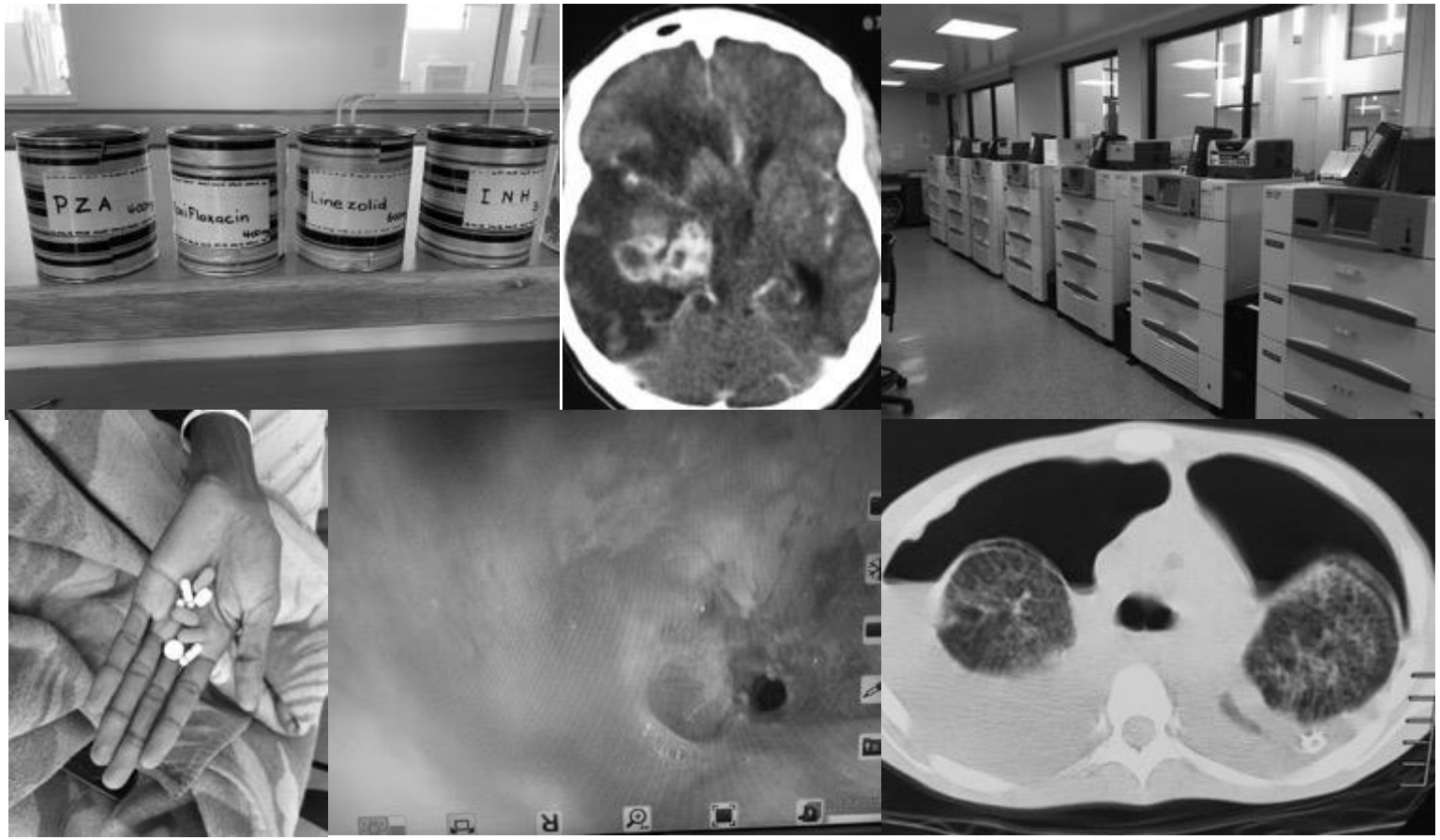
Tuberculosis update 2022



Gunar Günther
Inselspital Bern and University of Namibia, School of Medicine

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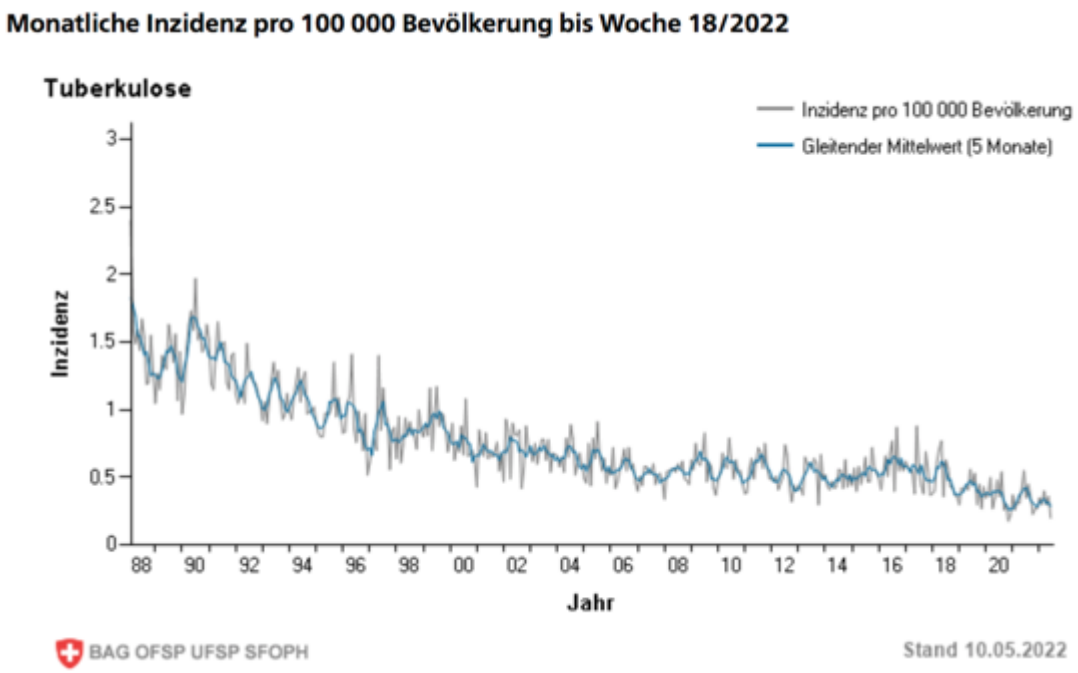
UNIVERSITY OF NAMIBIA

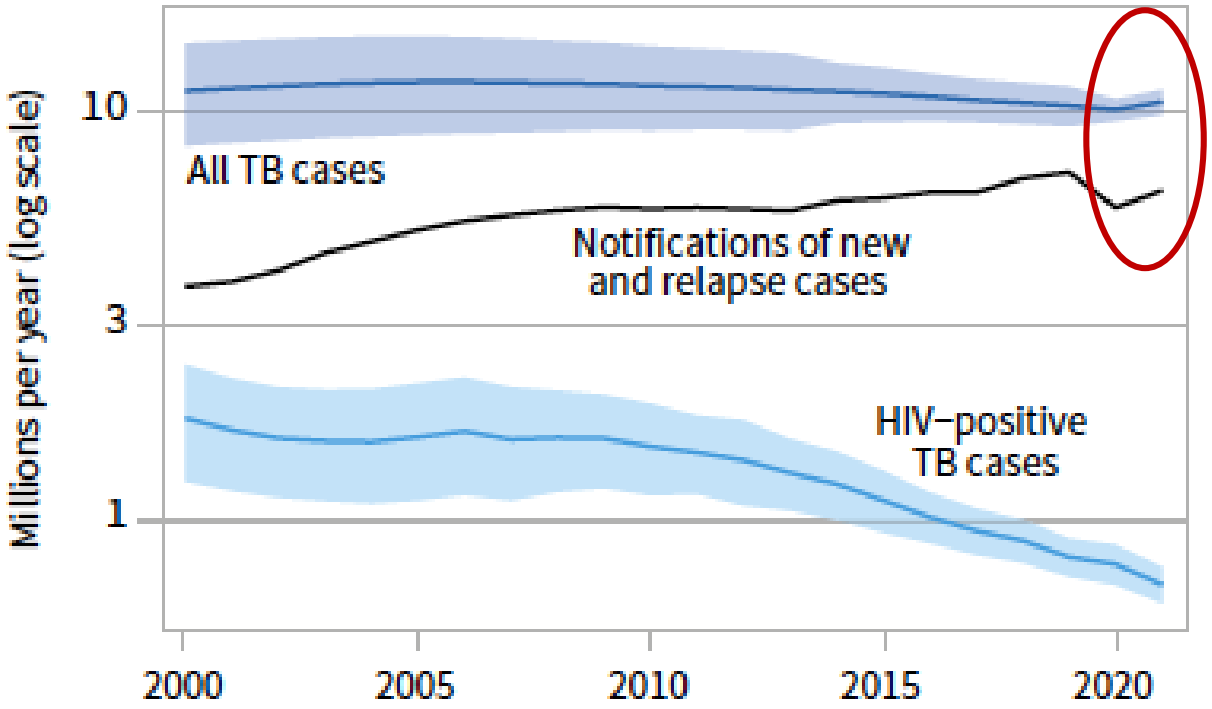
Tuberculosis in Switzerland



Year	Cases	Incidence/ 100.000	Cases RR-TB
2016	625	7.22	17
2017	557	6.27	11
2018	511	5.93	7
2019	440	4.99	20
2020	373	4.23	?
2021	366	4.20	5
2022	321	4.35	?

https://www.bag.admin.ch/bag/de/home/zahlen-und-statistiken/zahlen-zu-infektionskrankheiten.exturl.html/

Tuberculosis worldwide 2022

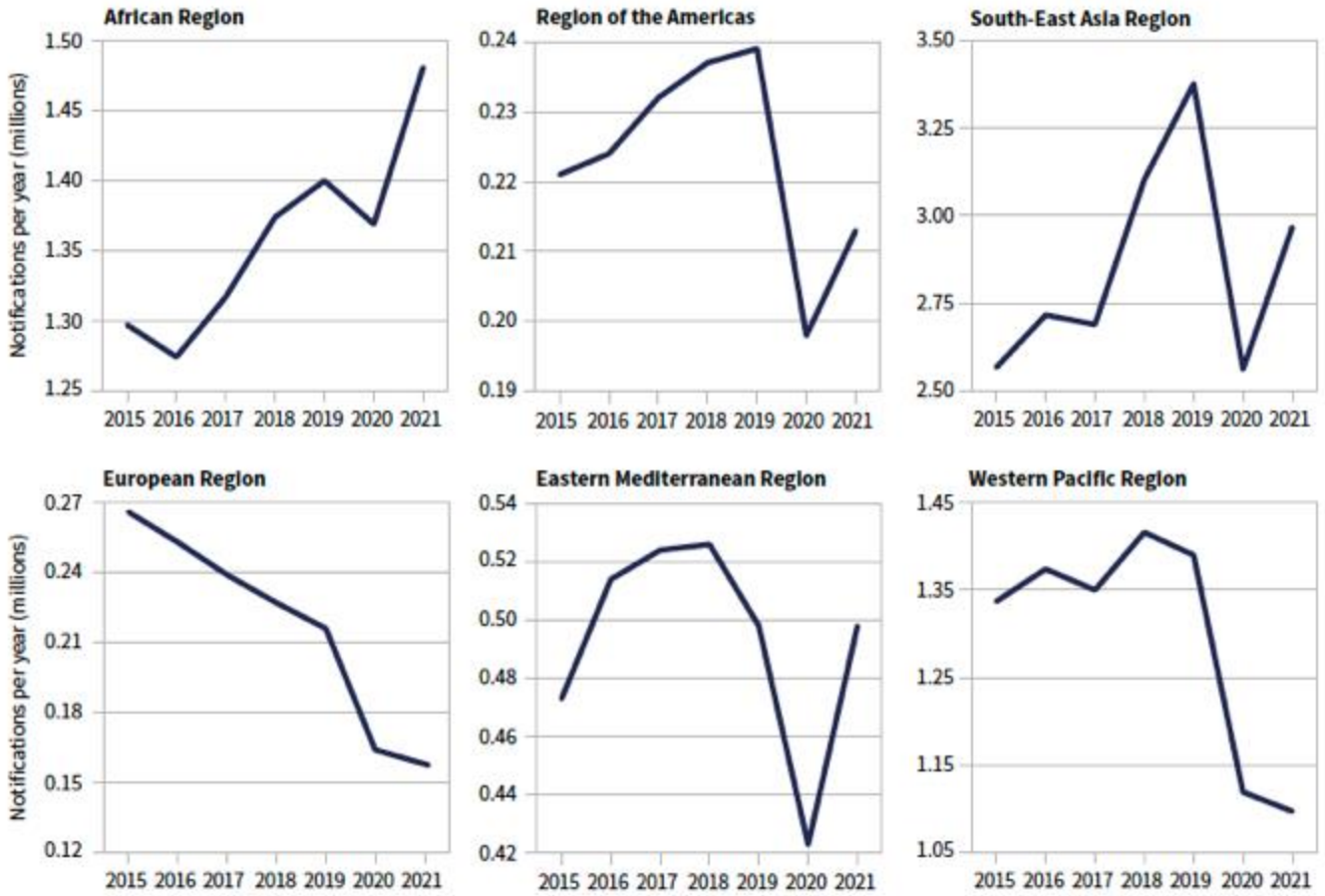


10.6 million new cases 2021
1.6 million deaths
incidence 127/100.000

- HIV+ 38.4 mill. worldwide
- 1.5 Mill. new infections
- 28.7 Mill. ART
- 650.000 mill. deaths

World TB Report 2022, UNAIDS 2022

Impact of COVID – 19 on global TB notifications



- 18% less notified cases 2020 compared to 2019
- from 7.1 million 2019 to 5.8 million 2020
- **First time in 20 years > in TB deaths**

WHO 2021

MDR-/ preXDR- / XDR-TB

Definition:
MDR: resistance to rifampicin und isoniazid
preXDR: MDR plus fluoroquinolone
XDR: MDR + fluoroquinolone + bedaquiline or linezolid

Global burden: 450.000 incident cases 2021 / 162.000 started treatment

	Europe[1]	**Africa**	**Ukraine[1]**	**Russia[1]**	**Switzer-land[1]**	**South-Afrika[1]**	**Namibia[2] 2015**
TB incidence 2020 (n/100.000)	25	220	73	46	4.7	554	460
New MDR (%)	18.0	2.5	28.0	32.0	1.25	3.4	3.9
MDR in retreatment (%)	54.0	12.0	55.0	67.0	ND	7.1	8.7

[1]WHO 2019/2021
[2]MOHSS Namibia 2016

IGRA/TST: PPV und NNT for the prevention of active TB

Table 3. Numbers needed to treat to prevent one case of TB in people with a positive IGRA or TST test result in different risk-groups in low incidence countries

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]

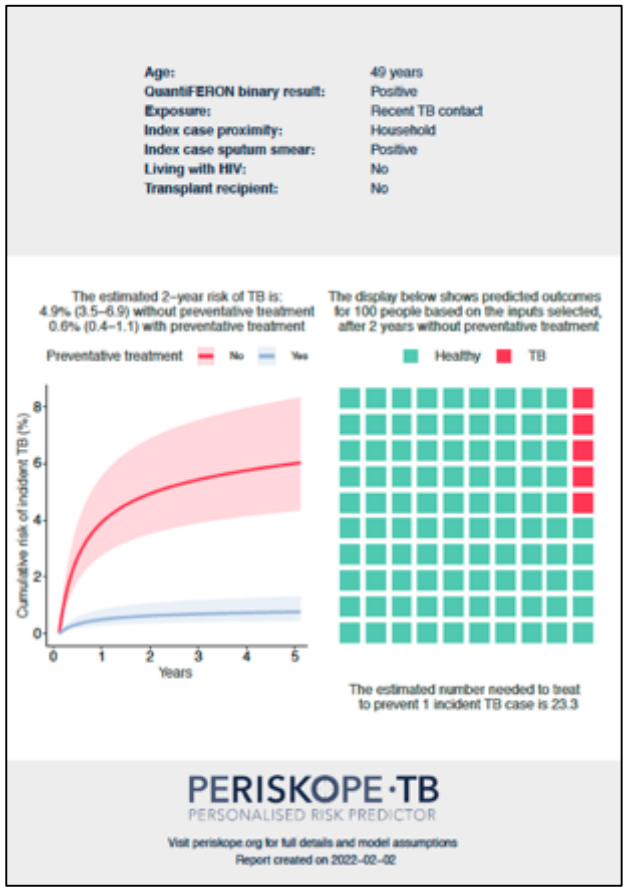
Lange et al, Pathogens und Immunity 2017

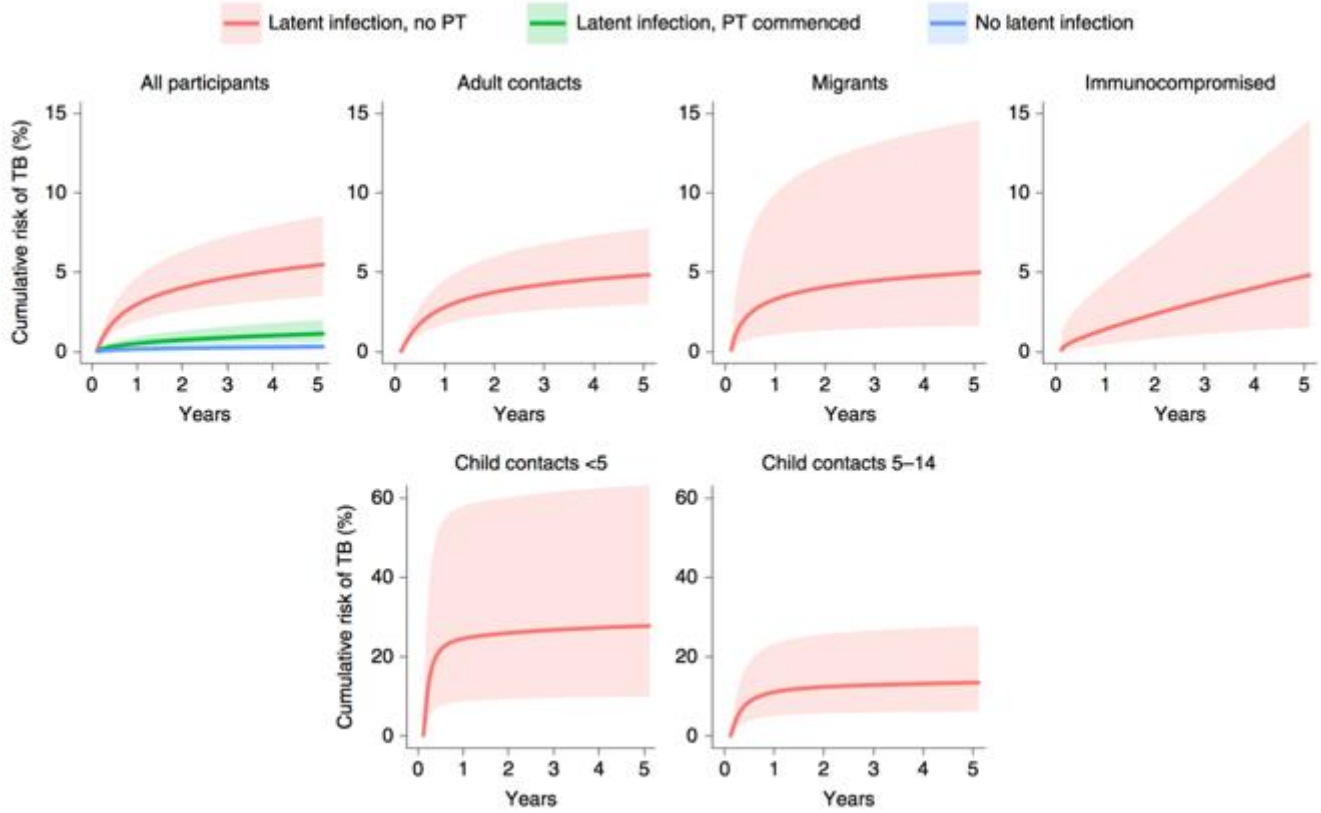
nature medicine

ARTICLES

https://doi.org/10.1038/s41591-020-1076-0

Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings





www.periskope.org

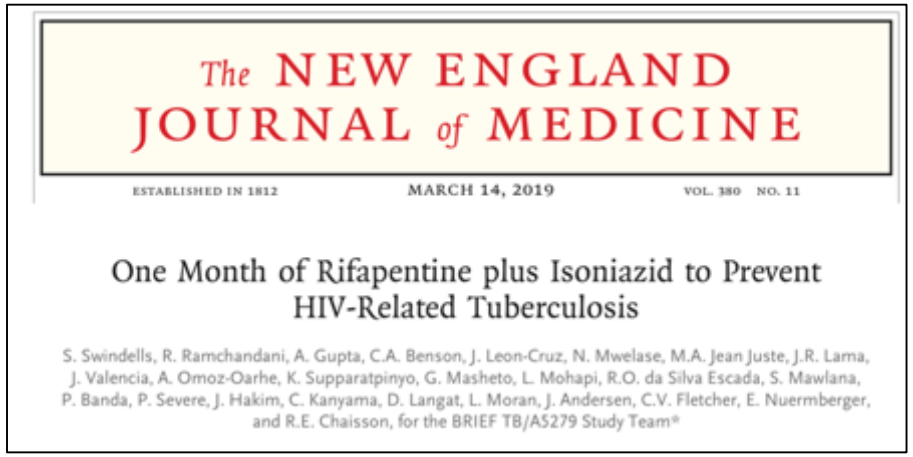
personlized calculator for risk of incident TB

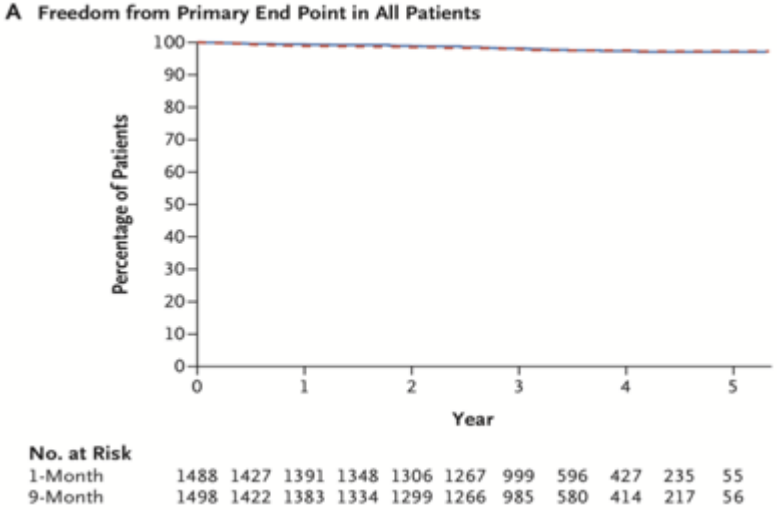
Gupta et al. Nature Medicine 2021

Treatment options for latent TB

- Isoniazid für 6 months / 9 months
- Rifampicin für 4 months
- Rifampicin /Isoniazid für 3 months
- *(Rifapentine / Isoniazid für 12 weeks 1 x weekly)*
- *Rifapentine / Isoniazid für 1 month daily*

But – Rifapentine not licensed in Europe





Swindells, NEJM 2019
ECDC 2019
WHO 2020

New concepts for sputum free diagnosis and risk prediction: host transcription signatures (RISK6, Sweeney3)

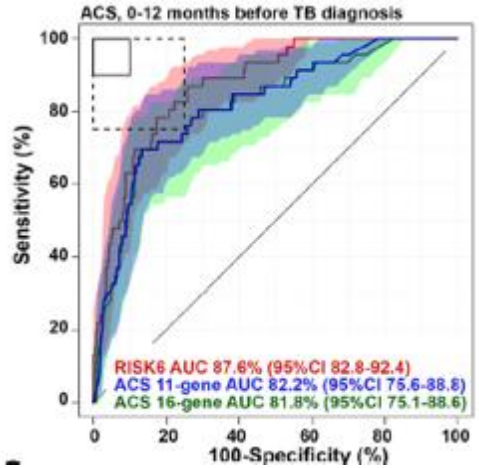
Requirements:
- Non sputum biomarker

- predicting progression to active TB,
- diagnosing disease
- monitoring the response to TB

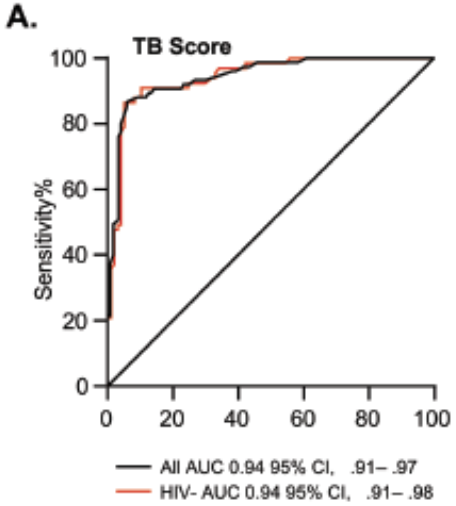
Concept:
- single, parsimonious host-blood transcriptomic signature

Methode: qRT- PCR – RNA expression analysis
Upregulated: GBP2, FCGR1B, SERPING1
Downregulated: TUBGCP6, TRMT2A, and SDR39U1

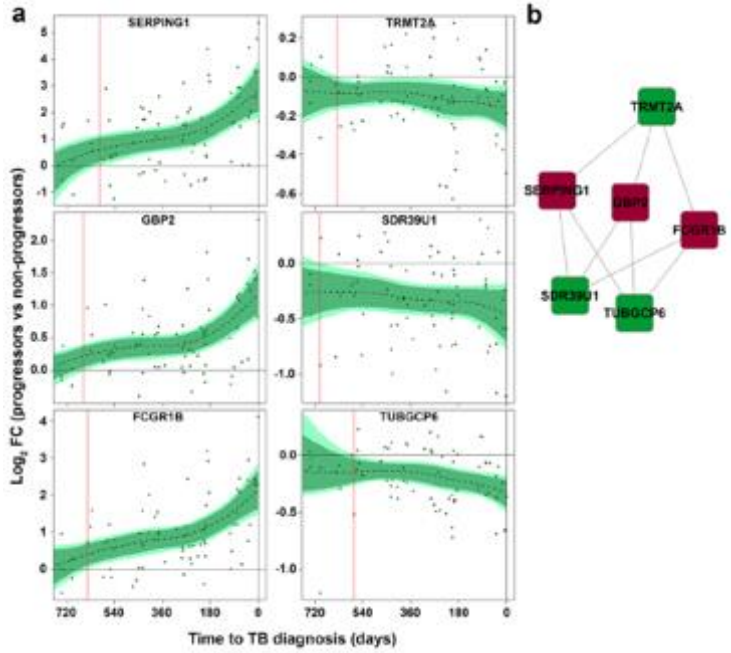
TB risk prediction of RISK6



Triage vs Xpert Ultra of Sweeney 3

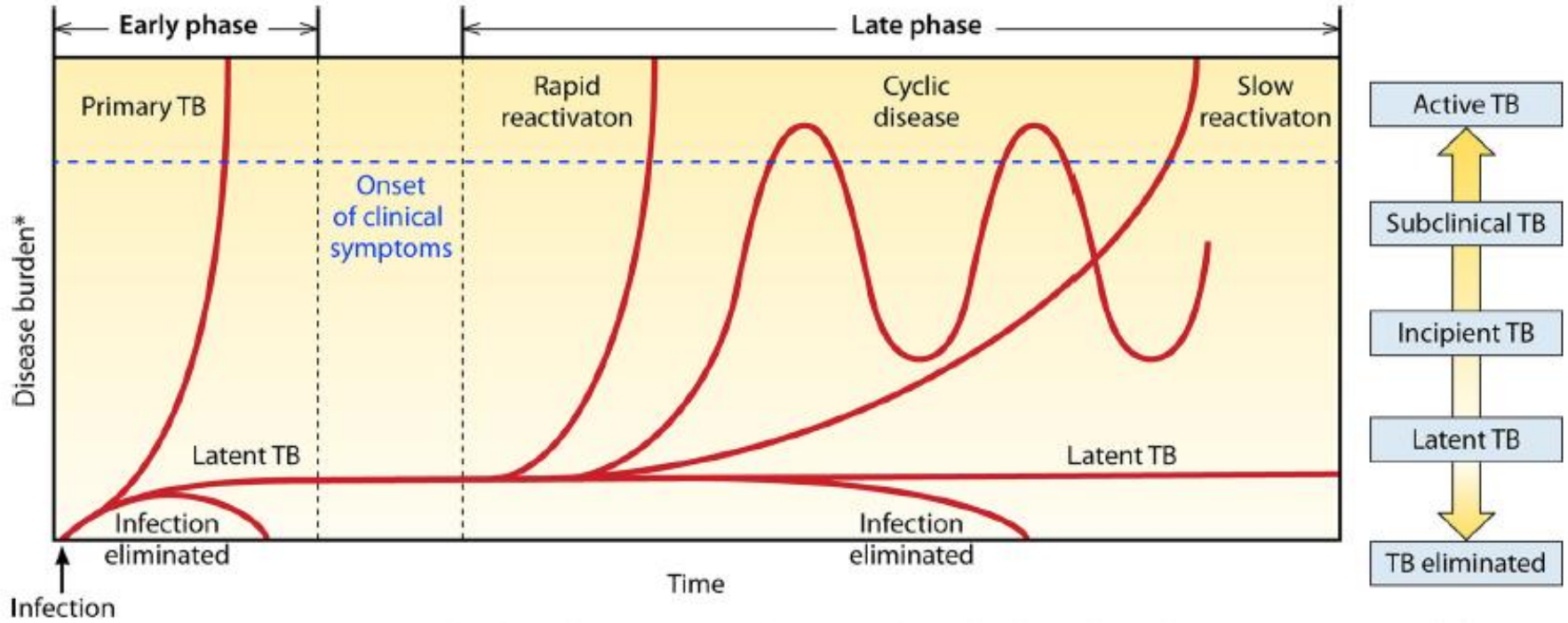


Transcript expression ratios in relation to time to TB diagnosis



Penn – Nicholson et al. Sci Rep 2020
Sutherland et al. CID 2021

Incipient and subclinical TB



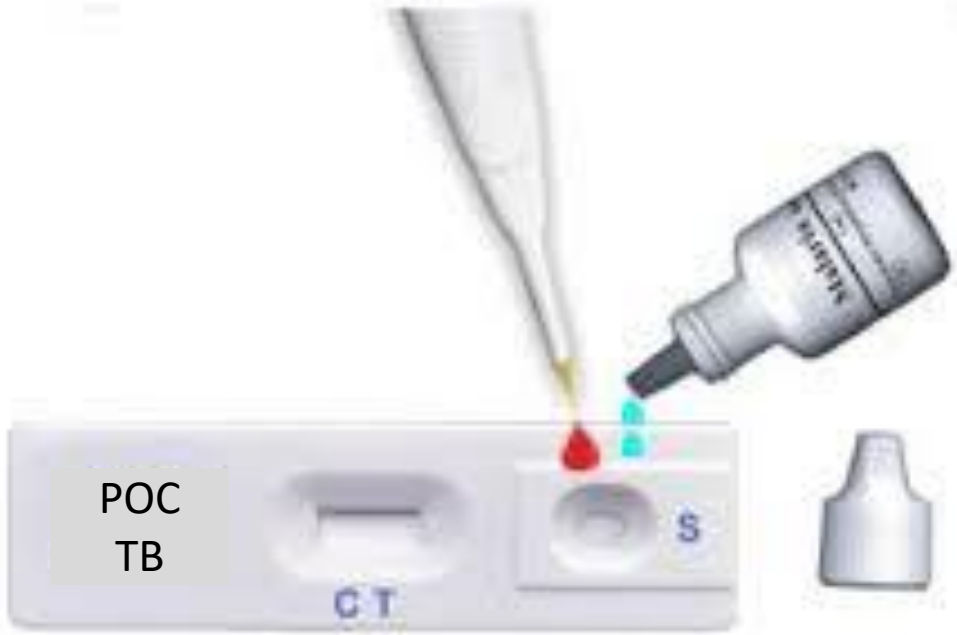
*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

50% of bacteriologically confirmed TB is subclinical in pooled prevalance survey data

Drain et. al; CMR 2018
Frascella et al. CID 2020

Point of care Test - TB

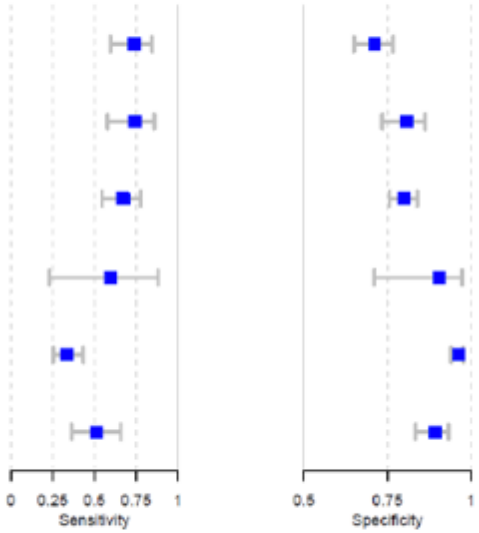
- with high sensitivity and specificity-



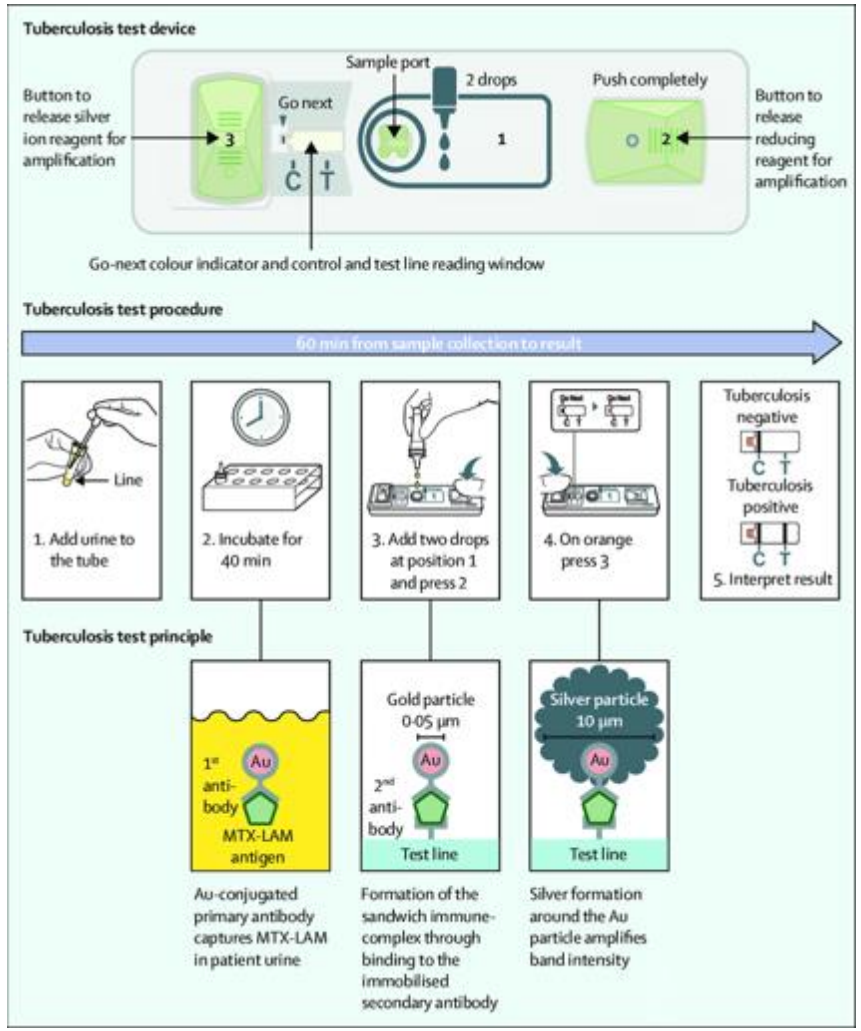
Fuji LAM in HIV + patients

Figure 2. FujiLAM performance by lot

Lot Number	N	TP	FP	FN	TN	Sensitivity [95%CI]	Specificity [95%CI]
19001	275	34	66	12	163	73.9 [59.7-84.4]	71.2 [65.0-76.7]
19002	180	26	28	9	117	74.3 [57.9-85.8]	80.7 [73.5-86.3]
19003	408	41	69	20	278	67.2 [54.7-77.7]	80.1 [75.6-84.0]
20002	26	3	2	2	19	60.0 [23.1-88.2]	90.5 [71.1-97.4]
20003	535	35	16	69	415	33.7 [25.3-43.2]	96.3 [94.1-97.7]
20004	191	21	16	20	134	51.2 [36.5-65.8]	89.3 [83.4-93.3]



FN, false negative; FP, false positive; N, number; TN, true negative; TP true positive.



Szekaly et al., medRxiv 2022

Xpert MTB/XDR

Gene – Targets:

Isoniazid (katG/inhA)

Flourquinolines (gyrA/gyrB)

Kanamycin (rrs/eis)

Amikacin (rrs/eis

Ethionamide (inhA)

vs. culture (MGIT 960)

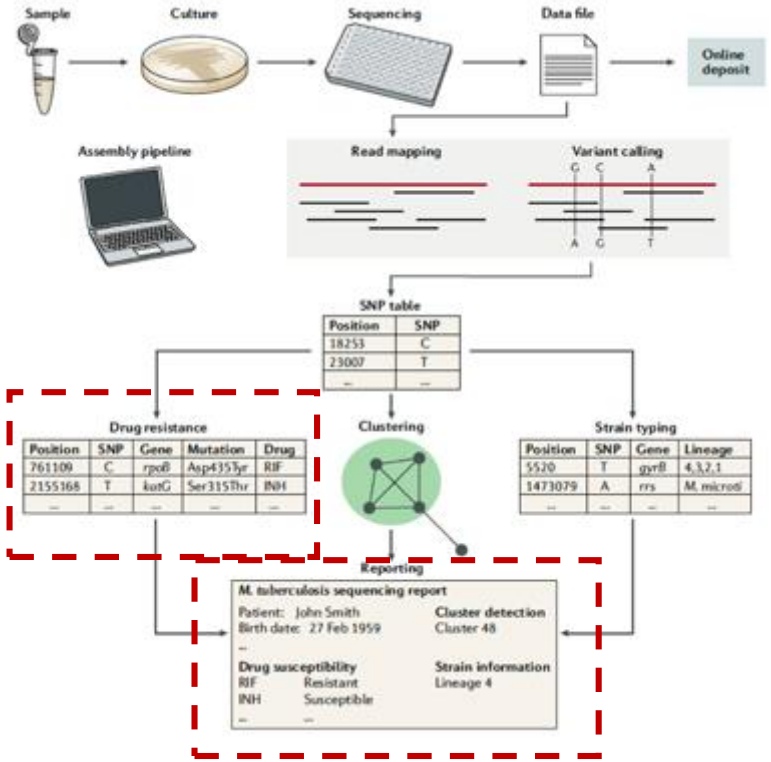
Drug	Investigational-Assay Result + Phenotypic Drug-Susceptibility Test Result*				Sensitivity		Specificity	
	R+R	R+S	S+R	S+S				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid†	150	1	30	122	150/180	83.3 (77.[illegible]–88.5)	122/123	99.2 (95.6–100.0)
Ofloxacin‡	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)

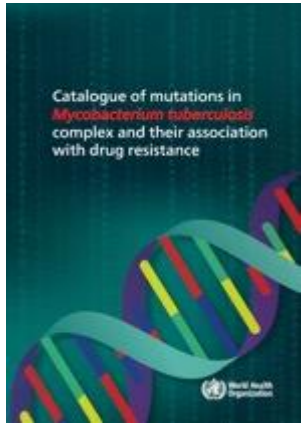
vs. sequencing

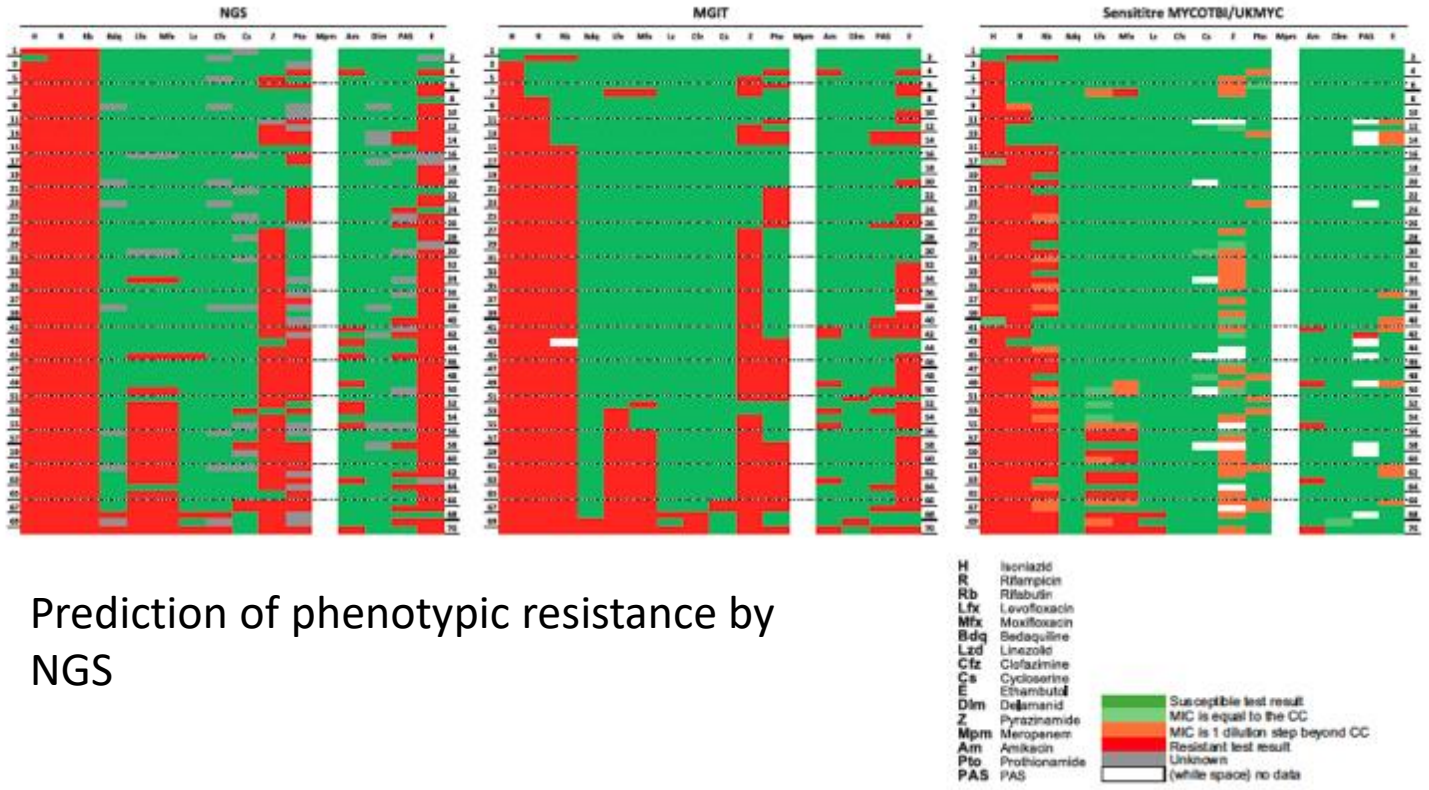
Drug	Investigational-Assay Result + DNA Sequencing Result†				Sensitivity		Specificity	
	M+M	M+NM	NM+M	NM+NM				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid‡	151	0	3	149	151/154	98.1 (94.4–99.6)	149/149	100.0 (97.6–100.0)
Fluoroquinolones§	91	0	4	208	91/95	95.8 (89.6–98.8)	208/208	100.0 (98.2–100.0)
Kanamycin¶	38	1	3	256	38/41	92.7 (80.1–98.5)	256/257	99.6 (97.9–100.0)
Amikacin¶	30	0	1	267	30/31	96.8 (83.3–99.9)	267/267	100.0 (98.6–100.0)

Xie et al, NEJM 2017

Sequencing based DST replaces pDST?

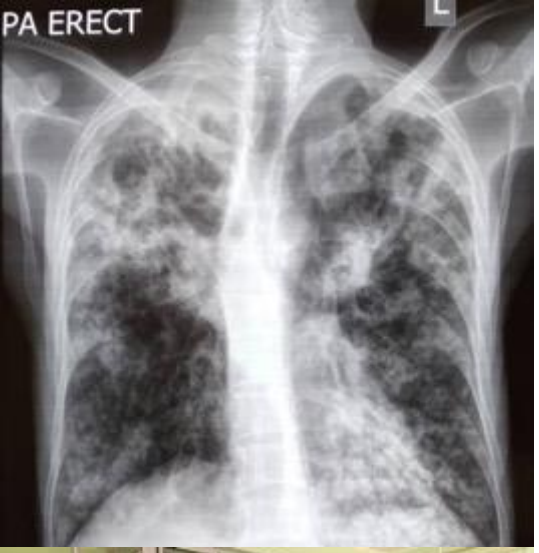






Prediction of phenotypic resistance by NGS

Groppel et. al. CID 2021
Mehaan et al. , Nature Microbiology 2019



tNGS in Namibia with Deeplex assay

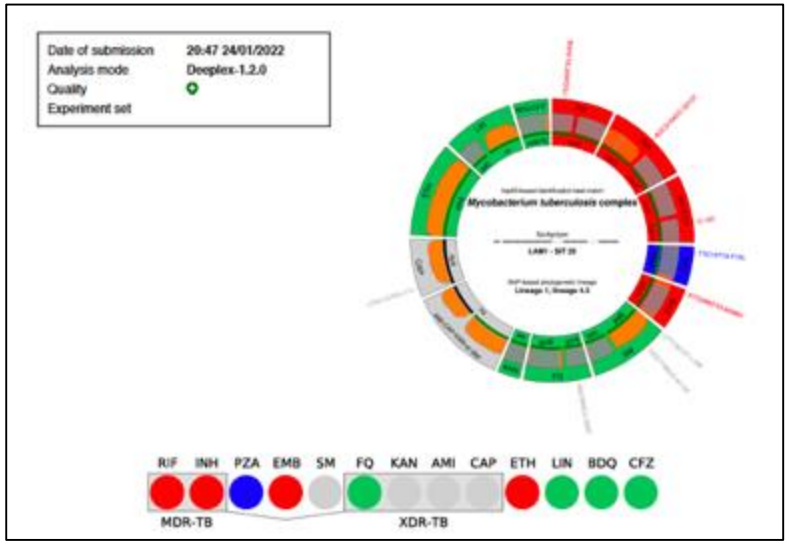
Drug resistance associated variants[3]

Gene	Genomic position	Codon change	% Variant	Dx-score	AA change	Drug*	Confidence	PMID
embB	4247429	ATG306GTG	100	18.25	M306V	EMB	High	
fabG1	1673425	C-15T	100	220.75	n/a	INH, ETH	Moderate // Moderate	ReSeqTb
katG	2155168	AGC315ACC	100	4.25	S315T	INH	High	ReSeqTb
rpoB	761155	TCG450TTG	100	2037.75	S450L	RIF	High	ReSeqTb

Uncharacterized variants[3]

Uncharacterized variants designate sequence variants of as yet unknown association with drug sensitivity or resistance.

Gene	Genomic position	Codon change	% Variant	Dx-score	AA change	Drug*
pncA	2289203	TTC13TTA	100	127.75	F13L	PZA



Shortening of standard TB treatment to 4 months now possible….

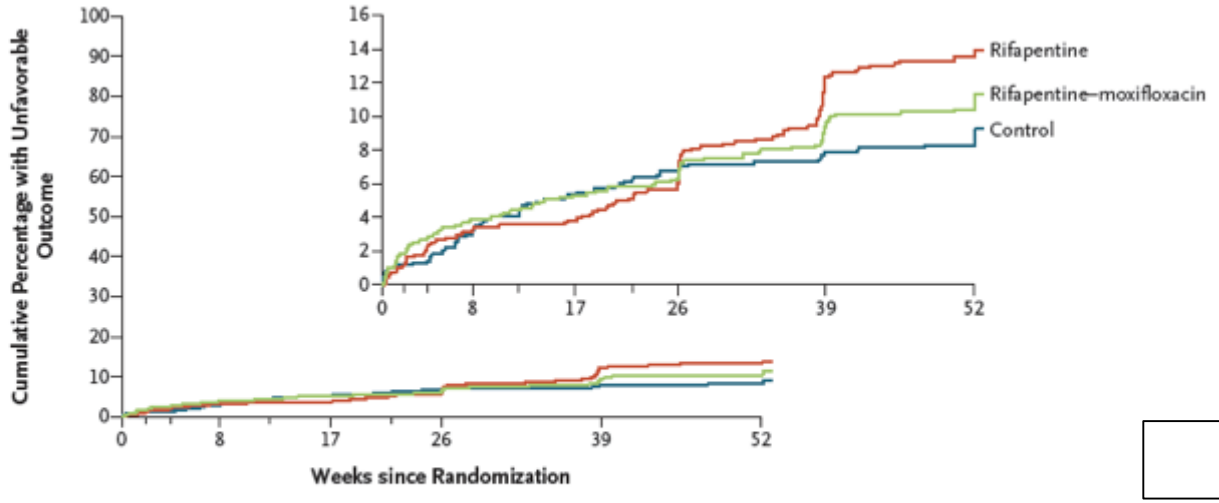
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

B



No. at Risk						
Rifapentine	784	758	749	727	660	644
Rifapentine–moxifloxacin	791	758	747	728	686	668
Control	768	742	724	711	675	658

Favourable outcomes:

- 4RHZE/2RH – **90.4%**
- 4 Rifapentine Moxifloxacin Isoniazid Pyrazinamide – **88.4%**
- 2 Rifapentine Isoniazid Pyrazinamid / 2 Rifapentine Isoniazid -**85.8%**

But Rifapentine not registered in Europe

Dorman et al. NEJM 2021

(Pre) XDR- TB Therapy for 6 months: (Ze)NIX TB - Pretomanid, Linezolid und Bedaquiline

	NIX- TB			ZeNIX-TB[1]	
	1200 mg Linezolid			1200 mg Linezolid 26 weeks	600 mg Linezolid 26 weeks
	XDR	MDR	All		
Favorable. (%)	89	92	90	93	91
Unfavorable (%)	11	8	10	7	9
Death (n)	6	1	7	0	0
Relapse(n)	1	1	2	0	1

[1] 41% XDR; 47% pre XDR, 12% MDR

2020: NiX TB: Linezolid 1200 mg (81% neuropathy, 42% myelosuppression)
2022: ZeNiX: Linezolid 600 mg (24% neuropathy, 2% myelosuppression)

Conradie et al, NEJM 2020
Conradie et al, NEJM 2022

RR -TB therapy for 6 months: TB PRACTECAL - Moxifloxacin, Pretomanid, Linezolid und Bedaquiline

	BPalM n=151	BPaL n=126	BPalC n=123	Standard of care n=152
Favorable. (%)	89	77	81	52
Unfavorable (%)	11	23	19	48
Recurrence (n)	0	3	1	
Deaths (n)	0	0	1	2
≥AE Grade III (%)	19	22	32	59

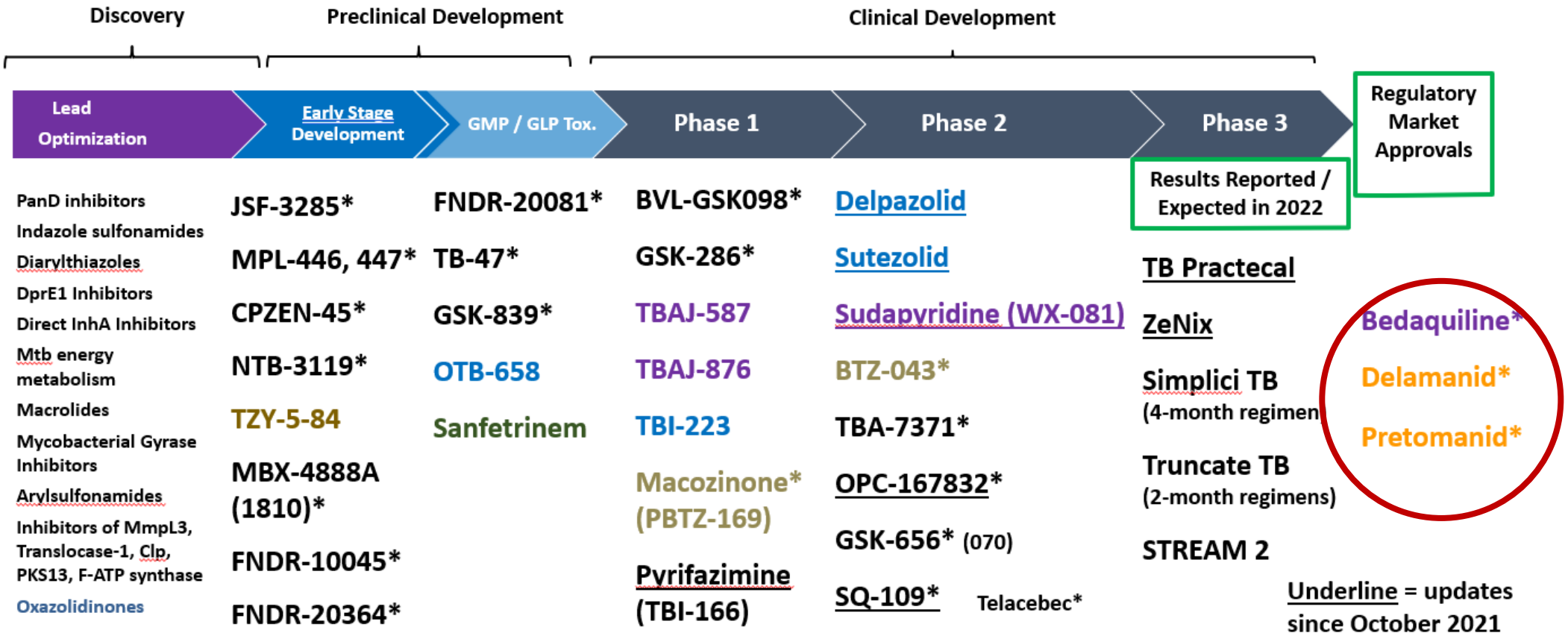
Linezolid 16 weeks 600 mg/ 8 weeks 300 mg

But: South Africa 3.8.% Bedaquline resistance prevalence

Moldova: 15% of patients with treatment emerging Bedaquiline resistance

Press release MSF Oct 2021
Abstract CROI 2022
Ismail et al. Lancet Inf Dis 2021
Chesov, ERJ 2021

2022 Global New TB Drug Pipeline[1]



Underline = updates since October 2021

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[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

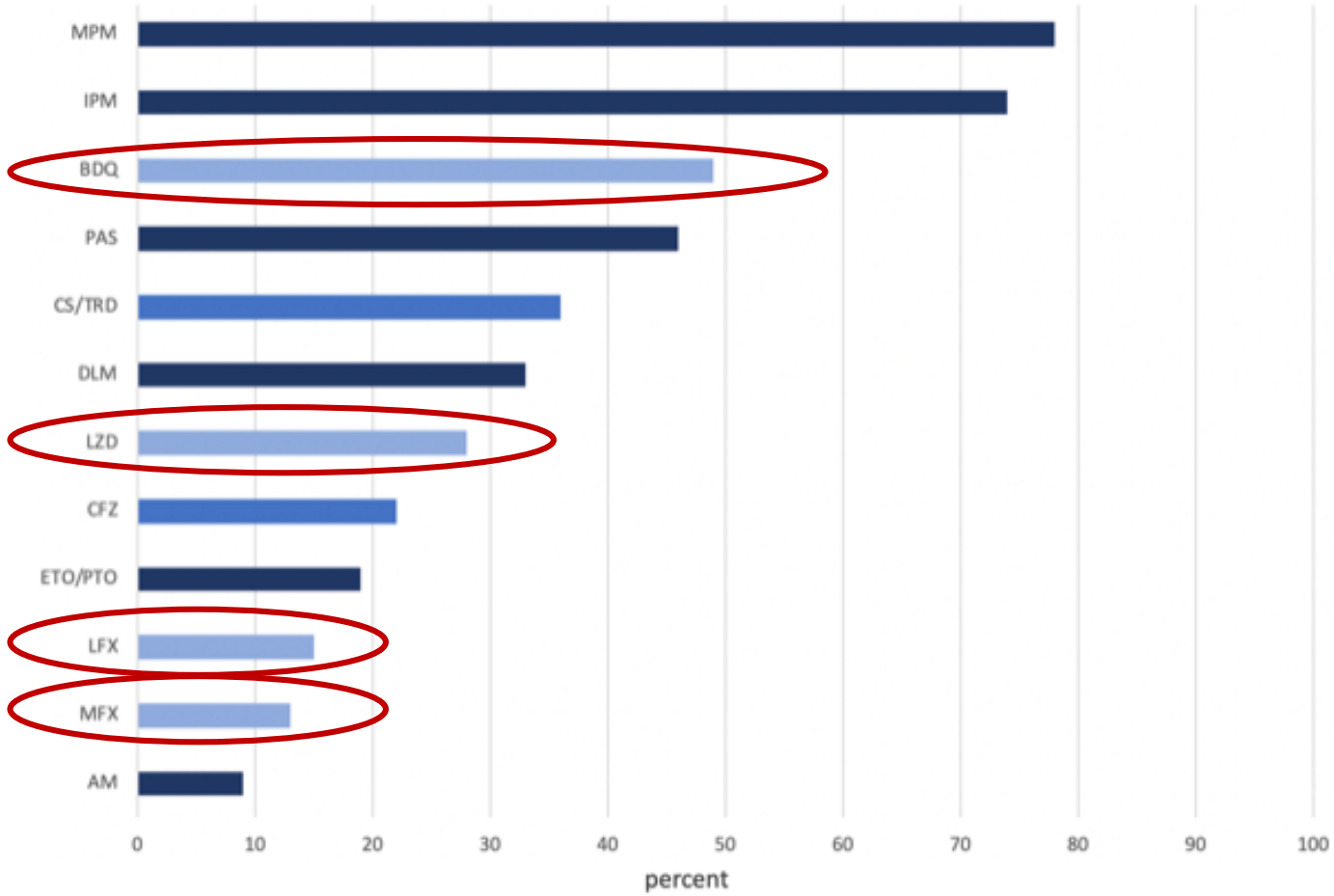
Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2022

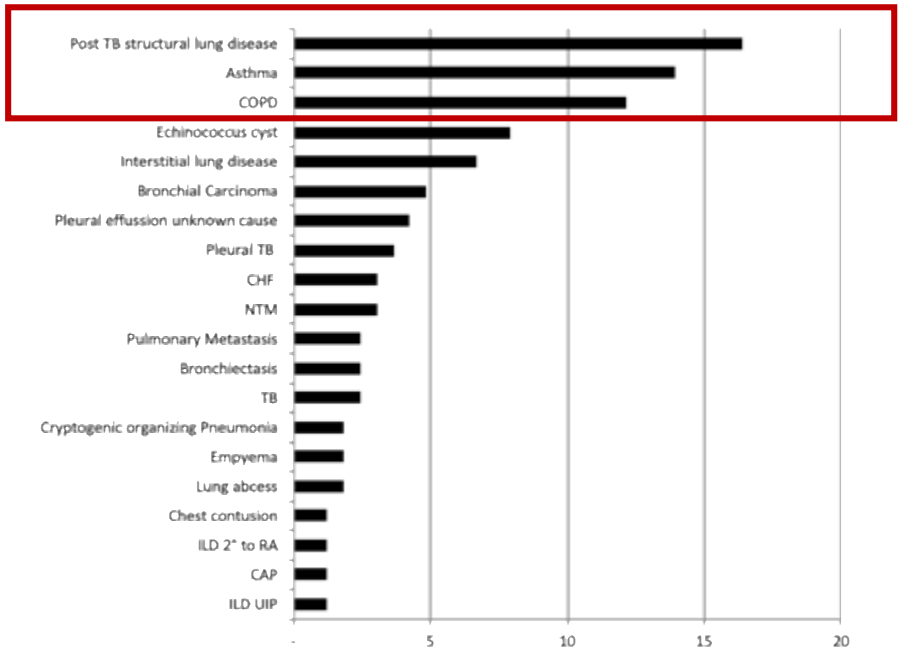
Proportion of countries where the drug is available, but no DST – 41 European countries 2021



- but since 2020 definition of XDR- TB: MDR-TB plus FQ plus BDQ or LQ

Günther et al. ,CMI 2022

Post TB lung disease in a African hospital chest service



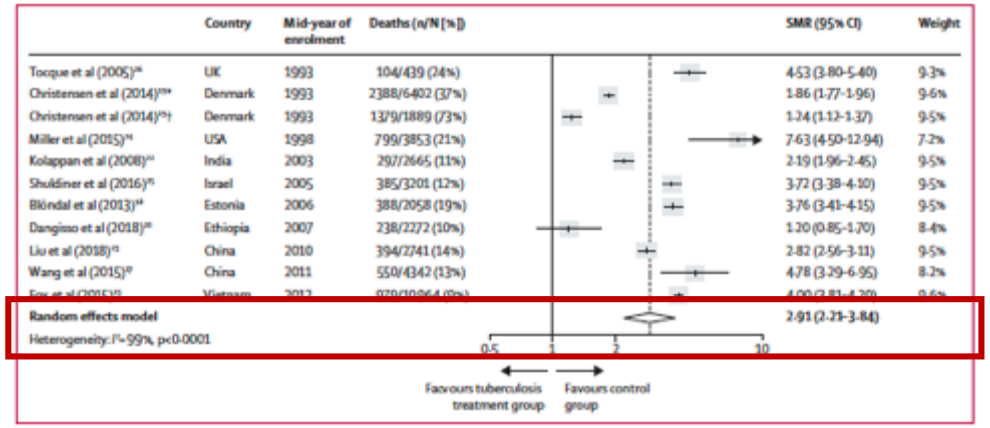
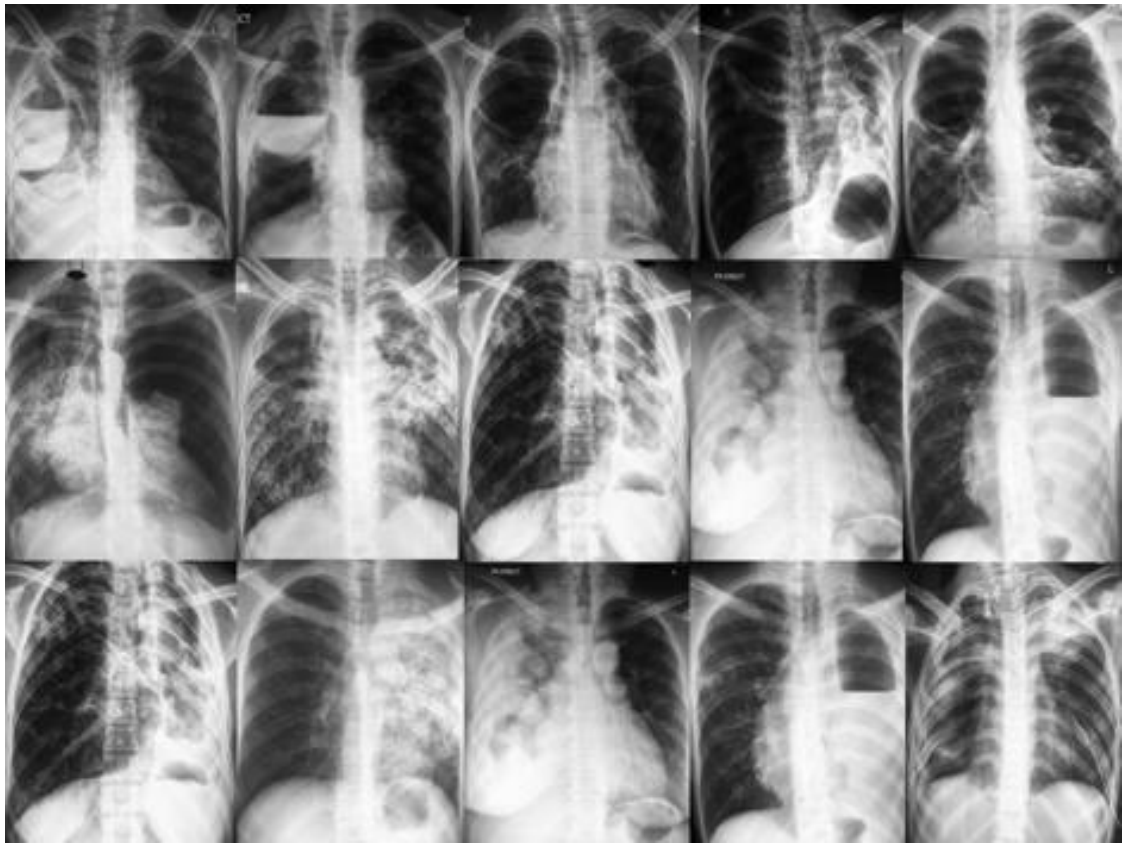


Figure 2: SMR for all-cause mortality after tuberculosis treatment
SMR=standardised mortality ratio. *Estimate for pulmonary tuberculosis. †Estimate for extrapulmonary tuberculosis.



Mortality after TB is approximately **3 x higher** then in the general population

Günther G, Ithete S, IJTLD 2021
Romanowski. Lancet Inf Dis 2019

Post / Long- tuberculosis vs Post / Long COVID in the literature

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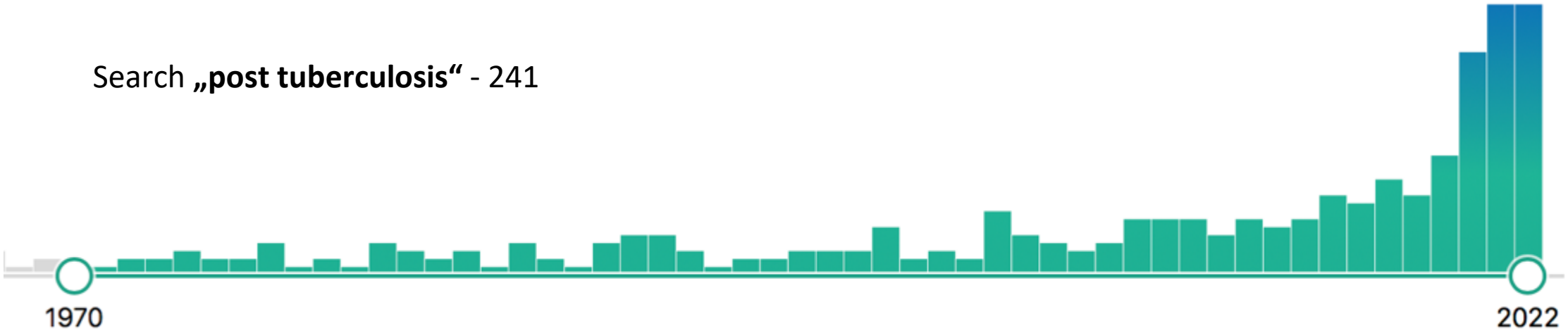

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