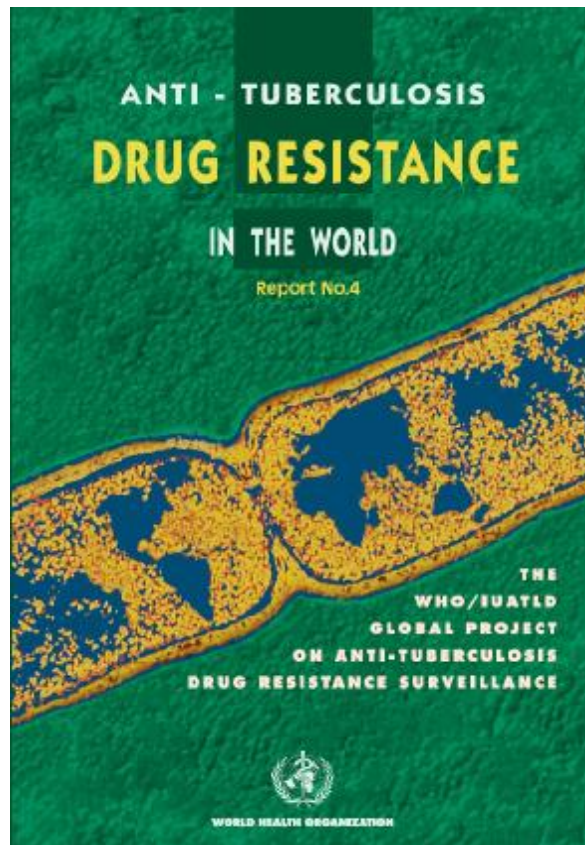
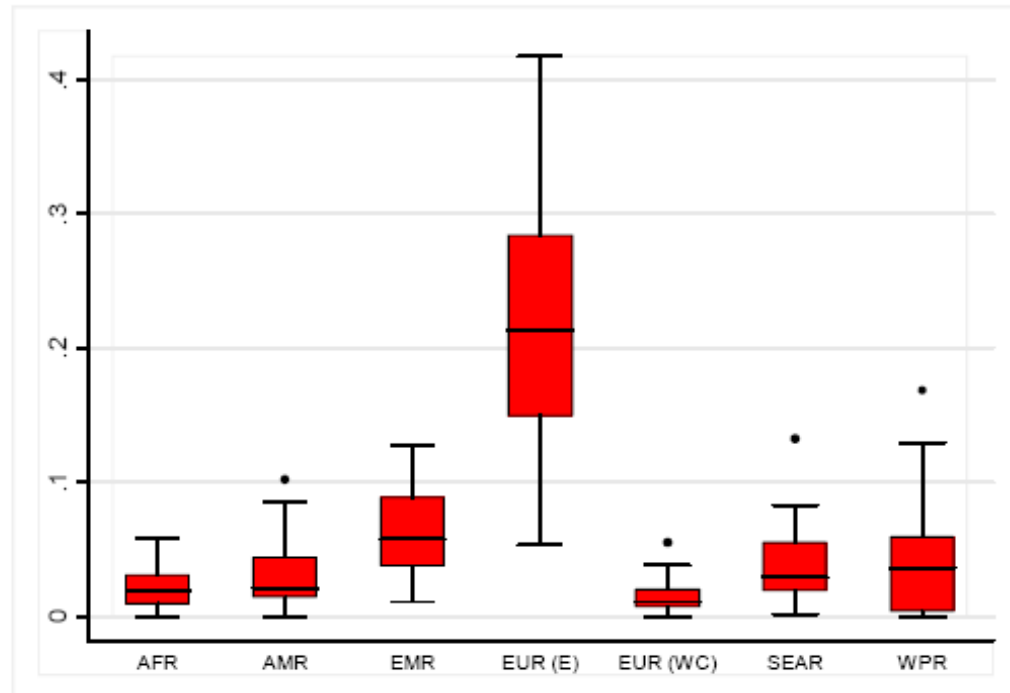


# Number of MDR/XDR TB Patients under Treatment: Implications for the Future

Megan Murray, MD, ScD  
Harvard School of Public Health  
Brigham and Women's Hospital

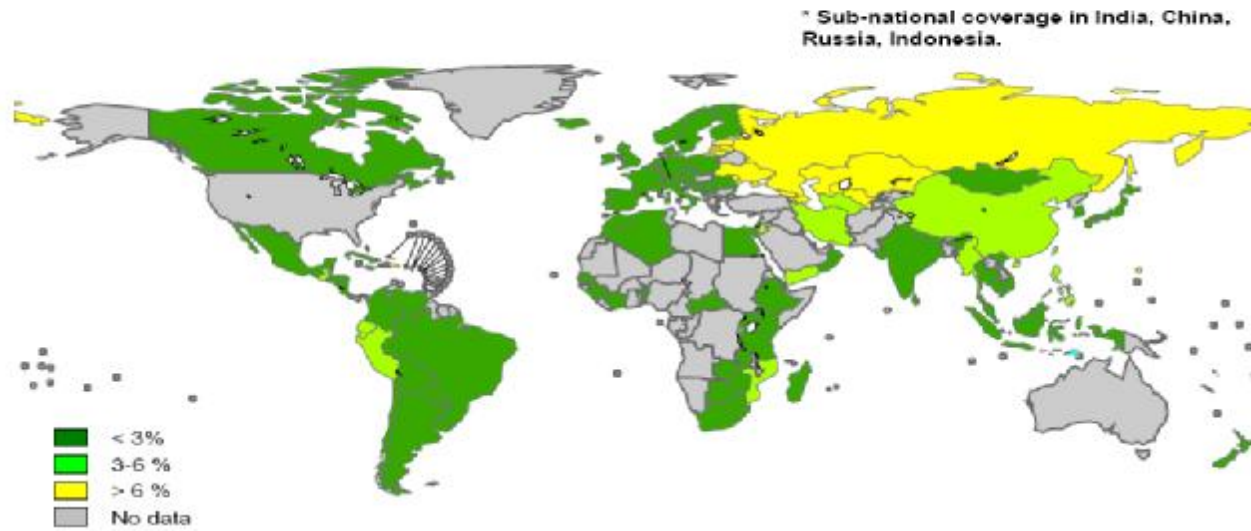


BOX PLOT DISTRIBUTION OF MDR-TB AMONG COMBINED TB CASES BY WHO REGION, 1994-2007

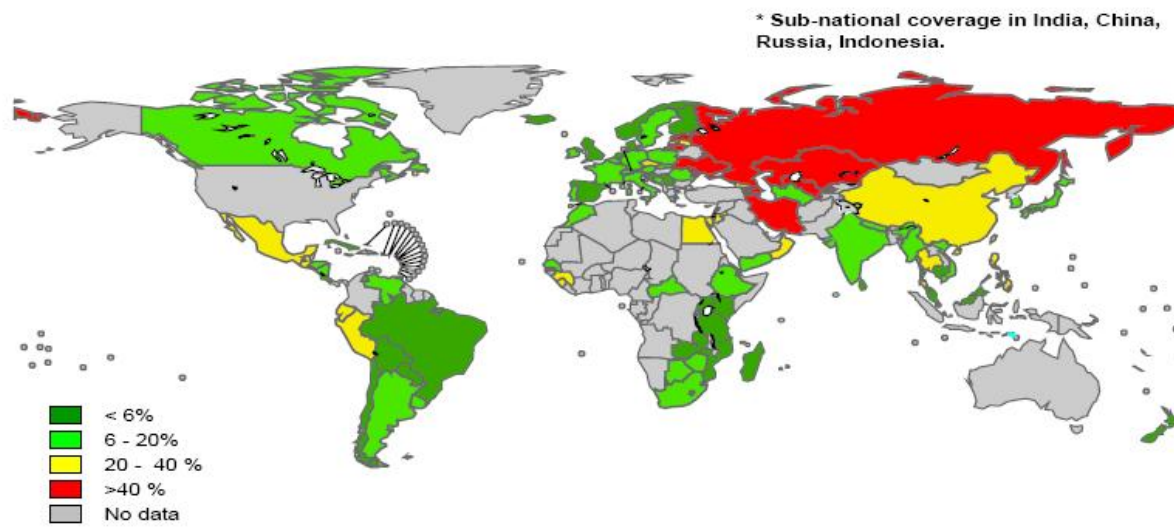


Regions	No. of All TB cases	No. of MDR TB cases		% MDR TB	Low 95% CL	High 95% CL
		Low 95% CL	High 95% CL			
Established Market Economies	105,795	1,317	1,147	1.2	1.1	1.5
Central Europe	50,502	1,201	623	2.4	1.3	7.2
Eastern Europe	416,316	80,057	71,893	19.2	18.0	22.2
Latin America	349,278	12,070	10,523	3.5	3.0	4.4
Eastern Mediterranean Region	601,225	25,475	15,737	4.2	2.6	11.9
Africa low HIV incidence	375,801	8,415	6,889	2.2	1.9	5.0
Africa high HIV incidence	2,856,422	58,296	48,718	2.2	1.9	4.5
South-east Asia	3,464,313	149,615	114,780	4.3	3.5	6.2
Western Pacific Region	2,173,333	152,694	119,886	7.0	6.1	8.1
Surveyed countries	7,953,603	408,325	361,264	5.1	4.7	5.7
Non surveyed countries	2,239,383	80,814	71,684	3.6	3.2	8.4
<b>All countries (n=185)</b>	<b>10,192,986</b>	<b>489,139</b>	<b>455,093</b>	<b>4.8</b>	<b>4.6</b>	<b>6.0</b>

Map 4: MDR-TB among new TB cases 1994-2007

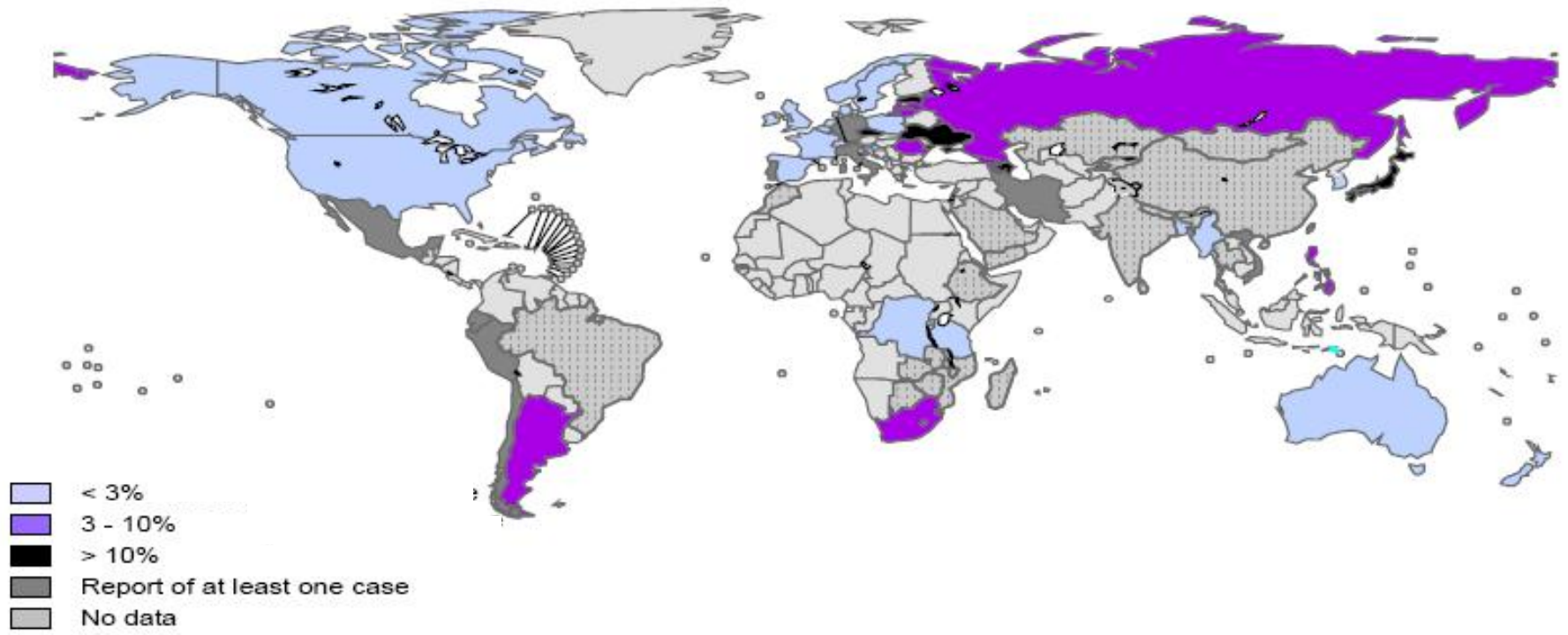


Map 6: MDR-TB among previously treated TB cases 1994-2007



Map 8: XDR-TB

\* Sub-national averages applied to Russia

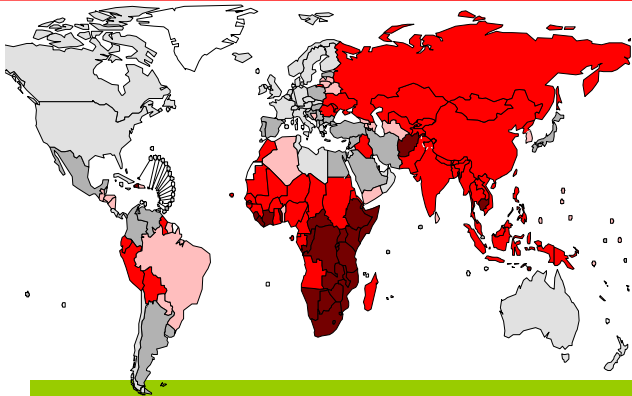


# Are Survey-Based Estimates of the Burden of Drug Resistant TB Too Low? Insight from a Simulation Study

**Ted Cohen<sup>1,2\*</sup>, Caroline Colijn<sup>2</sup>, Bryson Finklea<sup>2</sup>, Abigail Wright<sup>3</sup>, Matteo Zignol<sup>3</sup>, Alexander Pym<sup>4</sup>, Megan Murray<sup>1,2,5</sup>**

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# Latest global TB Estimates - 2006



## All forms of TB

Greatest number of cases in Asia;  
greatest rates per capita in Africa

Estimated  
number of  
cases

Estimated  
number of  
deaths

9.15 million

1.65 million

## Multidrug-resistant TB (MDR-TB)

489,000

120,000

## Extensively drug- resistant TB (XDR-TB)

40,000

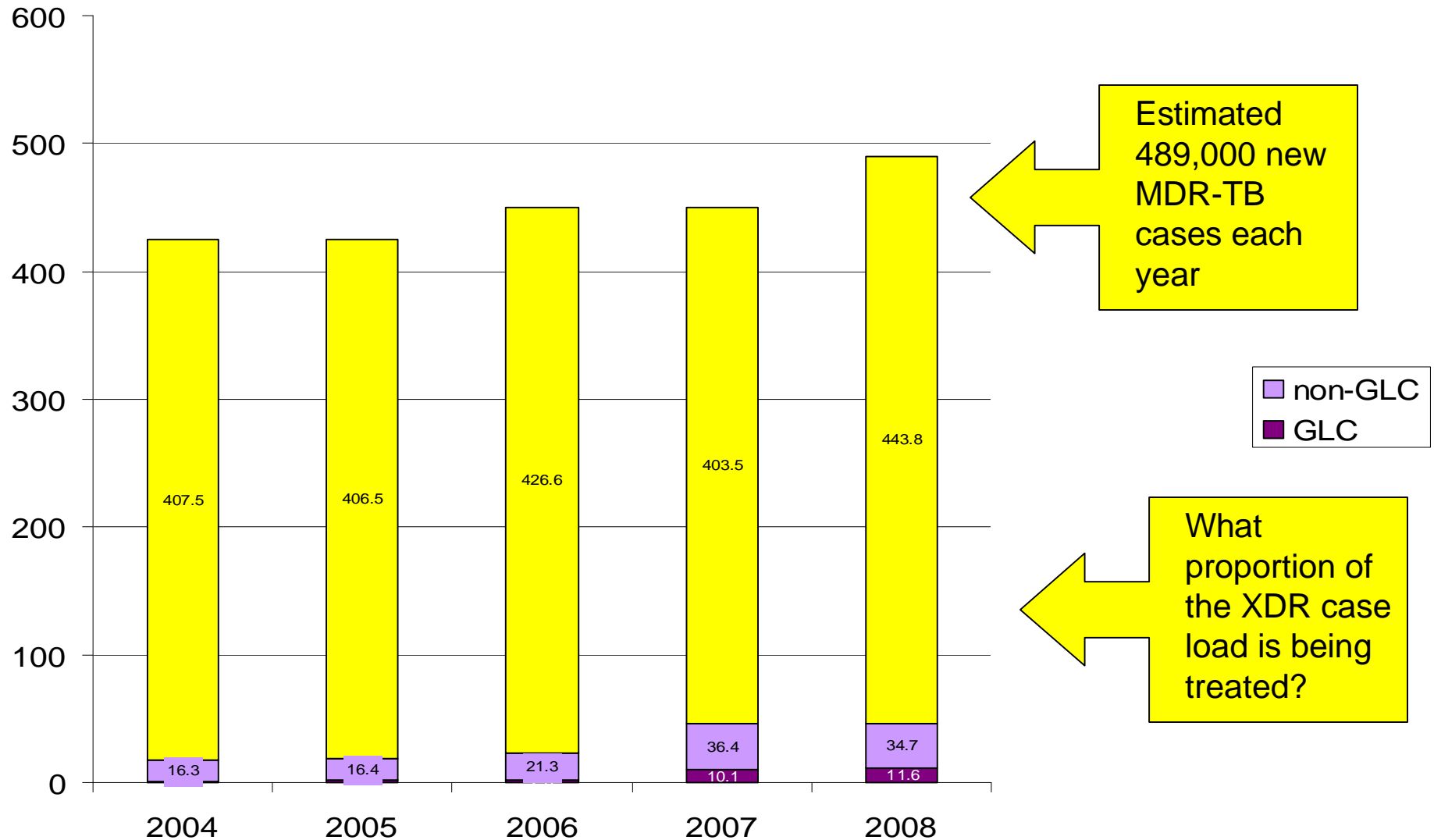
20,000

## HIV-associated TB

700,000

200,000

# Notified cases of MDR-TB (2004-2006) and projected patients to be treated (2007-2008) compared to estimated burden of MDR-TB



# Treatment outcomes for MDR

## MDR Outcomes

- 23 studies reviewed
- 15 countries
- Long term cure rates 33-83%
  - HIV predicts higher failure rates
  - FQ use and surgery associated with better outcomes
  - Worse outcomes with increasing number of drugs to which resistant

Chan E and Iseman MD, Multi-drug resistant and extensively drug resistant tuberculosis: a review. Current Opinion in Infectious Diseases. 2008, 21: 587-595

# XDR Outcomes

Study	Location	XDR Outcomes		MDR Outcomes	
		poor	%	poor	%
Banerjee et al, 2008, CID	California	5/18	.39	80/406	.20
Bonilla et al, 2008, CID	Peru	14/43	.48	89/494	.18
Jeon et al, 2008, CID	South Korea	13/16	.81	8/39	.21
Keshavjee et al, 2008, Lancet	Tomsk, Russia	11/29	.38	78/579	.14
Kim et al, 2008, AJRCCM	South Korea	32/75	.43	177/1332	.13
Migliori et al, 2008, Eur Respir J	Estonia, Germany, Italy, Russian Federation	26/48	.54	75/240	.31
Mitnick et al, 2008, NEJM	Peru	16/48	.35	136/603	.23

## MDR outcomes by drug resistance:

### Peru and Russia

Baseline R		Poor outcome	N	Risk	OR	95% CI
Streptomycin	R	199	911	0.22	0.91	.64-1.32
	S	27	113	0.24		
Capreomycin	R	63	175	0.36	1.87	1.47-2.38
	S	163	849	0.19		
Amikacin	R	27	77	0.35	1.45	1.03-2.05
	S	122	506	0.24		
Kanamycin	R	106	659	0.16	0.88	.69-1.12
	S	120	659	0.18		
Fluoroquinolone	R	41	115	0.36	1.75	1.33-2.32
	S	185	909	0.20		
Cycloserine	R	9	23	0.39	1.8	1.18-8.05
	S	217	1001	0.22		
P-amino sal acid	R	11	28	0.39	1.42	.84-2.38
	S	138	555	0.25		
Ethionamide/Prothionamide	R	84	232	0.36	1.65	1.36-2.00
	S	65	351	0.19		

## XDR outcomes by drug resistance:

### Peru and Russia

Baseline R		Poor outcome	N	Risk	OR	95% CI
Streptomycin	R	27.00	63.00	0.43	NA	
	S	0.00	1.00	0.00		
Capreomycin	R	21.00	45.00	0.47	1.48	.71-8.07
	S	6.00	19.00	0.32		
Amikacin	R	6.00	17.00	0.35	0.92	.41-2.06
	S	10.00	26.00	0.38		
Kanamycin	R	26.00	58.00	0.45	2.69	.44-16.44
	S	1.00	6.00	0.17		
Fluoroquinolone	R	27.00	64.00	0.42	NA	
	S	0.00	0.00	0.00		
Cycloserine	R	4.00	6.00	0.67	1.69	.88-8.21
	S	23.00	58.00	0.40		
P-amino sal acid	R	3.00	3.00	1.00	NA	
	S	13.00	40.00	0.33		
Ethionamide/Prot	R	11.00	25.00	0.44	1.58	.67-8.76
	S	5.00	18.00	0.28		

# Reproductive number

$R_0$ : the average number of secondary infectious cases directly infected by a single infectious case during the entire infectious period when s/he enters a totally susceptible population

$R_0 > 1$

Disease can spread

$R_0 < 1$

Disease cannot spread

# Epidemic potential

- $R_0 = bkD$

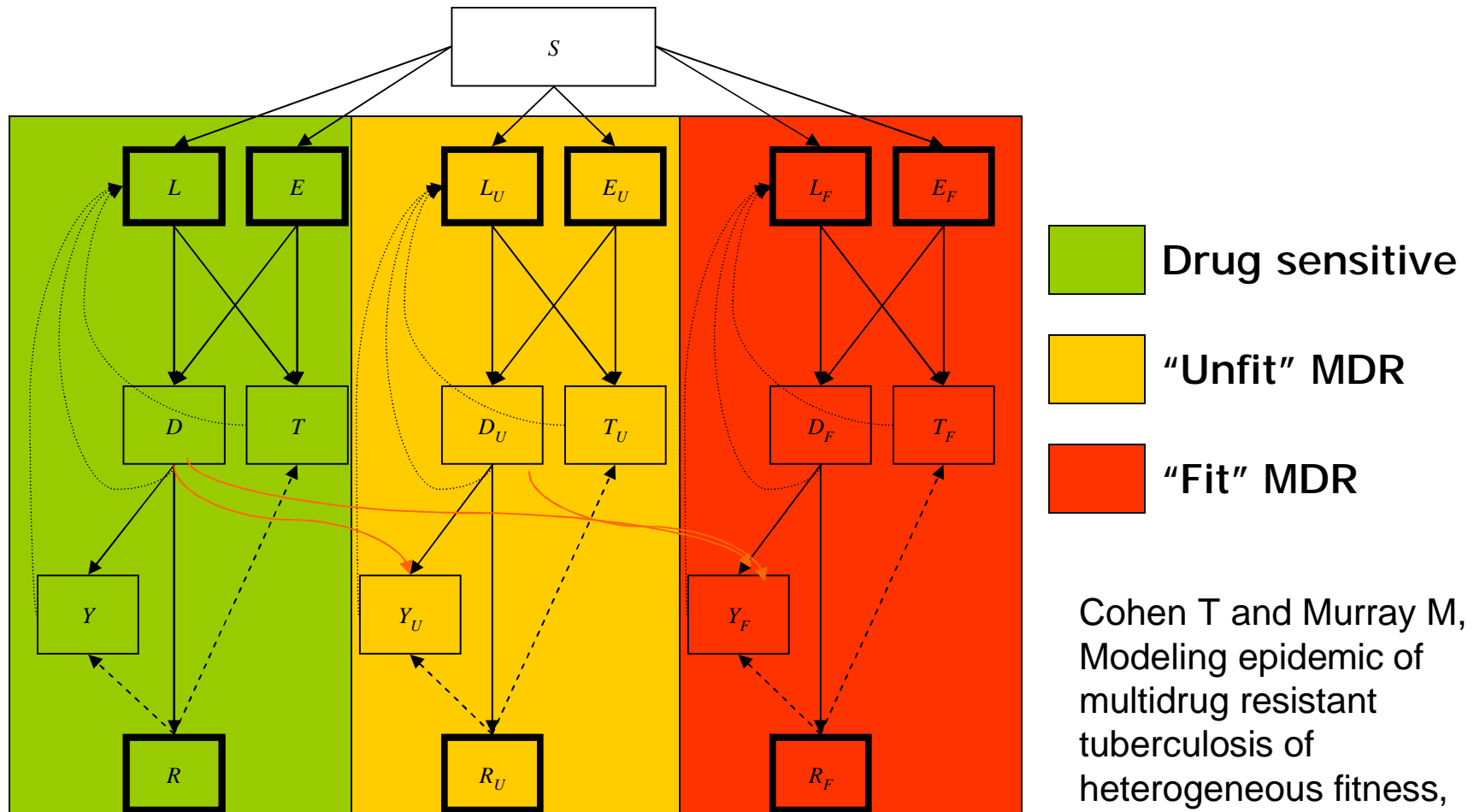
Where  $b$  = transmission probability

$k$  = contact rate

$D$  = average duration of infectiousness

- *Epidemic potential of MDR/XDR depends on:*
  - *Relative fitness or transmissibility of MDR/XDR*
  - *Average number of contact made between infectious cases and susceptible hosts*
  - *Duration of infectious state in those with disease*

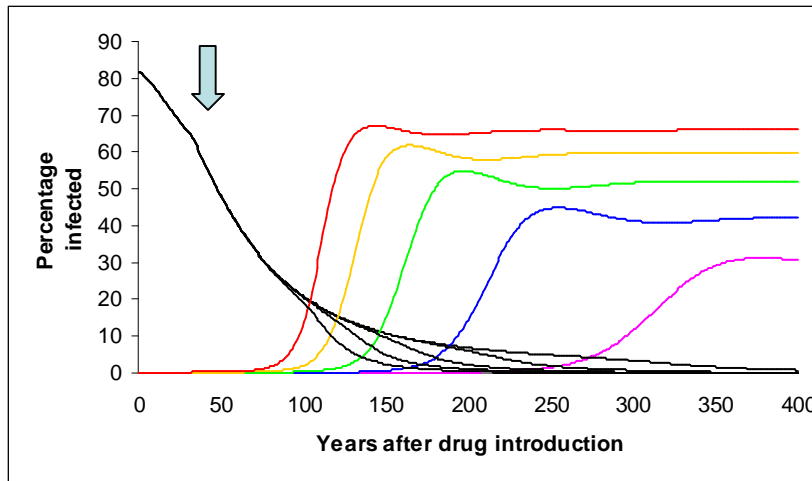
# Predicting the future



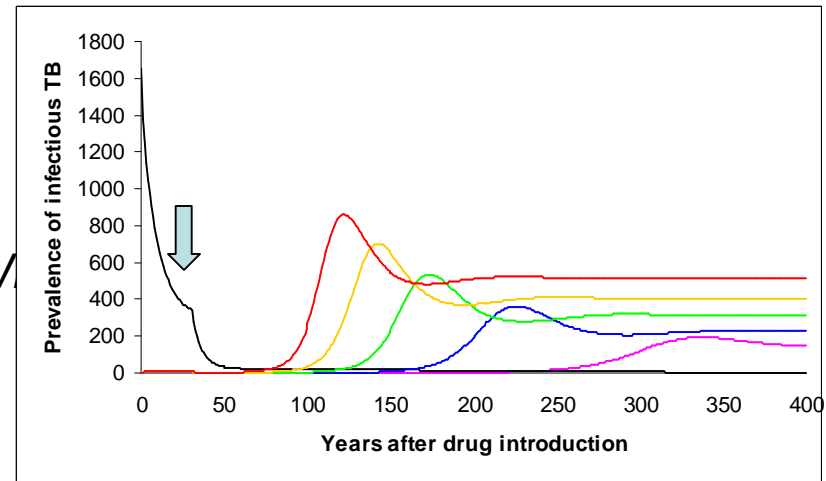
Cohen T and Murray M,  
Modeling epidemic of  
multidrug resistant  
tuberculosis of  
heterogeneous fitness,  
*Nat Med*, 2004

# Projections

## Latent Infection



## Active Disease

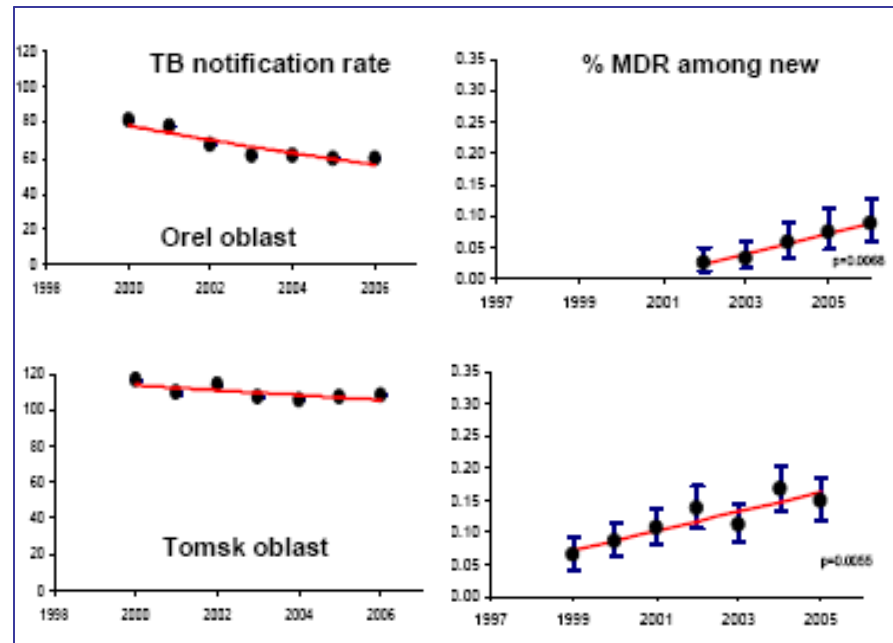
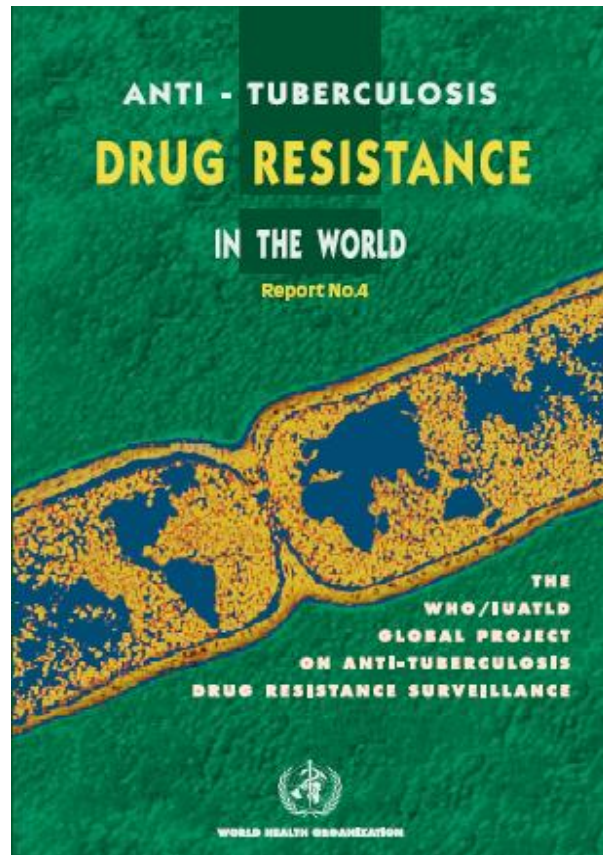


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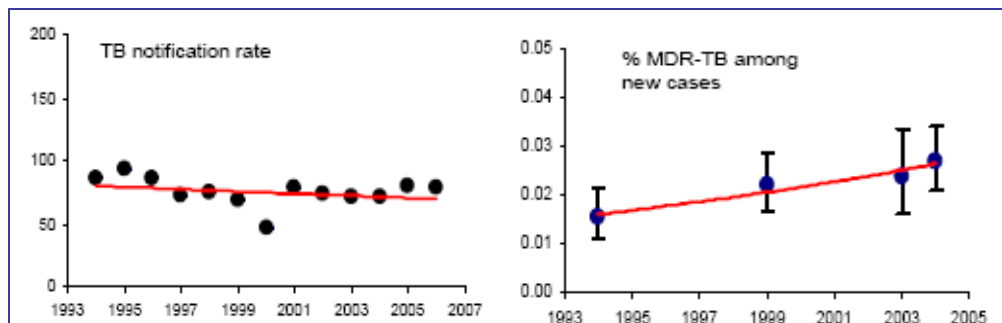
↓ = time of switch to DOTS strategy

- Drug sensitive
- MDR (RF=120%)
- MDR (RF=80%)

# New survey finds highest rates of drug-resistant TB to date



OBLASTS OF THE RUSSIAN FEDERATION, 1997-2007



Peru 1996-2005

# Thanks

- Theodore Cohen (Modeling)
- Christie Jeon (resistance prediction)
- Karen Jacobsen (XDR outcomes)
- Carole Mitnick, Salmaan Keshavjee, Sonya Shin and country teams (Peru and Russia data)