

THE GLOBAL BURDEN OF DRUG-RESISTANT TUBERCULOSIS:

REALITIES AND CHALLENGES

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MOSCOW, RUSSIAN FEDERATION

NOVEMBER 14, 2011



Photo: Open Society Institute/Pep Bonet

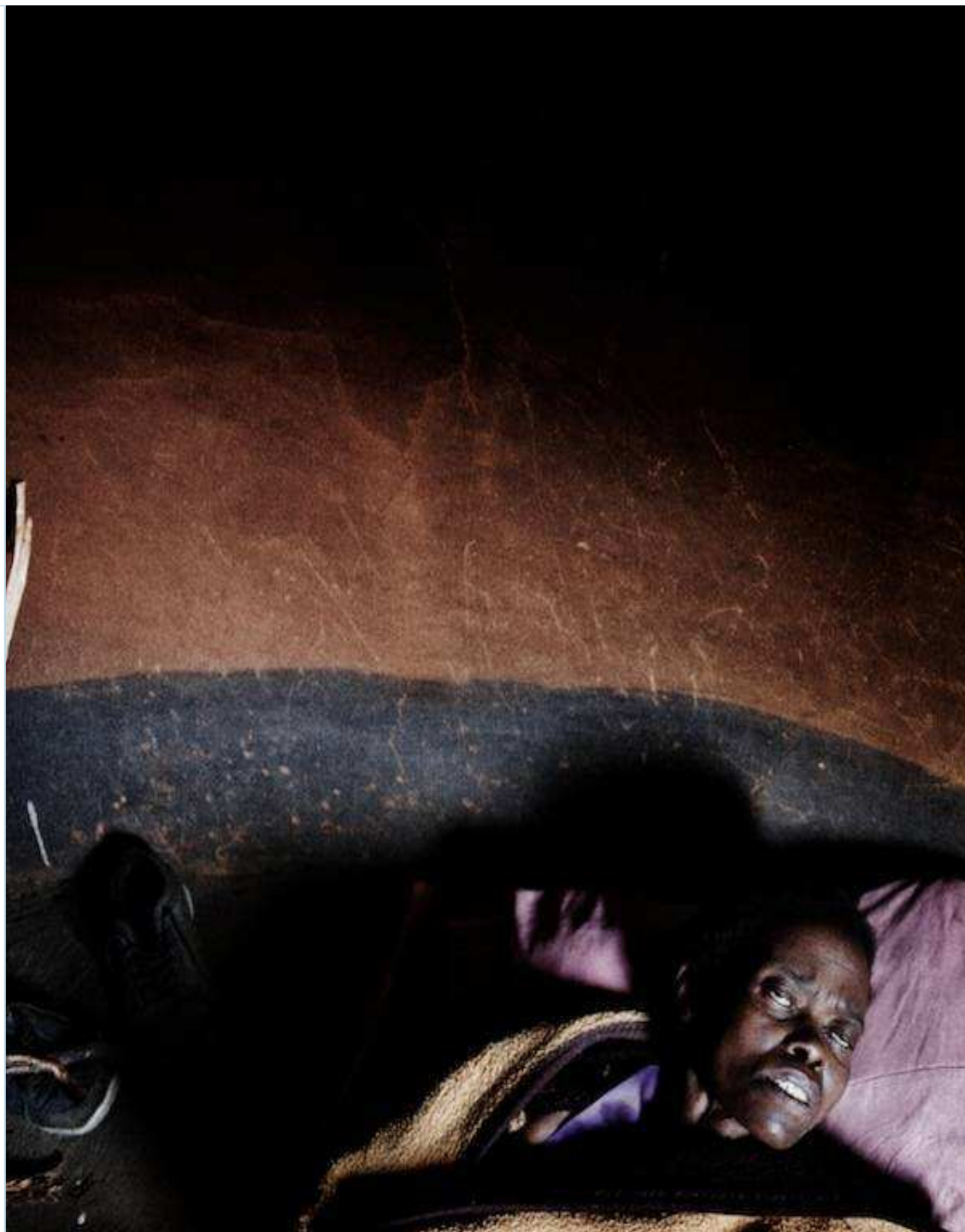
OVERVIEW

- I. CURRENT STATE OF AFFAIRS
- II. WHY ARE WE UNABLE TO RAPIDLY SCALE UP MDR-TB TREATMENT?
- III. CONSEQUENCES OF INACTION

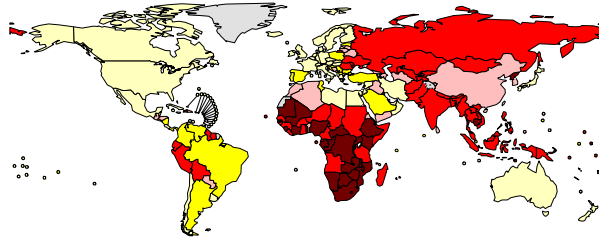


CURRENT STATE OF AFFAIRS

Photo: Open Society Institute/Pep Bonet



The global burden of TB in 2009



**Estimated
number of
new cases**

**Estimated
number of
deaths**

All forms of TB

9.4 million
(range 8.9–9.9 million)

1.7 million
(range 1.6–1.9 million)

HIV-associated TB

1.1 million (12%)

400,000

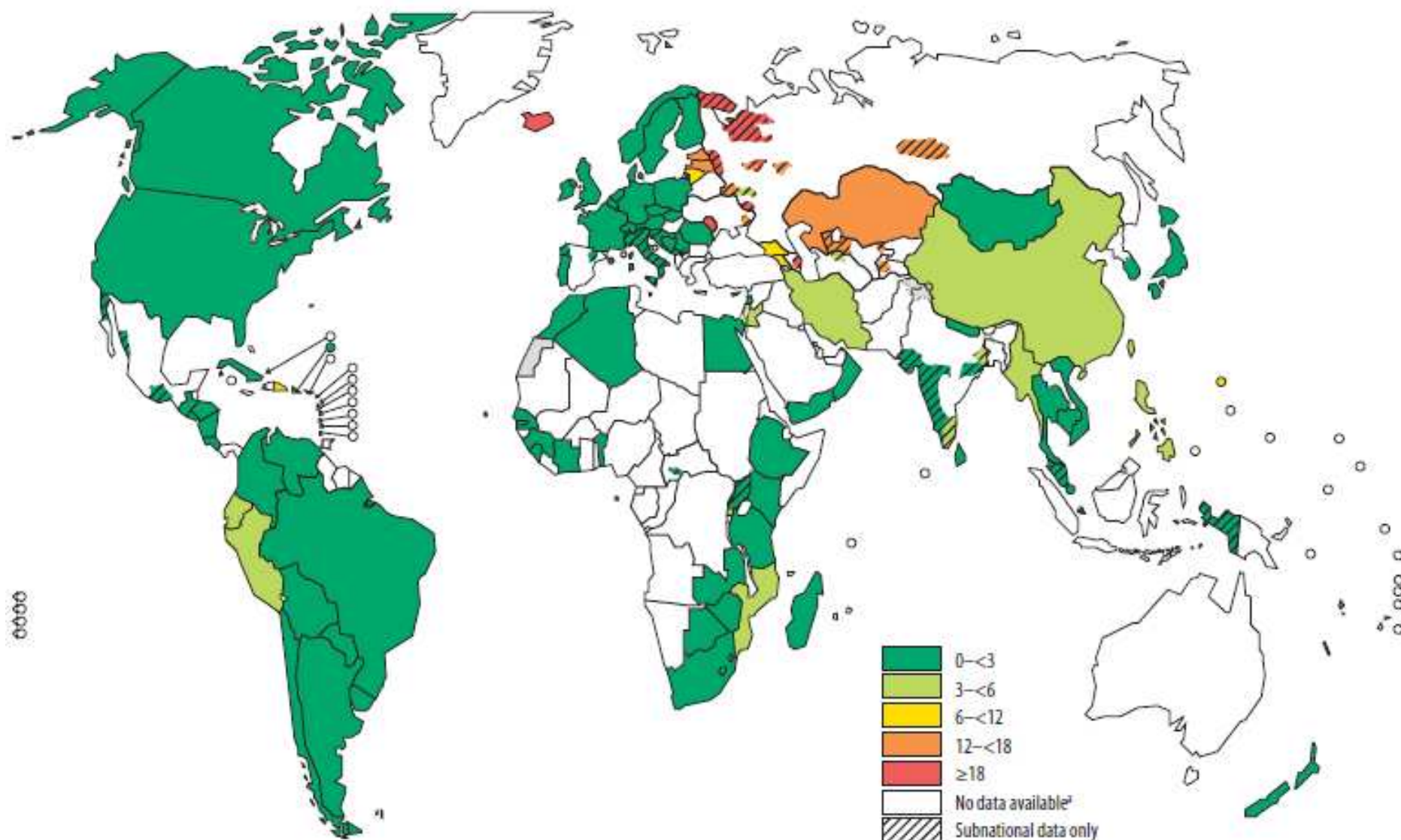
**Multidrug-resistant
TB (MDR-TB)**

440,000
(0.39-0.51 million)

150,000
(0.05–0.27 million)

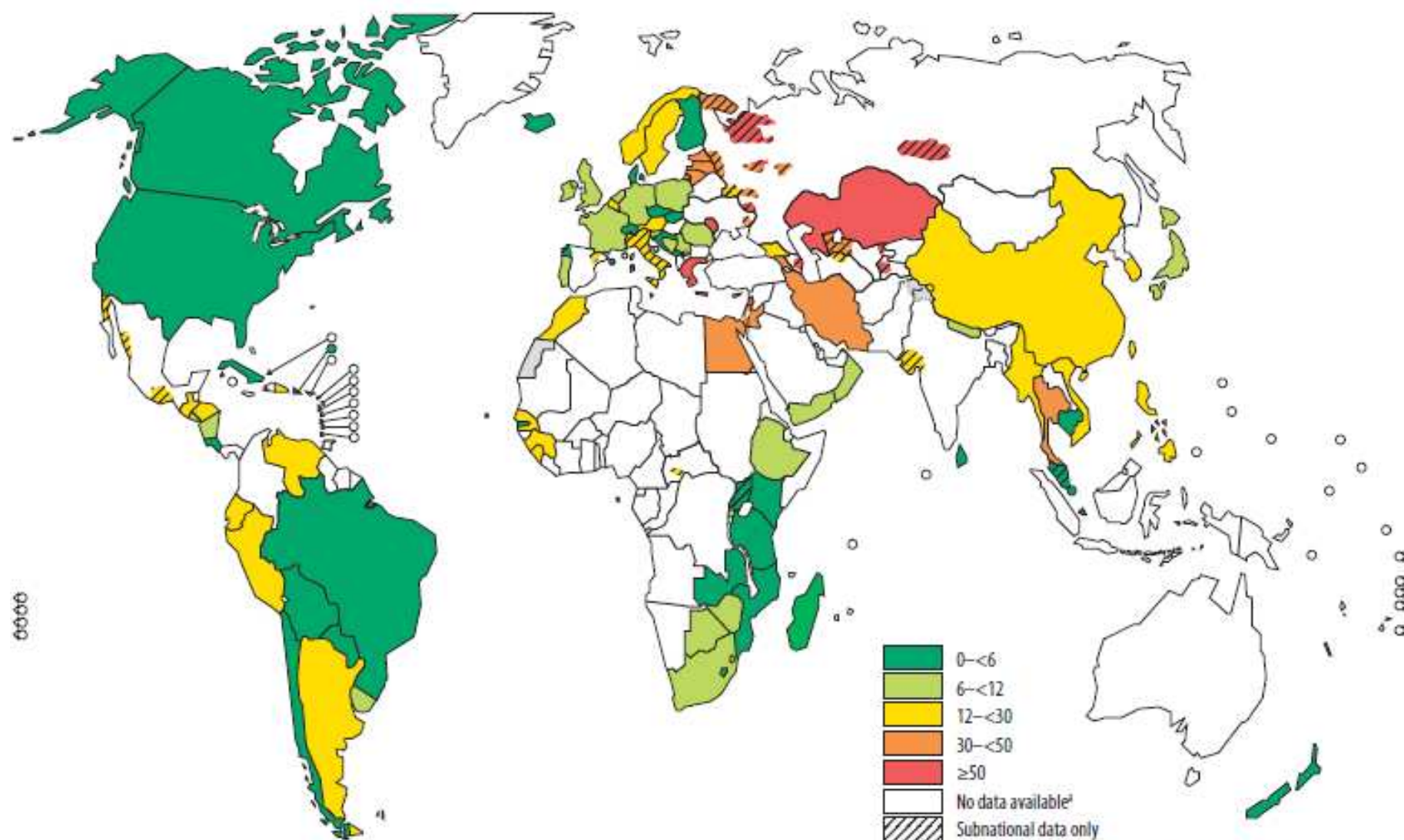


MAP 3 Distribution of proportion of MDR-TB among new TB cases, 1994–2009



^a Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.

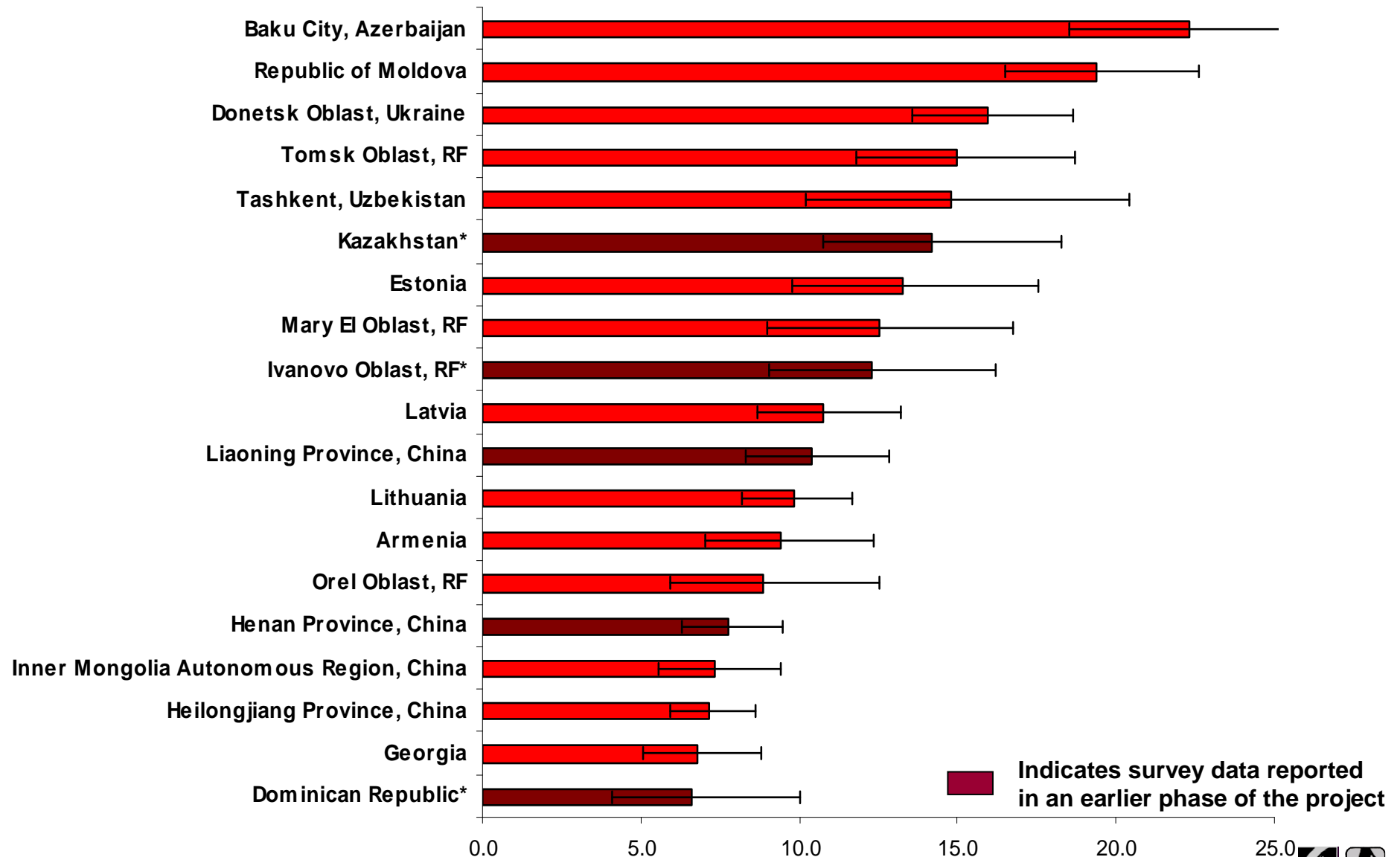
MAP 4 Distribution of proportion of MDR-TB among previously treated TB cases, 1994–2009



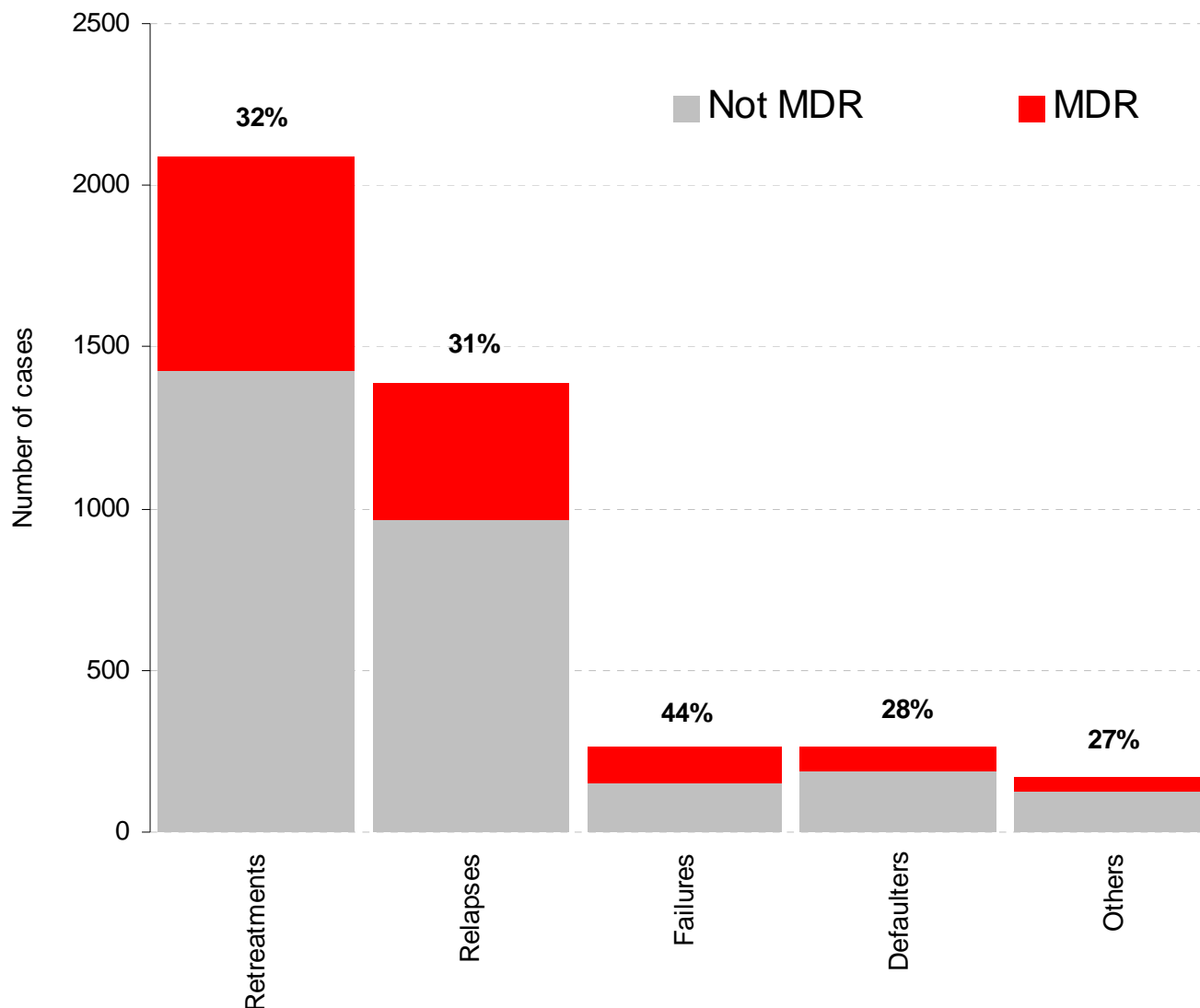
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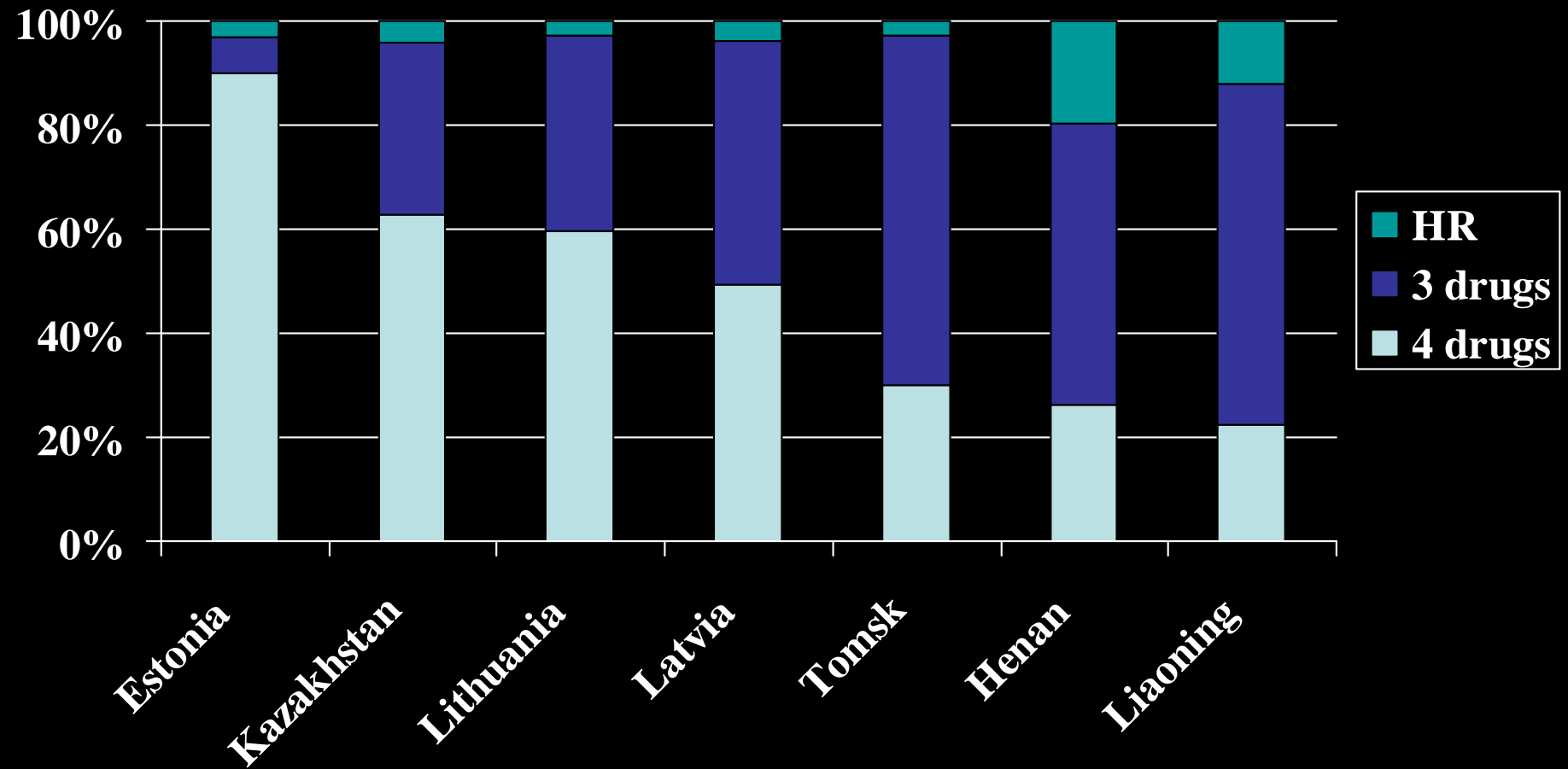
19 settings with $\geq 6\%$ MDR among new cases, 1994-2007



Cumulative figures of MDR-TB among subcategories of retreatment cases (9 settings)



Resistance pattern among new MDR cases in selected countries



Global distribution of countries reporting at least one XDR-TB case by March 2011



I. BIOSOCIAL HISTORY OF MDR-TB





SPECIAL ARTICLE

SELECTIVE PRIMARY HEALTH CARE

An Interim Strategy for Disease Control in Developing Countries

JULIA A. WALSH, M.D., AND KENNETH S. WARREN, M.D.

Abstract Priorities among the infectious diseases affecting the three billion people in the less developed world have been based on prevalence, morbidity, mortality and feasibility of control. With these priorities in mind a program of selective primary health care is compared with other approaches and suggested as the most cost-effective form of medical intervention in the least developed countries. A flexible program delivered by either fixed or mobile units might include measles and diphtheria-per-

tussis-tetanus vaccination, treatment for febrile malaria and oral rehydration for diarrhea in children, and tetanus toxoid and encouragement of breast feeding in mothers. Other interventions might be added on the basis of regional needs and new developments. For major diseases for which control measures are inadequate, research is an inexpensive approach on the basis of cost per infected person per year. (N Engl J Med 301:967-974, 1979)

Table 3. Priorities for Disease Control in the Developing World, Based on Prevalence, Mortality, Morbidity and Feasibility of Control.

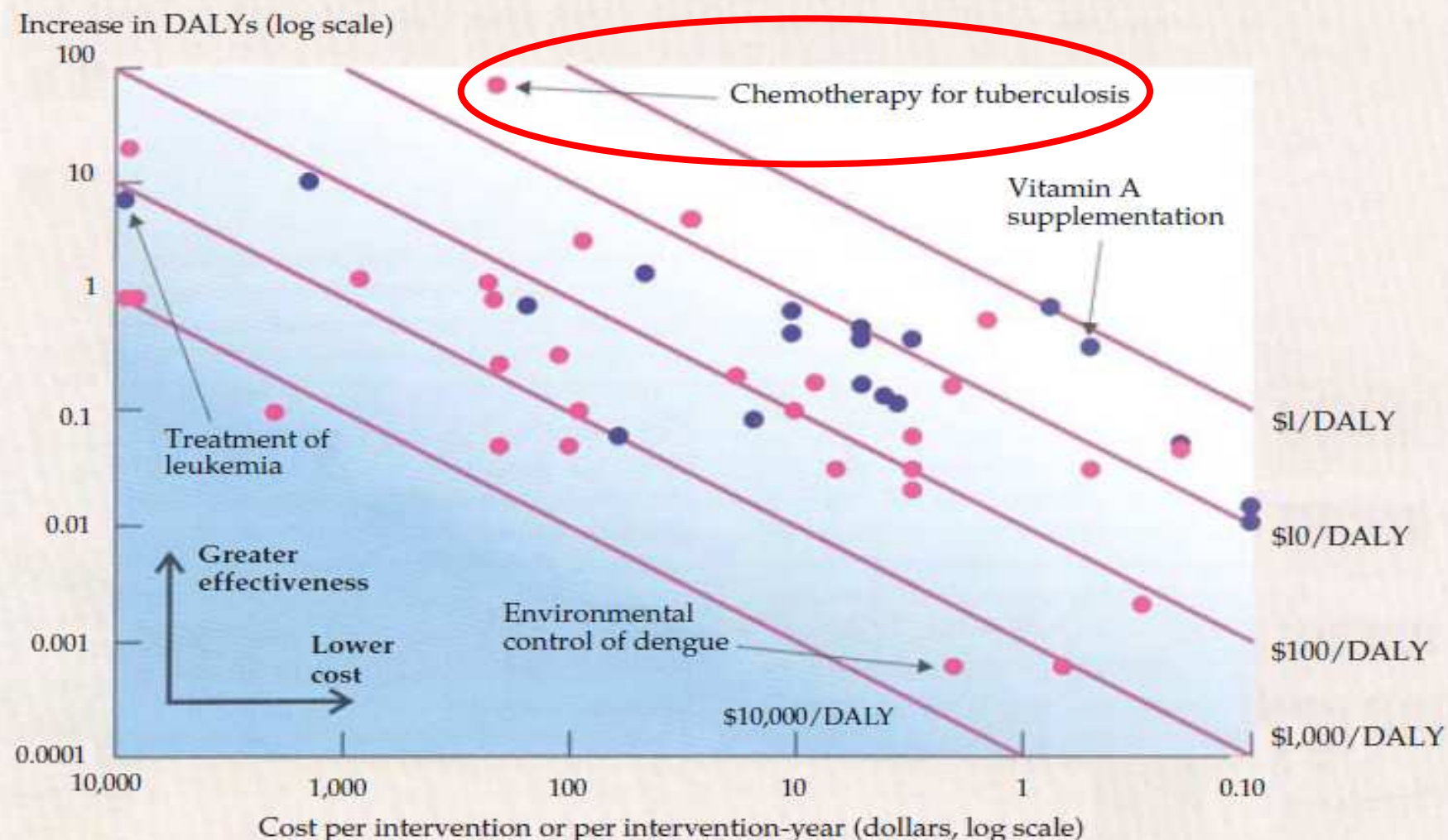
PRIORITY GROUP	REASONS FOR ASSIGNMENT TO THIS CATEGORY
I High	High prevalence, high mortality or high morbidity, effective control
Diarrheal diseases	
Measles	
Malaria	
Whooping cough	
Schistosomiasis	
Neonatal tetanus	
II Medium	
Respiratory infections	High prevalence, high mortality, no effective control
Poliomyelitis	High prevalence, high mortality, no effective control
Tuberculosis	High prevalence, high mortality, control difficult
Onchocerciasis	High prevalence, high mortality, control difficult
Meningitis	Medium prevalence, high mortality,

For a number of prevalent infections, treatment or preventive measures are expensive, difficult to administer, toxic or ineffective. These infections, which include Chagas' disease, African trypanosomiasis, leprosy and tuberculosis, may better be dealt with through an investment in research. In terms of the



WORLD DEVELOPMENT REPORT 1993

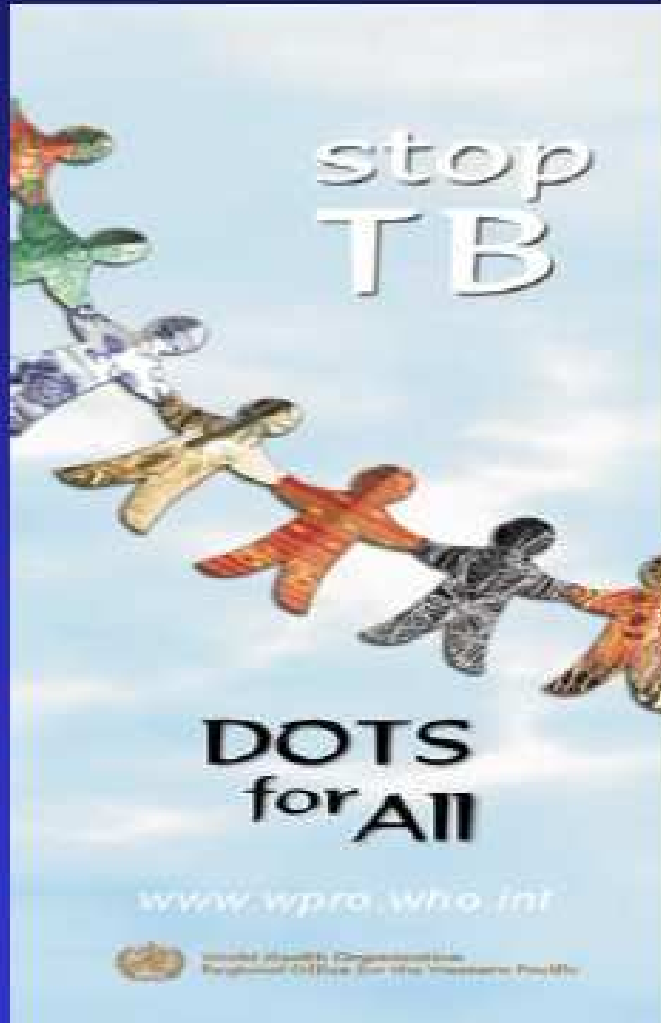
Figure 3.2 Benefits and costs of forty-seven health interventions



DOTS and the World Health Organization

1993: Press conference
to declare TB “a global
emergency”

International funding
increases from \$16
million to \$50 million
within 2 years



Adopted by 127
countries within 3
years

1999: TB Advocacy,
A Practical Guide:
guidelines for
community to
influence
policies/funding for
DOTS

IDEAS ENSHRINED IN DOTS

1. Political commitment
2. Diagnosis with sputum-smear microscopy
3. Standardized short-course chemotherapy
4. Regular supply of high-quality drugs
5. Standardized recording and reporting



IDEAS ENSHRINED IN DOTS

1. Political commitment
 - Focus on governments; limited engagement with private sector
2. Diagnosis with sputum-smear microscopy
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IDEAS ENSHRINED IN DOTS

1. Political commitment
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 - Finding those thought to be the most infectious cases
 - Smear microscopy was good enough; no need for new technology
 - Ignored children, people with HIV
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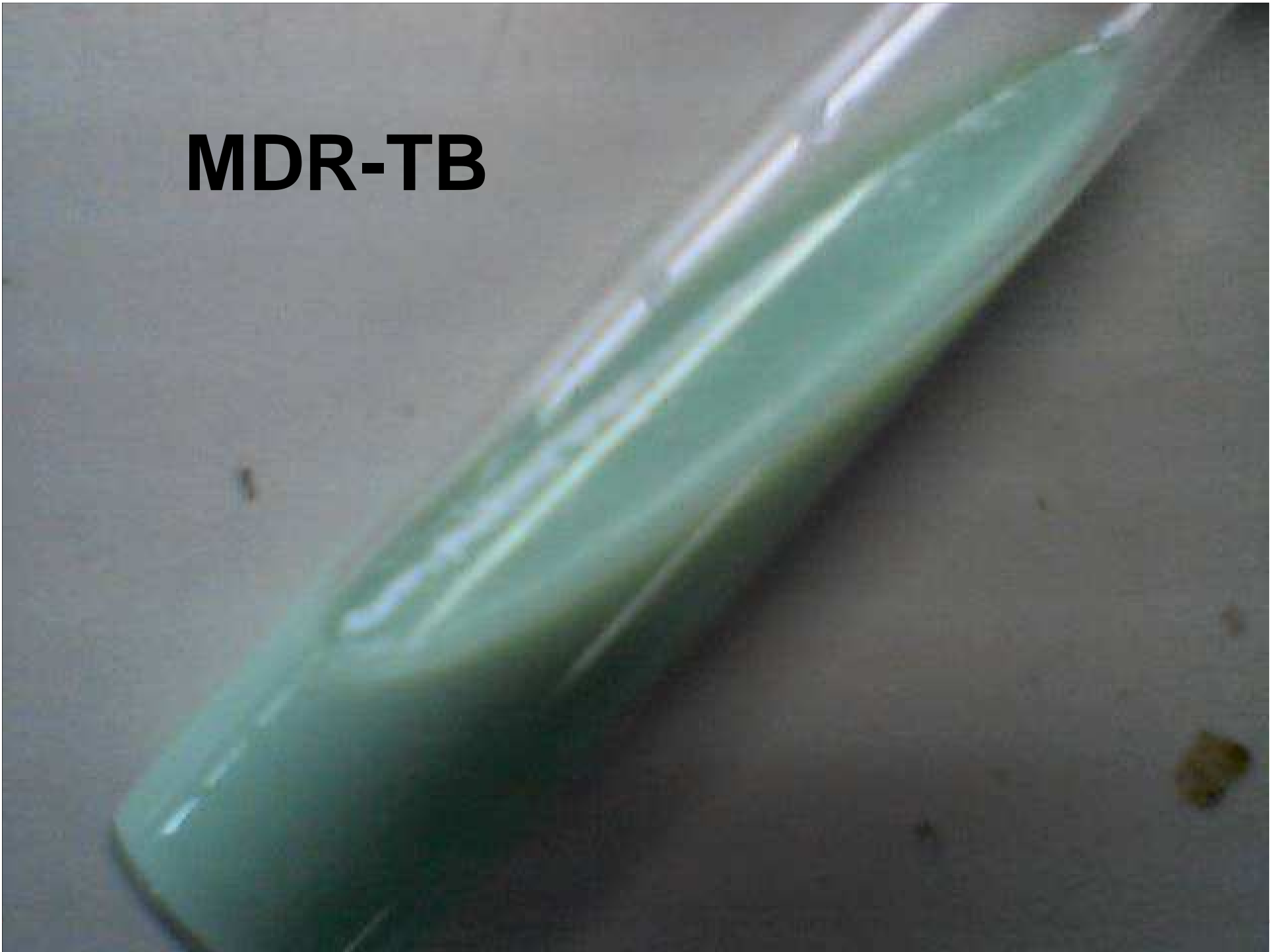


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4. Regular supply of high-quality drugs
 - Complex issues around procurement were not dealt with
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5. Standardized recording and reporting
 - Accountability for outcomes
 - Unable to capture complex data



MDR-TB



1993

Vol. 328 No. 8

TUBERCULOSIS RESISTANT TO ISONIAZID AND RIFAMPIN — GOBLE ET AL.

527

TREATMENT OF 171 PATIENTS WITH PULMONARY TUBERCULOSIS RESISTANT TO ISONIAZID AND RIFAMPIN

MARIAN GOBLE, M.D., MICHAEL D. ISEMAN, M.D., LORIE A. MADSEN, R.N.-C., B.S.N.,
DENNIS WAITE, M.D., LYNN ACKERSON, PH.D., AND C. ROBERT HORSBURGH, JR., M.D.

1995

Vol. 333 No. 4

TUBERCULOSIS IN NEW YORK CITY

229

SPECIAL ARTICLE

TUBERCULOSIS IN NEW YORK CITY — TURNING THE TIDE

THOMAS R. FRIEDEN, M.D., M.P.H., PAULA I. FUJIWARA, M.D., M.P.H., RITA M. WASHKO, M.D.,
AND MARGARET A. HAMBURG, M.D.


Abstract *Background.* From 1978 through 1992, the number of patients with tuberculosis in New York City nearly tripled, and the proportion of such patients who had drug-resistant isolates of *Mycobacterium tuberculosis* more than doubled.

Methods. We reviewed, confirmed, and analyzed data obtained during the surveillance of patients with tuberculosis.

Results. From 1992 through 1994, there was a 21 percent decrease in reported cases of tuberculosis in

among elderly and foreign-born persons, in whom the disease is likely to result from the reactivation of an infection acquired many years earlier. Enrollment in a program of directly observed therapy, in which health workers watch patients take their medications, increased from fewer than 100 patients to nearly 1300, with more than 32,000 patient-months of observation from 1992 through 1994.

Conclusions. Epidemiologic patterns strongly suggest that the decrease in cases resulted from an interruption in the ongoing spread of *M. tuberculosis* infection, primar-



“MDR-TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease.”

- World Health Organization
Groups at Risk, 1996

“DOTS makes it virtually impossible to cause a patient to develop the incurable forms of TB that are becoming more common. Other treatment strategies are actually causing multidrug-resistant TB, and may be doing more harm than good.”

— WHO, TB Treatment Observer, 1997



“...best practice SCC may even reduce the incidence of MDR-TB where it has already become endemic...”

- Dye et al.
Science 2002

A woman with dark hair, wearing a dark jacket over a light-colored top, stands in a library. She is looking towards the camera. Behind her are tall bookshelves filled with books. The lighting is warm, coming from the left, creating a soft glow on her face and the books.

1996

MDR-TB treatment initiated in Lima's Northern Cone by PIH/SES and Harvard Medical School, with the Peruvian National TB Program

1998

Major policy meeting held in Cambridge, Massachusetts

1998-2000

Creation of "DOTS-Plus" framework;
Five initial pilot projects

Early 2000s

Community-based delivery of MDR-TB treatment deemed feasible in resource-limited settings

2000: A mechanism to enable “DOTS-Plus”



Multi-institutional partnership

- created by Jim Kim and colleagues (PIH/Harvard) along with international partners (MSF, CDC, UNION, KNCV, and the WHO) in 2000.
- Shut down in 2011; replaced by a new mechanism

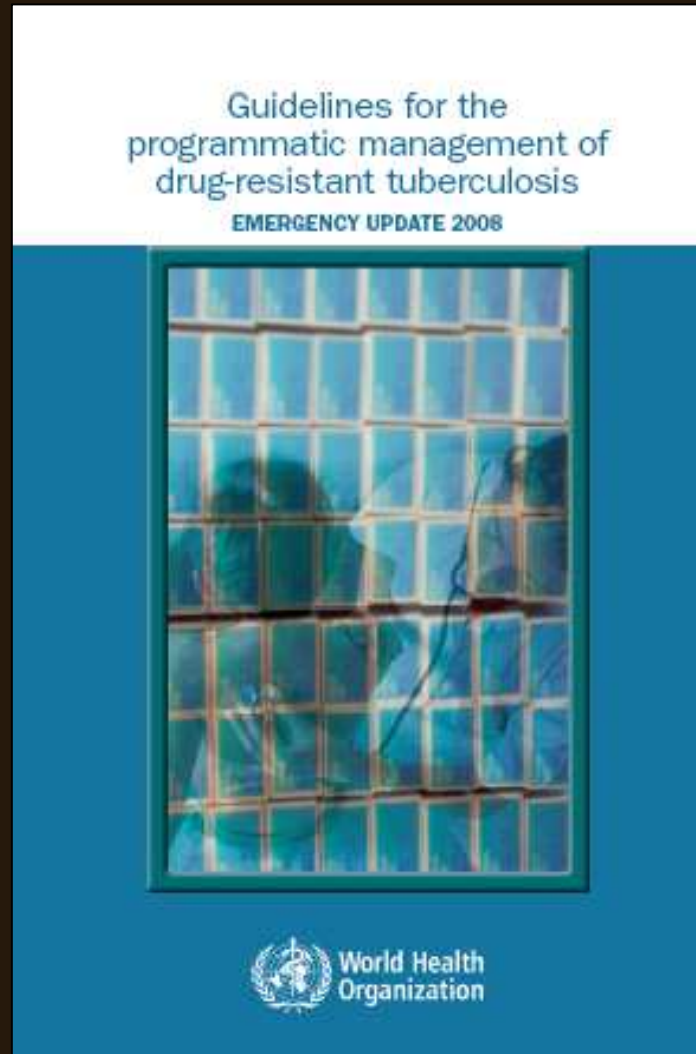
Mandate:

- Ensure access to affordable quality-assured second-line drugs
- Ensure that projects were able to use the drugs appropriately
- Use data from “DOTS-Plus” pilot projects to shape policy

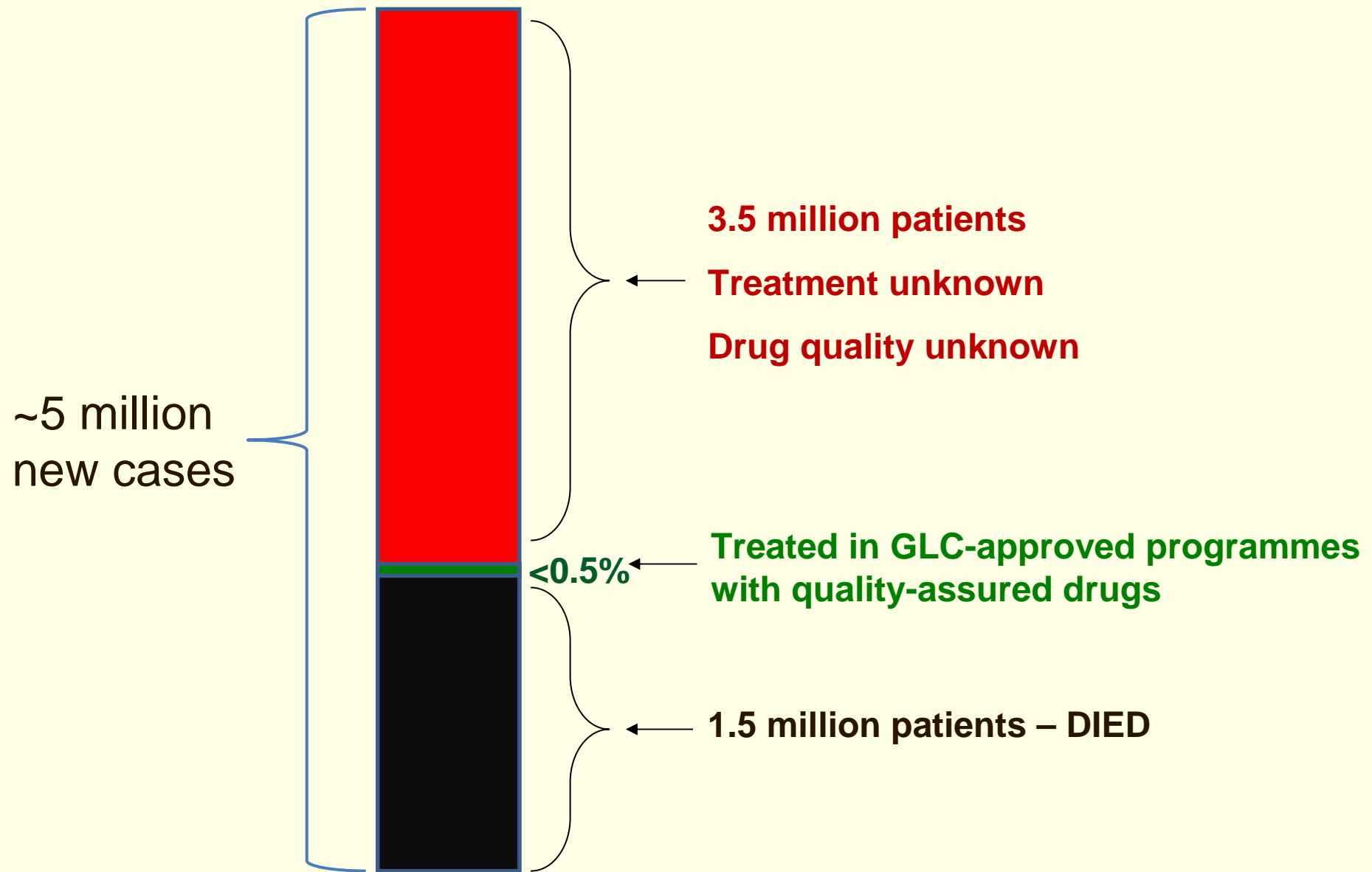


2006

WHO guidelines for DR-TB treatment informed by international pilot projects (2006)

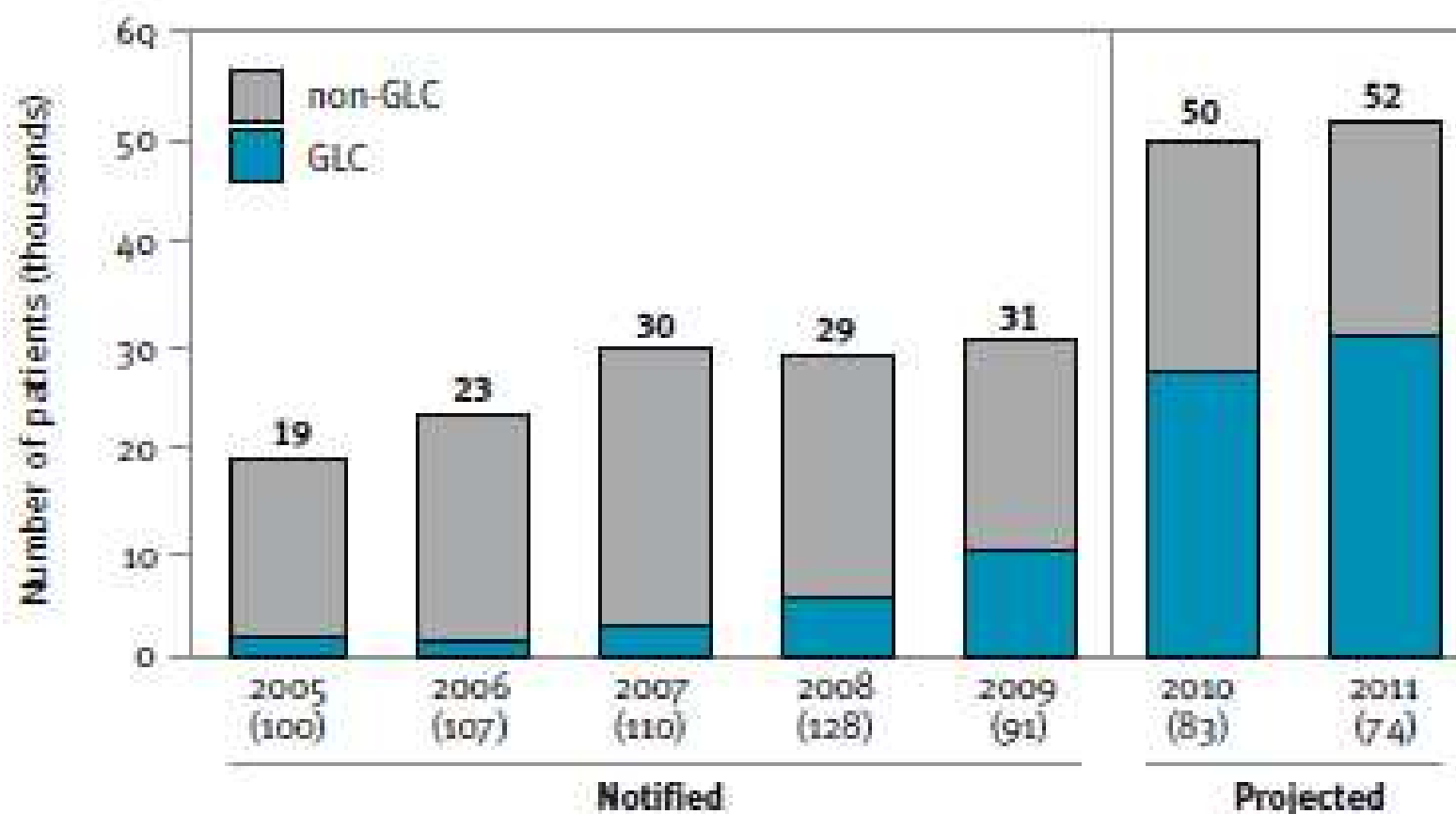


10 YEAR TOTAL: PATIENTS REQUIRING MDR-TB TREATMENT (2000 – 2009)



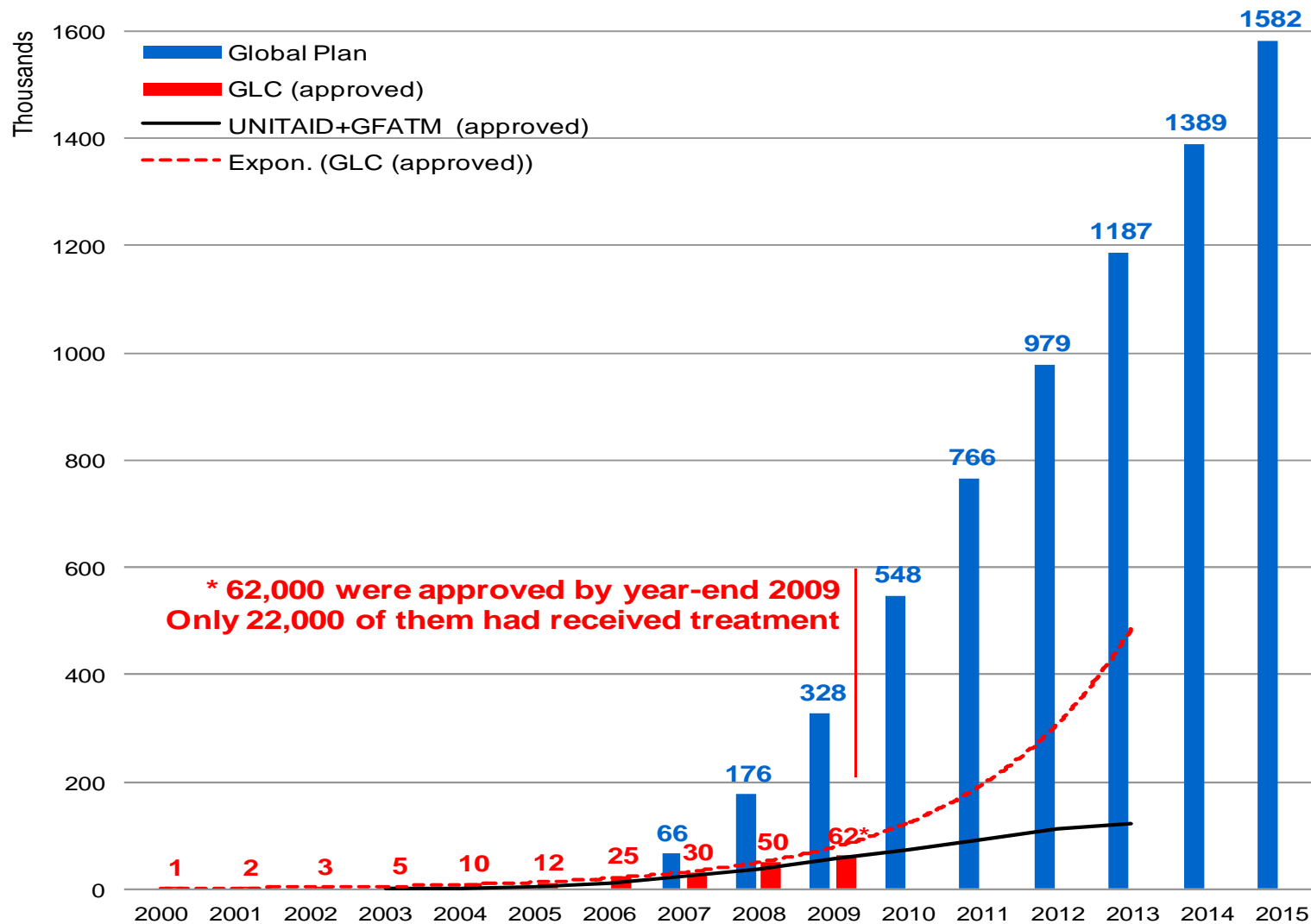
Source: based on WHO estimates 2008, 2009, 2010

Notified cases of MDR-TB (2005–2009) and projected numbers of patients to be enrolled on treatment (2010–2011)^a



^a Numbers under years show the number of countries reporting data.

Gap between the Global Plan, 2006-2015 and GLC projections



**WHY ARE WE UNABLE
TO RAPIDLY EXPAND
MDR-TB TREATMENT AND
STOP THE EPIDEMIC?**



INADEQUATE DIAGNOSTIC CAPACITY



CHALLENGES

Need rapid culture and drug-sensitivity testing

- Liquid bacterial culture → 2 weeks
- Molecular tests → 2 hours to 2 days
- Require laboratory infrastructure; need an approach that requires less infrastructure
- Need something that works on children and those with HIV

Need rapid point-of-care test

- Diagnose patients at health points/clinics
- Start treatment immediately to reduce transmission and increase successful treatment outcomes

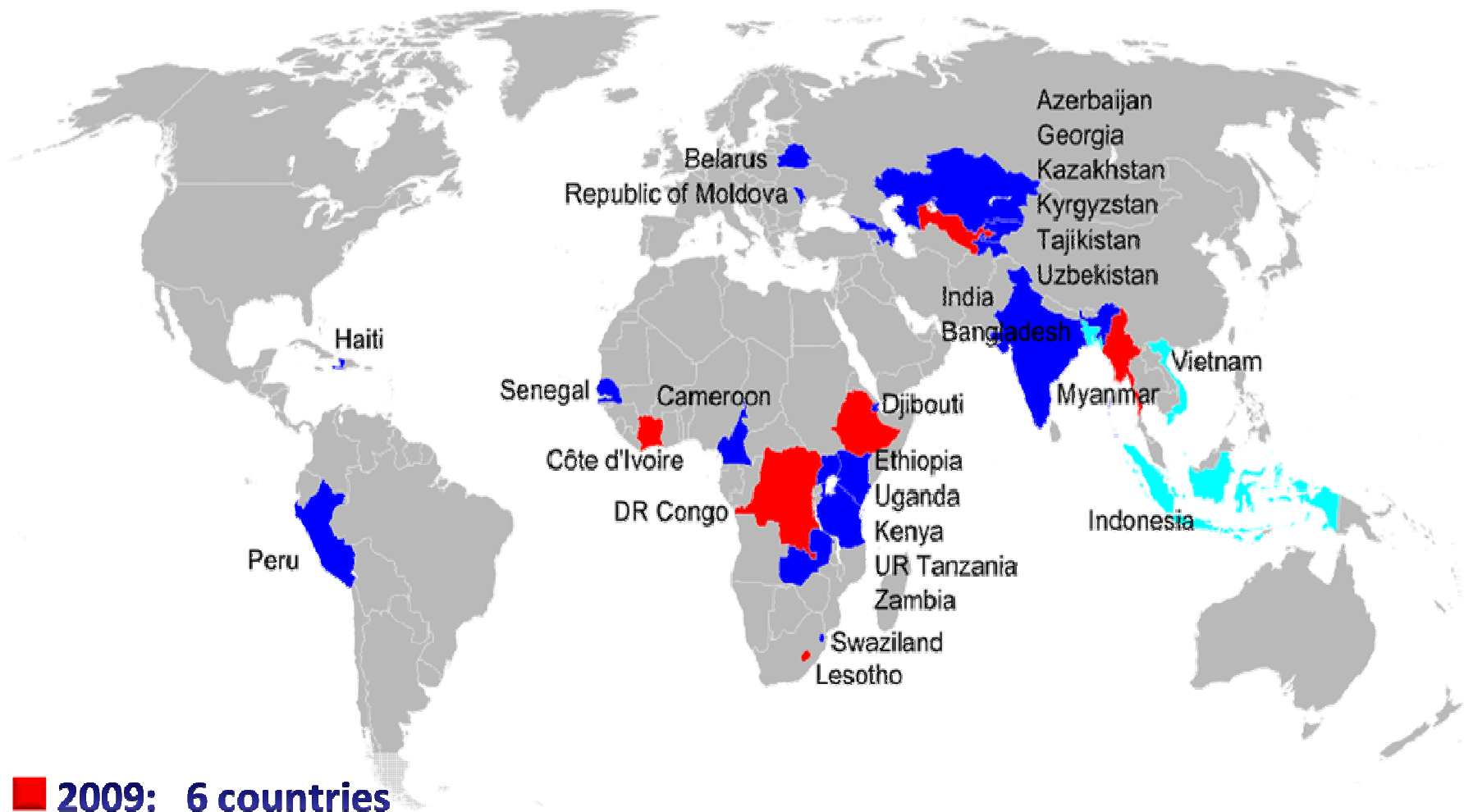


SOLUTION: BUILD CAPACITY

Lesotho example demonstrates what can be achieved in resource-limited settings



LAB CAPACITY BUILDING: EXPAND-TB

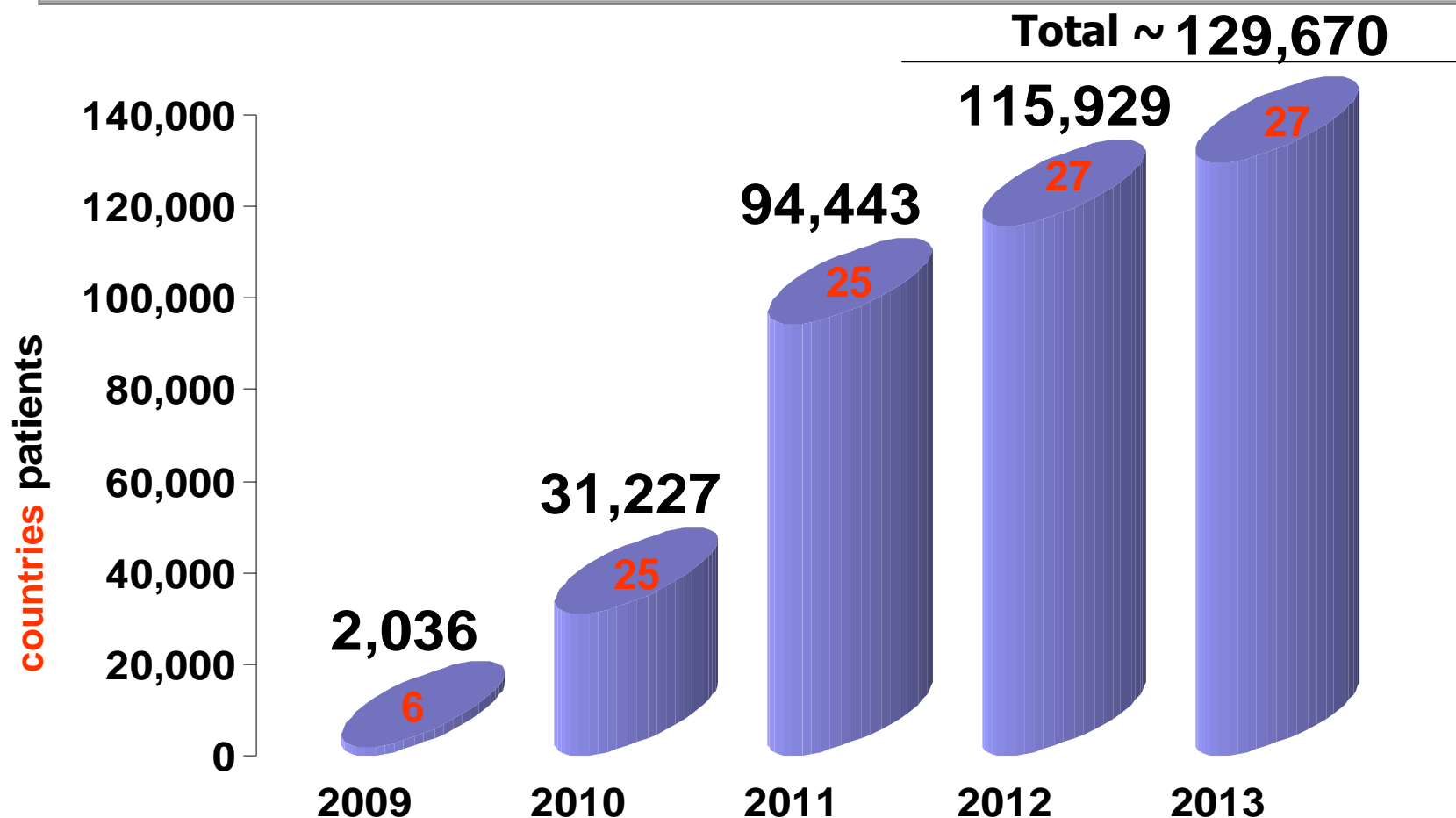


- 2009: 6 countries
- 2010: 18 countries including India (43 labs)
- 2011: 3 countries

EXPAND-TB is a joint project between FIND, the Stop TB Partnership and the World Health Organization under a Grant from UNITAID



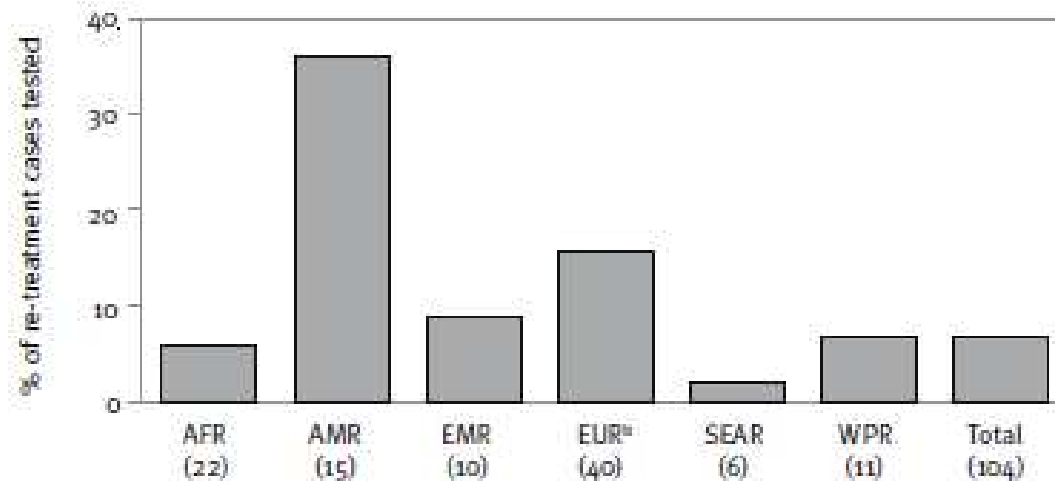
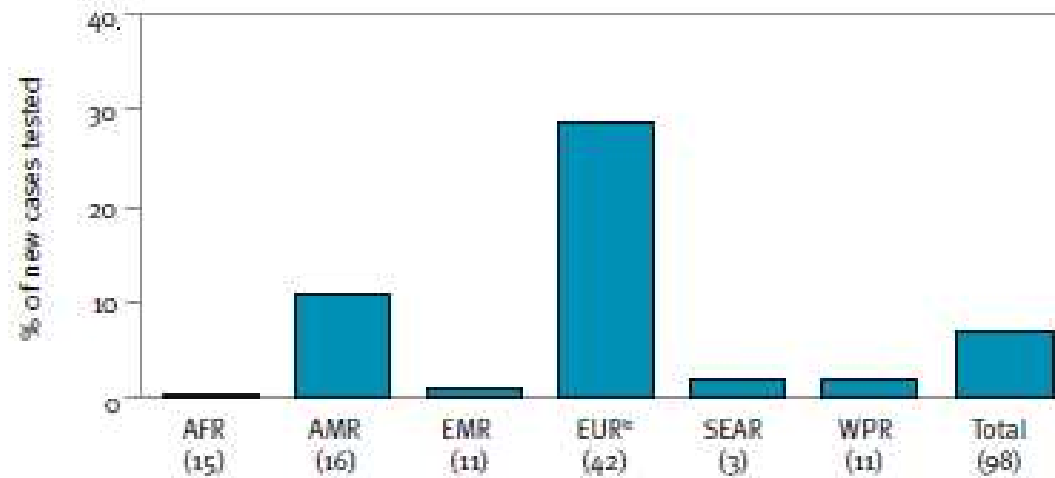
EXPAND-TB Project Targets



* Targets calculated as a % of the estimated MDR-TB burden, 80% for most countries; 35% for India and 60% for Zambia and Cameroon

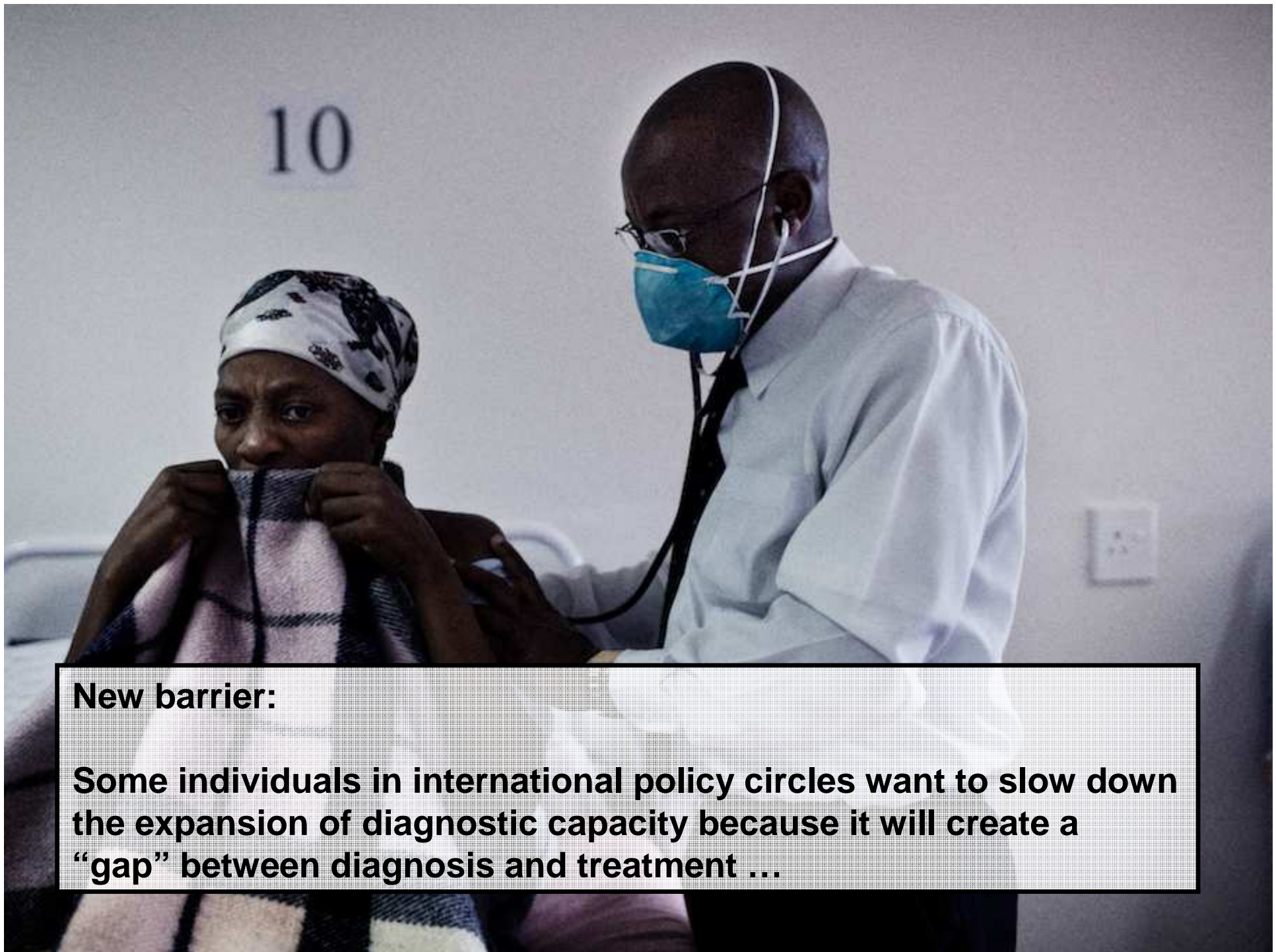


Diagnostic DST for new and re-treatment TB cases, by WHO region, 2009^a



^a The numbers under each bar show the number of countries in each region reporting data.

^b Data for EUR are from 2008 (data for 2009 were incomplete at the time of publication due to later deadlines for reporting).



New barrier:

Some individuals in international policy circles want to slow down the expansion of diagnostic capacity because it will create a “gap” between diagnosis and treatment ...

INADEQUTE SECOND-LINE DRUG SUPPLY



Reduced prices of second-line TB drugs (2000)

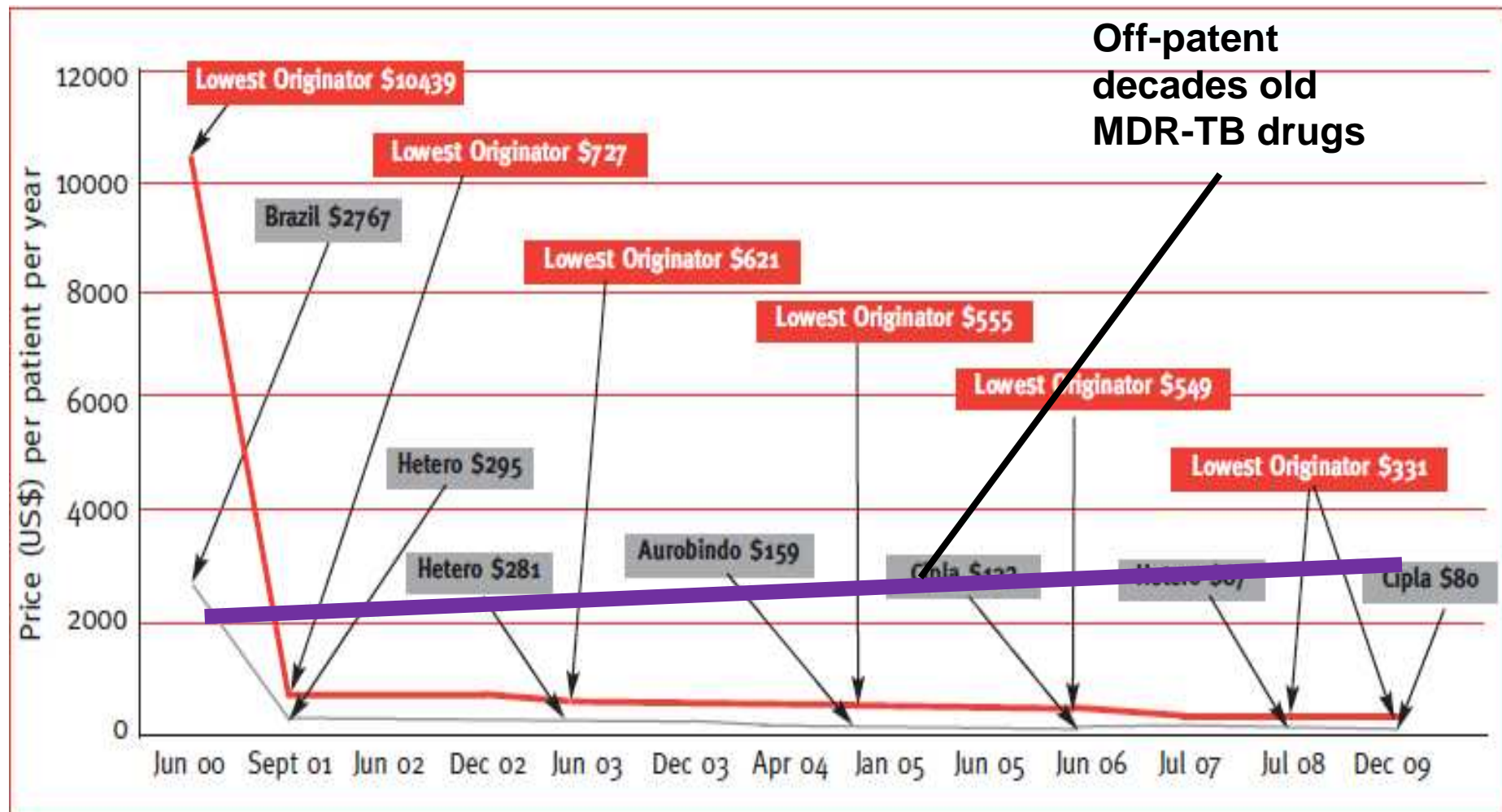
Result of negotiations based on plans for pooled procurement

Drug	Formulation	1997 price	2000 price	% Decline
Amikacin	1gm vial	\$9.00	\$0.90	90
Cycloserine	250mg tab	\$3.99	\$0.50	87
Ethionamide	250mg tab	\$0.90	\$0.14	84
Kanamycin	1gm vial	\$2.50	\$0.39	84
Capreomycin	1gm vial	\$29.90	\$0.90	97
Ofloxacin	200mg tab	\$2.00	\$0.05	98



Situation with second-line anti-TB drugs

- Competition tends to lower prices and allows affordable access to medical technologies... second-line anti-TB drugs have been an exception.

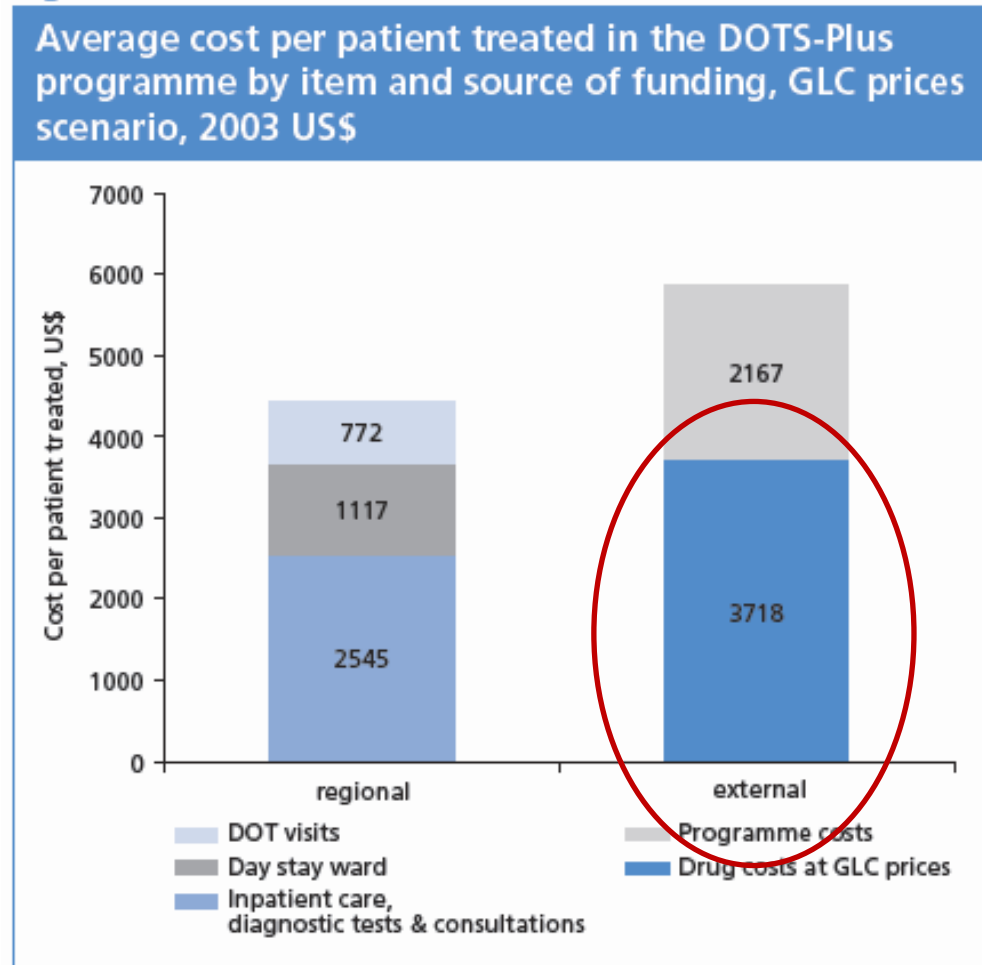


Prices available for GLC - approved programmes, in US\$

Products	July 2001	March 2011 (lowest price)	% Difference 2001/2011
Amikacin 500mg	0.11	1.20	+991%
Kanamycin 1g	0.36	2.58	+617%
Cycloserine 250mg	0.14	0.59	+321%
Capreomycin 1gr	1.02	4.00	+292%
Ethionamide 250mg	0.10	0.09	Stable
Prothionamide 250mg	0.10	0.10	Stable
PAS 4g sachet	1.51	1.57	Stable

Drugs cost significantly more than the provision of care...

Figure 3



⁶External sources means funding from both federal level and international agencies.



FIGURE 9 Costs of second-line anti-TB drugs and treatment as a percentage of gross national income (GNI) per capita in the 27 high MDR-TB burden countries



CHALLENGES

- Not enough manufacturers of quality-assured 2nd line drugs
- No pooled procurement
- Opaque market; insufficient forecasting
- Prices are very high for some drugs
- Serious delivery delays
- Overly centralized system
- Countries want local manufacturers
- No pediatric formulations!!!

- Access to quality-assured second-line anti-TB drugs remains a major barrier as countries increase their pace of enrolment
 - **Need to explore other mechanisms**
- Some new drugs are in clinical development for TB treatment (e.g. moxifloxacin, PA-824, TMC 207).
 - Need to ensure that pediatric dosages are known
 - Need to conduct prophylaxis trials

**INABILITY TO DELIVER
NECESSARY CARE
IN COUNTRIES**

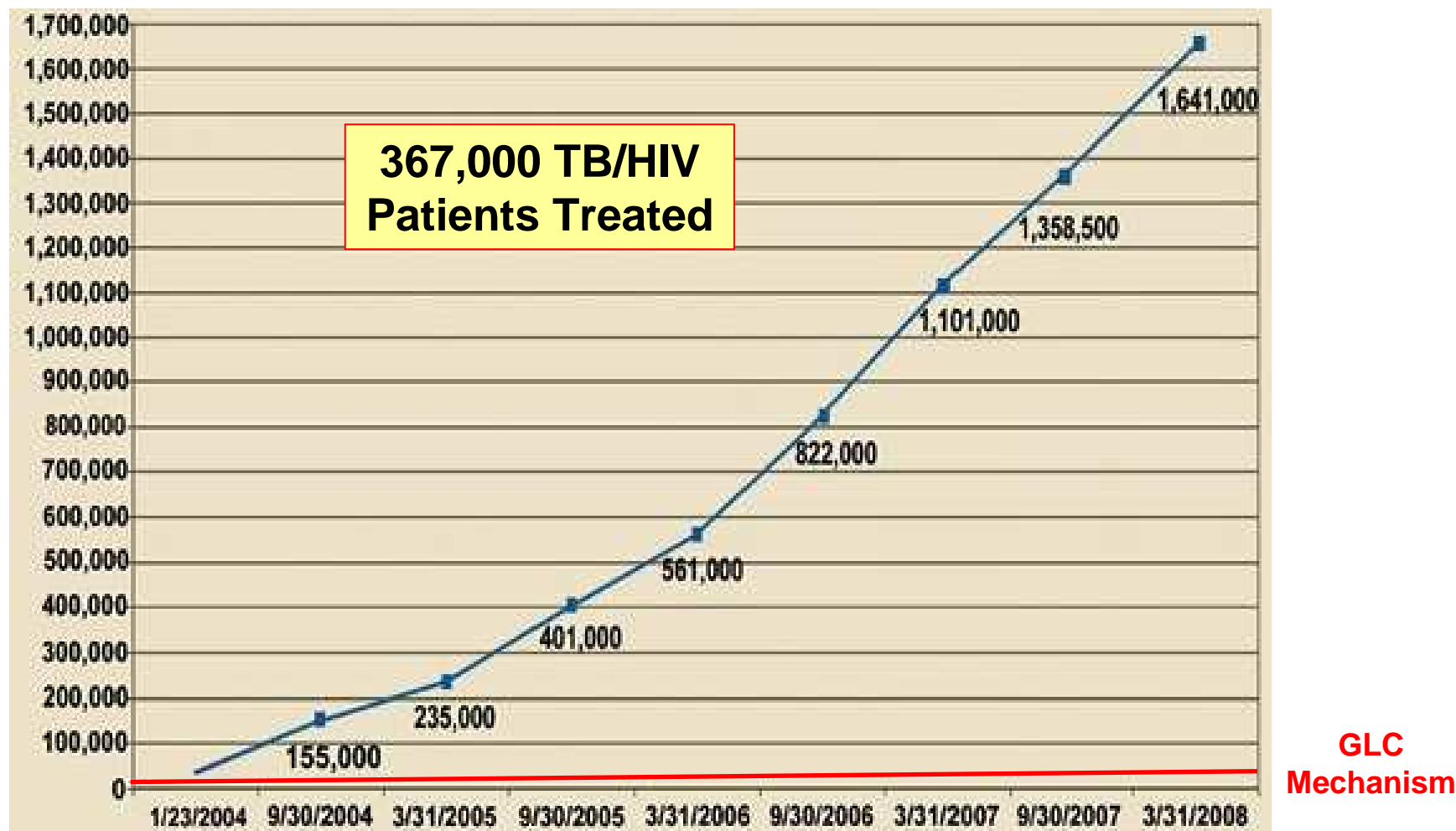


Table Number of MDR-TB cases, health system ranking, and poverty in the 27 MDR-TB high-burden countries

Country	Number of MDR-TB patients (2008)*	Health system overall performance ranking (N = 191; 1997) [†]	Living on <\$2/day (2000–2007) [‡] %
Africa			
Democratic Republic of the Congo	5 600	188	74.4
Ethiopia	5 200	180	77.5
Nigeria	11 000	187	83.9
South Africa	13 000	175	42.9
Europe & Eastern Mediterranean			
Armenia	480	104	43.4
Azerbaijan	4 000	109	<2
Belarus	800	72	<2
Bulgaria	460	102	2.4
Estonia	94	77	<2
Georgia	670	114	30.4
Kazakhstan	8 100	64	17.2
Kyrgyzstan	1 400	151	51.9
Latvia	170	105	<2
Lithuania	330	73	<2
Pakistan	15 000	122	60.3
Republic of Moldova	2 100	101	28.9
Russia	38 000	130	<2
Tajikistan	4 000	154	50.8
Ukraine	8 700	79	<2
Uzbekistan	8 700	117	76.7
South-East Asia & Western Pacific			
Bangladesh	9 800	88	81.3
China	100 000	144	36.3
India	99 000	112	75.6
Indonesia	9 300	92	53.8
Myanmar (Burma)	9 300	190	—
Philippines	13 000	60	45
Vietnam	5 900	160	48.4



The number of individuals receiving antiretroviral treatment in PEPFAR's 15 focus-countries compared to the GLC mechanism



**GLC
Mechanism**

Countries included: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam (added in 2004), Zambia



Delivery of treatment

Lack of infection/transmission control

Lack of systems to deliver care to patients over the 2-year period of treatment and to manage adverse events

Lack of systems to help countries scale-up treatment rapidly

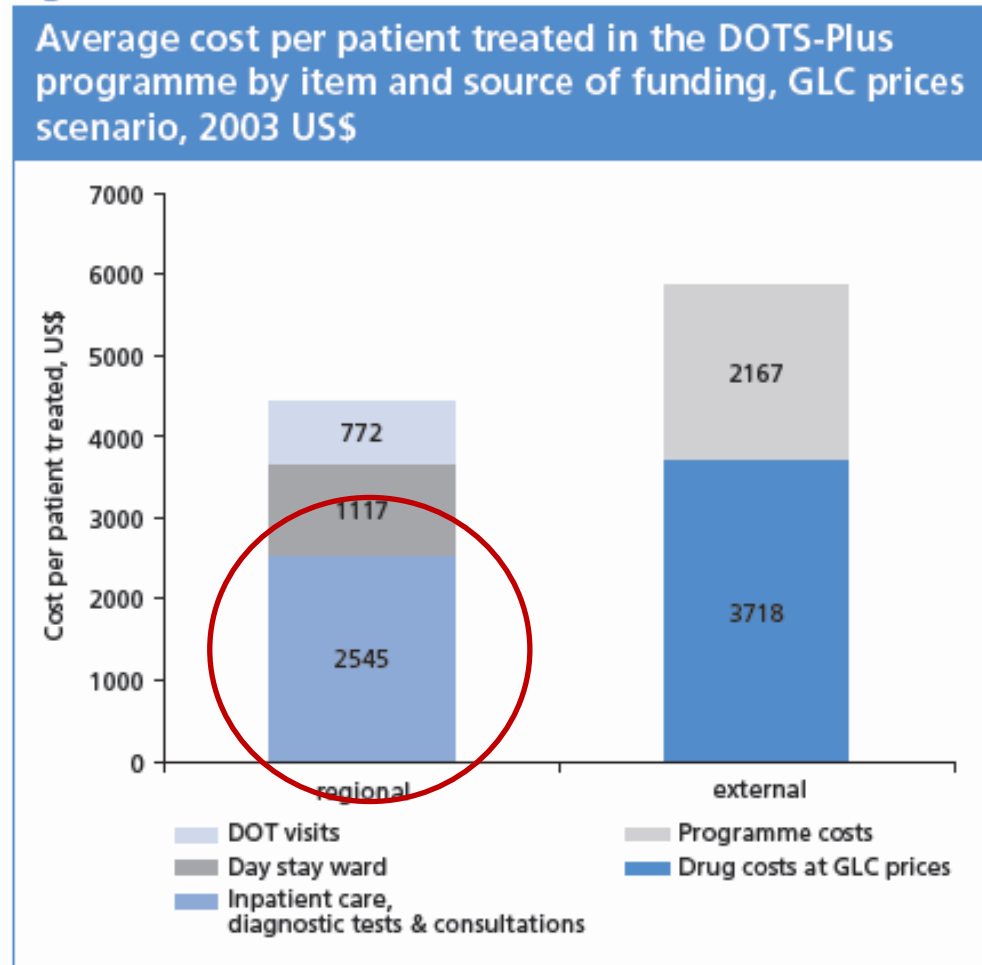


Infection control has to be made a priority



Ambulatory care costs less + less nosocomial transmission

Figure 3



⁶External sources means funding from both federal level and international agencies.



Community based care allows patients to receive care in their own communities; essential when treatment is up to two-years long





Photo: Open Society Institute/Pep Bonet



Photo: Open Society Institute/Pep Bonet

INEFFECTUAL TECHNICAL ASSISTANCE MODELS



U.S. INSTITUTE OF MEDICINE RECOMMENDATION (2008):

The system of international technical assistance provision is currently inadequate. It must be transformed in order to better draw on the experience of successful regional MDR-TB treatment programs, to include the provision of on-site, long-term technical assistance, and where necessary, to involve on-site implementation teams.



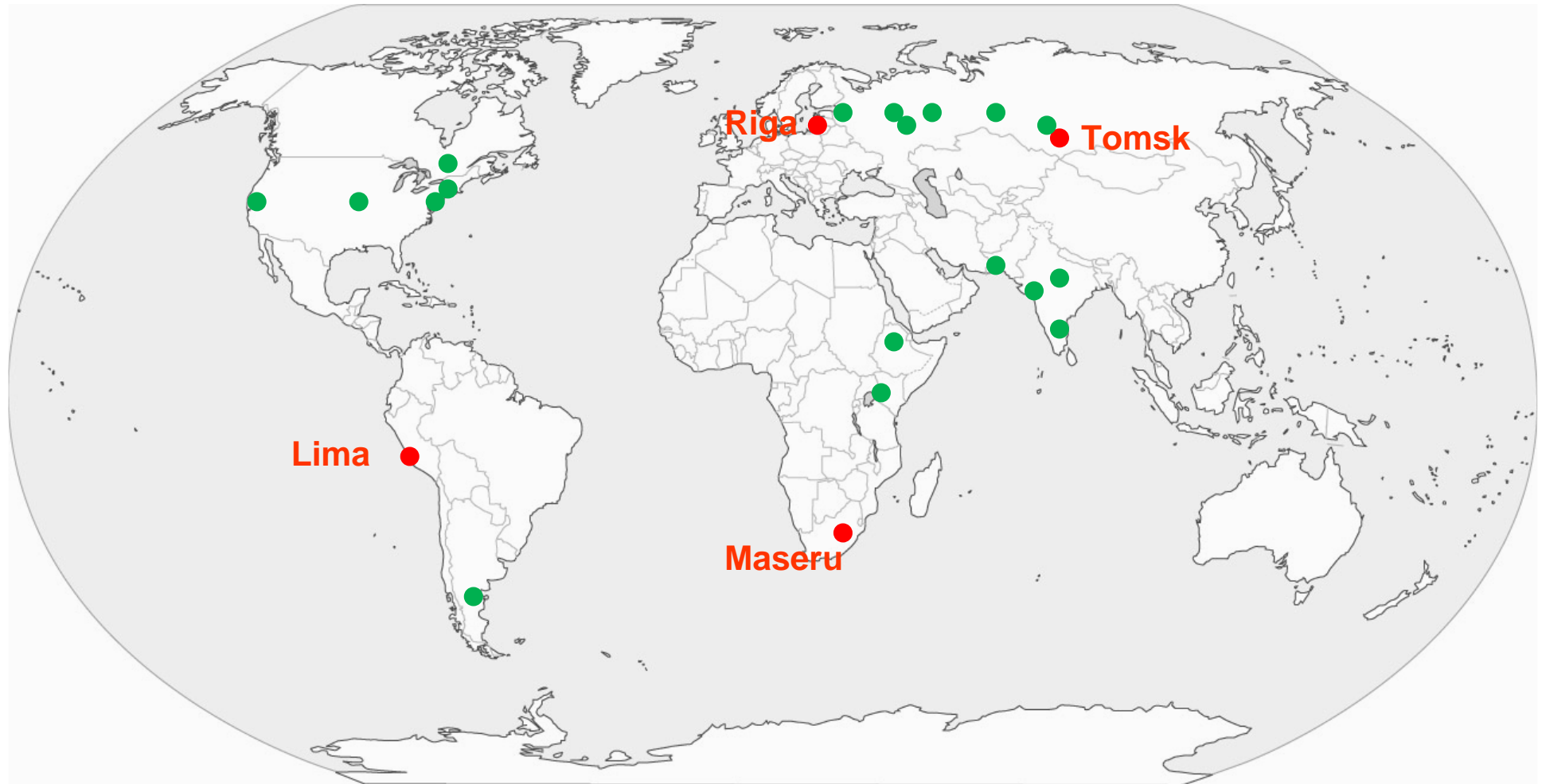
We have not made use of existing approaches...

Many of the successful GLC Pilot projects had strong technical partners helping on-site and long-term:

- Latvia worked with US CDC
- Tomsk (Russia) worked with PIH
- LHL worked with Arkhangelsk
- Orël (Russia) worked with CDC and WHO
- PIH assisted the NTP in Peru with national scale-up
- TDF is the NTP's main technical partner in the Philippines
- Lesotho received technical assistance from PIH and FIND
- MSF worked with Uzbekistan, Georgia, Armenia



We have not made use of existing knowledge hubs...



**WE HAVE MAJOR GAPS
IN OUR STRUGGLE
AGAINST TB**



We have no preventive therapy for MDR-TB contacts...

Comstock's studies in Alaska 1960s

- Isoniazid preventive therapy effective in preventing TB in different populations
- protective effect persistent for more than 19 years (as of 1979); perhaps lifelong

INH prophylaxis in patients infected with HIV

- highly effective in preventing mortality
- greater effect seen in PPD+ people
- 36 month therapy (continuous IPT) was more effective for prevention of TB than 6 month IPT in people with HIV (2011)

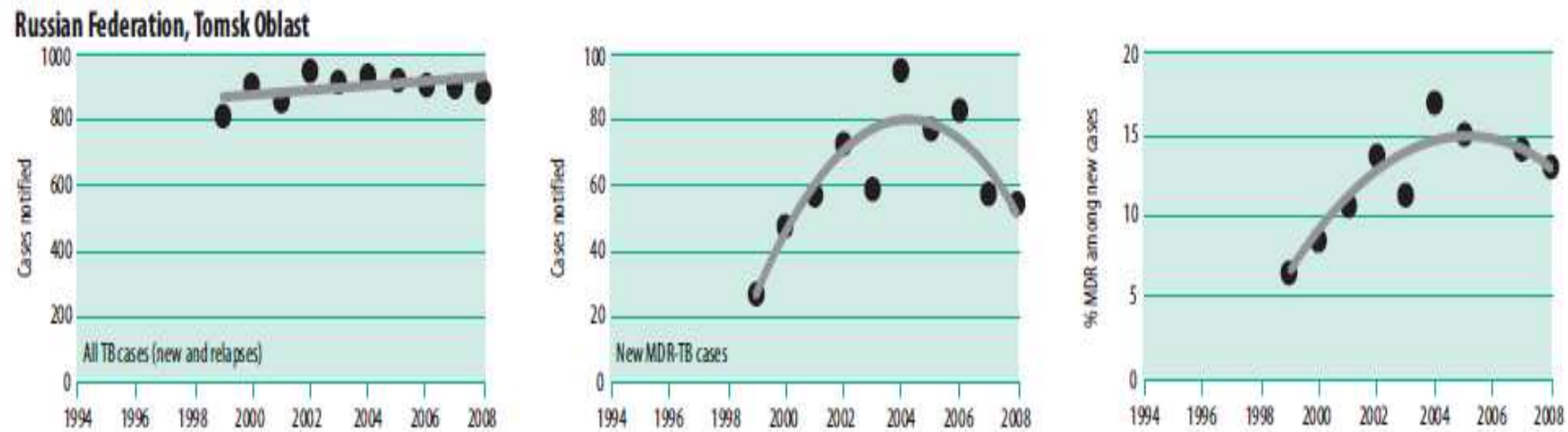
Is there a role for prophylaxis of MDR-TB contacts?

- children?
- people infected with HIV?
- all contact?
- New drugs



We are not fighting for universal access to MDR-TB care...

Universal access—and transmission interruption—has to be a priority

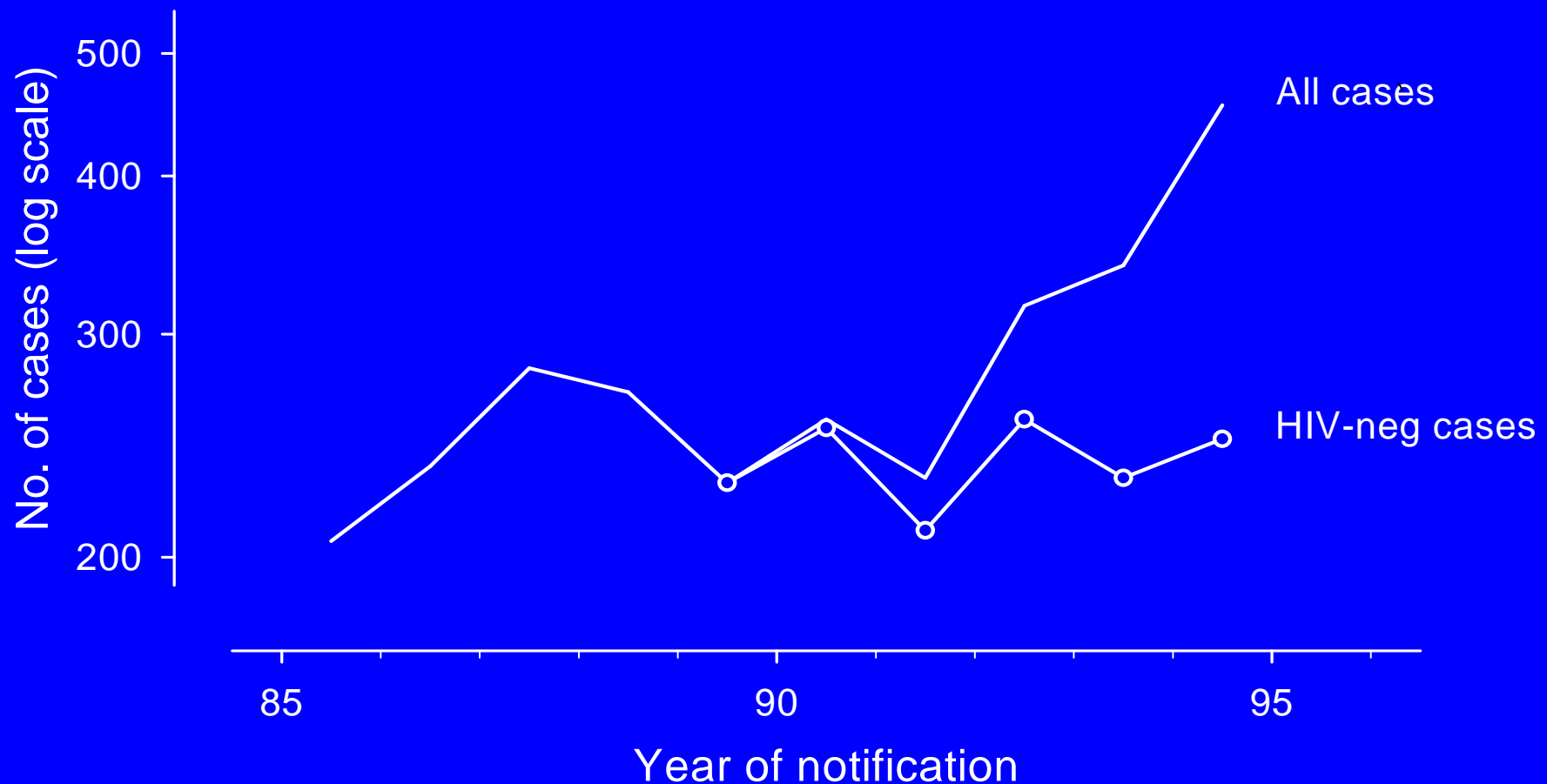


Ambulatory care and community based approaches provide a way to treat large numbers of patients rapidly, and safely



We have not focused enough on the HIV epidemic...

Impact of HIV Infection on Tuberculosis Notifications in Chiang Rai, Thailand, 1985 - 1994



Yanai H, et al. AIDS 1996;10:527-31

Intensified TB case-finding among HIV-positive people, 2005–2009. The percentage of estimated HIV-positive people who were screened for TB is shown above the line.^a



^a Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people accounted for by reporting countries.



we have not addressed MDR-TB in Children...



Between 10% and 30% of patients

- Diagnostics poor
- Treatment has not been optimized
- Outcomes/deaths not properly measured

Our case detection is low...

Estimates of the case detection rate for all cases (%), 1995–2009*

	1995			2000			2005			2009		
	BEST ^b	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
High-burden countries	44	41	47	42	39	45	55	52	59	64	60	68
AFR	38	36	40	38	36	40	42	40	45	50	48	53
AMR	68	63	74	70	66	76	75	70	80	79	74	85
EMR	23	20	26	25	22	28	46	41	53	70	62	79
EUR	62	58	67	76	70	82	80	74	86	80	74	85
SEAR	53	47	60	49	44	56	58	51	66	65	58	74
WPR	41	35	48	40	35	46	66	59	74	70	64	78
Global	46	43	49	45	43	48	56	53	59	63	60	67

Low case detection:

- one third of patients (over 3 million) are not detected each year
- mortality has stayed roughly the same

Reasons for low case detection:

- No point of care test
- Poor program performance
- Lack of integration with health system
- Lack of engagement with the private sector



We have no aspirational goal...

**UNICEF
(2008-)**



**UNAIDS
(2010-)**

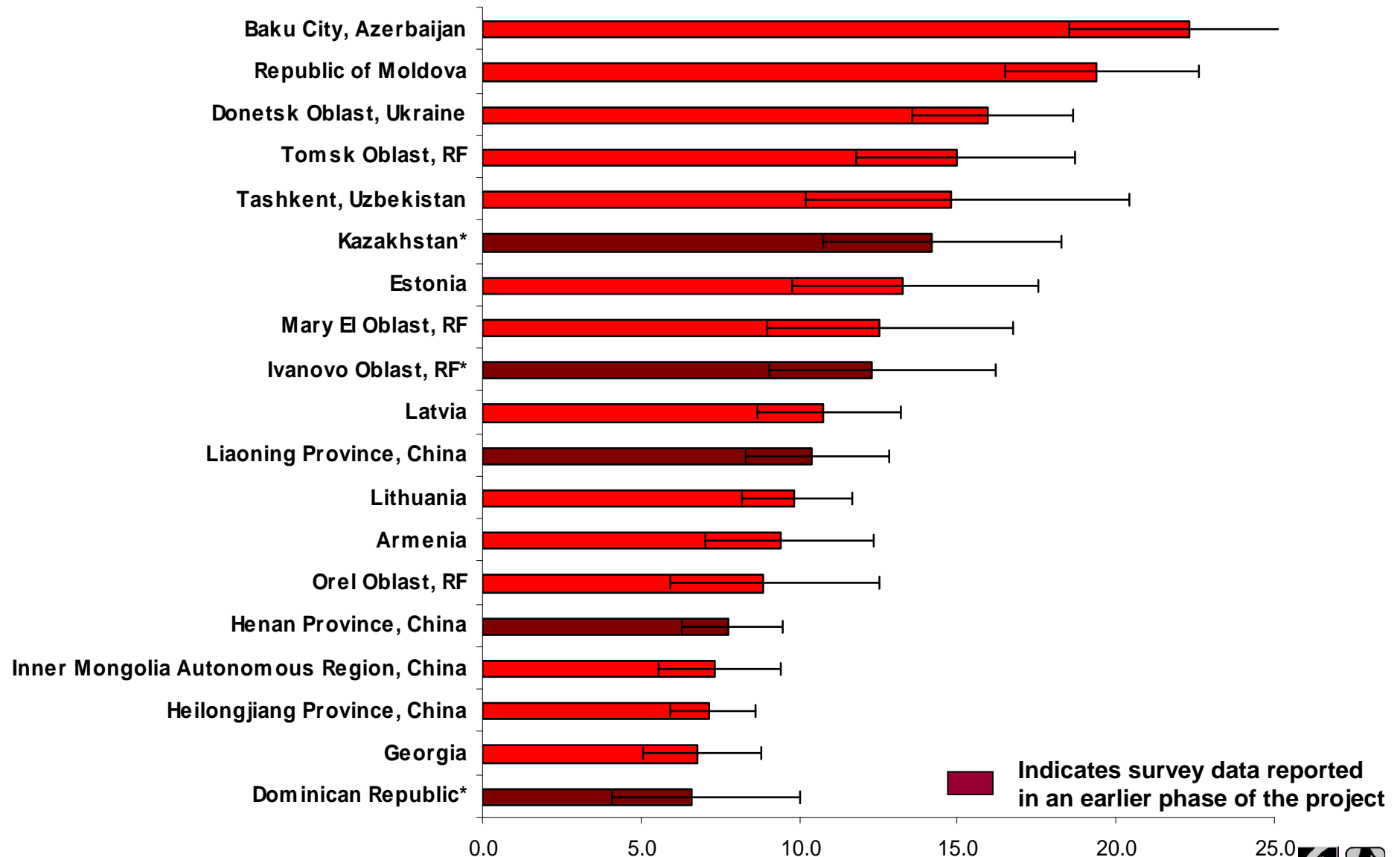


CONSEQUENCES OF INACTION



Photo: Open Society Institute/Pep Bonet

19 settings with $\geq 6\%$ MDR among new cases, 1994-2007



New data from Minsk, Belarus

- “Results: Multidrug-resistant tuberculosis was found in 35.3% (95%CI: 27.7-42.8) of new patients and 76.5% (95%CI: 66.1-86.8) of those previously treated. Overall nearly one in two patients enrolled had multidrug-resistant tuberculosis. Extensively drug-resistant tuberculosis was found in 15 of the 107 multidrug-resistant tuberculosis patients (14.0%; 95%CI: 7.3-20.7). Patients under 35 years old have shown a 2 times higher odds of MDR-TB than those 35 and older.”

Skrahina et al., *European Respiratory Journal* (e-pub Oct 20th)



Global distribution of countries reporting at least one XDR-TB case by March 2011

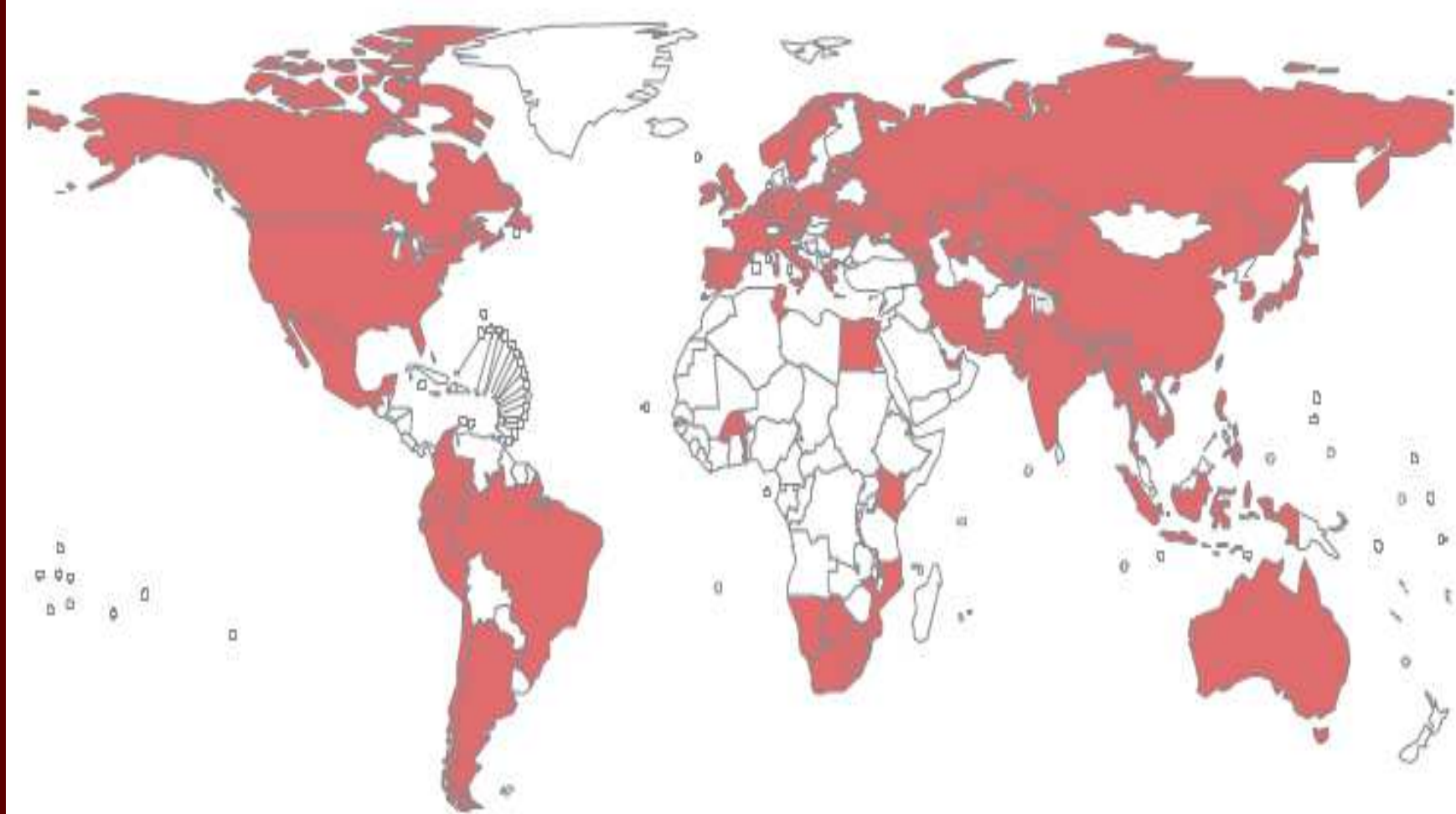




Photo: Tara Lloyd

WE ASPIRE TO A WORLD WITH
ZERO TB DEATHS

Thank you

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