

THE THREAT OF EMERGING DRUG RESISTANCE IN TUBERCULOSIS

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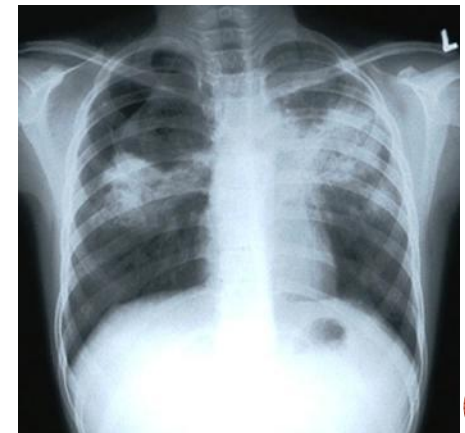
Harvard Medical School



I have no financial or other potential conflicts of interest to disclose

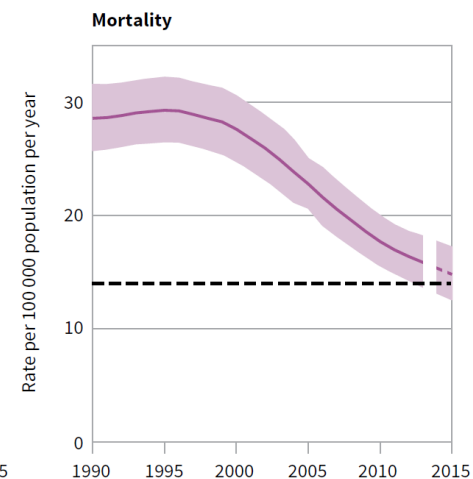
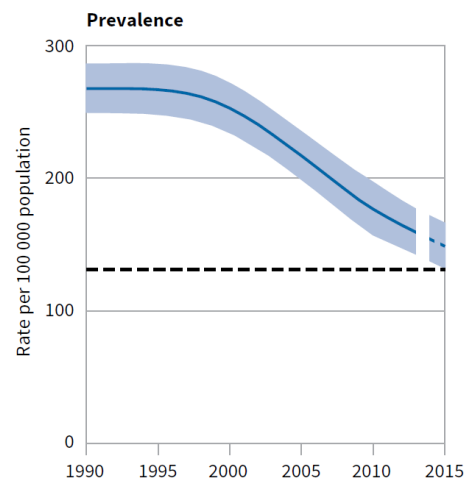
OUTLINE

- Update on the epidemiology of TB drug resistance
- Success and challenges of new diagnostics
- Results of Genome Wide Association Studies and their implications for drug resistance diagnostics
- Overview and prospects of new therapeutics

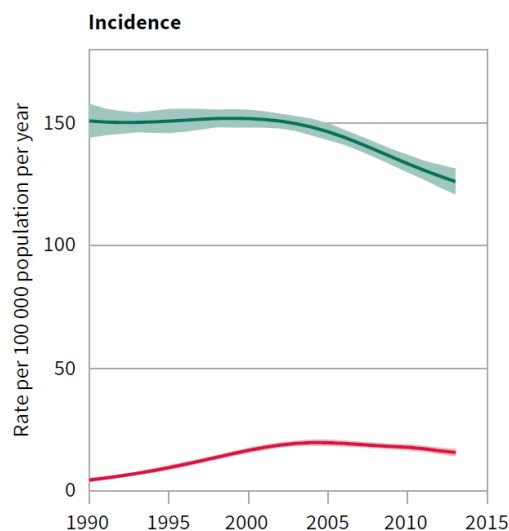


THE GLOBAL TB BURDEN

- Between 1990-2013
 - Prevalence decreased by 41%
 - Mortality decreased by 45%



- Between 2000-2013
 - Incidence decreased by 1.5%/year



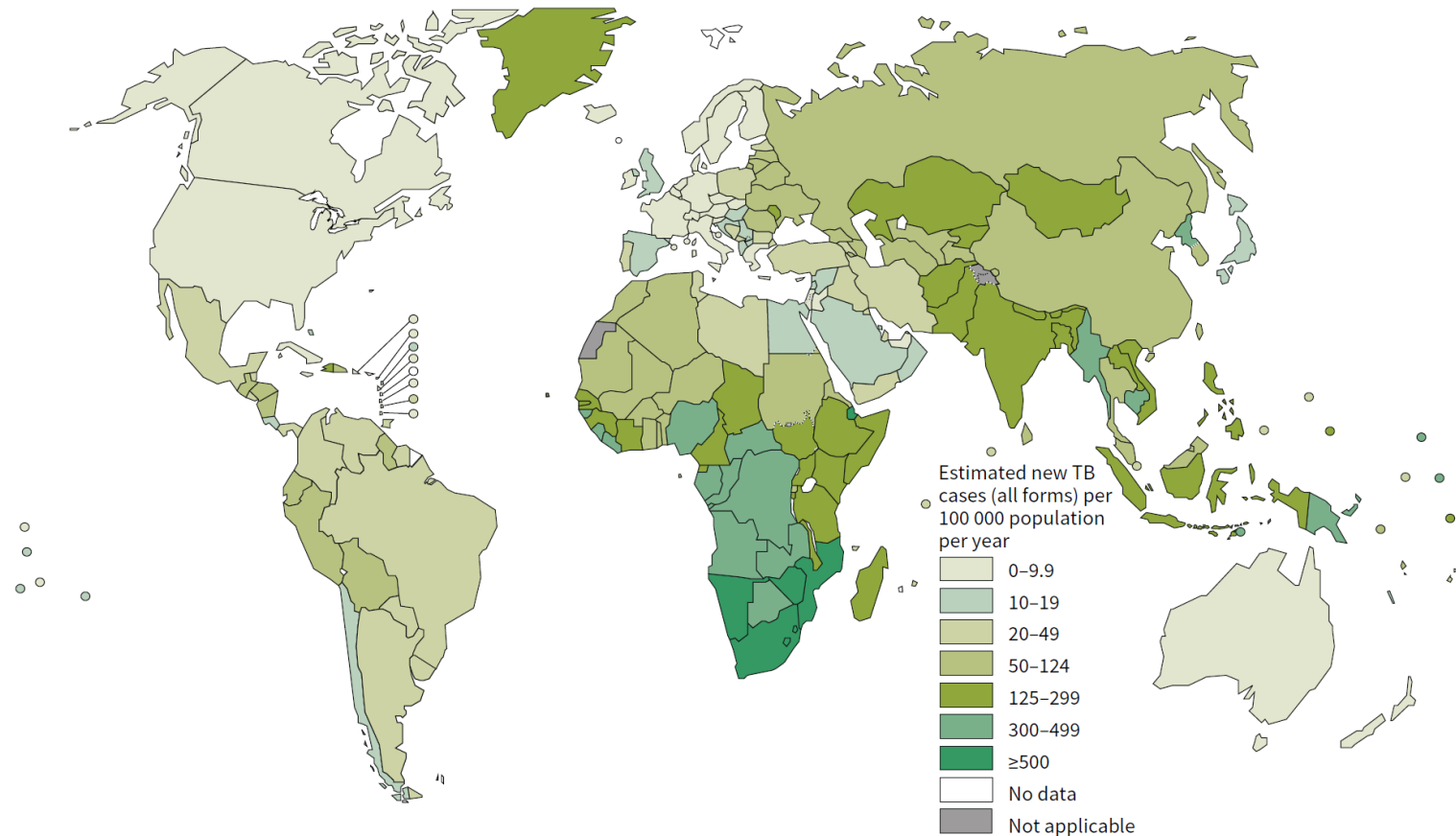
Increase in global total for new TB cases and deaths with the use of improved national data

Decline in prevalence, incidence and mortality less than target in 4/6 world regions

■ In 2013

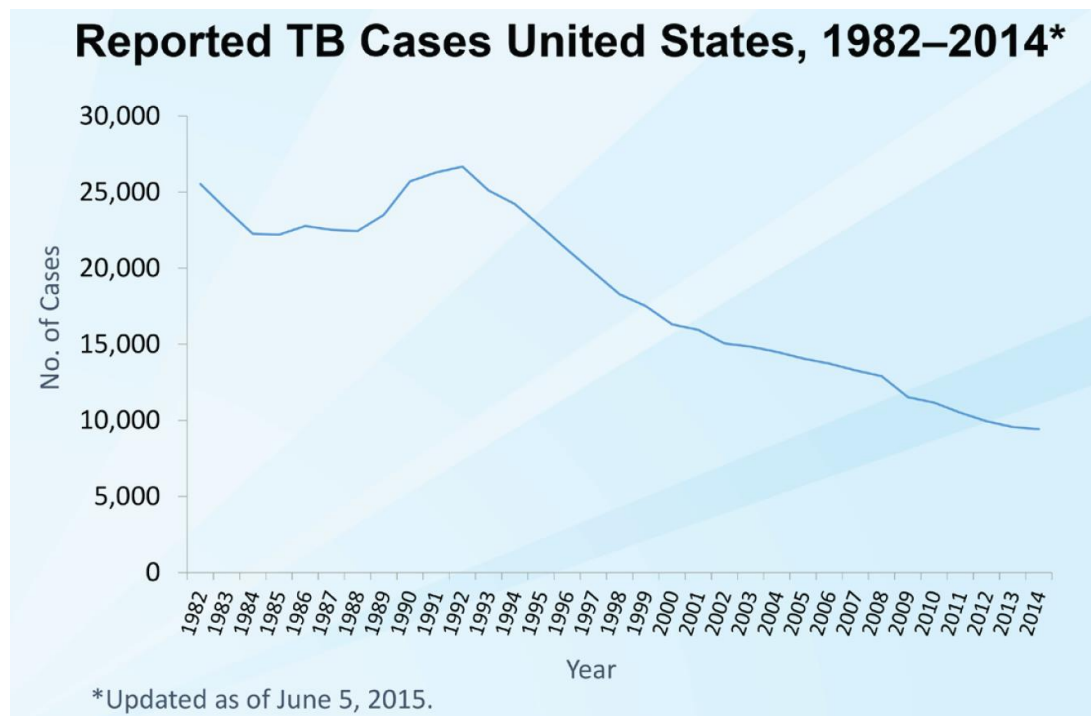
9,000,000 new cases

1,500,000 deaths



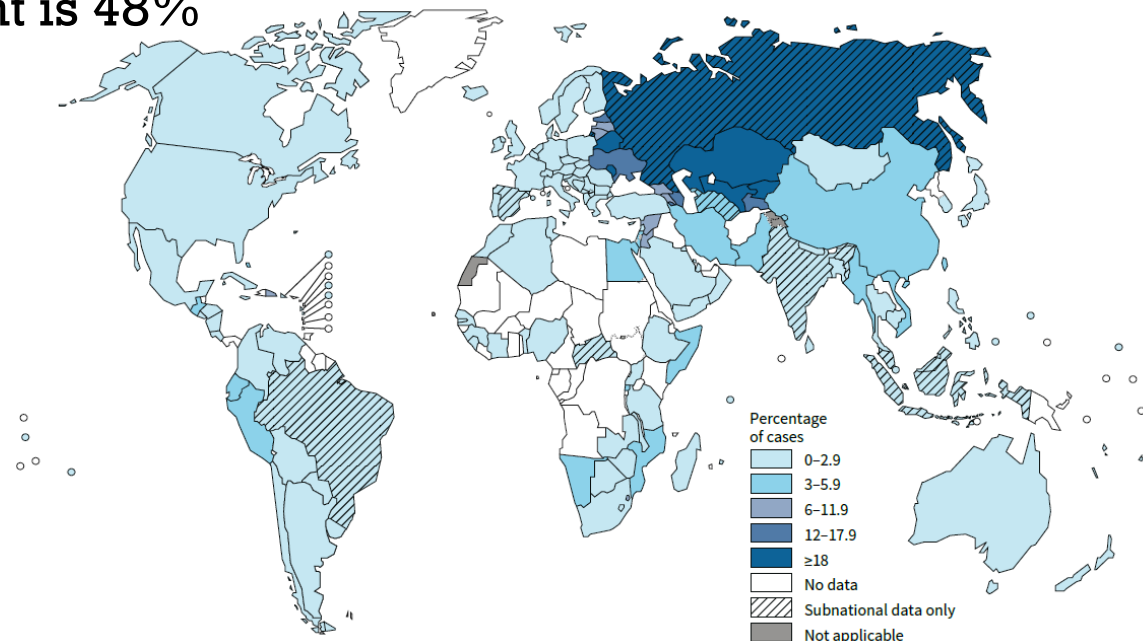
TB BURDEN IN THE US

- 9,421 cases in 2014 (1.5% decrease compared with 2013)
- Lowest decline in incidence in >10 years
- 66% foreign born
- 550 deaths



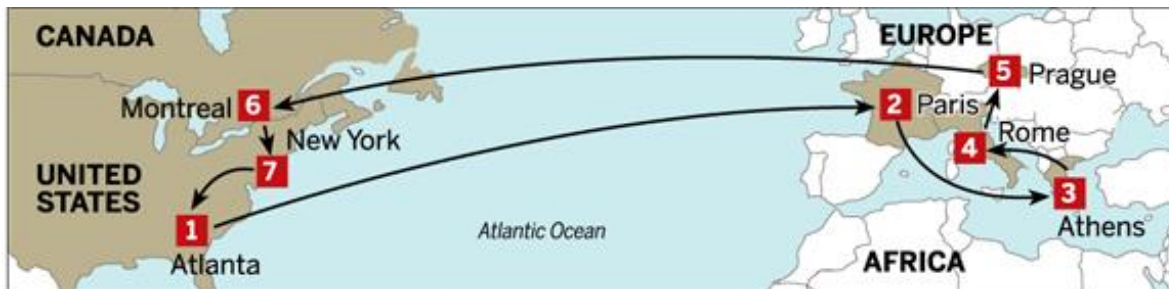
DRUG RESISTANT TB

- 480,000 cases globally, 3.5% of new cases
- Several countries have serious epidemics
- Treatment duration: 18-24months long at 5-10x the cost of treating drug sensitive TB
- 136,000 or 45% of cases were diagnosed
- Only 70% of diagnosed cases receive treatment
- The cure rate on treatment is 48%



DRUG RESISTANT TB IN THE US

- 10% of TB is resistant to 1 or more drugs, 7% is resistant to INH
- 1% of TB in the US is MDR (91 cases in 2014)
- Increasingly MDR is diagnosed in the foreign born, 88% in 2014 vs 33% in 1993



- Drug resistance is estimated to be associated with 50 deaths annually (2013)

ADDRESSING THE MDR-TB CRISIS

- Prevention
- Infection control
- Expanding rapid diagnostics for TB/MDR-TB
- Providing immediate access to effective therapy



Prevent the development of drug resistance through high quality treatment of drug-susceptible TB



Expand rapid testing and detection of drug-resistant TB cases



Provide immediate access to effective treatment and proper care

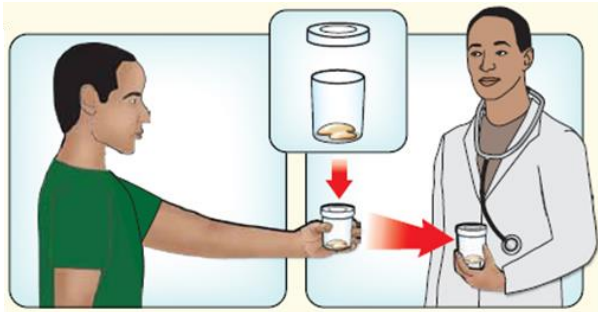


Prevent transmission through infection control



Increase political commitment with financing

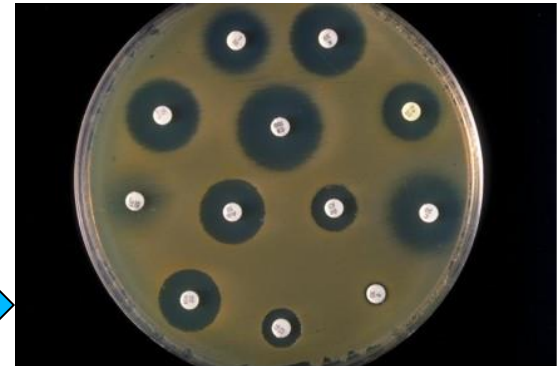
DRUG SENSITIVITY TESTING (DST):



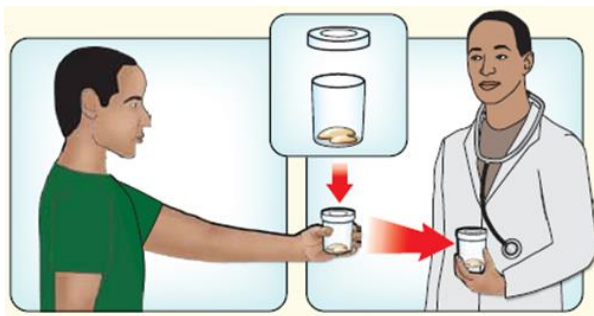
Sputum collection

De-
contamination
Replicate
cultures
with
different
antibiotics

minimum 2 weeks,
up to 2 months



DST results



Sputum collection

Rapid molecular
testing

(0-2 days)

Mutations
detected:

rpoB S531L

Drug
Sensitivity:

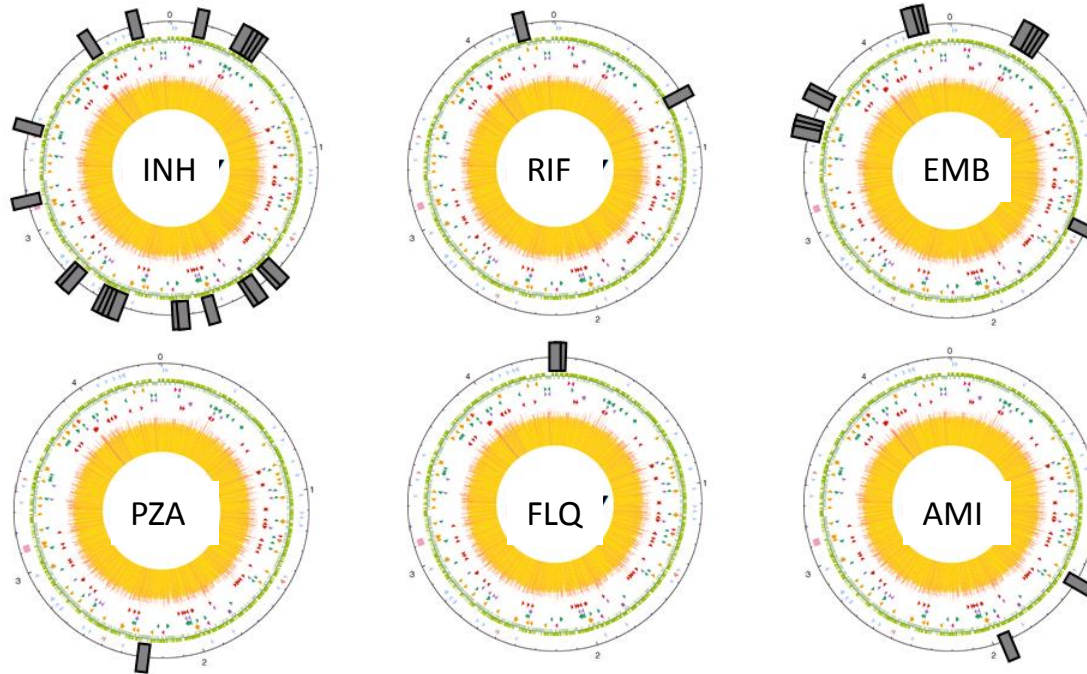
Rifampicin=R



XPRT MTB/RIF



GENETIC BASIS OF DRUG RESISTANCE



TB DRUG RESISTANCE

Drug	Locus	No. of isolates				Accuracy values	
		Resistant		Susceptible		Sensitivity (%)	Specificity (%)
		With mutation	Without mutation	With mutation	Without mutation		
RIF	<i>rpoB</i>	169 ^a	5	9	131	97.1	93.6
INH	<i>katG</i>	181	31	0	102	85.4	100
	<i>inhA</i>	35	177	0	102	16.5	100
	<i>katG</i> and/or <i>inhA</i>	192	20	0	102	90.6	100
EMB	<i>embB</i>	121 ^b	33 ^c	11 ^d	149 ^e	78.6	93.1
PZA ^f	<i>pncA</i>	55	10	15 ^g	109 ^h	84.6	85.8
CIP and OFX	<i>gyrA</i>	80	18	5	211	81.6	97.7
KAN	<i>ms</i>	64	47	2	201	57.7	99.0
	<i>eis</i>	32	79	6	197	28.8	97.0
	<i>ms</i> or <i>eis</i>	96	15	8	195	86.5	96.1
AMK	<i>ms</i>	63	7	3	241	90.0	98.8
CAP	<i>ms</i>	38	31	28	217	55.1	88.6
	<i>tlyA</i>	7	62	3	242	10.1	98.8
	<i>ms</i> and/or <i>tlyA</i>	42 ⁱ	27	31	214	60.9	87.3
MDR (RIF and INH)	<i>rpoB</i> and <i>katG</i> and/or <i>inhA</i>	148	15	NA ^j	NA	90.8	94.7



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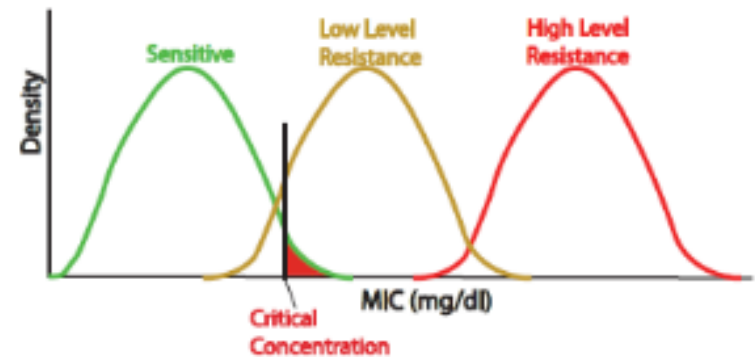
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HOW GENETIC MUTATIONS ASSOCIATE WITH THE RESISTANCE PHENOTYPE?

1. Single mutation with large effect: *katG* S315T
2. Multiple mutations with cumulative effects: *embB* + *Rv3806c*
3. Mutations with no effect on MIC but improve bacterial fitness: *rpoB* + *rpoC*; *embB* + *Rv3792*



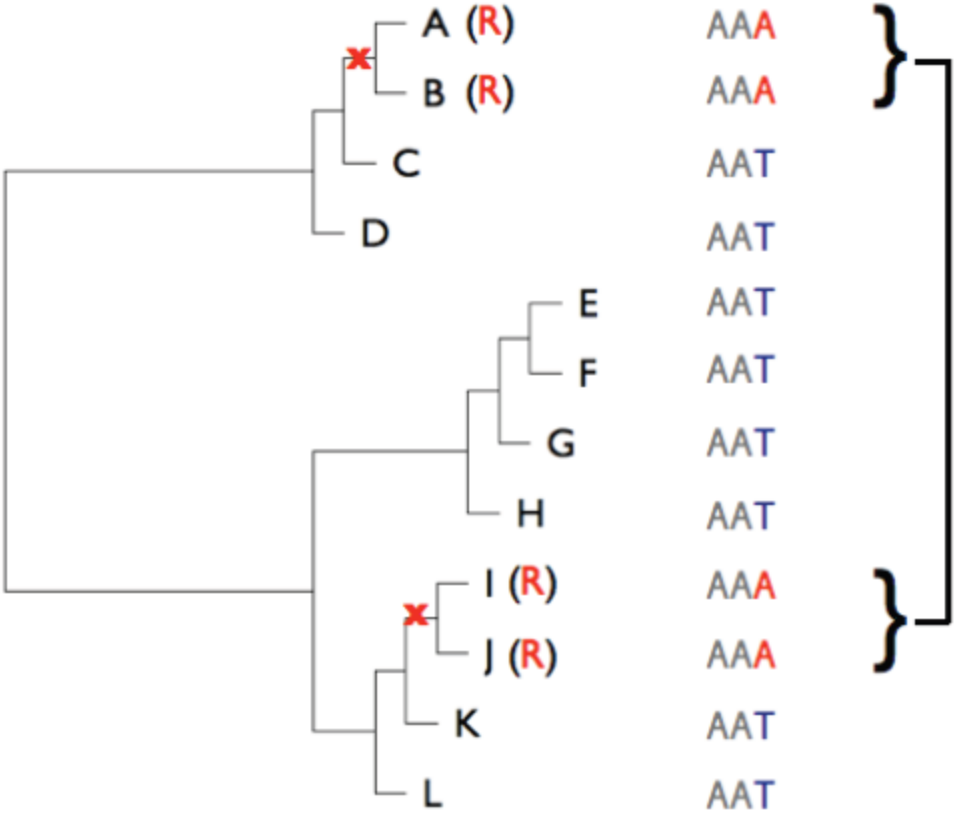
Pym A et al. *Infec Imm* 2002
Safi H et al. *Nat Gen* 2013
Comas I et al. *Nat Gen* 2011



Drug	Selected Mutations
Isonaizid	19
Rifampicin	14
Pyrazinamide	124
Ethambutol	18
Streptomycin	39
Ethionamide	20
Kanamycin	3
Capreomycin	5
Amikacin	2
Ciprofloxacin	7
Levofloxacin	8
Ofloxacin	6
p-aminosalicylic acid	4
Total	250



CONVERGENCE OF CHANGES ALONG THE PHYLOGENETIC TREE

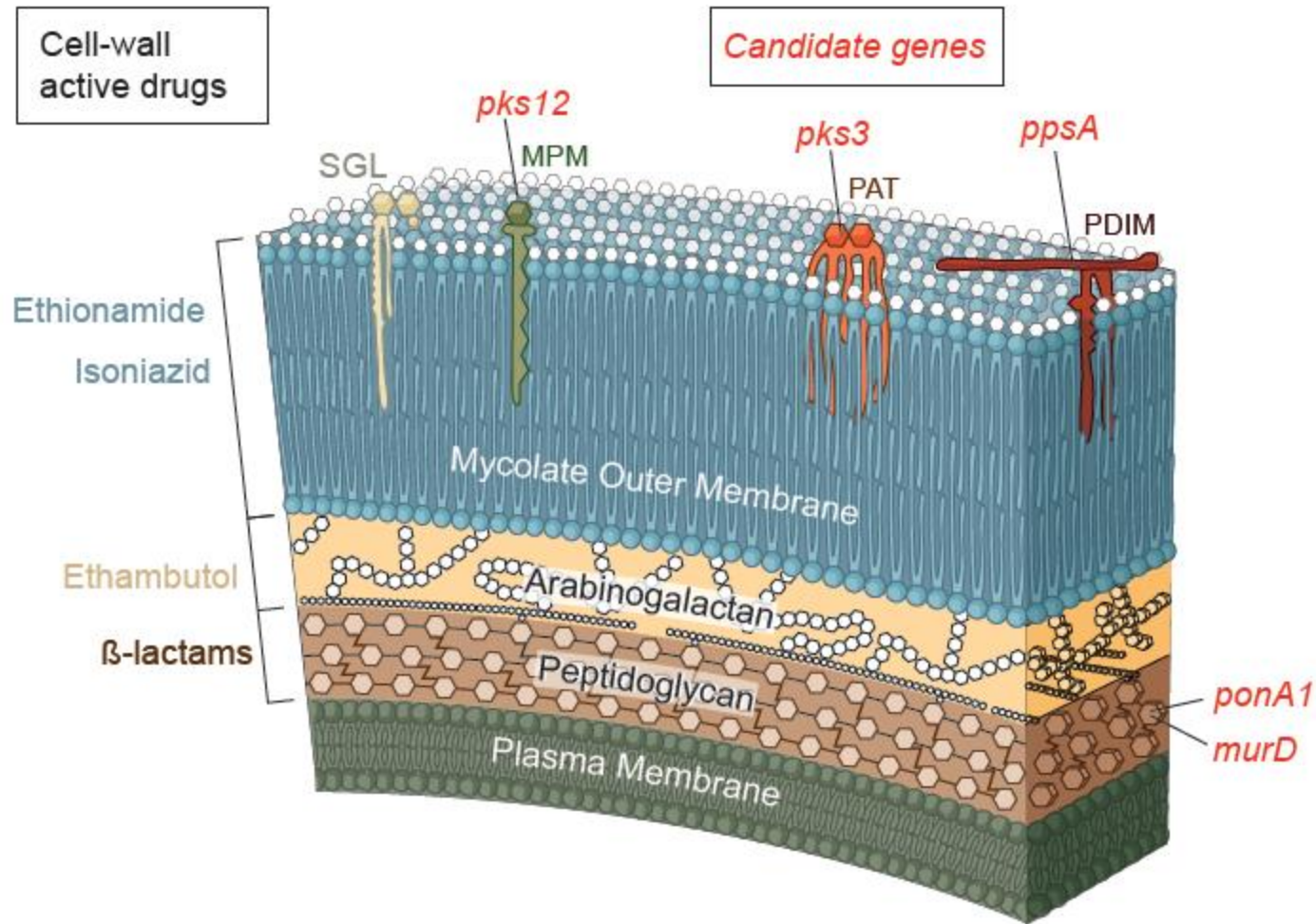


RESULTS

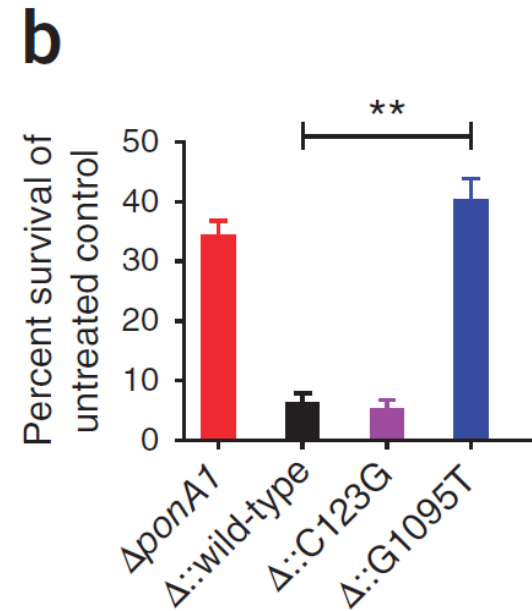
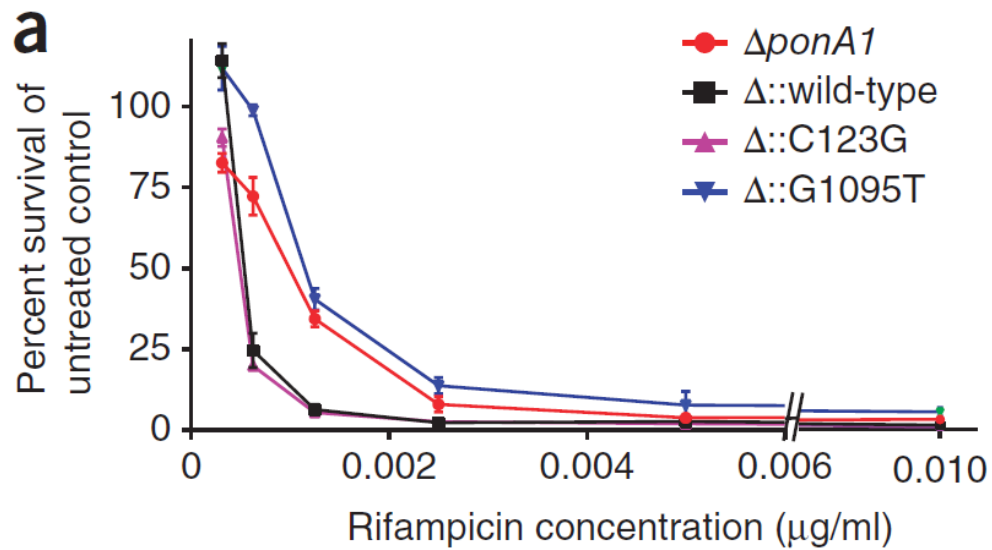
Convergent Gene/Site	Description	Permutation p-value	Nucleotide Site
katG	catalase-peroxidase	0.00000	944GC
rpoB	RNA polymerase beta chain	0.00071	1349CT, 1304AT
rpsL	30S ribosomal protein S12	0.00075	128AG
rrs	16S ribosomal RNA	0.00105	1401AG
embB	membrane indolylacetyltransferase	0.00841	916AG, 918GA
pncA	pyrazinamidase/nicotinamidase	0.00000	multiple
gid	glucose-inhibited division protein B	0.00003	multiple
ethA	monooxygenase	0.00073	multiple
gyrA	DNA gyrase subunit A	0.00410	multiple
inhA promoter	NADH-dependent enoyl-[acyl-carrier-protein] reductase promoter	0.011	multiple
eis promoter	enhanced intracellular survival protein	0.00200	multiple



MYCOBACTERIAL CELL WALL



ALLELIC EXCHANGE



Coming to an office/lab near you: The USB Sequencer



New Tuberculosis Drugs 2012

Bedaquiline

Delamanid



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT



**World Health
Organization**

> **PRESS RELEASES:**

First New TB Drug Approved In 50 Years Must Be Made Widely Available

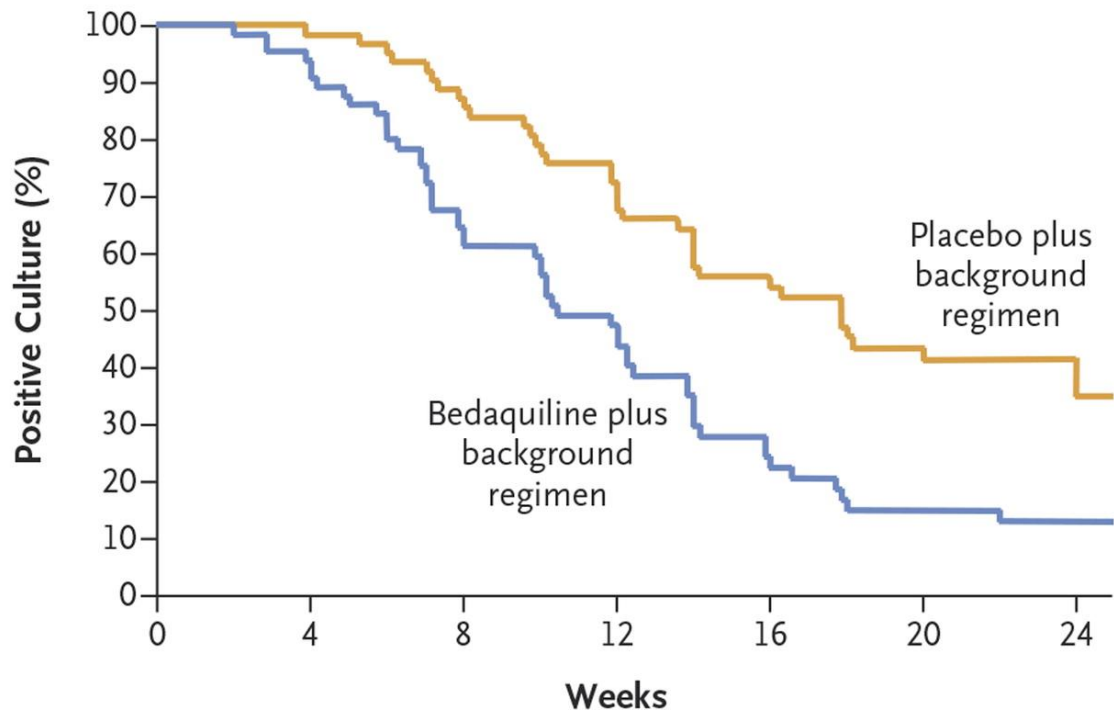
December 31, 2012



Works On Drug Resistant Forms Of The Disease; MSF Calls For Rapid Registration In Countries With High Drug-Resistant TB Burden

An important new TB treatment approved by the US Food and Drug Administration must be made available in countries with high levels of the drug-resistant form of the disease.

Time to Culture Conversion



No. at Risk

Bedaquiline	58	37	25	12	7	3
Placebo	61	53	40	30	22	5



NEW DRUG PIPELINE HIGHLIGHTS

- Nitroimidazole:
 - PA-824 (Pretomanid)
 - TBA-354
 - Delamanid
- ATP Synthase inhibitors
 - Bedaquiline (TMC207) a diarylquinoline
- Oxazolidinones:
 - Linezolid
 - Sutezolid



REFERENCES:

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- 2. Centers for Disease Control. Tb-trends 2014
- 3. Centers for Disease Control. Antibiotic Resistance Threats in the United States, 2013
- 5. Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review. *Eur Respir J.* 2014 Jun;43(6):1763–75.
- 6. Diacon AH et al. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *N Engl J Med* 2014;371:723-732





Clinical Course of the 14-Year-Old Patient with Fulminant Meningoencephalitis

