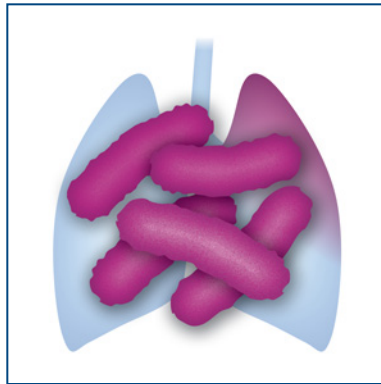


Pneumo Update Europe 2018

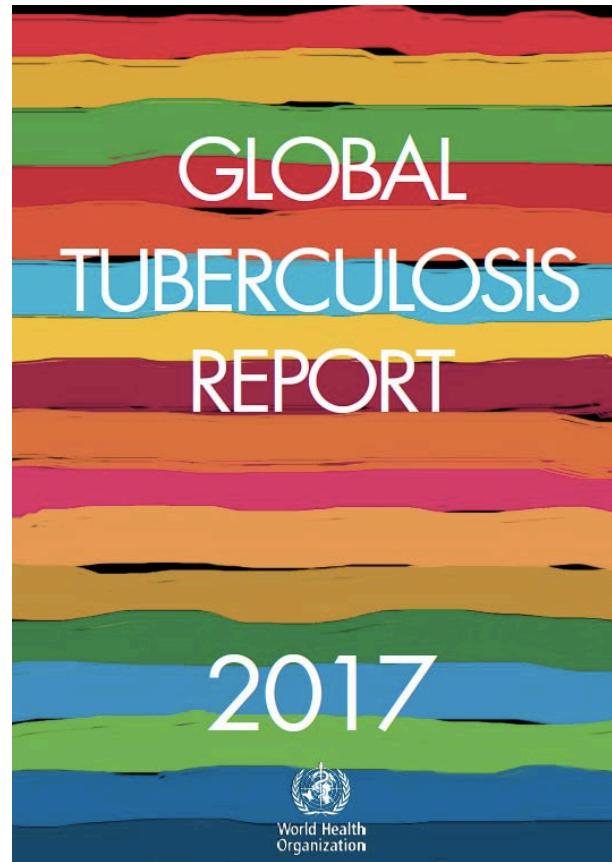
15 - 16 June, Budapest

Tuberculosis



Christoph Lange, Germany

Epidemiology



END TB

2015

by

2035

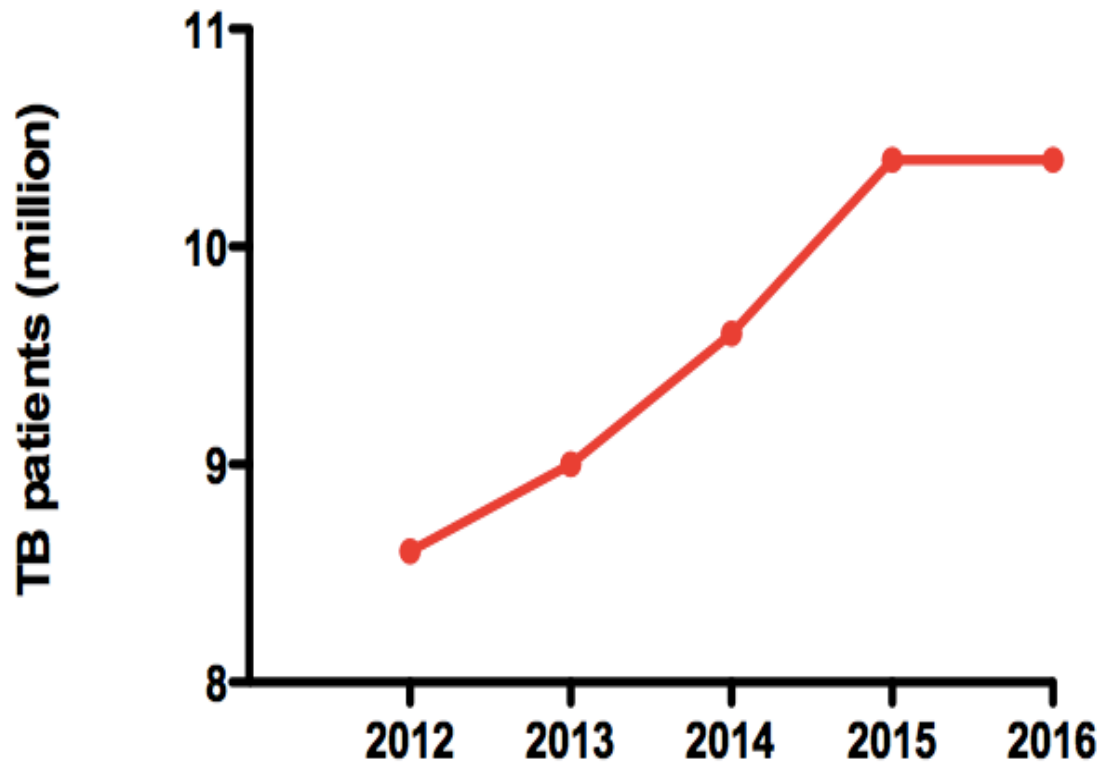


- 95 % reduction in deaths due to TB
- 90 % reduction in TB incidence
- 0 % of affected families facing catastrophic costs due to TB

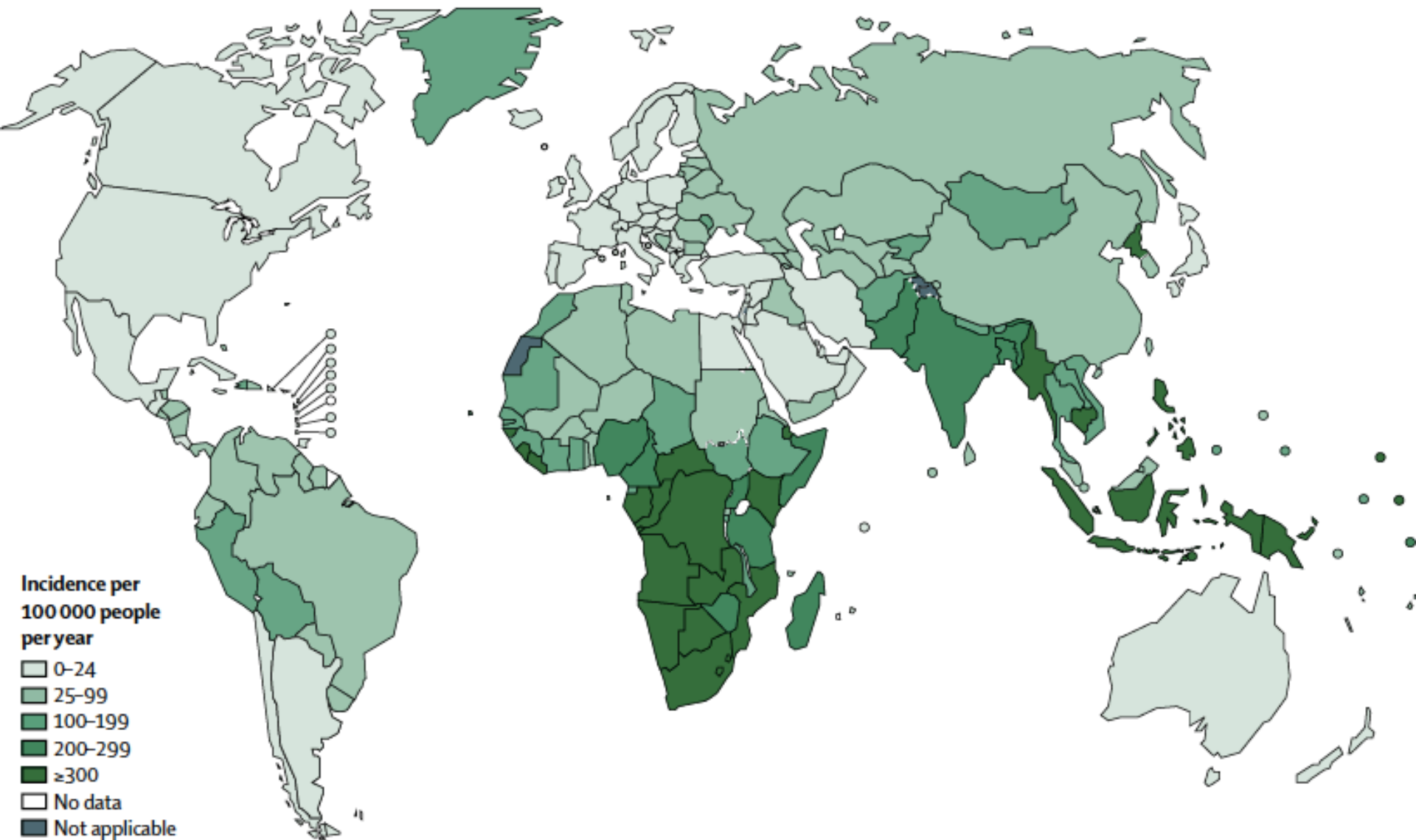
Epidemiology

- #1 cause of death by an infectious disease
- ¼ of the world's population infected
- Increasing *M. tuberculosis* drug resistance

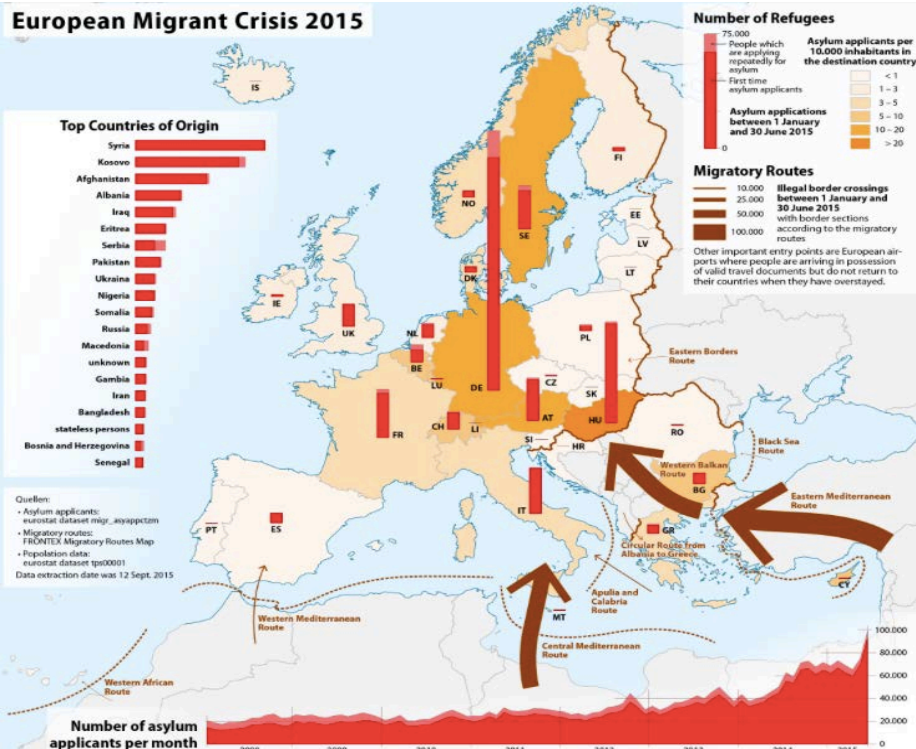
highest number of TB patients in history



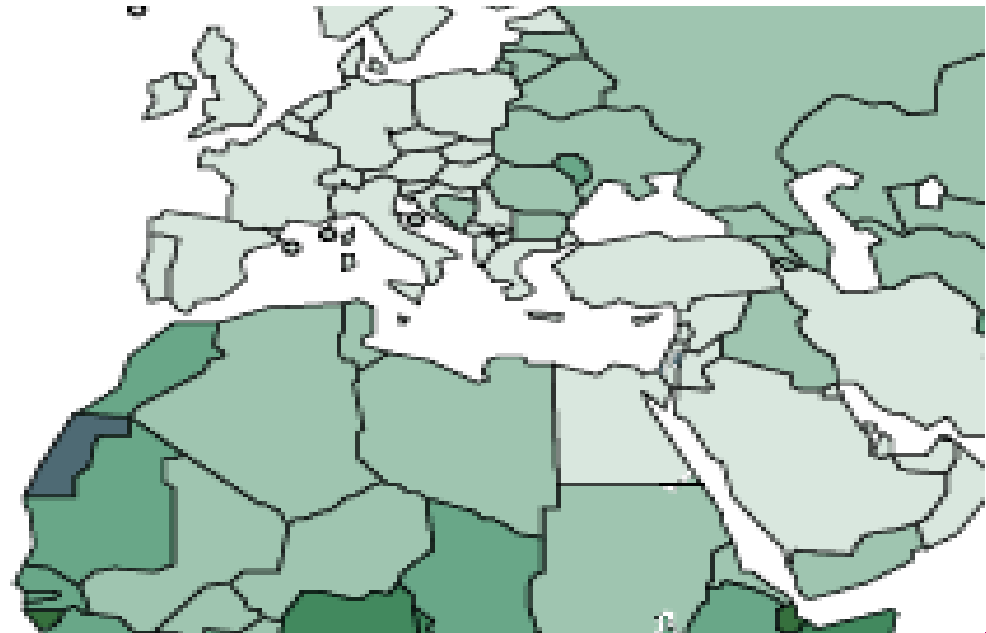
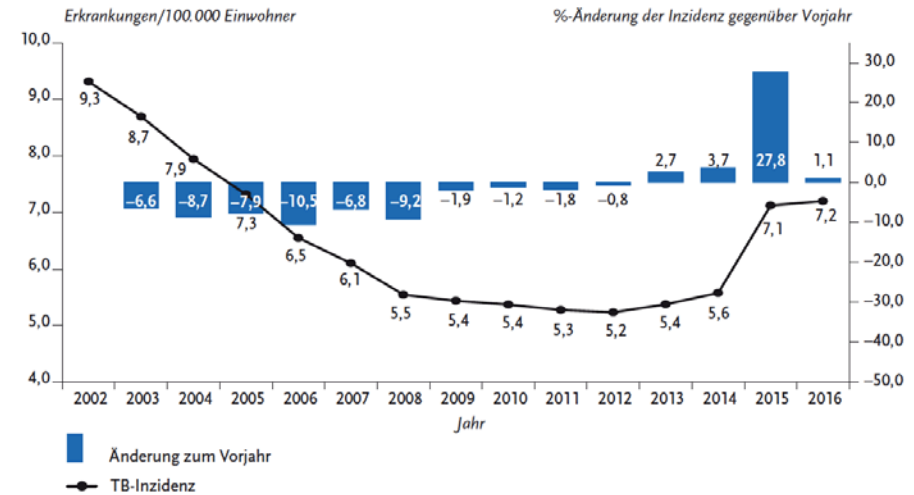
TB is not equally distributed in the world



European Migrant Crisis 2015



Tuberculosis trends Germany 2002-2016



TB-prevalence in migrants to Germany

- selection -

Country	TB prevalence when entering Germany
Somalia	1.871/100.000
Ethiopia	1.037/100.000
Eritrea	822/100.000
Pakistan	616/100.000
Syria	48/100.000

Number needed to screen to detect one case of TB

- in migrants to Germany -

Country	number needed to screen
Somalia	146
Ethiopia	n/a
Eritrea	216
Pakistan	729
Syria	3434

„AMR represents a growing threat to public health and economic growth ...



G20 GERMANY 2017
HAMBURG

... we highlight the importance of fostering R&D, in particular for priority pathogens as identified by the WHO and **tuberculosis**“.

Definitions: MDR- and XDR-TB



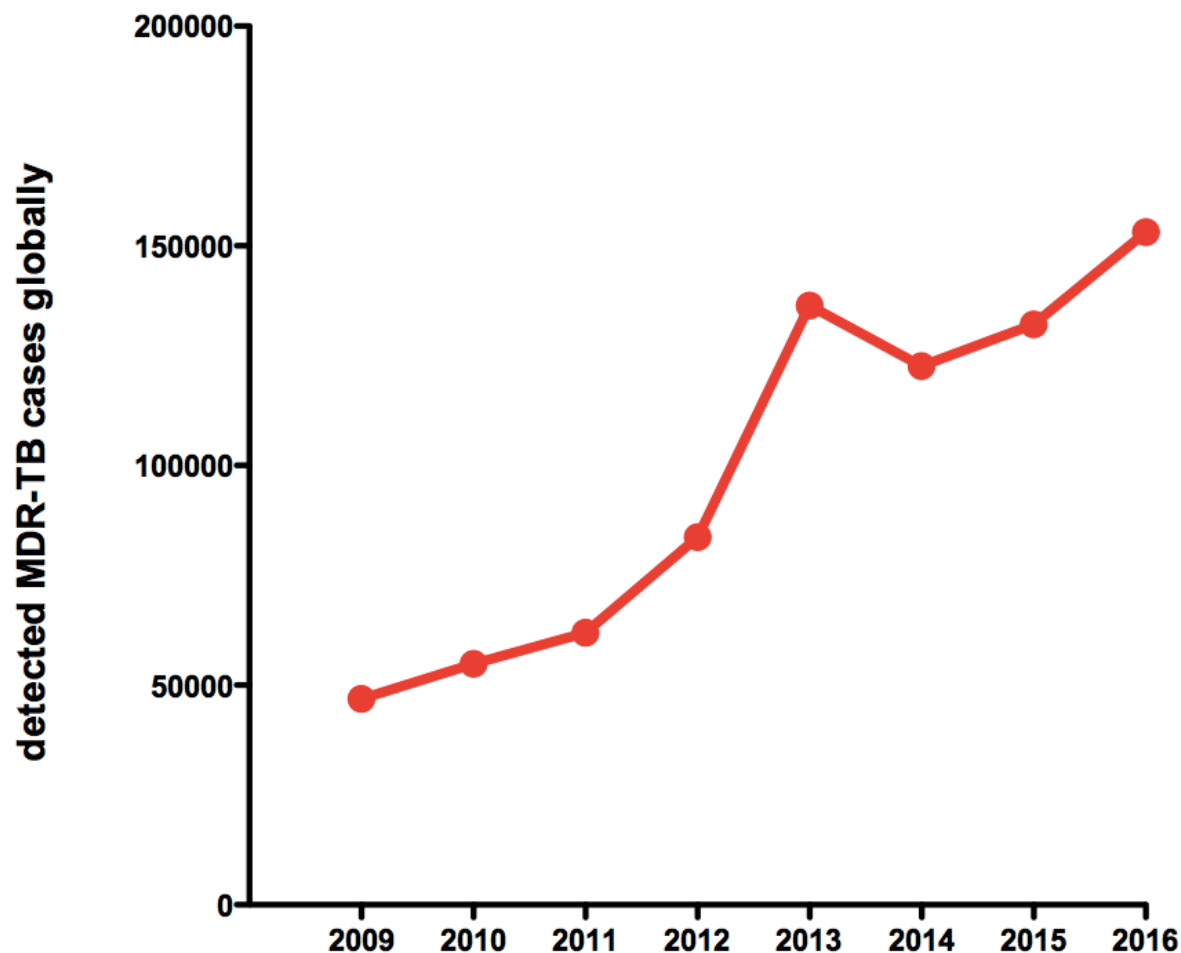
MDR

- Rifampicin
- Isoniazid

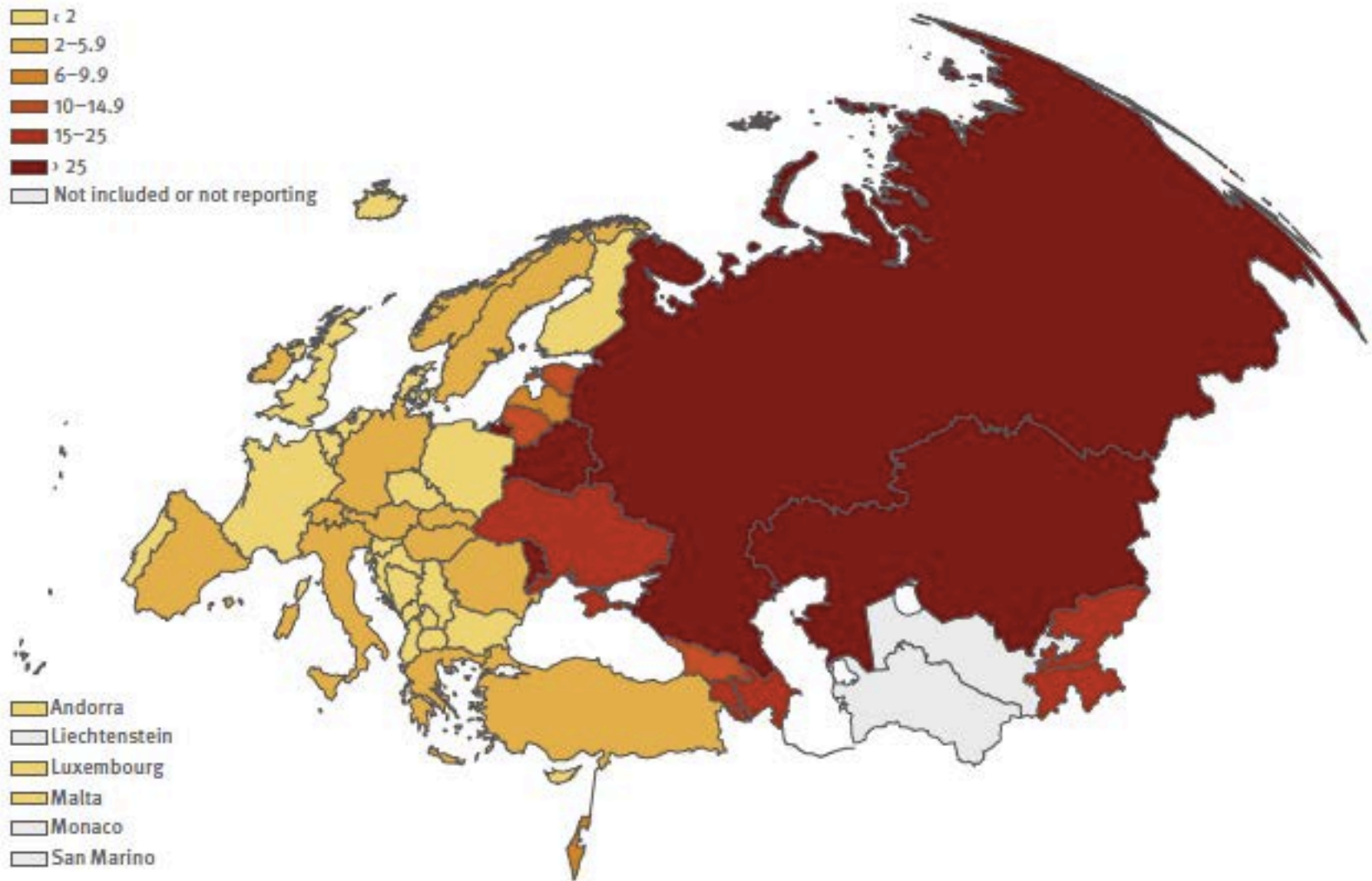
XDR

- MDR
- ≥ 1 Fluoroquinolones
- ≥ 1 „2nd-line injectables“
 - Amikacin
 - Capreomycin
 - Kanamycin

> 20% annual increase in MDR-TB world-wide



MDR-TB in Europe

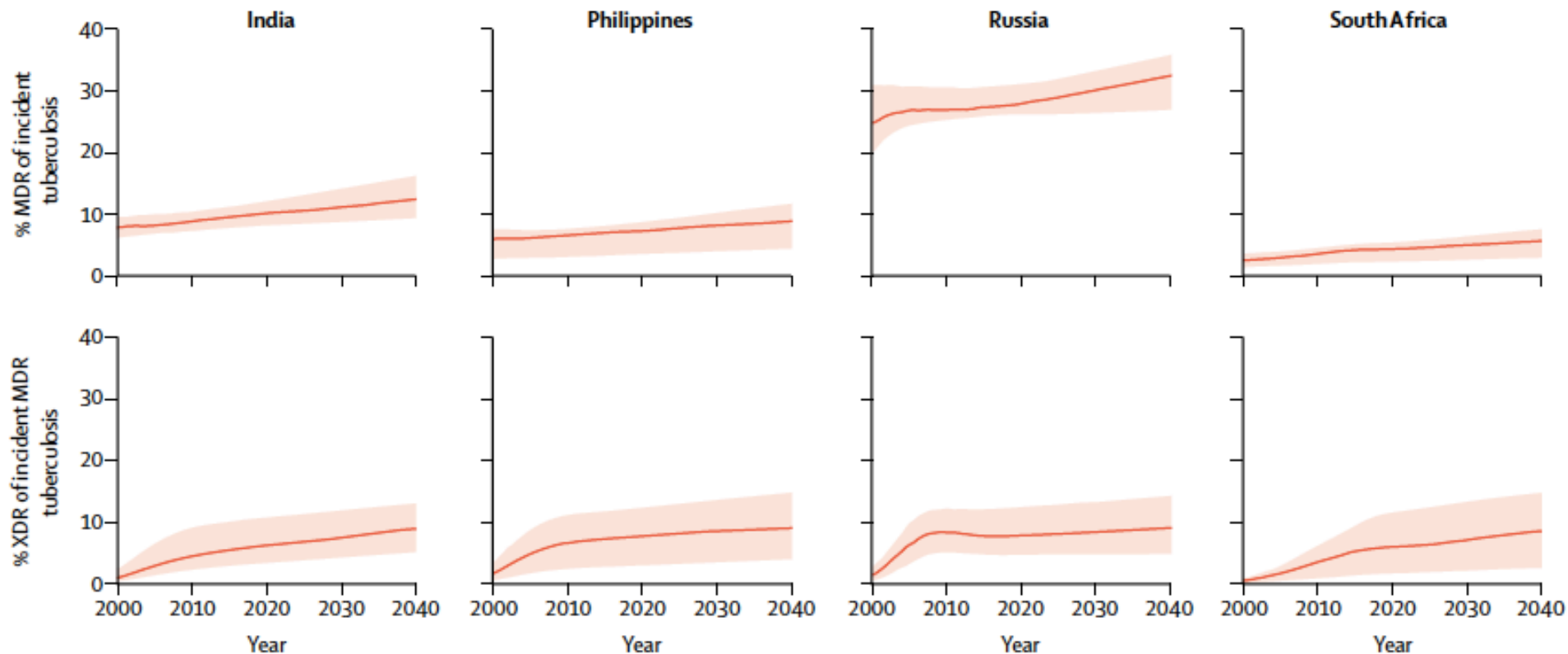


Prevalence of MDR-TB in Europe (selection)

- 2016 -

countries	new	retreatment	total	
Germany	2.2%	23%	160	EU
Hungary	2.9%	8.1%	27	
Latvia	7.6%	23%	62	
Lithuania	12%	47%	260	
Romania	2.8%	17%	730	
Belarus	38%	72%	1600	EU neighbors
Moldova	26%	56%	1400	
Russian Federation	27%	65%	47000	
Ukraine	27%	47%	10000	

Prediction of the development of M/XDR-TB



THE

END TB

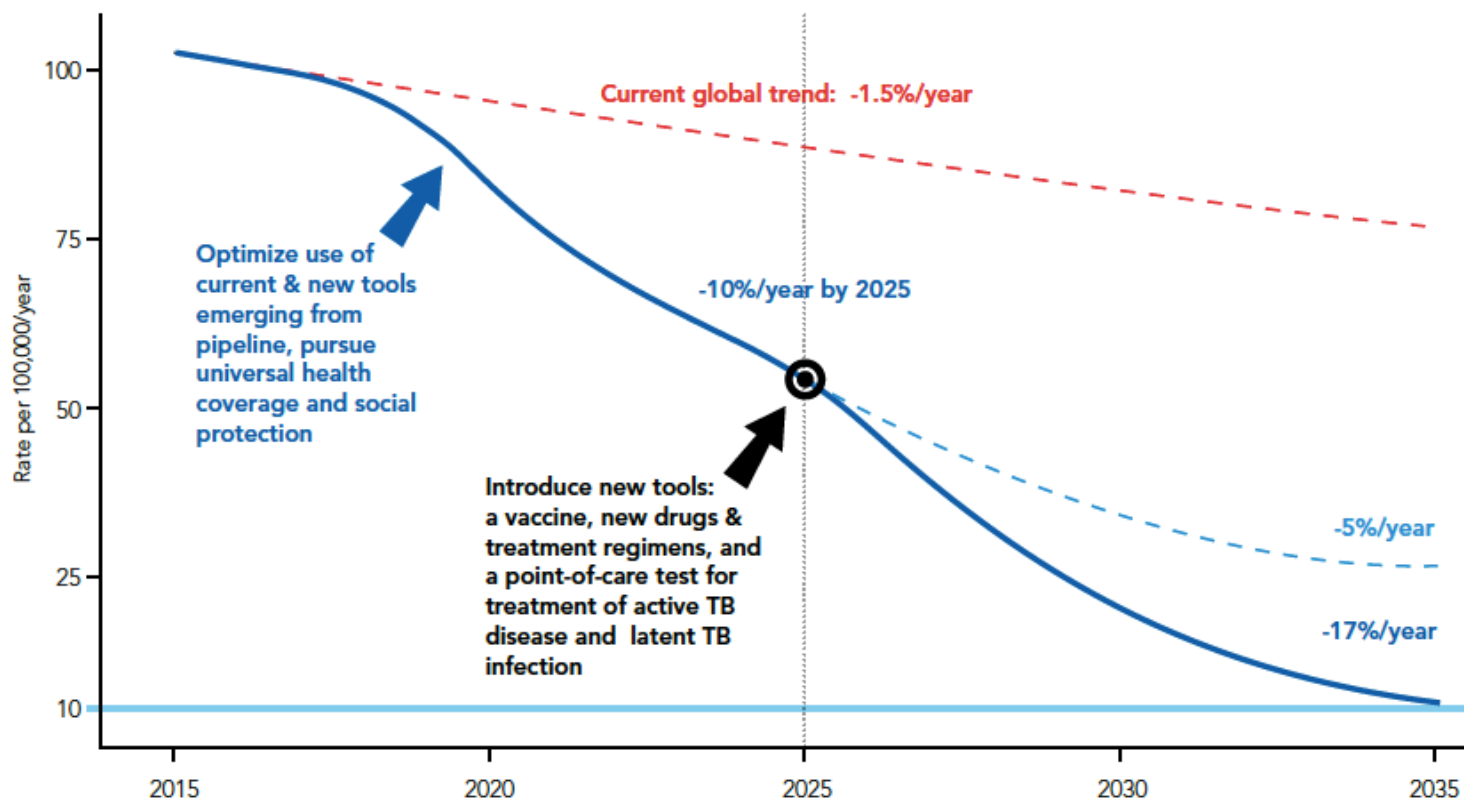
STRATEGY

Take-Home Message I

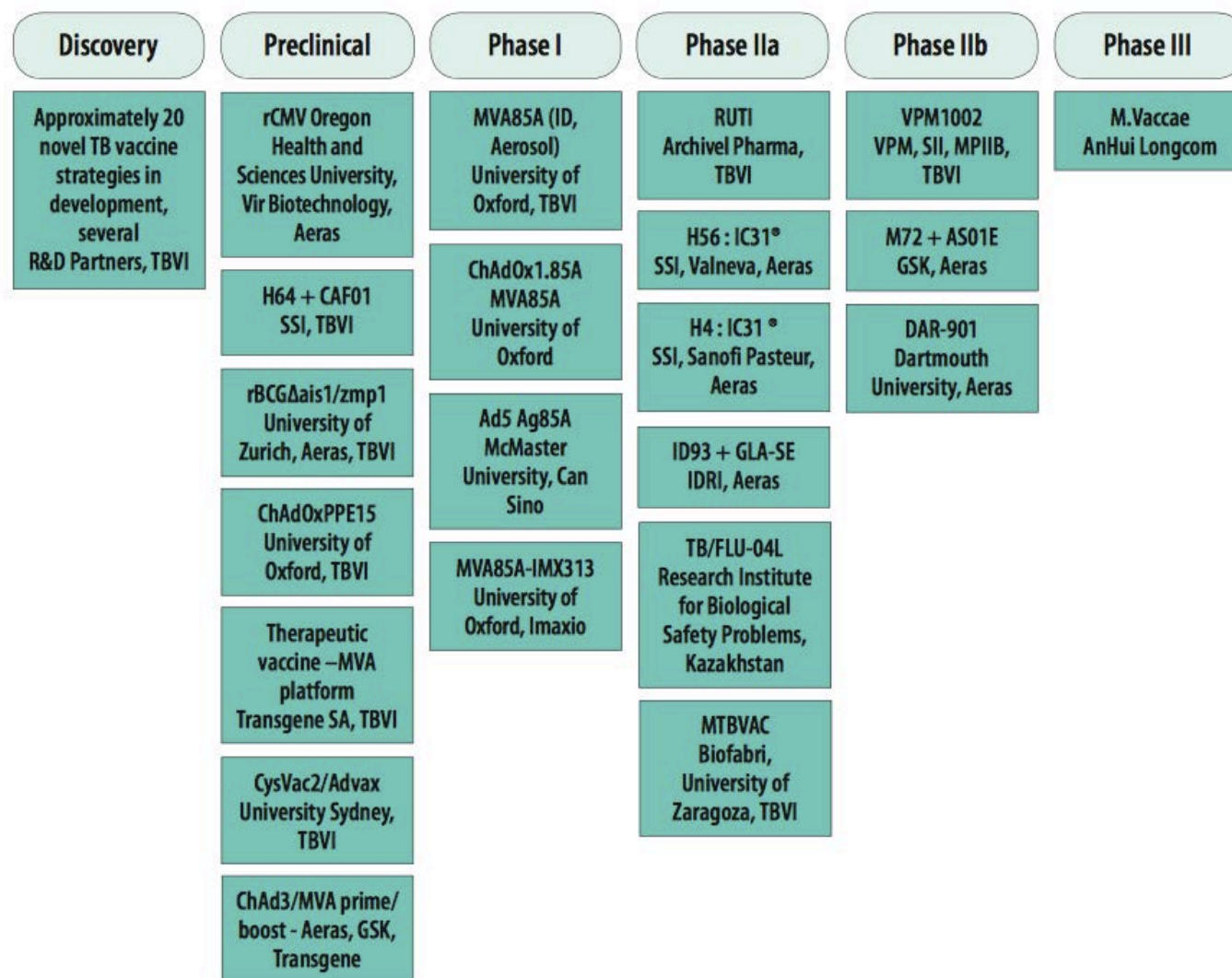
- ... historical „world record“ of TB patients
- ... increase in M/XDR-TB
- ... EndTB strategy is failing

Prevention

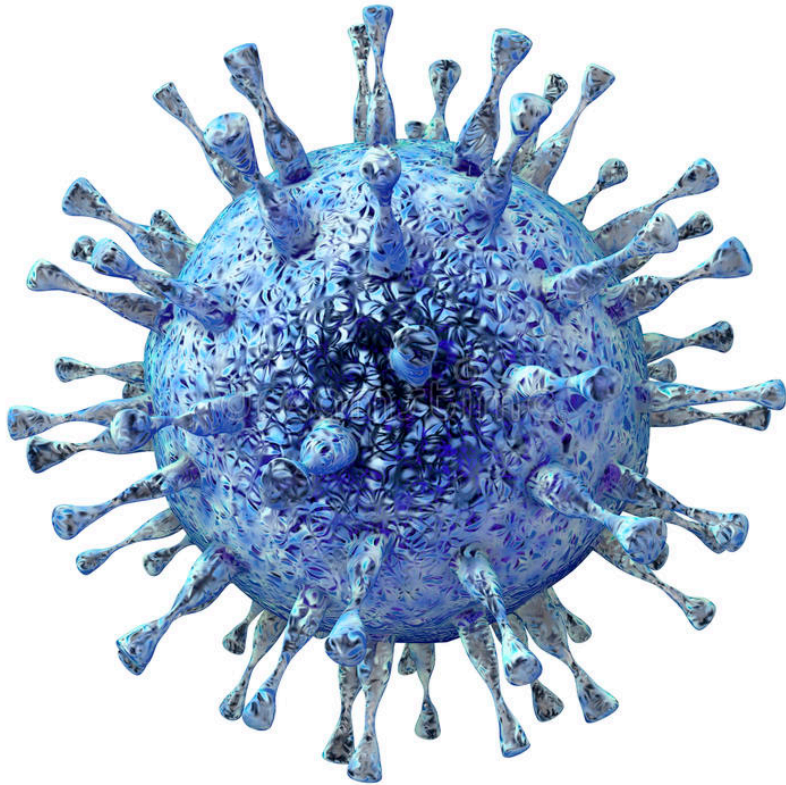
Goal of TB elimination plan



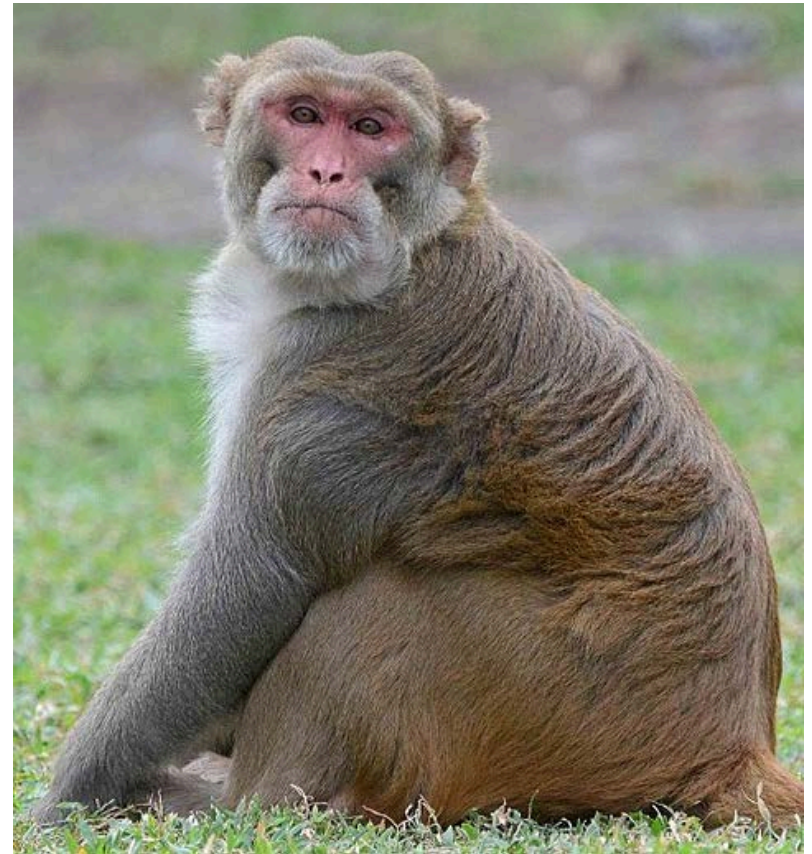
22 TB vaccine candidates in development



CMV-TB vaccine



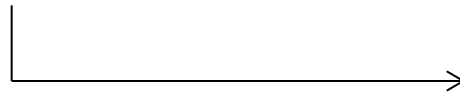
<https://www.dreamstime.com>



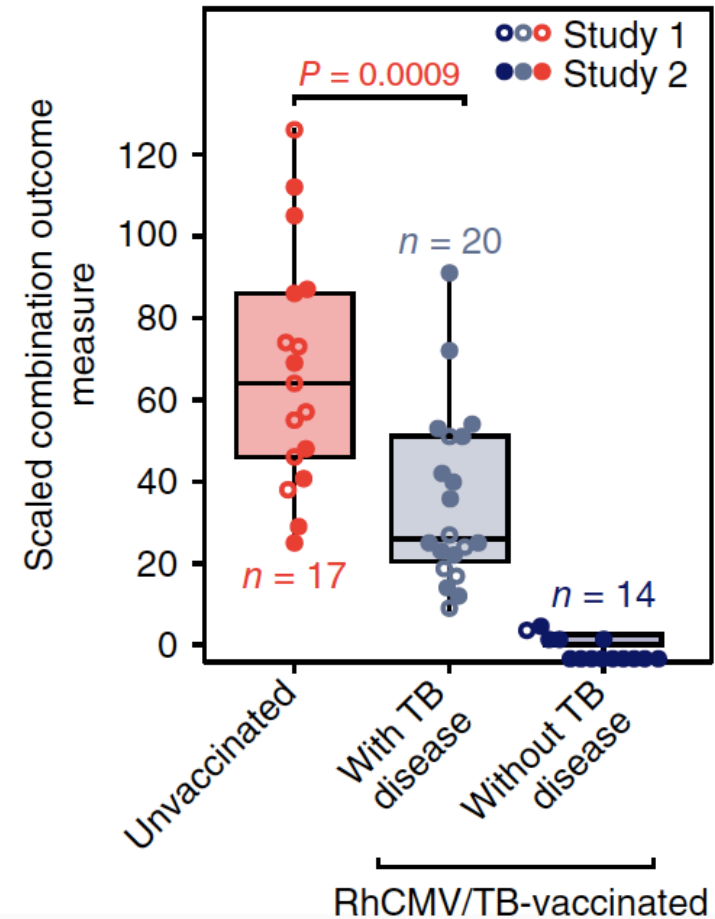
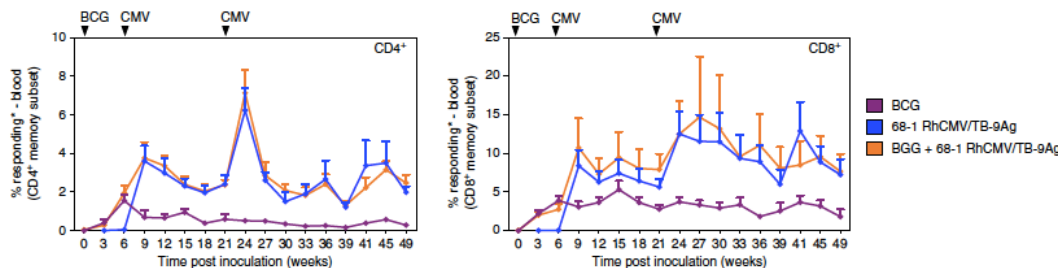
<https://commons.wikimedia.org>

CMV-TB vaccine

- all unvaccinated animals developed TB
- 14/34 (41%) of vaccinated animals protected

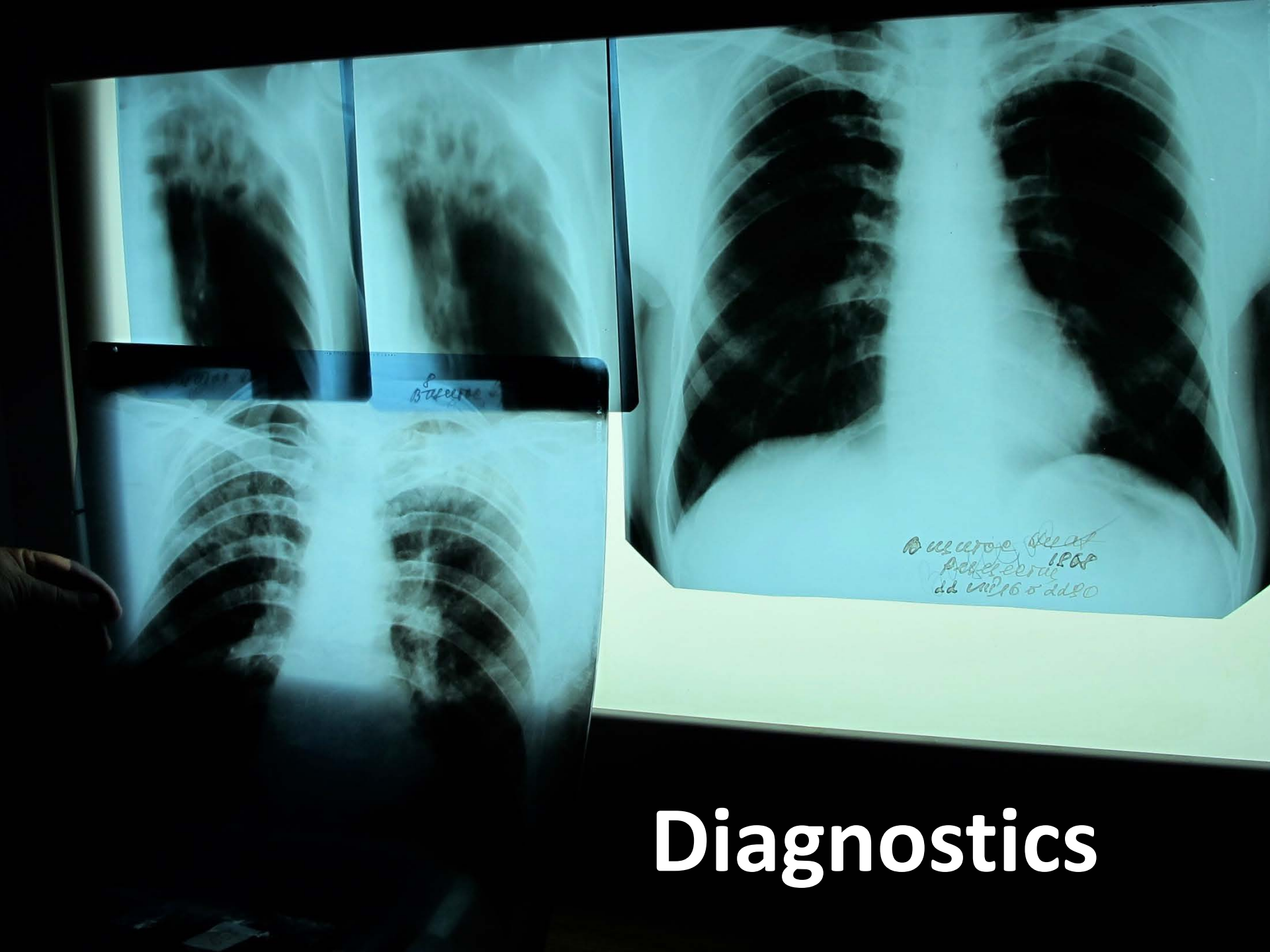


- Strong CD4+ and CD8+ cell responses



Take-Home Message II

- ... BCG does not protect from tuberculosis
- ... 22 vaccine candidates in the development pipeline
- ... RhCMV/TB: shows promising pre-clinical results



Diagnostics

Xpert MTB/Rif „ULTRA“ pulmonary TB

2368 patients, 8 countries, new cartridge

	Tuberculosis detection*				Detection of rifampicin resistance†	
	Sensitivity: all culture-positive (95% CI; n/N)	Sensitivity: smear-negative (95% CI; n/N)	Sensitivity: HIV-negative (95% CI; n/N)‡	Sensitivity: HIV-positive (95% CI; n/N)‡	Specificity (95% CI; n/N)	Specificity (95% CI; n/N)
Xpert	83% (79 to 86; 383/462)	46% (37 to 55; 63/137)§	90% (84 to 94; 143/159)	77% (68 to 84; 88/115)	98% (97 to 99; 960/977)	95% (91 to 98; 167/175)
Xpert Ultra	88% (85 to 91; 408/462)	63% (54 to 71; 86/137)§	91% (86 to 95; 145/159)	90% (83 to 95; 103/115)	96% (94 to 97; 934/977)	98% (97 to 99; 370/376)
Difference (Xpert Ultra minus Xpert)	5.4% (3.3 to 8.0; 25/162)	17% (10 to 24; 23/137)	1.3% (-1.8 to 4.9; 2/159)	13% (6.4 to 21; 15/115)	-2.7% (-3.9 to -1.7; 36/977)	0.3% (-0.7 to 1.5; 1/376)

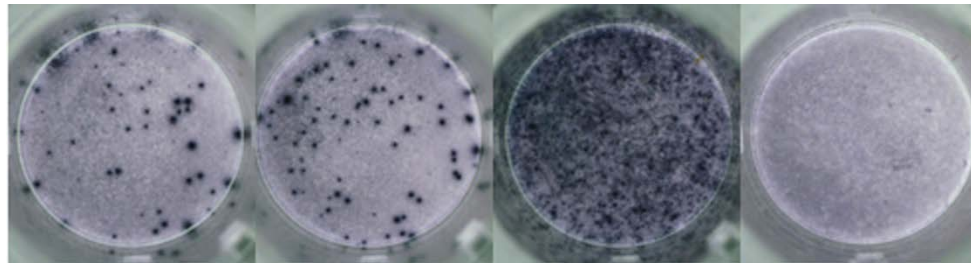
Xpert MTB/Rif „ULTRA“

TB-meningitis (csf)

129 patients, HIV+, Uganda, new cartridge

	Sensitivity vs composite endpoint (95% CI; n/N)	Sensitivity vs case definition (95% CI; n/N)	Assay error rate
Xpert Ultra	95% (77-99; 21/22)	70% (47-87; 16/23)	2.3% (3/129)
Xpert	45% (24-68; 10/22)	43% (23-66; 10/23)	4.7% (6/129)
MGIT culture	45% (24-68; 10/22)	43% (23-66; 10/23)	1.6% (2/129)

Xpert MTB/RIF + BAL-ELISpot



Smear negative TB: Xpert + BAL-ELISpot

98 % correctly classified diagnoses in 3 days



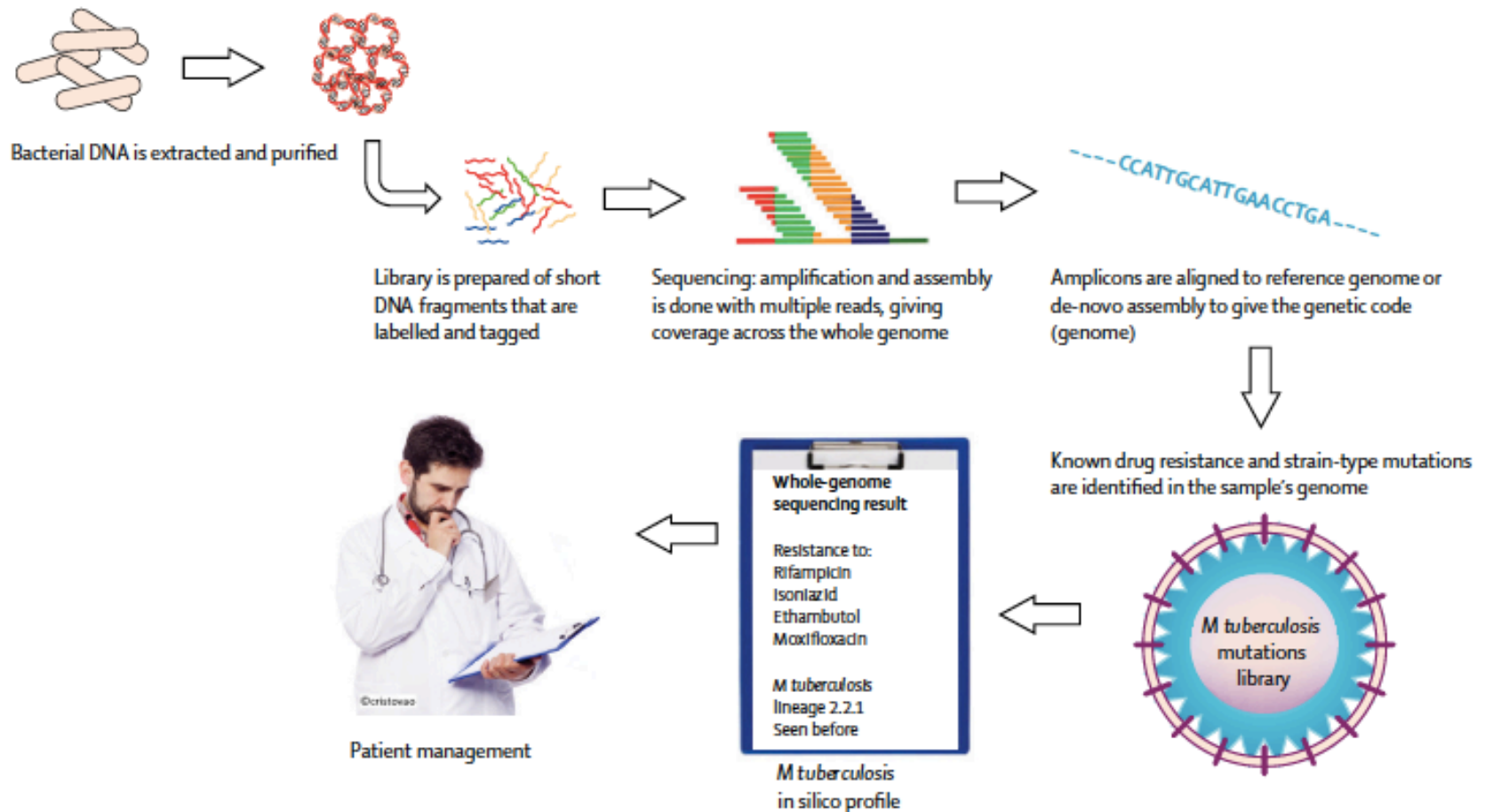
Cut-off	Sensitivity in % (95% CI)	Specificity in % (95% CI)	PPV in % (95% CI)	NPV in % (95% CI)	CC in %	LR+ in % (95% CI)	LR- in % (95% CI)	False positive -> treated unnecessarily
Combined GeneXpert and ELISpot >4000 BAL-Ly	99 (96-100)	98 (94-100)	98 (94- 100)	99 (96-100)	98.2	42 (10.7-165.2)	0.01 (0-0.1)	2/166 (1.2%)

Xpert „XDR-TB“

308 patients, 2 countries, other new cartridge

Drug	Investigational-Assay Result + Phenotypic Drug-Susceptibility Test Result*				Sensitivity		Specificity	
	R+R	R+S	S+R	S+S	no./total no.	% (95% CI)	no./total no.	% (95% CI)
	no. of specimens							
Isoniazid†	150	1	30	122	150/180	83.3 (77.1–88.5)	122/123	99.2 (95.6–100.0)
Ofloxacin‡	84	7	11	201	84/95	88.4 (80.2–94.1)	201/208	96.6 (93.2–98.6)
Moxifloxacin, 0.5 µg/ml‡§	78	12	11	200	78/89	87.6 (79.0–93.7)	200/212	94.3 (90.3–97.0)
Moxifloxacin, 2.0 µg/ml‡	51	40	2	210	51/53	96.2 (87.0–99.5)	210/250	84.0 (78.9–88.3)
Kanamycin¶	35	4	14	245	35/49	71.4 (56.7–83.4)	245/249	98.4 (96.0–99.6)
Amikacin¶	29	1	12	256	29/41	70.7 (54.5–83.9)	256/257	99.6 (97.9–100.0)

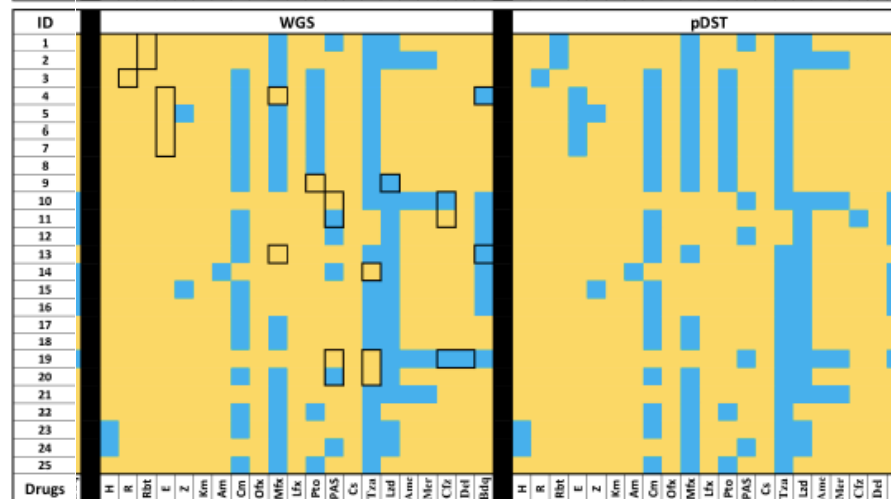
Whole genome sequencing



whole genome sequencing

Drug (phenotypic testing)	Gene	High-confidence mutations	Moderate-confidence mutations	Minimal-confidence mutations	No association with resistance
First-line					
Rifampicin [R]	<i>rpoB</i>	F505V+D516Y, S512T, Q513H+L533P, Q513-F514ins, Q513K, Q513L, Q513P, F514dupl , M515I+D516Y, D516A, D516F, D516G , D516G+L533P, D516ins, D516N, D516V , Del N518, S522Q, H526C, H526D, H526F, H526G, H526L, H526R, H526Y S531F, S531L, S531Q, S531W, S531Y, D626E	D516Y, S522L, H526P, L533P	L511P, H526N, I572F	
Isoniazid [H]	<i>inhA-mabA</i>	g-102a ^{a,†}	c-15t		g-102a^{a,†} , t-80g, g-47c, T4I
	<i>katG</i>	S315I, S315N, S315T , pooled frameshifts and premature stop codons			A110V, R463L , L499M
	<i>furA</i>		A187V ^{a,†}		L68F
	<i>mshA</i>				N111S
Second-line (group A)					
Moxifloxacin (MXF)	<i>gyrA</i>	G88C, A90V, S91P, D94A, D94G, D94N, D94Y			E21Q, S95T , G247S, G668D, V712L
Ofloxacin (OFX)/levofloxacin (LFX)	<i>gyrA</i>	G88A, G88C, S91P, A90V, D94A, D94G, D94H, D94N, D94Y	D89N		E21Q, T80A, S95T , G247S, G668D, V712L
	<i>gyrB</i>	E459K, A504V			
Second-line (group B)					
Amikacin (AM)	<i>rrs</i>	a1401g, g1484t			
Kanamycin (KM)	<i>eis</i>	c-14t, g-10a		g-37t, c-12t	a1338c
	<i>rrs</i>	a514c [#] , a1401g , c1402t, g1484t			
	<i>rrs+eis</i>	<i>rrs</i> c517t [#] + <i>eis</i> g-37t			
Capreomycin (CM)	<i>rrs</i>	a1401g, c1402t, g1484t			c517t
	<i>tlyA</i>	N236K , pooled frameshifts and premature stop codons			D149H
Streptomycin (S)	<i>rpsL</i>	K43R, K43T, K88Q, K88R, T40I			
	<i>rrs</i>	a1401g [#] , a514c , a514t, c462t, c513t, c517t			
	<i>gidB</i>		E92D^{a,†}		L16R, V110G , pooled frameshifts and premature stop codons
Second-line (group C)					
Ethionamide and prothionamide (ETO/PTO)	<i>inhA</i>	c-15t+I194T, c-15t+S49A	c-15t		Q347Stop
	<i>ethA</i>				
Second-line (group D)					
Pyrazinamide (Z)	<i>pncA</i>	t-12c, a-11g, t-7c, A3E , L4S, I6T, V7G, D8E, D8G , D8N, Q10P, D12A, D12N, C14R , G17D, L19P, G24D, Y34D, A46V, K48T, D49G , D49N, H51Q, H51R , P54S, H57D[†] , H57P, H57R, H57Y , S59P, P62L, P62Q, D63G, S66P, S67P , W68C, W68R, H71D, H71Q, H71Y, C72R, T76P, H82R, L85P, L85R, F94L, F94S , K96N, K96R, G97C, G97D, G97S , Y103H, S104R, G108R , L116P, L116R, L120P , R123P, V125F, V125G, V128G , G132A, G132D, G132S, A134V, T135N, T135P , H137P, C138Y, V139G, V139L, Q141P, T142A, T142K, T142M , indel - R148ins (inframe), L151S, V155G , L159P, T160P, G162D, T168P, L172P , M175T, M175V , V180F, V180G, Pooled frameshifts and premature stop codons	V7G , Q10R, P54L, W68G , K96E, K96T, A171E, M175I	D12G , F58L, H71R, I133T, V139A	indel - c-125del, I31T, L35R, T47A, I6L , K48T, T114M

diagnosis



Take-Home Message III

- ... automated Mtb PCR become more sensitive
- ... automated PCR expand to XDR-TB diagnosis
- ... genotype2phenotype DST is the future

Treatment

RHIZE

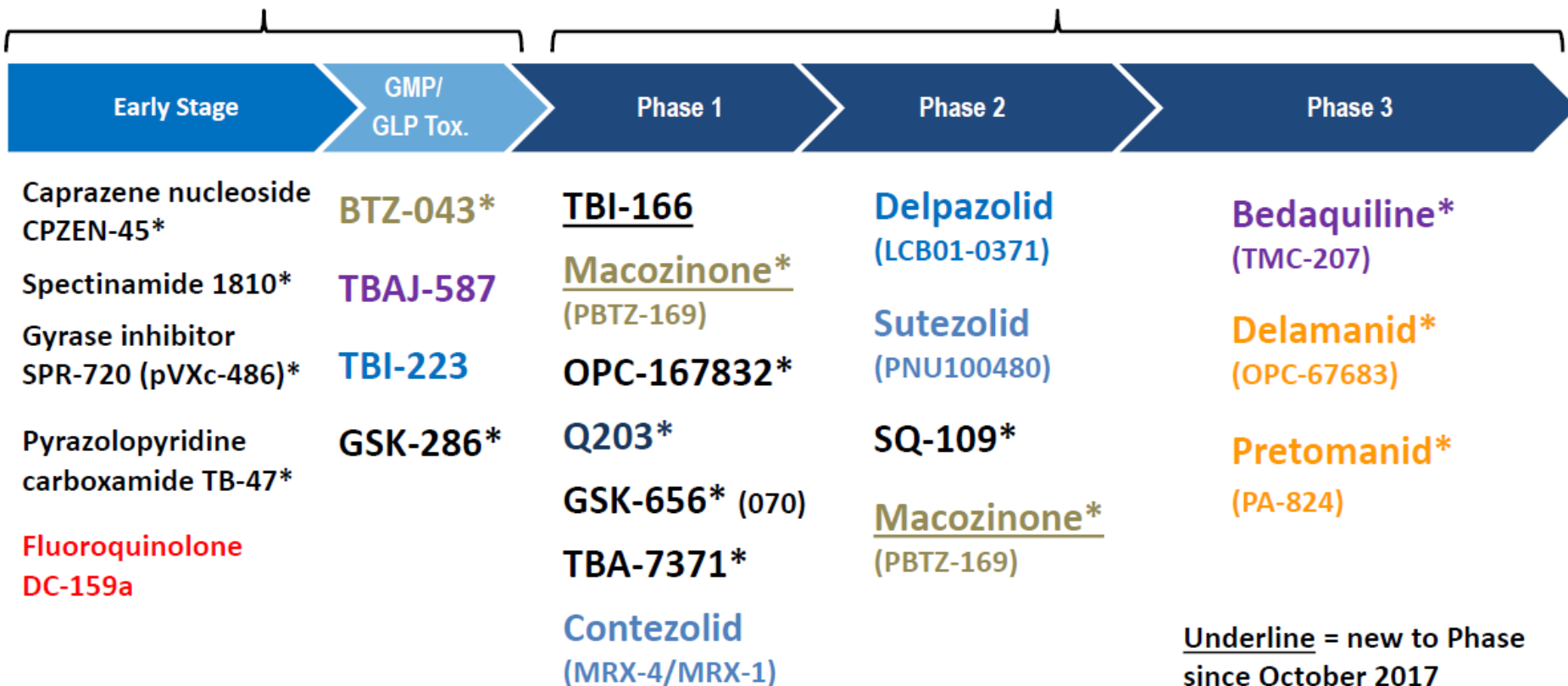
Number of new TB drugs licenced since 1966

2

TB drug pipeline

Preclinical Development

Clinical Development



New chemical class* Known chemical classes for any indication are color coded:

fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

¹ New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline/clinical>



WORKING GROUP


ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2018

TB treatment outcomes

	New and relapse, 2015 cohort		Previously treated, excluding relapse, 2015 cohort		HIV-positive TB, 2015 cohort		MDR/RR-TB, 2014 cohort		XDR-TB, 2014 cohort	
	Cohort (Number)	Success (%)	Cohort (Number)	Success (%)	Cohort (Number)	Success (%)	Cohort (Number)	Success (%)	Cohort (Number)	Success (%)
Global	5 918 965	83	195 859	69	470 051	78	102 903	54	6 777	30



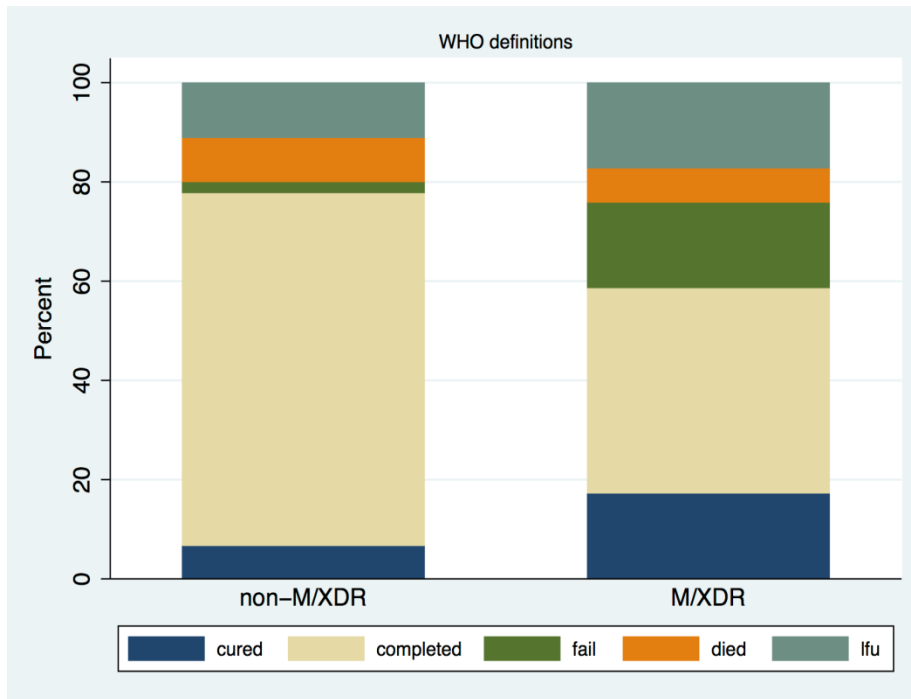
Two horizontal arrows point from the 'Success (%)' column for the 'New and relapse, 2015 cohort' (83%) to the 'Success (%)' column for the 'XDR-TB, 2014 cohort' (30%).

How is cure from TB defined



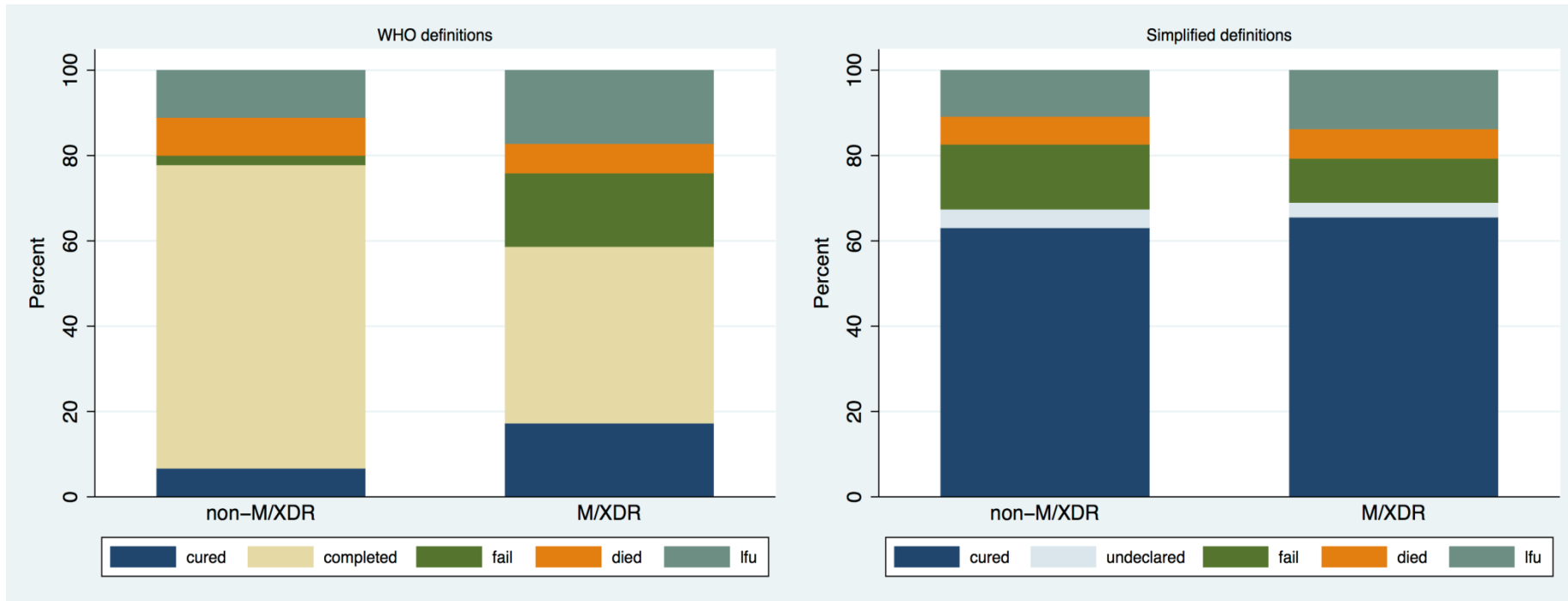
Treatment outcome is a matter of definition

46 dsTB; 29 MDR-TB



Treatment outcome is a matter of definition

46 dsTB; 29 MDR-TB



Take-Home Message

- ... 2HRZE/4HR is still the standard of care for ds-TB
- ... WHO treatment outcome definitions need revision
- ... cure from M/XDR-TB is possible

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List of Abbreviations

AMR = antimicrobial resistance

BAL = bronchoalveolar lavage

BCG = Bacille Calmette Guérin

CC = correctly classified

CMV = cytomegalovirus

CSF = cerebrospinal fluid

DS = drug susceptible

DST = drug susceptibility testing

E = ethambutol

ELISpot = enzyme-linked immunospot

EU = European Union

H = isoniazid

HIV = human immunodeficiency virus

LR = likelihood ratio

Ly = lymphocytes

MDR = multidrug-resistant

MGIT = mycobacterium indicator tube

MTB = Mycobacterium tuberculosis

NPV = negative predictive value

PCR = polymerase chain reaction

PPV = positive predictive value

R = resistant

R = rifampicin

RhCMV/TB = rhesus Macaque CMV/TB vaccine

RIF = rifampicin

S = susceptible

TB = tuberculosis

WGS = whole genome sequencing

XDR = extensively drug-resistant

Z = pyrazinamide