Can Tuberculosis Be Eradicated?

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Center for TB Research

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CENTER FOR AIDS RESEARCH
JOHNS HOPKINS UNIVERSITY

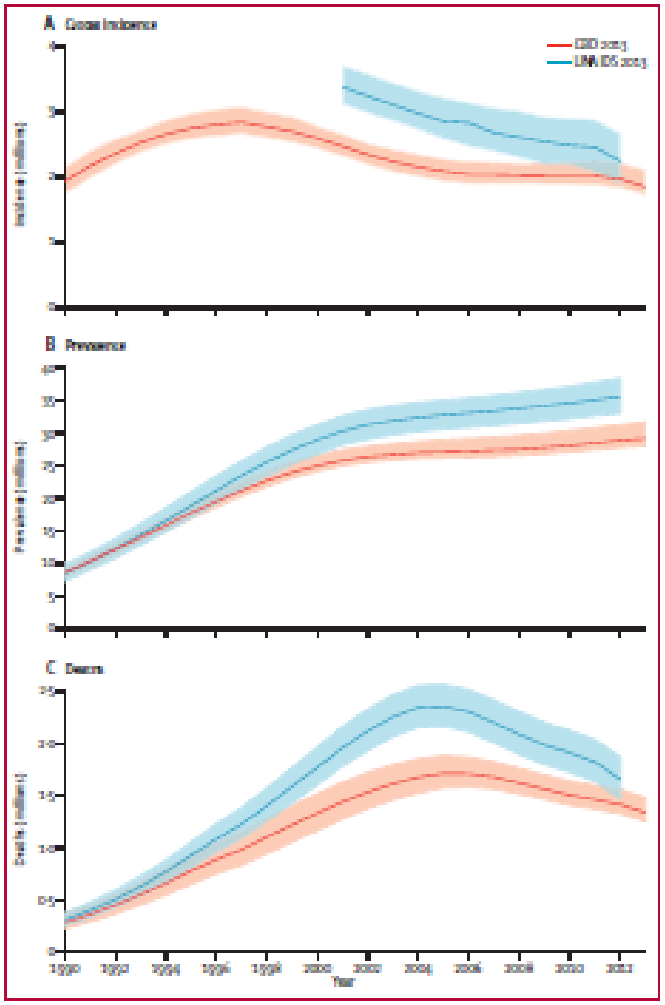
CREATE
Consortium to Respond Effectively to the AIDS TB Epidemic

Eradication, elimination or control?

- **Eradication – complete absence of the disease from the planet.**
- **Elimination – ending the disease as a public health problem.**
  - Defined as TB incidence of <1 per million and TB deaths <1 per 10 million
- **Control – making it a much smaller problem than it currently is.**

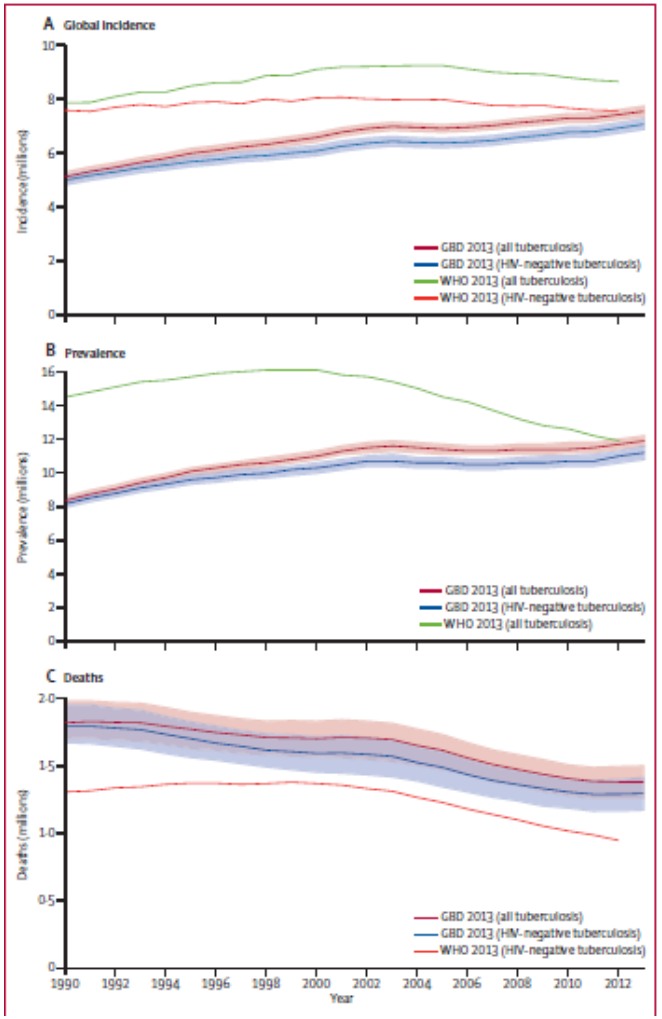
Global Burden of Disease Estimates of Incidence, Prevalence and Mortality from HIV and TB

HIV



1.3 million deaths in 2012

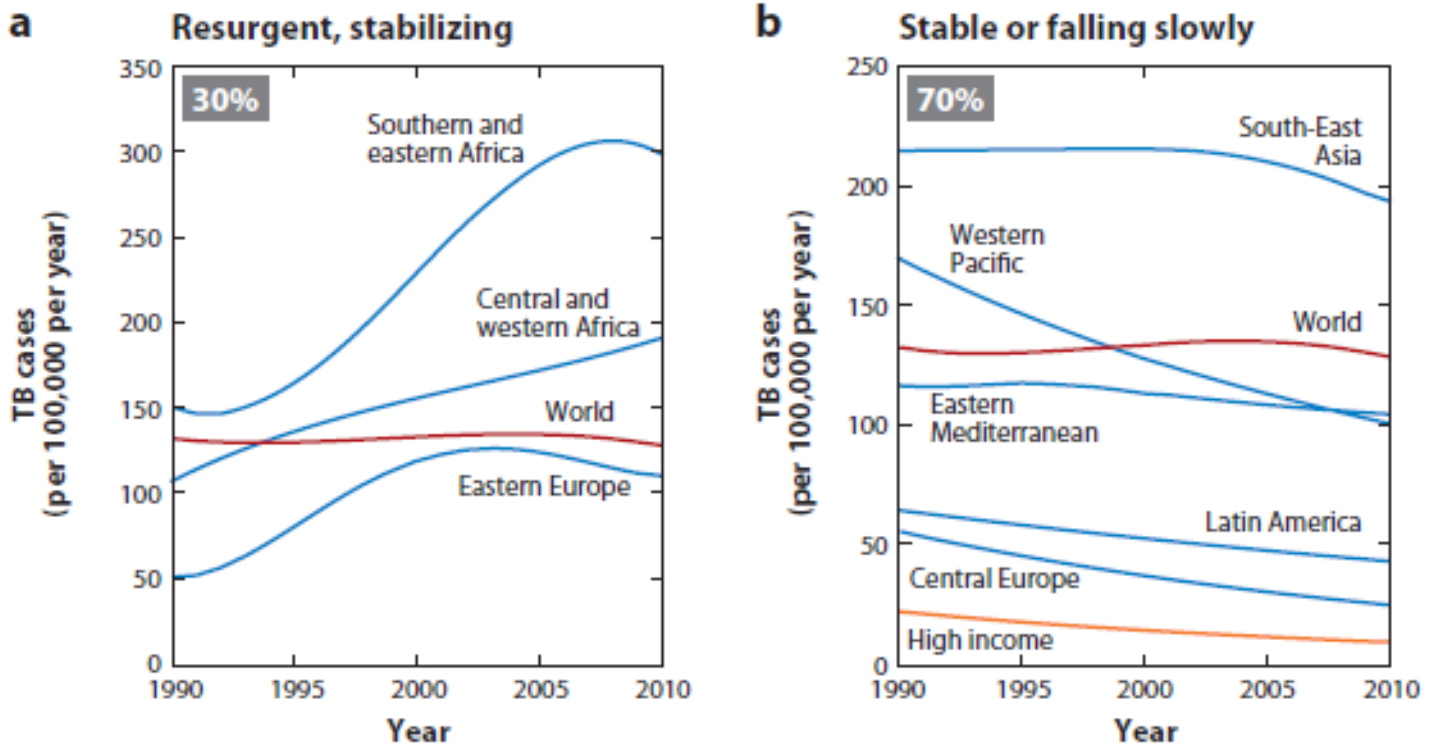
Tuberculosis



1.4 million deaths in 2012

CJL Murray et al., Lancet, Sept 12, 2014

The World in 2 Acts
"Controlled" and Uncontrolled TB

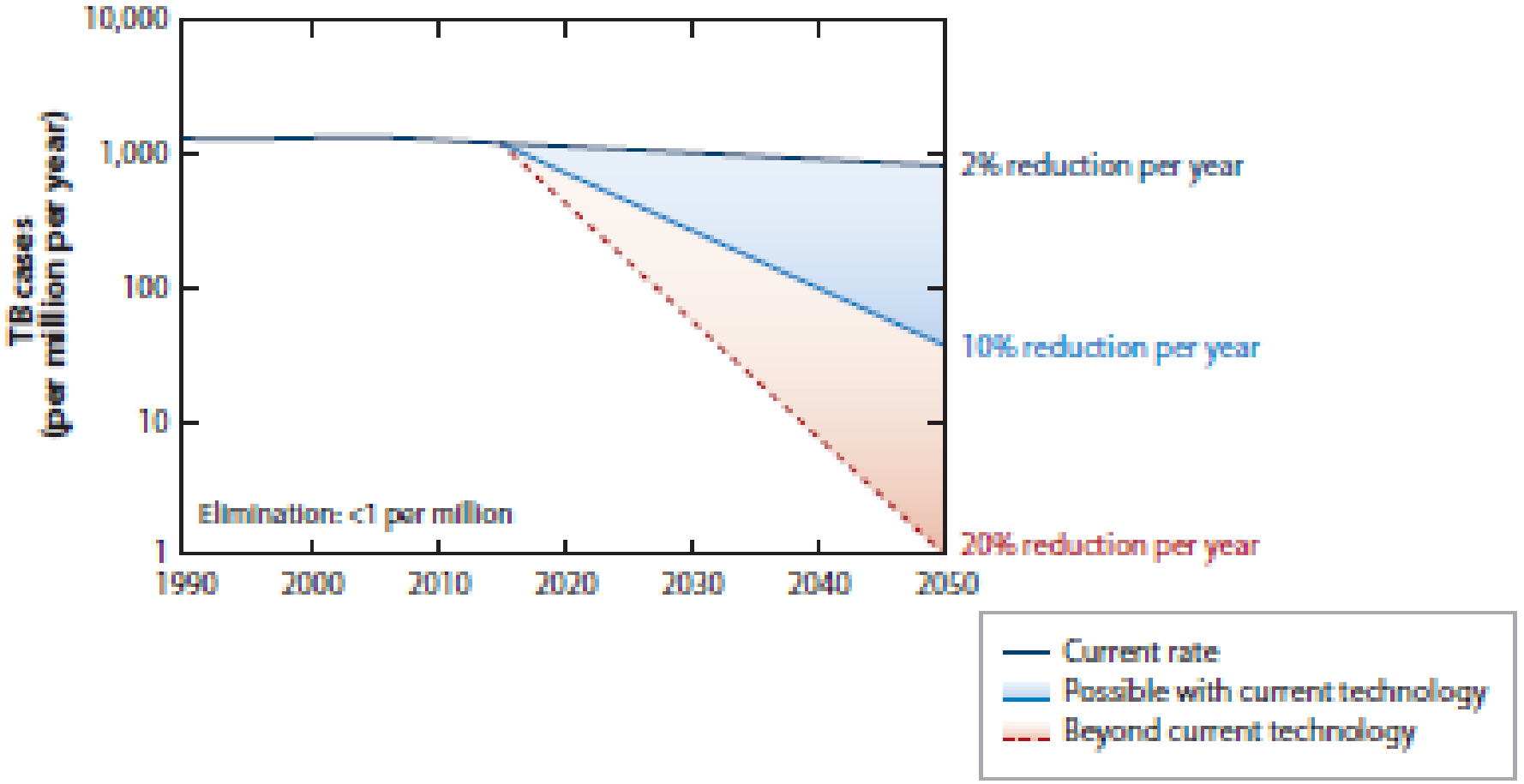


Dye, et al., Ann Rev Publ Health 2013

Tools to Control of Tuberculosis
Why hasn't TB already been eliminated?

- Global failure to apply biomedical tools effectively
  - Weaknesses in health systems
- Inadequacies of existing tools
  - Smear detection of cases ~50%
  - Adherence to regimens is poor
  - BCG vaccine does not prevent adult TB
- Changing epidemiological situation
  - HIV epidemic
  - MDR
- Global policies that lack understanding of best epidemiologic approaches

The Path to Elimination



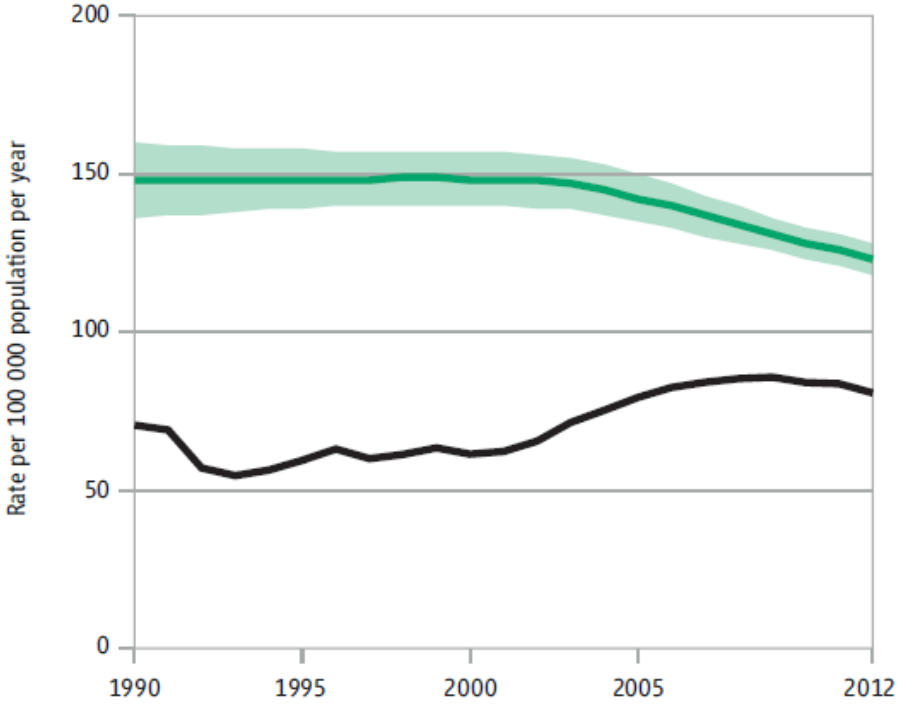
Dye, et al., Ann Rev Publ Health 2013

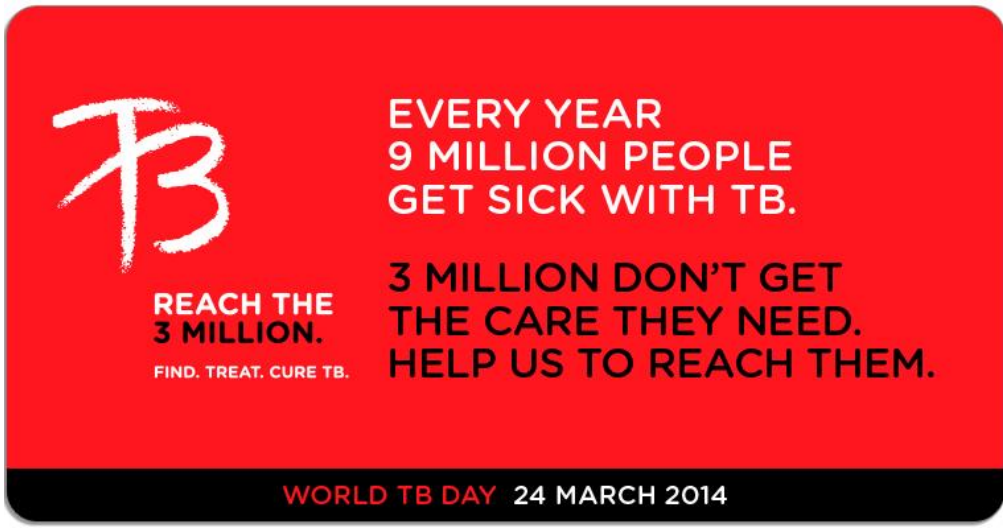
Drivers of tuberculosis

- Population level drivers
  - Force of infection (transmission)
  - Crowding and mixing
  - Inadequate diagnostic/treatment services
  - (Drug resistance)
- Individual level drivers
  - HIV/immunosupression
  - Diabetes
  - Smoking
  - Silicosis
  - Malnutrition

TB Case Detection: Mind the Gap

Global trends in case notification (black) and estimated TB incidence (green) rates, 1990–2012.
Case notifications include new and relapse cases (all forms).





WHO Global Tuberculosis Report 2013

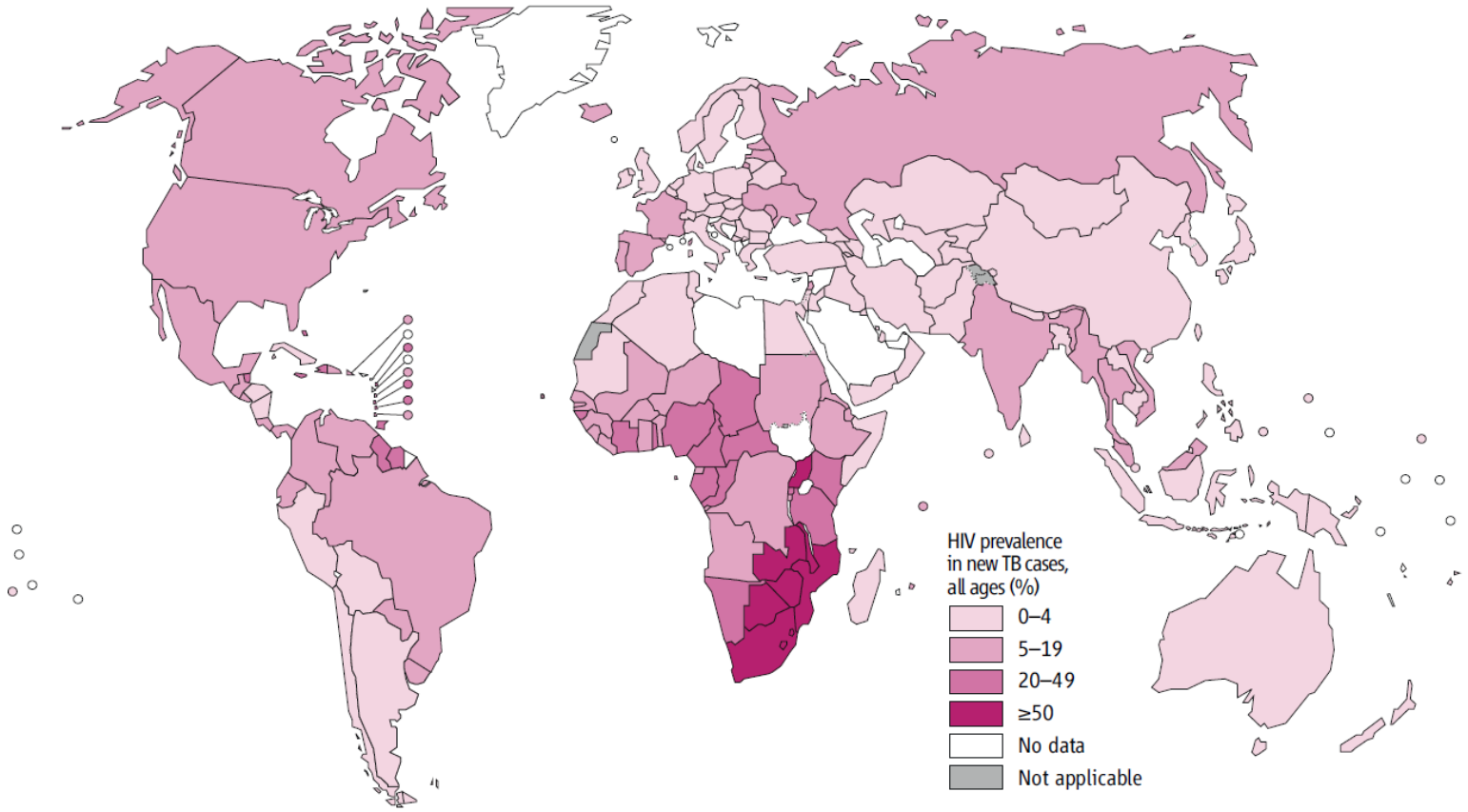
Tuberculosis in South African Adults Dying at Home without a Medical Diagnosis

- Adults dying at home, no diagnosis
- (18% excluded, known to have TB)
- Consent from family
- Bilateral axillary Tru-Cut biopsy
- Modified bronchoalveolar lavage

Post-Mortem Diagnosis	**N=85 (%)**
TB on ≥1 lab test	**29 (34.1)**
TB on ≥2 lab tests	**22 (25.9)**
Biopsy	
Histology	16/29 (55.2)
AFB positive (ZN)	13/16 (81.3)
Xpert	13/29 (44.8)
MGIT	**18/29 (62.1)**
BAL	
AFB+ (Auramine)	9/29 (31.0)
Xpert	**20/29 (69.0)**
MGIT	19/29 (65.5)

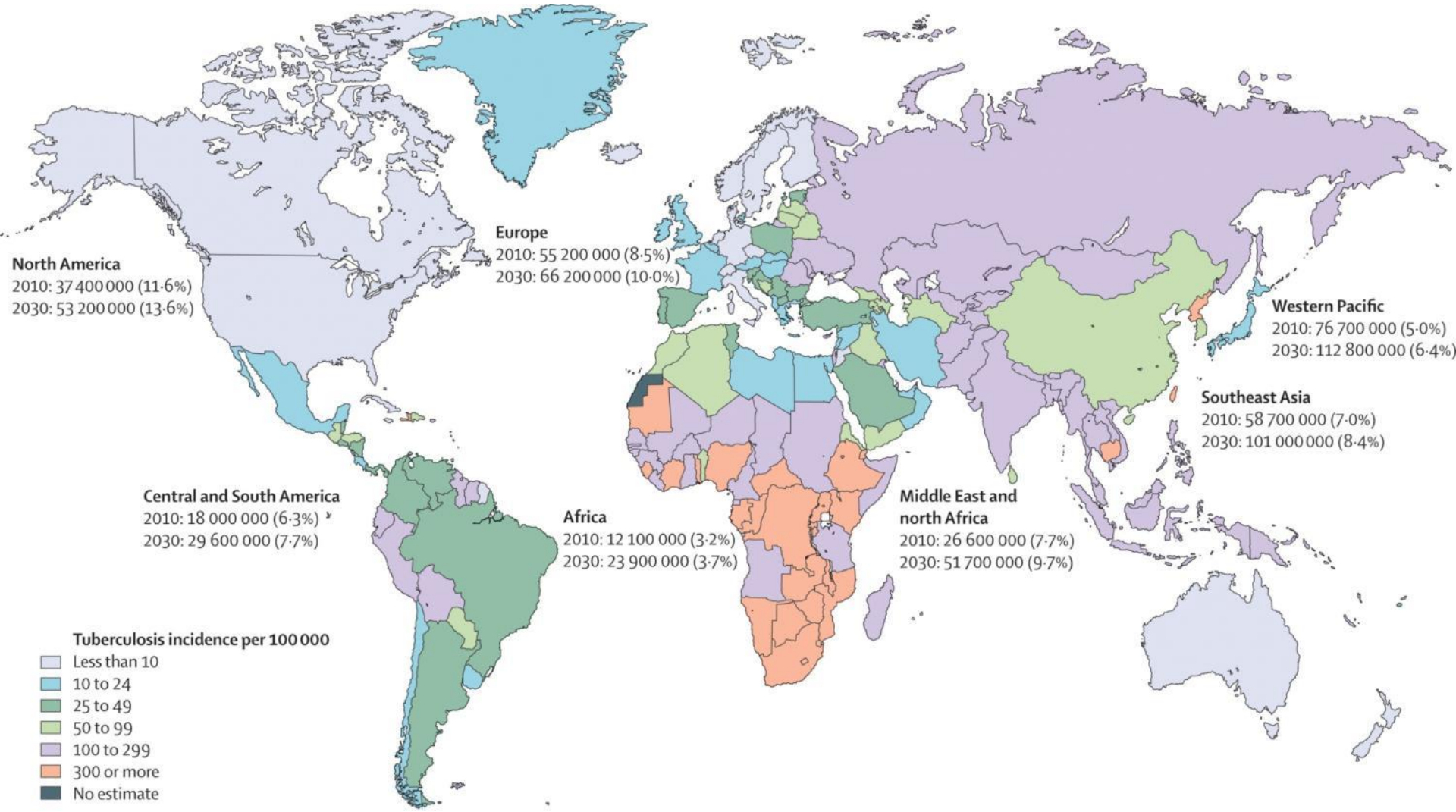
Martinson et al., CROI 2013

Estimated HIV prevalence among new TB cases, 2012



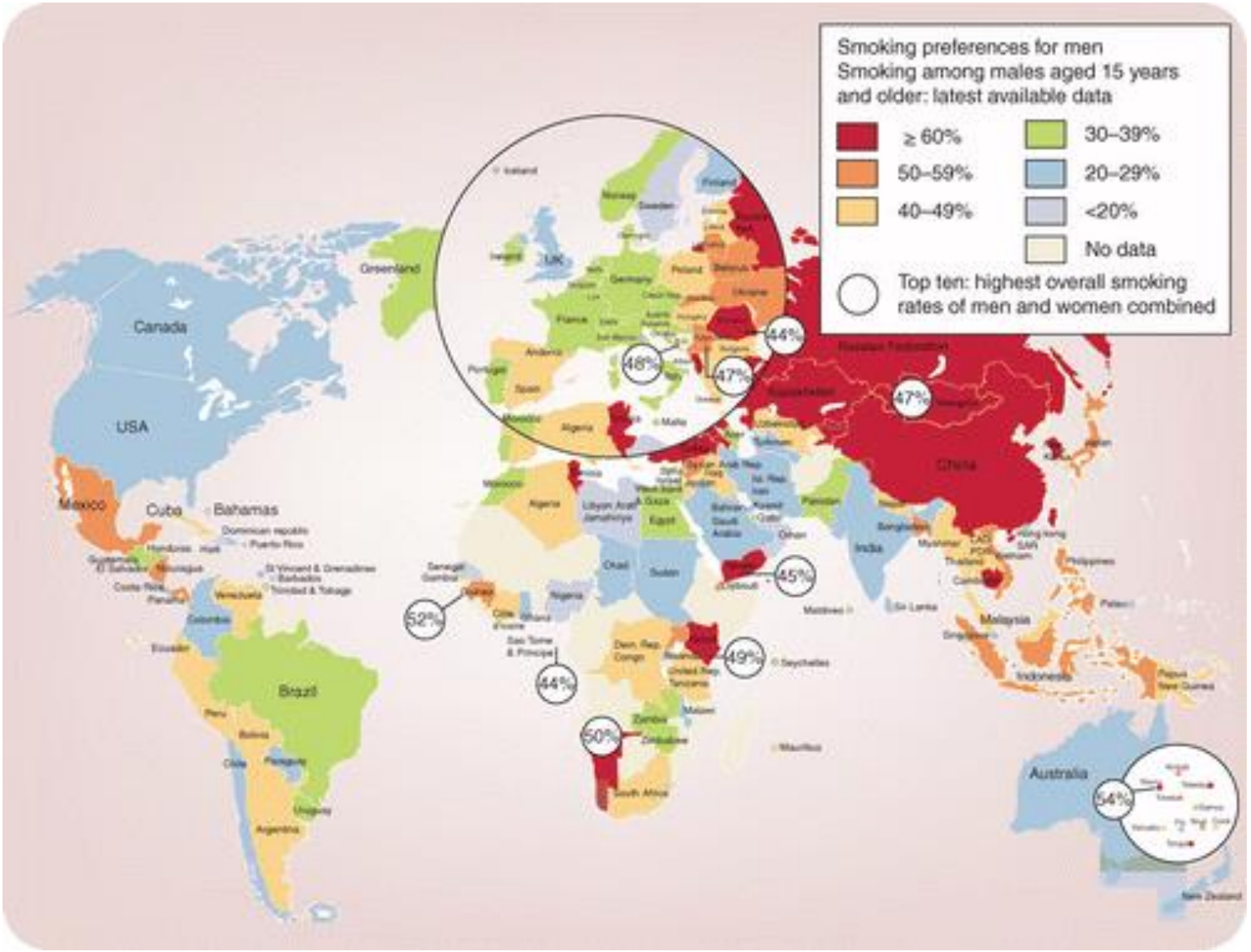
WHO Global Tuberculosis Report 2013

TB Incidence and Prevalence of Diabetes, 2010 and 2030



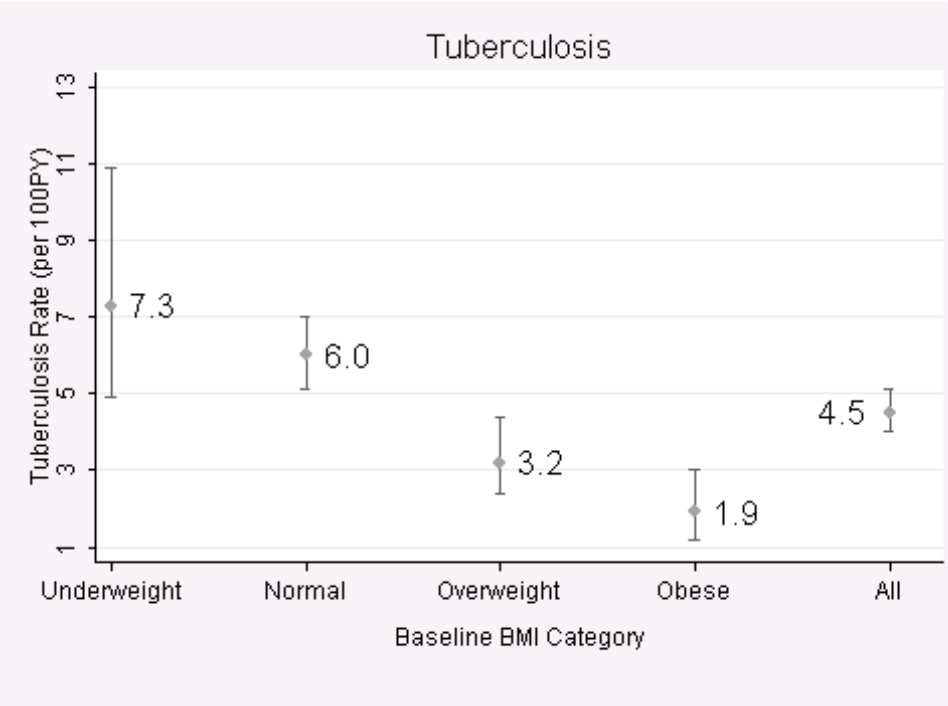
Dooley and Chaisson, Lancet Infect Dis, 2009; 9: 737–46

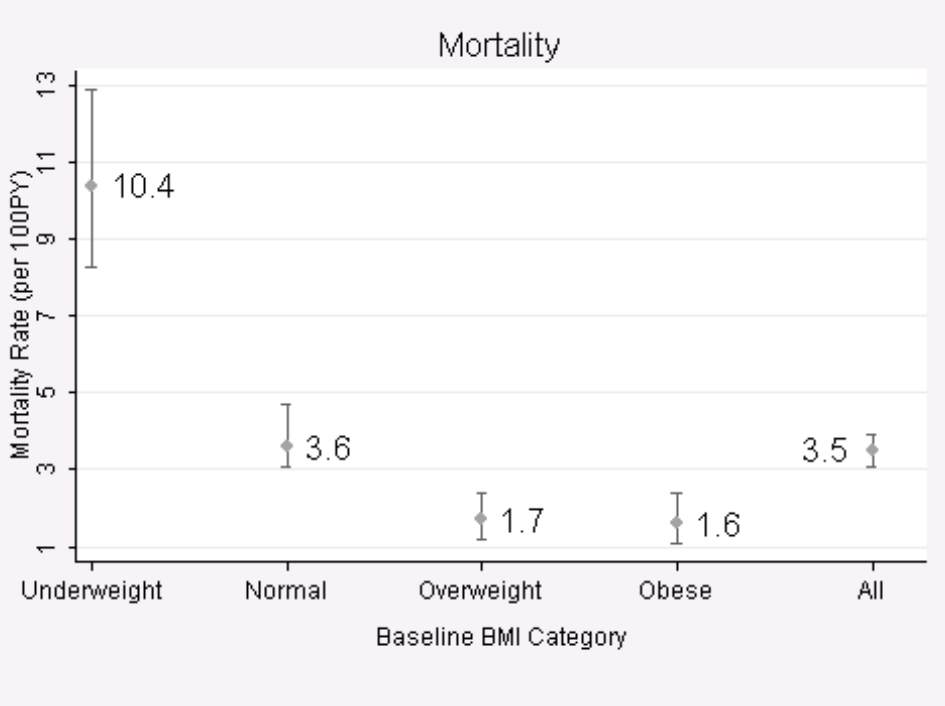
Global Prevalence of Tobacco Smoking by Men



From: Mackay J, Ericksen M. The tobacco atlas. WHO, Geneva, Switzerland (2002).

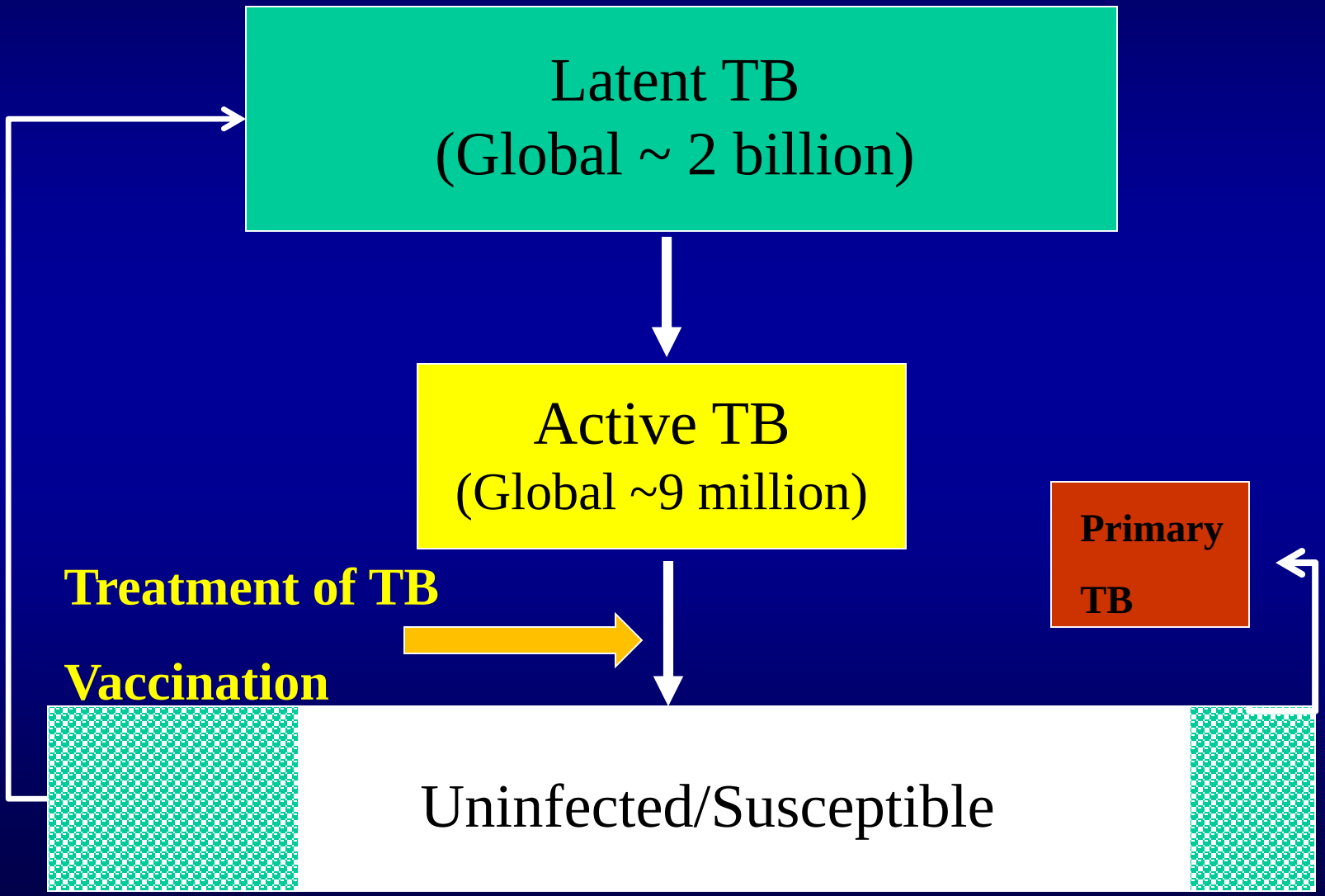
Body Mass Index with Risk of Tuberculosis and Death in HIV+ Patients in Soweto, South Africa



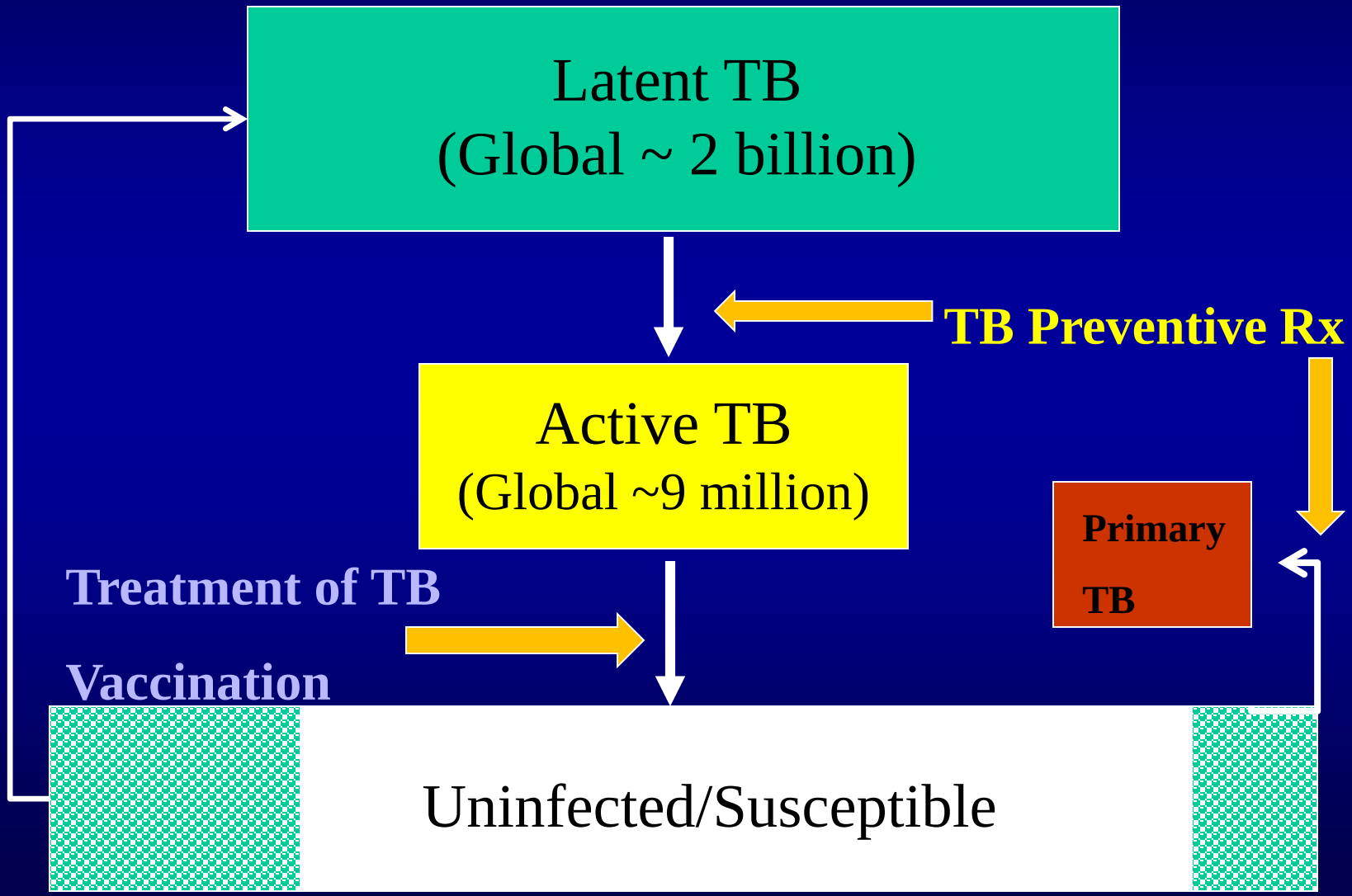


Hanrahan et al., AIDS 2010

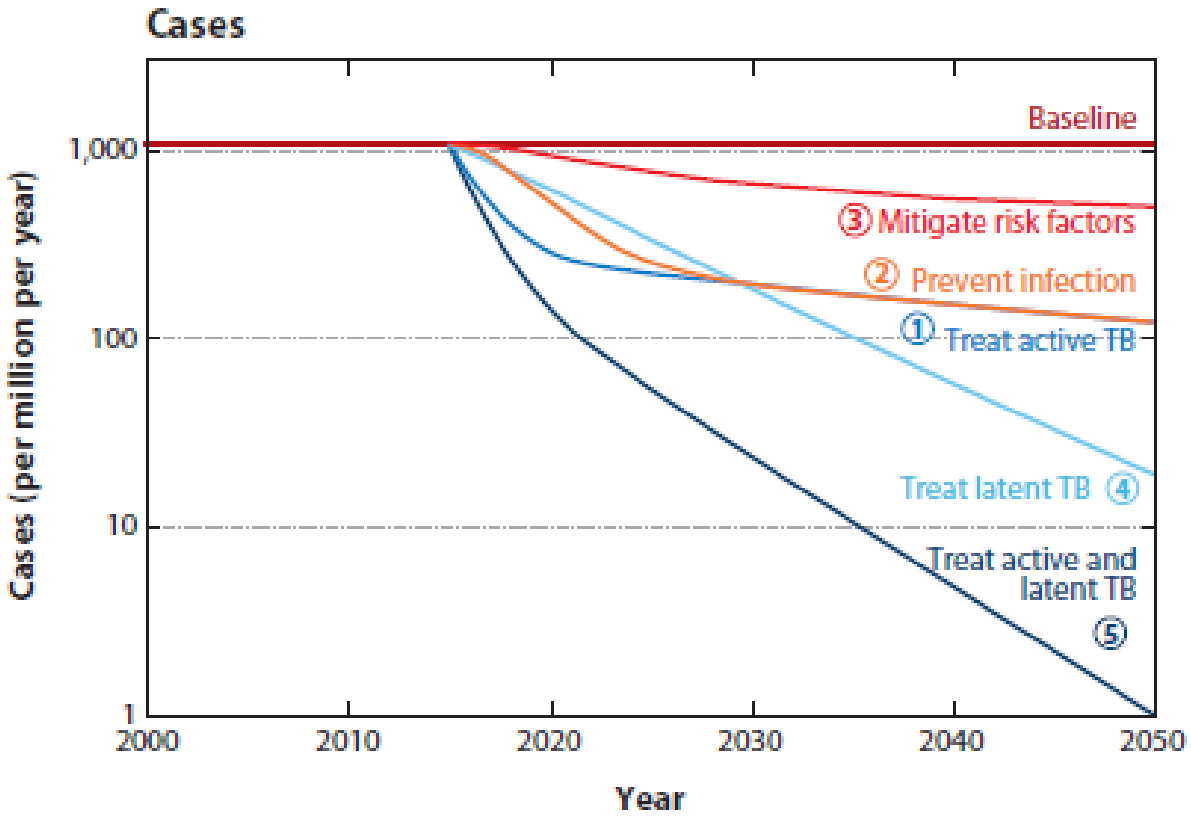
Population-level Control Strategies for TB



Population-level Control Strategies for TB



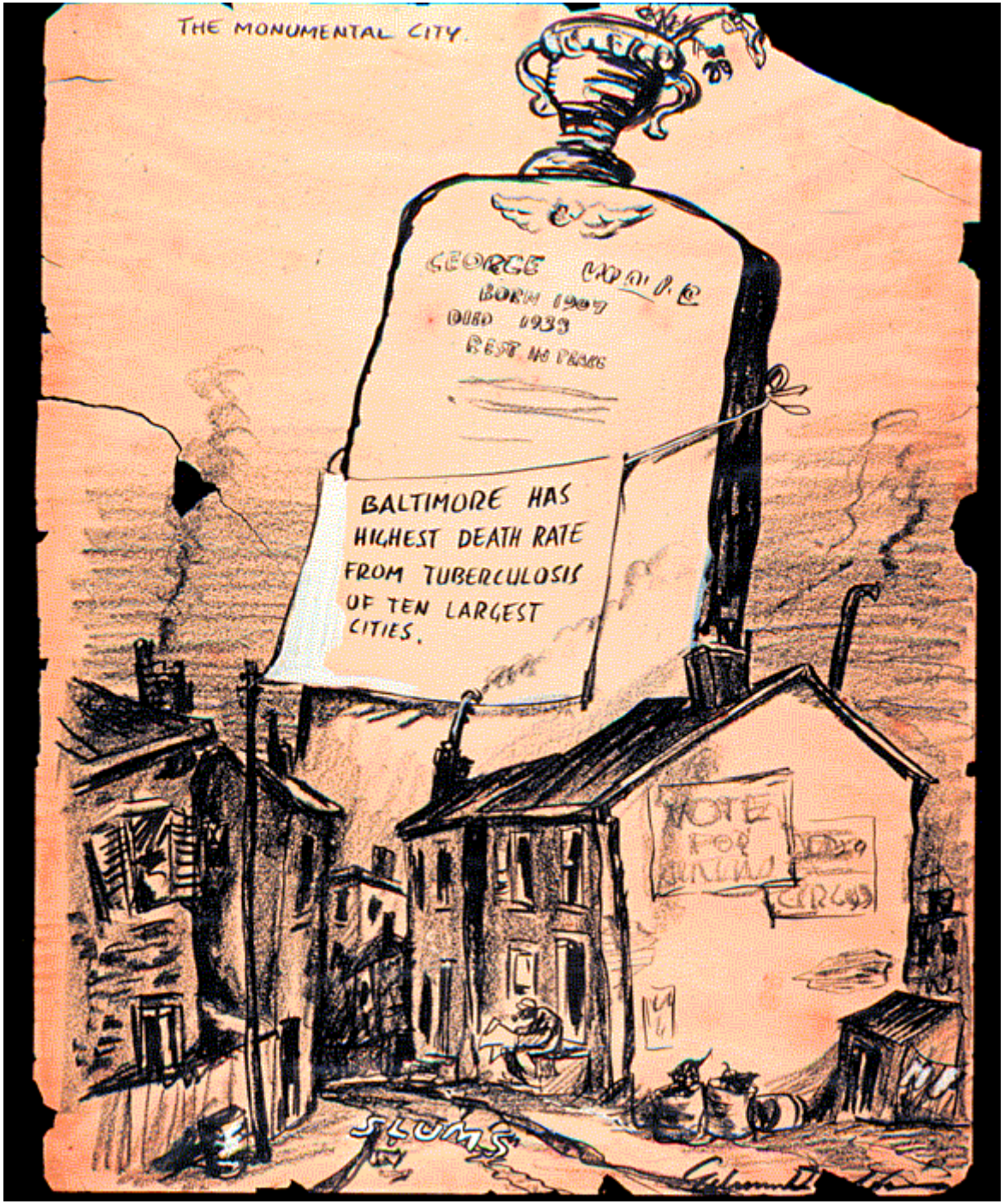
Modeled approaches to reaching TB elimination



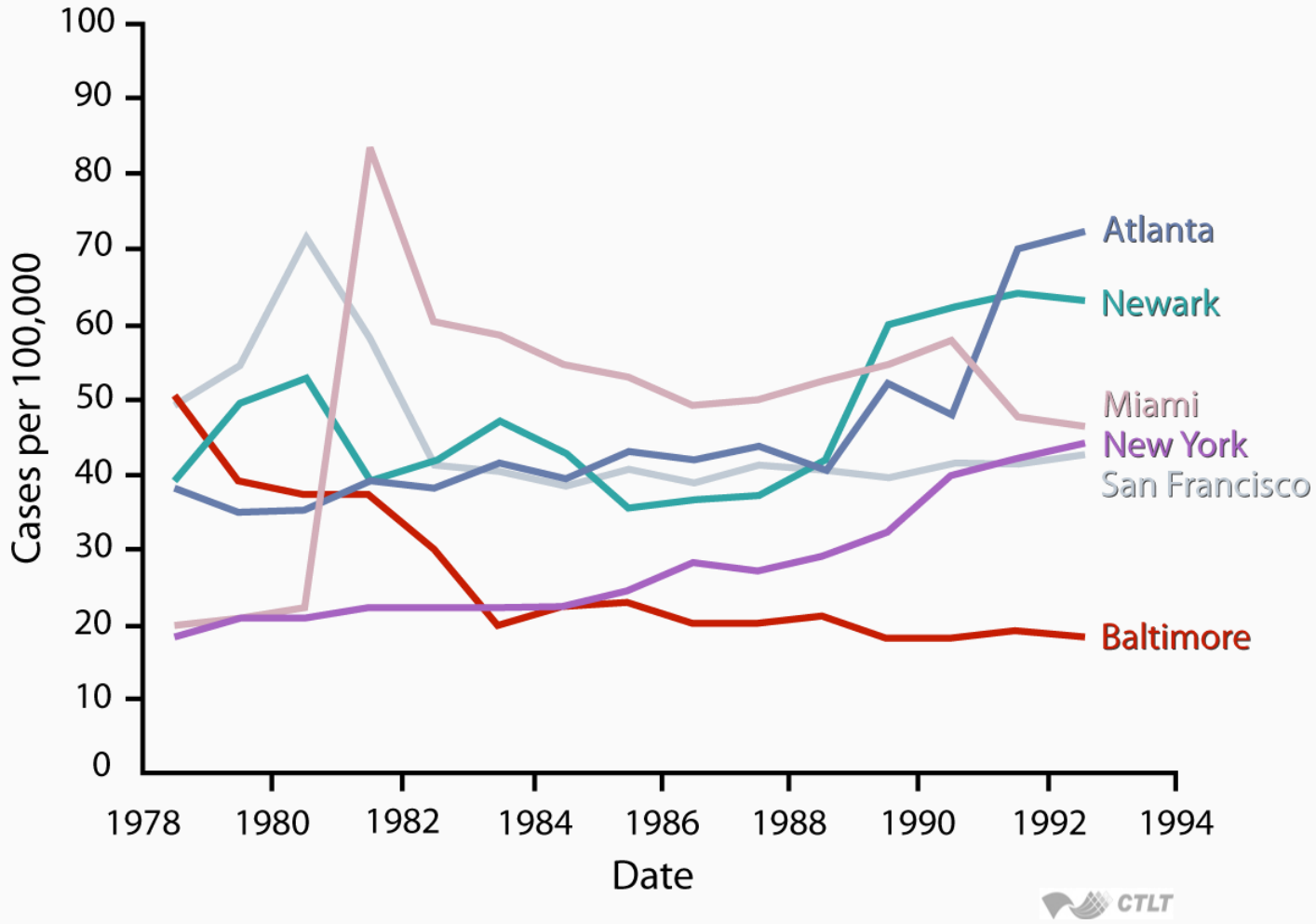
Dye, et al., Ann Rev Publ Health 2013

Control of TB: Historical Precedents

- Remembering how it was done!


THE MONUMENTAL CITY.
GEORGE
BORN 1907
DIED 1939
BALTIMORE HAS HIGHEST DEATH RATE FROM TUBERCULOSIS OF TEN LARGEST CITIES.
VOTE FOR
SLUMS

Impact of DOT and Rigorous TB Contorl in Baltimore
TB Rates: Six US Cities with Highest TB Incidence, 1978-92

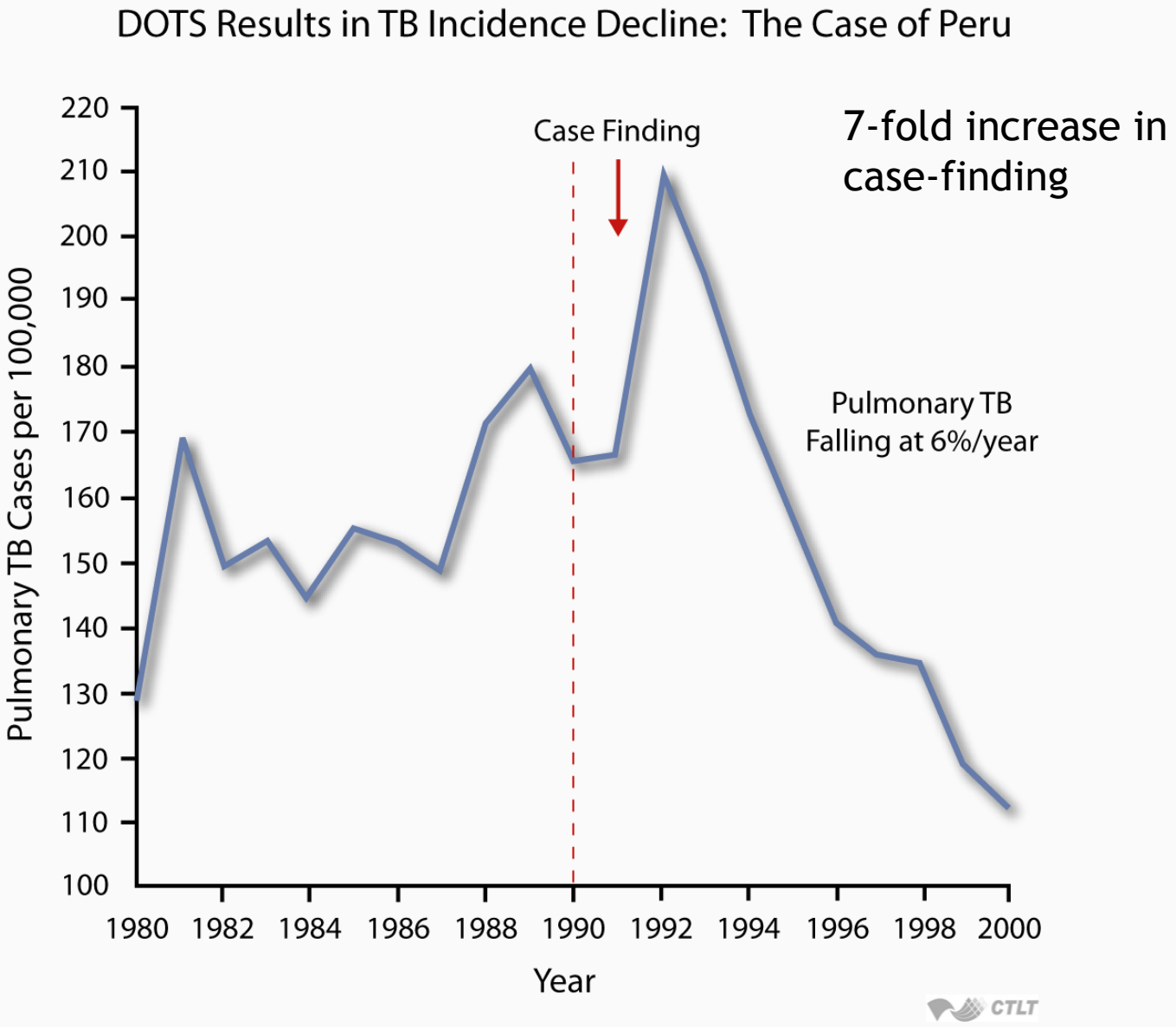


Chaulk PC, Moore-Rice K, Rizzo T, Chaisson RE, JAMA 1995, 274:945-951

Keys to success in reducing TB in Baltimore

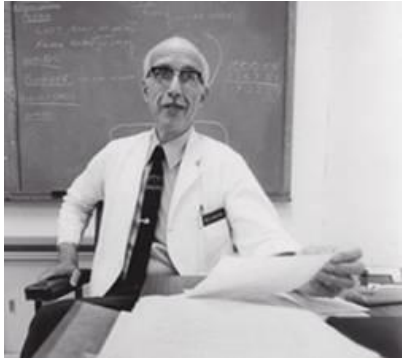
- Essentially complete case-finding
- Community-based directly observed therapy
- High rates of contact evaluation
- High rates of completion of IPT for contacts
- Outreach program to drug treatment centers and injection drug users
- 20 years later, Baltimore's rate = national rate (~4-5 cases/100,000), 90% reduction
  - 80+% in foreign-born individuals

DOTS Results in TB Incidence Decline



Adapted from Suarez et al., J Infect Dis. 2001; 184:473-8.

George W. Comstock and the Conquest of Tuberculosis in Alaskan Eskimos

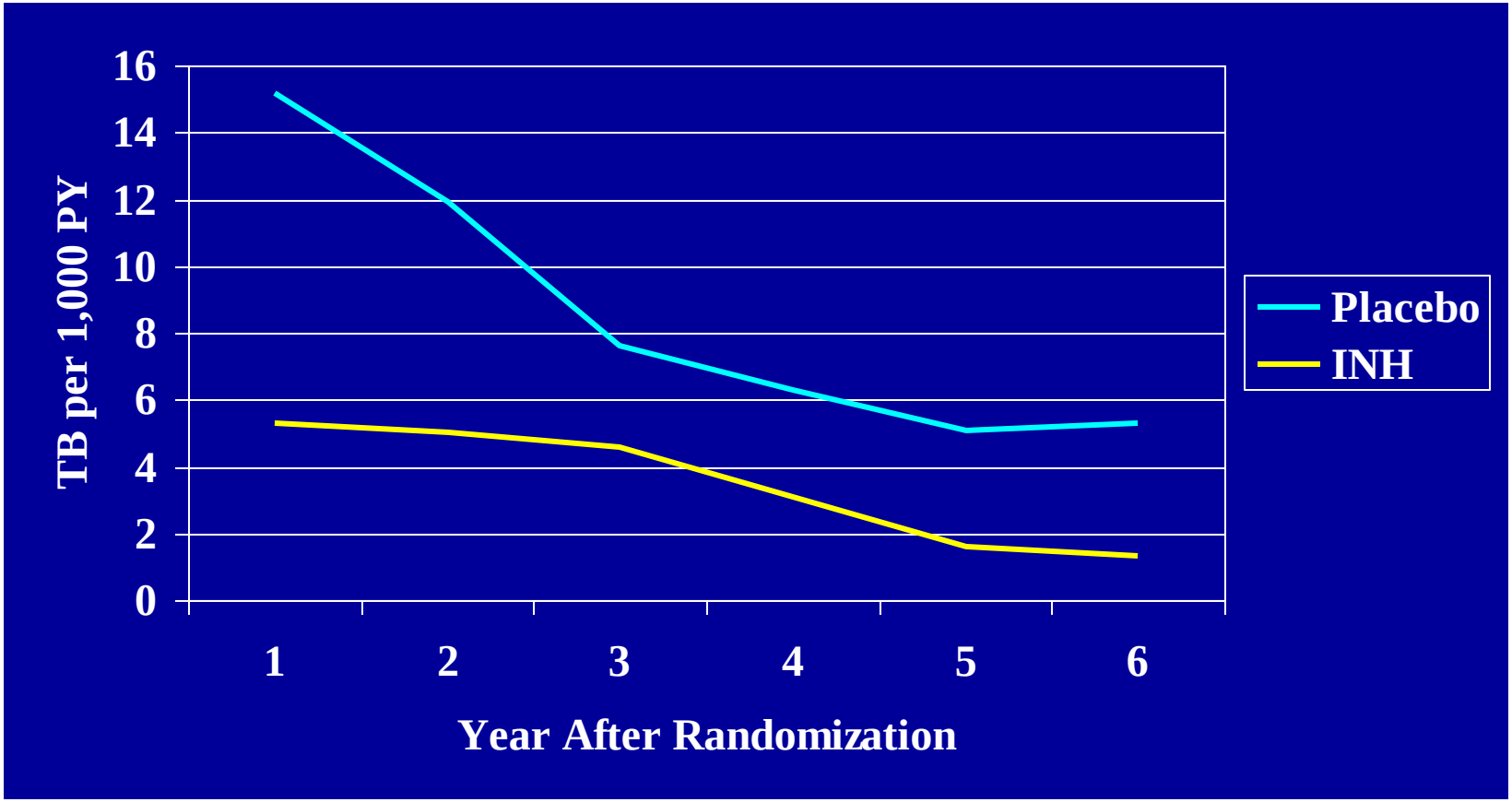


INH Preventive Therapy in an Undeveloped Area: The Bethel Study

- the Bethel [trial] was designed to test the prophylactic usefulness of isoniazid among entire communities in an undeveloped area with a serious tuberculosis problem."
- 28 villages, ~7000 residents
- Pertinent features of the Bethel area in 1957:
  - High rate of poverty
  - 2% prevalence of active TB
  - Annual risk of TB infection ~8 percent
  - Average household size 6, 2/3rd of homes 1 room
  - "a climate that discourages ventilation"

GW Comstock, Isoniazid in an Undeveloped Area. Am Rev Respir Dis 1962;86:810

TB Rates in the 6 Years After Treatment with INH or Placebo in the Bethel Trial

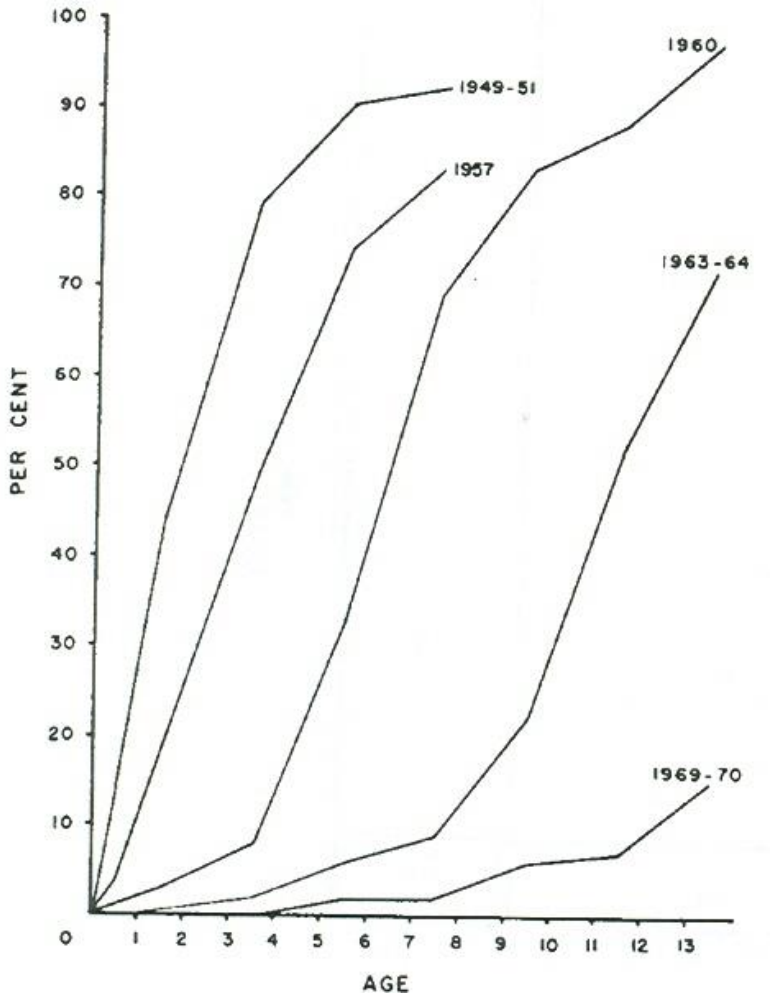


Cumulative reduction 5.1% → 2.1% = 60%

GW Comstock, Ferebee SH, Hammes LM. Am Rev Respir Dis 1967;95:935-43.

Tuberculosis in Alaska, 1970: The Continued Decline of the Tuberculosis Epidemic

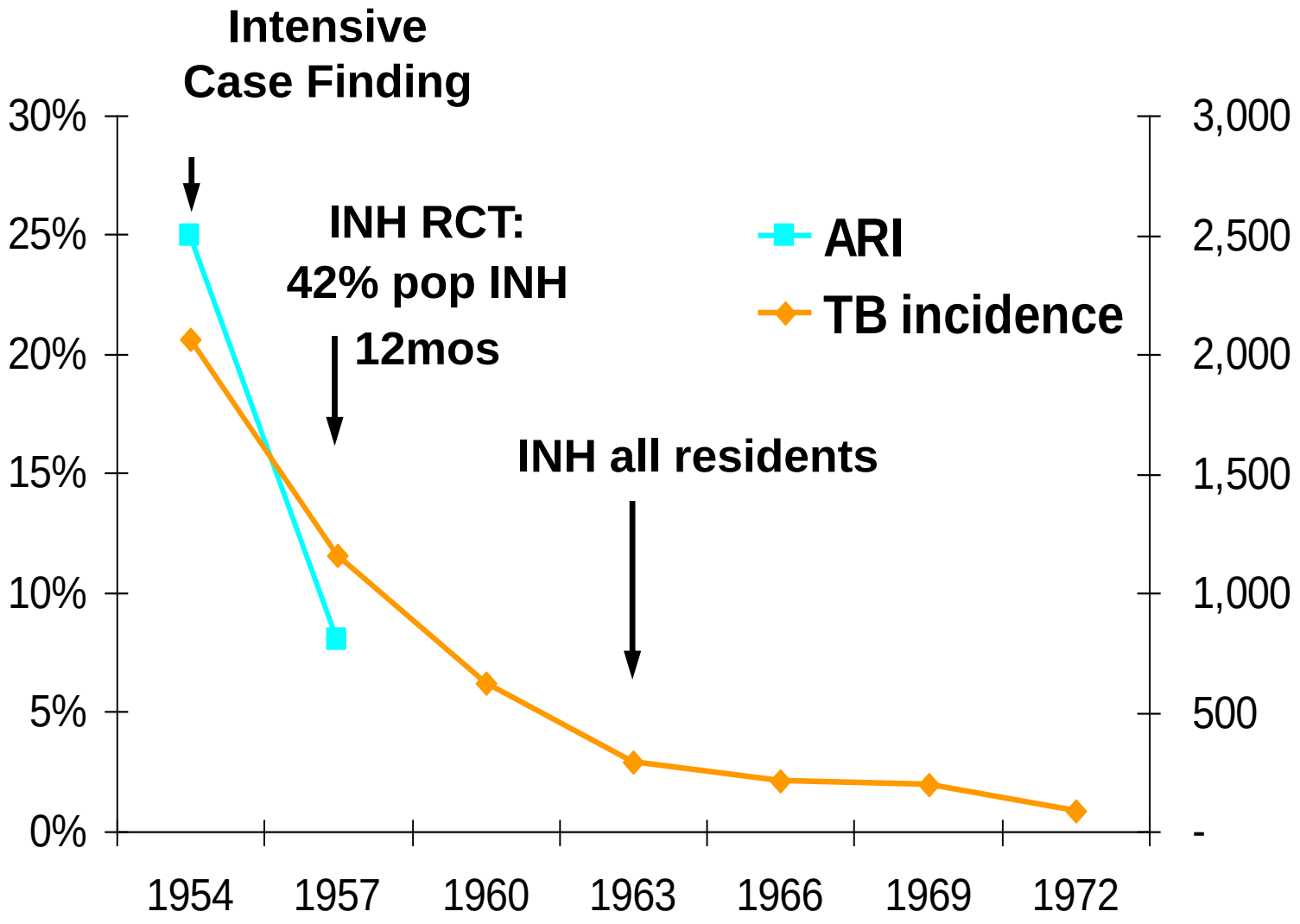
Prevalence of Positive Skin Test Reactions in Children, 1949-1970



Kaplan GJ, Fraser RI, Comstock GW. ARRD 1972,105:920

Interventions and impact: Bethel 1950s & 60s

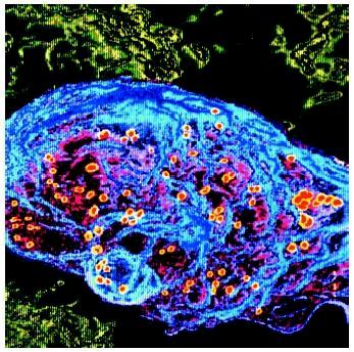
Annual Risk of Infection (%) and incidence rates per 100,000

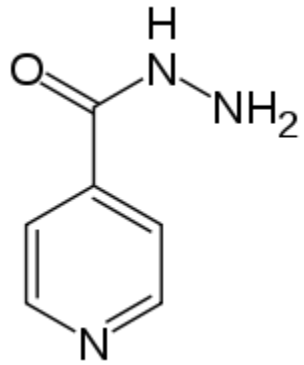


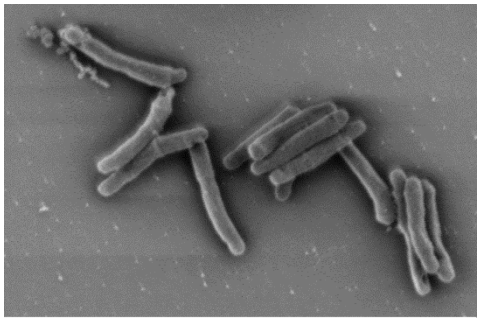
A Platform for Controlling Global Tuberculosis

- **FIND** the TB that is there
  - Passive case detection is not sufficient
  - Intensified (active case finding essential)
  - Improved diagnostic technologies
- **TREAT** the TB that is found
  - Treatment success is unacceptably low
  - Treatment for M/XDR is abysmal
  - New drugs and treatment strategies urgently needed
- **PREVENT** the TB that hasn't occurred yet
  - Preventive therapy essential for high risk populations
  - Infection (transmission) control critical
  - Control susceptibility (antiretrovirals, diabetes control)
  - New vaccine

Preventive Interventions in TB







Prevent Infection

Reduce Susceptibility

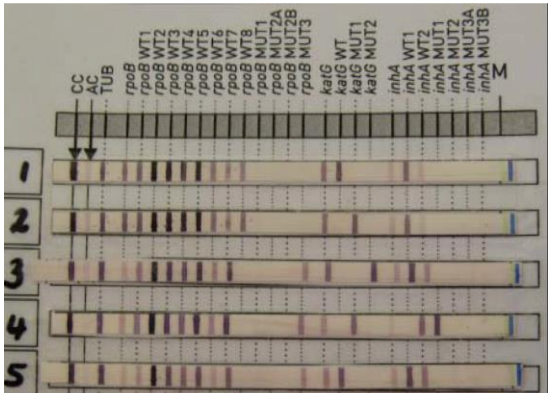
Chemoprophylaxis

TB and HIV vaccines obvious additional strategies, but not currently available

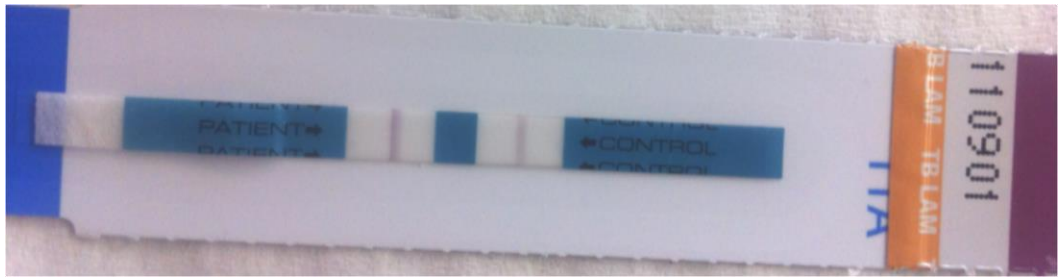
The March of Diagnostic Technology

- LED Microscopy*

- Line probe assays for MDR



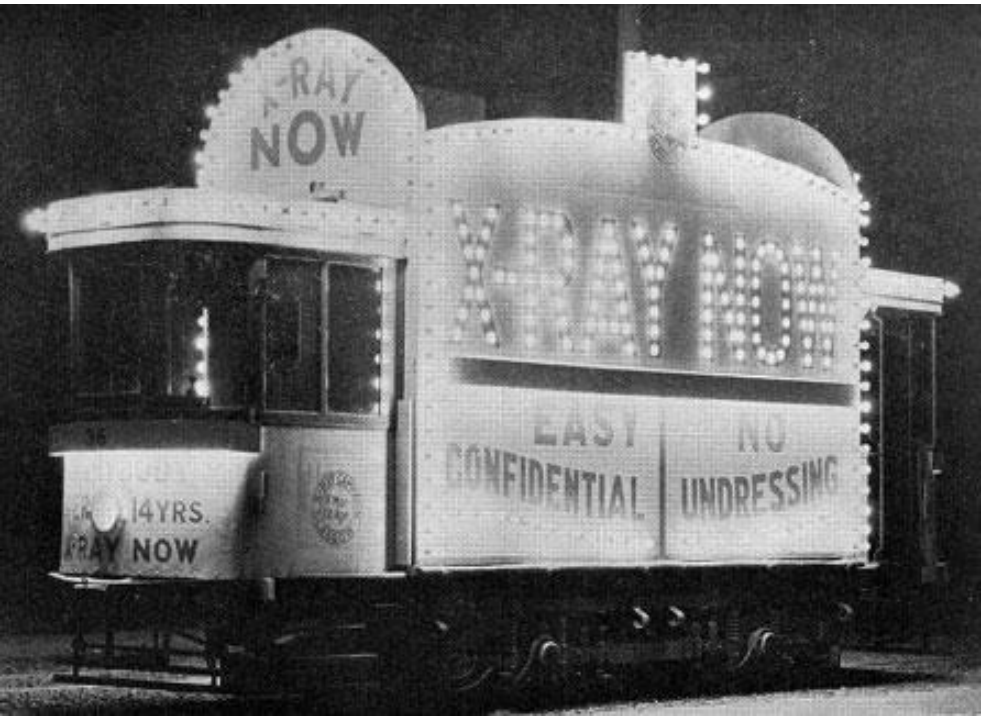
- Urine LAM dipstick**



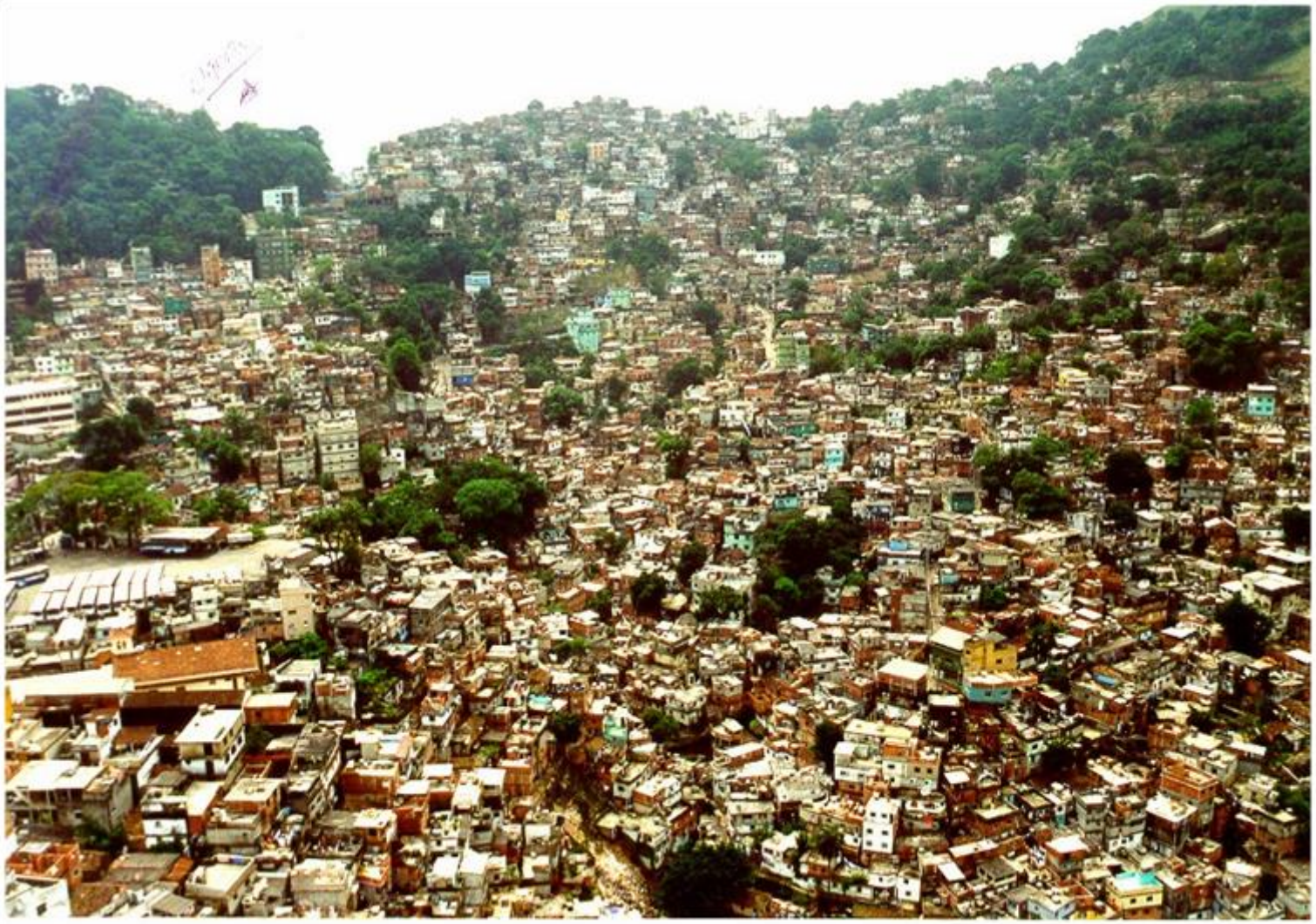
- GeneXpert TB/RIF*

*BSL-3 not required
** Point of care test

Campaigns to detect prevalent, untreated TB cases?



Rocinha *favela*, Rio de Janeiro

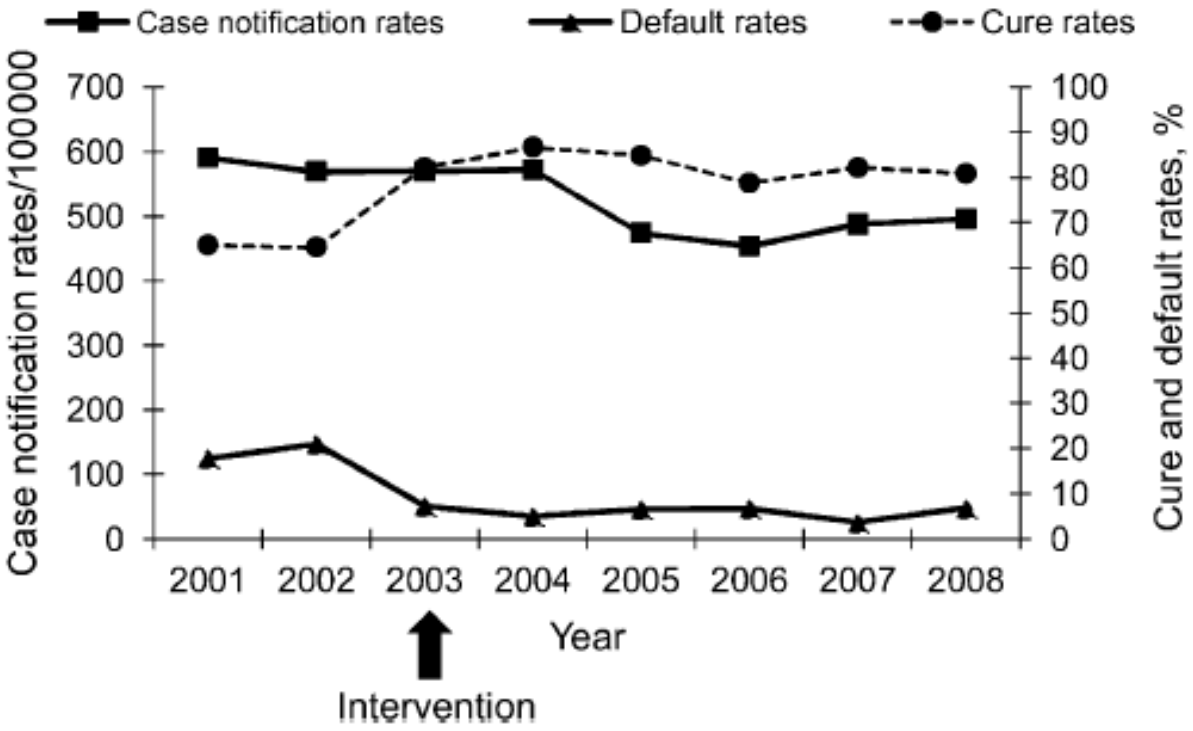


A cluster-randomized trial of door-to-door active case finding for TB in Rio de Janeiro (14 neighborhoods, 58,587 residents)

	Household Case Finding	Pamphlet Only	Rate ratio (95% CI)
TB incidence during intervention	9.34/1000 py	6.04/1000 py	1.55 (1.10, 1.99)

Miller et al., IJTLD 2010

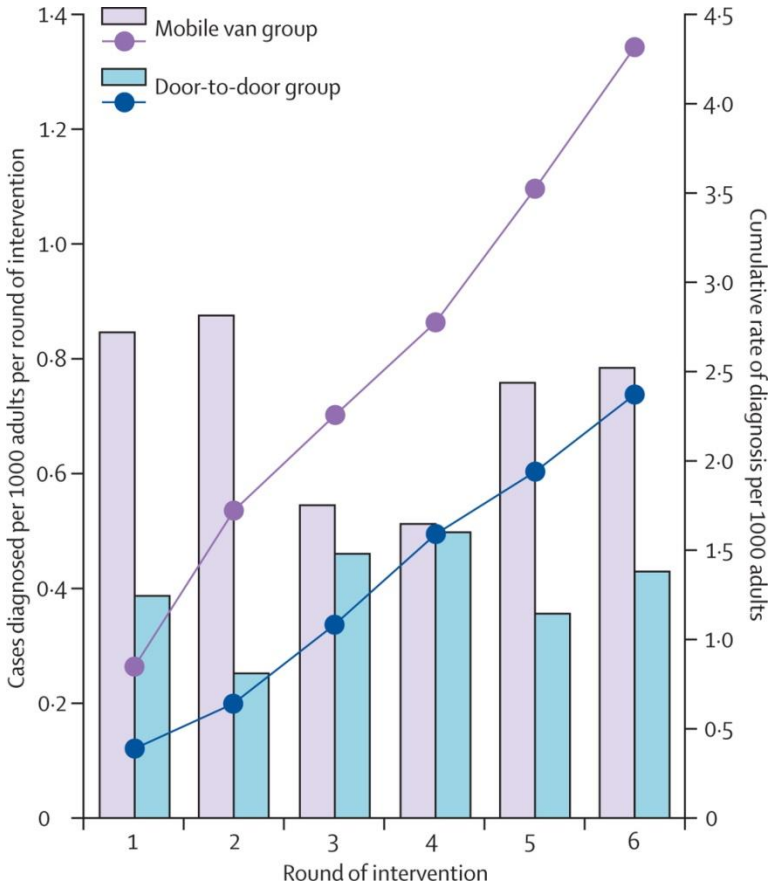
TB in Rocinha before and after intervention – 16% decline in incidence



Soares et al., Int J TB Lung Dis, 2013, 17:1581-6.

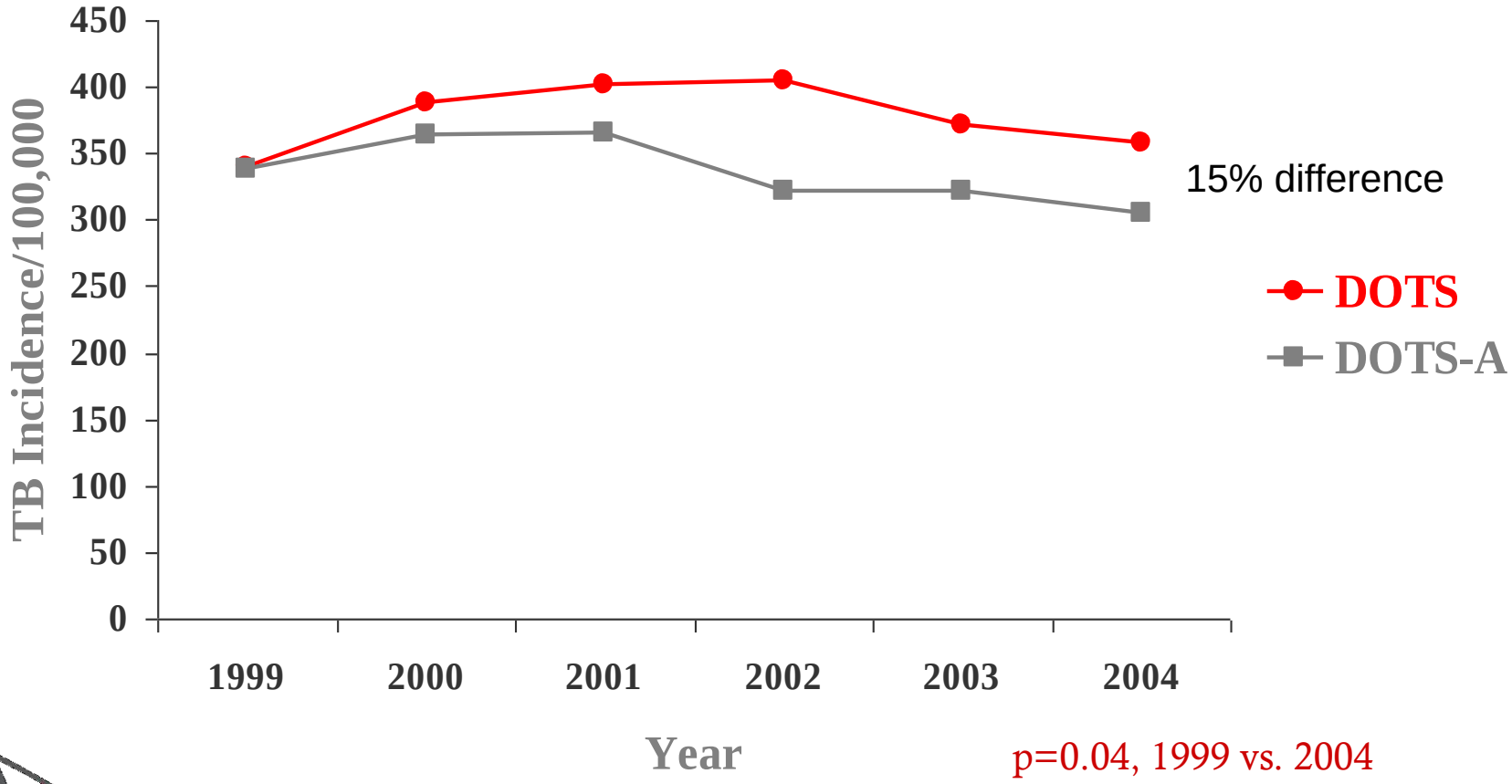
DETECTB Community-Based TB Case Finding in Harare, Zimbabwe

- Multiple rounds of ACF in community
  - Door to door vs mobile vans
- Findings after 6 rounds:
  - 59% reduction in HIV- TB prevalence
  - 22% reduction in HIV+ TB prevalence



Corbett et al. Lancet 2010

Community-Randomized Trial of Household Contact Evaulation and Preventive Therapy (DOTS-A) vs DOTS in Rio de Janeiro



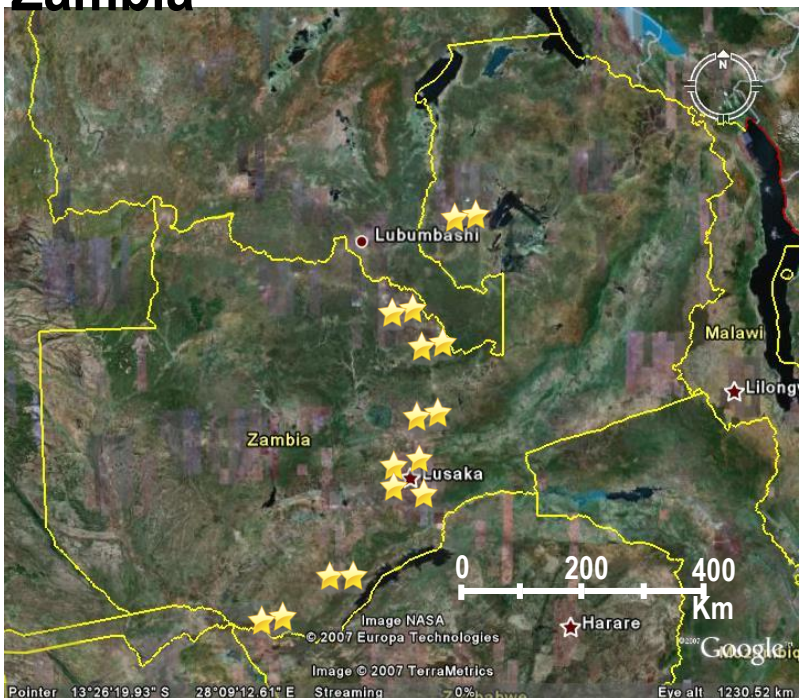
p=0.04, 1999 vs. 2004

Cavalcante et al., Int J TB Lung Dis 2010:14:203-9

Cluster-randomized trial of TB control interventions

Western

Zambia



TB/HIV at the clinic: 257,698

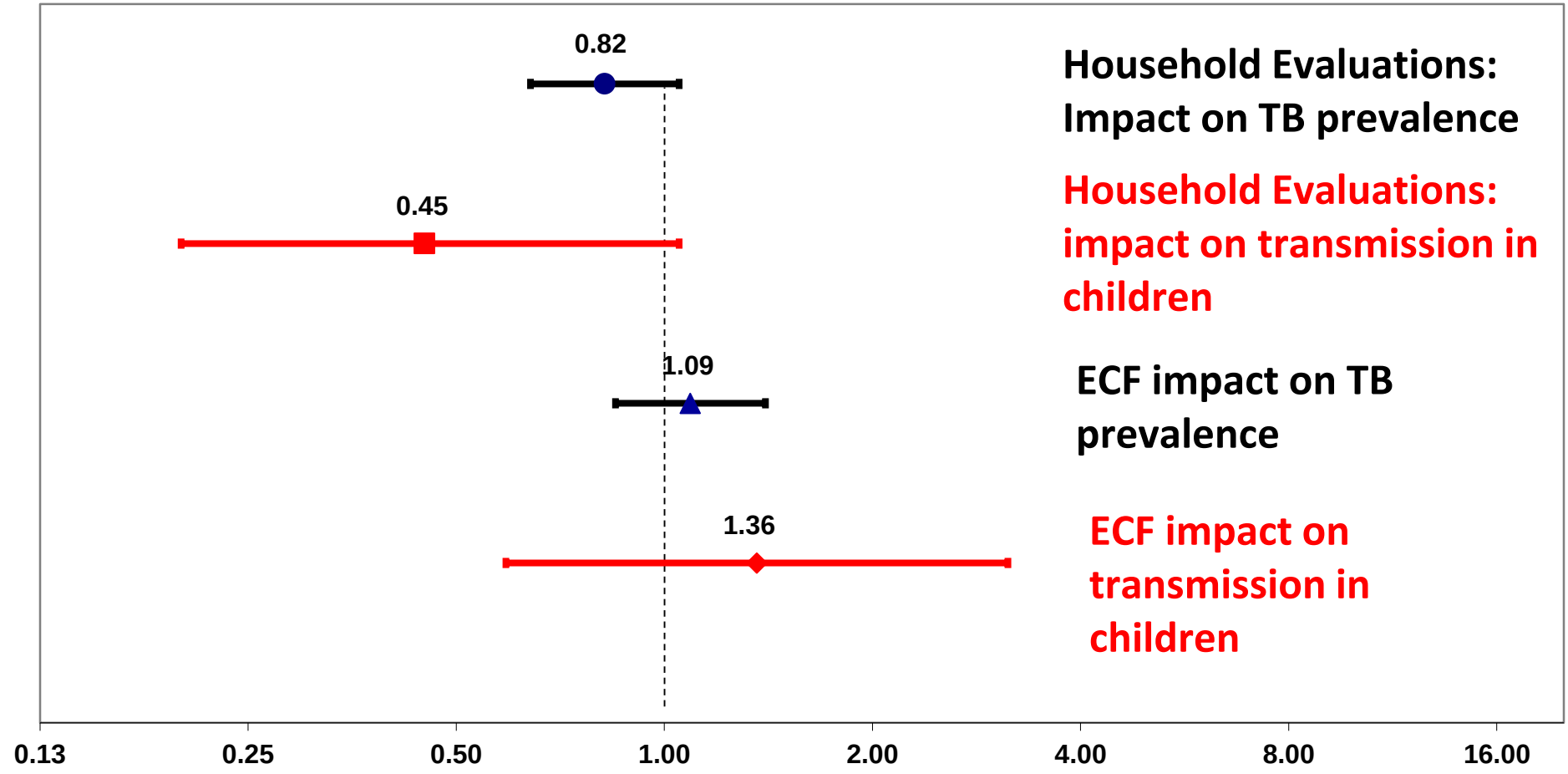
Enhanced Case Finding: 148,090

Household: 257,729

ECF & Household: 299,138

H. Ayles, et al., Lancet, 2013

Impact of Household Contact Evaluations for New TB Patients or Community Active TB Case (ECF) Finding in High Burden Areas

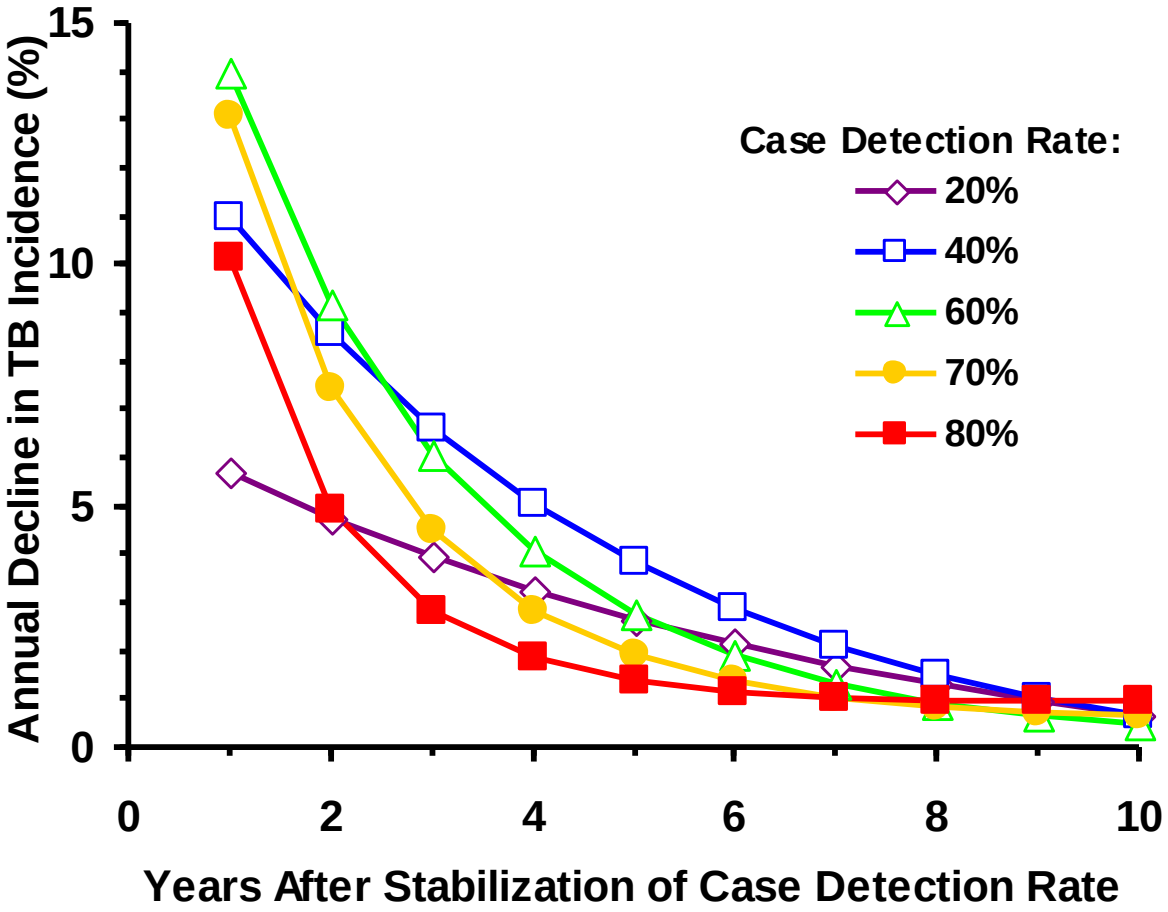


Risk ratios (for prevalence) and Rate ratios (for transmission)

ZAMSTAR

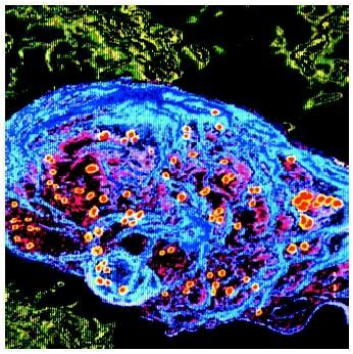
H. Ayles, et al., Lancet, 2013

Impact of Improving Case Finding and Treatment on Tuberculosis Control: A Mathematical Model



Dowdy and Chaisson, Bull WHO 2009, 87:296–304

Preventive Interventions in TB
Impact of ART on TB Incidence in HIV+ People



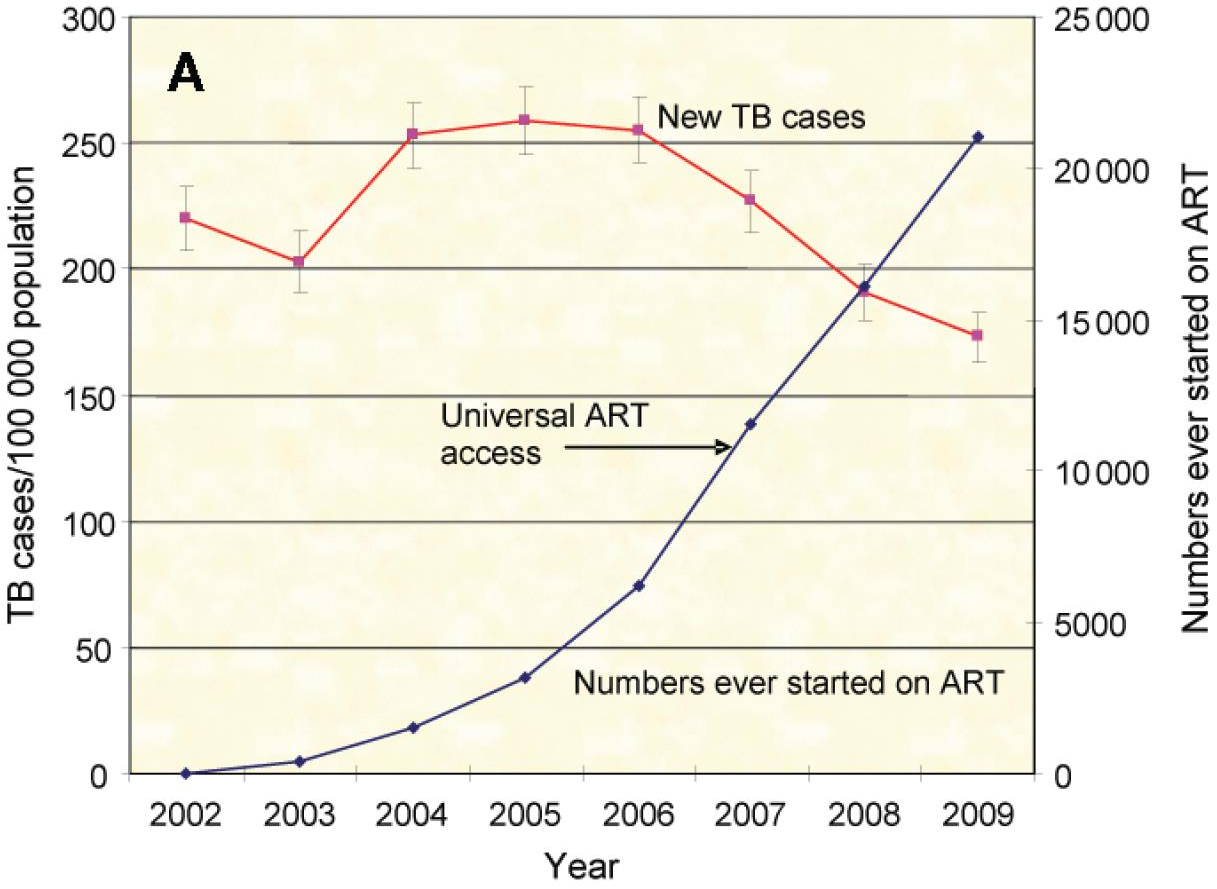
Reduce Susceptibility

	ART		Control		HR (95% CI)
	TB cases	PY at risk	TB cases	PY at risk	
All baseline CD4 counts					
Badri (2002) *	9	375.1	82	848.2	0.19 (0.09 - 0.38)
Cohen (2011) *, †	17	1661.9	33	1641.8	0.51 (0.28 - 0.91)
Golub (2007)	221	11627	155	3865	0.41 (0.31 - 0.54)
Golub (2009)	44	952	200	2815	0.36 (0.25 - 0.51)
Jerene (2006)	6	162.6	9	80.9	0.11 (0.03 - 0.48)
Lannoy (2008)	-	-	-	-	0.10 (0.02 - 0.45)
Miranda (2007)	-	-	-	-	0.20 (0.10 - 0.60)
Samandari (2011) †	-	-	-	-	0.33 (0.11 - 0.94)
Santoro-Lopes (2002)	1	-	42	-	0.19 (0.03 - 1.09)
Severe (2010) †	18	-	36	-	0.50 (0.28 - 0.83)
Zhou (2009)	57	5186	40	985	0.40 (0.26 - 0.61)
All studies					**0.35 (0.28 - 0.44)**

Effect: Z = 9.19, p < 0.001; Heterogeneity: I^2 = 31% (22% - 44%) , p = 0.151

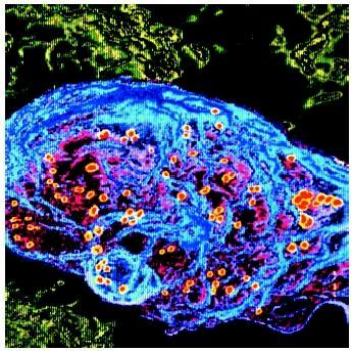
A.B Suthar, et al. PLoS Medicine, 2012

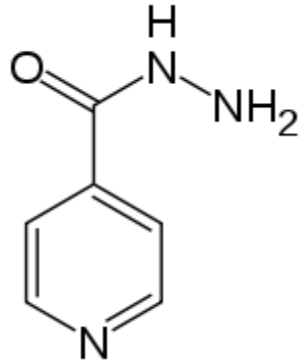
TB rates in relation to ART scale up in rural Malawi

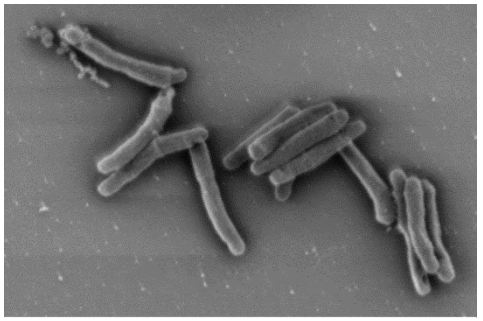


Zachariah, et al., 2011, Int J Tuberc Lung Dis

Preventive Interventions in TB







Prevent Infection

Reduce Susceptibility

Chemoprophylaxis

The THRio Study: Implementation of TB Screening and INH Preventive Therapy in HIV Clinics

	Outcome	Cases	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Intent To Treat	TB	475	0.87 (0.69-1.10)	0.24	**0.73 (0.54-0.99)**	0.04
	TB or Death	1313	0.76 (0.66-0.87)	<0.001	**0.69 (0.57-0.83)**	<0.001
Per-protocol (Stayers)	TB	399	0.43 (0.31-0.58)	<0.001	**0.42 (0.31-0.58)**	<0.001
	TB or Death	1055	0.50 (0.41-0.60)	<0.001	**0.50 (0.41-0.60)**	<0.001

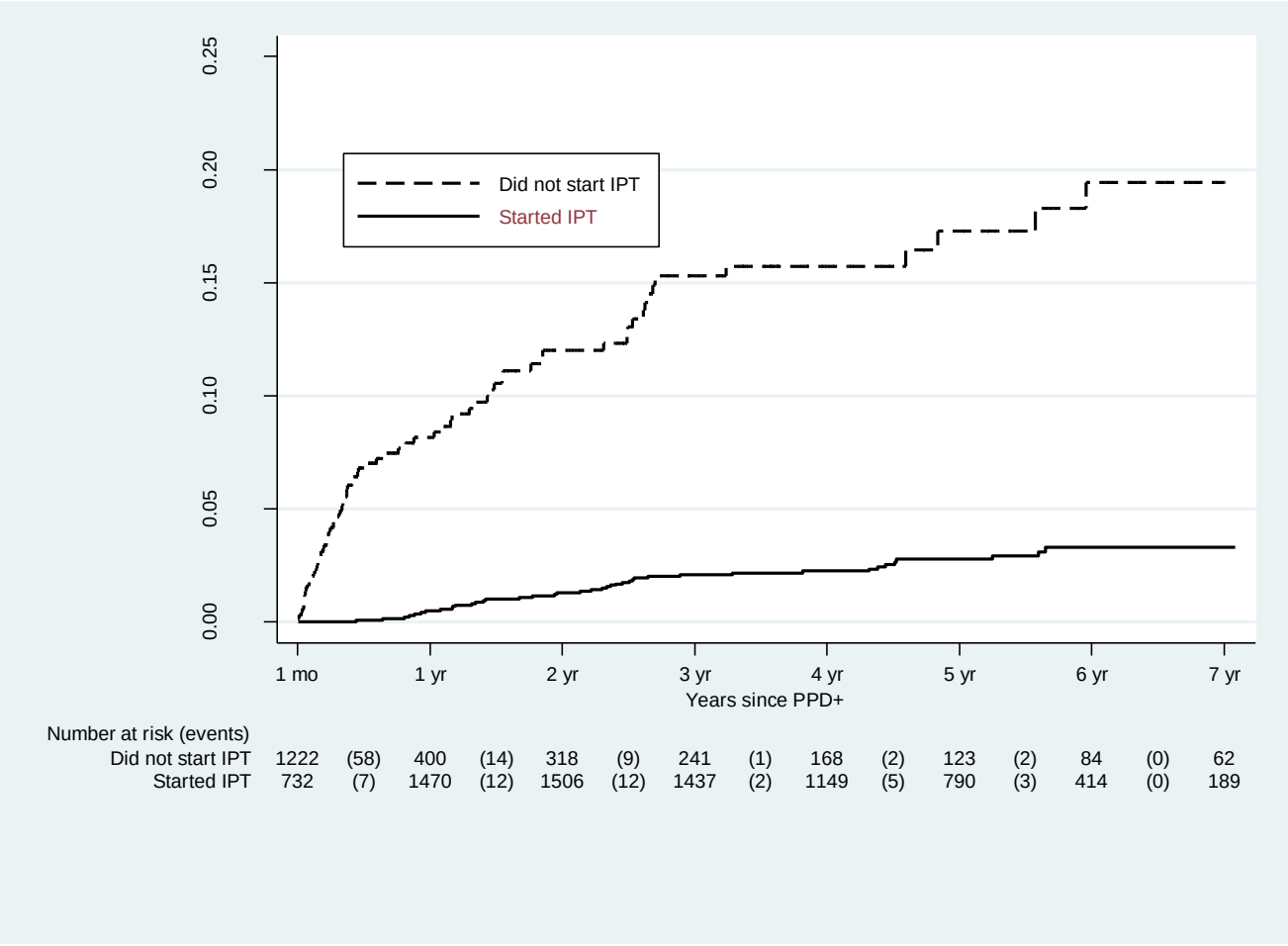
Stayers – per-protocol - Among those remaining in clinic contact
(Patients censored after one year without a clinic contact)

THRio TB/HIV NO RIO

Durovni et al., Lancet Infect Dis. 2013;10:852-8

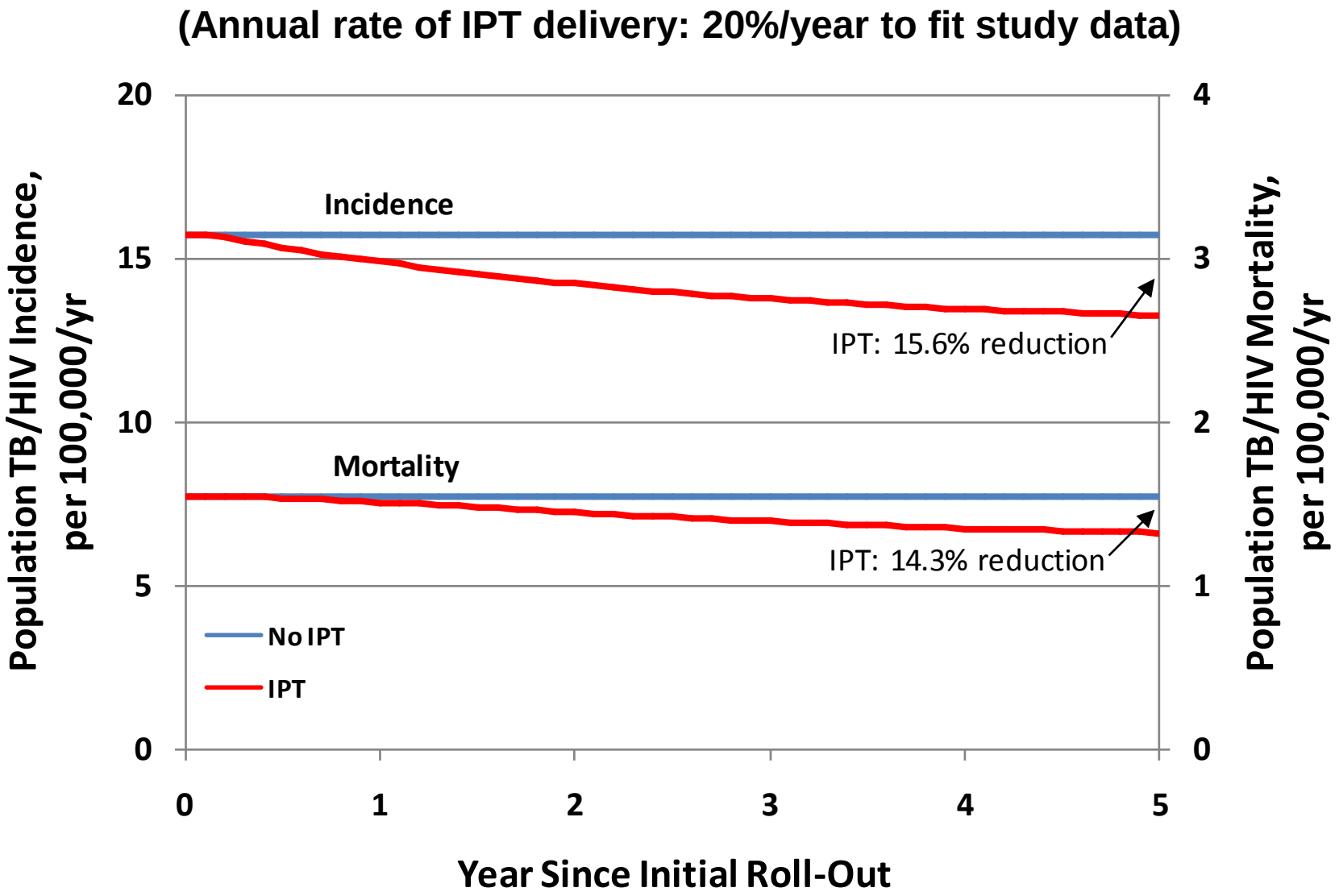
CREATE Consortium to Respond Effectively to the AIDS TB Epidemic

Long term efficacy of IPT in HIV-infected persons in a medium TB burden setting: Rio de Janeiro



(Golub, CID, 2014, In press)

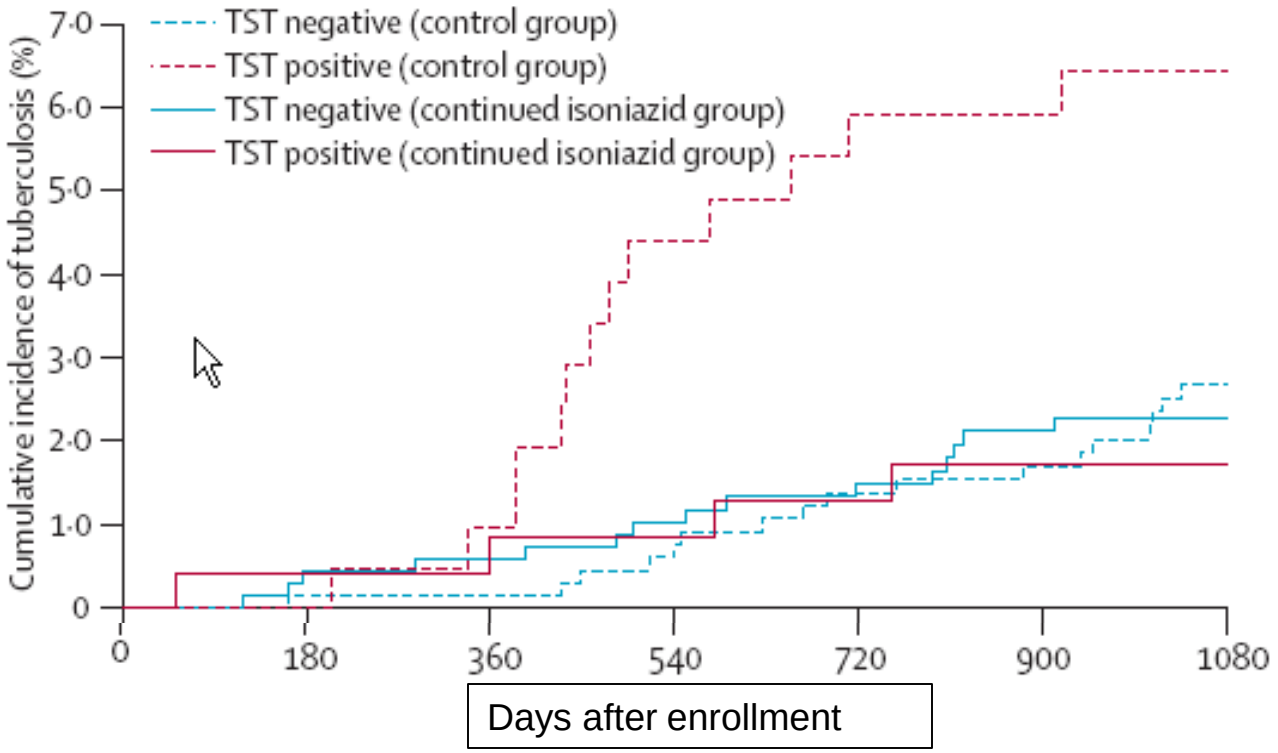
5-Year Impact of IPT for HIV+ Patients in Rio de Janeiro on Population TB Incidence



Dowdy, et al., JAIDS 2014. 66:552-8.

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Taraz Samandari, Tefera B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margarett K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H Kilmarx, Kenneth G Castro, Charles D Wells

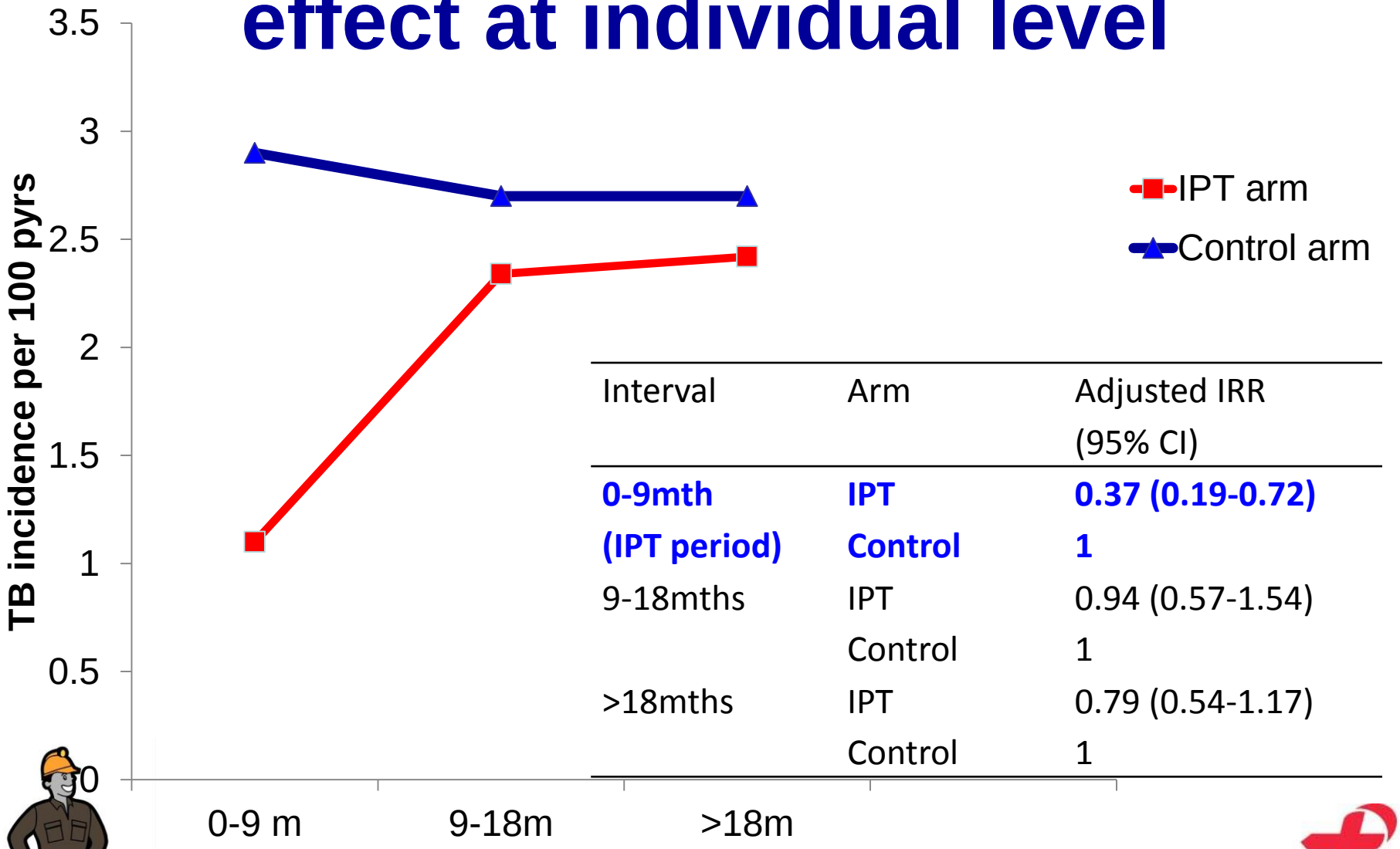


TST-positive, 6 months IPT

TST- negative, 6 months IPT
TST-negative, 36 months IPT
TST-positive, 36 months IPT

Lancet. 2011;377:1588-1598.

Thibela TB: durability of IPT effect at individual level



Interval	Arm	Adjusted IRR (95% CI)
0-9mth	**IPT**	**0.37 (0.19-0.72)**
(IPT period)	**Control**	**1**
9-18mths	IPT	0.94 (0.57-1.54)
	Control	1
>18mths	IPT	0.79 (0.54-1.17)
	Control	1

Churchyard et al., NEJM 2014

THIBELA Team up against TB

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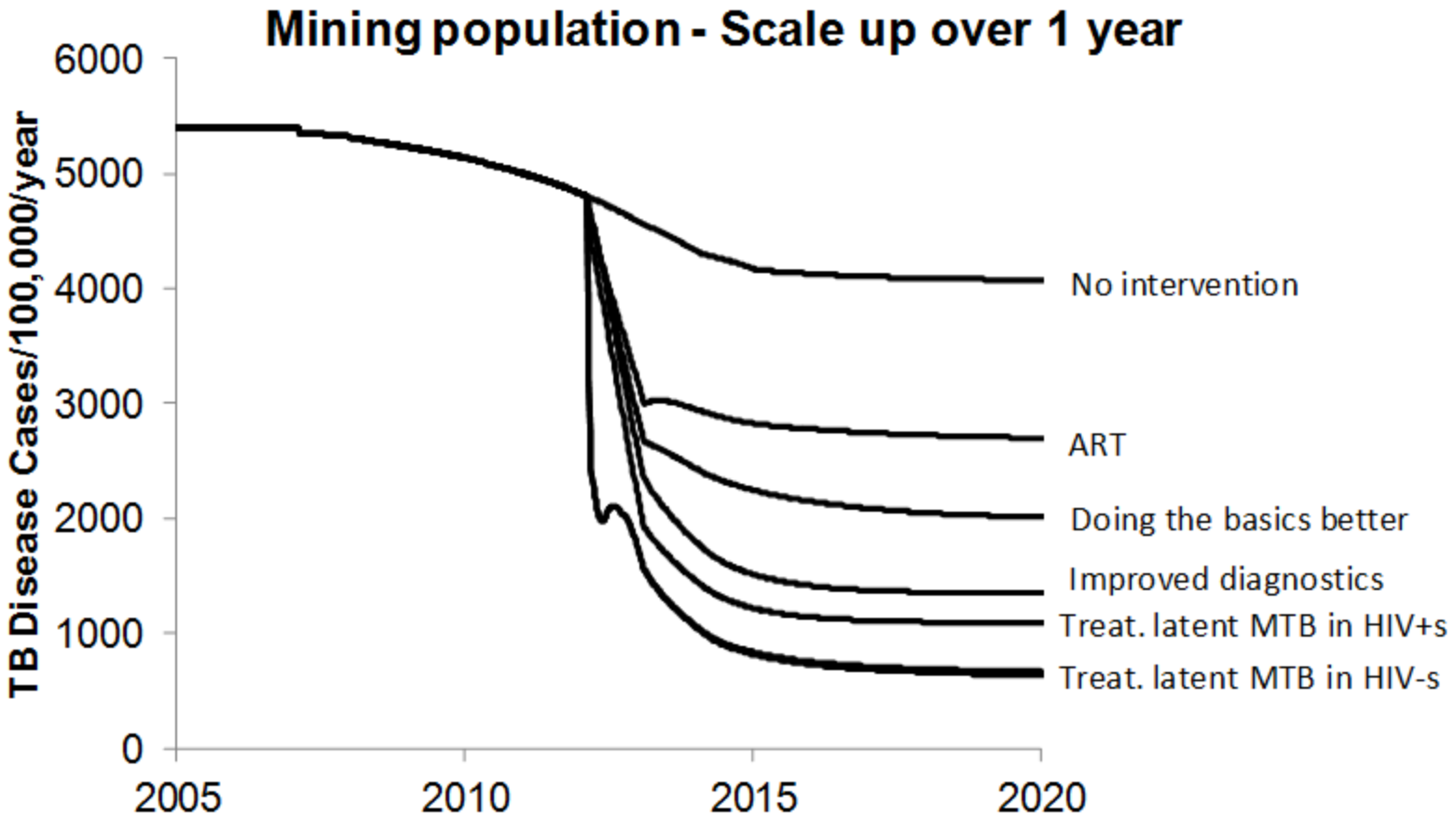
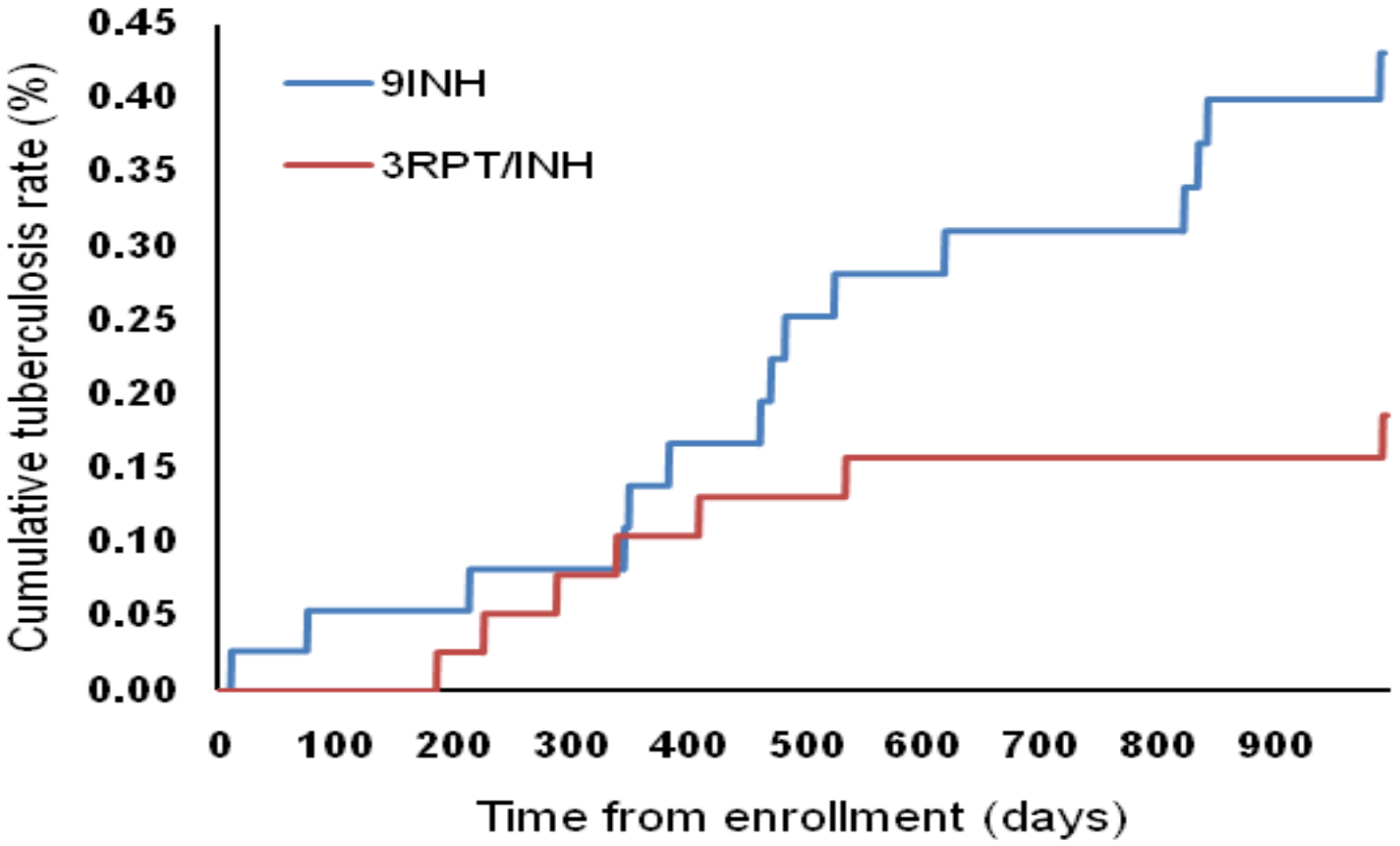
Thibela TB: what will it take to control TB in gold mines?



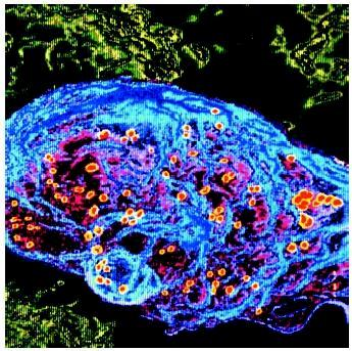
Reid, et al., Int J. Tuberc Lung Dis. 2014. In press

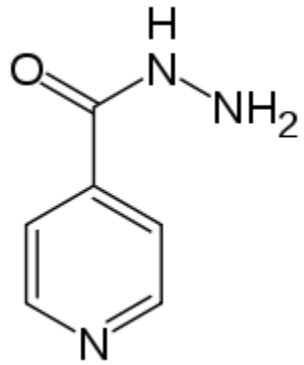
Short-course, sterilizing regimen for latent TB: Rifapentine/INH x 12 weekly doses vs INH x 9 mos. Cumulative TB Rates

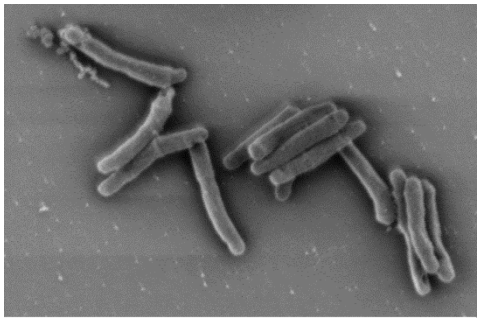


Log-rank P-value: 0.06

Preventive Interventions in TB







Prevent Infection

Reduce Susceptibility

Chemoprophylaxis

TB and HIV vaccines urgently needed

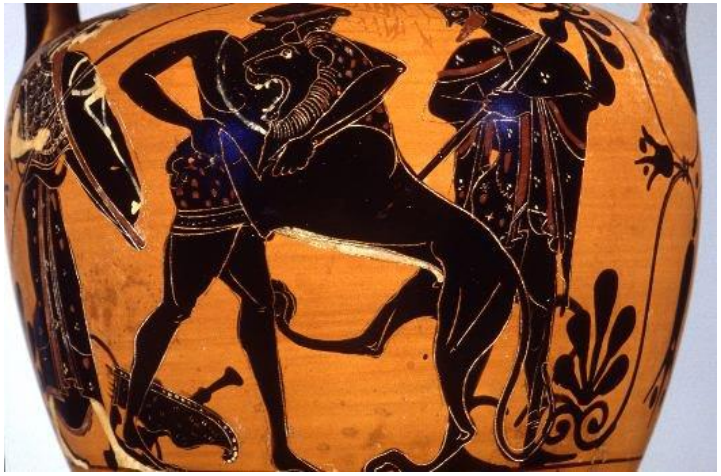
Can TB be eliminated? Probably not by 2050.

Can TB be controlled? Yes, with investment in epidemiologically sound strategies and tools.

Strategies and tools to control TB

- Improved diagnostics (↑case finding,↓transmission)
  - Better tests
  - Campaigns to find prevalent cases (e.g., contacts)
- Improved therapy (↑treatment completion)
  - Shorter duration regimens to assure adherence
  - New drugs for MDR/XDR TB
- Prevention
  - INH or novel preventive therapy
  - Reduction of susceptibility (ART, diabetes, smoking)
  - Effective vaccine
- Combination of approaches essential

Tuberculosis:
The Nemean Lion



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Fogarty Int'l Center

CDC

FDA

Bill and Melinda Gates Foundation

THE CENTER FOR TB RESEARCH JOHNS HOPKINS UNIVERSITY

TBTC TB Trials Consortium CDC

CENTER FOR AIDS RESEARCH JOHNS HOPKINS UNIVERSITY

ACTG AIDS CLINICAL TRIALS GROUP

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