

Global Approaches Combating MDR-TB



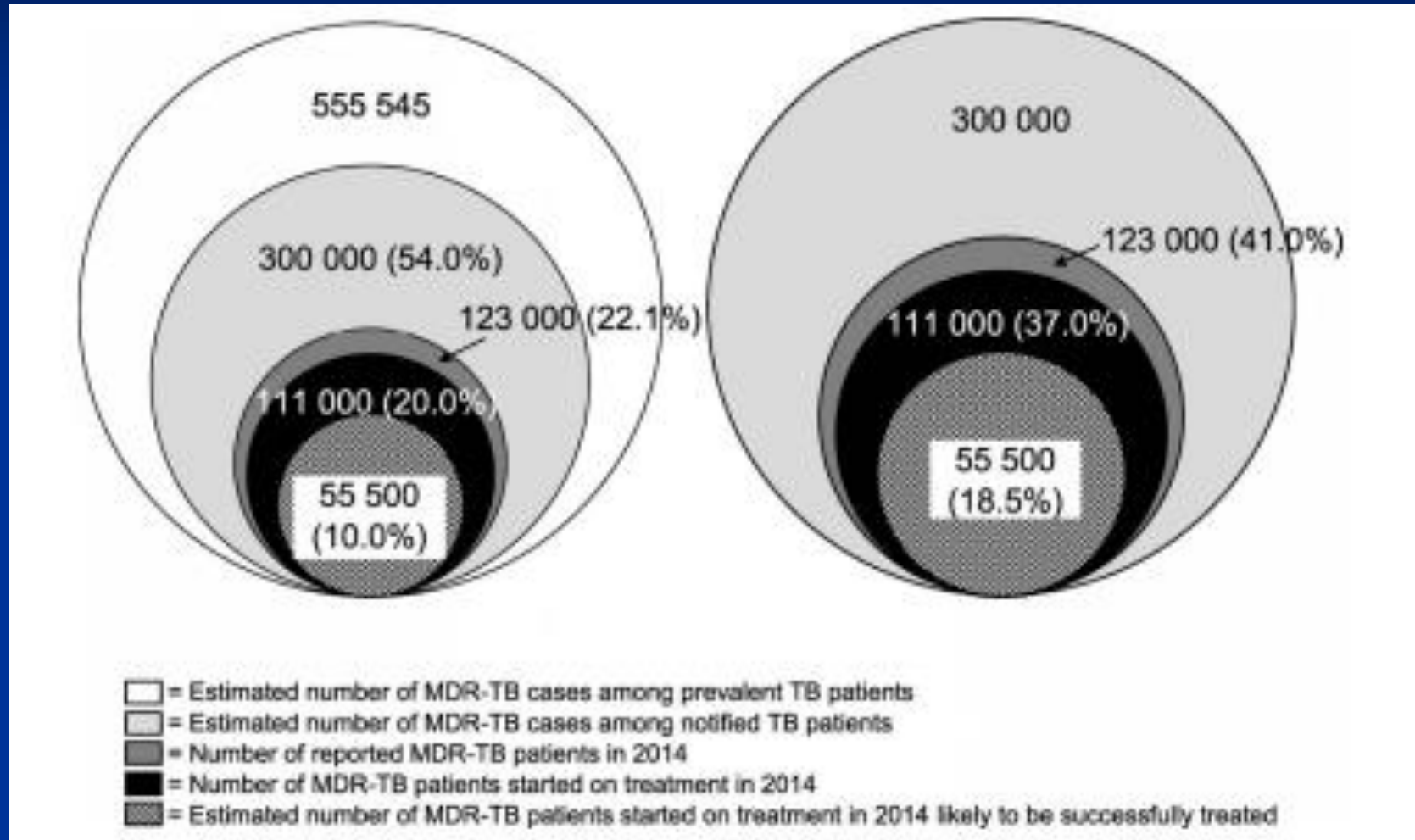
Jing Bao, MD, PhD

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6th Conference of International Union
Against Tuberculosis and Lung Disease, Asia Pacific Region

March 22-25, Tokyo, Japan

Estimated number of cases of MDR-TB occurring, reported, treated, and successfully treated among global total notified and prevalent TB cases in 2014

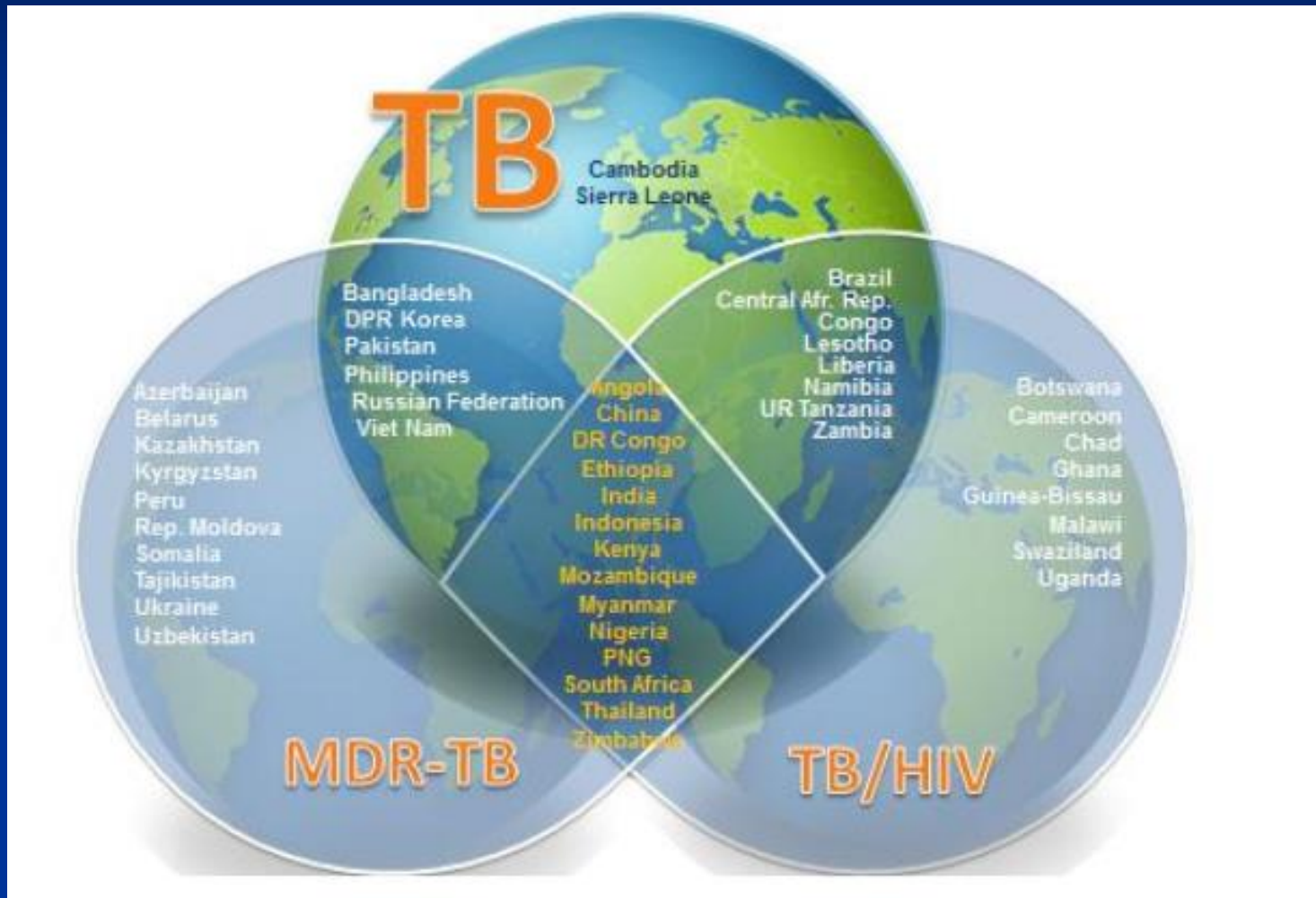


Estimating the global burden of multidrug-resistant tuberculosis among prevalent cases of tuberculosis, S. Nourzad,* H. E. Jenkins,†‡ M. Milstein,§¶ C. D. Mitnick†§#

MDR-TB Epidemiology

- **MDR-TB** is a form of **TB** that is resistant to treatment with at least two of the most powerful first-line anti-**TB** medications (drugs), isoniazid and rifampin.
- According to WHO's Global TB Report, there are **580,000** MDR-TB new cases in the world and **250,00** death due to MDR-TB in 2015.

The three HBC lists of 30 countries each that will be used by WHO 2016 - 2020

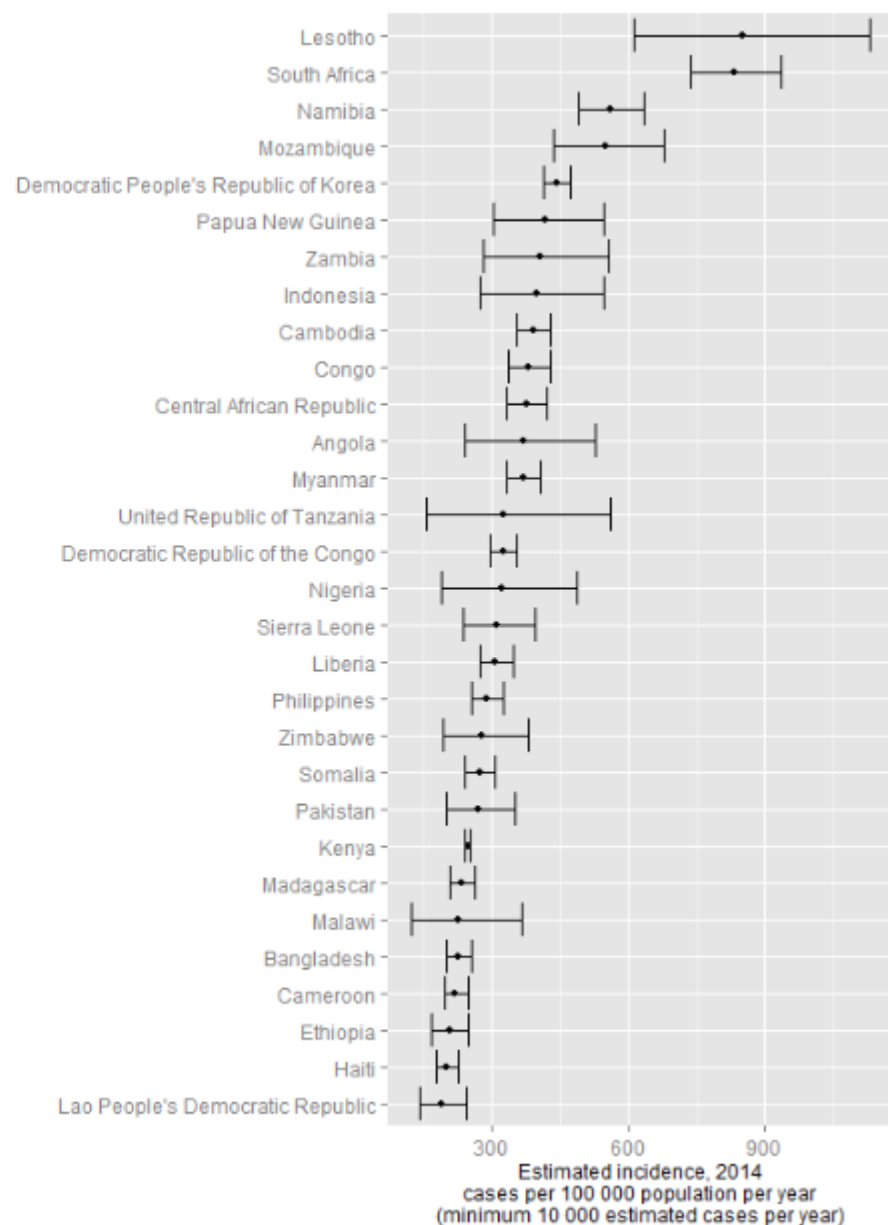
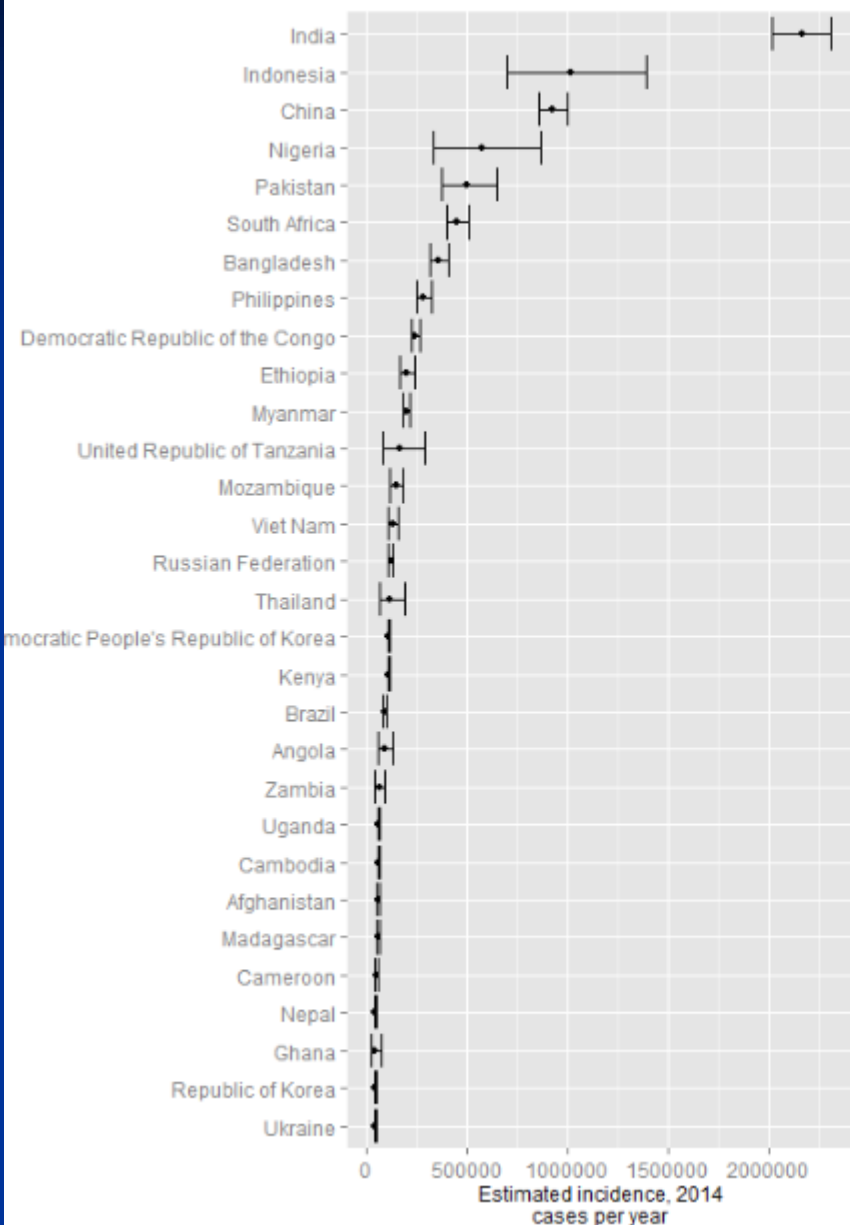


MDR-TB

Top 20, MDR-TB number	% global total	Top 20, MDR-TB rate per capita	% global total
India	23.7	Sao Tomé & Príncipe	0.1
China	17.3	Rep. Moldova	0.5
Russian Fed.	13.0	Swaziland	0.1
Ukraine	4.3	Kyrgyzstan	0.7
Pakistan	4.0	Ukraine	4.3
Philippines	3.7	Kazakhstan	1.6
Myanmar	3.0	Russian Fed.	13.0
Uzbekistan	2.3	Namibia	0.2
Indonesia	2.3	Uzbekistan	2.3
South Africa	2.1	Kiribati	0.0
Viet Nam	1.7	Belarus	0.6
Kazakhstan	1.6	Myanmar	3.0
Bangladesh	1.6	Lesotho	0.1
DPR Korea	1.3	Georgia	0.2
Nigeria	1.1	DPR Korea	1.3
DR Congo	0.9	Azerbaijan	0.4
Kenya	0.8	Gabon	0.1
Thailand	0.7	PNG	0.3
Mozambique	0.7	South Africa	2.1
Peru	0.7	Philippines	3.7
	87		35***
	76		23

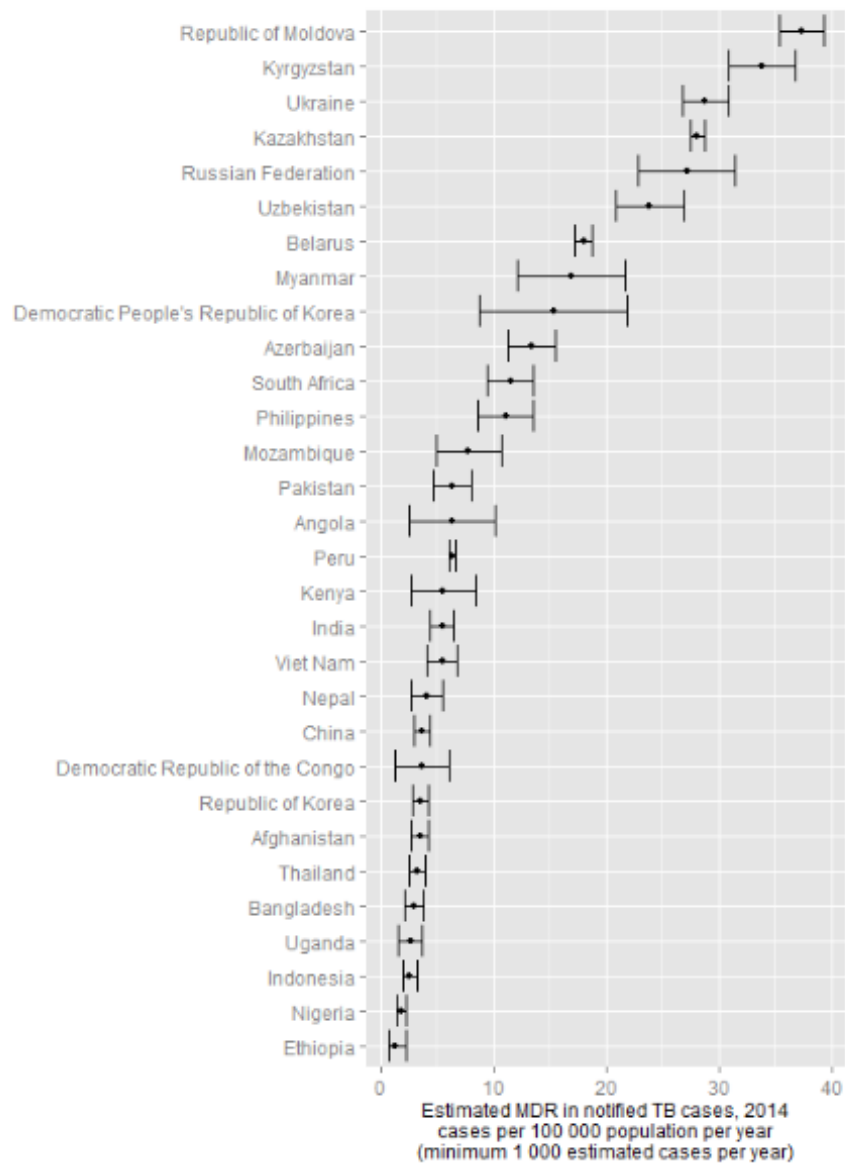
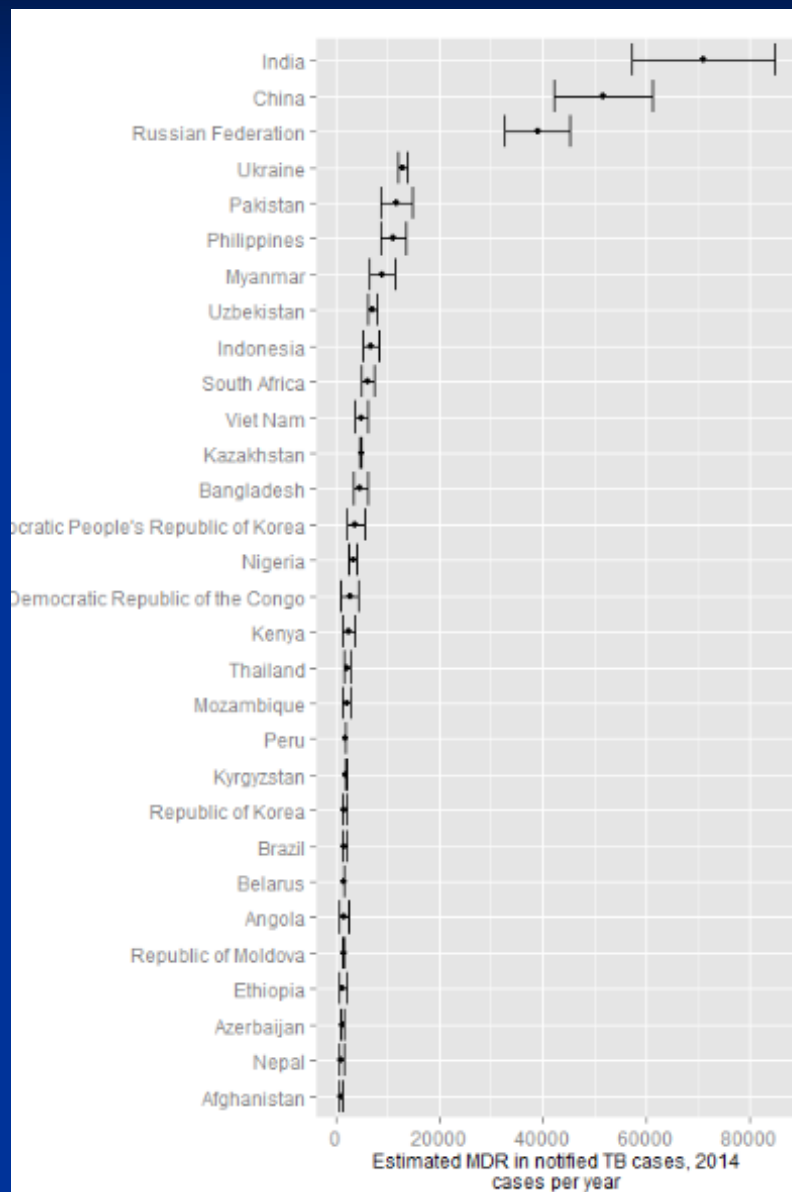
Use of high burden country lists for TB by WHO in the post 2015 era

Top 30 countries: absolute TB numbers and rates

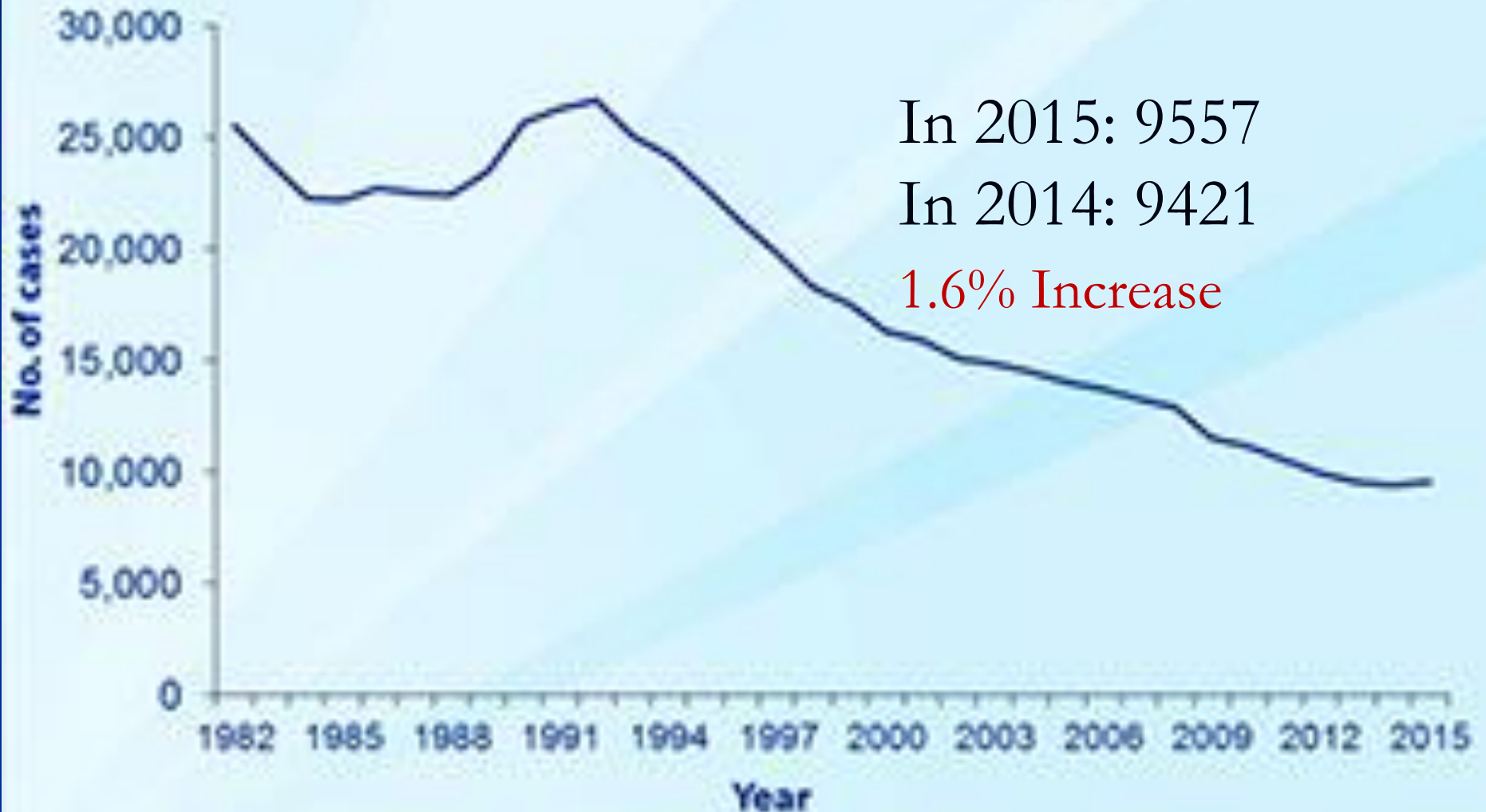


Top 30 countries in terms of absolute numbers and rates

MDR-TB



Reported Tuberculosis (TB) Cases United States, 1982–2015*



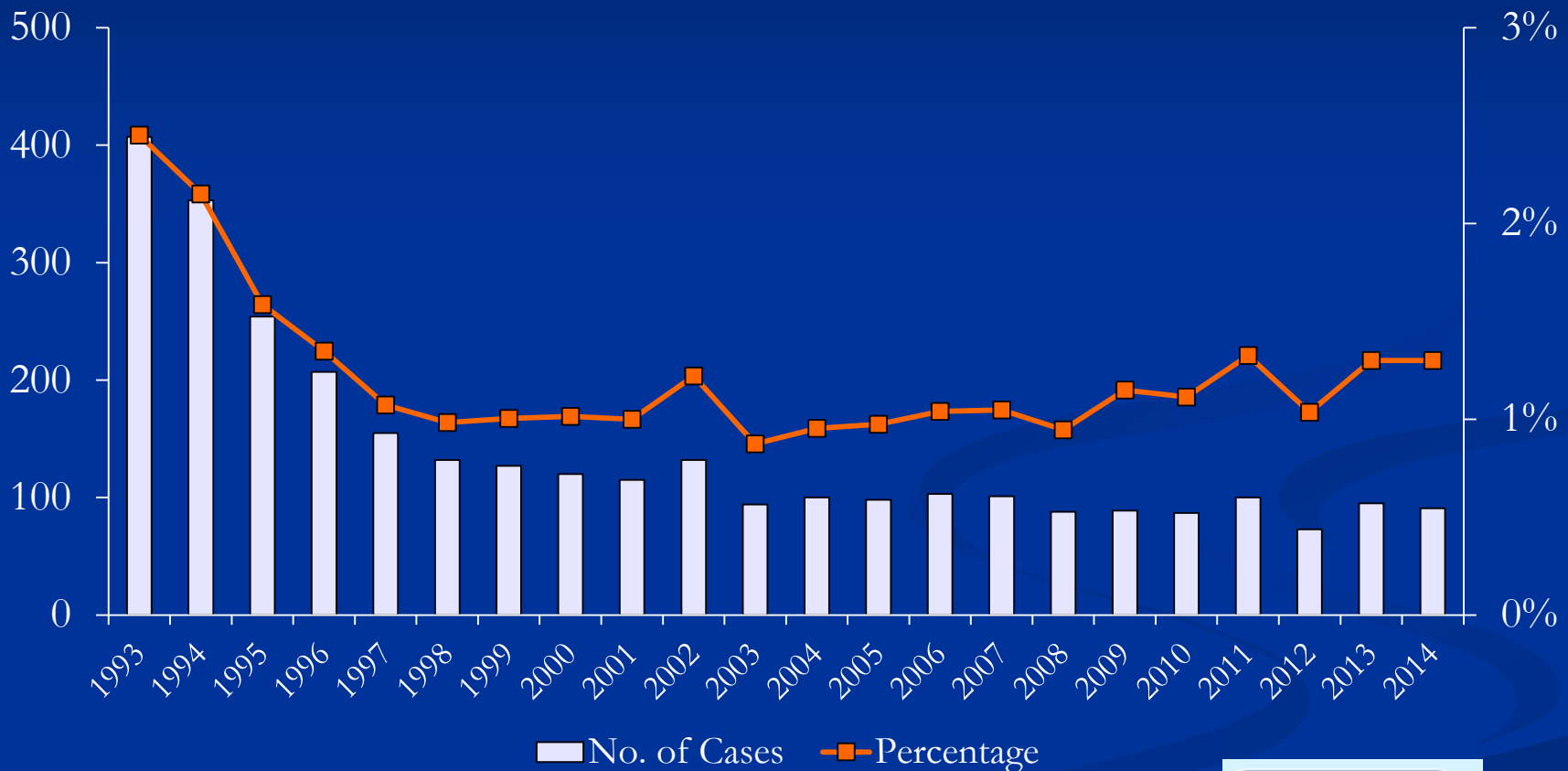
In 2015: 9557

In 2014: 9421

1.6% Increase

*As of June 9, 2016.

Primary MDR TB, United States, 1993 – 2014*

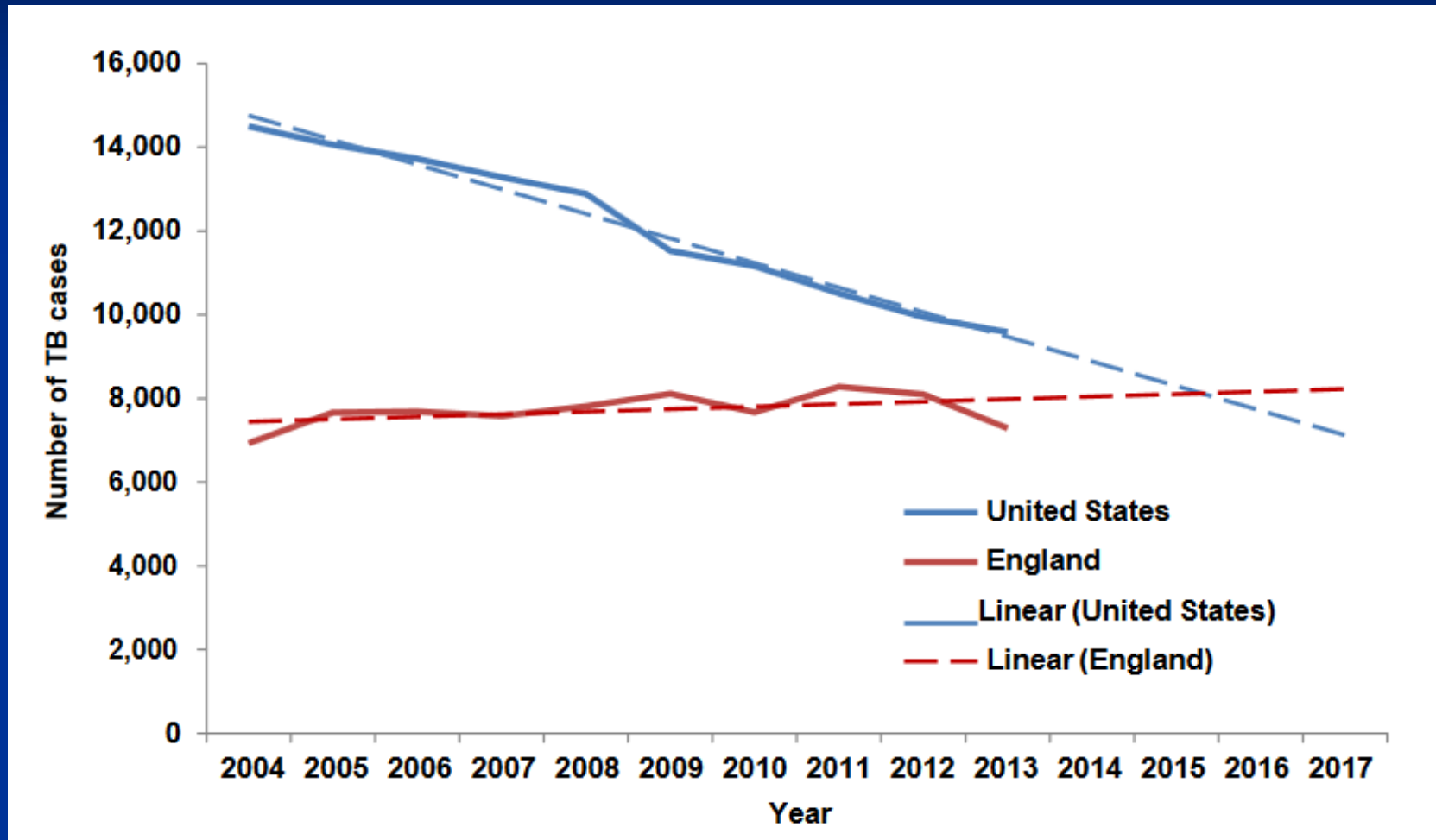


*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.



Numbers of TB cases in England versus the US (Collaborative TB Strategy for England 2015-2020)



The Cost Burden of Drug-Resistant TB in the U.S.

- While MDR and XDR TB are relatively rare in the US, their treatment comes at a terrible price
 - expensive
 - takes a long time,
 - disrupts life,
 - and has potentially life threatening side effects.

THE COSTLY BURDEN OF DRUG-RESISTANT TB IN THE U.S.

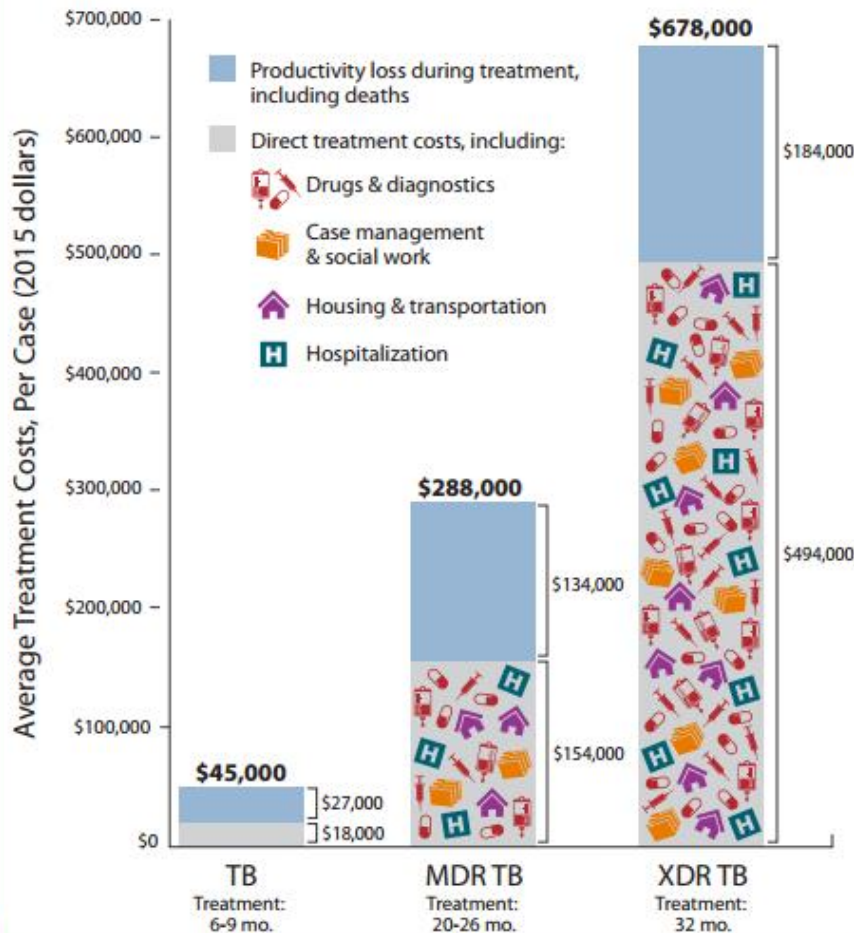
Multidrug-resistant (MDR) tuberculosis is a major health threat globally. Nearly half a million MDR TB¹ cases are estimated to occur worldwide annually, including cases that are extensively drug-resistant (XDR).²

While MDR and XDR TB are relatively rare in the U.S., their treatment comes at a terrible price – it is very expensive, takes a long time to treat, disrupts lives, and has potentially life-threatening side effects.

The Cost Burden of MDR-TB in the U.S.

The Outsized Financial Toll of MDR and XDR TB

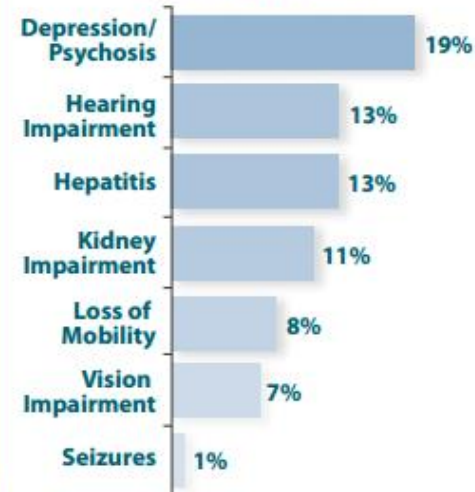
Cost increases with greater resistance:



A Major Human Cost Of those treated for drug-resistant TB:



Severe Treatment Side Effects



Preventing and Controlling MDR and XDR TB in the U.S.

Requires:

Preventing and Controlling MDR and XDR TB in the U.S. Requires:

**BETTER
TREATMENT
OPTIONS**

**RAPID
DIAGNOSIS**

**EXPERT
TREATMENT
OF EVERY
TB CASE**

**IMPROVING
GLOBAL TB
DIAGNOSIS AND
TREATMENT**

Footnotes

¹ Multidrug-resistant TB is resistant to at least two of the best and most important anti-TB drugs (isoniazid and rifampin).

² Extensively drug-resistant TB is resistant to isoniazid and rifampin among first-line drugs, resistant to any fluoroquinolone and at least one second-line injectable drug.

Source: Marks S et al. Treatment Practices, Outcomes, and Costs of Multidrug-resistant and Extensively Drug-resistant Tuberculosis in the United States. *Emerg Infect Dis.* 2014;20(5); additional estimates for TB and XDR TB productivity losses due to premature deaths. Updated to 2015 dollars.



Centers for Disease
Control and Prevention
National Center for HIV/AIDS,
Viral Hepatitis, STD, and
TB Prevention

October 2016

<http://www.cdc.gov/nchhstp/newsroom>

WHO The End TB Strategy at a glance

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*	END TB 2035
Percentage reduction in the absolute number of TB deaths <i>(compared with 2015 baseline)</i>	35%	75%	90%	95%
Percentage reduction in the TB incidence rate <i>(compared with 2015 baseline)</i>	20%	50%	80%	90% (approximately 10 per 100 000 population)
Percentage of TB-affected households experiencing catastrophic costs due to TB <i>(level in 2015 unknown)</i>	0%	0%	0%	0%

United States Government Global TB Strategy 2015-2019

VISION



The U.S. Government and the global community share a vision of a world free from tuberculosis (TB), as set forth in the World Health Assembly's Post-2015 Global TB Strategy.¹

To achieve this vision and end all deaths due to TB, the U.S. Government will work with its partners around the world to **reach** every person with TB, **cure** those in need of treatment, and **prevent** the spread of disease and new infections.

NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS: Six-Month Progress Report and Future Direction



National Institutes
of Health

The U.S. NAP

- On December 22, 2015, the White House National Security Council officially released a plan to address MDR-TB) domestically and internationally and to advance research on this critical public health issue through a National Action Plan for Combating MDR-TB
- The release was followed by a launch event on January 7, 2016, which was open to the general public.
- The NAP, which will build on the WHO END TB Strategy and the U.S. Government's (USG) domestic and global TB strategies, will contribute to the success of these existing strategies.

Three Goals of USG NAP

1

Strengthen
domestic
capacity

2

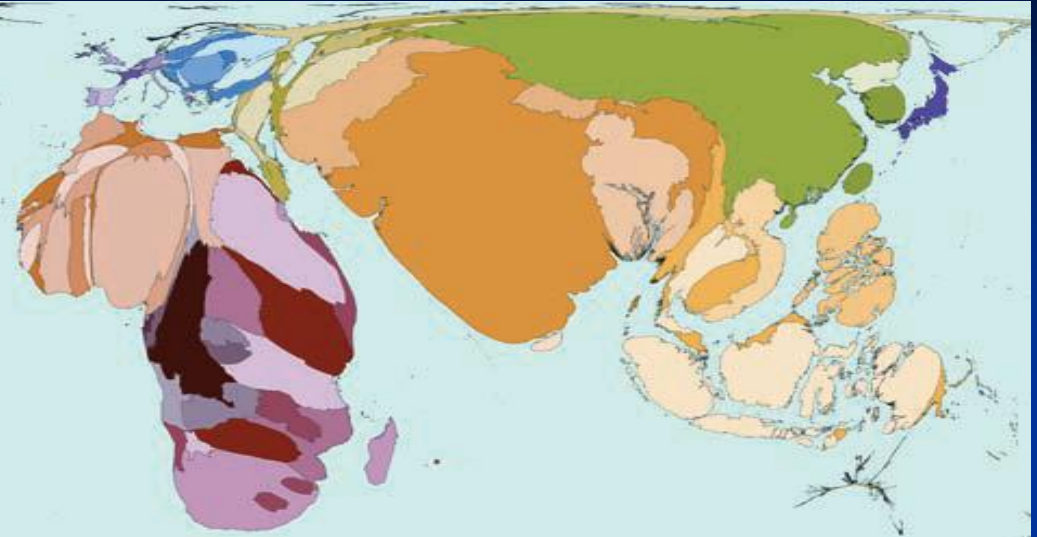
Improve
international
capacity

3

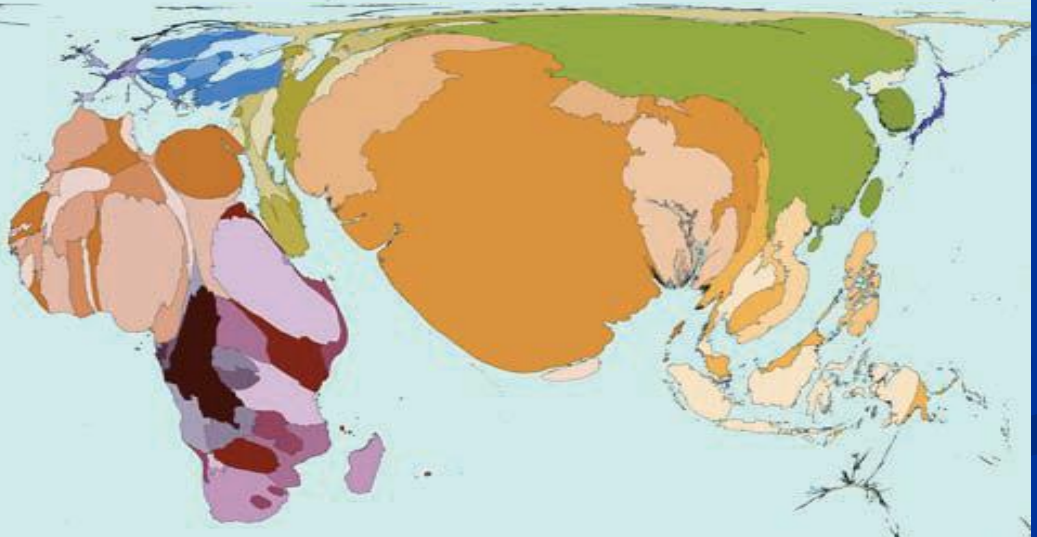
Accelerate
basic and
applied
research and
development

TB is Disease of Poverty

The world map of
poverty



The world map of
tuberculosis



Geographical Distribution of TB in China

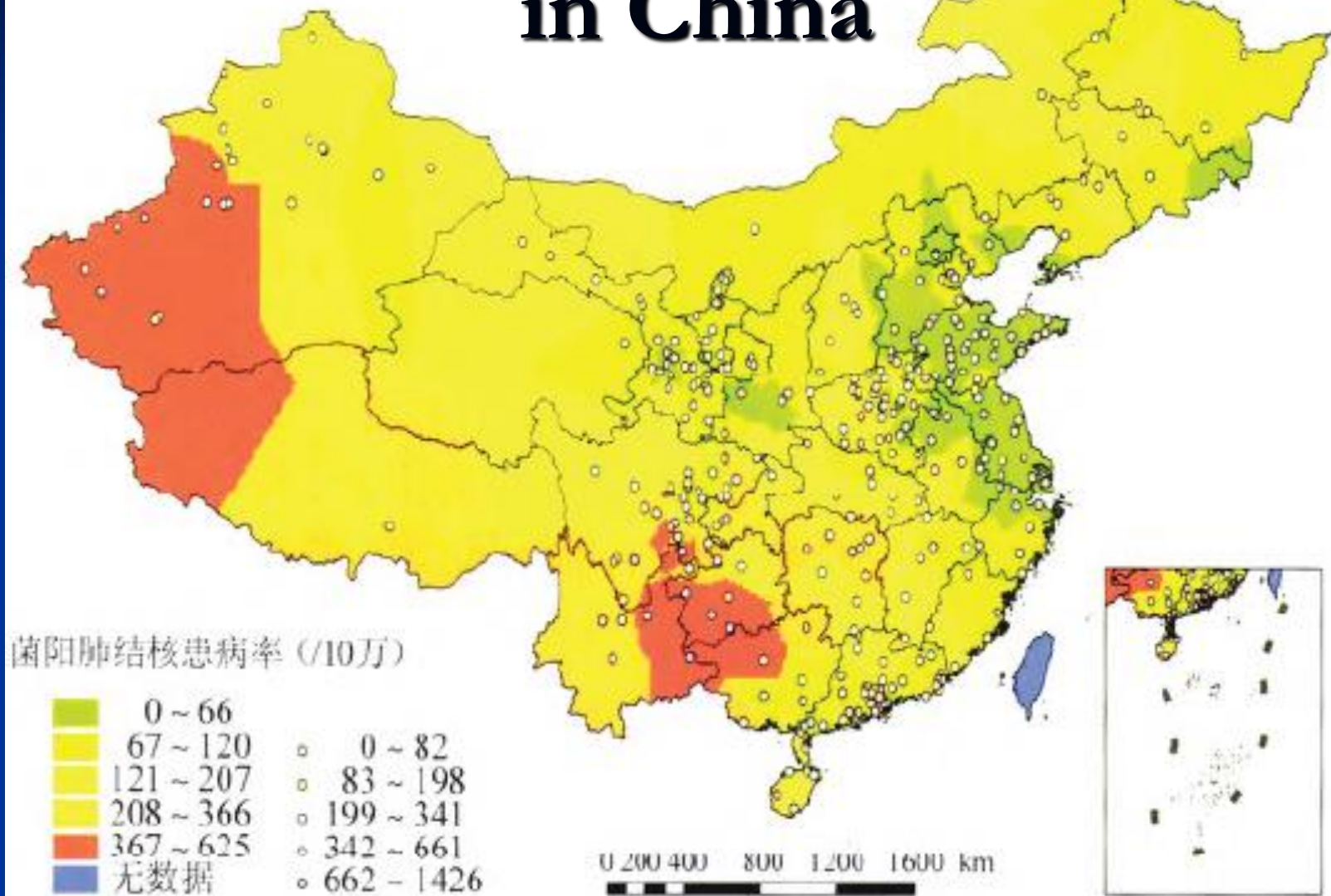


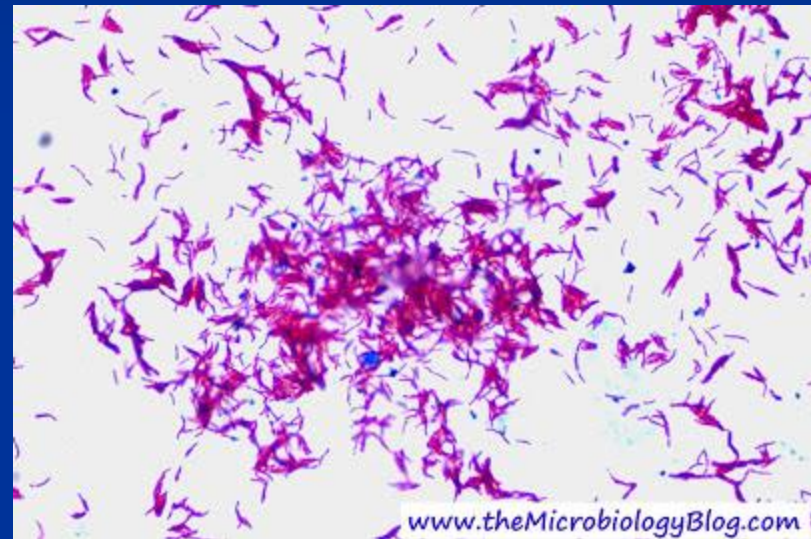
图4 我国菌阳肺结核患病率的地理分布

LX Wang, et al., Chin J Epid, Oct., 2013

A Beautiful Dancer in Shanghai



Multi-Drug Resistant Tuberculosis

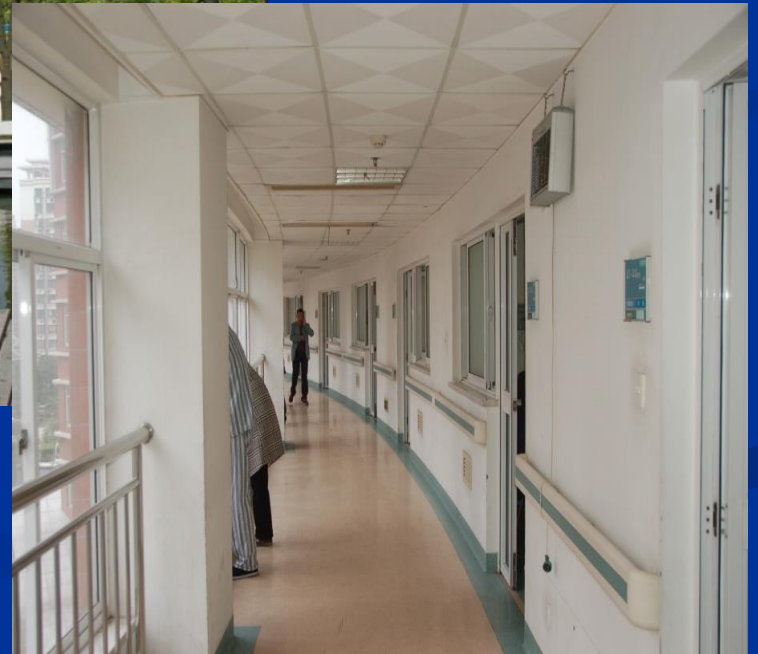
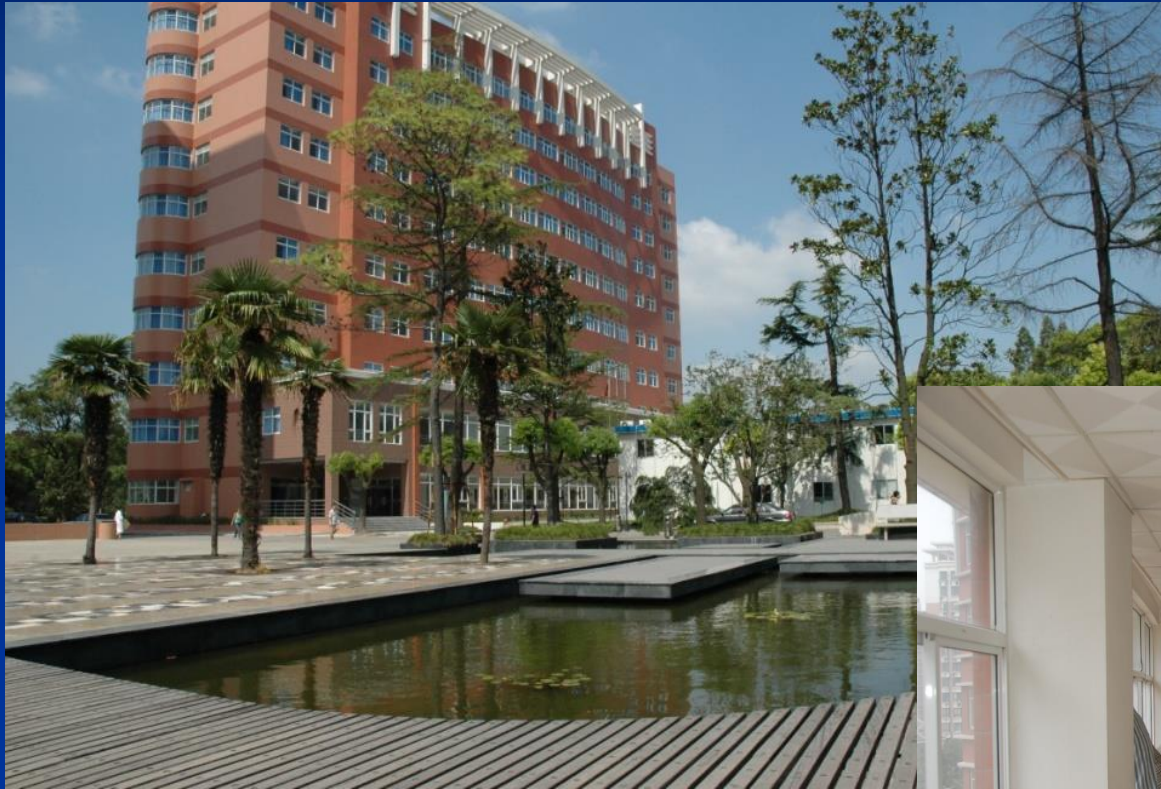


Shanghai 'most popular city' for migrants



http://www.chinadaily.com.cn/china/2014-05/19/content_17516078.htm

Shanghai Chest Hospital



He Should Not Have Died

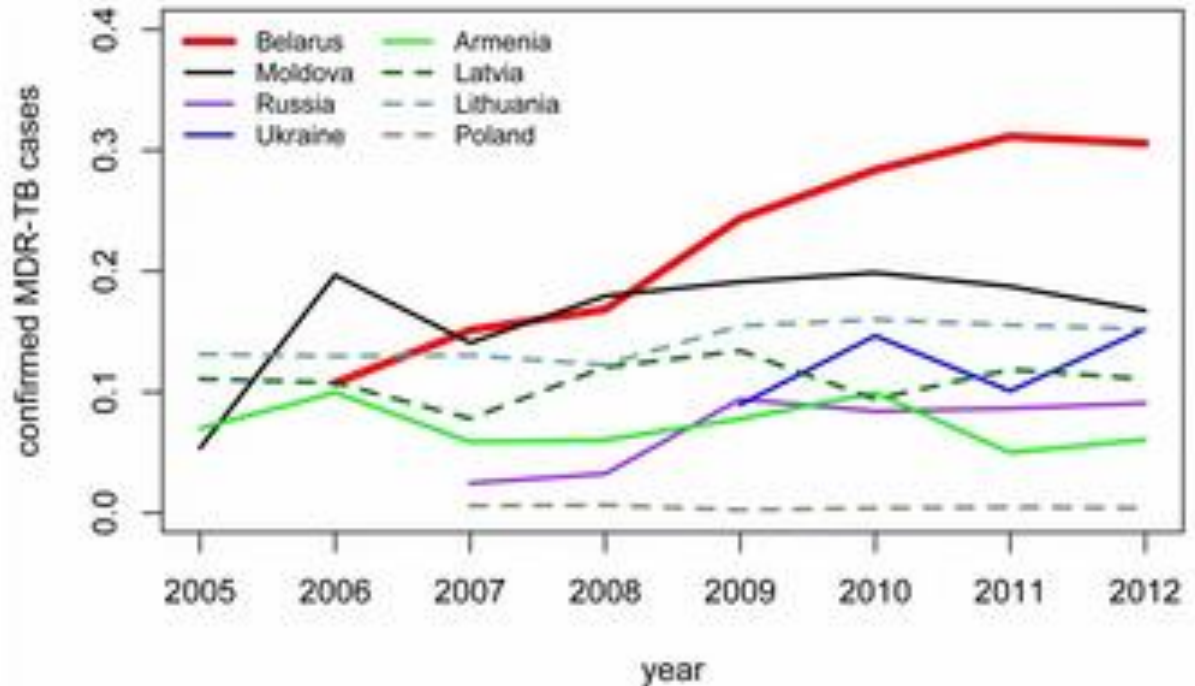
*Global Health Implication of Multi-Drug Resistant
Tuberculosis*

The World Is Flat, there is no country boundaries for MDR TB

MDR-TB in Belarus



Rate of MDR-TB per all notified TB cases



<http://belarusdigest.com/story/fighting-tuberculosis-western-myths-and-belarusian-reality-18541>

Financial barriers and coping strategies: a qualitative study of accessing MDR TB and TB care in Yunnan, China

- Five focus group discussion / 47- indepth interviews for sampled TB, MDR-TB, and health care providers 2014-2015
- **Financial constrains** are the most common barriers to accessing care
- Rural residents, farmers, and ethnic minorities were most vulnerable.
- Patients selling assets or borrowing money



Hutchison et al. BMC Public Health (2017) 17:221 DOI 10.1186/s12889-017-4089-y

MDR-TB Comorbidities

- Of 1970 patients with drug-resistant tuberculosis
 - 486(24,7%) had one or more comorbidity
 - 223 patient(11,3%) had liver diseases
 - DM-104(5,2%)
 - HIV-72(3,7%)
 - Psychiatric diseases - 53(2,7%),
 - Other-55(2,9%).

Comorbidities and MDR-TB treatment outcomes in Georgia- 2009-11 cohort
Marina Kikvidze, Lali Ikiashvili European Respiratory

Journal 2014 44: P1444; DOI:



MDR TB Diagnosis GeneXpert



[J Clin Microbiol. 2007 Apr; 45\(4\): 1081–1086.](#)

The Impact

COLLAPSE



Impact on Patient Isolation Pathway*

* Refer to the Xpert MTB/RIF package insert for details

^ Example with one Xpert® MTB/RIF negative result

MOTT: Mycobacteria Other Than Tuberculosis; DST: Drug Susceptibility Test



Xpert® MTB/RIF

Two-hour detection of MTB and rifampin resistance mutations

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[Critical Infectious Diseases](#), [Clinical IVD Tests](#)

Related Products
[Xpert EV](#), [Xpert Flu](#), [Xpert Flu/RSV XC](#)

OVERVIEW

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FAQS



Because the MTB/RIF test can detect TB better than the smear, results from one or two MTB/RIF tests can be used in the decision to remove patients from isolation.”

- FDA News Release

FDA. New data shows test can help physicians remove patients with suspected TB from isolation earlier. Press Release. 2015 Feb 12. Accessed Feb 2015.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434226.htm>

MDR-TB Global Clinical Trials

- **Nix-TB:** A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis (TBA and Janson)

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>	LOCATION
Pulmonary Tuberculosis MDR / XDR	Drug: Bedaquiline Drug: PA-824 Drug: Linezolid	Phase 3 6 m (optional 9 m)	SA: Cape Town Johannesburg Kwazulu-Natal

THE NIX-TB TRIAL OF PRETOMANID, BEDAQUILINE AND LINEZOLID TO TREAT XDR-TB (CROI, Feb. 27, 2017, Seattle)

Francesca Conradie¹, Andreas H. Diacon², Daniel Everitt³, Carl Mendel³, Christo van Niekerk⁴,
Pauline Howell⁵, Kyla Comins⁶, Mel Spigelman³

- 61 participants have been enrolled as of 15 December 2016 at 2 sites.
- 49% of the participants are HIV positive,
- 79% have XDR-TB and 21% have MDR TI or Fr to prior therapy.
- 34 have completed the 6 months of therapy with the drug regimen and 20 have been followed to the primary endpoint at 6 m after treatment.
- All surviving patients were culture negative by 4 mos, with 74% negative at 8 wks.
- 4 participants died within the first 8 wks of therapy; 3 had multi-organ TB on autopsy and 1 had a GI bleed due to erosive esophagitis.
- 27% had serious adverse events (AE). No surviving participants have withdrawn from the study due to any clinical AE or lab abnormalities.
- As of 15 December, 2016, there has been 1 microbiological relapse.

Two new drug therapies might cure every form of tuberculosis



Together, the new treatments, called **BPaMZ** and **BPaL**, could make treating TB much simpler and more effective

Caution needed

<https://www.newscientist.com/article/2121354-two-new-drug-therapies-might-cure-every-form-of-tuberculosis/>

Tipple AAA Principle

Available



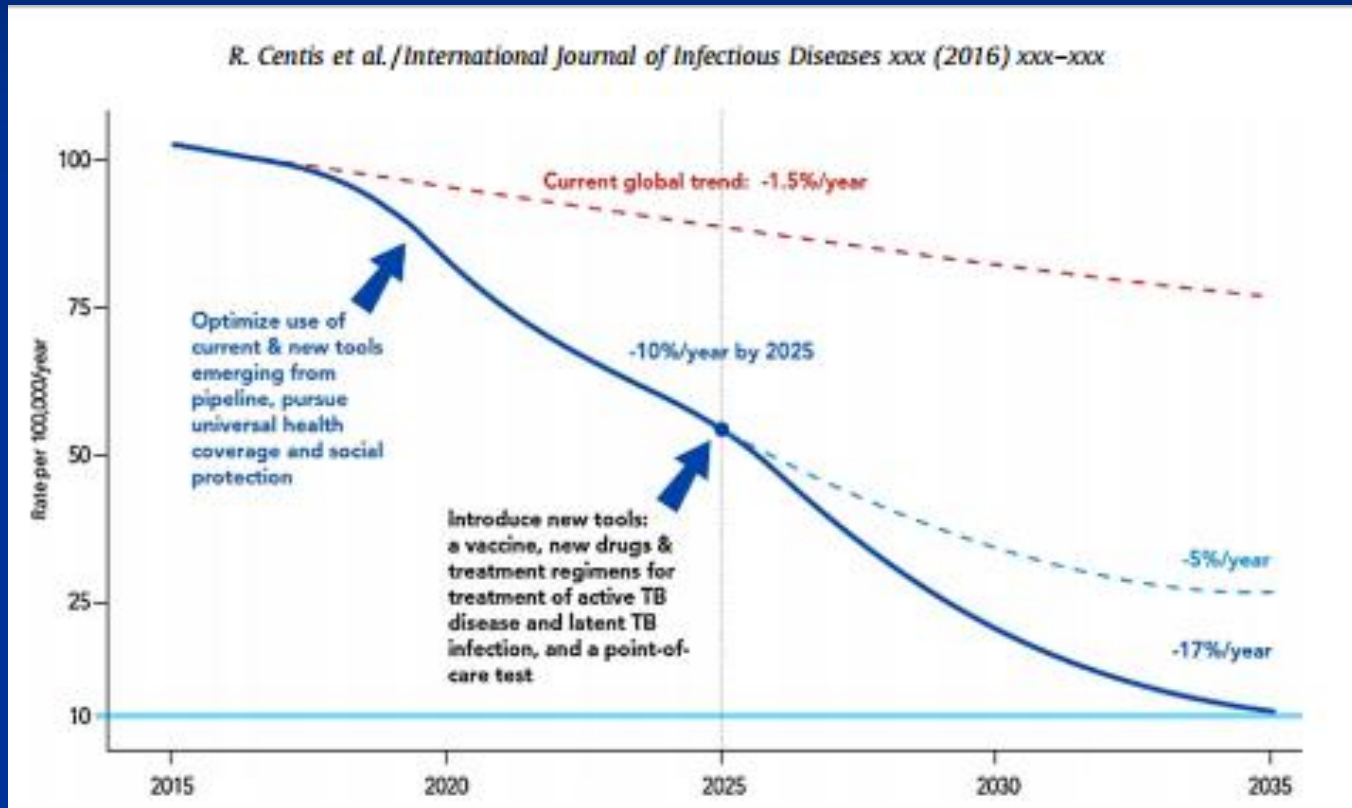
Affordable



Accessible



Projected acceleration in the decline of global tuberculosis incidence rates to target levels

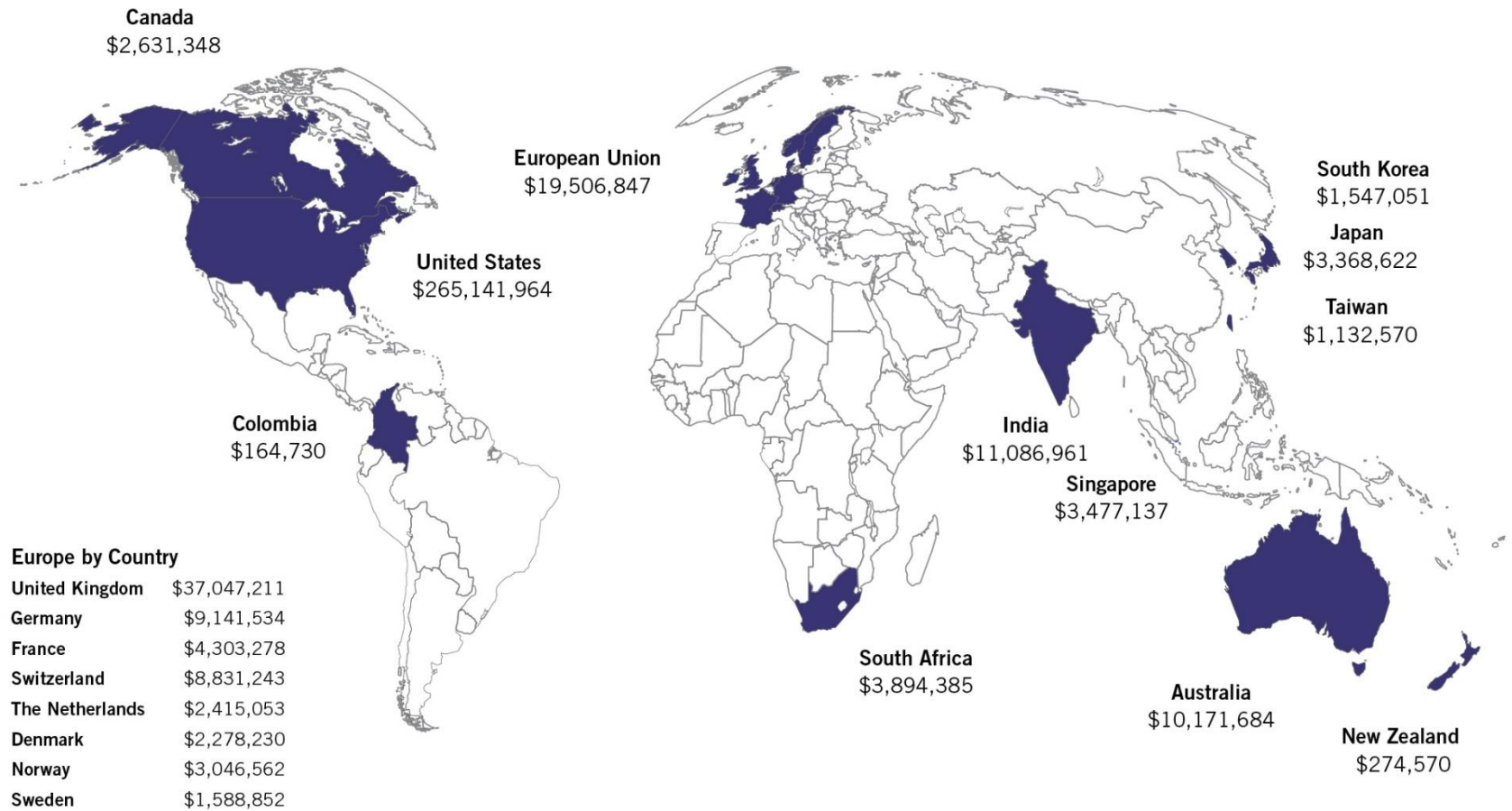


Shifting from tuberculosis control to elimination: Where are we? What are the variables and limitations? Is it achievable?

Rosella Centis^{a, 1}, Lia D'Ambrosio^{a, b, 1}, Alimuddin Zumla^c, Giovanni Battista Migliori^{a, 1}

2016 Report on TB Research Funding, TAG

Country Contributions to TB R&D, 2015



MDR TB is a global health threat



Joint Effort Combating MDR-TB



Discussion Points

- What are top 3 priorities for MDR-TB?
- How to control MDR- TB in migrant population?
- What are the major comorbidities of MDR-TB?
HIV/AIDS, DM, COPD, smoke, cancer, etc.
- How to share and coordinate / partner with MDR-TB National strategies?
- How to best inform WHO about country specific issues and make joint strategies?
- How to enhance efficacy and reduce cost?
- How to discover/control the most risky populations?