Treating both active TB disease and latent TB infection to achieve TB elimination

Myanmar Medical Association TB Forum

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Yangon

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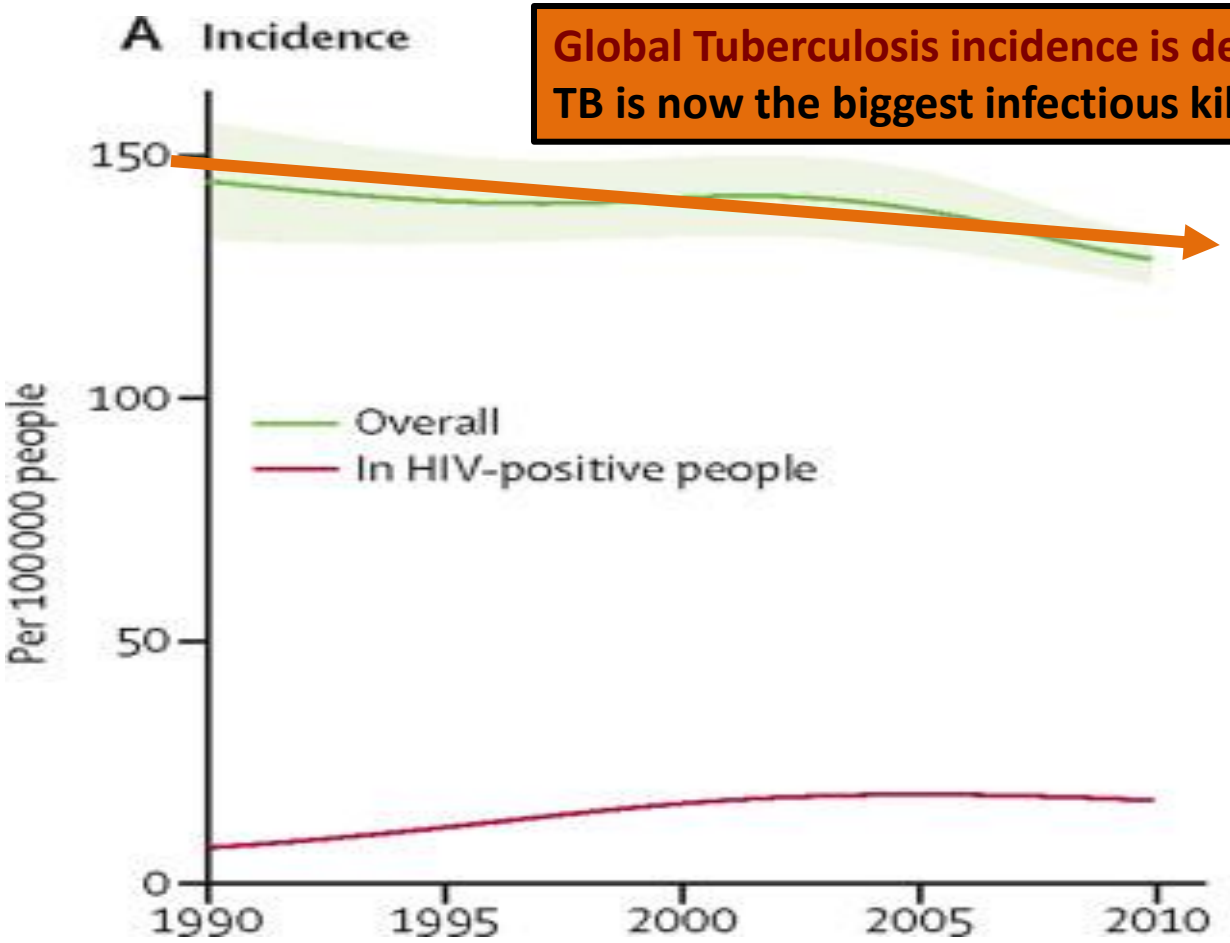
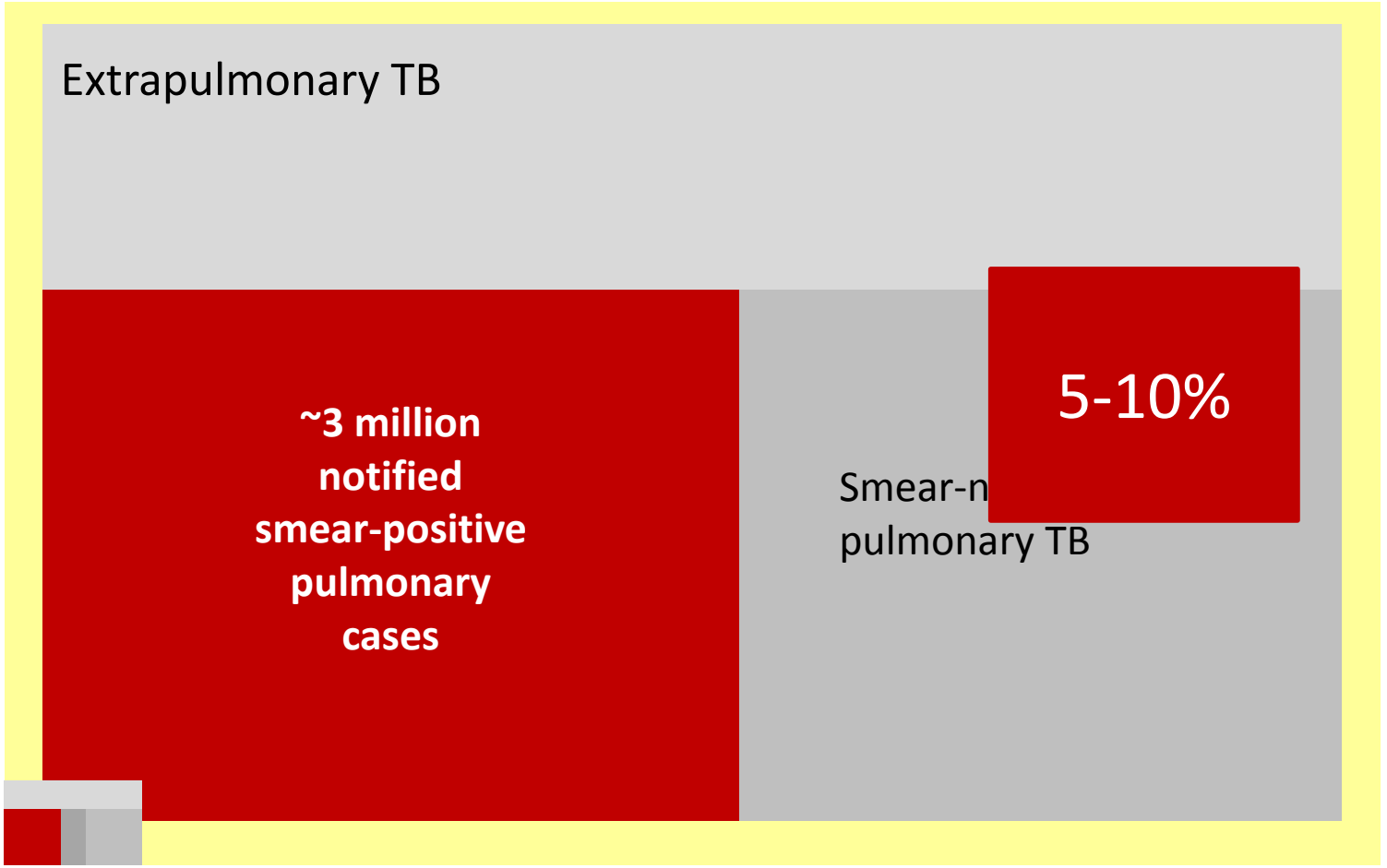
Global TB incidence

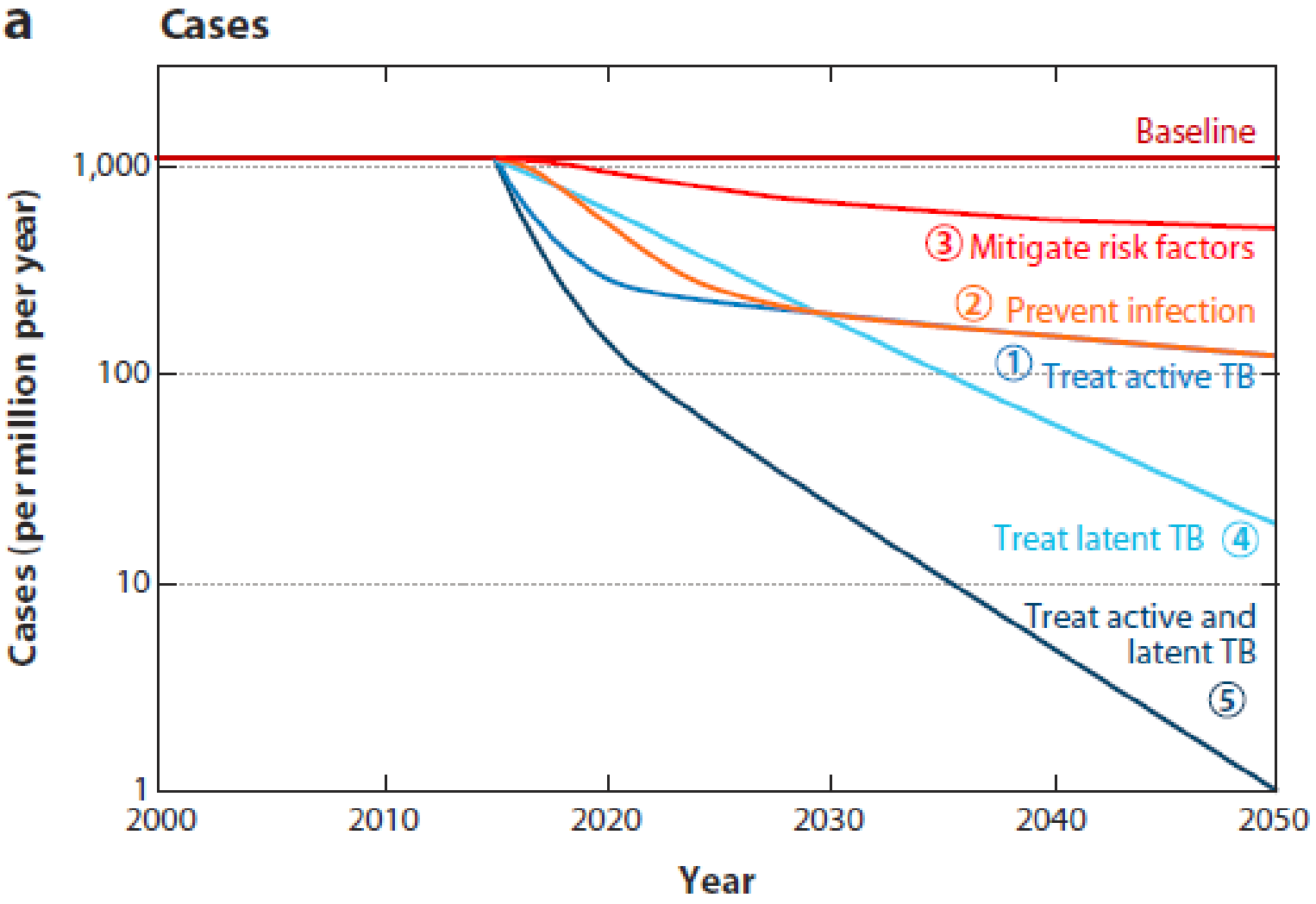
Global Tuberculosis incidence is declining at only 1.5% per year
TB is now the biggest infectious killer of adults worldwide



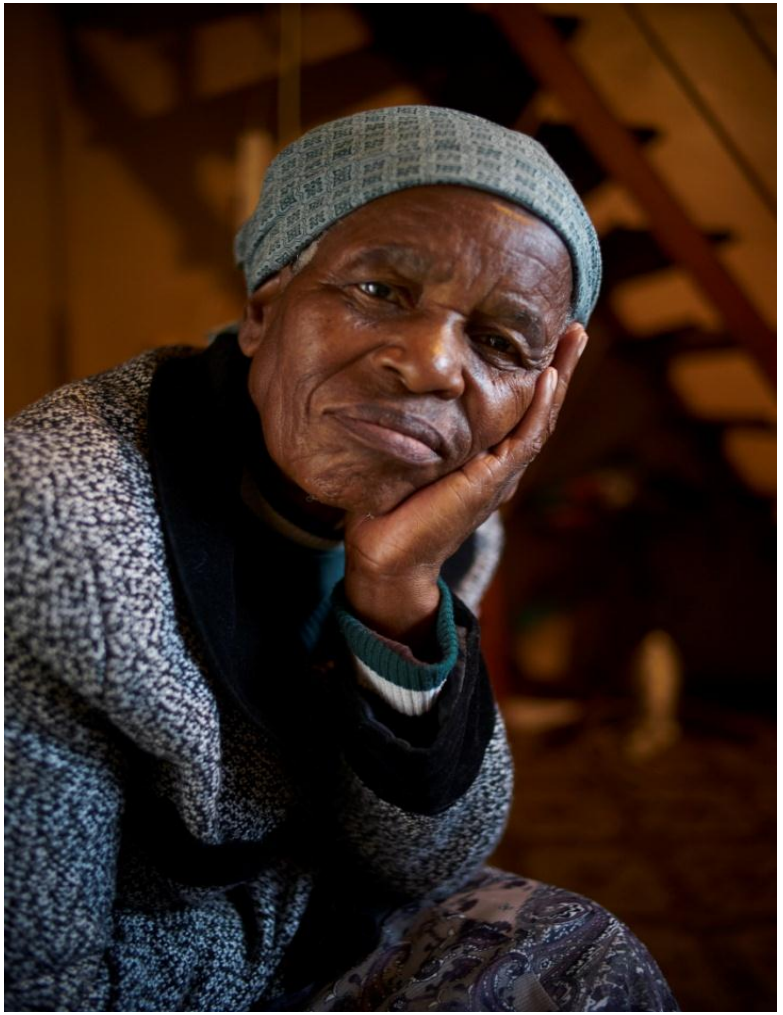
Date Source: Raviglione et al., *The Lancet*, 2012


Extrapulmonary TB
~3 million notified smear-positive pulmonary cases
Smear-n
pulmonary TB
5-10%

Strategies for eliminating TB



Dye, 2013



What is achievable ?

Photo Credit: SAF-IRD-2016-Noorani-0219

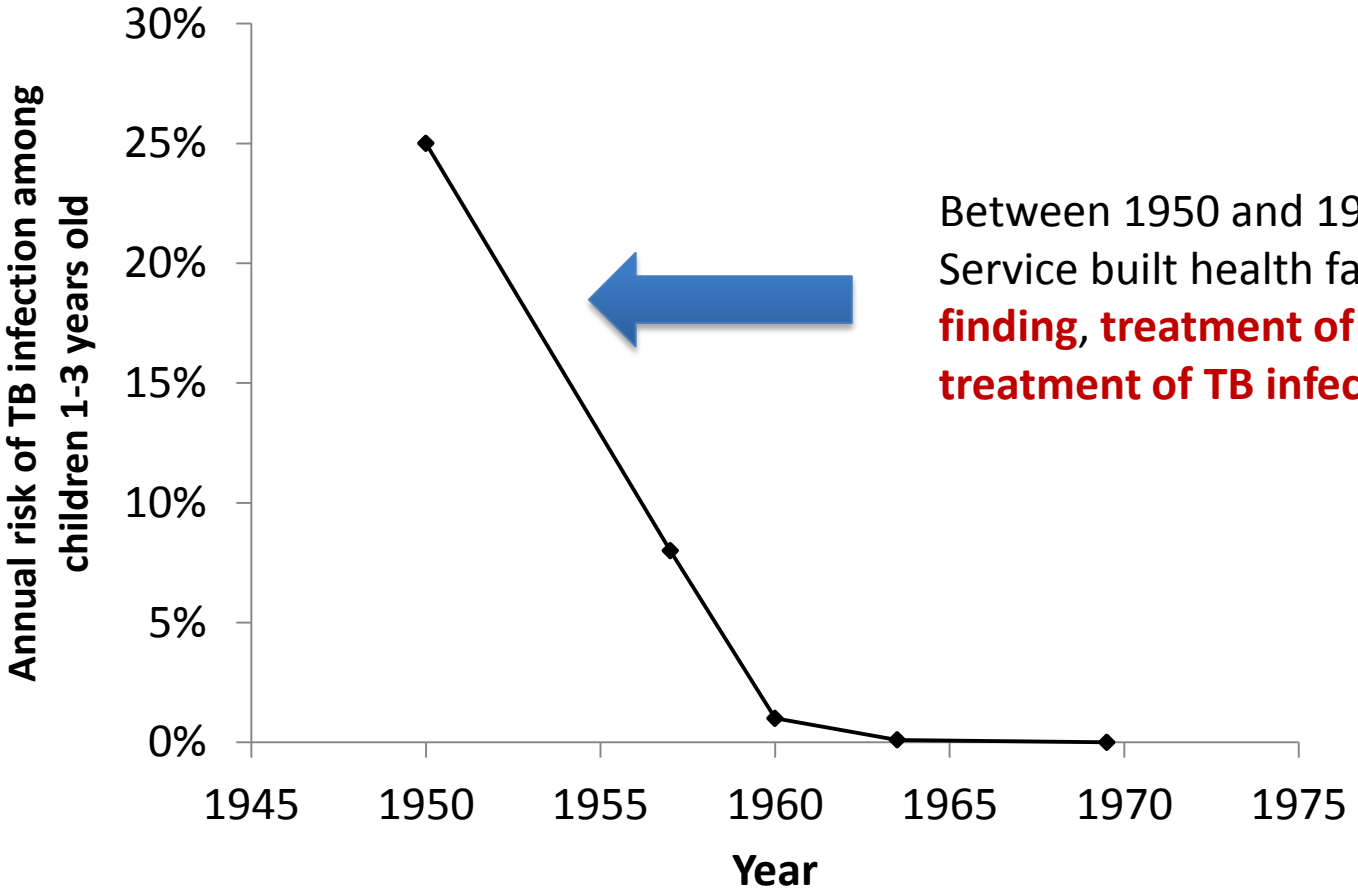
Bethel, Alaska

Alaska
1950s and 1960s

Source:
http://wikitravel.org/upload/shared//thumb/7/7b/Bethel Alaskabanner.jpg/1800px-BethelAlaskabanner.jpg

ZERO TB

Decline in TB transmission in Alaska, United States

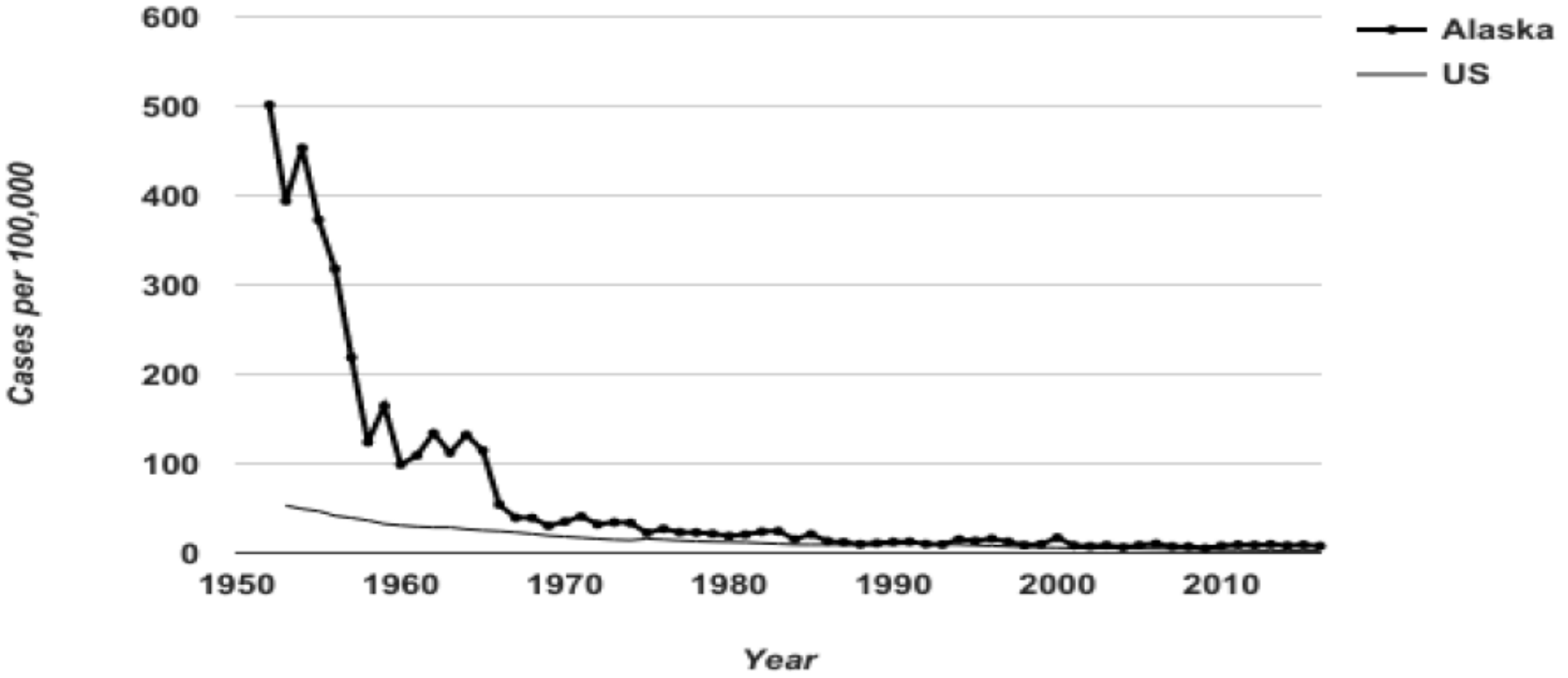


Between 1950 and 1960, the US Public Health Service built health facilities, started **active case finding**, **treatment of all forms of disease**, and **treatment of TB infection**

Kaplan, Fraser, and Comstock.
Am Rev Resp Crit Care. 1972

TB incidence rates: Alaska and US

Figure 1. Alaska and the United States TB Incidence Rates, 1952–2016



Source: Chandler 2017

Source: http://travelnoire.com/wp-content/uploads/2014/12/o-NEW-YORK-CITY-WRITER-facebook.jpg

New York City
1988

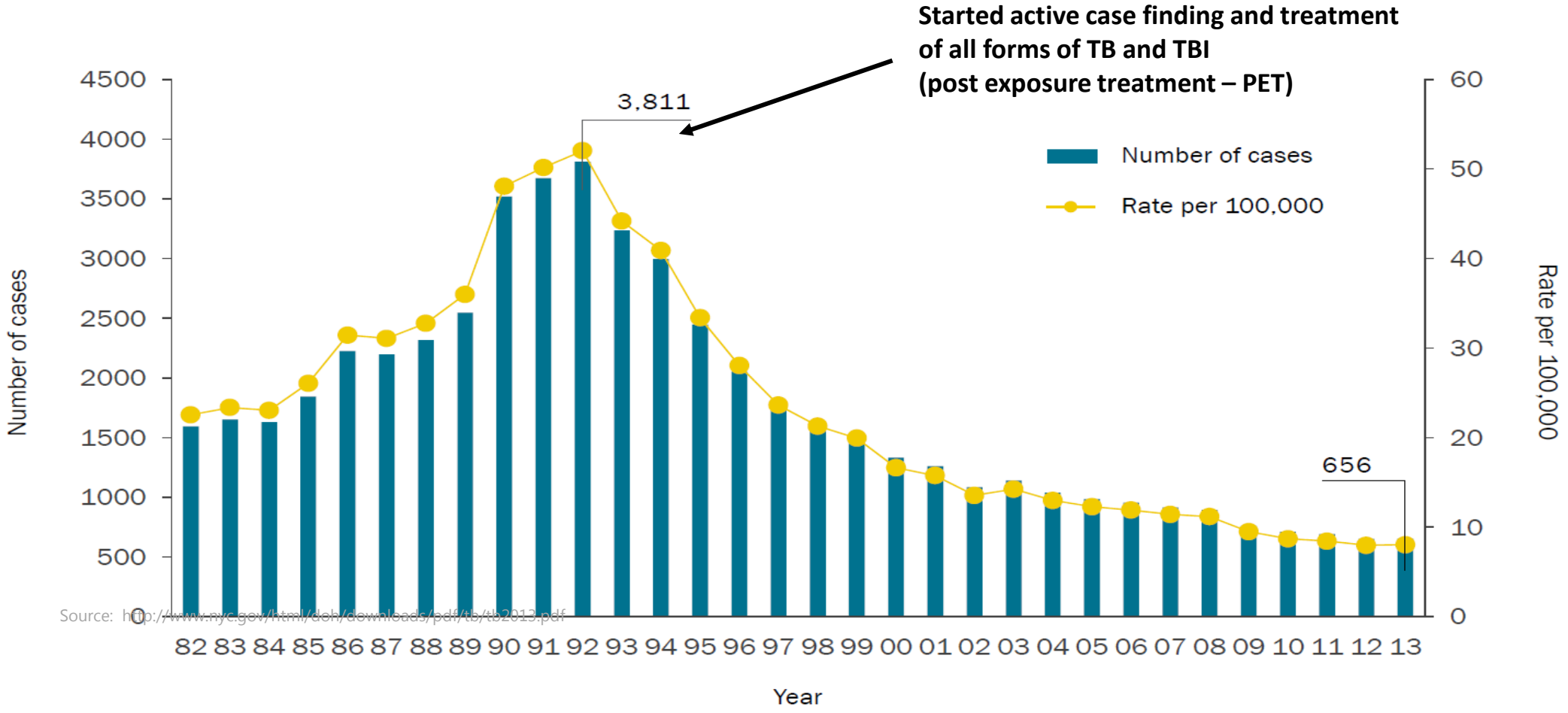
ZERO TB

- TB cases had nearly tripled in 15 years
  - In central Harlem, the case rate of >150 per 100,000 people exceeded that of many developing countries
  - Nearly 1 in 5 TB patients had MDR-TB
    - MDR-TB had more than doubled in 7 years
    - In 1991 NYC was home to 3% of the country's population, but accounted for 61% of all MDR-TB cases in U.S.

Source: Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. NEJM 1995; 333(4): 229-233.

New York City: TB cases and rates

FIGURE 1: Tuberculosis cases and rates,[1] New York City, 1982-2013



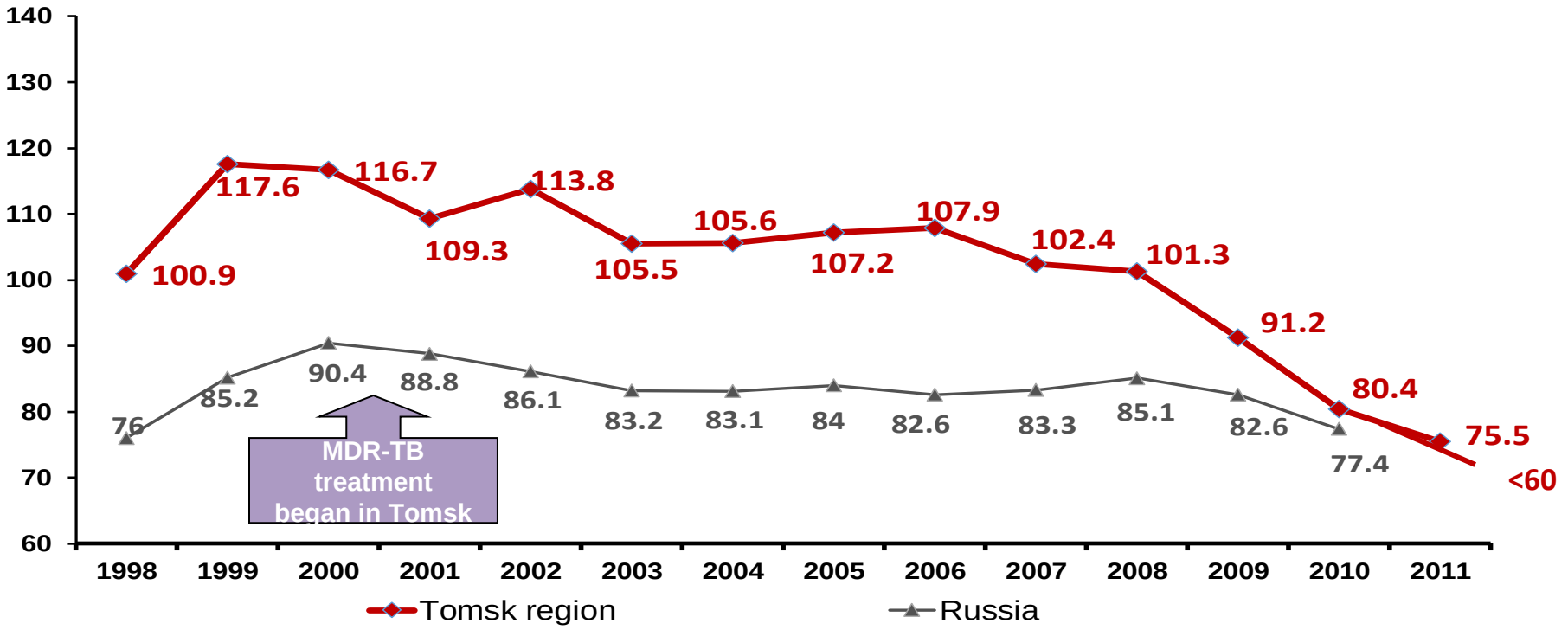
Source: http://www.nyc.gov/html/doh/downloads/pdf/tb/tb2013.pdf

Russia
2000s

ZERO TB

Tomsk, Russia

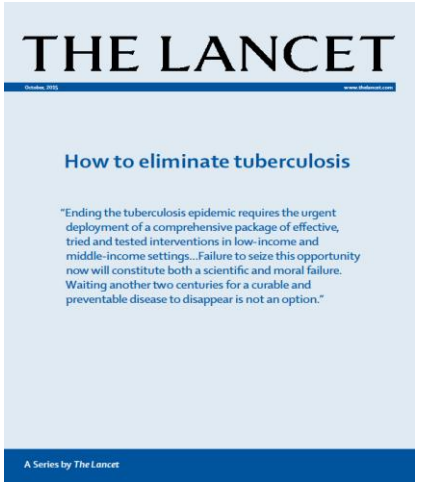
Tuberculosis notification rate in Tomsk Oblast, Siberia, and Russian Federation (per 100,000 population)



Source: Tomsk Oblast TB Services

What do these programmes have in common?

A comprehensive approach is required



ZERO TB

Search/ Treat/ Prevent

- SEARCH
  - Myanmar has a 79% case detection rate (NSP)
- TREAT
  - Early appropriate treatment saves lives
    - Optimise adherence/ differentiated care
  - Treatment reduces transmission
- PREVENT
  - TB infection control
  - ART
  - TB infection treatment

What is the evidence for Preventive Therapy?

Evidence for Communities

- Bethel, Alaska in 1950s Comstock, 1962 & 1967
  - Community wide 30% reduced TB incidence

- Community cluster randomised trial in Rio Cavalcante, 2010
  - 8 neighbourhoods: comparing standard DOTs to enhanced DOTs.
  - Enhanced DOTs
    - Household visits for contacts
    - TST, CXR, clinical exam
    - Results
      - 4% of contacts had active TB
      - 72% of contacts had latent TB
      - 70% received PT
  - Over 5 years: 15% reduction in TB incidence

Evidence for PLWH

- 1998: WHO and UNAIDS endorsed targeted IPT Wilkinson 1998, Bucher, 1999
- Cochrane reviews
  - 2004: Decreased risk of TB (33% overall) 64% (TST+ ve) Woldehanna, 2004
  - 2010: Efficacy similar for all regimens; regardless of drug type, frequency or duration
  - But short-course multi-drug regimens much more likely to require discontinuation due to A/E than INH alone Akolo, 2010

Evidence for PLWH Cont.

- TRIO, PLWH in Rio clinics Durovni, 2013
  - Step wedge, cluster randomised in 29 clinics over 2.5 years.
  - Screened, TST, IPT
  - Followed pre and post intervention.
    - 27% reduction in TB incidence
    - 31% reduction in TB or death among entire population of PLWH- not just those who received INH
    - TST pos: 7 year durable protection, no rebound as seen in Sub-Saharan Africa

IPT and ART

- Prospective study in South Africa Golub, 2009
  - ART reduced TB by 64%/ ART+ IPT : 89% reduction

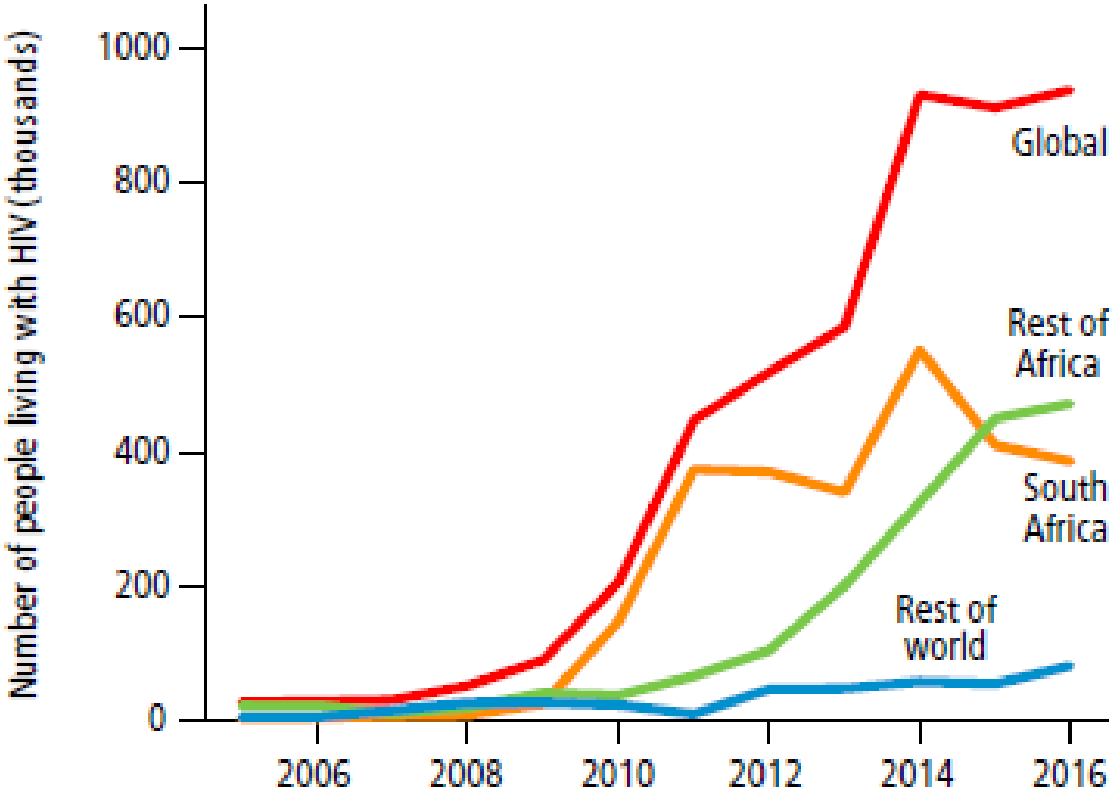
- Randomised, double blind, placebo controlled, South African ART clinic under field conditions Rangaka, 2014
  - 12 months of INH reduced TB incidence by 37%

IPT and ART cont.

- Temprano Cluster Randomised, PLWH in Cote d'Ivoire
  - Over 78 months — Badje, 2017
    - No IPT/ deferred (CD4<350) : 8% mortality
    - No IPT, immediate ART: 6.6% mortality
    - IPT, deferred ART: 4.9% mortality
    - IPT, immediate ART: 3.2% mortality
  - IPT reduced risk of death by 37%; independent of ART
- REALITY trial in 4 African countries; PLWH and children with CD4<100 starting ART — Hakim, 2017
    - "Enhanced": 3 months of IPT, flucon, azithro, albednazole, TMP-SMZ
    - Control: ART and TMP-SMZ
  - Even with "substandard" 3 month regimen of INH; reduction in TB by 33%

940 269 PLWH receiving infection treatment

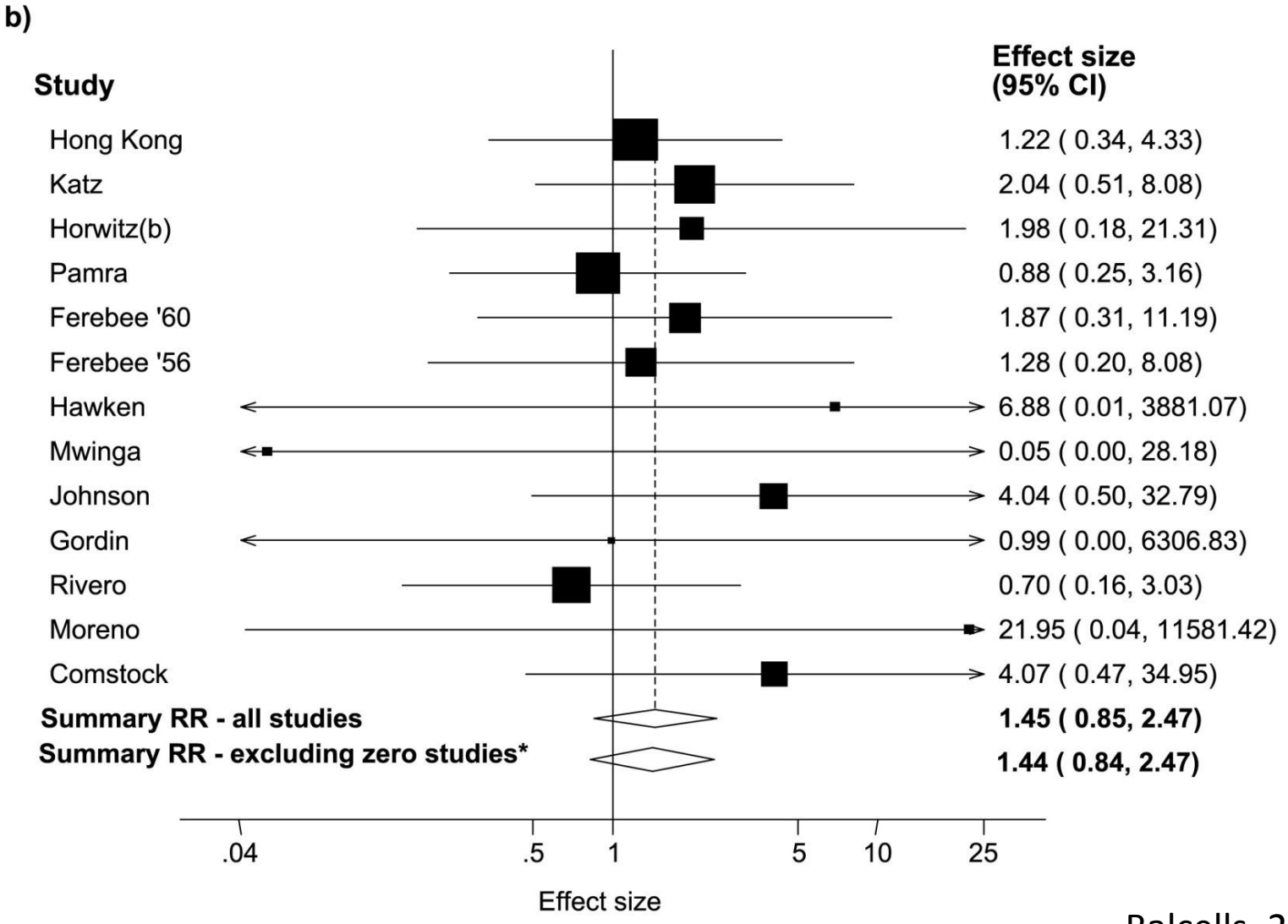
Provision of TB preventive treatment to people living with HIV, 2005–2016



WHO: Global TB report:2017

Why are we not providing this life saving treatment for our patients?

Is there a risk of drug resistance?



Balcells, 2006

Is there a risk of hepatotoxicity?

- Isoniazid carries some risk of hepatotoxicity, but risk of TB is higher: 28,000 Eastern European adults with TB history

Thompson 1982

Risk of TB in placebo arm	1.4%
Risk of hepatitis in placebo arm	0.12%
Risk of hepatitis in 6-month isoniazid arm	0.36%
Risk of hepatitis in 12-month isoniazid arm	0.52%

- Hepatotoxicity is reduced with 3HP vs INH

WHO 2015; Bliven Sizemore, 2015

How long does protection last?

- A comprehensive approach is required
  - In trials with South African mine workers and PLWH in Botswana, with a high background TB prevalence; IPT was protective only while people received it

    Churchyard 2014, Samandari 2015
- Protection can be durable
  - In Alaska those who received isoniazid had a reduced risk of TB disease over the next 19 years Comstock 1967
  - A regimen containing Rifamycin may be more beneficial in terms of sterilisation than INH alone
  - Trio trial, with PLWH; effect endured for 7 years have not seen the rebound as we have seen in Sub-Saharan Africa Cavalcante, 2013

New shorter regimens are as effective and improve adherence

Regimen	Number of doses
Isoniazid Daily, 6-9 months	180 or 270
Rifampicin Daily, 3-4 months	90 or 120
Rifampicin and isoniazid Daily, 3-4 months	90 or 120
Rifapentine and isoniazid Weekly, 3 months	12

WHO 2015

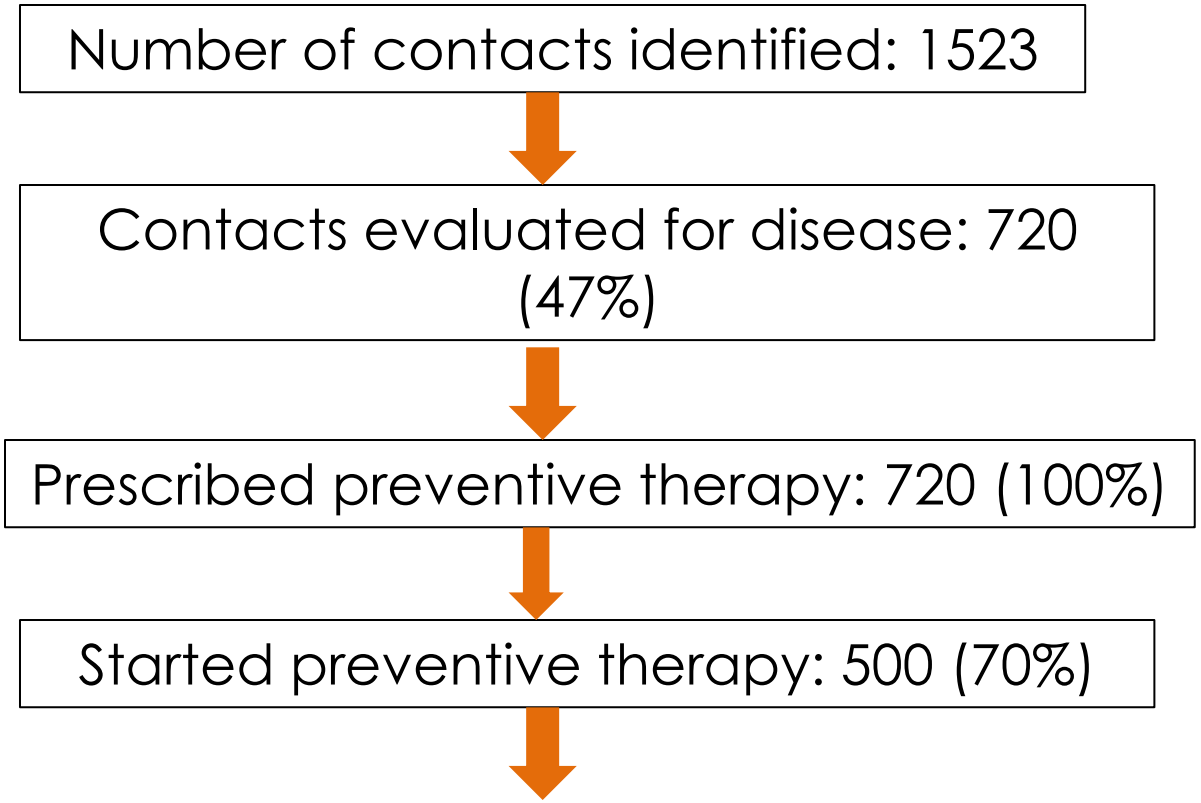
MDR prevention: 3 trials

- Phoenix (ACTG and IMPAACT)
  - Global study of Household contacts
  - Delaminid vs. INH
- V-Quin
  - Vietnam
  - Contacts > 15 years
  - Levofloxacin vs. placebo
- TB CHAMP
  - South Africa
  - Child contacts
  - Levofloxacin vs. placebo

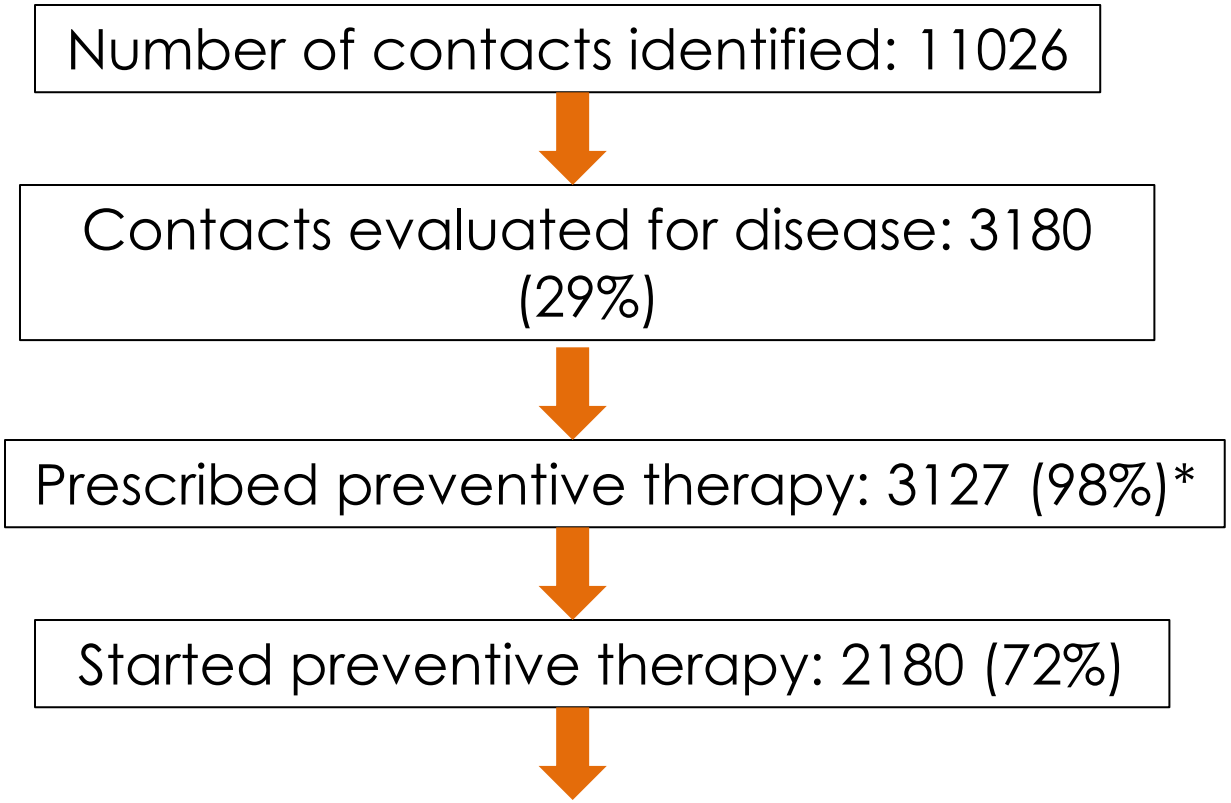
CENTER FOR GLOBAL HEALTH DELIVERY–DUBAI
HARVARD MEDICAL SCHOOL


KARACHI
22 MILLION PEOPLE

Prevention Cascade - DRTB (Oct '16-Dec'17)



Prevention Cascade – DSTB (Oct '16-Dec'17)



51 TB
3 Hep C Rx

6 months INH vs. 3HP

Indicators		6 Months INH				3HP				Grand Total
	Less than 2 Years	2-4 years	5-14 years	≥15 years	Total	2-4 years	5-14 years	≥15 years	Total	
Contacts offered treatment	167	121	423	608	1319	196	567	732	1495	2814
Contacts started on treatment	103	102	302	436	943 **(71%)**	110	370	644	1124 **(75%)**	2067 **(73%)**
Contacts refused after started on PET	24	23	72	106	225 **(24%)**	2	6	14	22 **(2%)**	247 **(12%)**
Contacts not completed the treatment	0	25	45	70	140 **(15%)**	3	5	15	23 **(2%)**	163 **(8%)**
Treatment Completed	13	35	121	129	298 **(32%)**	27	98	145	270 **(24%)**	568 **(27%)**
Still on treatment	66	19	64	131	280 **(30%)**	78	261	470	809 **(72%)**	1089 **(53%)**

Further reading

Barriers to implementation of tuberculosis preventive therapy and proposed responses

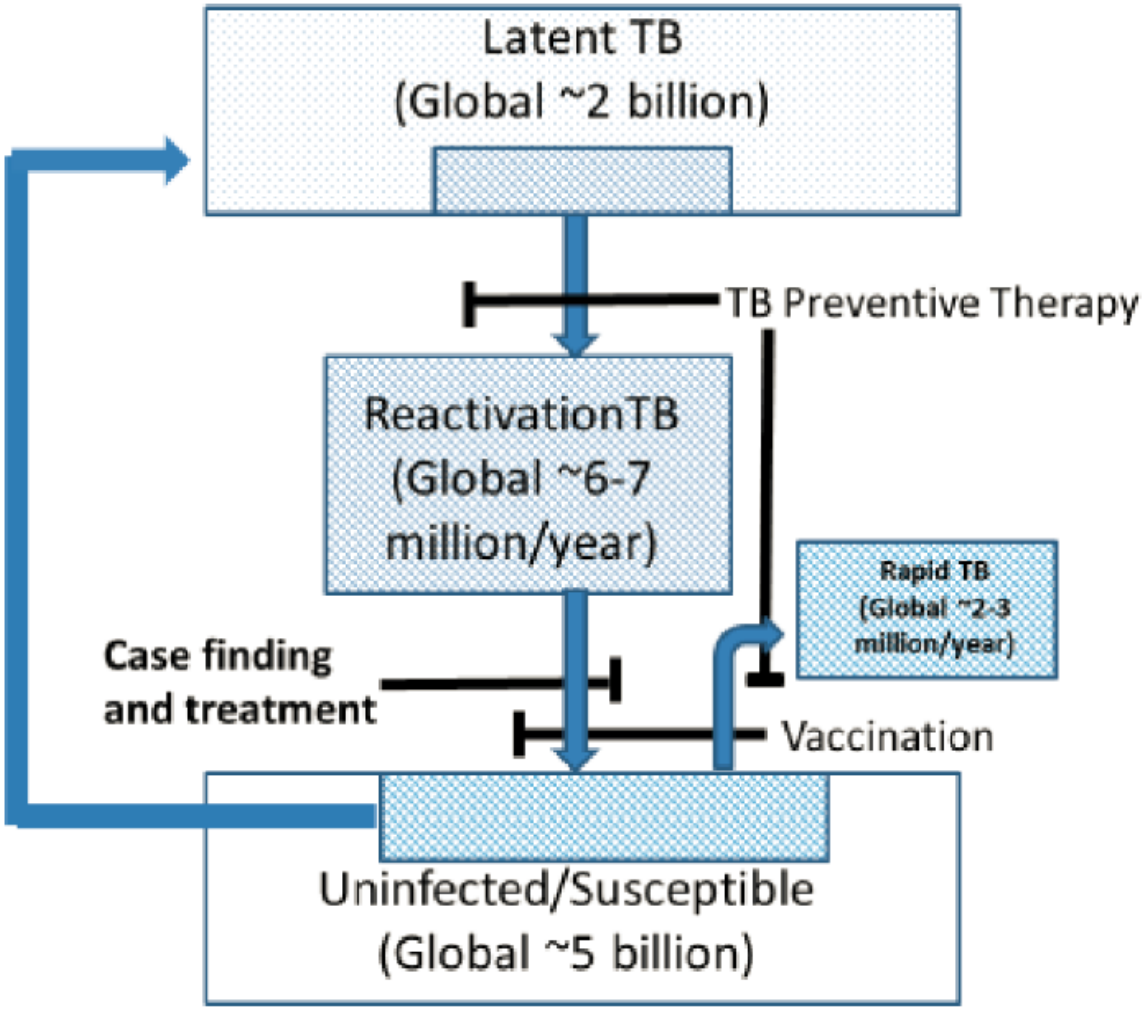
Category	Barriers	Proposed responses
Clinical	Excluding active tuberculosis, especially in HIV+ patients	Use of clinical algorithms, more use of chest x-rays
	Need for tuberculin or other testing (IGRA)	Develop new simpler tests that are more predictive of subsequent active TB, improve global production of tuberculin, treat high-risk patients without testing
	Poor adherence and completion of preventive therapy	Use of short-course regimens Supervision of therapy
	Drug toxicity	Encourage monthly monitoring, patient education
	Perceived risk of acquiring drug resistance	Available evidence suggests this is not a problem
Health System	Lack of consistent guidelines	Harmonized global and national guidelines Development of preventive therapy toolkit
	Inadequately trained staff	Enhanced training for doctors, nurses and other health workers
	Stock-outs of drugs and diagnostics (TST and IGRAs)	Strengthened supply chain
	Poor surveillance and reporting	Better health information systems, increased monitoring and evaluation
	Inadequate funding	a. Expansion of vertical health programs to address TB prevention (e.g., HIV PMTCT), with benchmarks for disease control b. More integration of tuberculosis control into primary health care
Policy/Advocacy	Lack of priority for prevention, with emphasis on proportion of active cases treated	Realignment of TB Control Programs to incorporate prevention, with performance evaluation linked to incidence
	Inadequate investment in basic, clinical and implementation research and training	Increased funding for research
	Lack of advocacy and demand from groups most at risk	Education and empowerment of at-risk group, including people with HIV, families

Published in final edited form as:
Lancet. 2015 December 5; 386(10010): 2344–2353. doi:10.1016/S0140-6736(15)00323-2.

Controlling the Seedbeds of Tuberculosis: Diagnosis and Treatment of Tuberculosis Infection

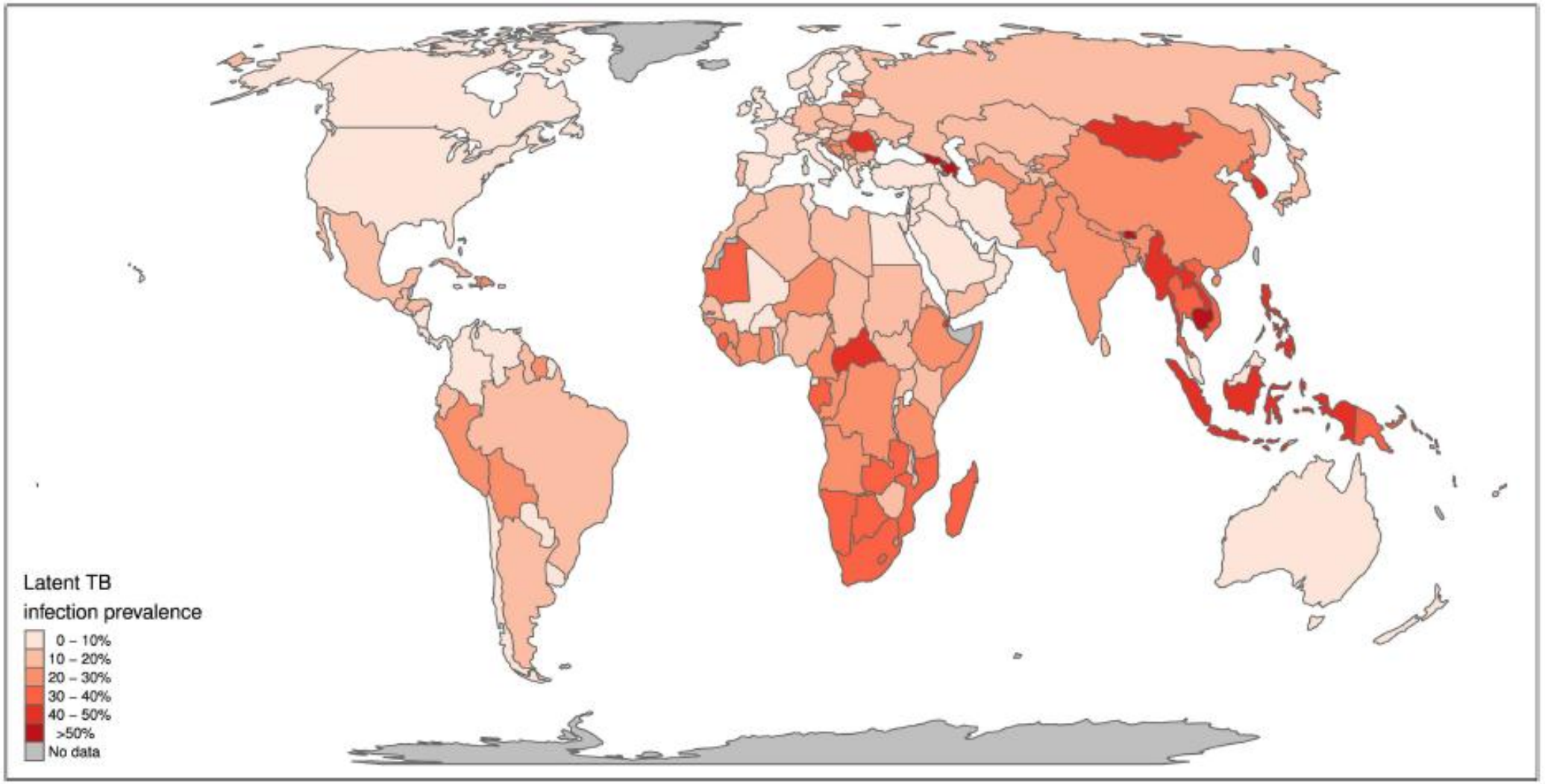
Molebogeng X. Rangaka, PhD, Solange C. Cavalcante, PhD, Ben J. Marais, PhD, Sok Thim, MD, Neil A. Martinson, MBBCh, Soumya Swaminathan, PhD, and Richard E. Chaisson, MD

A reminder of our challenge



Rangaka , 2015

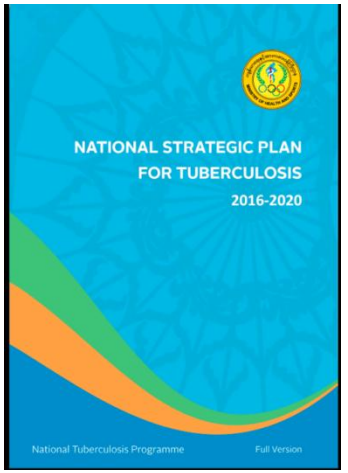
Global map of prevalence of latent TB infection: 2014



Who is will benefit most from TB infection treatment?

- Child contacts < 5 years (5-40%)
- PLWH: pre-Art and on ART (2-10%/ year)
- Miners and people with silicosis
- Expected new WHO guidelines
  - All household contacts (72% infected in Brazil and Phoenix study)
    - ? With evidence of infection
- Other populations at high risk e.g.
  - Congregate settings such as prisons
  - HCWs regardless of HIV status

Myanmar National Strategic plan 2016-2020



- Eligible
  - Child contacts of smear positive < 5 years
  - PLWH
    - 35 townships reported. 17% received IPT
    - 2014: 36% of PLWH accessed ART
- Plans include
  - Assessment of provider, patient and family concerns
    - Education, training and mentoring
  - Drug supply chain including paediatric formulations and pyridoxine
  - Improved monitoring and evaluation

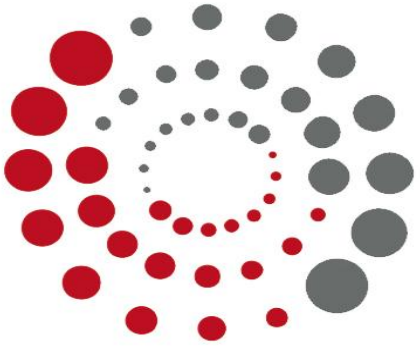
WHO 2017: Top 10 Nationals indicators towards meeting the END TB Strategy

	INDICATOR	RECOMMENDED TARGET LEVEL	MAIN RATIONALE FOR INCLUSION IN TOP 10
5	Latent TB infection (LTBI) treatment coverage *Number of people living with HIV newly enrolled in HIV care and the number of children aged <5 years who are household contacts of cases started on LTBI treatment, divided by the number eligible for treatment, expressed as a percentage (separately for each of the two groups).*	≥90%	Treatment of LTBI is the main treatment intervention available to prevent development of active TB disease in those already infected with *Mycobacterium tuberculosis*.

Conclusion

- We need to significantly increase our effort to Eliminate TB
- It has been done and can be done again
- A comprehensive approach is required
  - Search: Find the missing cases
  - Treat: Early and appropriately
  - **Prevent: Infection treatment**

Acknowledgements



ZERO TB Initiative

Stop TB Partnership

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