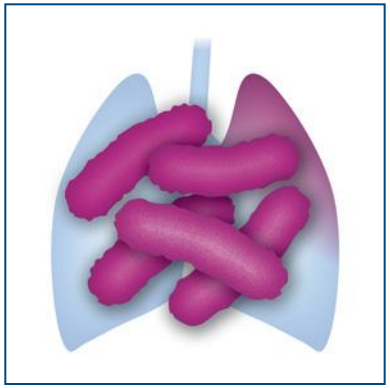
Pneumo Update Europe 2017

9-10 June, Vienna

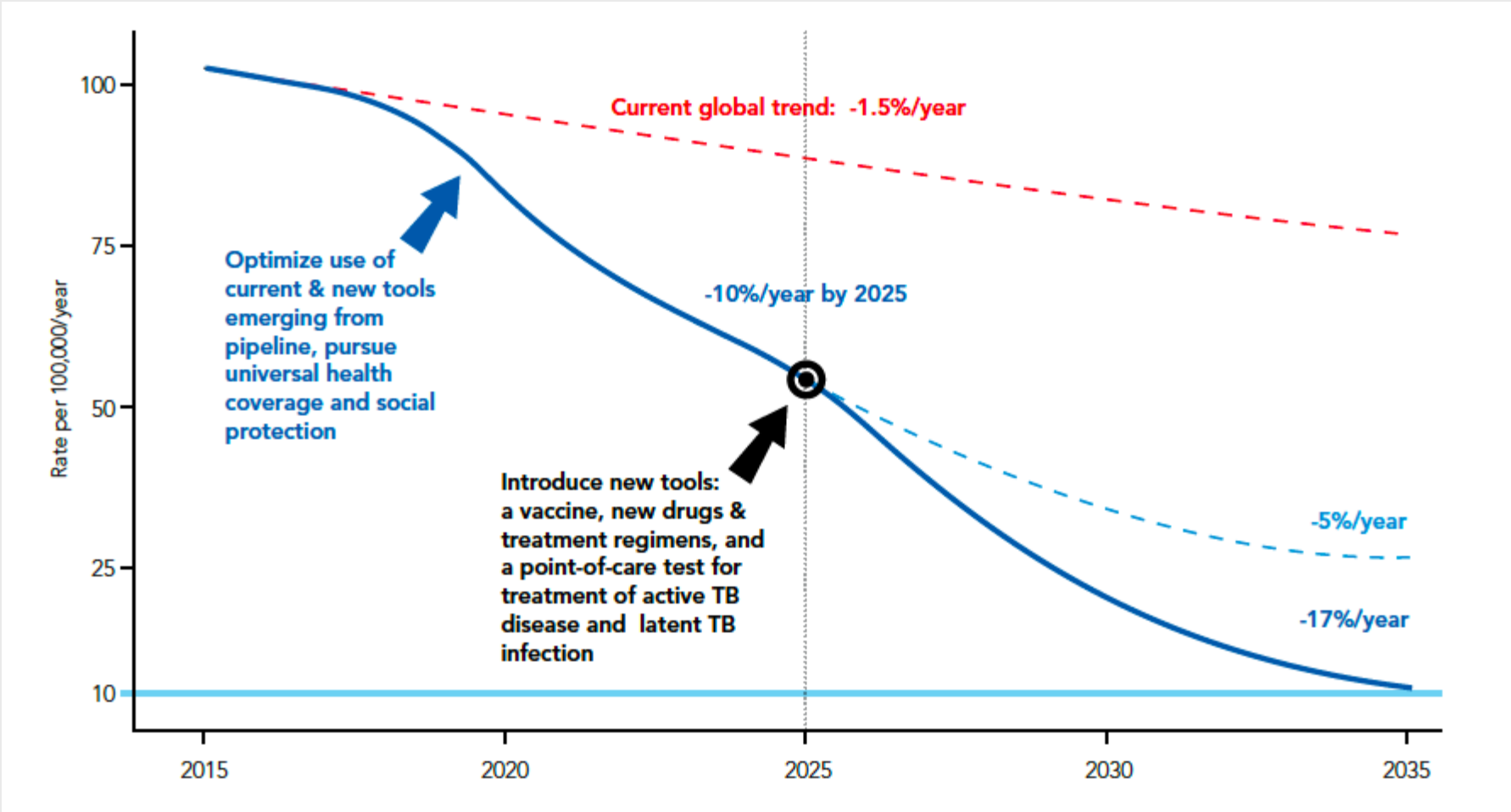
Tuberculosis



Christoph Lange, Germany

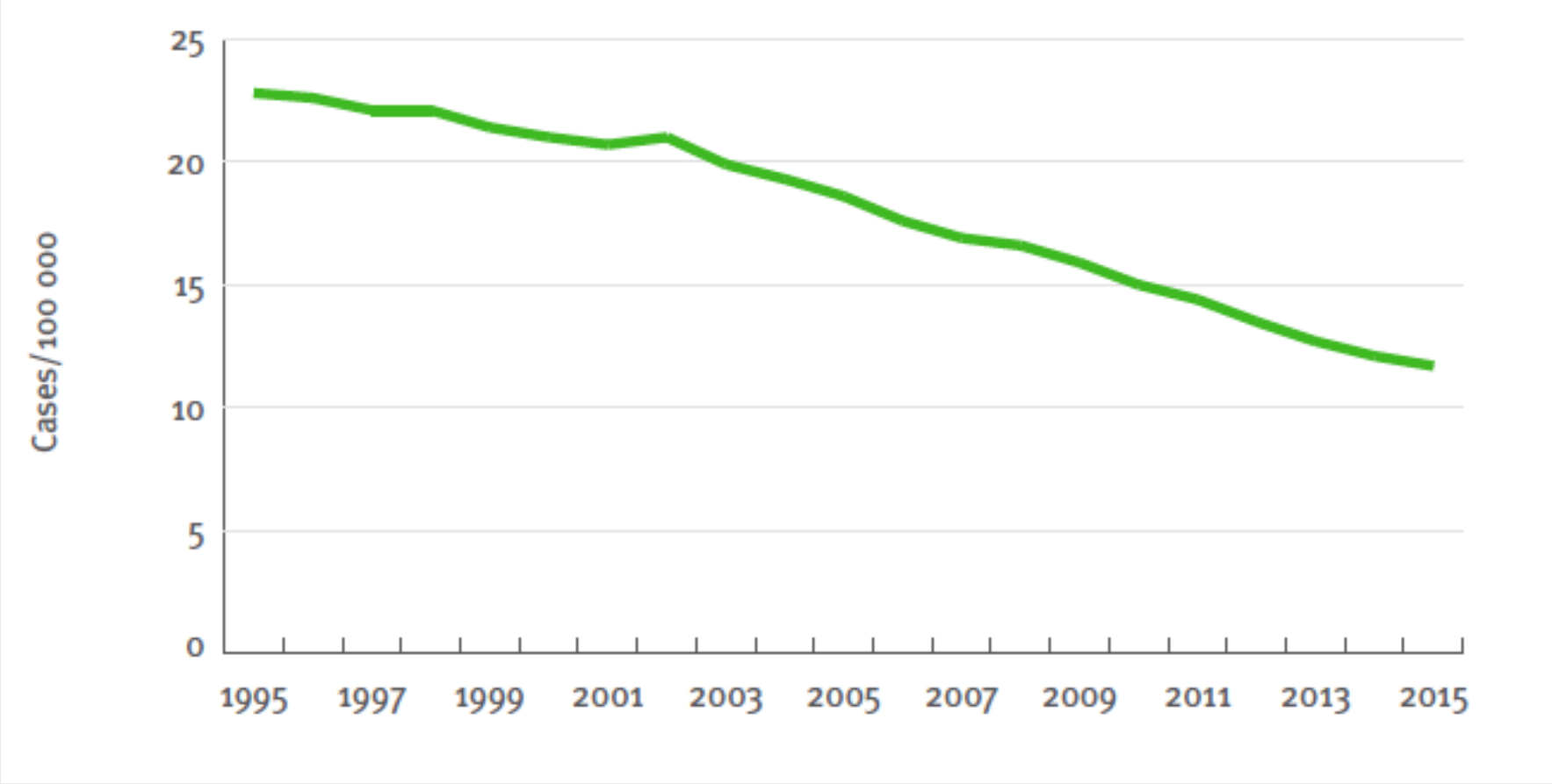
Epidemiology

Goal of TB elimination plan



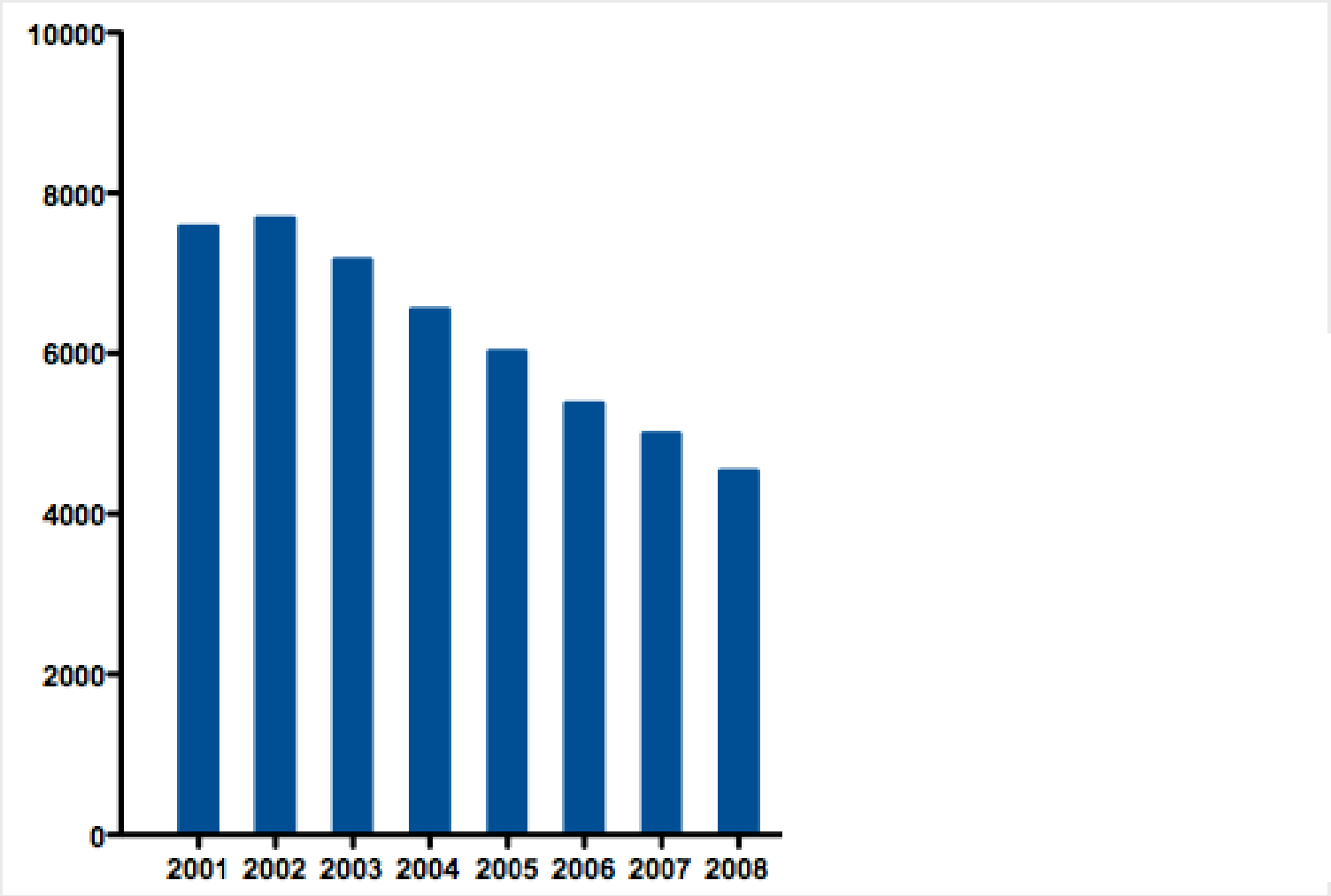
WHO: End TB Strategy http://www.who.int/tb/post2015_strategy/en/

New TB cases in Europe



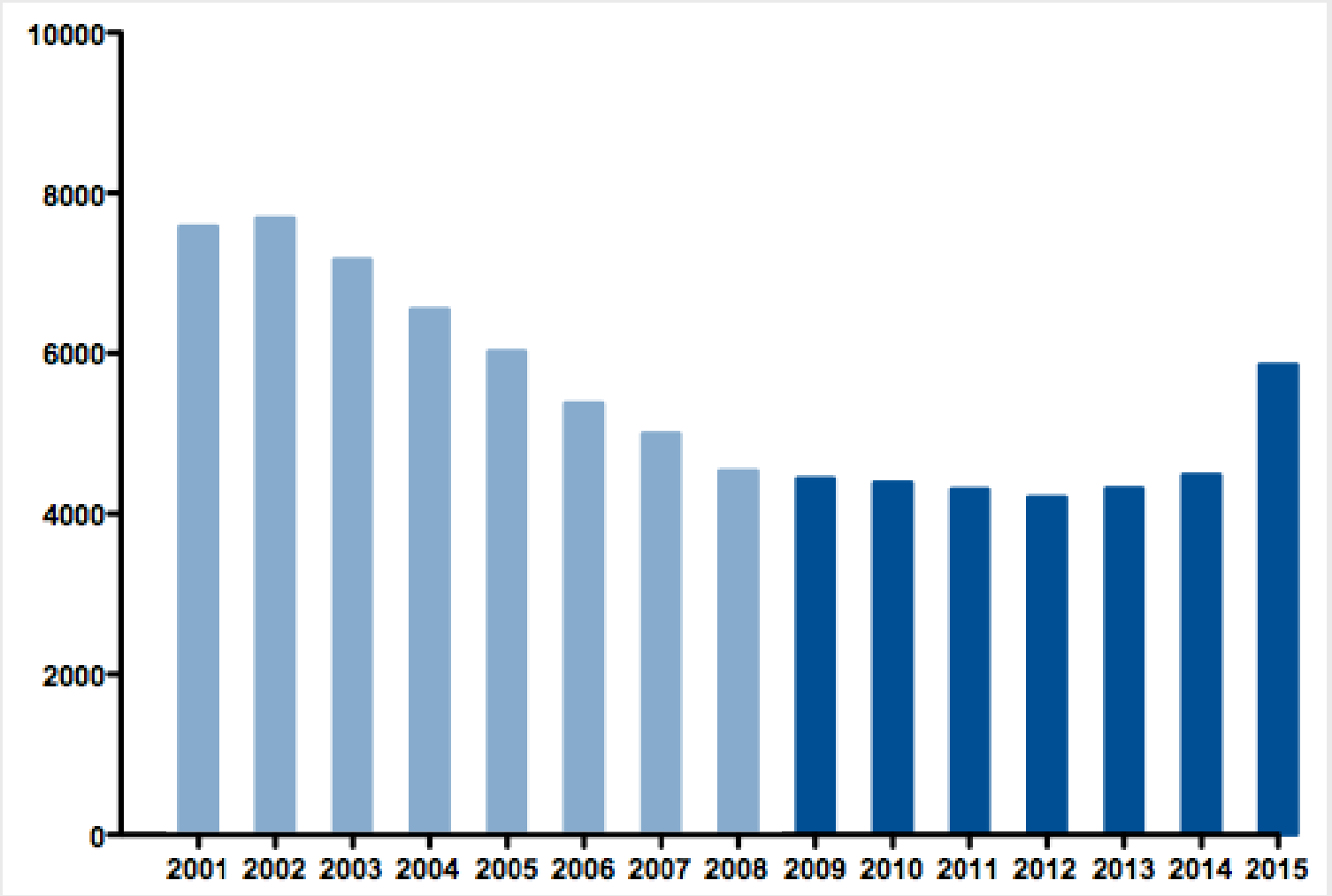
European Centre for Disease Prevention and Control/WHO Regional Office for Europe.
Tuberculosis surveillance and monitoring in Europe 2017

New TB cases in Germany



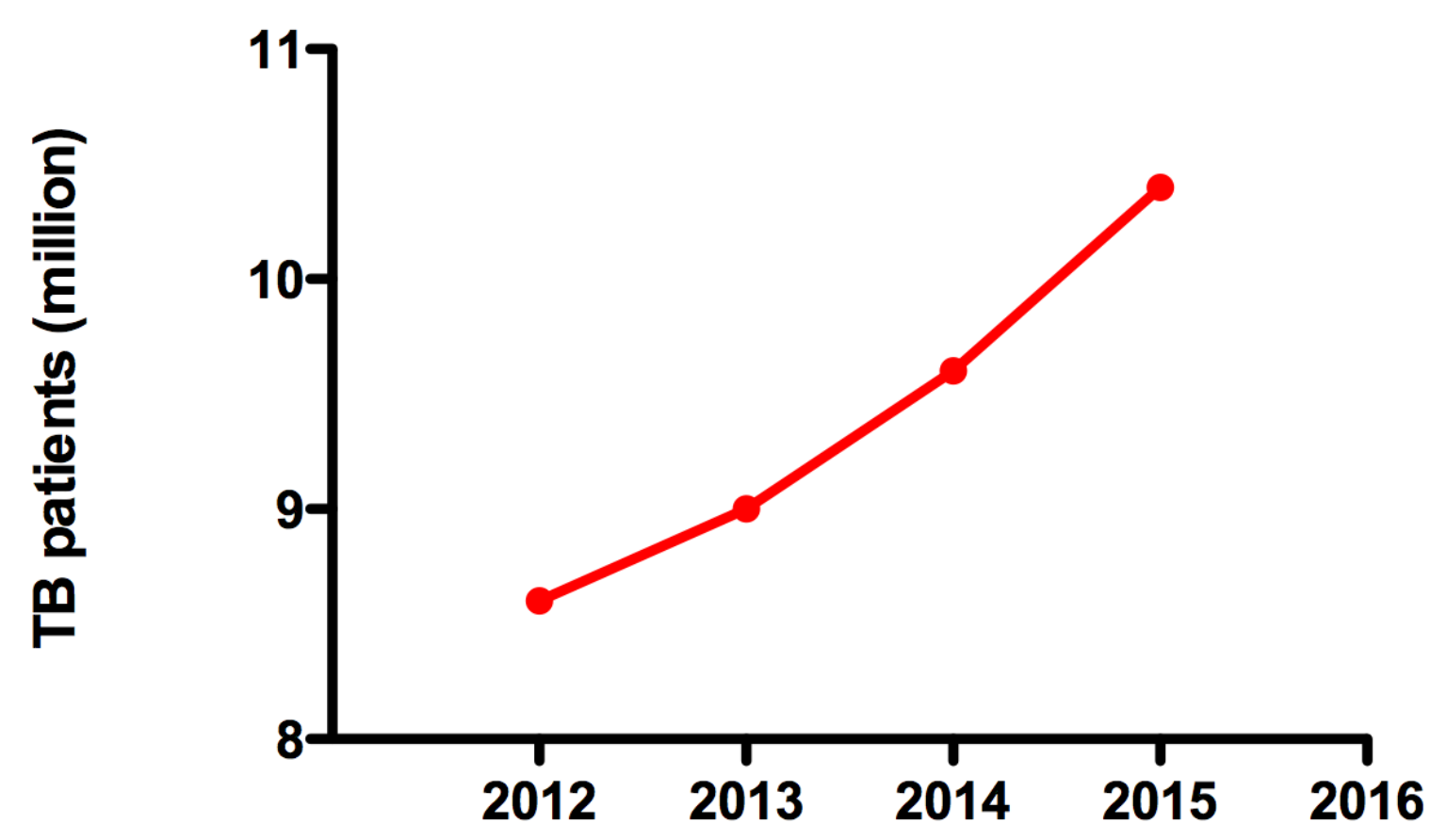
Robert Koch Institute 2017

New TB cases in Germany



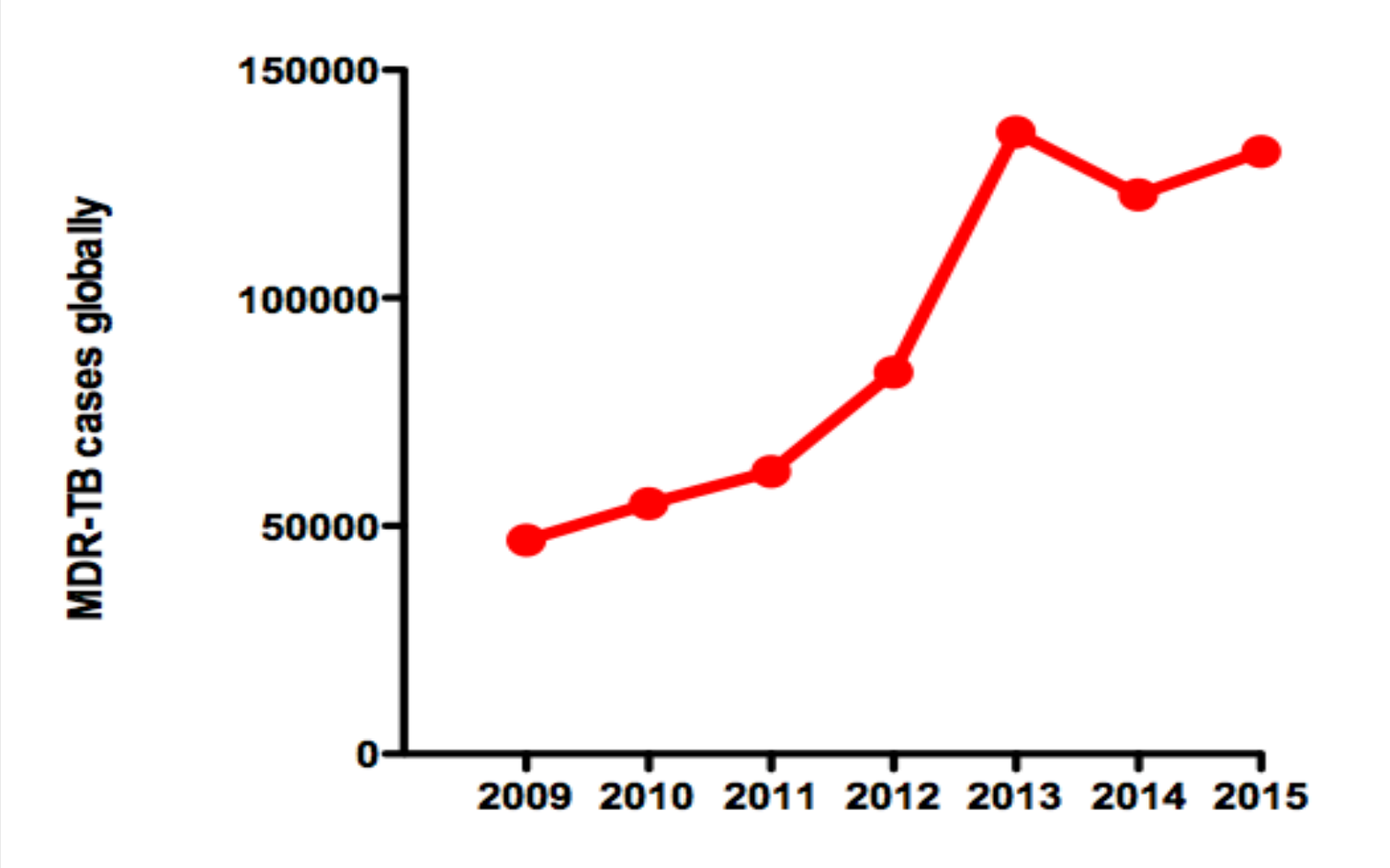
Robert Koch Institute 2017

17% increase in new TB cases since 2012



WHO Global TB Reports 2013-2016

21% annual increase in MDR-TB 2009-2015



WHO Global TB Reports 2010-2016

Transmission of Extensively Drug-Resistant Tuberculosis in South Africa

ABSTRACT

BACKGROUND

Drug-resistant tuberculosis threatens recent gains in the treatment of tuberculosis and human immunodeficiency virus (HIV) infection worldwide. A widespread epidemic of extensively drug-resistant (XDR) tuberculosis is occurring in South Africa, where cases have increased substantially since 2002. The factors driving this rapid increase have not been fully elucidated, but such knowledge is needed to guide public health interventions.

METHODS

We conducted a prospective study involving 404 participants in KwaZulu-Natal Province, South Africa, with a diagnosis of XDR tuberculosis between 2011 and 2014. Interviews and medical-record reviews were used to elicit information on the participants' history of tuberculosis and HIV infection, hospitalizations, and social networks. *Mycobacterium tuberculosis* isolates underwent insertion sequence (IS)*6110* restriction-fragment–length polymorphism analysis, targeted gene sequencing, and whole-genome sequencing. We used clinical and genotypic case definitions to calculate the proportion of cases of XDR tuberculosis that were due to inadequate treatment of multidrug-resistant (MDR) tuberculosis (i.e., acquired resistance) versus those that were due to transmission (i.e., transmitted resistance). We used social-network analysis to identify community and hospital locations of transmission.

RESULTS

Of the 404 participants, 311 (77%) had HIV infection; the median CD4+ count was 340 cells per cubic millimeter (interquartile range, 117 to 431). A total of 280 participants (69%) had never received treatment for MDR tuberculosis. Genotypic analysis in 386 participants revealed that 323 (84%) belonged to 1 of 31 clusters. Clusters ranged from 2 to 14 participants, except for 1 large cluster of 212 participants (55%) with a LAM4/KZN strain. Person-to-person or hospital-based epidemiologic links were identified in 123 of 404 participants (30%).

CONCLUSIONS

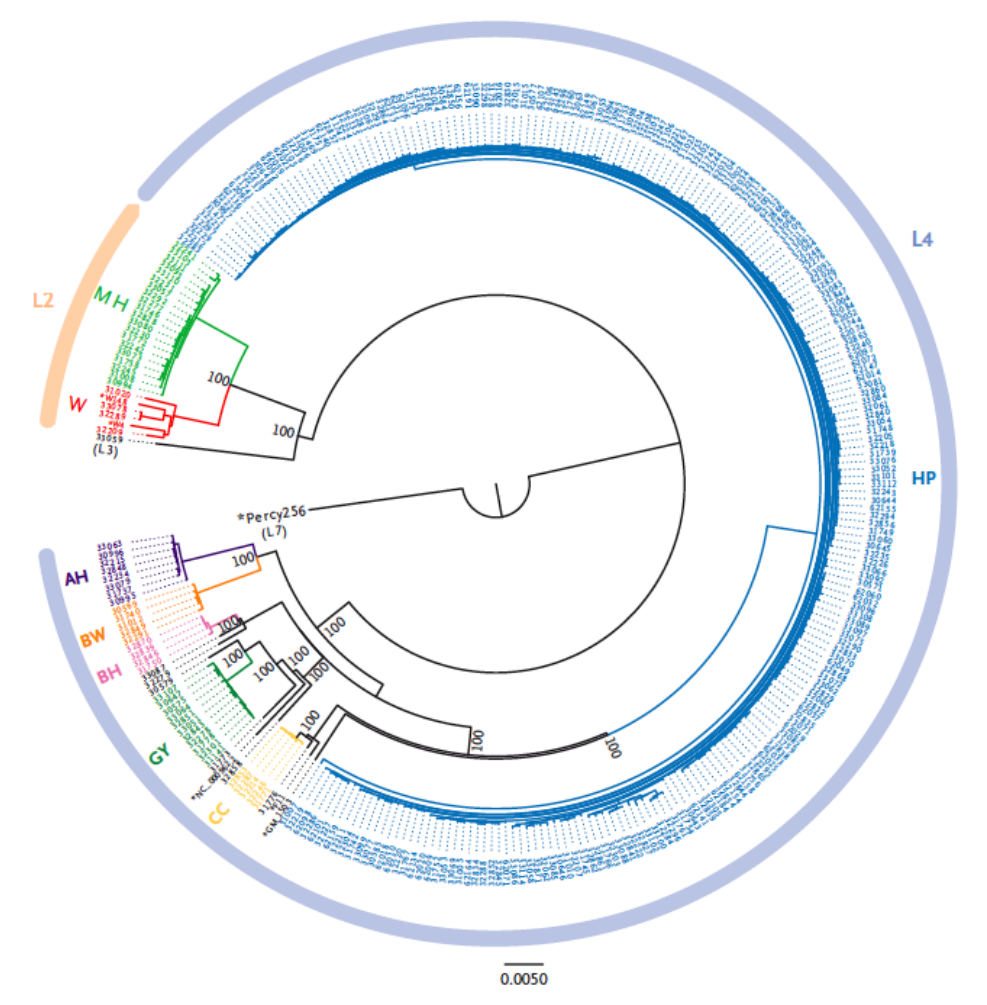
The majority of cases of XDR tuberculosis in KwaZulu-Natal, South Africa, an area with a high tuberculosis burden, were probably due to transmission rather than to inadequate treatment of MDR tuberculosis. These data suggest that control of the epidemic of drug-resistant tuberculosis requires an increased focus on interrupting transmission. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

From the Emory University Rollins School of Public Health and School of Medicine (N.S.S., S.C.A., S.A., A.C., N.R.G.) and the Centers for Disease Control and Prevention (N.S.S.) — both in Atlanta; Albert Einstein College of Medicine and Montefiore Medical Center (N.S.S., J.C.M.B., N.R.G.), Columbia University Mailman School of Public Health (B.M., T.S.B.), and the American Museum of Natural History (A.N.) — all in New York; the National Institute for Communicable Diseases, Johannesburg (N.I., H.M., S.V.O.), University of KwaZulu-Natal and National Health Laboratory Service, Durban (P. Moodley, K.M., T.M., P. Mpangase), and the South African Medical Research Council, Cape Town (N.M., T.K.) — all in South Africa; and the Public Health Research Institute, New Jersey Medical School–Rutgers University, Newark (E.S., B.K.). Address reprint requests to Dr. Gandhi at the Rollins School of Public Health, Emory University, 1518 Clifton Rd. NE, Claudia Nance Rollins Bldg., Rm. 3031, Atlanta, GA 30322, or at neel.r.gandhi@emory.edu.

N Engl J Med 2017;376:243-53.
DOI: 10.1056/NEJMoa1604544

Shah NS et al. N Engl J Med. 2017 Jan 19;376(3):243-253.

Community transmission of XDR-TB



Shah NS et al. N Engl J Med. 2017 Jan 19;376(3):243-253.

Take-Home Message

- **... all time „world record“ of TB patients**
- **... increase and transmission of M/XDR-TB**
- **... success of the EndTB strategy is unlikely**

Prevention

Safety and efficacy of the C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial

Ruhwald M et al. Lancet Respir Med 2017; 5:259-68

C-Tb has QFT comparable test performance

	Negative controls (n=263)	Occasional contacts (n=299)	Close contacts (n=319)	Patients with tuberculosis (n=101)
C-Tb skin test				
Positive	9 (3%)	49 (16%)	136 (43%)	68 (67%)
Negative	253 (96%)	250 (84%)	180 (57%)	32 (32%)
Not done	1 (<0·5%)	0	0	1 (1%)
QuantiFERON-TB Gold In-Tube interferon γ release assay				
Positive	10 (4%)	57 (21%)	122 (42%)	82 (81%)
Negative	253 (96%)	227 (82%)	166 (57%)	19 (19%)
Indeterminate	0	2 (<1%)	2 (<1%)	0
Not done	0	13	26	0
Tuberculin skin test				
Positive	46 (22%)	80 (27%)	162 (51%)	90 (90%)
Negative	167 (78%)	219 (73%)	154 (49%)	10 (10%)
Not done	50 (19%)	0	0	1 (1%)

Ruhwald M et al. Lancet Respir Med 2017; 5:259-68

A blood RNA signature for tuberculosis disease risk:

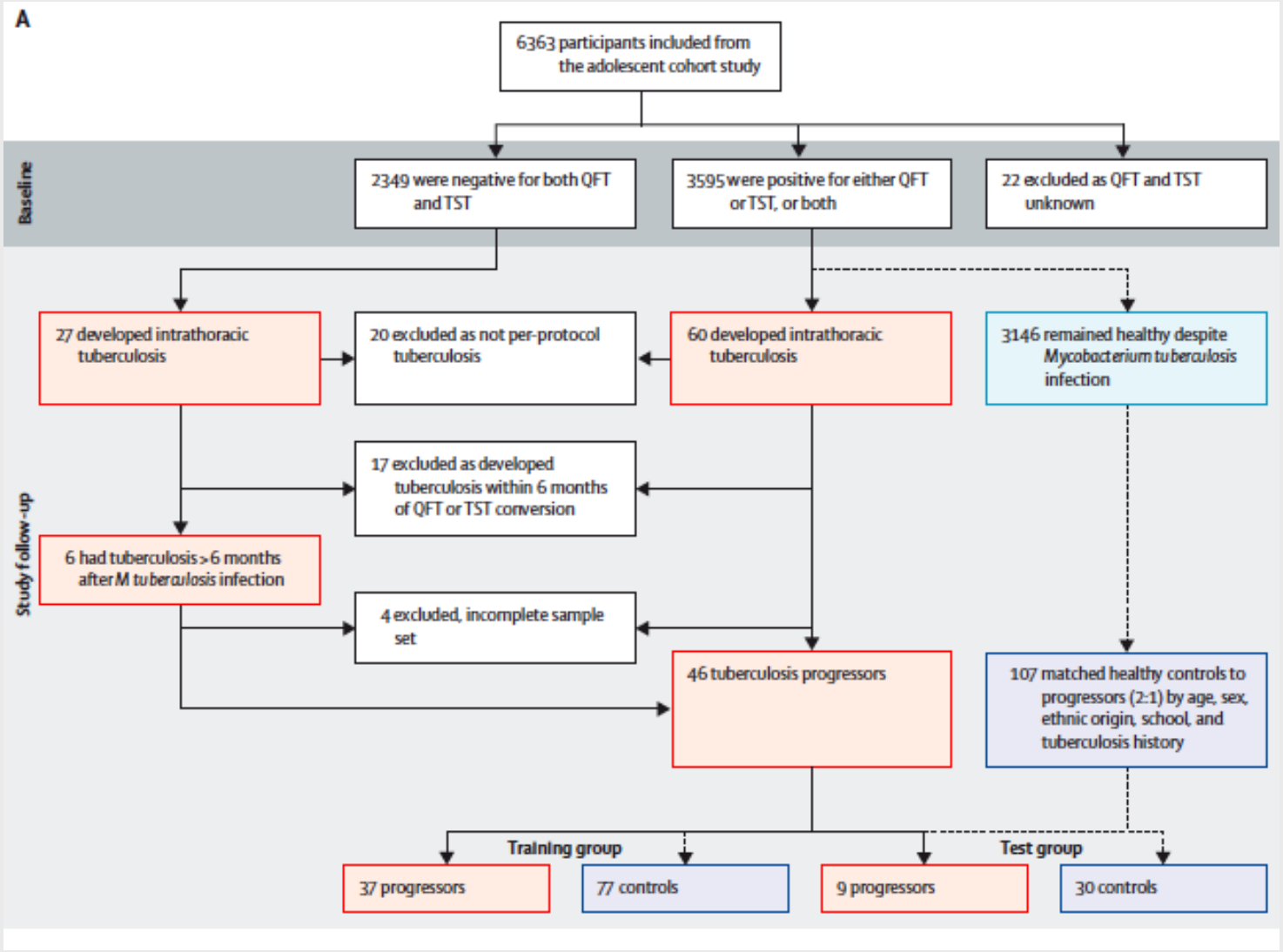
A prospective cohort study

Summary

Background Identification of blood biomarkers that prospectively predict progression of *Mycobacterium tuberculosis* infection to tuberculosis disease might lead to interventions that combat the tuberculosis epidemic. We aimed to assess whether global gene expression measured in whole blood of healthy people allowed identification of prospective signatures of risk of active tuberculosis disease.

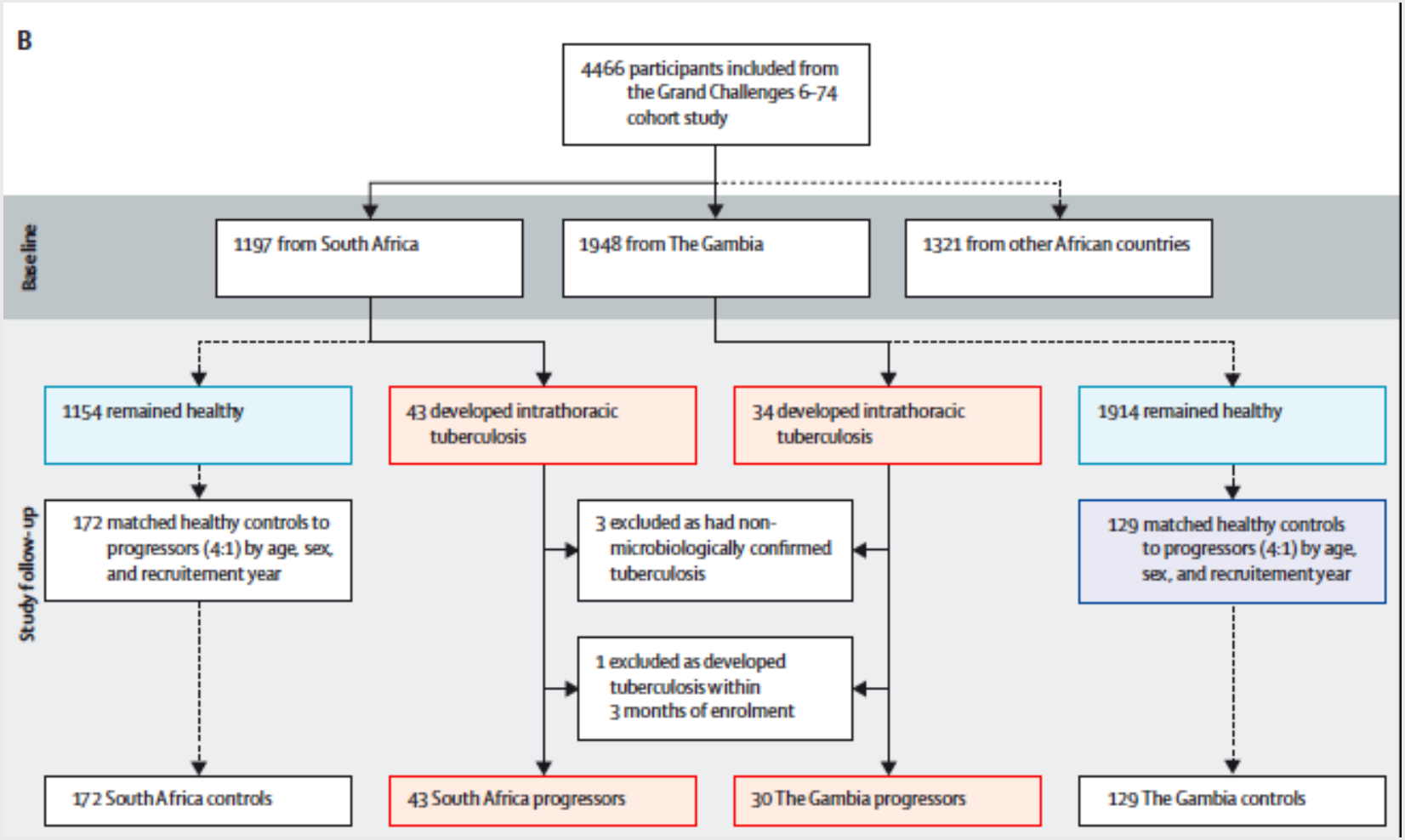
Zak DE et al. Lancet 2016; 387: 2312–22

mRNA signature to predict future TB



Zak DE et al. Lancet 2016; 387: 2312–22

mRNA signature to predict future TB



Zak DE et al. Lancet 2016; 387: 2312–22

Moderate sensitivity, high specificity

	Platform	Days before tuberculosis diagnosis	ROC AUC (95% CI)	ROC p value	Sensitivity (95% CI)	Specificity (95% CI)	Threshold
ACS test							
All ACS test	RNA sequencing	..	0·69 (0·52–0·85)	0·018	41·7% (22·3–64·5)	89·9% (82·6–94·0)	82%
All ACS test	qRT-PCR	..	0·69 (0·54–0·85)	0·0095	46·7% (27·8–66·6)	90·9% (83·8–94·7)	76%
GC6-74							
All GC6-74	qRT-PCR	1–720	0·69 (0·63–0·76)	<0·0001	48·8% (39·9–57·7)	82·8% (78·7–86)	76%
South Africa	qRT-PCR	1–720	0·72 (0·63–0·81)	<0·0001	43·2% (31·7–55·5)	87·7% (82·7–91·2)	79%
The Gambia	qRT-PCR	1–720	0·67 (0·56–0·78)	0·001	50·0% (37·1–62·8)	81·9% (75·5–86·7)	78%
All GC6-74	qRT-PCR	1–360	0·72 (0·64–0·80)	<0·0001	53·7% (42·6–64·3)	82·8% (78·7–86·0)	76%
All GC6-74	qRT-PCR	361–720	0·65 (0·53–0·76)	0·0048	39·3% (25·8–54·8)	85·5% (81·7–88·5)	79%

Zak DE et al. Lancet 2016; 387: 2312–22

Predicting tuberculosis risk

Predicting tuberculosis risk

A diagnostic test that more reliably predicts which people with latent tuberculosis are likely to progress to active disease would be an important contribution to efforts to end tuberculosis. We therefore read with interest the Article by Daniel Zak and colleagues (June 4, p 2312)[1] describing a blood RNA signature of tuberculosis risk. The investigators report relative risks of progression to active tuberculosis for people with a positive versus negative risk signature of between 6 and 14, compared with around 2 for interferon gamma release assays (IGRA) or the tuberculin skin test.

Despite sounding promising, this risk signature is unlikely to translate into major clinical benefits because of low specificity. In the populations used to validate the risk signature, the risk of disease progression at 24 months was 1–2%. If this RNA signature (sensitivity 66% and specificity 81% in the adolescent cohort) was used to identify risk of progression in a population with a 1% risk of disease progression, its positive predictive value would be 3·4%, meaning that for every 100 people with a positive signature, around three will progress to disease and 97 will not. This compares to a positive predictive value of 1·5% for IGRA in the adolescent cohort.[2] Even with a very high progression risk of 4%, the positive predictive value of the signature would be 12·6% versus 5·8% for IGRA (table). Thus, this RNA signature is likely to perform only slightly better than existing tests in predicting disease progression. A transformative new test to predict active tuberculosis would need substantially higher specificity (table).

We declare no competing interests.

*Sandra V Kik, Frank Cobelens, David Moore
sandra.kik@kncvtbc.org

	Sensitivity	Specificity	True positive	False positive	False negative	True negative	Positive predictive value
1% progression rate							
TST	0·77*	0·45*	769	54 450	231	44 550	1·4%
IGRA	0·75*	0·49*	750	50 193	250	48 807	1·5%
RNA signature	0·66*	0·81*	660	18 810	340	80 190	3·4%
Hypothetical test	0·75	0·95	750	4950	250	94 050	13·2%
4% progression rate							
TST	0·77*	0·45*	3076	52 800	924	43 200	5·5%
IGRA	0·75*	0·49*	3000	48 672	1000	47 328	5·8%
RNA signature	0·66*	0·81*	2640	18 240	1360	77 760	12·6%
Hypothetical test	0·75	0·95	3000	4800	1000	91 200	38·5%

Data in the table are from or calculated from the indicated references. IGRA=interferon gamma release assay. TST=tuberculin skin test.

Table: Performance characteristics of tests predicting active tuberculosis (cohort size 100 000)

KNCV Tuberculosis Foundation, The Hague 2501 CC, Netherlands (SVK, FC); Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, Netherlands (SVK, FC); and TB Centre, London School of Hygiene & Tropical Medicine, London, UK (DM)

1 Zak DE, Penn-Nicholson A, Scriba TJ, et al, for the ACS and GC6-74 cohort study groups. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet 2016; 387: 2312–22.

2 Mahomed H, Hawkridge T, Verver S, et al, on behalf of the SATVI Adolescent Study Team. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. Int J Tuberc Lung Dis 2011; 15: 331–36.

Authors' reply

Sandra V Kik and colleagues question the potential value of our RNA signature of tuberculosis risk for targeted intervention on a population basis.[1] They point out that the positive predictive value (PPV) of the RNA signature depends on the rate of progression to active tuberculosis disease; prognostic utility would therefore be greatest in settings of high tuberculosis incidence. The Foundation for Innovative New Diagnostics and the New Diagnostics Working Group of the Stop TB Partnership have drafted an Intervention target product profile (ITPP) for a new prognostic test for tuberculosis risk. This ITPP proposes that a new test would have to be compared with an interferon gamma release assay (IGRA). The test would need a sensitivity and specificity in the range 75–90% in order to at least double the PPV, and halve the number needed to treat with preventive therapy, compared with IGRA.[2] As Kik and colleagues explain, the RNA signature achieves this goal, and therefore is likely to be substantially more useful than an IGRA. It should be noted that other ITPP characteristics such as practicality and low cost would have to be addressed for ultimate application.

The signature had higher sensitivity at the timepoints most proximal to tuberculosis diagnosis, suggesting that timing of the test is a key factor in performance. Disease resolution has been recognised since the prechemotherapy era, and arrest or even reversal of disease without therapy—particularly in children with subclinical, culture-positive, or radiographic tuberculosis—has been described.[3] Incipient disease that is detected early might be more likely to spontaneously halt or resolve than active disease detected at late stages, and thus timing will likely affect specificity of the signature.

Our next step is to develop a practical, low-cost assay. In parallel, performance of the signature should be assessed beyond the highly selected case-control cohorts reported, which were ideal for discovery and validation. An initial follow-up study, in which the signature was applied to

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/

Kik SV et al. Lancet 2016; 388: 2233

... little added value

	Sensitivity	Specificity	True positive	False positive	False negative	True negative	Positive predictive value
1% progression rate							
TST	0·77[2]	0·45[2]	769	54 450	231	44 550	1·4%
IGRA	0·75[2]	0·49[2]	750	50 193	250	48 807	1·5%
RNA signature	0·66[1]	0·81[1]	660	18 810	340	80 190	3·4%
Hypothetical test	0·75	0·95	750	4950	250	94 050	13·2%
4% progression rate							
TST	0·77[2]	0·45[2]	3076	52 800	924	43 200	5·5%
IGRA	0·75[2]	0·49[2]	3000	48 672	1000	47 328	5·8%
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Hypothetical test	0·75	0·95	3000	4800	1000	91 200	38·5%

Data in the table are from or calculated from the indicated references. IGRA=interferon gamma release assay. TST=tuberculin skin test.

Table: **Performance characteristics of tests predicting active tuberculosis (cohort size 100 000)**

Kik SV et al. Lancet 2016; 388: 2233

Clinical Application of Interferon-γ Release Assays for the Prevention of Tuberculosis in Countries with Low Incidence

STANDFIRST
In this article, we discuss the principles and use of IGRAs, and we provide recommendations for their use in countries with low incidence of tuberculosis.

Lange C et al. Pathog Immun. 2016;1(2):308-329

Numbers needed to treat to prevent TB

Study	Country	Population	LTBI test	LTBI positive (%)	Number followed longitudinally	TB cases incident	Sensitivity %	Specificity %	PPV %	NPV %	NNT
Zellweger et al [36]	Europe	contacts	QFT-G-IT	1067 (27.4%)	3425	20	85.0	74.0	1.9	99.9	37
			T-SPOT.TB	299 (26.6%)	1061	4	50	73.6	0.7	99.7	37
Geis et al [47]	Germany	contacts	QFT-G-IT[c]	306 (19.3%)	254	6	100	n.d.	2.5	n.d.	34
Sloot et al [48]	Netherlands	contacts	TST/QFT-G-IT	739 (15.5%)	4716	17	76.5	85.8	1.9	99.9	89
		Close contacts	TST/QFT-G-IT		1622	10	90	79	2.6	99.9	30
Kik et al [51]	Netherlands	Migrant contacts	TST[d]	339	339	8	87.5	n.d.	3.8	n.d.	26
			QFT-G-IT	178	327	8	62.5	n.d.	2.8	n.d.	36
			T-SPOT.TB	181	299	8	75	n.d.	3.3	n.d.	30
Hermansen et al [49]	Denmark	Mixed[a]	QFT-G-IT	1703 (10.7%)	15980	40	50	88.7	1.32	99.9	68[e]
Sester et al [8]	Europe	Immuno-compromised[b]	TST	212 (14.1%)	1404	6	50	86.2	1.5	99.8	50
			QFT-G-IT	239 (15.6%)	1342	4	50	84.1	0.9	99.8	80
			T-SPOT.TB	266 (17.7%)	1310	6	50	81.3	1.3	99.7	64
		HIV only	TST	55 (8.7%)	626	6	50	93.7	7.1	99.5	14
			QFT-G-IT	83 (13.1%)	621	4	50	92.1	3.9	99.6	26
			T-SPOT.TB	101 (15.9%)	561	6	50	89	4.7	99.4	21
		HIV positive HIV load	TST	24 (8.1%)	291	6	50	92.6	12.5	98.9	8
			QFT-G-IT	25 (8.4%)	289	4	50	91.9	8	99.2	13
			T-SPOT.TB	31 (10.4%)	255	6	50	88.8	9.7	98.7	10
Schablon et al [50]	Germany	HCW	QFT-G-IT	317 (8.3%)	3823	0	0	91.7	0	100	n.a.[f]
Slater et al [43]	USA	HCW	QFT-G-IT	853 (9.3%)	9153	0	0	90.7	0	100	n.a.[f]
Dorman et al [42]	USA	HCW	TST	125 (5.2%)	2418	0	0	94.8	0	100	n.a.[f]
			QFT-G-IT	118 (4.9%)	2418	0	0	95.1	0	100	n.a.[f]
			T-SPOT.TB	144 (6.0%)	2418	0	0	94	0	100	n.a.[f]

Lange C et al. Pathog Immun. 2016;1(2):308-329

Take-Home Message

- **... new skin test (C-Tb) is not better than QFT**
- **... mRNA signatures predict TB better than QFT**
- **... MUCH room for improvement for a biomarker**

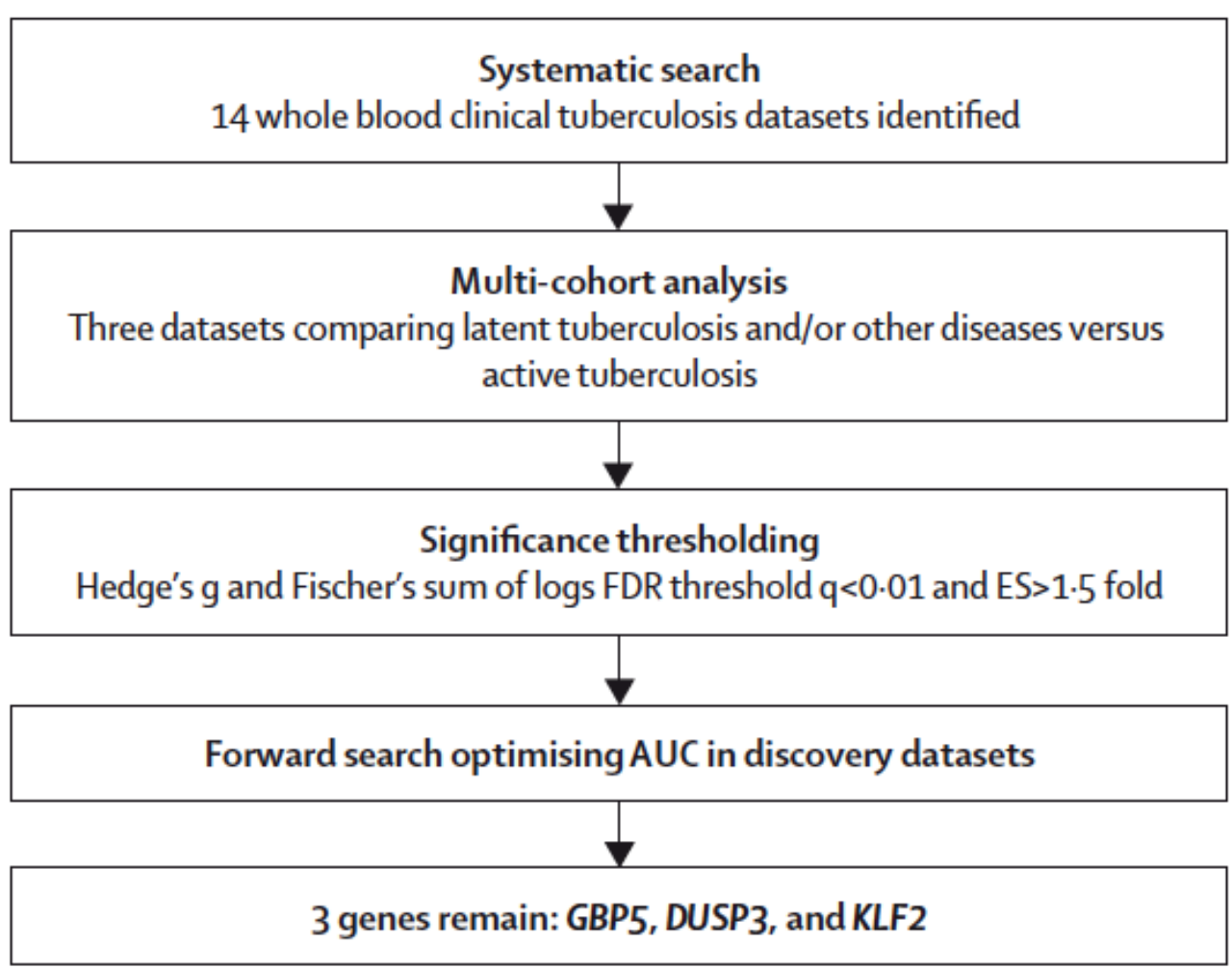
Diagnosis

Genome-wide expression for diagnosis of pulmonary tuberculosis:

a multicohort analysis

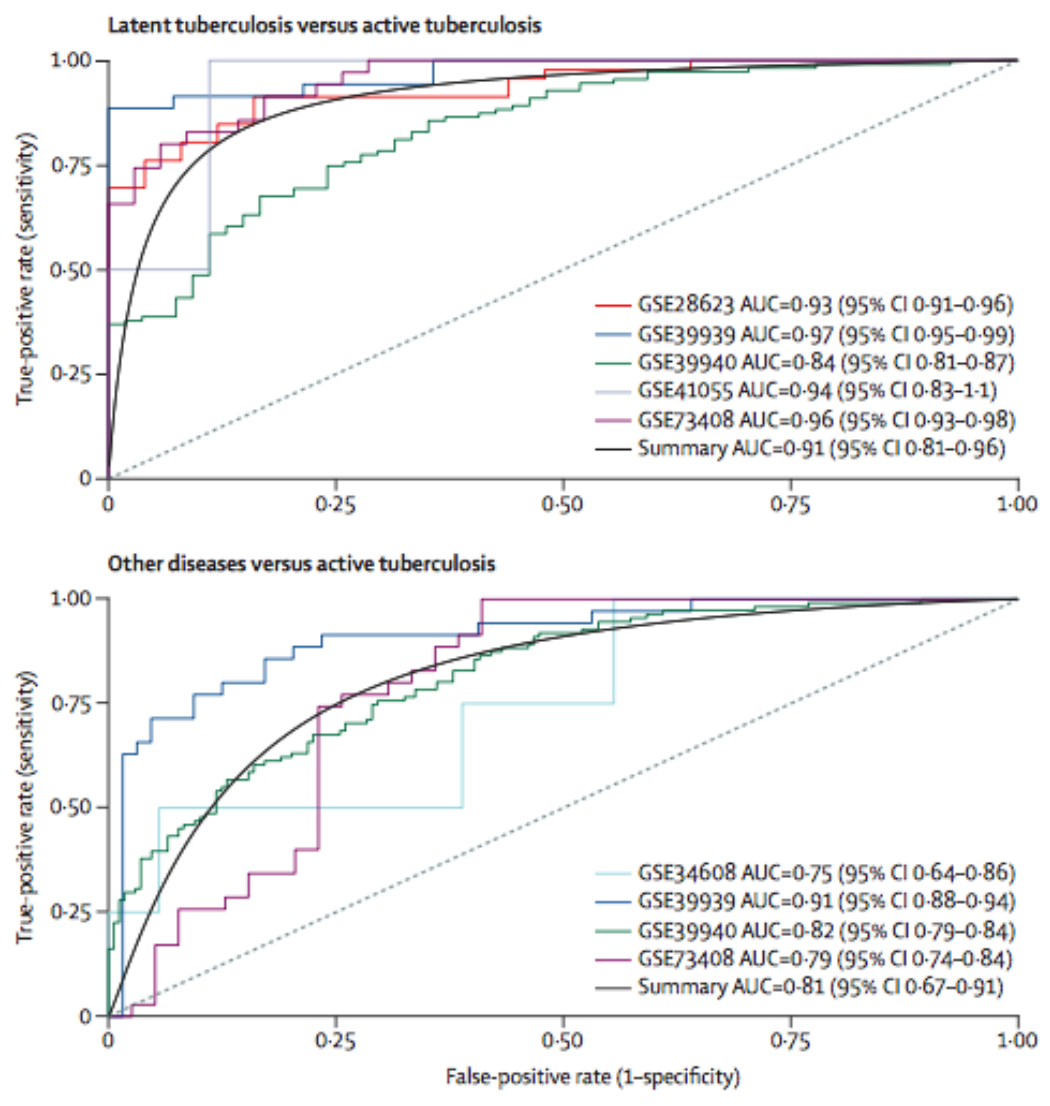
Sweeney TE et al. Lancet Respir Med. 2016 Mar;4(3):213-24

Study Design



Sweeney TE et al. Lancet Respir Med. 2016 Mar;4(3):213-24

ROC curve analyses of 3 gene signature

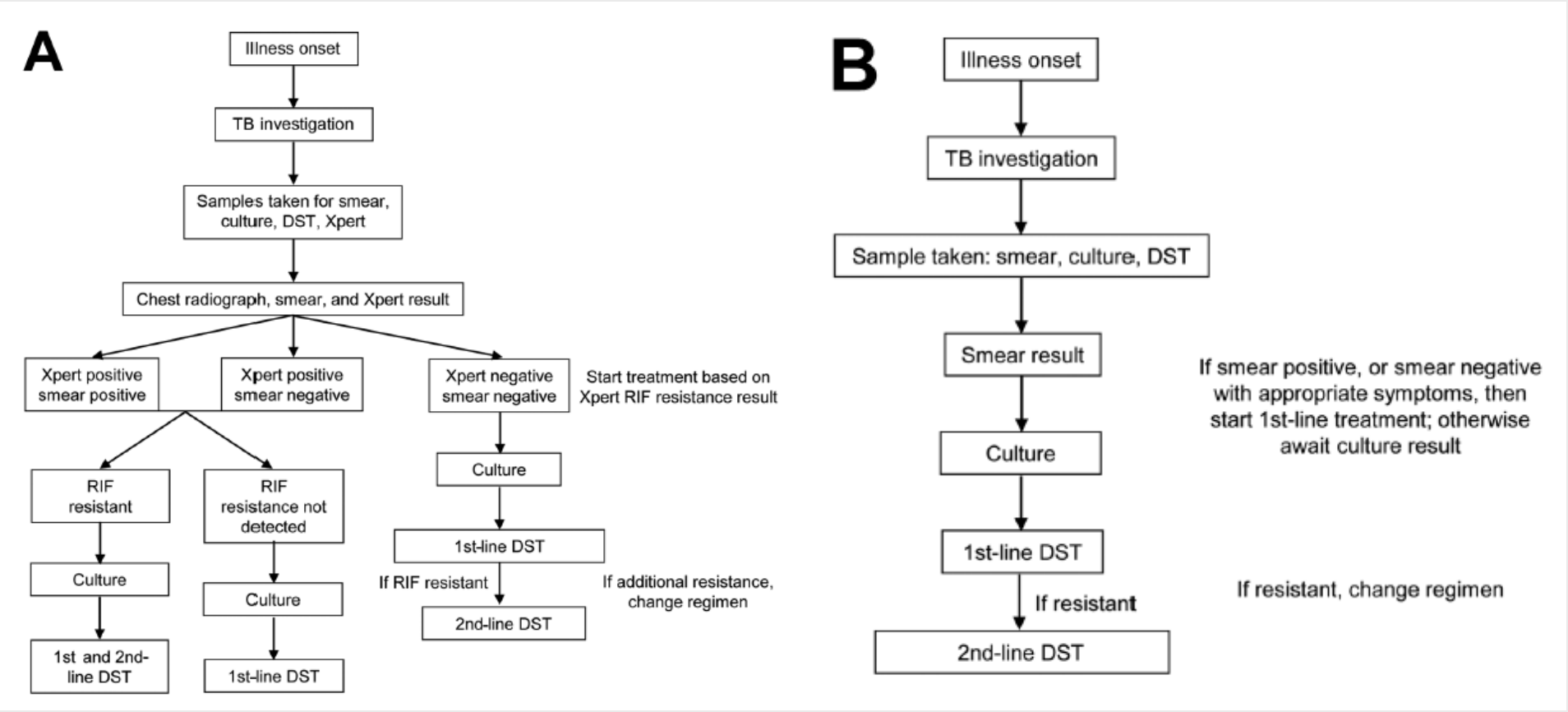


Sweeney TE et al. Lancet Respir Med. 2016 Mar;4(3):213-24
Sweeney TE et al. Lancet Respir Med. 2016 Jun;4(6):e29

Decreased Time to Treatment Initiation for Multidrug-Resistant Tuberculosis Patients after Use of Xpert MTB/RIF Test, Latvia

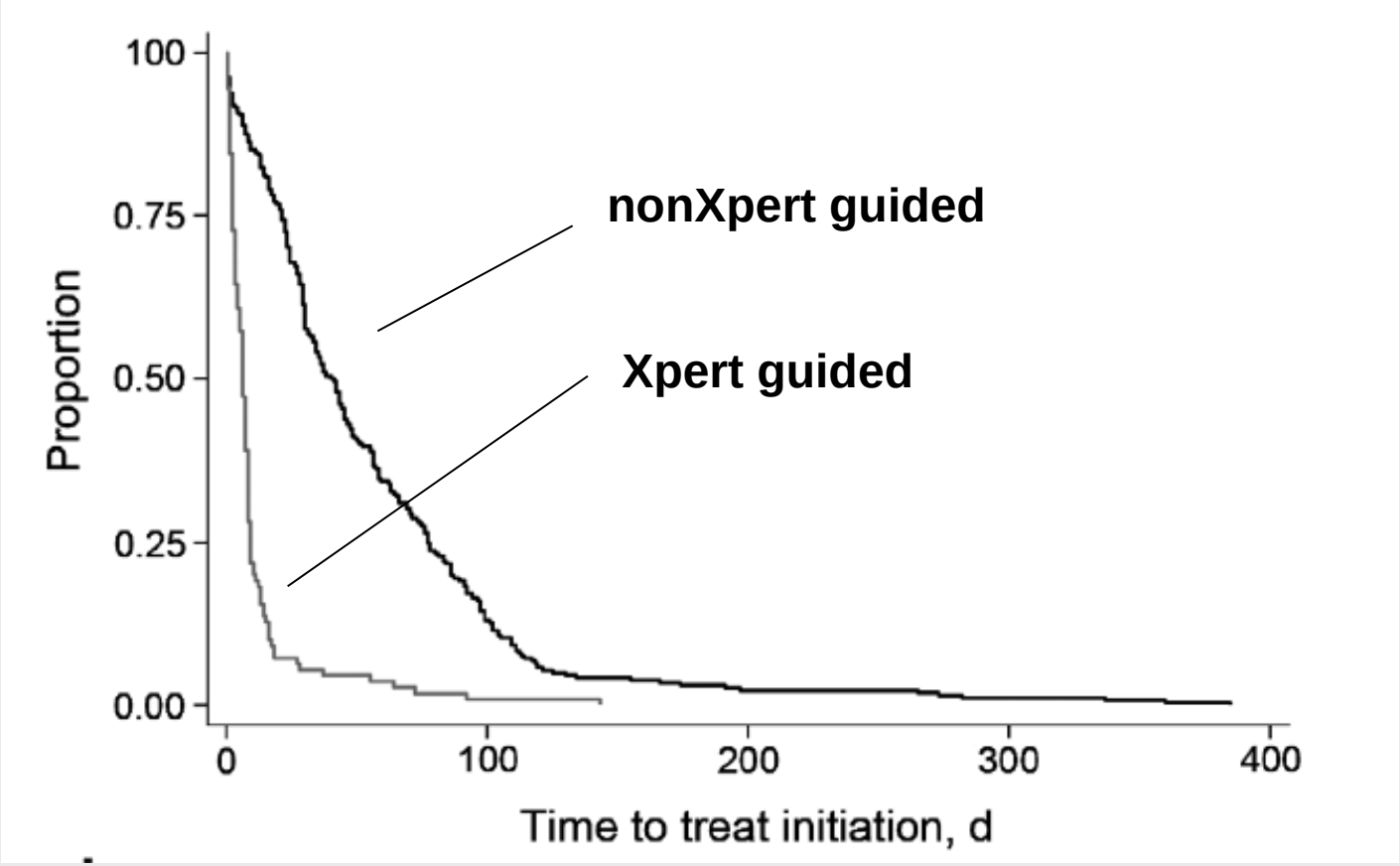
Stagg HR et al. Emerg Infect Dis. 2016 Mar;22(3):482-90.

Xpert (A) vs nonXpert (B) guided diagnosis



Stagg HR et al. Emerg Infect Dis. 2016 Mar;22(3):482-90.

Xpert reduces time to treatment initiation in MDR-TB

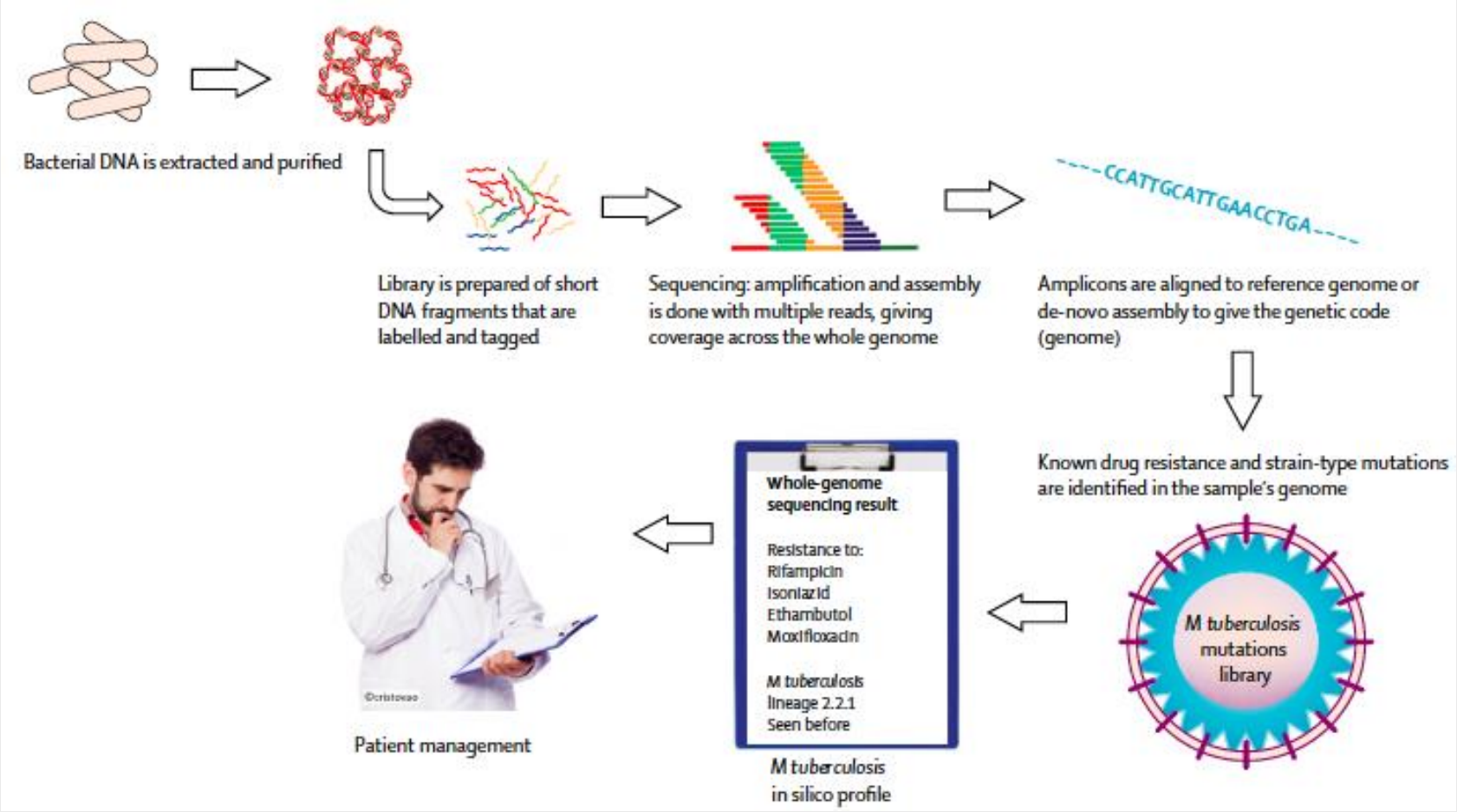


Stagg HR et al. Emerg Infect Dis. 2016 Mar;22(3):482-90.

The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis

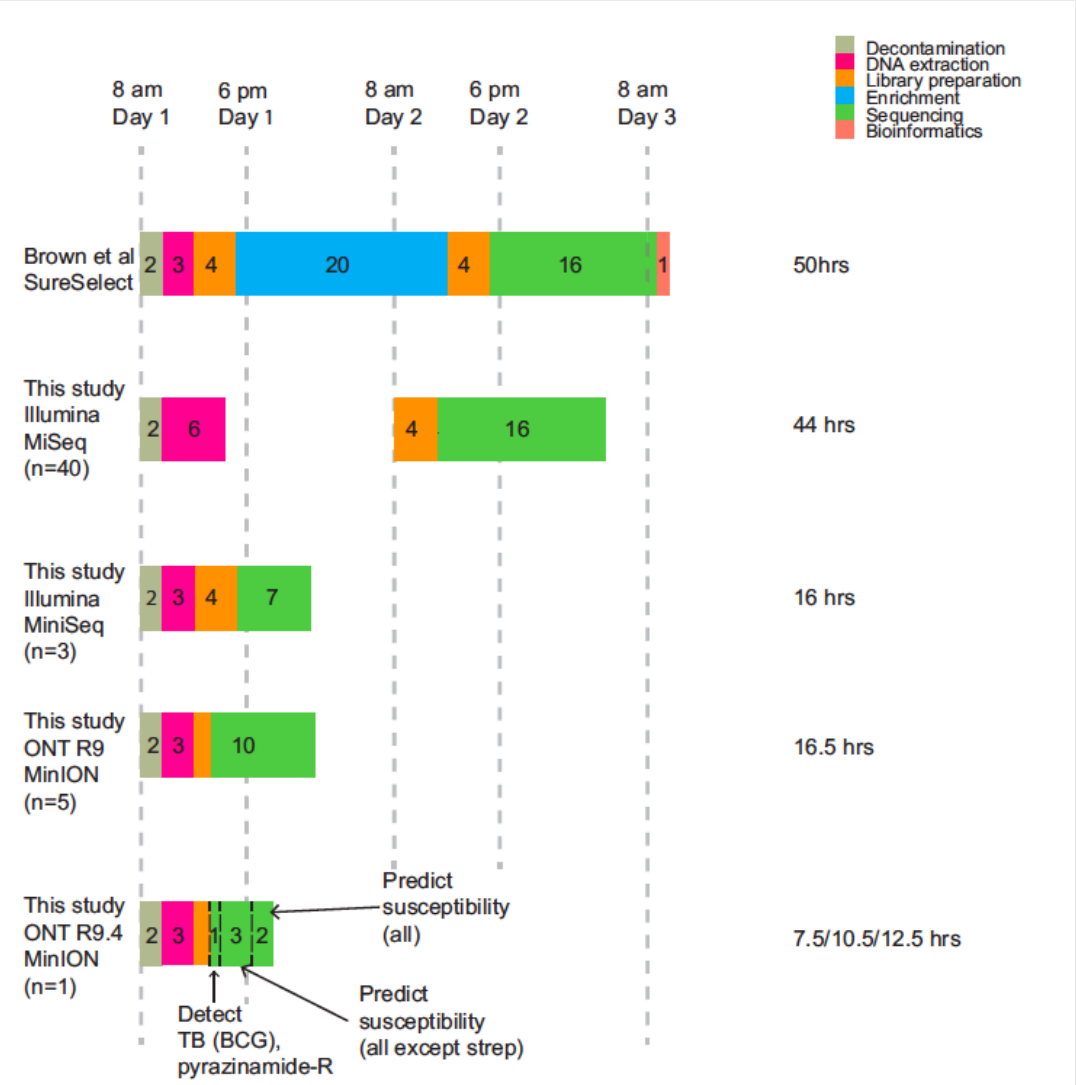
Dheda K et al. Lancet Respir Med. 2017 Mar 15. pii: S2213-2600(17)30079-6

Whole genome sequencing



Dheda K et al. Lancet Respir Med. 2017 Mar 15. pii: S2213-2600(17)30079-6

Proof of principle: Result in one day!



Votintseva AA et al. J Clin Microbiol. 2017 May;55(5):1285-1298.

WGS-report

antibiotic	polymorphisms	result
isoniazid	katG S315T1 (agc/aCc)2	R
rifampicin, rifabutin	rpoB S450L (tcg/tTg)	R
streptomycin	rpsL K43R (aag/aGg)	R
ethambutol	embA -12c/t embB M306V (atg/Gtg)	I R
pyrazinamide	pncA1 182S1 (ttg/tCg)2	R
moxifloxacin, gatifloxacin, ofloxacin, levofloxacin, ciprofloxacin	gyrA D94G (gac/gGc)	R
amikacin	rrs 1401 a/g	R
kanamycin	rrs 1401 a/g	R
capreomycin	rrs 1401 a/g	R
Ethionamide, prothionamide	ethA A89E (gcg/gAg) ethA S266R (agc/agG)	I
delamanid	wt	S
PA-824	wt	S
bedaquiline	Rv0678 E55D (gaa/gaC)	unknown
clofazimine	Rv0678 E55D (gaa/gaC)	unknown
linezolid	rplC T71T (acc/acT)	S
cycloserine	wt	S
PAS	thyX A220A (gcc/gcT)	S
possible enhanced growth rate	rpoC G332S (ggc/Agc)	yes
Genotype	Beijing2 Ancestral3 2	

Courtesy: C. Lange

Take-Home Message

- **... diagnosis of active TB by 3-gene signature**
- **... Xpert reduces time to treatment in MDR-TB**
- **... WGS is entering clinical practice**

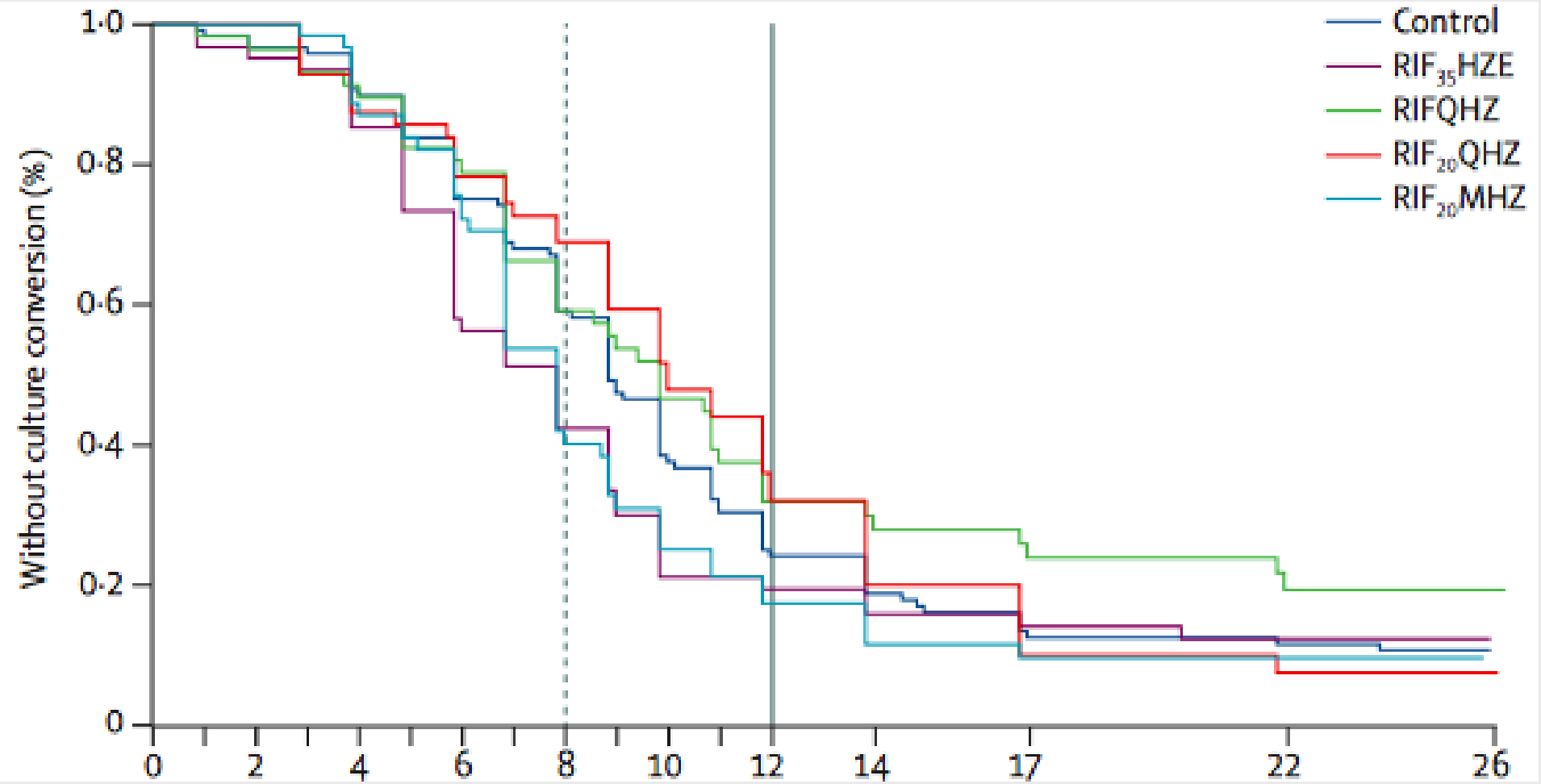
Treatment

High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis:

a multi-arm, multi-stage randomised controlled trial

Boeree M et al. Lancet Infect Dis. 2017 Jan;17(1):39-49.

Benefits of high dose rifampicin therapy

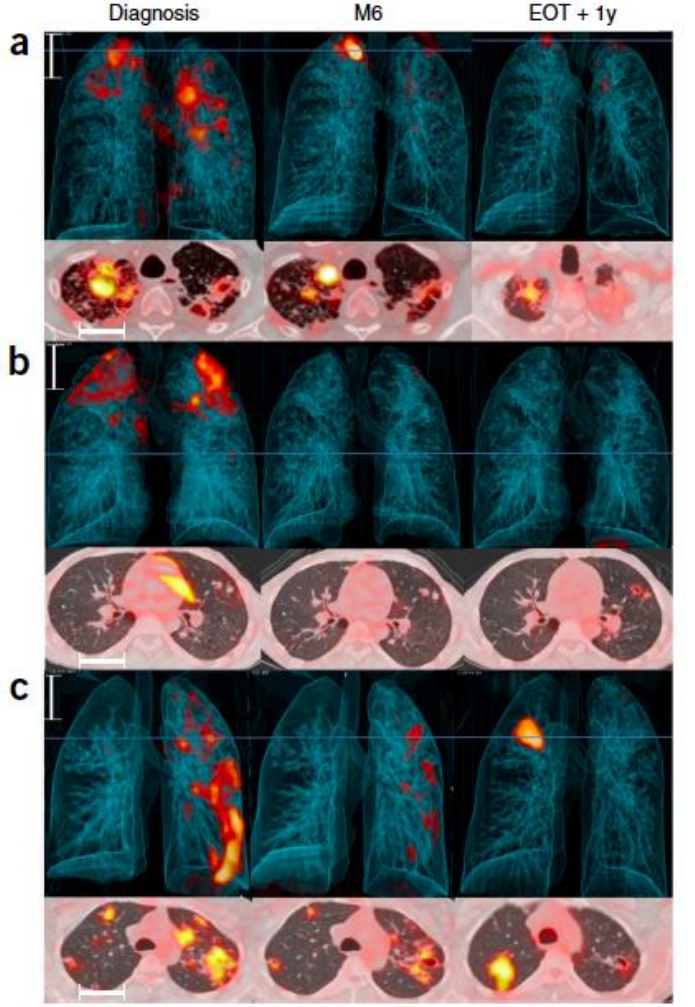


Boeree M et al. Lancet Infect Dis. 2017 Jan;17(1):39-49.

Persisting positron emission tomography lesion activity and *Mycobacterium tuberculosis* mRNA after tuberculosis cure

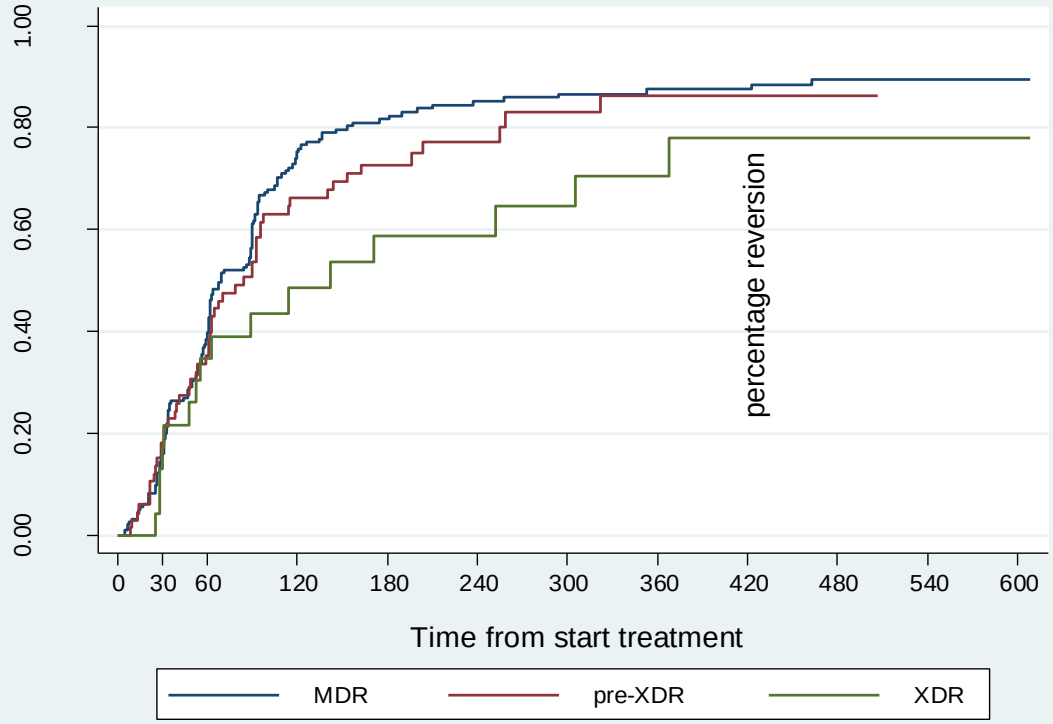
Malherbe M et al. Nat Med. 2016 Oct;22(10):1094-1100.

Only 14% of patients have resolved inflammation at the end of treatment (PET-CT)



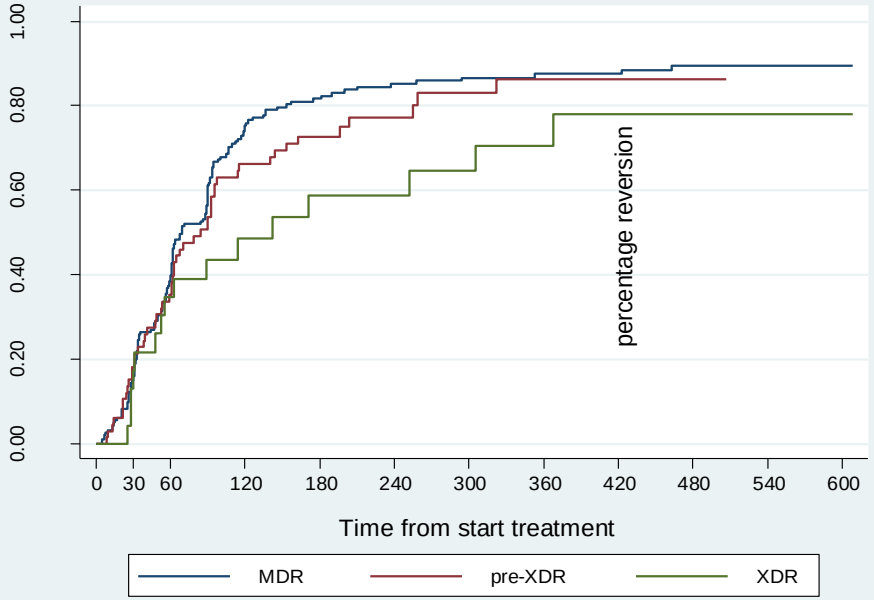
Malherbe M et al. Nat Med. 2016 Oct;22(10):1094-1100.

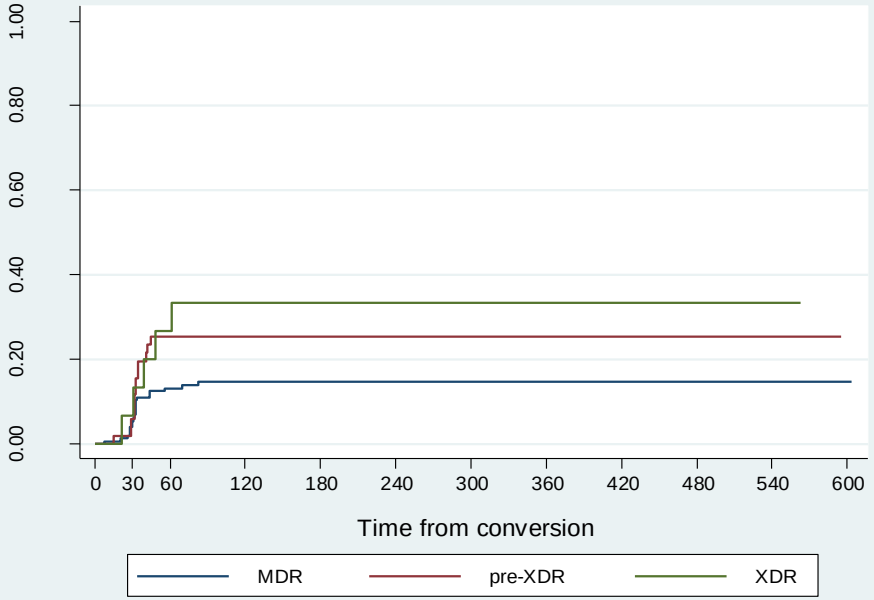
Treatment outcome in M/XDR-TB



Günther G et al. N Engl J Med. 2016 Sep 15;375(11):1103-5

Treatment outcome in M/XDR-TB





Günther G et al. N Engl J Med. 2016 Sep 15;375(11):1103-5

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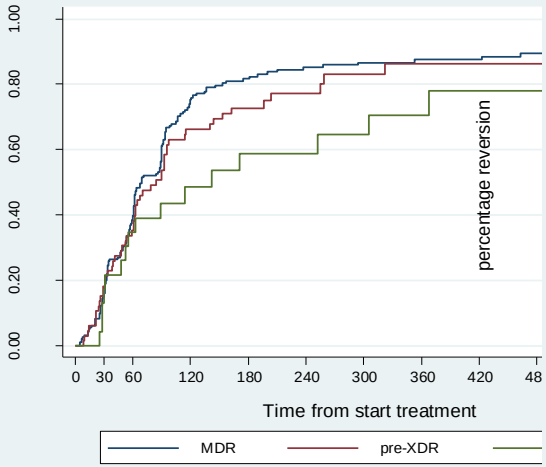
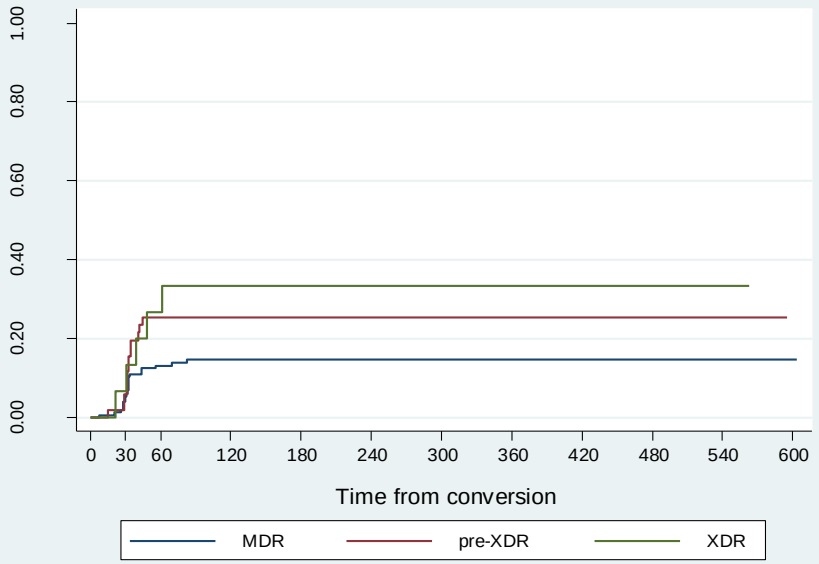
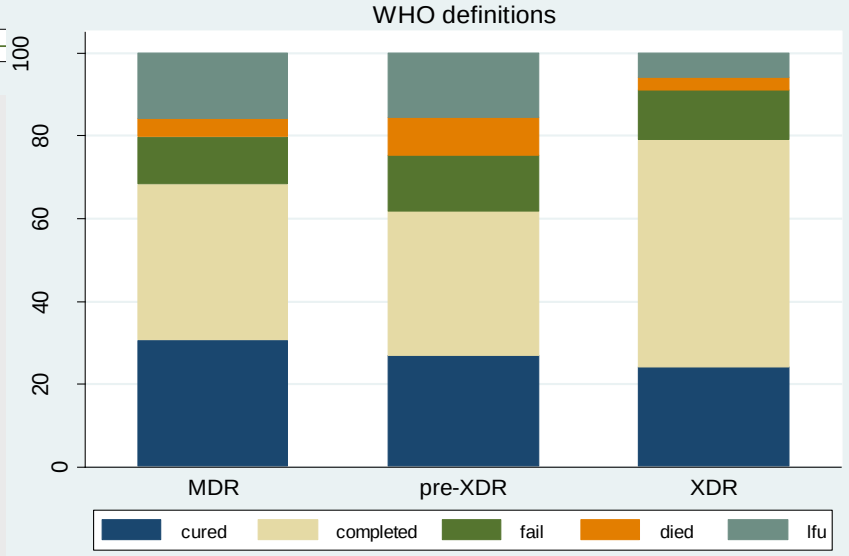
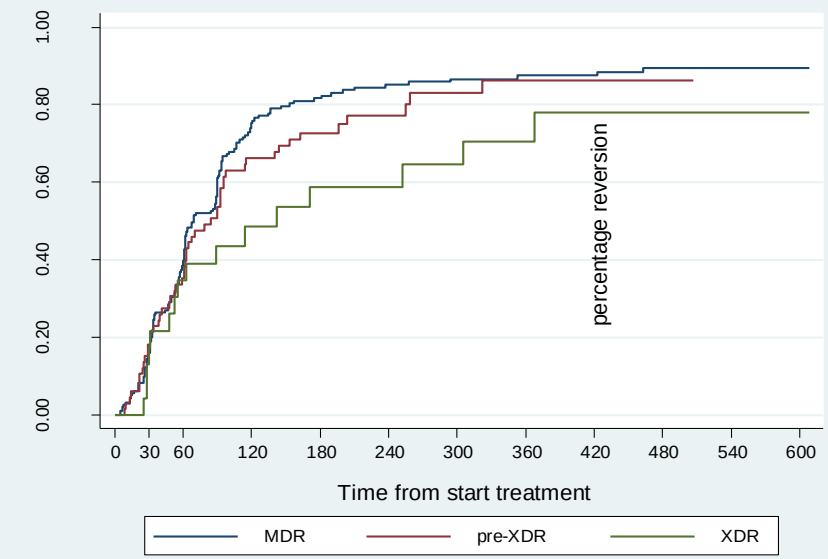
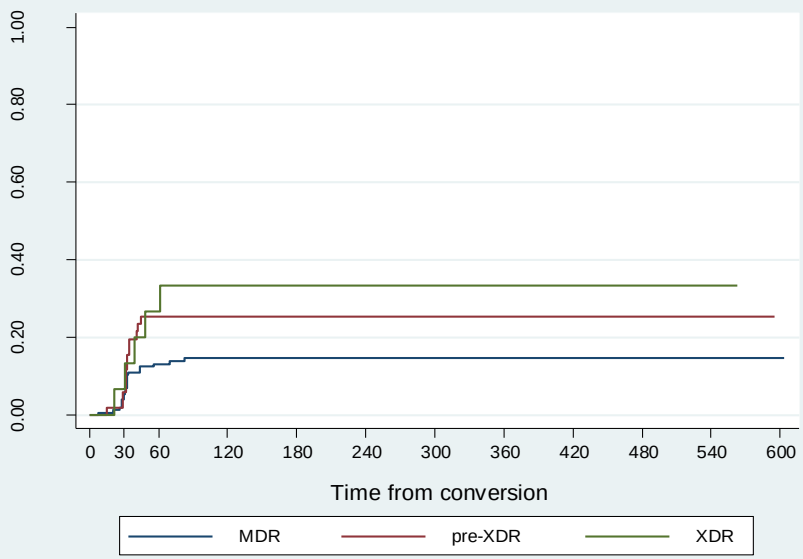


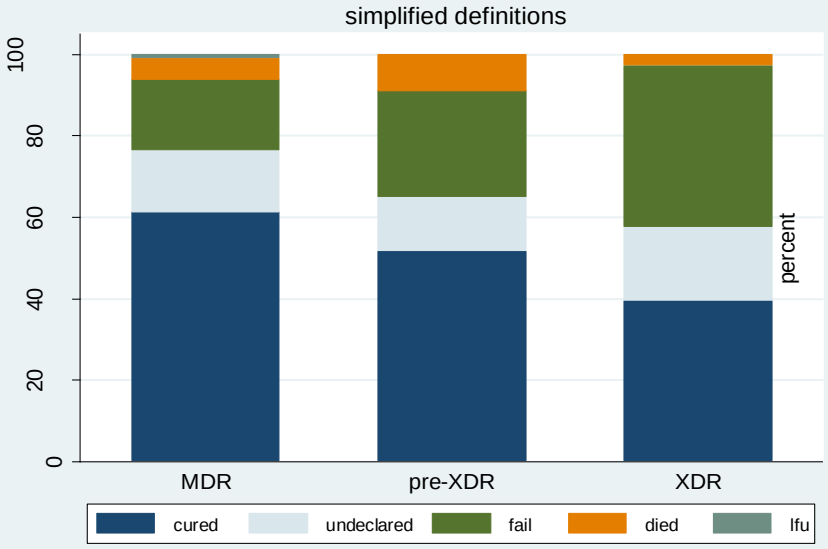


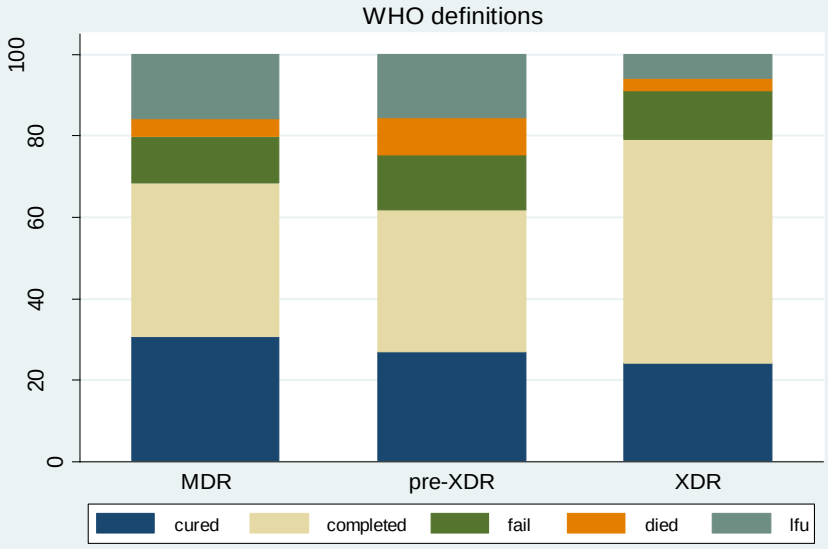


Günther G et al. N Engl J Med. 2016 Sep 15;375(11):1103-5









Günther G et al. N Engl J Med. 2016 Sep 15;375(11):1103-5

Take-Home Message

- **... high-dose Rifampicin is safe and effective**
- **... PET-CT may help to define radiological cure**
- **... treatment outcome definitions should be revised**

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List of Abbreviations

ACS = Adolescent cohort study
AUC = Area under the curve
CT = Computated tomography
DST = drug susceptibility testing
E = ethambutol
ES = Effect Size
FDR = False discovery rate
GC6 = Grand Challanges 6-74
GEO = Gene expression omnibus
GSExxxx = Gene expression datasets in GEO
I = intermediate
IGRA = interferon-γ release assay
H = isoniacid
LTBI = Latent infection with M. tuberculosis
M = Moxifloxacin
MDR = multidrug-resistance
Mfx = moxifloxacin
NNT = number needed to treat to prevent one case
NPV = Negative predictive value
PET = Positron emission tomography
PPV = Positive predictive value
Q = SQ109 (a investigonal TB drug)
QFT = Quantiferon Gold in tube test
TB = tuberculosis
R = resistance
RIF = rifampicin
RNA = Ribonucleic acid
ROC = Receiver operator curves
S = susceptible
TST = Tuberculin Skin Test
WGS = whole genome sequencing
WT = wild type
XDR = extensively drug-resistance
Z = pyrazinamide