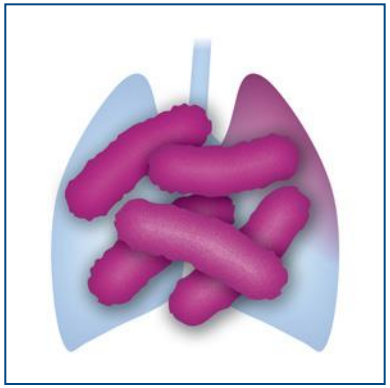
Pneumo Update Europe 2016

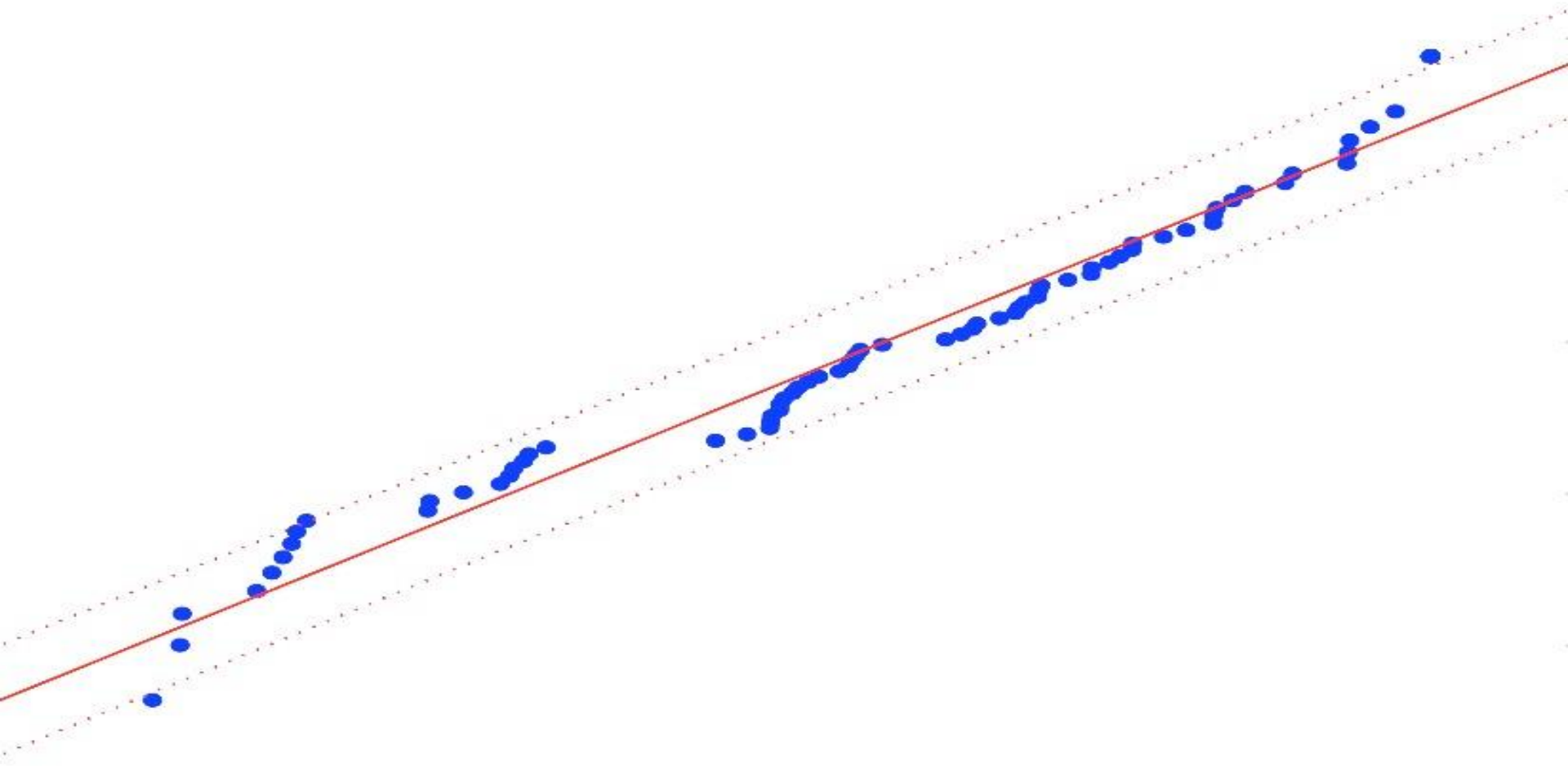
24-25 June, Prague

Tuberculosis & Infection



Christoph Lange, Germany

Epidemiology



9.6 million

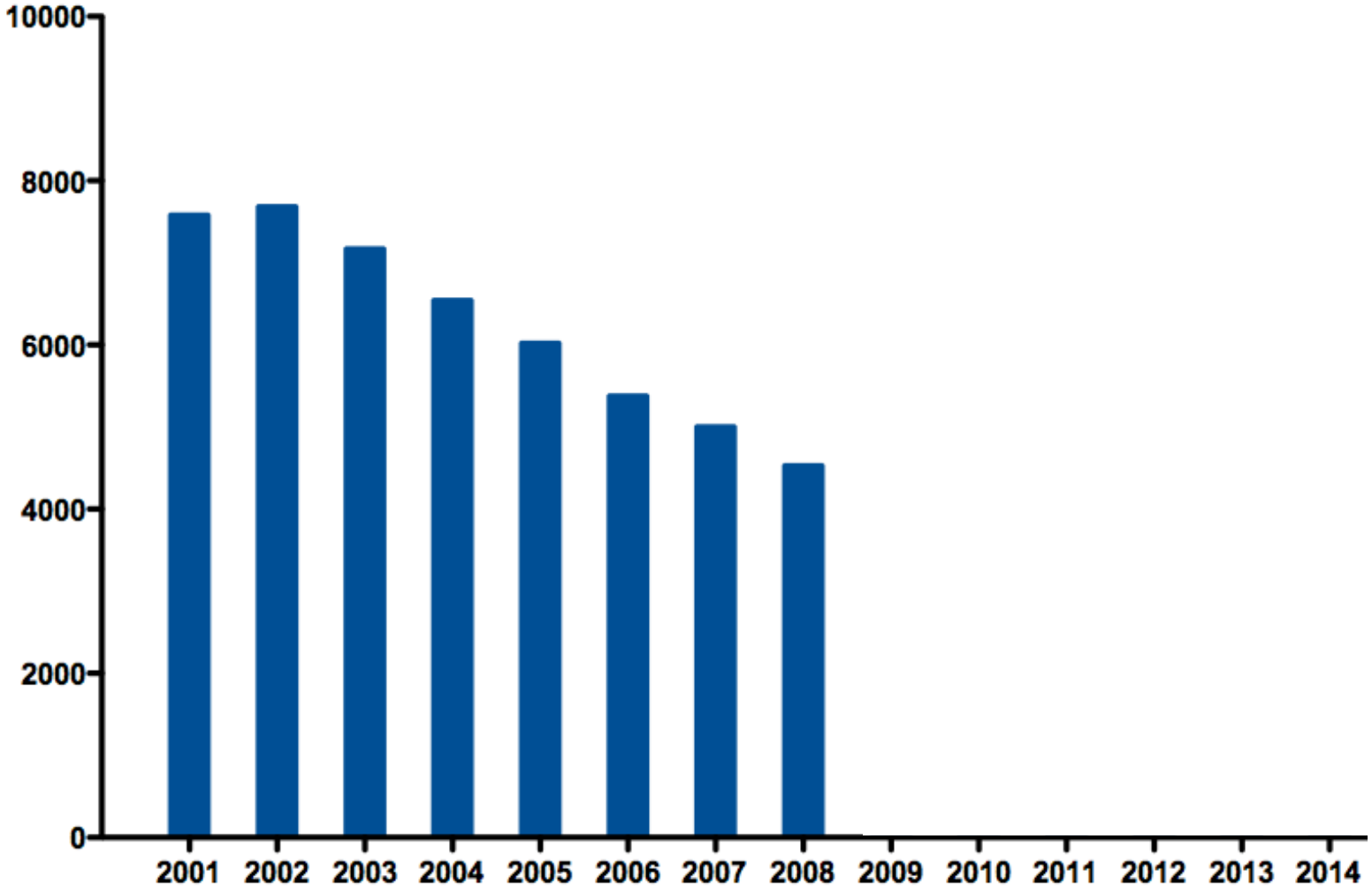
people are estimated to have fallen ill with tuberculosis in 2014

WHO: Global tuberculosis report 2015, Geneva Switzerland

Never before in human history...

... was the number of patients affected by tuberculosis larger than today!

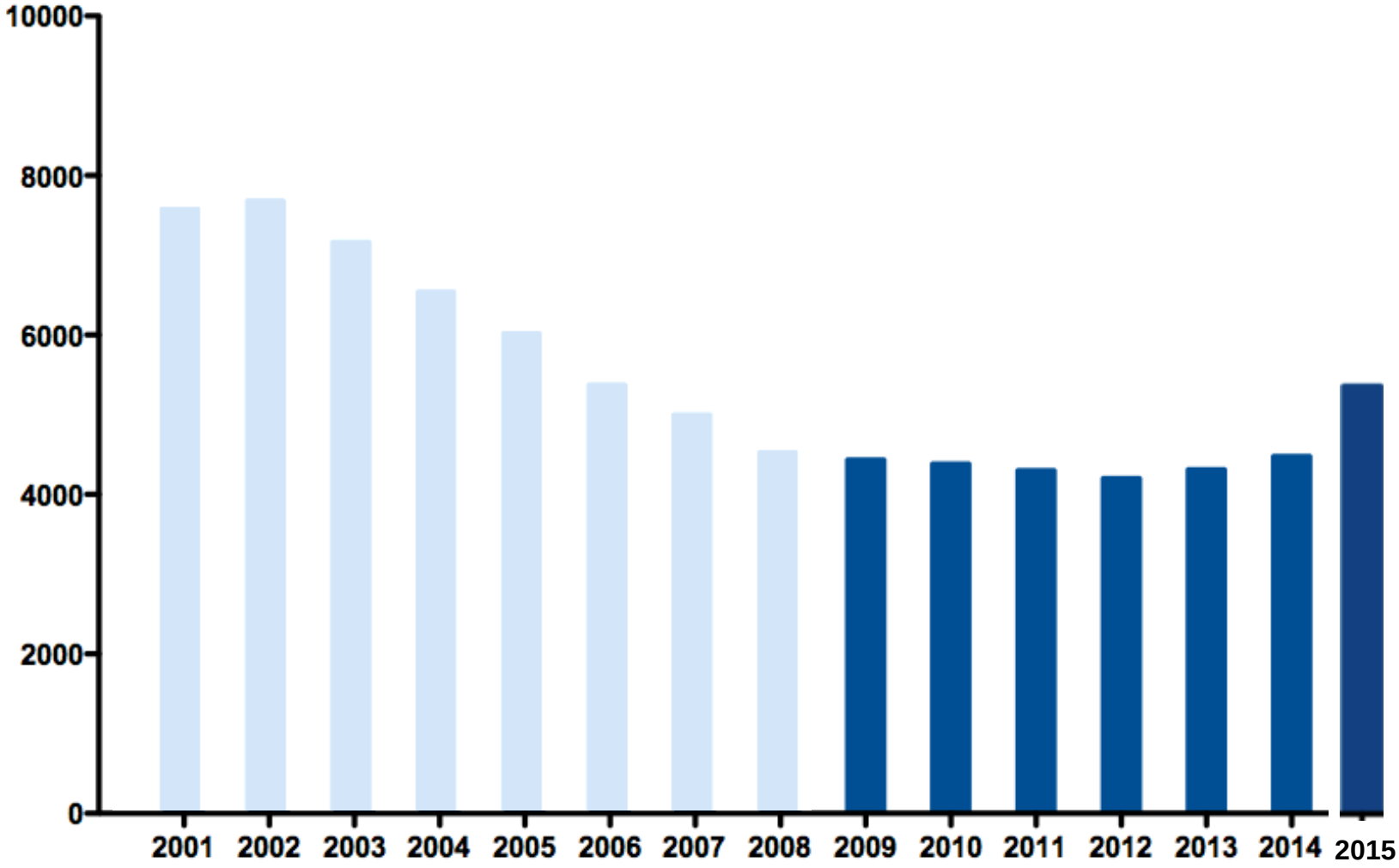
Numbers of tuberculosis cases in Germany



Robert Koch Institute 2015

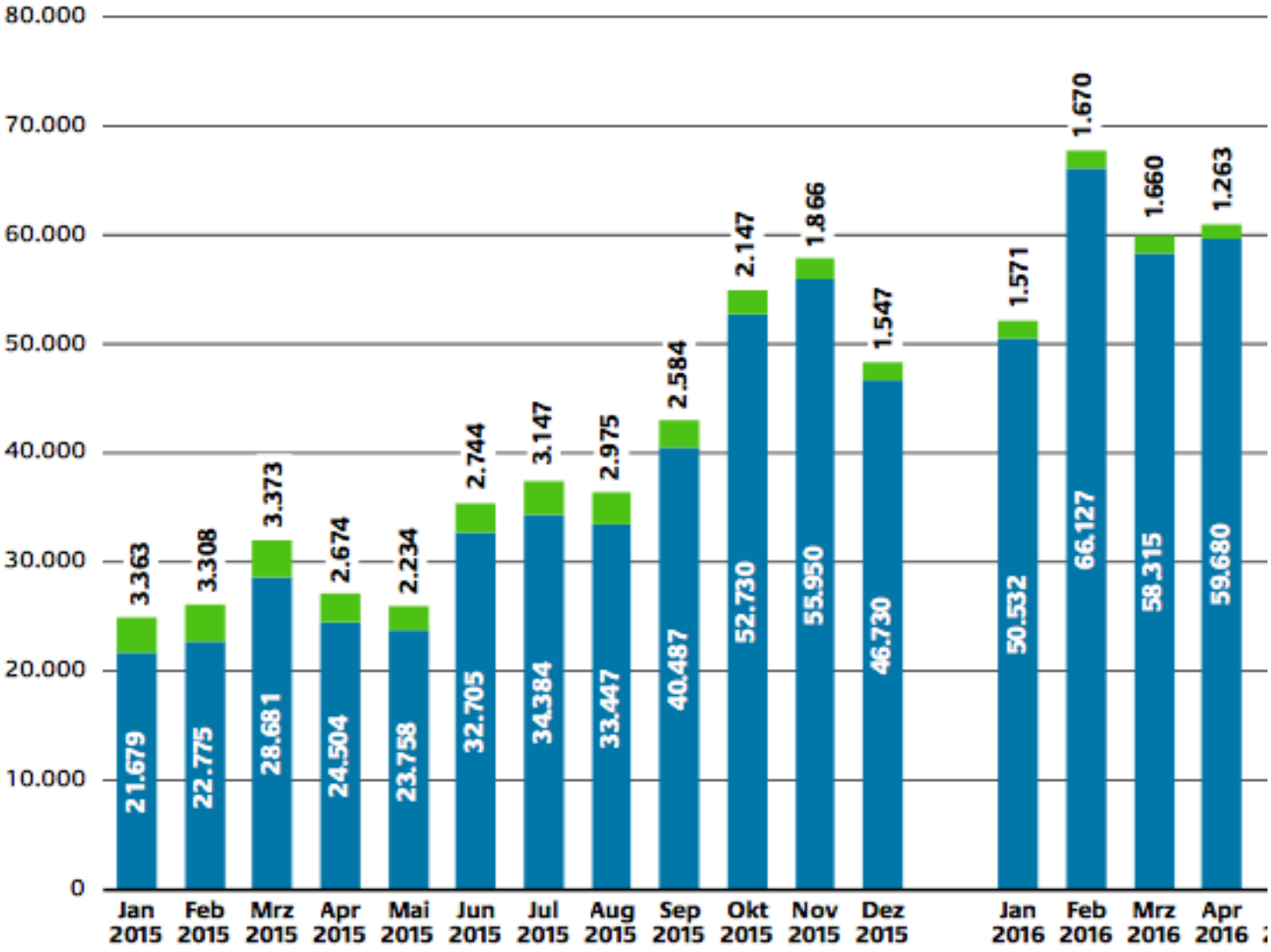
Numbers of tuberculosis cases in Germany

no decline since 2008

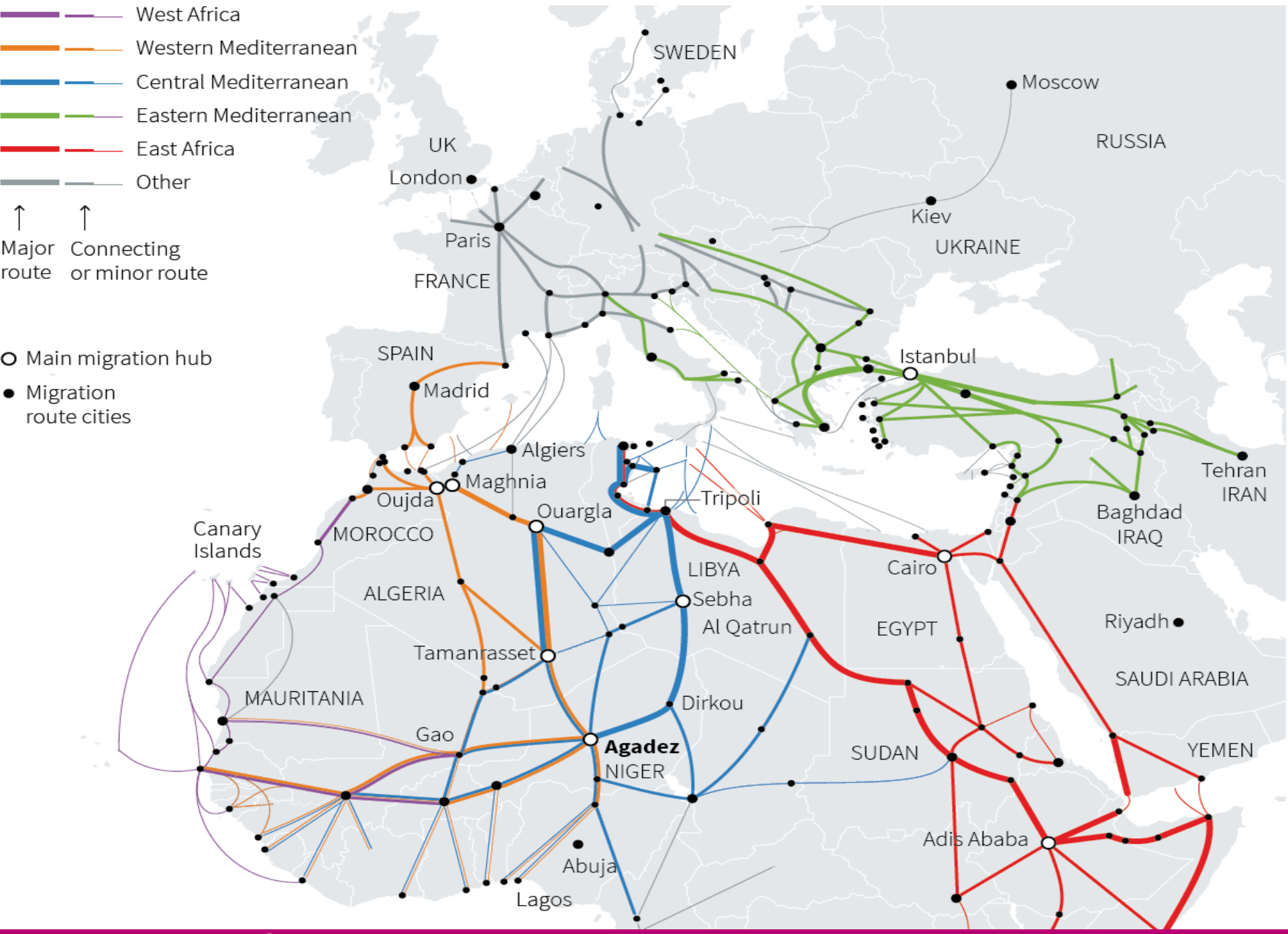


Robert Koch Institute 2015/6

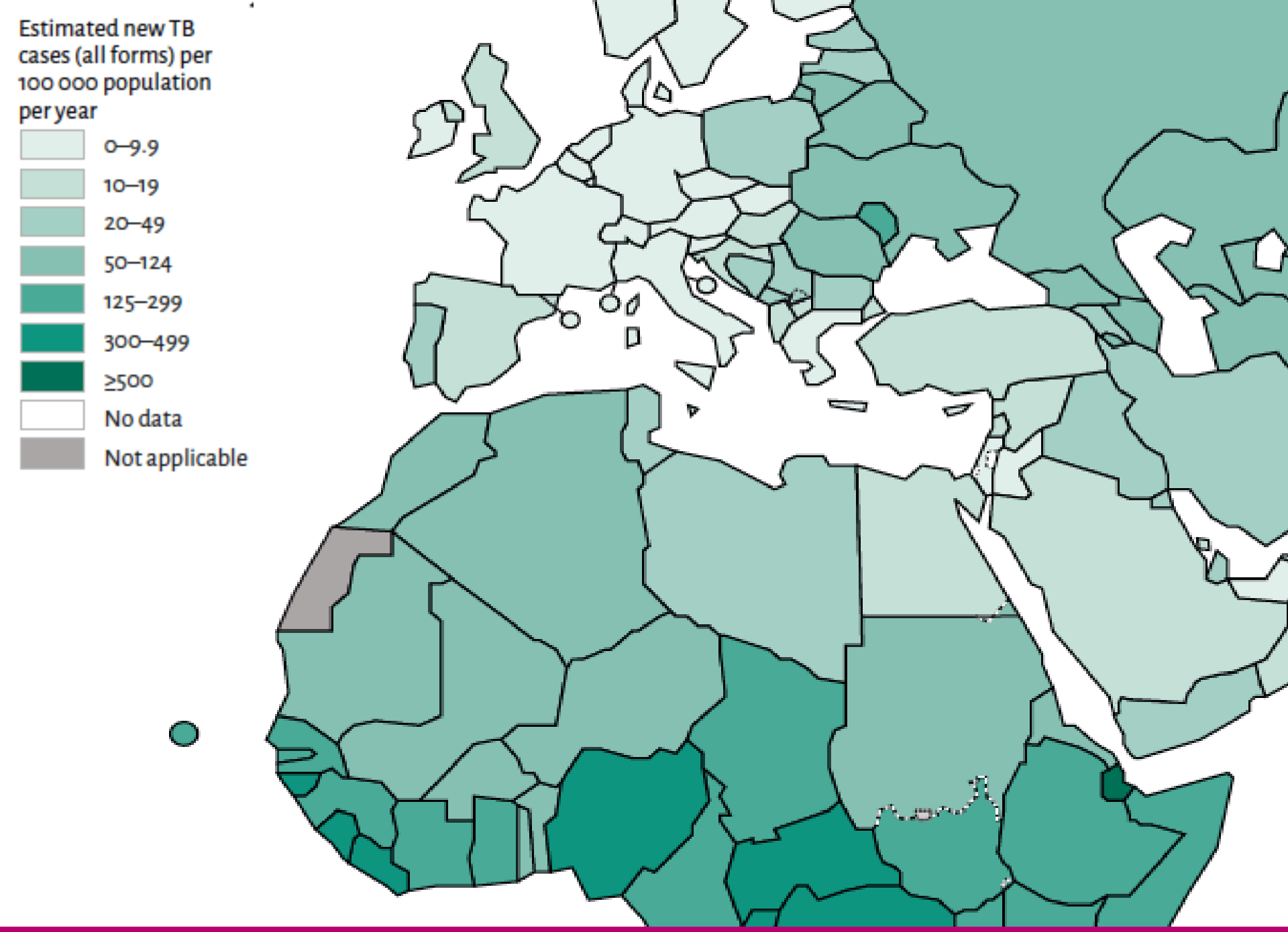
Asylum seekers to Germany



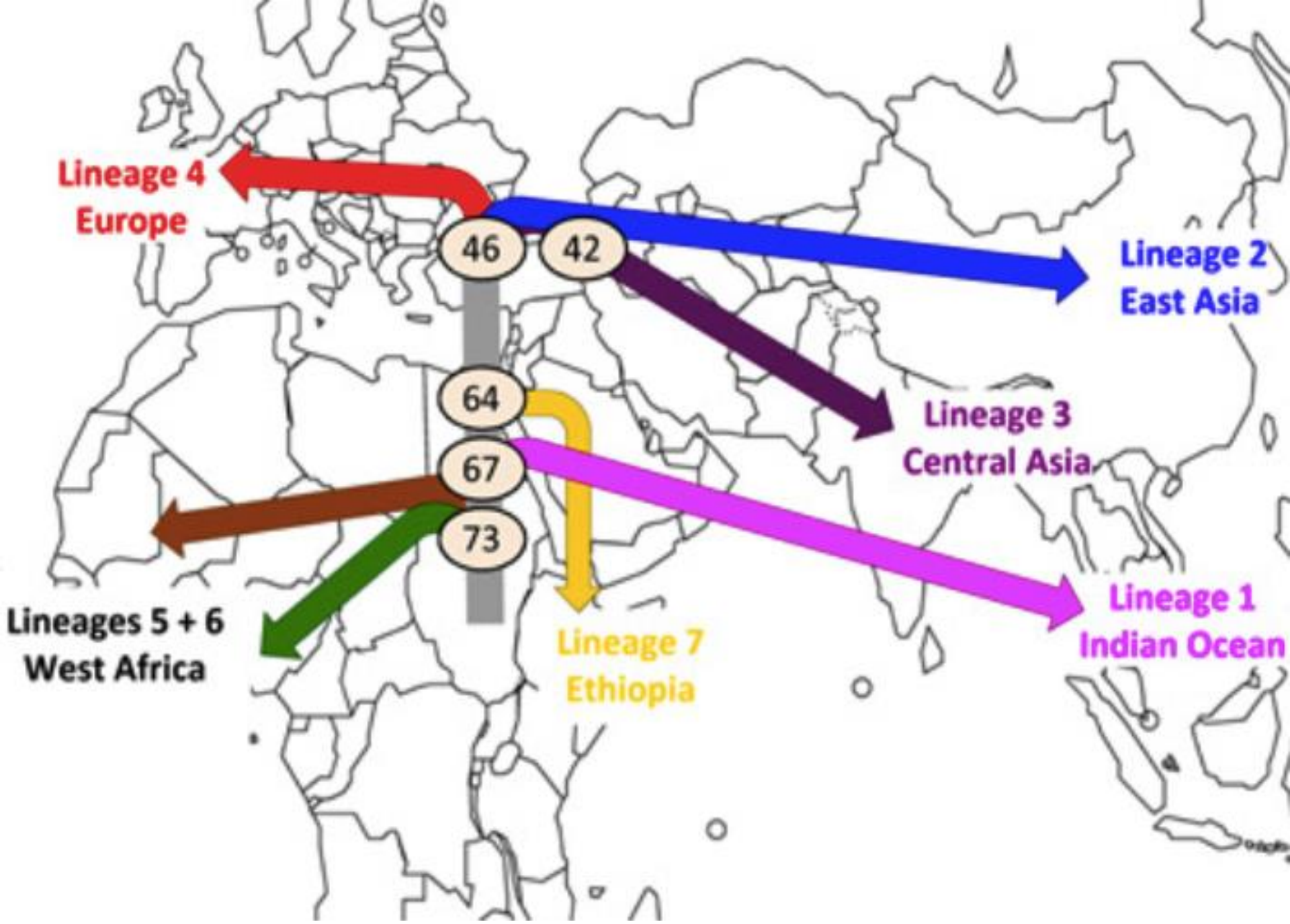
Bundesamt für Migration 2016



International Centre for Migration Policy, 2016

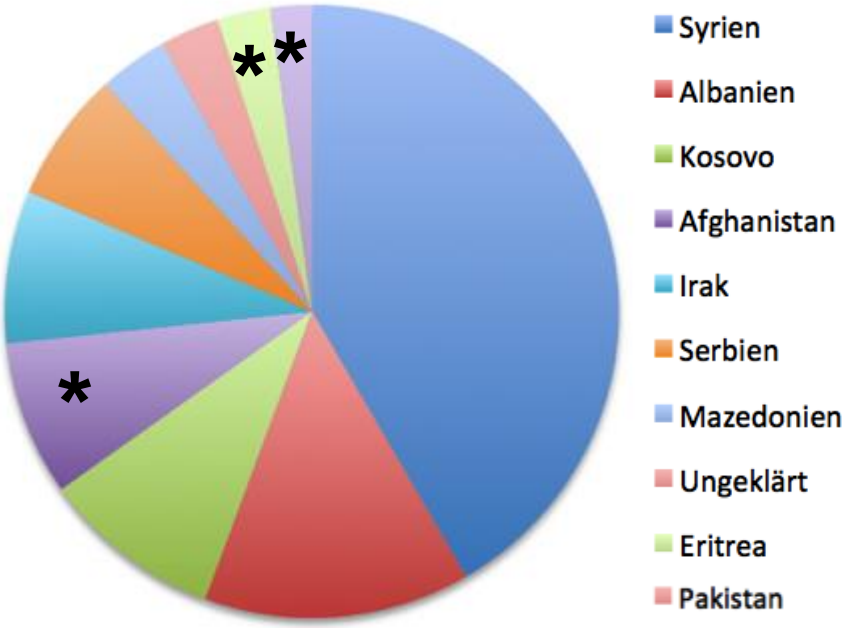


WHO: Global tuberculosis report 2015, Geneva, Switzerland



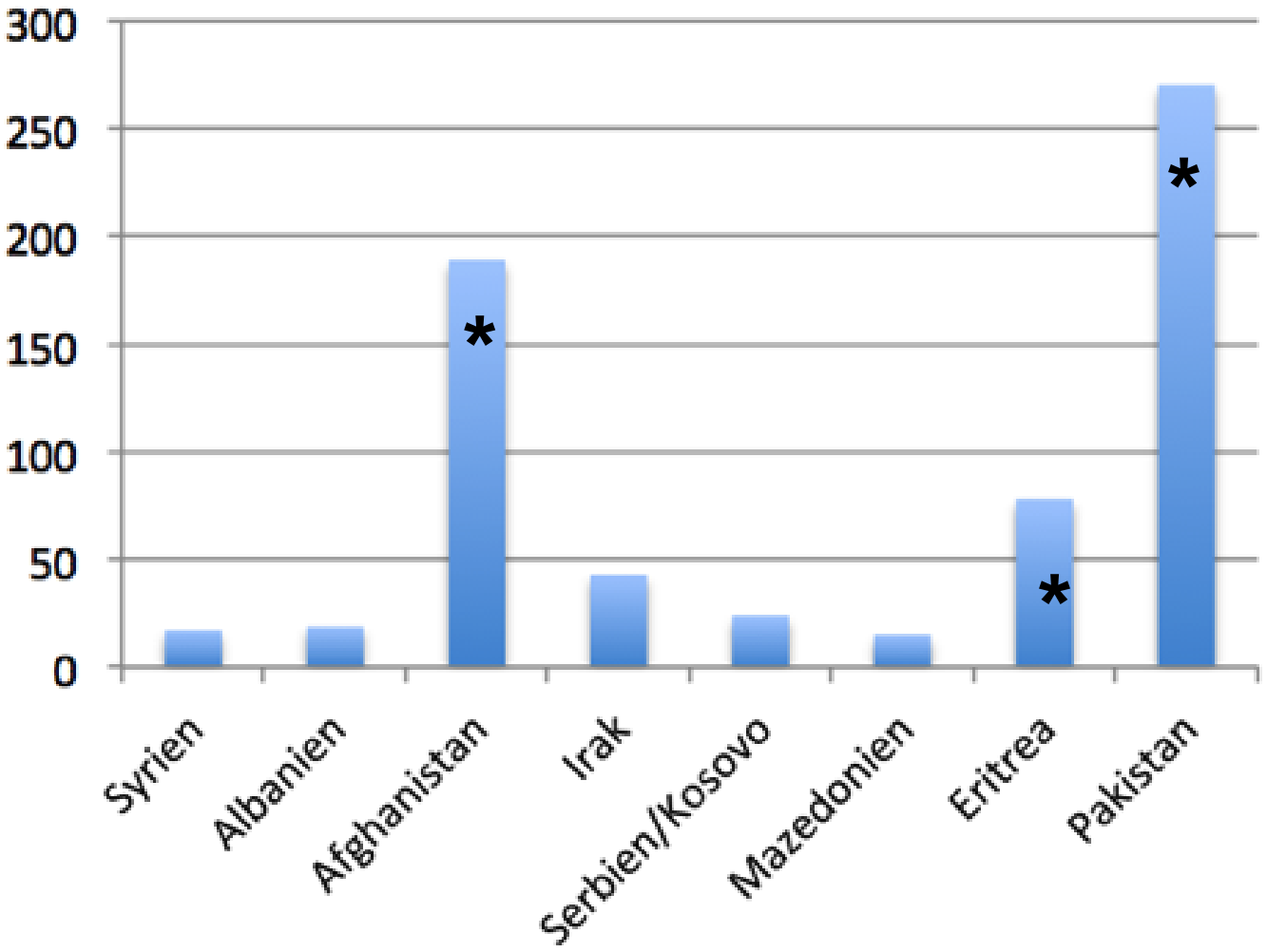
Comas I et al. Nat Genet. 2013 Oct;45(10):1176-82

Applications for asylum
Germany 2015



Bundesamt für Migration 2016

TB notification rates



WHO: Global tuberculosis report 2015, Geneva, Switzerland

TB among foreign-born in Germany

	2010		2011		2012		2013		2014	
Geburtsland	Anzahl	Anteil	Anzahl	Anteil	Anzahl	Anteil	Anzahl	Anteil	Anzahl	Anteil
Somalia	59	1,4%	59	1,4%	60	1,5%	118	2,9%	282	6,7%
Türkei	263	6,2%	241	5,8%	229	5,6%	207	5,0%	201	4,8%
Rumänien	87	2,1%	121	2,9%	125	3,1%	178	4,3%	181	4,3%
Eritrea	16	0,4%	37	0,9%	20	0,5%	42	1,0%	173	4,1%
Indien	121	2,9%	104	2,5%	107	2,6%	135	3,3%	151	3,6%
Russische Föderation	160	3,8%	126	3,0%	117	2,9%	190	4,6%	122	2,9%
Pakistan	66	1,6%	52	1,3%	67	1,6%	92	2,2%	81	1,9%
Kasachstan	100	2,4%	106	2,6%	84	2,1%	71	1,7%	80	1,9%
Polen	96	2,3%	96	2,3%	110	2,7%	105	2,5%	71	1,7%
Afghanistan	59	1,4%	58	1,4%	70	1,7%	68	1,6%	71	1,7%
Andere Länder	975	23,0%	1.026	24,8%	1.044	25,6%	1.146	27,8%	1.222	28,9%
Ausland	2.002	47,3%	2.026	48,9%	2.033	49,8%	2.352	57,0%	2.635	62,4%
Deutschland	2.235	52,7%	2.114	51,1%	2.046	50,2%	1.772	43,0%	1.591	37,6%
Gesamt	**4.237**	**100,0%**	**4.140**	**100,0%**	**4.079**	**100,0%**	4.124	100,0%	**4.226**	**100,0%**

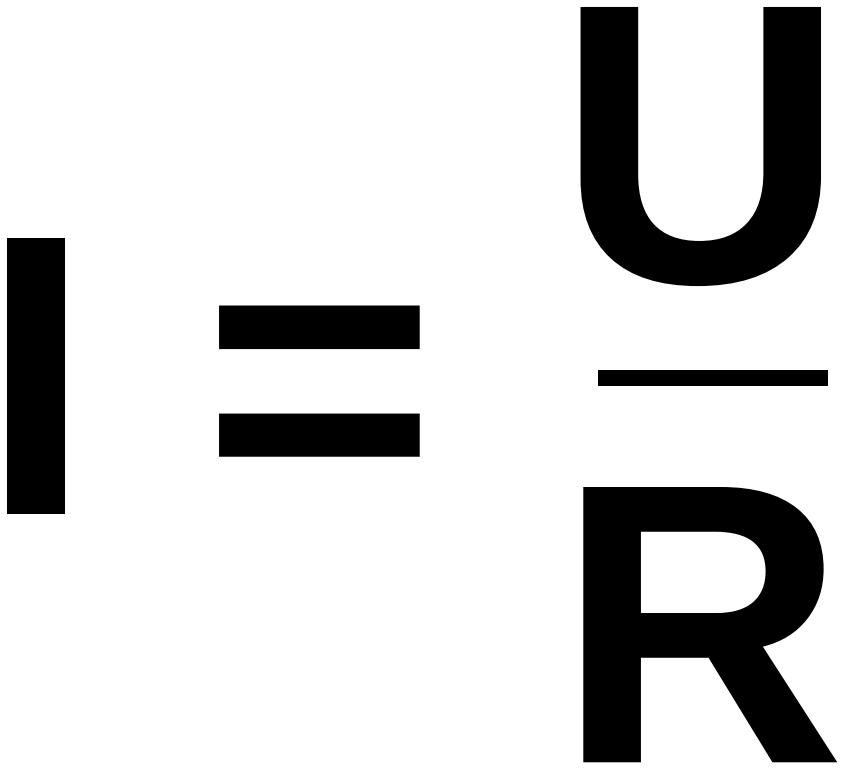
Robert Koch Institute 2015

TB in migrants, Germany (2014)

	# of TB cases	# of asylum seekers	incidence when in Germany	incidence in country of origin	factor
Senegal	13	759	1713	138	11.3
Somalia	86	5528	1556	274	6.3
Georgia	24	2873	835	106	7.9
Eritrea	68	13198	515	78	6.6
Russian Fed.	18	4411	408	84	4.9
Pakistan	13	3968	328	270	1.2
Kosovo	12	6908	174	24	7.3
Afghanistan	15	9115	165	189	0.87
Serbia	22	17172	128	24	5.3
Syria	19	39332	48	17	2.8

Bundesamt für Migration 2016

WHO: Global tuberculosis report 2015, Geneva, Switzerland


I = U/R

Take-Home Message

- **... increasing number of patients with tuberculosis**
- **... migration follows Ohm´s law**
- **... elimination of tuberculosis in unlikely**

0.7-1.9%

is the PPV of IGRAs that recent contacts develop TB within 2 years

Zellweger et al. Am J Respir Crit Care Med 2015; 191(10):1176–1184

Numbers needed to treat to prevent a case: contacts (1)

	Test result	Prophylaxis	N	PY at risk	TB cases	Inc	NNT
QFT G-IT	negative	no	2419	6349.8	3	**0.047**	**807**
	negative	yes	104	326.4	0	0	
	positive	no	421	1169.1	14	**1.198**	**38**
	positive	yes	481	1296.5	3	0.231	
TSPOT-TB	negative	no	722	1790.1	2	**0.112**	**361**
	negative	yes	58	316.1	0	0	
	positive	no	73	247.8	2	**0.807**	**37**
	positive	yes	208	829.7	0	0	

Zellweger et al. Am J Respir Crit Care Med 2015; 191(10):1176–1184

Numbers needed to treat to prevent a case: contacts (2)

QFT G-IT / TST

Test result	Prophylaxis	N	TB cases	NNT
negative	no	1275	1	**1275.0**
negative	yes	0	0	
positive	no	201	8	**30.4**
positive	yes	146	1	

Close contacts

Sloot R. et al. Am J Respir Crit Care Med 2014; 190 (9):1044–1052,

Numbers needed to treat to prevent a case: contacts (3)

QFT G-IT

Test result	Prophylaxis	N	TB cases	NNT
positive	no	207	6	34.5
positive	yes	47	0	

No info given for negative tests

Geis et al. Eur Respir J 2013: 42: 1743

Numbers needed to treat to prevent a case: contacts (4)

QFT G-IT

Test result	Prophylaxis	N	TB cases	NNT
negative	no	13405	20	**670.3**
positive	no	970	18	**67.6**
positive	yes	530	2	

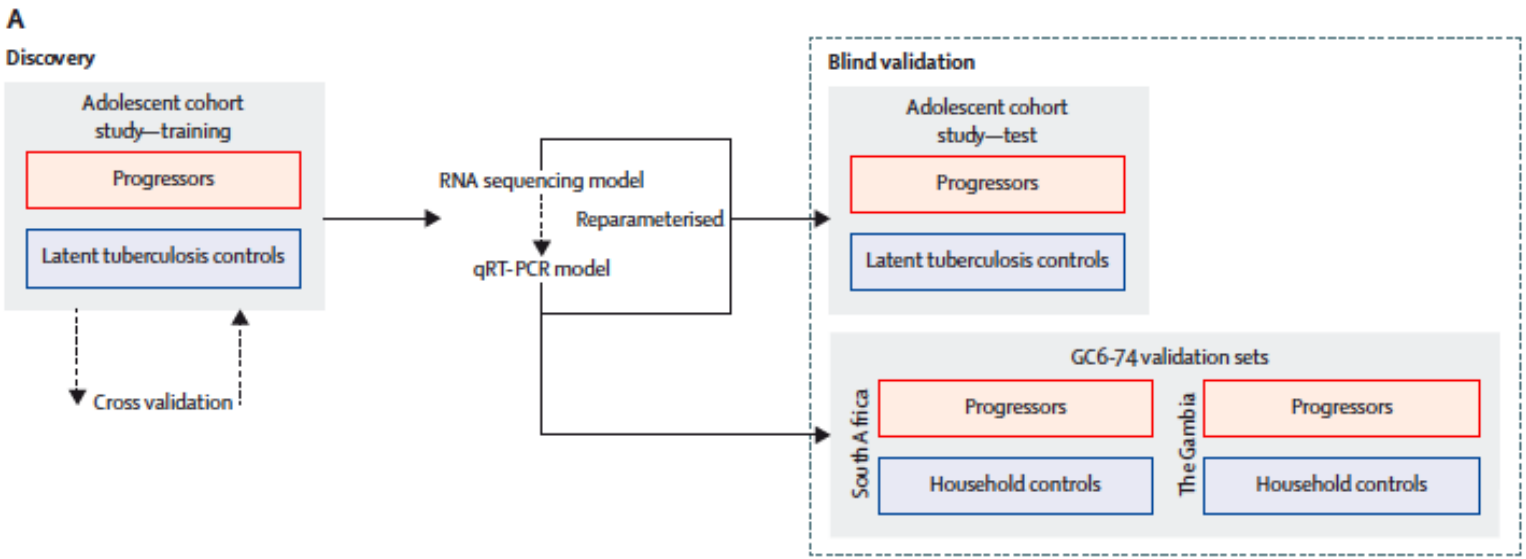
Hermansen TS et al. Thorax 2016: doi:10.1136/thoraxjnl-2015-208228

Numbers needed to treat to prevent a case: immunocompromized hosts

		All patients	HIV infected	HIV infected with positive HIV load
TST	positive	49.7	14.0	8.0
	negative	377.7	194.7	89.0
QFT G-IT	positive	79.5	25.5	12.5
	negative	539.5	285.0	132.0
TSPOT-TB	positive	64.3	21.3	10.3
	negative	341.3	164.7	74.7

Sester M et al. Am J Respir Crit Care Med 2014; 190(10): 1168–1176

mRNA signature predicts TB



Period (days)	Sensitivity (95% CI)	ROC AUC (95% CI)
1-180	71.2% (66.6-75.2%)	0.79 (0.76-0.82)

Zak DE et al. Lancet 2016 http://dx.doi.org/10.1016/ S0140-6736(15)01316-1

Take-Home Message

- **... PPV (IGRAs) for TB development = poor**

- **... NNT to prevent one case of TB**

  HCW, CRF, RA = >100

  adult TB contacts = >1 in 35

  HIV (VL+) = ± 10

- **... transcriptomic signatures predict TB**

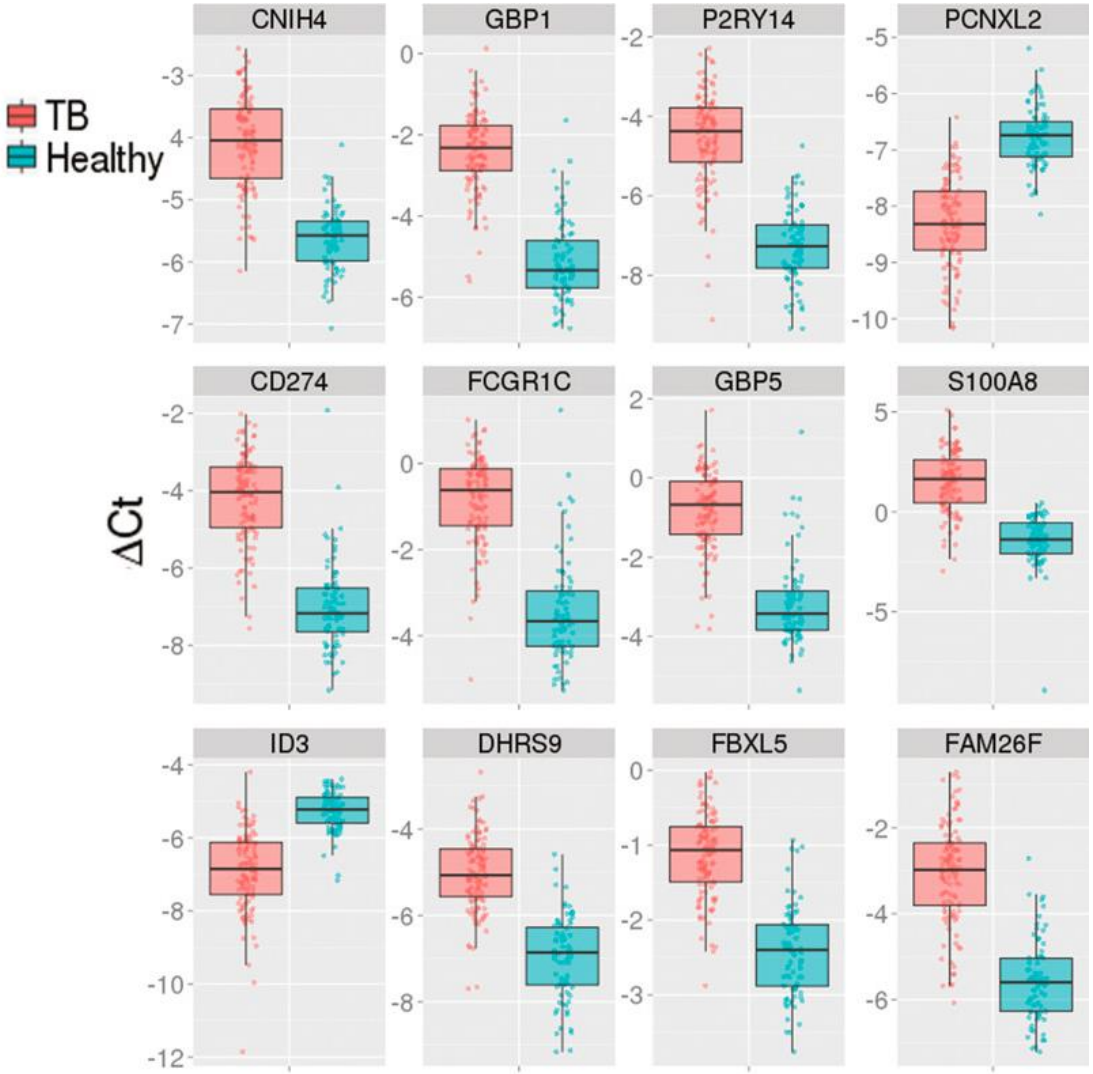
Diagnosis

13 000

Are estimated to live with MDR-TB in the Ukraine in 2014

WHO: Global tuberculosis report 2015, Geneva Switzerland

Gene-signature for POC diagnosis of TB



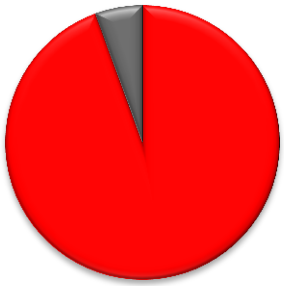
Maertzdorf J et al. EMBO Mol Med 2016; 8: 86–95

Gene-signature for POC diagnosis of TB

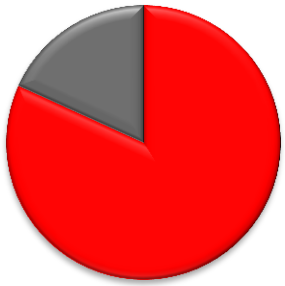
Platform	Classification	Cohort	*N*	4 gene AUC (95% CI)
RT–PCR	TB vs. healthy	India (test set)	89	0.95 (0.90–0.99)
		India (full dataset)	189	0.98 (0.97–1.00)
		The Gambia	75	0.89 (0.81–0.96)
		Uganda	62	0.82 (0.71–0.93)
Microarray	TB vs. healthy (HIV^-)	Bloom	148	0.99 (0.98–0.99)
		Berry	228	0.91 (0.86–0.91)
		Kaforou	180	0.91 (0.87–0.91)
		Maertzdorf	26	0.99 (0.95–0.99)
	TB vs. healthy (HIV^+)	Kaforou	182	0.84 (0.79–0.84)
		Dawany	44	0.72 (0.56–0.72)
	TB vs. ODs (pulmonary)	Bloom (pneumonia)	49	0.94 (0.87–0.94)
		Bloom (lung cancer)	51	0.95 (0.88–0.95)
		Bloom (sarcoidosis)	96	0.72 (0.62–0.72)
		Maertzdorf (sarcoidosis)	26	0.58 (0.34–0.58)
		Kaforou (others)	180	0.71 (0.63–0.71)

Maertzdorf J et al. EMBO Mol Med 2016); 8: 86–95

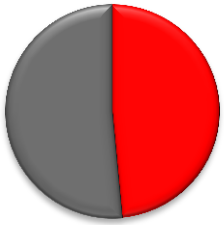
Additional drug-resistance in XDR-TB in Europe



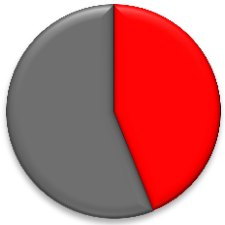
Pyrazinamide 94.4%



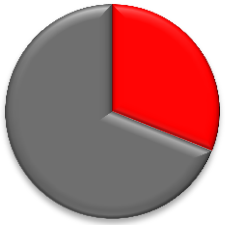
Ethambutol 81.8%



Prothionamid 48.5%



Cycloserin 44.0%

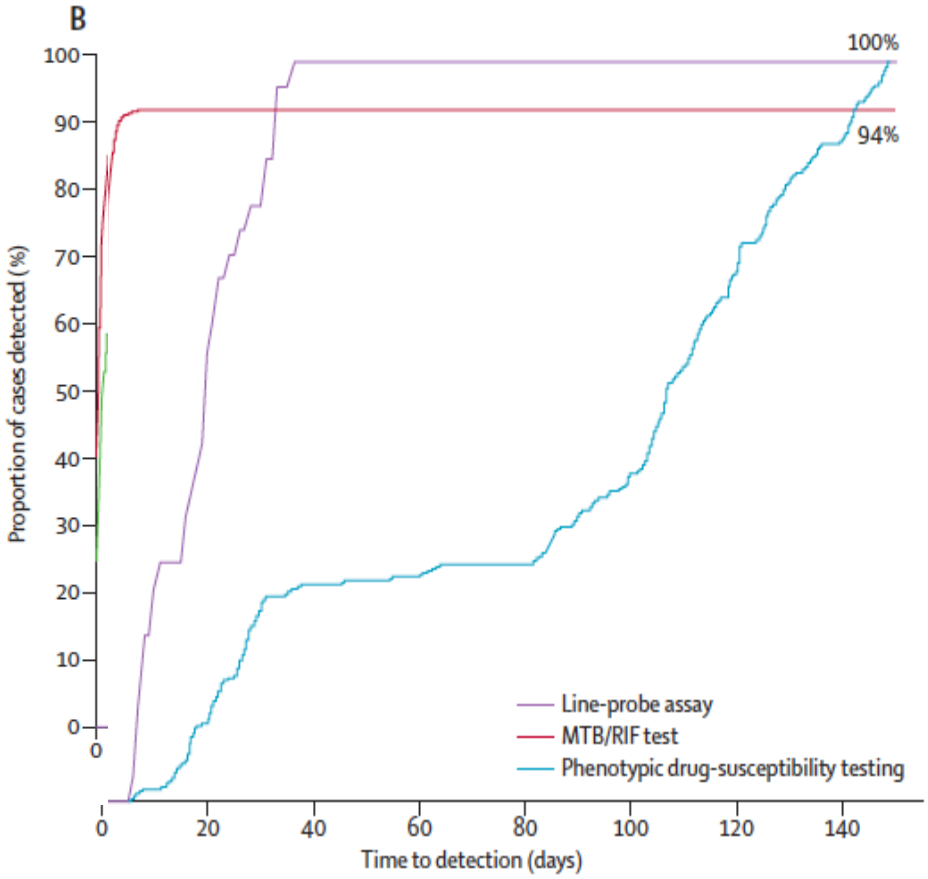


PAS 31.0%

Guenther G et al. INT J TUBERC LUNG DIS 2015;19:1524-27

Xpert MTB/RIF (rpoB)

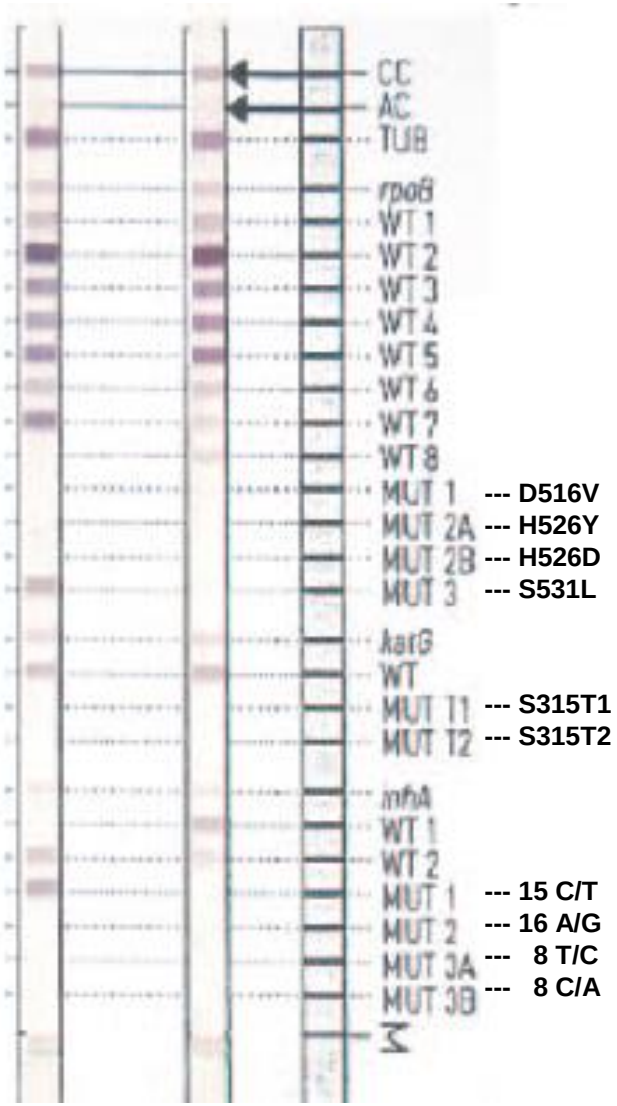
- R -



 Boehme C et al. Lancet 2011DOI:10.1016/S0140- 6736(11)60438 -8

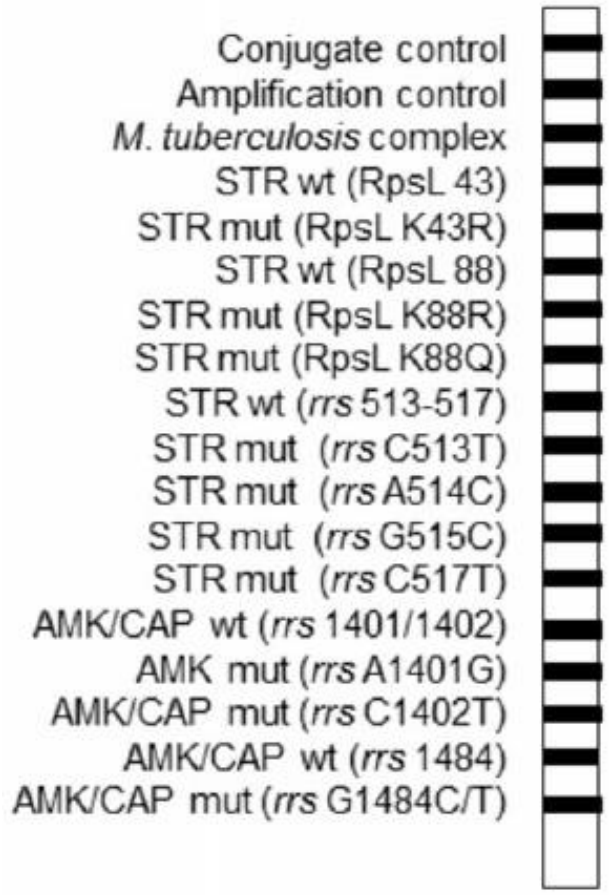
Line probe assays (rpoB, katG, inhA)

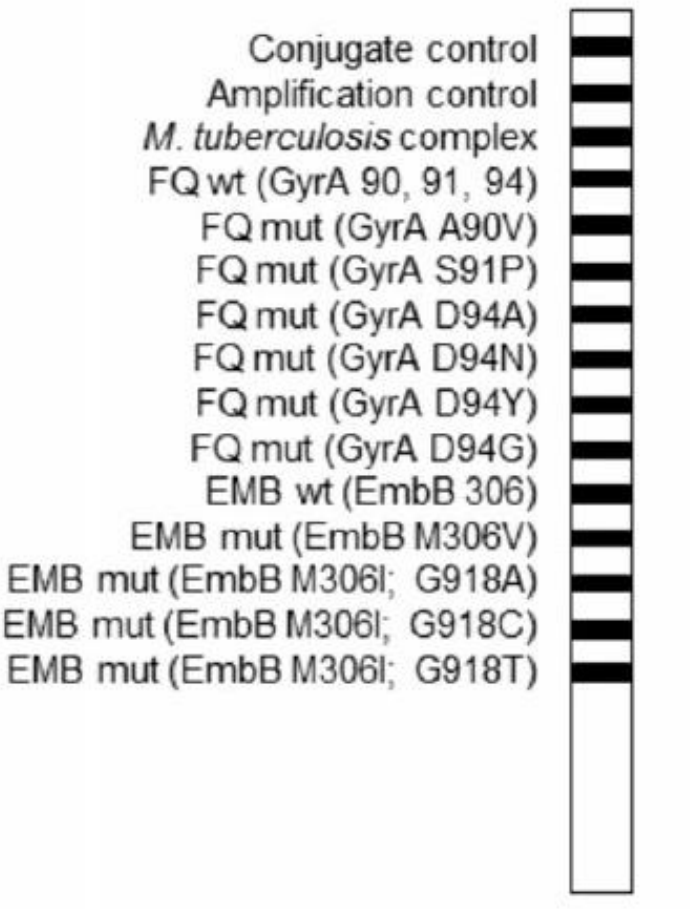
- R, H -



Hillemann D et al. J Clin Microbiol 2007; Aug.: 2635–2640

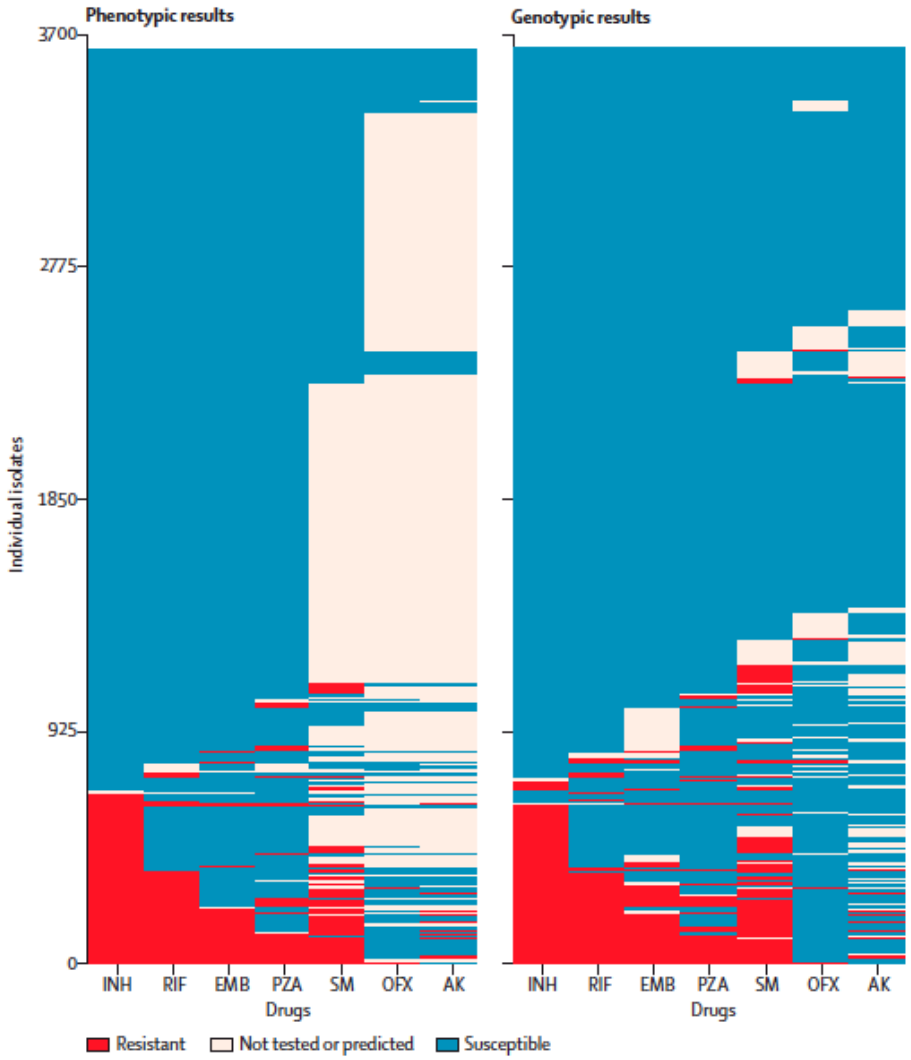
Line probe assays (RpsL, rrs, GyrA, EmbB)
- Sm, Am, Cm, Km, FQs, E -





Ritter C et al. J Clin Microbiol 2014; 52(3).: 940-46

Whole genome sequencing
- genotypic predicts phenotypic DST -



Walker TM et al. Lancet Infect Dis 2015; 15: 1193–1202

Whole genome sequencing
- genotypic DST directly on sputum-

Patient	Sputum positivity	Sample	Type	Rif	Inh	Emb	Pza	Str*	Ofl*	Pas*	Amg*	Thi*
1	3+		Culture phenotype	S	S	S	S	NA	NA	NA	NA	NA
		MTB-27	Culture genotype									
		MTB-17	Sputum genotype									
2	2+		Culture phenotype	S	S	S	S	NA	NA	NA	NA	NA
		MTB-28	Culture genotype							R		
		MTB-18	Sputum genotype							R		
3	2+		Culture phenotype	S	S	S	S	NA	NA	NA	NA	NA
		MTB-29WE	Culture genotype									
		MTB-19	Sputum genotype									
4	3+		Culture phenotype	R	R	R	R	R	S	S	R (Kan)	S
		MTB-30WE	Culture genotype	R	R	Low R	R	R			R	
		MTB-20	Sputum genotype	R	R	Low R	R	R			R	
5	3+		Culture phenotype	S	R	S	R	R	R	S	R (Kan & Amk)	R
		MTB-31WE	Culture genotype	R	R	Low R		R	R		R	
		MTB-21	Sputum genotype	R	R	Low R		R	R		R (Kan)	
6	3+		Culture phenotype	R	R	S	R	R	R	S	R (Kan)	R
		MTB-32WE	Culture genotype	R	R	Low R	R	R	R		R	R
		MTB-22	Sputum genotype	R	R	Low R	R	R	R		R	R
7	3+		Culture phenotype	R	R	R	R	R	R	R	R (Cap)	R
		MTB-33WE	Culture genotype	R	R	R		R	R			
		MTB-23	Sputum genotype	R	R	R		R	R			
8	3+		Culture phenotype	R	R	R	R	R	R	R	S	S
		MTB-34WE	Culture genotype	R	R	Low R	R	R	R			
		MTB-24	Sputum genotype	R	R	Low R	R	R	R			
9	3+		Culture phenotype	R	R	R	NA	R	NA	NA	NA	NA
		MTB-35WE	Culture genotype	R	R	R	R	R				
		MTB-25	Sputum genotype	R	R	R	R	R				
10	3+		Culture phenotype	R	R	R	R	R	R	S	S	S
		MTB-36WE	Culture genotype	R	R	Low R	R	R	R			
		MTB-26	Sputum genotype	R	R	Low R	R	R	R			

Brown AC et al. J Clin Microbiol 53: 2230–2237

Consensus statement: Implications of molecular DST

	Drug	
Mutation	**Isoniazid**	**Ethionamide**
katG S315T	–	+
inhA - 16G - 15T - 8A/C	+	–
	Rifampicin	**Rifabutin**
rpoB S531L H526mut	–	–
rpoB D516mut	–	+
rpoB L533mut	+	+
	Ethambutol	
embB M306mut	(+)	

	Drug	
	Amikacin	**Capreomycin**
rrs A1408G* (1401)	–	+
rrs C1409T* (1402)	+	–
rrs G1491C/T* (1484)	–	–
	Streptomycin	
rpsL K43R	–	
rrs A523C* (514) C526T* (517)	–	
	Moxifloxacin	
gyrA D94mut	–	
gyrA A90mut	(+)	

Dominguez J et al. Int J Tuberc Lung Dis 2016 (1):24–42

Take-Home Message

- **... M/XDR-TB = ↑↑ problem in Eastern Europe**
- **... Revolution in molecular diagnostics**
- **... Molecular diagnostics → personalized treatment**

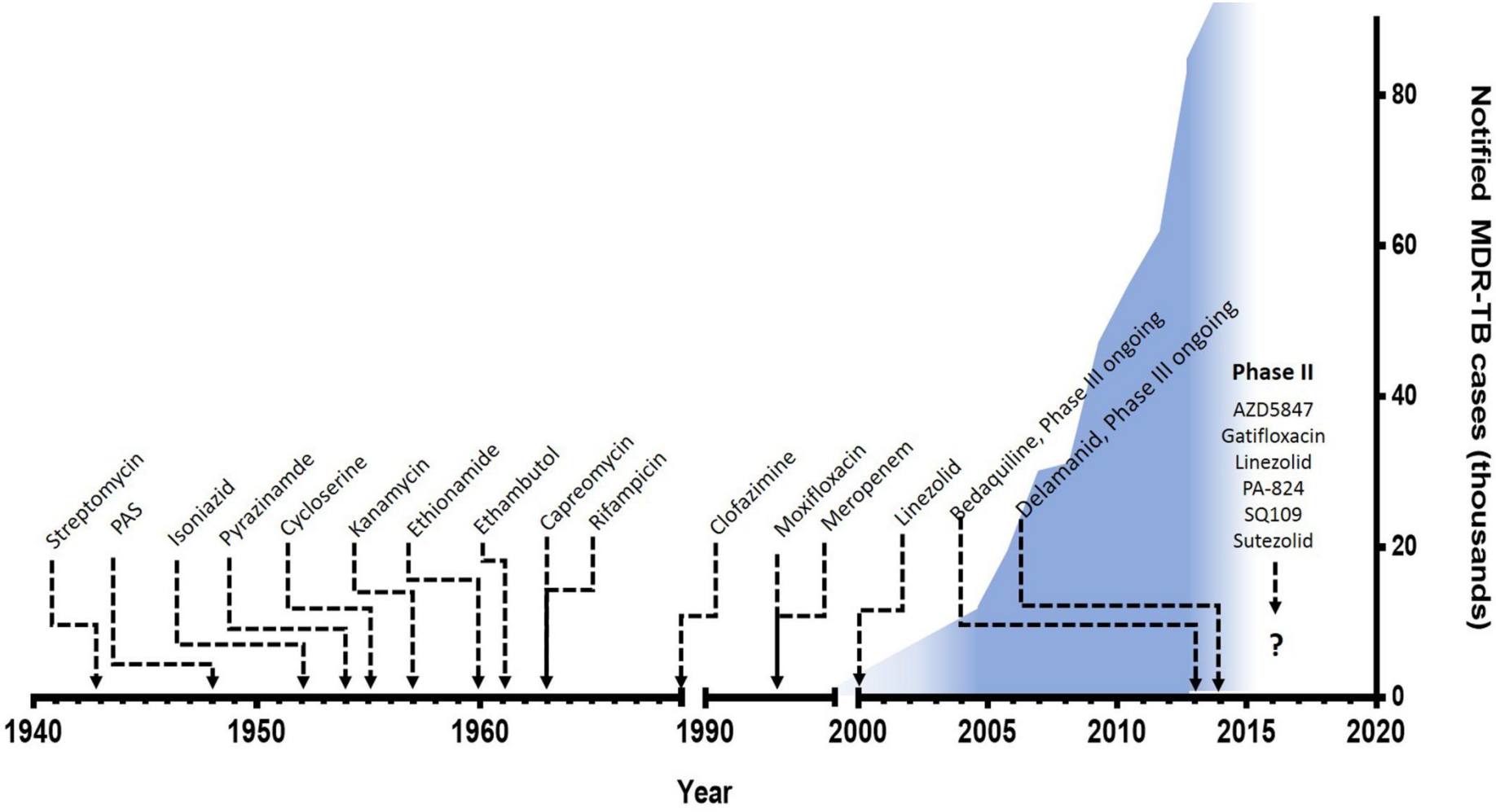
Treatment

>85 %

treatment success can be achieved in MDR-TB by personalized therapy

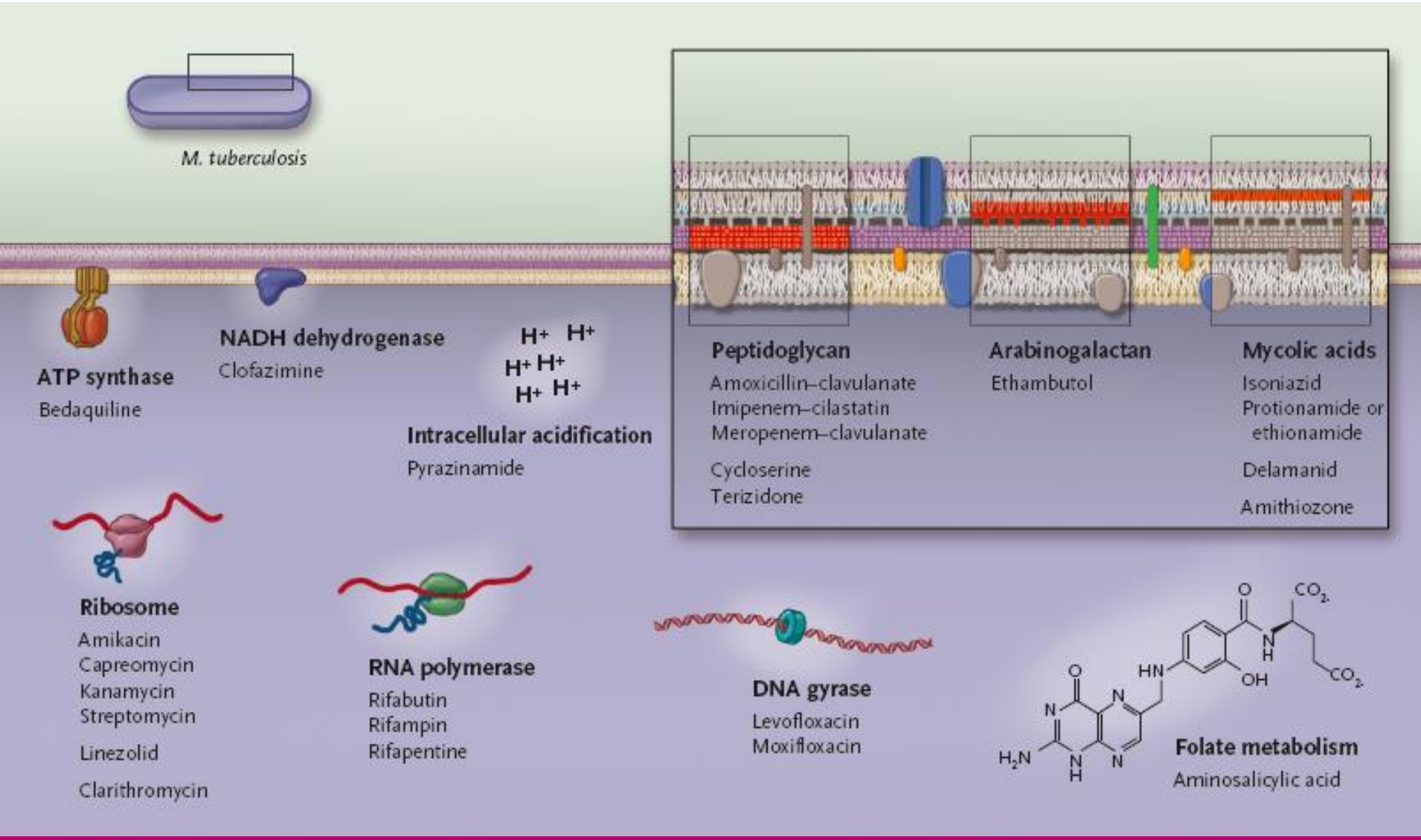
Olaru ID et al. Ann Am Thoracic Soc 2016 (in press)

Development of anti-TB drugs



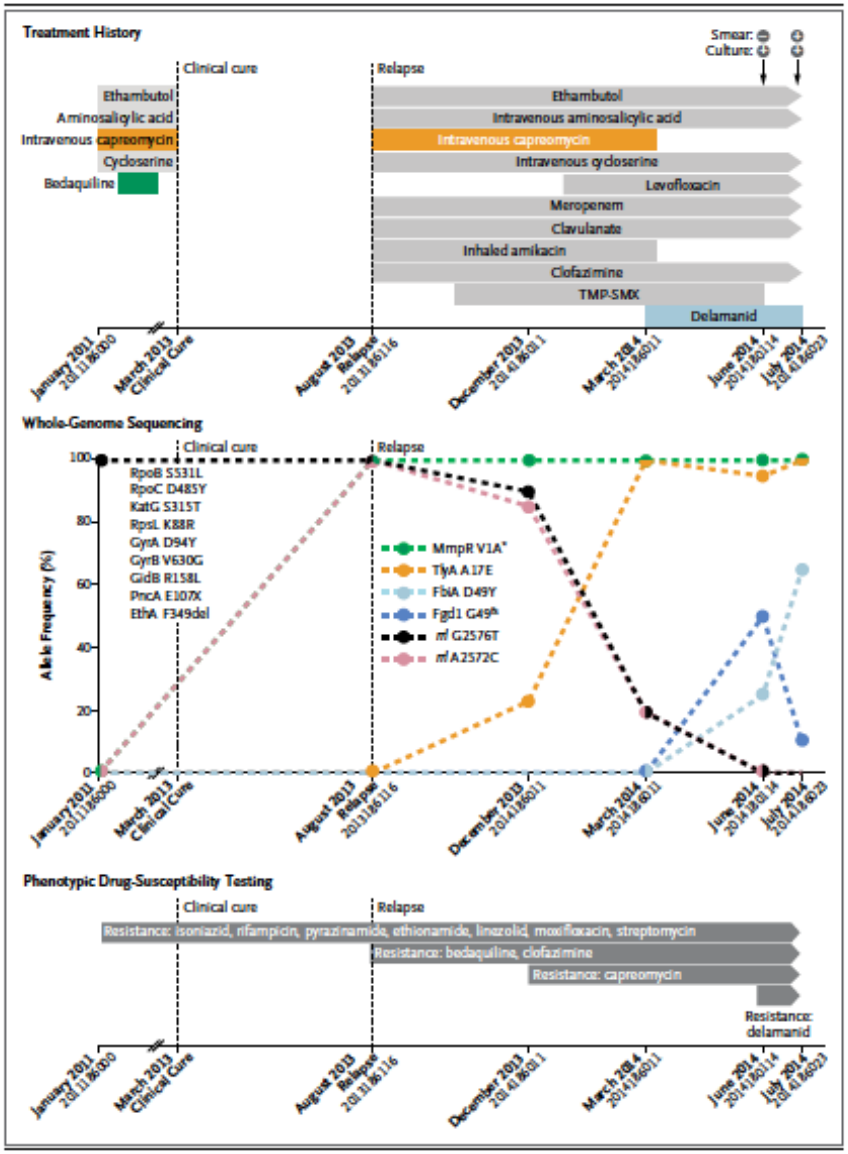
Olaru ID et al. Eur Respir J 2015; 45: 1119–1131

Targets of therapeutics



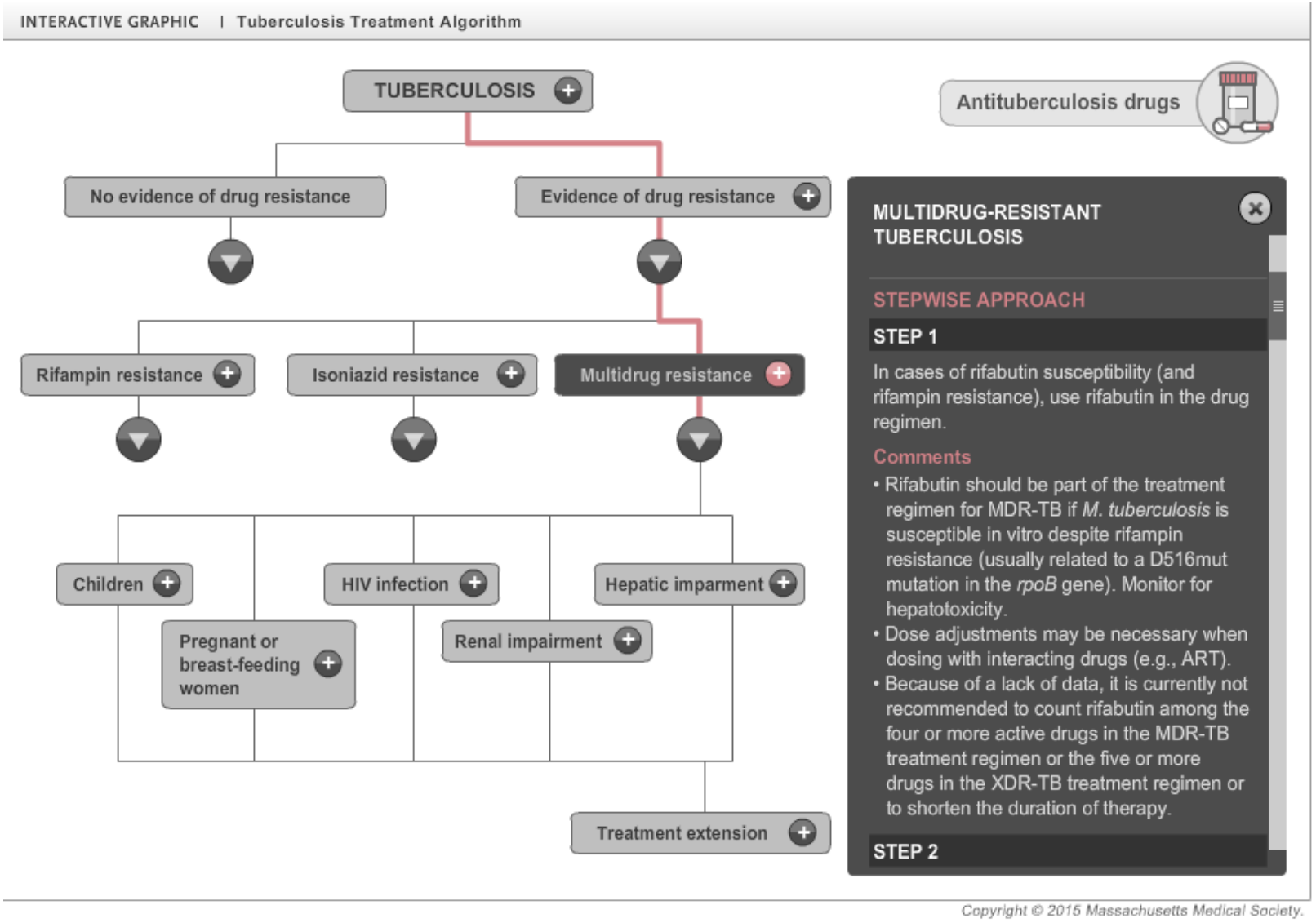
Horsburgh CR et al. N Engl J Med 2015;373:2149-60.

Resistance against new drugs



Bloemberg G et al. N Engl J Med 2015;373 (20):1986-88.

Treatment algorithm for TB



Horsburgh CR et al. N Engl J Med 2015;373:2149-60.

8 steps für choosing a drug regimen
(≥4 active drugs for MDR-TB, ≥5 for XDR-TB)

1. **Is there low level rifampicin-resistance? Y: Use high dose R or Rb**

Horsburgh CR et al. N Engl J Med 2015;373:2149-60.

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4. In case of later generation FQ-resistance: Use Bdq

Horsburgh CR et al. N Engl J Med 2015;373:2149-60.

8 steps für choosing a drug regimen
(≥4 active drugs for MDR-TB, ≥5 for XDR-TB)

1. Is there low level rifampicin-resistance? Y: Use high dose R or Rb

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7. **Add Mero/Clv, Clf and/or Dlm if necessary**

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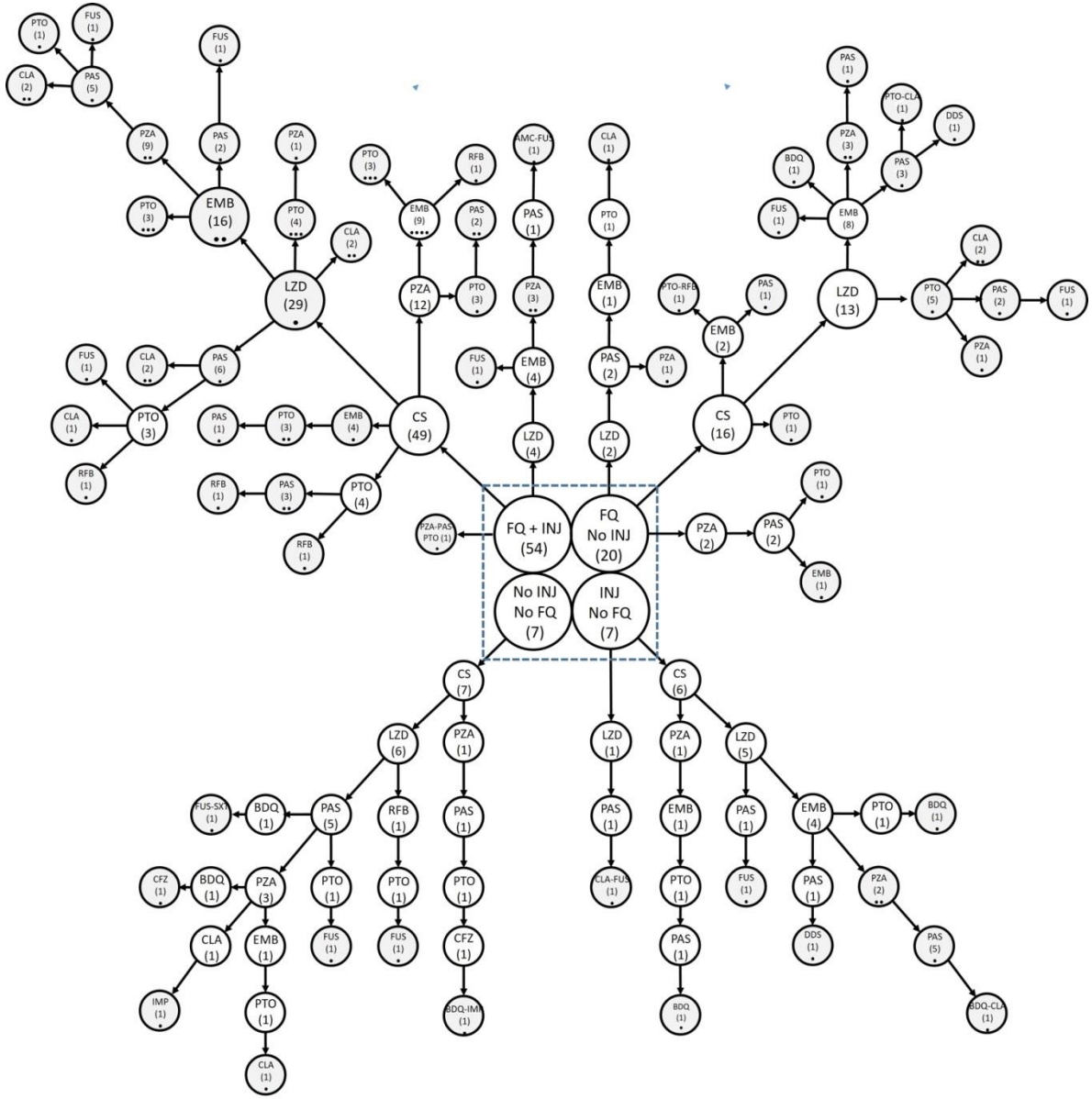
6. Can Pto, Cs, PAS or Lzd be used: Y: A combi. of up to 3 drugs is often used
7. Add Mero/Clv, Clf and/or Dlm if necessary
8. **Add Z and E to all regimen if suggested by DST (not counted)**

Horsburgh CR et al. N Engl J Med 2015;373:2149-60.

Highly individualized treatment regimens



Olaru ID et al. Ann Am Thoracic Soc 2016 (in press)

THE SHORTER
MDR-TB REGIMEN

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line dru

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line dru

Supported by selected first-line TB drugs

Future management of TB

	Standard	Advanced	Perspective
Molecular drug resistance testing	R	R, H, FQ, SLID	WGS
Quantitative drug resistance testing	-	MIC	TDM
Dosing of drugs	„one4all“ weight-based	by plasma levels	TDM
Duration of therapy	standardized	severity of disease	biomarker
Prediction of adverse events	-	-	host genetics
Immunotherapy	-	IFN-g, IL2, VitD	immune signatures
Clinical care	uniform	consillary	multidisciplinary

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Take-Home Message

- **... BDQ/DLM: Emergence of resistant mycobacteria**
- **... the future of TB medicine will be personalized**
- **... high M/XDR-TB cure rates possible**

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List of Abbreviations

Am = amikacin
Bdq = bedaquiline
CI = confidence intervall
Clf = clofazimine
CM = capreomycin
CRF = chronic renal failure
Cs = cycloserin
Del = delamanid
DST = drug susceptibility testing
E = ethambutol
FQ = fluoroquinolone
I = current
IGRA = interferon-γ release assay
H = isoniacid
HCW = healthcare worker
Inc = incidence
Km = kanamycin
Lfx = levofloxacin
Lzd = linezolid
MDR = multidrug-resistance
Mero/Clv = meropenem/clavulanic acid
MIC = minimal inhibitory concentration
Mfx = moxifloxacin
NNT = number needed to treat to prevent one case
PAS = P-aminosalicylic acid
POC = point of care
PPV = Positive predictive value
Pto = protionamide
PY = patient years
RA = rheumatoid arthritis
Sm = streptomycin
TB = tuberculosis
U = voltage
R = resistance
R = rifampicin
Rb = rifabutin
SLID = second line injectable drug
TDM = therapeutic drug monitoring
WGS = whole genome sequencing
XDR = extensively drug-resistance
Y = yes
Z = pyrazinamide