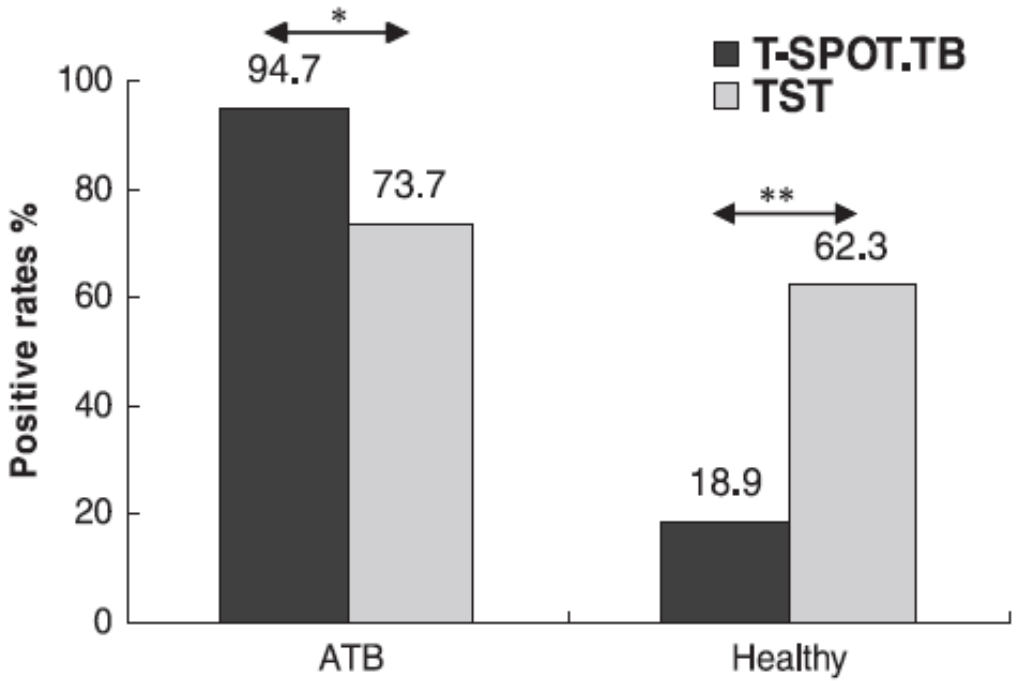
Yingda L. Xie, M.D., Soumitesh Chakravorty, Ph.D., Derek T. Armstrong, M.H.S., Sandra L. Hall, M.P.H., Laura E. Via, Ph.D., Taeksun Song, Ph.D., Xing Yuan, M.D., Xiaoying Mo, Ph.D., Hong Zhu, M.D., Peng Xu, Ph.D., Qian Gao, Ph.D., Myungsun Lee, M.D., et al.

Table 2. Sensitivity and Specificity of the Investigational Assay, with Phenotypic Drug-Susceptibility Testing as the Reference Standard, in the Main Analysis Population for Drug-Susceptibility Testing.

Drug	Investigational-Assay Result + Phenotypic Drug-Susceptibility Test Result*				Sensitivity		Specificity	
	R+R	R+S	S+R	S+S				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid†	150	1	30	122	150/180	83.3 (77.1–88.5)	122/123	99.2 (95.6–100.0)
Ofloxacin‡	84	7	11	201	84/95	88.4 (80.2–94.1)	201/208	96.6 (93.2–98.6)
Moxifloxacin, 0.5 μg/ml‡§	78	12	11	200	78/89	87.6 (79.0–93.7)	200/212	94.3 (90.3–97.0)
Moxifloxacin, 2.0 μg/ml‡	51	40	2	210	51/53	96.2 (87.0–99.5)	210/250	84.0 (78.9–88.3)
Kanamycin¶	35	4	14	245	35/49	71.4 (56.7–83.4)	245/249	98.4 (96.0–99.6)
Amikacin¶	29	1	12	256	29/41	70.7 (54.5–83.9)	256/257	99.6 (97.9–100.0)

N Engl J Med 2017;377:1043-54. DOI: 10.1056/NI

IGRA (TB-SPOT) to diagnose LTBI in China



LTBI prevalence: 18%-20%

Zhang S, et al. **Zhang W.** CLINICAL AND VACCINE IMMUNOLOGY, Dec. 2010, p. 1985–1990

Latent tuberculosis infection in rural China: baseline results of a po

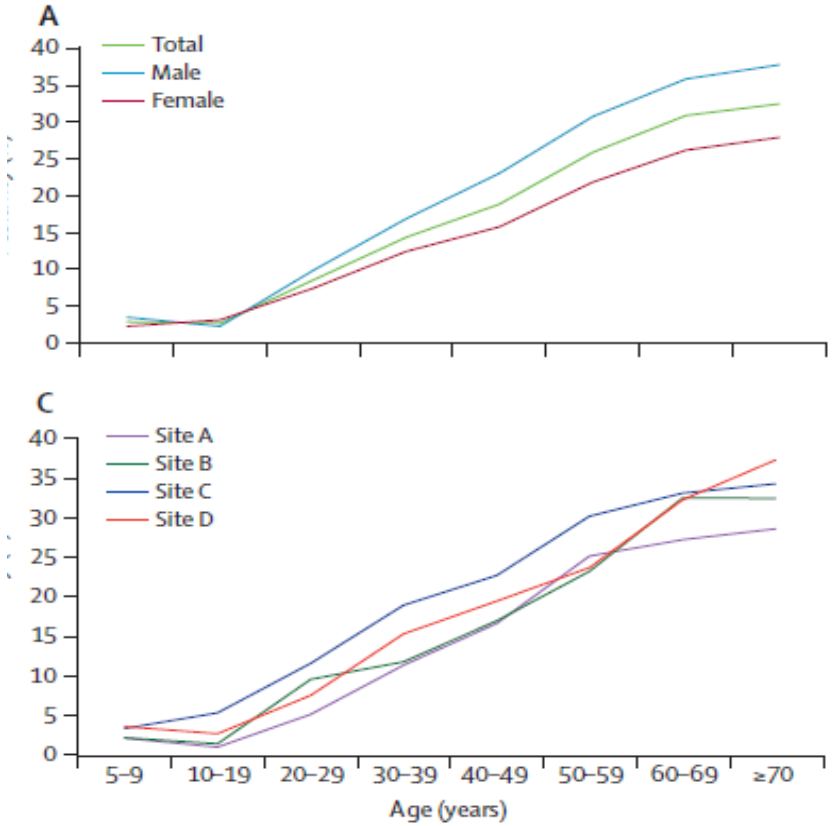
Latent tuberculosis infection in rural China: baseline results of a population-based, multicentre, prospective cohort study

Lei Gao*, Wei Lu
Yinyin Xia, Mufe

30 M LTBI

1.5M-3.0M New cases / whole life

300K-600K/y, 50y



Funding The National Science and Technology Maj
Innovative Research Team in University of China.

GAOL， *et al. Lancet Infect Dis* 2015;15: 310–19

Anti-TNFα：LTBI is a real story

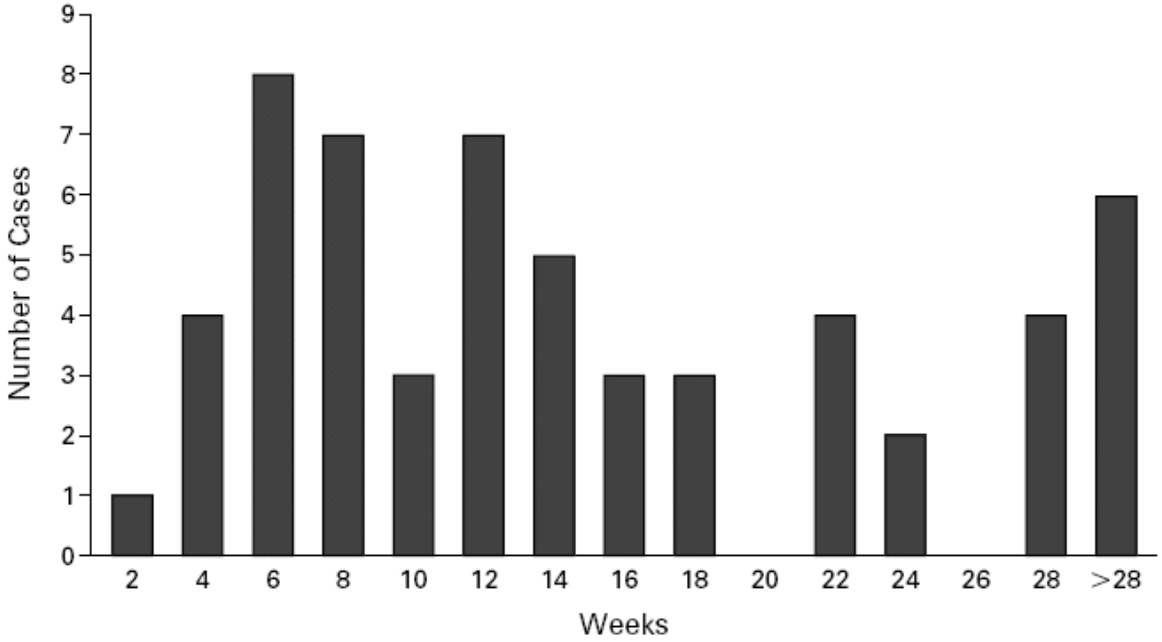


Figure 1. Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.
Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

N Engl J Med, Vol. 345, No. 15 ·October 11, 2001

Stratety of Preventive treatment

The Journal of Rheumatology

The Journal of Rheumatology Volume 42, no. 12

The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor- α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

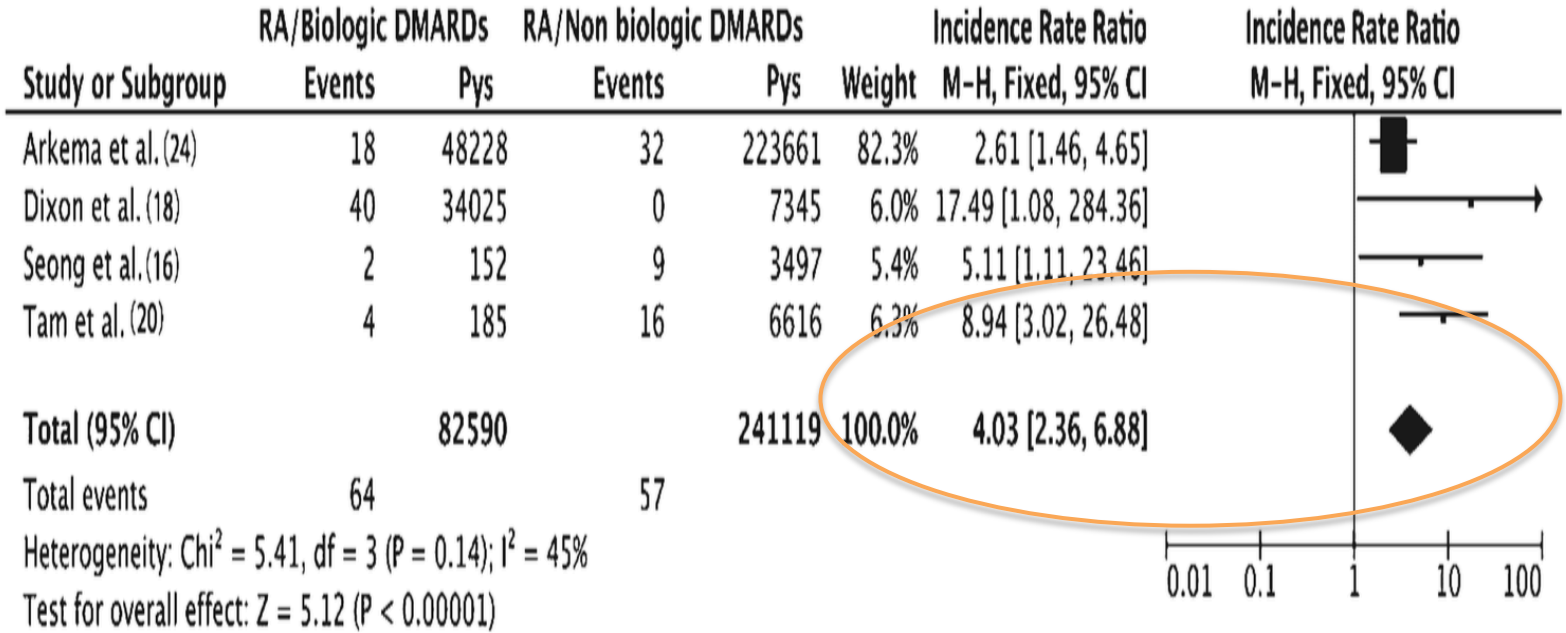
Jing-Wen Ai, Shu Zhang, Qiao-Ling Ruan, Yi-Qi Yu, Bing-Yan Zhang, Qi-Hui Liu and Wen-Hong Zhang

J Rheumatol. 2015 Dec;42(12):2229-37. doi: 10.3899/jrheum.150057. Epub 2015 Oct 15.

The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies.

Ai JW[1], Zhang S[1], Ruan QL[1], Yu YQ[1], Zhang BY[1], Liu QH[1], Zhang WH[2].

Author information



Study or Subgroup	RA/Biologic DMARDs Events	Pys	RA/Non biologic DMARDs Events	Pys	Weight	Incidence Rate Ratio M-H, Fixed, 95% CI
Arkema et al. (24)	18	48228	32	223661	82.3%	2.61 [1.46, 4.65]
Dixon et al. (18)	40	34025	0	7345	6.0%	17.49 [1.08, 284.36]
Seong et al. (16)	2	152	9	3497	5.4%	5.11 [1.11, 23.46]
Tam et al. (20)	4	185	16	6616	6.3%	8.94 [3.02, 26.48]
Total (95% CI)		**82590**		**241119**	**100.0%**	**4.03 [2.36, 6.88]**
Total events	64		57			

Heterogeneity: $Chi^2 = 5.41$, $df = 3$ ($P = 0.14$); $I^2 = 45\%$

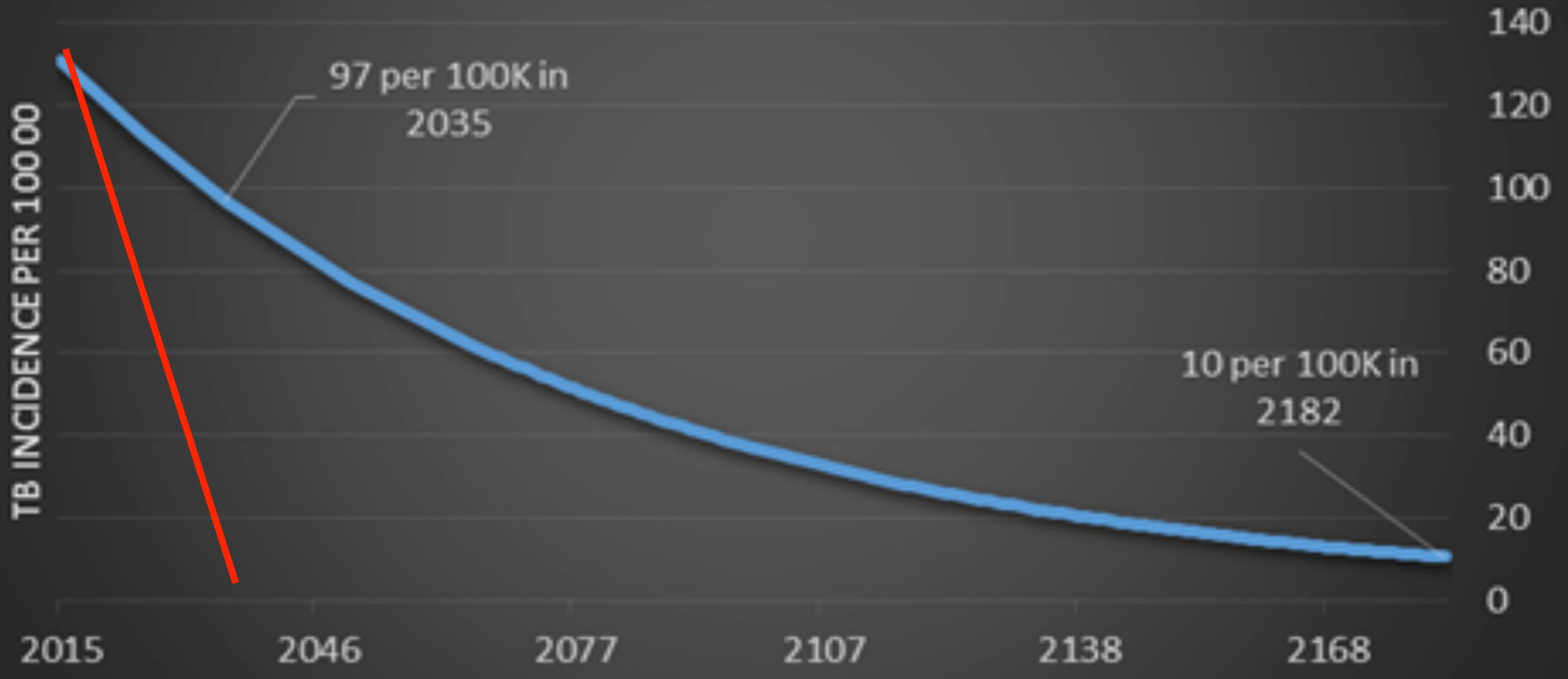
Test for overall effect: $Z = 5.12$ ($P < 0.00001$)

End of TB：a strategy or a slogan?

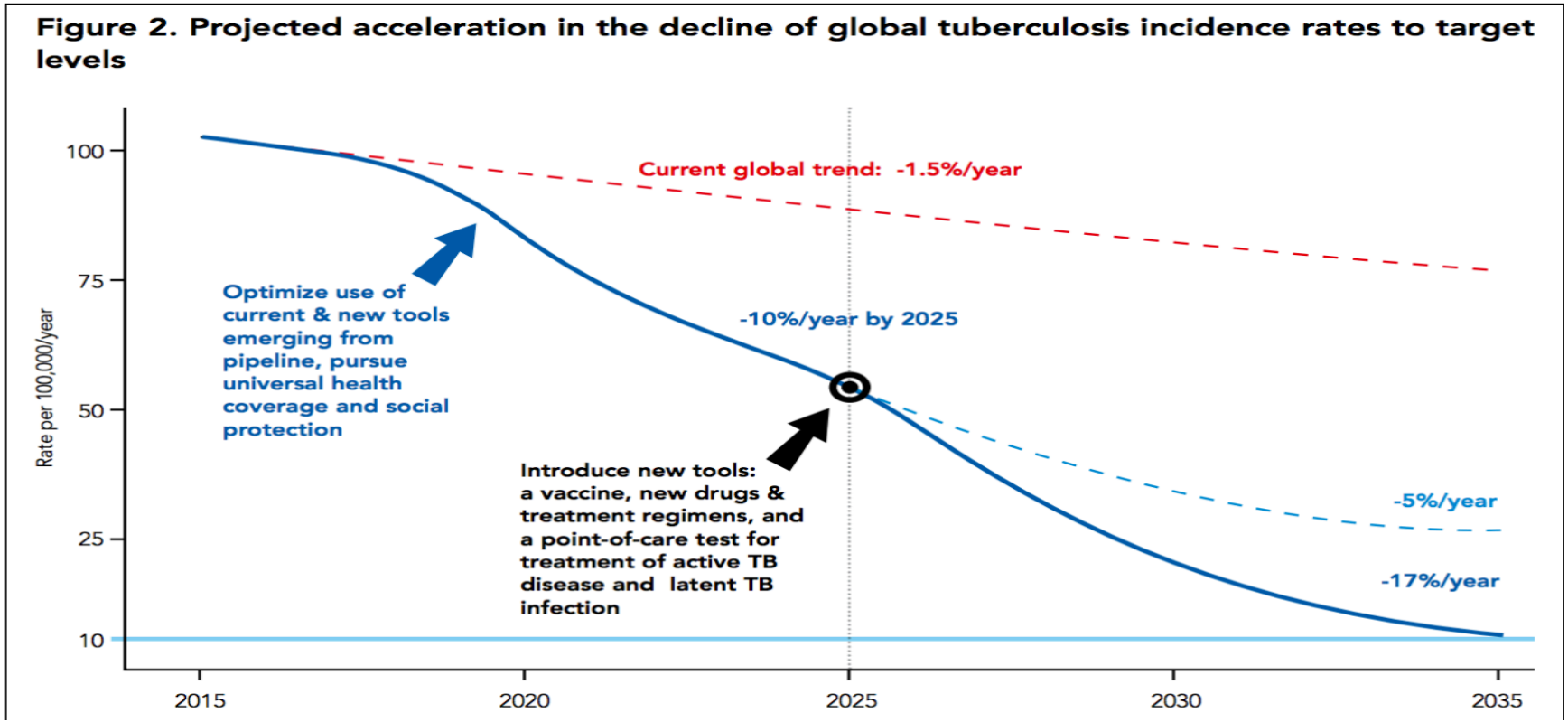
1.3 The *End TB Strategy* at a glance (2016–2035)

VISION	**A WORLD FREE OF TB** — zero deaths, disease and suffering due to TB			
GOAL	**END THE GLOBAL TB EPIDEMIC**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	2025	SDG 2030[a]	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0	0	0	0

Current efforts will not end TB by 2035 but by 2182

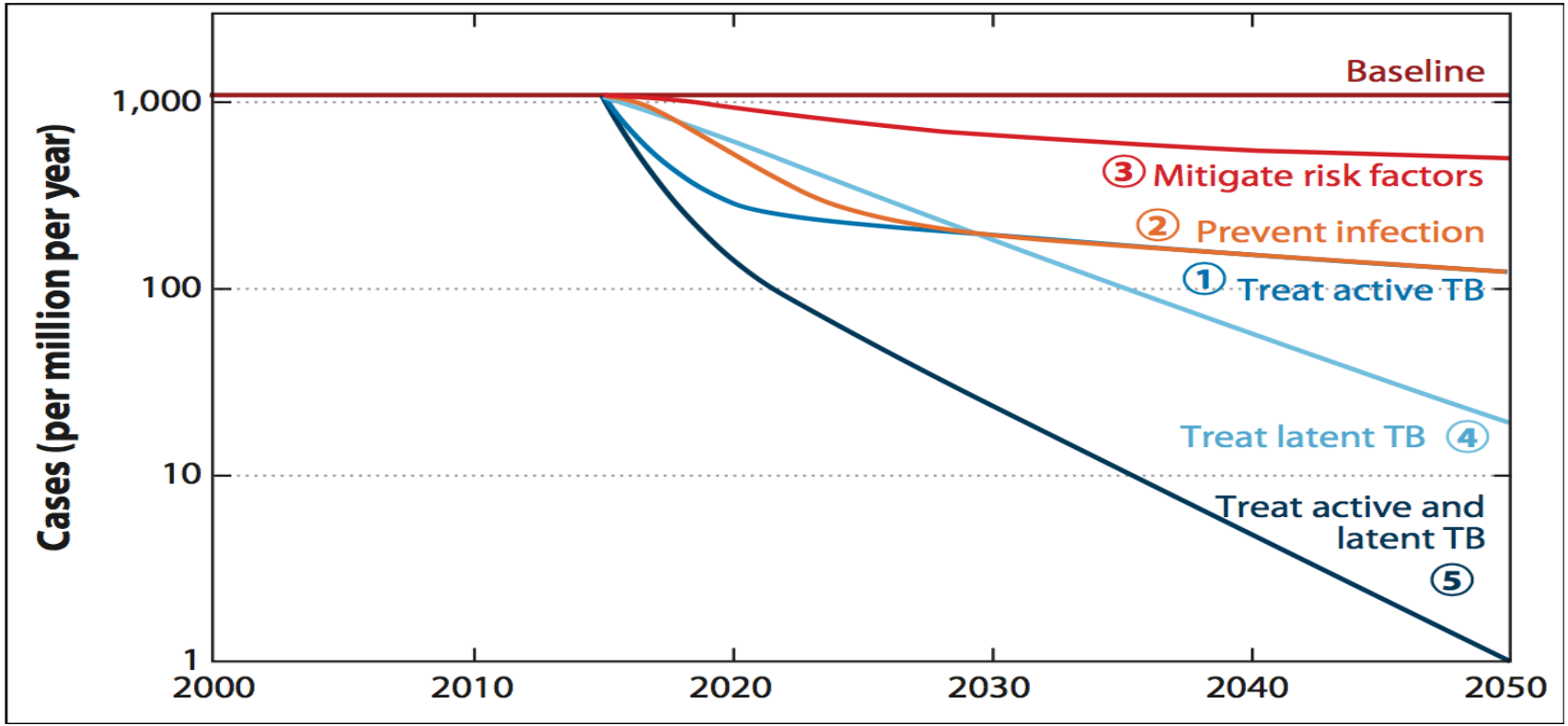


Goal of WHO END-TB strategy



Global strategy and targets for tuberculosis prevention, care and control after 2015。 WHO 2017

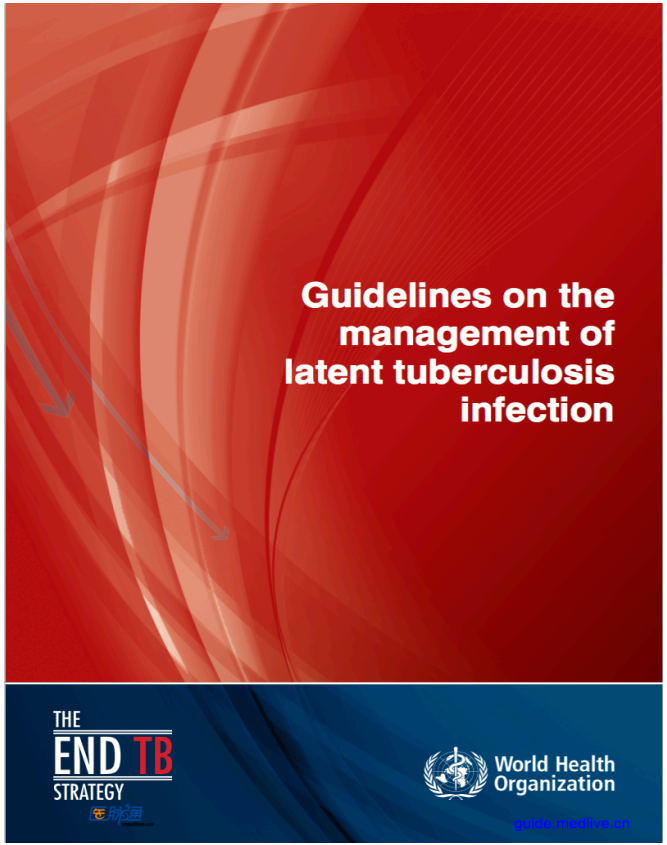
Elimination Strategy



Dye C, et al. Annu Rev Public Health 2013;34: 271-86.

High risk for active tuberculosis from LTBI

- WHO 2015年首次推出潜伏性结核的指南
- 根据国家收入，结核病发病率等指标将各个危险因素及相关的筛查治疗手段



OPEN

Emerging Microbes and Infections (2016) 5, e10; doi:10.1038/emi.2016.10

www.nature.com/emi

REVIEW

Updates on the risk factors for latent tuberculosis reactivation and their managements

Jing-Wen Ai, Qiao-Ling Ruan, Qi-Hui Liu and Wen-Hong Zhang

WHO recommendations

Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5 mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults= 10 mg/kg Children = 10 mg/kg	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin= 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Adults and Children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg	Isoniazid = 900 mg Rifapentine = 900 mg

Latent TB Infection Prevention in Silicosis Patients

Cross-sectional study has been performed among 1 227 silicosis patients in Wenling, Zhejiang, China

Active TB prevalence was 7 300/100 000 among silicosis patients （high TB risk population）

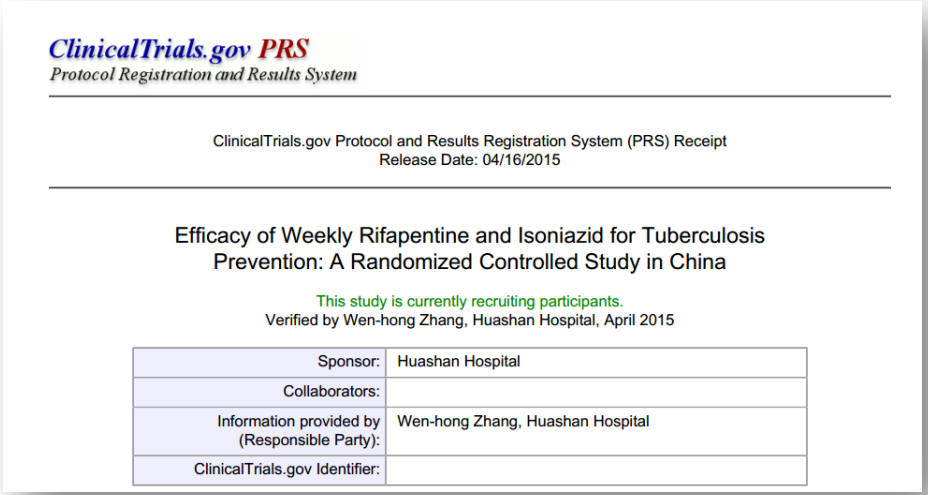
- **RCT for Prevention Study ： Regimen：**

  3RPT/INH by DOT

Rifapentine: 15mg/kg， up to 900mg

Isoniazide: 15mg/kg， up to 900mg

ClinicalTrials.gov Identifier:NCT02430259



ClinicalTrials.gov PRS
Protocol Registration and Results System

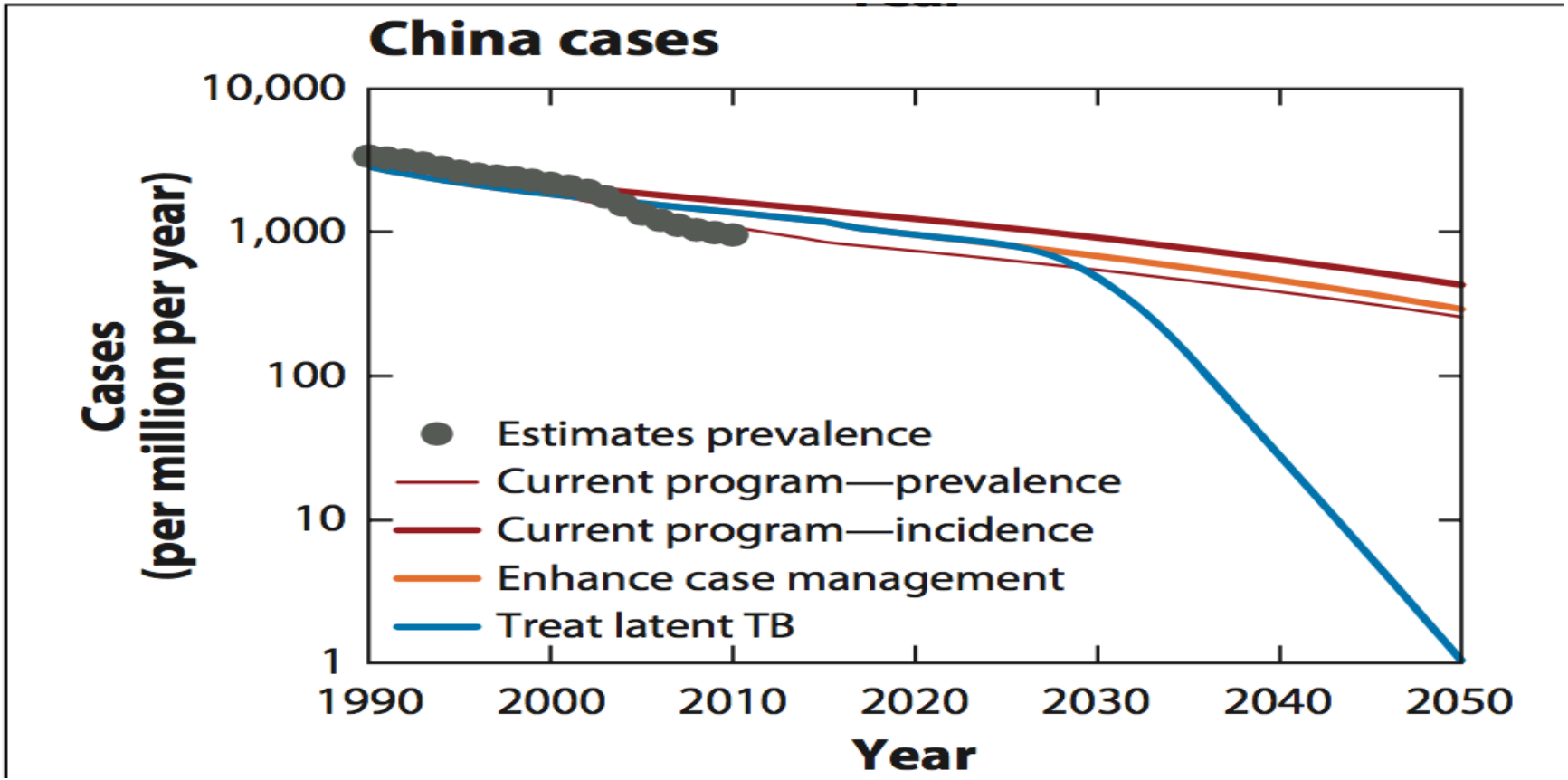
ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 04/16/2015

Efficacy of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention: A Randomized Controlled Study in China

This study is currently recruiting participants.
Verified by Wen-hong Zhang, Huashan Hospital, April 2015

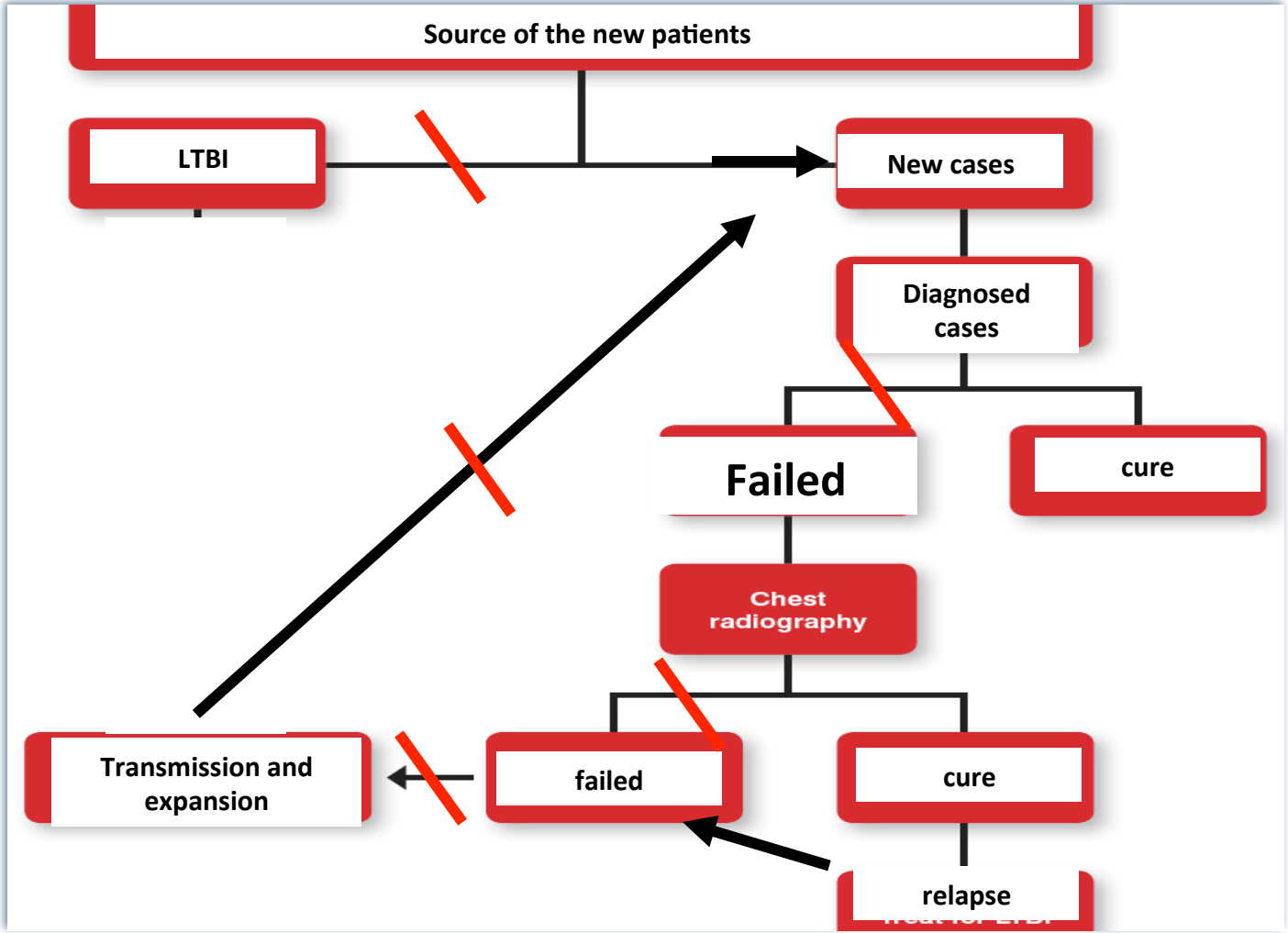
Sponsor:	Huashan Hospital
Collaborators:	
Information provided by (Responsible Party):	Wen-hong Zhang, Huashan Hospital
ClinicalTrials.gov Identifier:	

Elimination Strategy in China: time points



Dye C, et al. Annu Rev Public Health 2013;34: 271-86.

Strategy to end TB



WE WILL END TB