Herzlich Willkommen zum 29. Virtuellen Tuberkulose-Symposium

Bienvenue au 29e Symposium Tuberculose virtuel

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
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LIA PULMUNARA SVIZRA

Kompetenzzentrum Tuberkulose
Centre de compétence tuberculose

THE CLOCK
IS TICKING

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Willkommensgruss
Mot de bienvenue

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Mot de bienvenue

lic. jur. Thomas Burgener
Präsident Lungenliga Schweiz, Bern

Président Ligue pulmonaire suisse, Berne

Dauer des Spitalaufenthalts von Tuberkulose-Patienten in der Schweiz

Sebastian Tonko, Florent Baty, Martin Brutsche, Otto D. Schoch

Kantonsspital St.Gallen

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Length of hospital stay for TB varies with comorbidity and hospital location

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[2]Tuberculosis Competence Centre, Swiss Lung Association, Berne, Switzerland

SUMMARY

Hintergrund

Spitalaufenthalt bei Tuberkulosepatienten

- Ambulante Patientenabklärung und Behandlung ist empfohlen
- International (WHO) und national (Handbuch Tuberkulose LLS)
- Bundesamt für Statistik erhebt Hospitalisations-Statistik mit ICD-10 codes
- Bundesamt für Gesundheit sammelt Meldungen der Tuberkulose Fälle

Jährliche Tuberkulosefälle 2002 - 2015

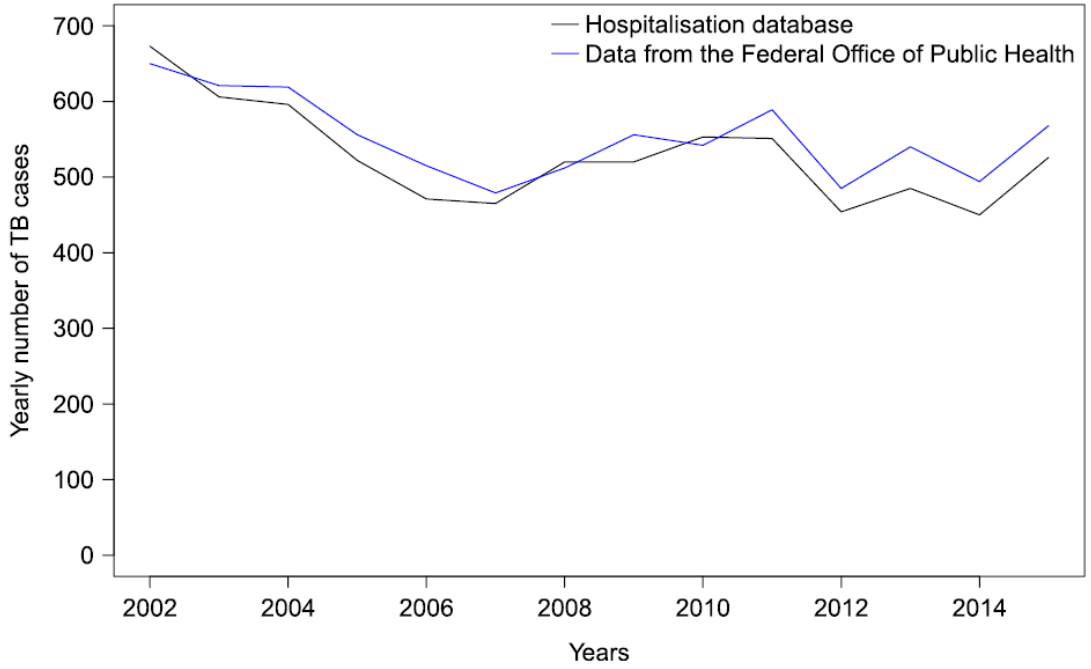


Figure 1 Annual TB cases reported to the Swiss Federal Office of Public Health (Bern, Switzerland) and annual number of patients hospitalised for TB (main diagnosis), 2002–2015. TB = tuberculosis.

Spitalstatistik

19 mio Spitaleintritte

7395 mit TB code

6234 Pers, Re-Hosp. 14%

Meldesystem BAG/ TB

7726 TB Fälle gemeldet

Hospitalisierungsrate

- **81%**

Table 1 Characteristics of hospitalisation cases with TB as primary diagnosis

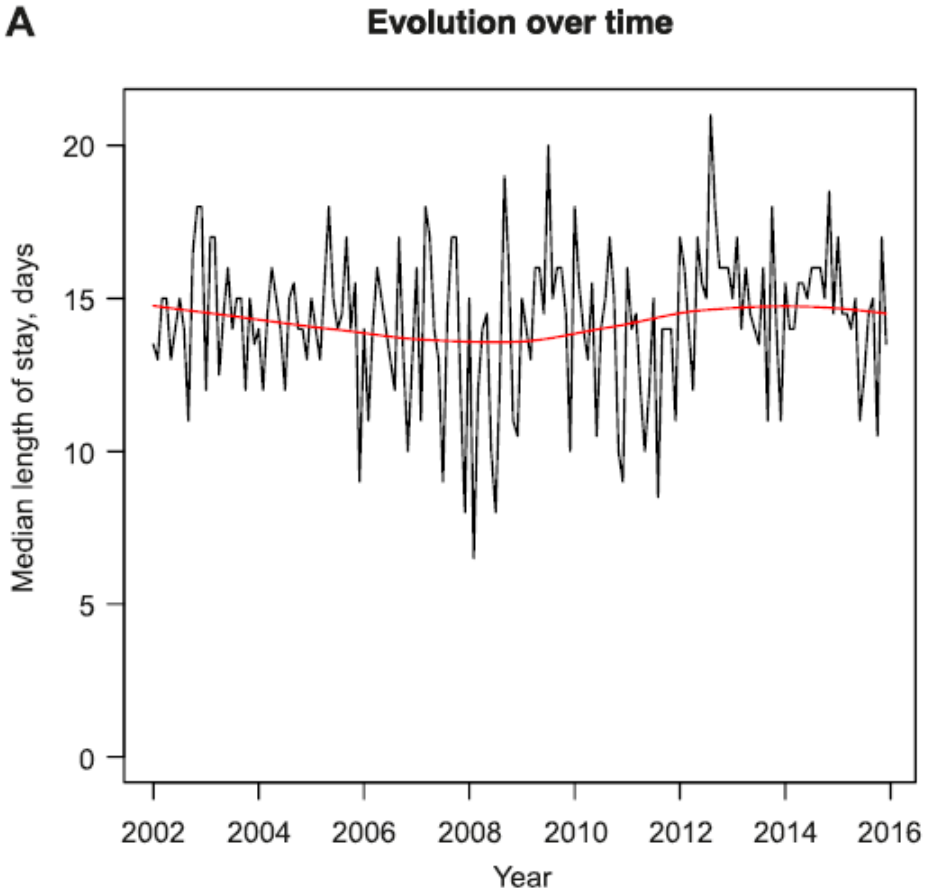
	n (%)
Number of unique patients	6234
Number of hospitalisations	7395
Rate of rehospitalisation, %	14
Age, years, median [IQR]	40 [27–62]
Male sex, %	59
Organ affected (ICD-10 code in brackets)	
Respiratory TB, confirmed (A15)	3247 (52)
Respiratory TB, not confirmed (A16)	1483 (24)
TB of nervous system (A17)	114 (2)
TB of other organs (A18)	1096 (18)
Miliary TB (A19)	292 (5)
Resistance pattern	
Resistance to one or several first-line TB drugs (U820)	28 (0.4)
Multidrug-resistant TB (U821)	44 (0.7)

TB = tuberculosis; IQR = interquartile range; ICD = International Classification of Disease.

Spitalaufenthalte mit TB codes 2002-2015

76% Atemwege

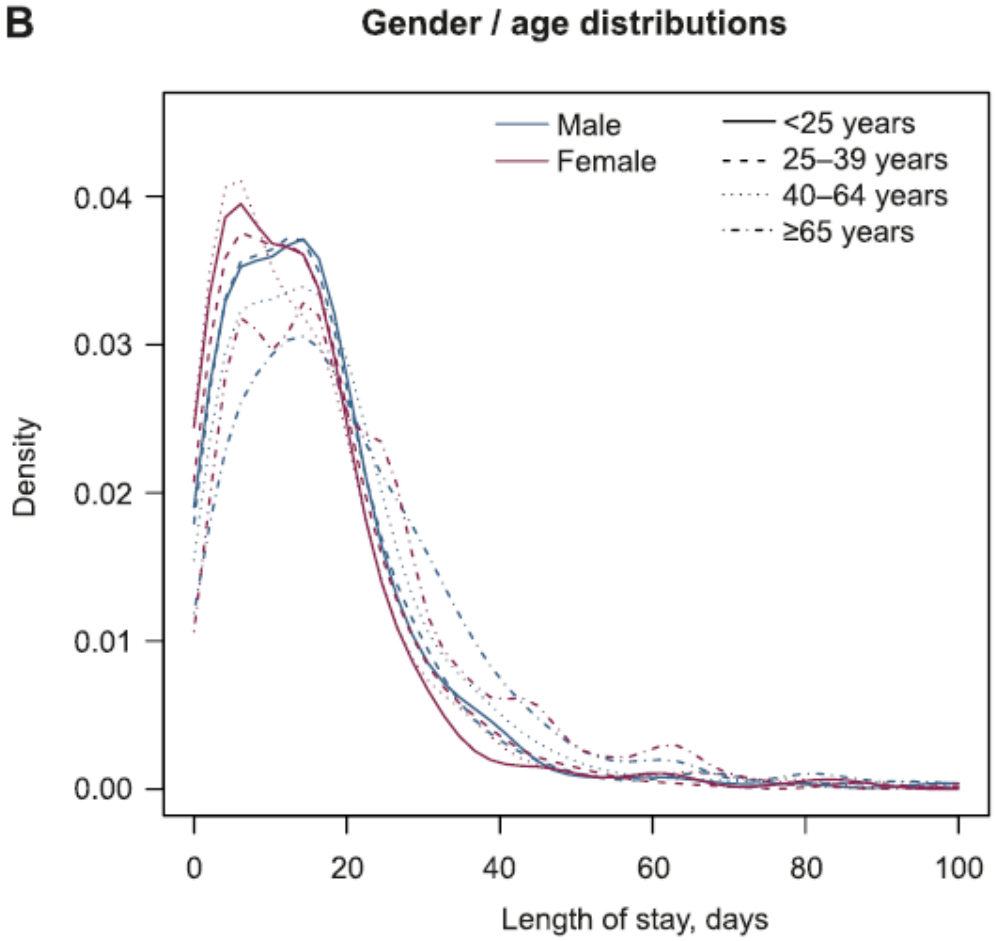
0.4% Mono- und 0.7% Multi-Resistenz



Dauer der Spitalaufenthalte

Median 14 Tage (IQR 7-22)

M 15 Tage, W 14 Tage (p<0.001)



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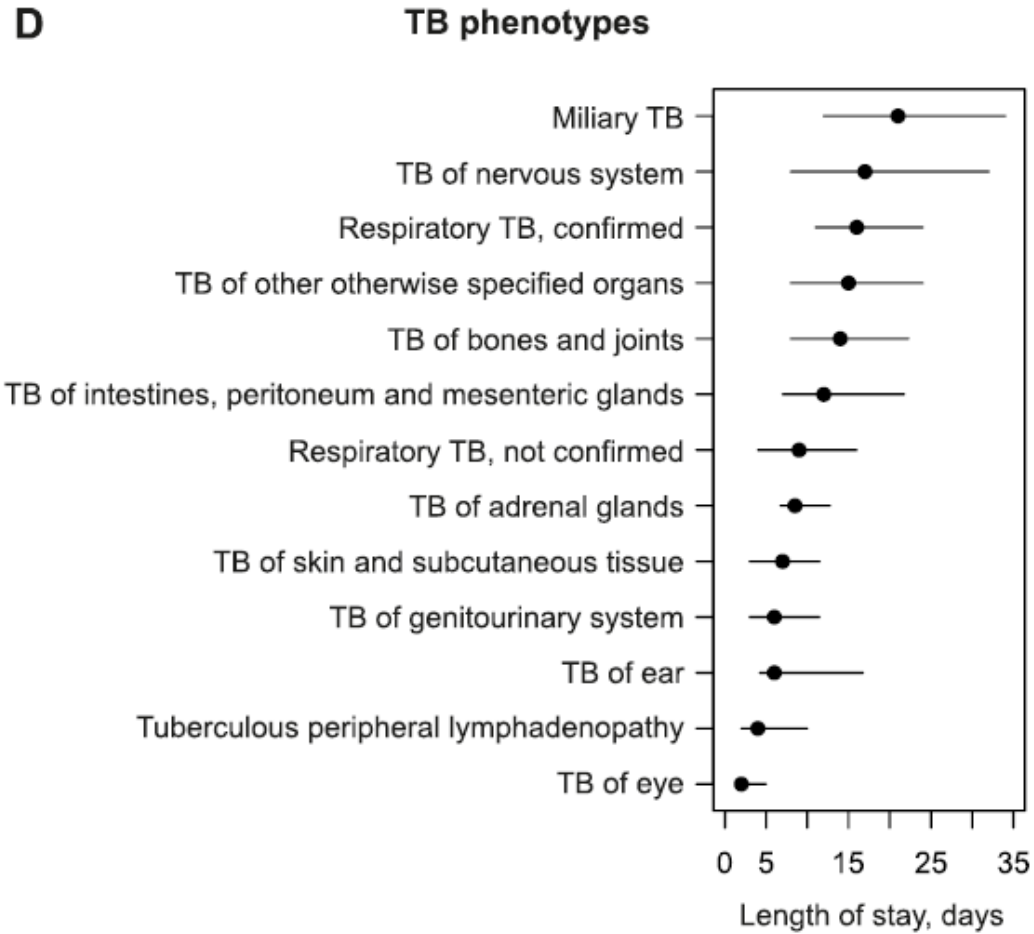
Länger bei >65 j



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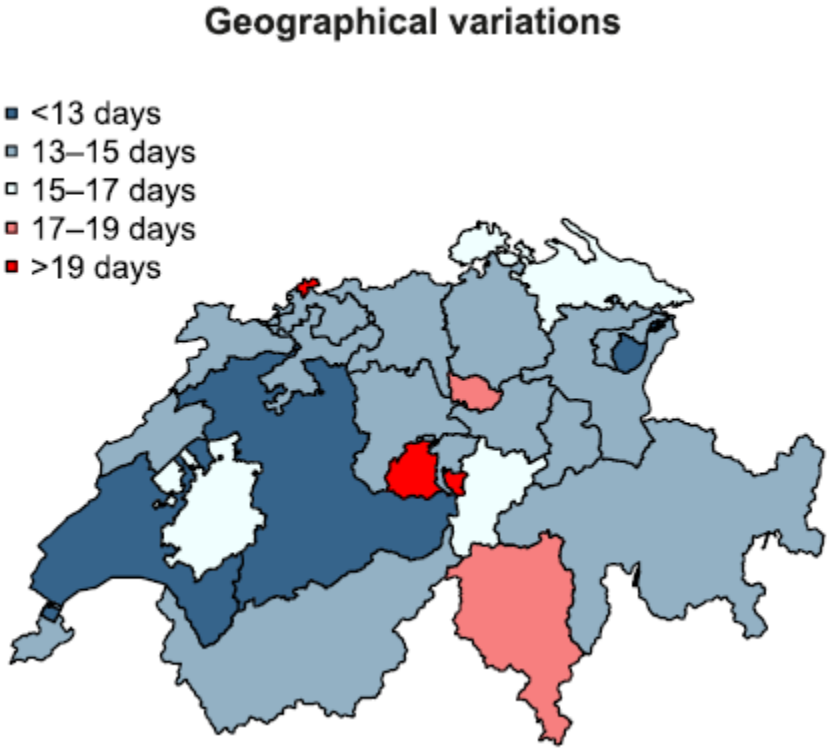
Länger bei >65 j, Resistenzen

Phänotypen: Miliar, ZNS



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Länger bei >65 j, Resistenzen

Phänotypen: Miliar, ZNS

Sehr grosse Regionale Unterschiede

-Basel Stadt 21 (9-29) Tage

-Waadt 11 (4-19) Tage

Aufenthaltsdauer und Resistenzen gegen Tuberkulose Medikamente

Resistenzen auf TB Medikamente wurden bei 72 Fällen codiert (1.1 %)

92% betrafen pulmonale Tuberkulosen

Die mittlere Aufenthaltsdauer lag bei 26 Tagen (IQR 16-42) (Rest 14 Tage)

Die längste erfasste Aufenthaltsdauer lag bei 92 Tagen

Prädiktoren für Aufenthaltsdauer von >14 Tagen

Table 2 Patient characteristics with regard to LOS. The population is split into short stayers (LOS < 14 days) vs. long stayers (LOS > 14 days)

	<14 days	>14 days	OR	95% CI	*P* value
Total number of cases	3154	3980			
Age, years					
<25	699 (55.3)	564 (44.7)			
25–39	1012 (52.7)	908 (47.3)	1.11	0.96–1.28	0.145
40–64	896 (52.5)	810 (47.5)	1.12	0.97–1.3	0.127
≥65	547 (40.7)	798 (59.3)	1.81	1.55–2.11	<0.001
Sex					
Female	1387 (54.4)	1162 (45.6)			
Male	1767 (48)	1918 (52)	1.3	1.17–1.43	<0.001
Organs affected					
Respiratory (confirmed) (A15)	1220 (37.6)	2027 (62.4)			
Respiratory (not confirmed) (A16)	1049 (70.7)	434 (29.3)	0.25	0.22–0.28	<0.001
Nervous system (A17)	43 (37.7)	71 (62.3)	0.99	0.68–1.47	0.975
Other organs (A18)	754 (68.8)	342 (31.2)	0.27	0.24–0.32	<0.001
Miliary (A19)	88 (30.1)	204 (69.9)	1.4	1.08–1.82	0.012
Resistance pattern					
No resistance	3139 (50.9)	3023 (49.1)			
Single/multiple resistance (U820/U821)	15 (20.8)	57 (79.2)	3.95	2.29–7.24	<0.001
Comorbidities					
No comorbidity	943 (64.3)	524 (35.7)			
One comorbidity	644 (58.2)	462 (41.8)	1.29	1.1–1.52	0.002
Several comorbidities	1567 (42.8)	2094 (57.2)	2.4	2.12–2.73	<0.001
Region of institution					
Capital (BE, SO, FR)	499 (53.7)	431 (46.3)			
Central (ZH, ZG, SZ, LU, UR, NW, OW, TI, SH)	826 (45.8)	976 (54.2)	1.37	1.17–1.6	<0.001
East (SG, AR, AI, TG, GR, GL)	344 (47.8)	376 (52.2)	1.27	1.04–1.54	0.018
North-West (BS, BL, AG)	346 (43.1)	456 (56.9)	1.53	1.26–1.85	<0.001
West A (GE, VS)	529 (53.4)	461 (46.6)	1.01	0.84–1.21	0.923
West B (VD, NE, JU)	610 (61.6)	380 (38.4)	0.72	0.6–0.86	<0.001

LOS = length of (hospital) stay; OR = odds ratio; CI = confidence interval. BE = Bern, SO = Solothurn, FR = Fribourg, ZH = Zürich, ZG = Zug, SZ = Schwyz, LU = Luzern, UR = Uri, NW = Nidwalden, OW = Obwalden, TI = Tessin, SH = Schaffhausen, SG = St.Gallen, AR = Appenzell Ausserrhoden, AI = Appenzell Innerrhoden, TG = Thurgau, GR = Graubünden, GL = Glarus, BS = Basel Stadt, BL = Basel Land, AG = Aargau, GE = Genève, VS = Valais, VD = Vaud, NE = Neuchâtel, JU = Jura.

Alter >65 Jahre

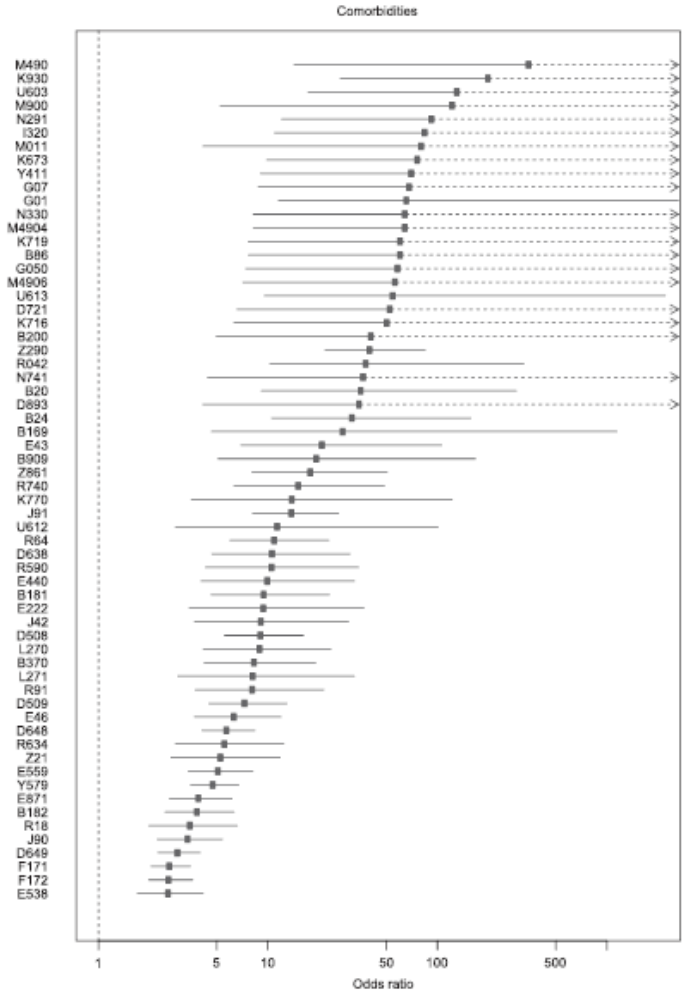
Männlich

Betroffenes Organsystem

Resistenz

Co- Morbiditäten

Region in der Schweiz



Ko-Morbiditäten (KM)

- 23% ohne KM, 62 assoziiert mit Tuberkulose
- Signifikanter Einfluss auf Aufenthaltsdauer:
  1 KM OR 1.3(1.2-1.4)/ 2 KM OR 2.4(2.1-2.7)
- Ko-Morbiditäts-‘clusters’:

1) HIV infection
2) Endokrinologische KM, Malnutrition und metabolische Krankheiten
3) Leber- und Lungenpatholgie
4) Arzeimittel-Nebenwirkungen

Figure 3 ICD-10 codes over-represented in patients hospitalised for tuberculosis in comparison to a nested matched control population. The ORs with 95% CIs are represented on a log-scale. The Haldane-Anscombe correction was used to avoid infinity values in the calculation of the ORs. Infinite upper limits of the 95% CIs are represented with dashed line and arrows (for decoding of ICD-10 codes, see Supplementary Table S1). ICD = International Classification of Disease; OR = odds ratio; CI = confidence interval.

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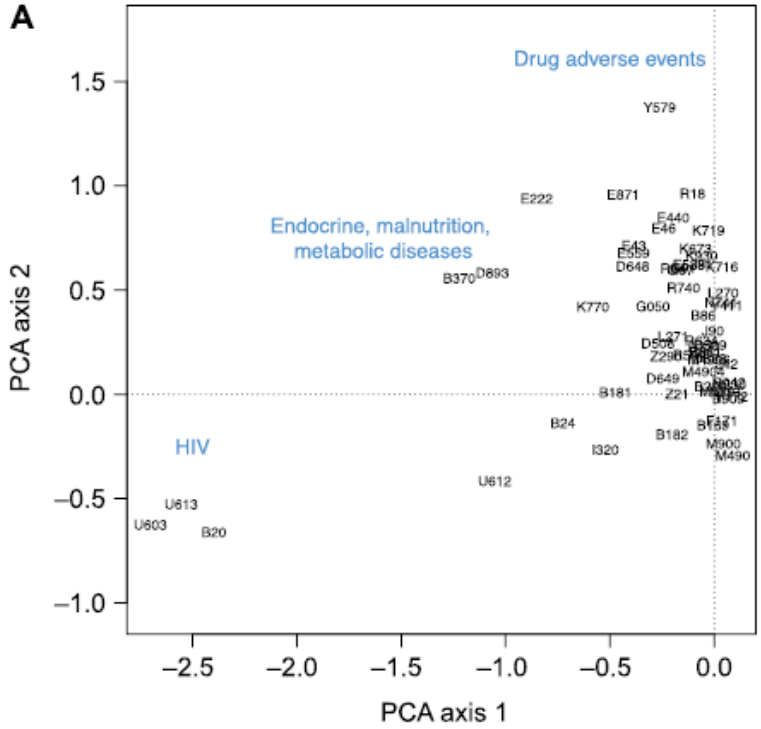
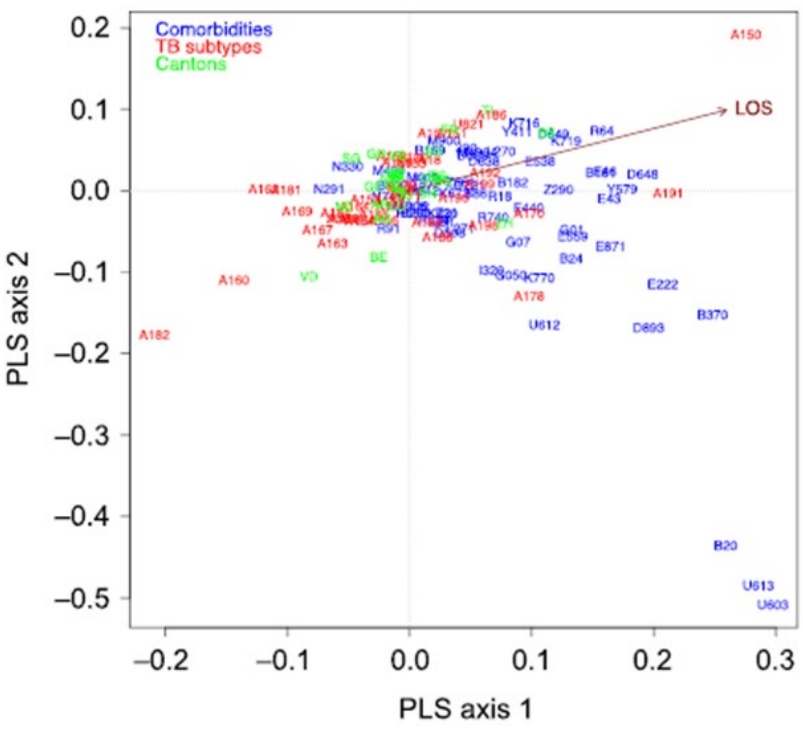
Principle component analysis
Partial least square regression





Diskussion / Schlussfolgerung

- >80% der Tuberkulose-Patienten 2002-2015 in der CH wurden hospitalisiert
- Alter, Geschlecht, TB-Typ, Komorbiditäten sind mit Aufenthaltsdauer assoziiert
- Grossen Einfluss auf die Aufenthaltsdauer hat die Region in der Schweiz

> Potential für Schulung bezüglich Empfehlungen der ambulanten TB Betreuung und Therapie respektive dem frühen Übergang zu ambulanter Betreuung mit Verkürzung der Hospitalisationsdauer

Kompetent
Umfassend
Nah

Herzlichen Dank
für Ihre Aufmerksamkeit.

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Accès aux soins pour les patients tuberculeux en situation de vulnérabilité

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29e Symposium Tuberculose virtuel Jeudi 25 mars 2021, 13.20 – 13h40

Plan

- Vulnérabilité?
- Un cas clinique
  - Et s'il était migrant («people on the move») ?
  - Et s'il était en prison?
  - Et s'il était «pauvre» ?
  - Fin du cas
- Conclusion

Vulnérabilité?

- Personnes vulnérable
  - Liste OFSP covid-19? (vulnérabilité biologique)
  - Fragile ou plus facilement atteint par une maladie? (vulnérabilité socio-économiques)

Vulnérabilité?

VULNERABILITE MEDICALE

Somatique

Mentale

Comportement à risque

Handicap

+

VULNERABILITE SOCIALE

Précarité socio-économique

Faibles compétences en santé

Migration forcée

Minorité

VULNERABILITE CLINIQUE

Risque de prise en charge inadéquate en termes de qualité
(accès, prévention, diagnostic, qualité du soin, orientation, suivi)

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Bodenmann P, Madrid C, Wolff. **Vulnérabilités et santé : une nouvelle rubrique**, *RMS*, 2009

«Vagueness»

Si la cause de l'inéquité n'est pas claire, chacun aura sa propre interprétation du terme «vulnérabilité».

Risque de penser que la vulnérabilité est décidé *biologiquement* ou par *les choix ou comportements* de chacun et de négliger les mécanismes et relations de pouvoir **structurels**. On pourrait alors voir la vulnérabilité non pas comme une résultante de barrières structurelles mais uniquement exacerbée par ces barrières.

Amy S. Katz , Billie-Jo Hardy , Michelle Firestone , Aisha Lofters & Melody E. Morton-Ninomiya (2020) Vagueness, power and public health: use of 'vulnerable' in public health literature, Critical Public Health,

Vignette

- H, Gambien, 46ans.
- Parcours migratoire: Espagne, Italie.
- En CH pour chercher des soins car dorsalgie depuis 8 mois. Multiples consultations en Italie pour ce motif. N'a eu que paracétamol/AINS. Pas d'autres examens (sans papiers).
- Perte de 10kg en qlques mois.
- 1m86. 59 kg.

Migration «People on the move»

Vulnérabilité Systémique

Pré-migratoire: **Epidémiologie** différente, **vaccinations,** niveaux socio-économique et d'éducation, profession, exposition à des pratiques rituelles (mutilations génitales féminines, mariage forcé). Motifs de la migration, exposition à la **violence organisée** (guerre, torture, violence psychologique et/ou sexuelle).

Péri migratoires : Les **conditions** (seul, en famille, exode de masse) et **modalités** du voyage (durée totale, nombre d'étapes). Dépendance aux filières de passeurs (+/-exposition à des violences y compris sexuelles).

Dans le pays d'accueil:

Statut administratif et conditions de vie (**accès au travail**, risque de traite des êtres humains).

Isolement social VS **communauté** structurée dans le pays d'accueil

Logement : accès, hébergements collectifs des pays d'accueil et favorise la transmission d'infections.

Complexité et durée de la procédure d'asile (**facteur de stress)**.

Accords de Dublin => interruption prise en charge + questions éthiques aux professionnels de santé

Vulnérabilité Individuelle

Risque élevé de **rupture de traitement**.

Sans-papiers: la survie dépend de la capacité à travailler. Santé = unique capital, => risque de retard ou renoncement aux soins.

La santé mentale a impact majeur et à long terme sur la capacité d'intégration. Il est influencé, en général de manière négative, par le parcours migratoire et les conditions de vie dans le pays d'accueil et, de façon plus positive, par la capacité de résilience.

Durieux-Paillard S., Jackson Y-L.,. **Migrants en situation vulnérable : leur accès aux soins correspond-il à leurs besoins de santé ?** *RMS,* 2019

Asile

Centre fédéraux (dès 1.03.2019)

- «Procédure accélérée» (durée jours/semaine).
- Fonctionnement propre à chaque centre
- Utilisation fréquente du TB score
- Durée maximal avant renvoie «Dublin»: 6mois

Dans les cantons: exemple Vaud (USMI)

- Consultation par IPL (délaie ~ 1 semaine) : Prévention, vaccination. Santé mentale et physique.
- Patient assuré, accès à tous les services (urgent ou électif). Traducteurs.
- Consultation par médecin généraliste (délaie 1-4 semaines).
- «Créer des réseaux de professionnels actifs dans le domaine de l'asile, en prenant exemple sur le modèle du canton de Vaud» (Rapport «*Soins médicaux pour les requérants d'asile dans les centres de la Confédération et les centres d'hébergement collectif cantonaux*»)

«Sans papiers»: sans assurance!

- Soins urgents: pris en charge.

=> Importance que les soignants identifient: douleurs intenses, multiples consultations, perte de 10kg, déformation colonne, épidémiologie différente dans le pays d'origine

- Si classé «non urgent»=> accès aux soins difficiles (pas d'IRM élective possible p.ex).
- Une fois le diagnostique posé: Permis N ou F le temps du traitement et pour la durée du traitement.

Prisons du canton de Vaud

- Anamnèse infirmière ciblée à l'entrée
- Algorithme dédié pour les médecins, avec «TB-score» pour prioriser ceux qui doivent avoir une RX (+/- isolement) rapidement.
- RX faites sur place par médecin ou TRM.
- RX d'entrée proposée systématiquement
- Expectoration faites sur place ou transfert au «dispensaire antituberculeux» (expectorations induites).
- Traitement sous surveillance 1x/j.
- Appuie à l'enquête d'entourage DAT.

Pauvreté

- En 2019, 8,7% de la population suisse ou quelque 735'000 personnes touchées par la pauvreté en termes de revenu.
- «Working poor»: 4,2% des personnes actives occupées en Suisse sont touchées par la pauvreté, soit 155'000 personnes.

Equité et renoncement aux soins

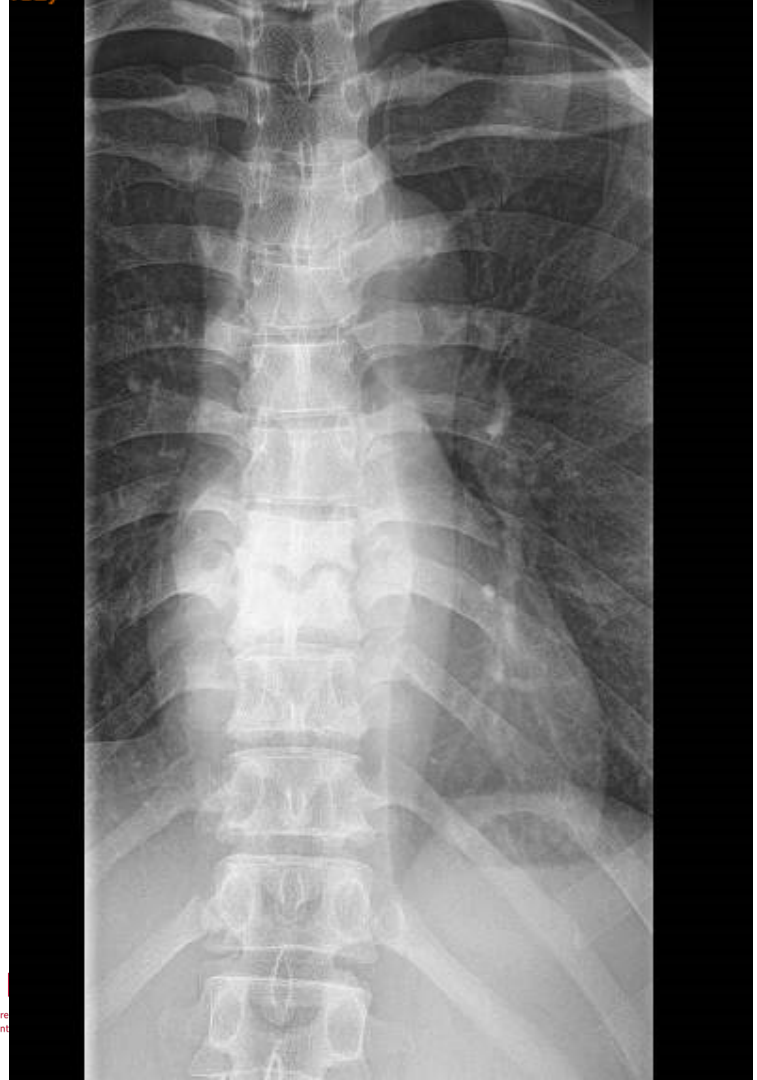
- Comparativement à dix autres pays industrialisés, la Suisse est classée quatrième pour l'équité et huitième pour l'accès aux soins.
  (Schneider EC, et al. Mirror, mirror : how the US health care system compares internationally at a time of radical change. The Commonwealth Fund, 2017.)
- Renoncement aux soins:

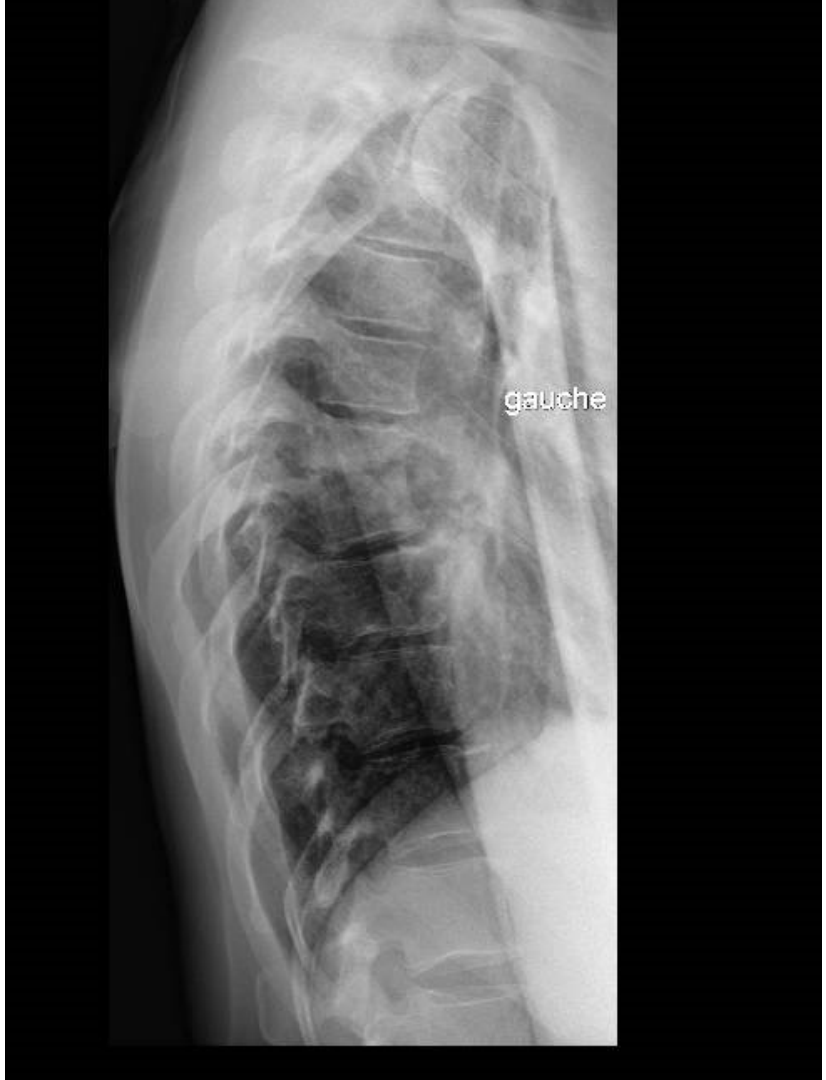
Schoen C et al, Health Affairs 2010 :	**10,8 %**
Wolff H et al, SMW 2011 :	**14,5 %**
Guessous I et al, Preventive Med 2012 :	**13 %**
Bodenmann P et al, Plos One 2014 :	**10,7 %**
Panorama de la santé 2017. Les indicateurs de l'OCDE:	**22 à 31%**

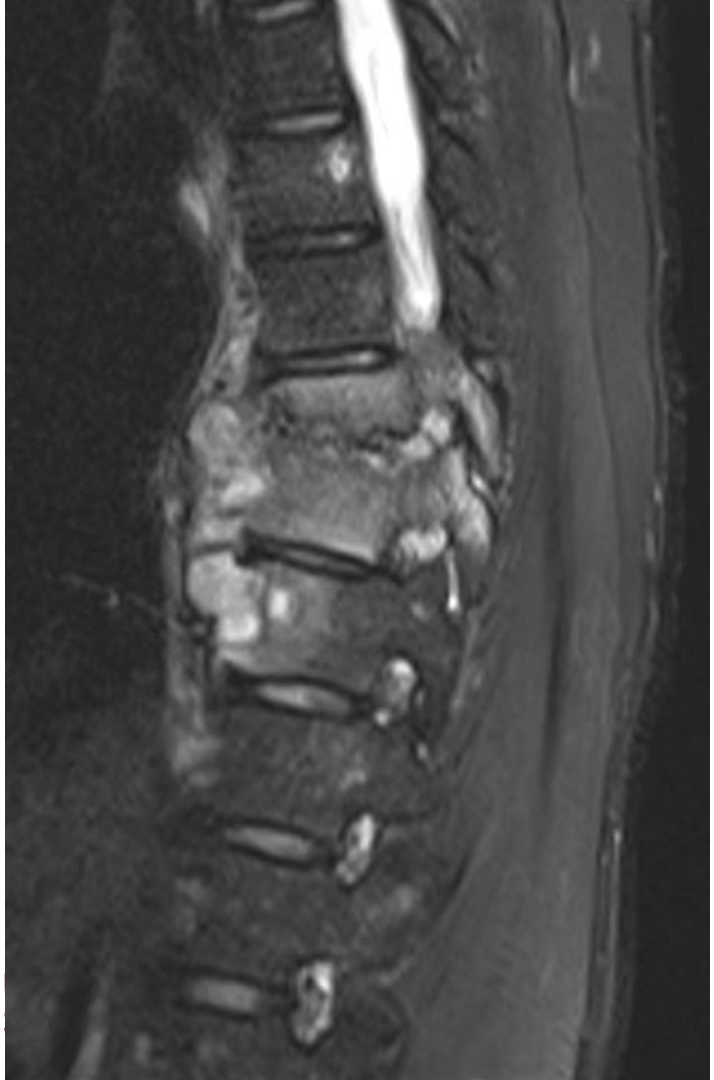
« **Durant les 12 derniers mois, avez-vous eu de la peine à payer les factures de votre ménage (impôts, assurances, téléphone, électricité, carte de crédit)** ? » VPN : 96.3% => Si réponse positive, aller plus loin dans l'anamnèse sociale BMJ Open. 2012;2(1):e000692

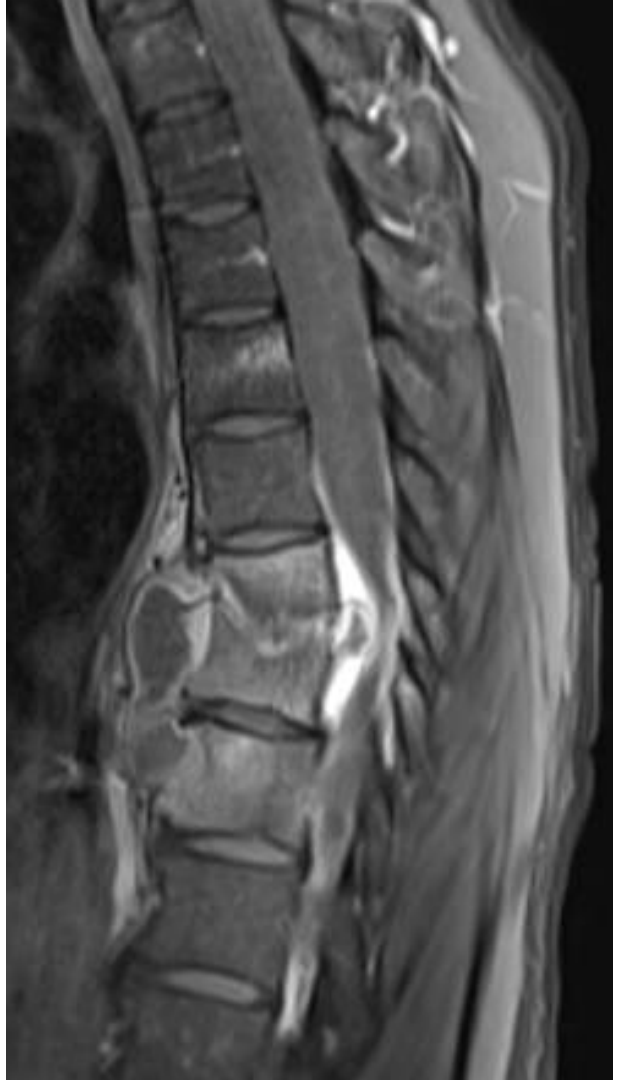
Vignette (suite)

- Arrêté en fin juin 2016. le 24.06: entrée infirmière.
- Entrée médicale en prison le 04.07: Dorsalgies à prédominance nocturne. Cyphose non harmonieuse/cassure=> antalgie et RX.
- Pas de symptôme pulmonaire.
- RX le 14.07
- Complété par IRM le 28.07




gauche





Vignette (fin)

- Hospitalisé aux HUG début aout.
- Ponction + quadrithérapie.
- Corset
- Sevrelong

Puis relaxé le 5.10. et «réadmission Dublin» en Espagne. Essai de planifier au mieux le contact avec un centre TB en sur place pour le suivi

Conclusion : accès aux soins?

- Rôle central des soignants!

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Merci !

Chirurgie thoracique, ce qu'elle apporte aujourd'hui pour la tuberculose

Dr Jean Y Perentes MD-PhD, PD-MER
Médecin Adjoint
Service de Chirurgie Thoracique
CHUV, Lausanne

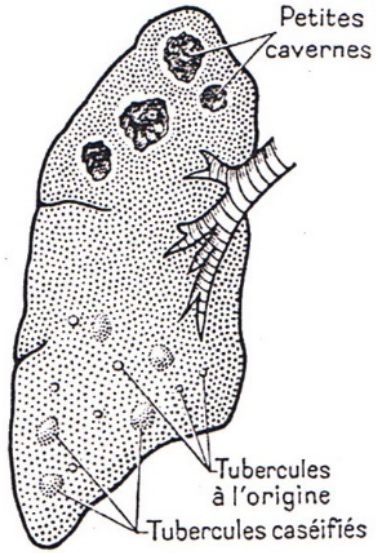
Sommaire

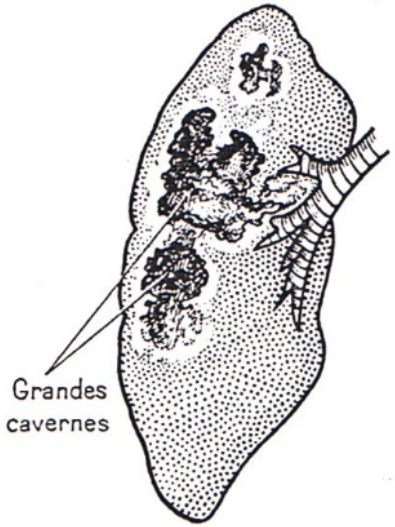
- Tuberculose (ère pré-antibiotiques): concepts chirurgicaux
- Evolution de la situation épidémiologique
- Quelles indications de prise en charge chirurgicale en 2021?
- Conclusion

Concepts historiques

Ere pré-antibiotique

Primo-infection (BK) → Latence (infection contenue par immunité) → Réactivation et progression





Tubercule: BK viable contenu par système immunitaire

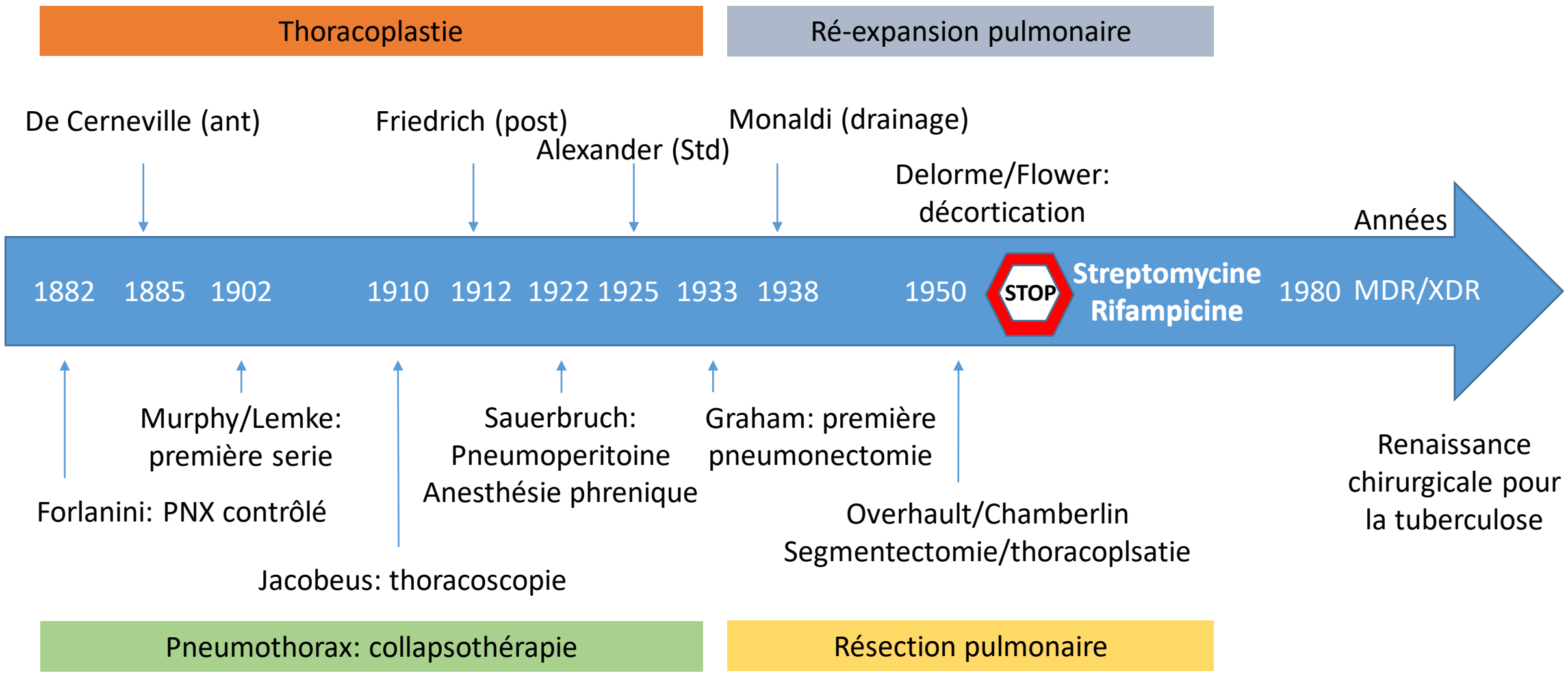
Baisse immunité→progression

Nécrose caséeuse→bronche/plèvre/vx

Destruction du parenchyme→cavernes

BK est un aérobe exclusif: développement de traitements pour priver le BK d'oxygène

Concepts historiques: chirurgie thoracique



La collapsothérapie

- Affaisser le poumon → Collapsus cavernes

Insufflation d'air ou d'azote

Répété une fois par semaine pour 4 ans

Bons résultats simplicité de l'approche

Mortalité de la tuberculose ttt par PNX: 20 à 44% à 5 ans

Complications: 10% des patients (adhérences)

Références: Srug LH et al, Dis Chest 1951; Forlanini CA et al Gaz Osp Clin Milan 1882, Floranini CA et al, Deutch Med Wochschr 1906

Dévelopement de la thoracoscopie

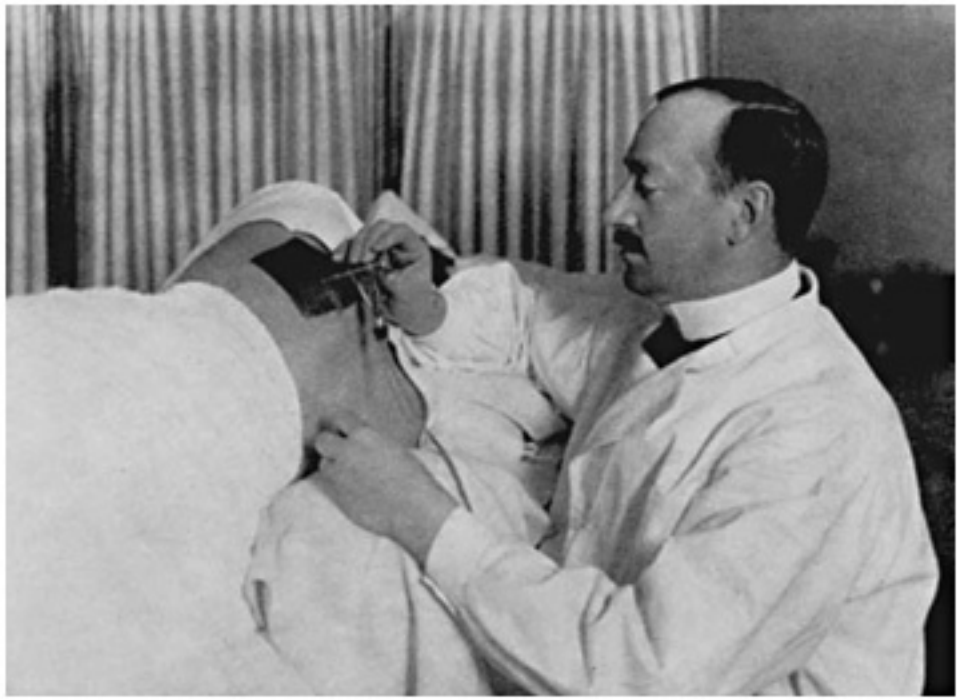
- 1910: thoracoscopie (Jacobaeus)→ but: sectionner brides pour favoriser l'affaissement pulmonaire

Aus dem westlichen Krankenhause der Allgemeinen Fürsorge-anstalt in Stockholm (Oberarzt: Dr. G. Wilkens).

Ueber die Möglichkeit die Zystoskopie bei Untersuchung seröser Höhlungen anzuwenden.

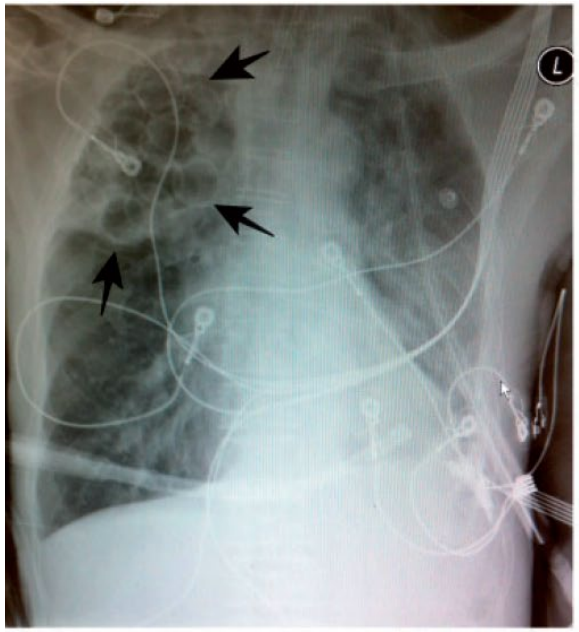
Vorläufige Mitteilung.

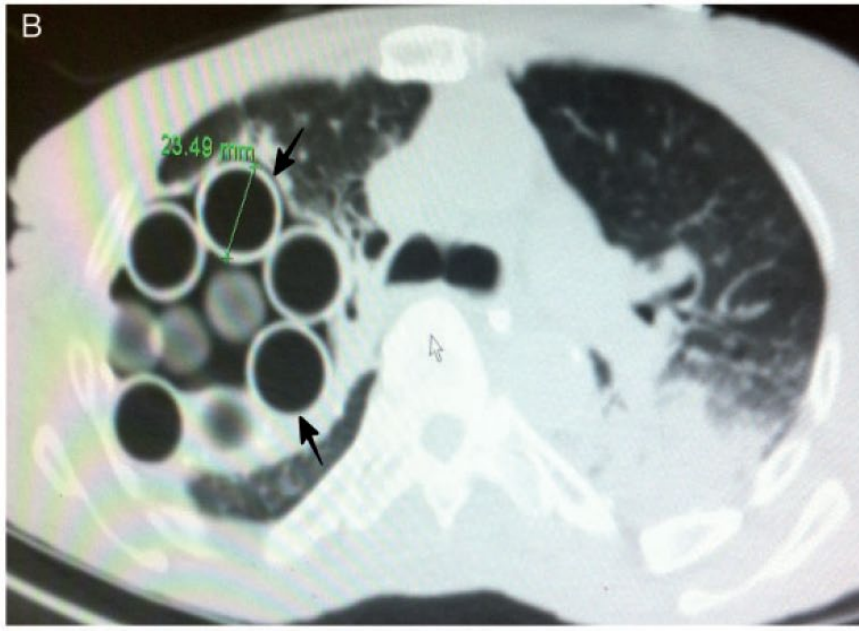
Von H. C. Jacobaeus, Privatdozent in Stockholm.



Références: Jacobeus HC, Munch Med Wchschr 1910

Autres approches de collapsothérapie



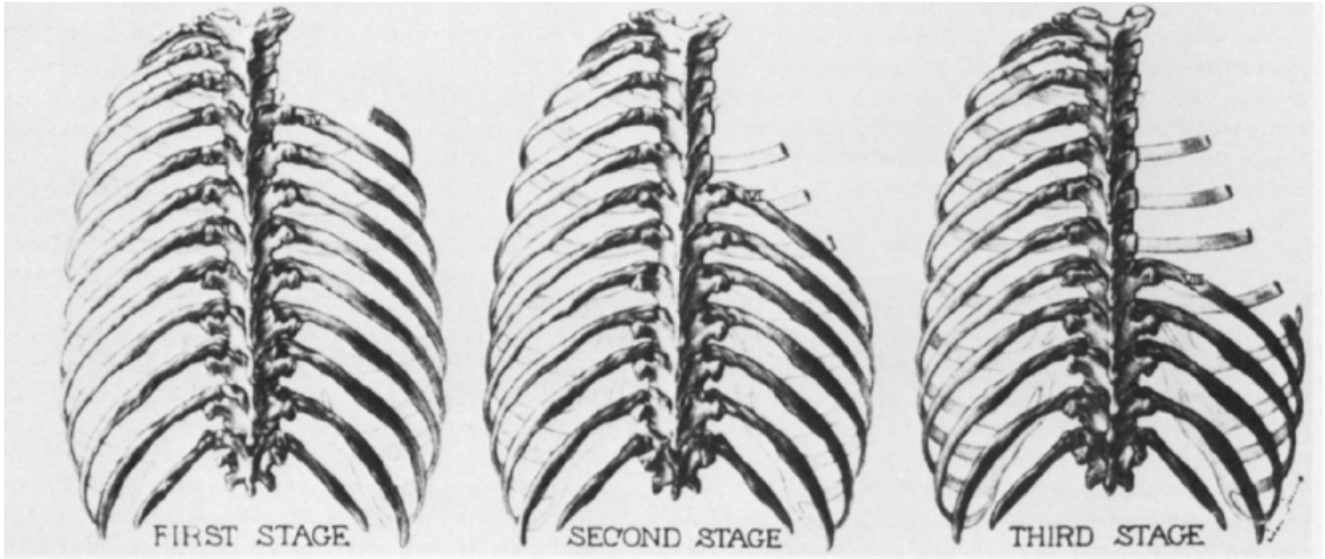


- Paralysie phrenique/pneumoperitoine
- Oléothorax/paraffin
- Boules de lucith
- **Transfert muscles en intrathoracique**

Références: Herbsman H, J Hist Med Allied Sci 1958

Développement de la thoracoplastie

- Concept: affaisser la paroi sur le poumon malade



Affaissement de la paroi par étapes

Mobilisation active des patients + bonne nutrition

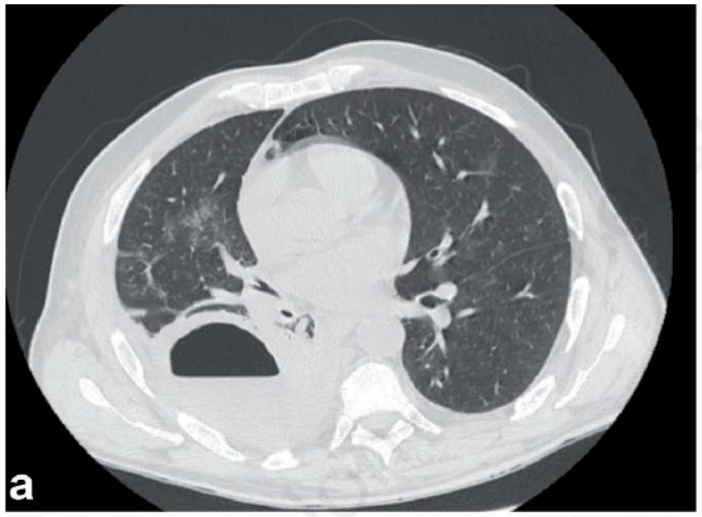
Première côte/Résection paravertebrale

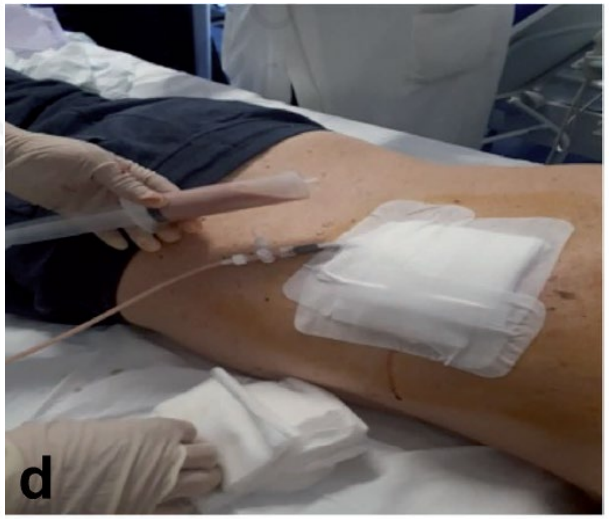
Epargne ant côtes sur niveaux inférieurs

Stabilisation de la maladie tuberculeuse chez 70% des malades
Approche sûre mais mutilante

Références: Shede M et al, Congen Innere Med 1890, Friedrich PL et al, Surg Gyn Obset 1908

Résection pulmonaire/Expansion



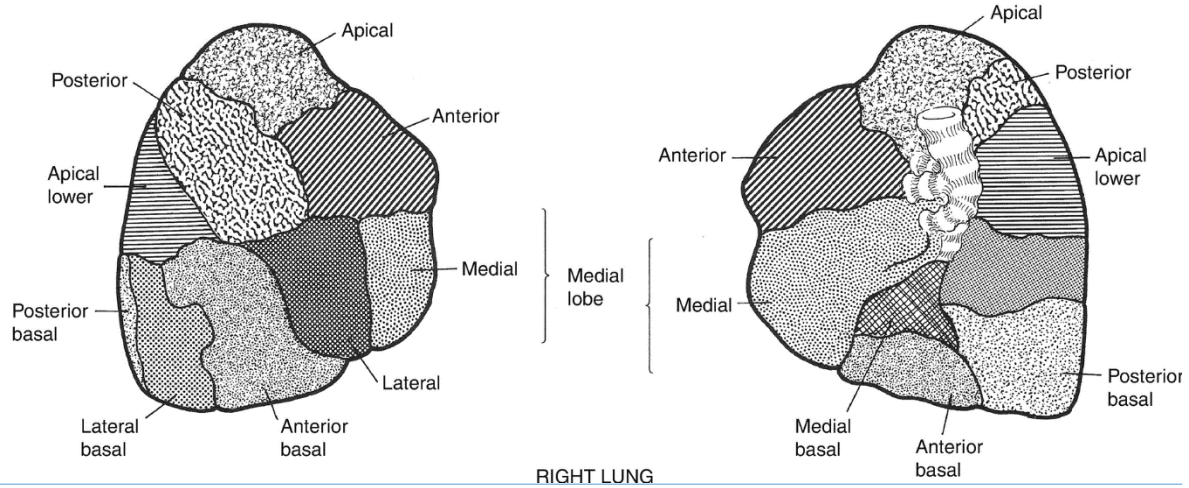


Drainage percutané → évacuation abcès

Résection pulmonaire: lobe ou segment

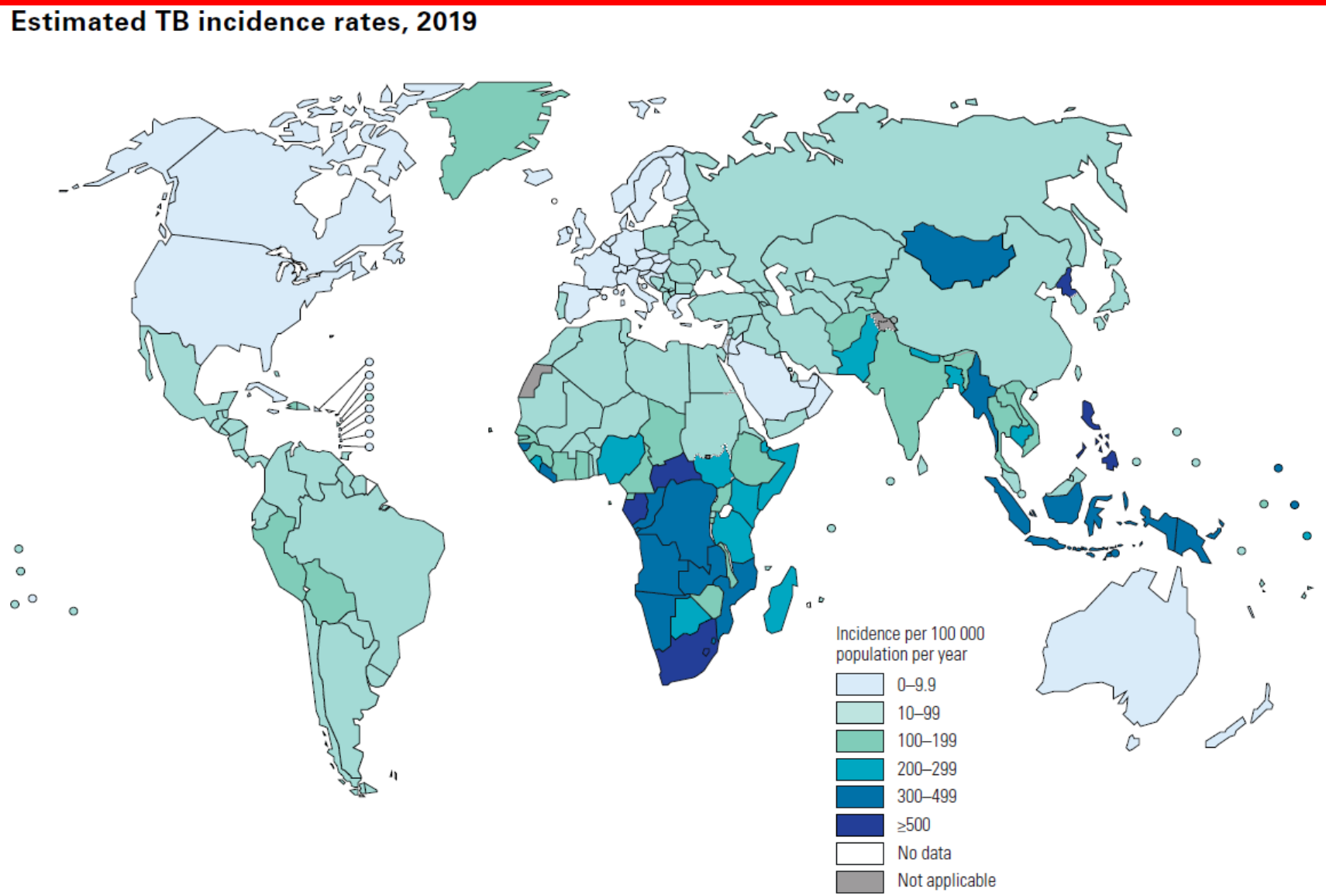
→ Développement anesthésie thoracique + gestion hile

Remplace la collapsotherapie des années 1950 mais changement de la donne avec les antibiotiques

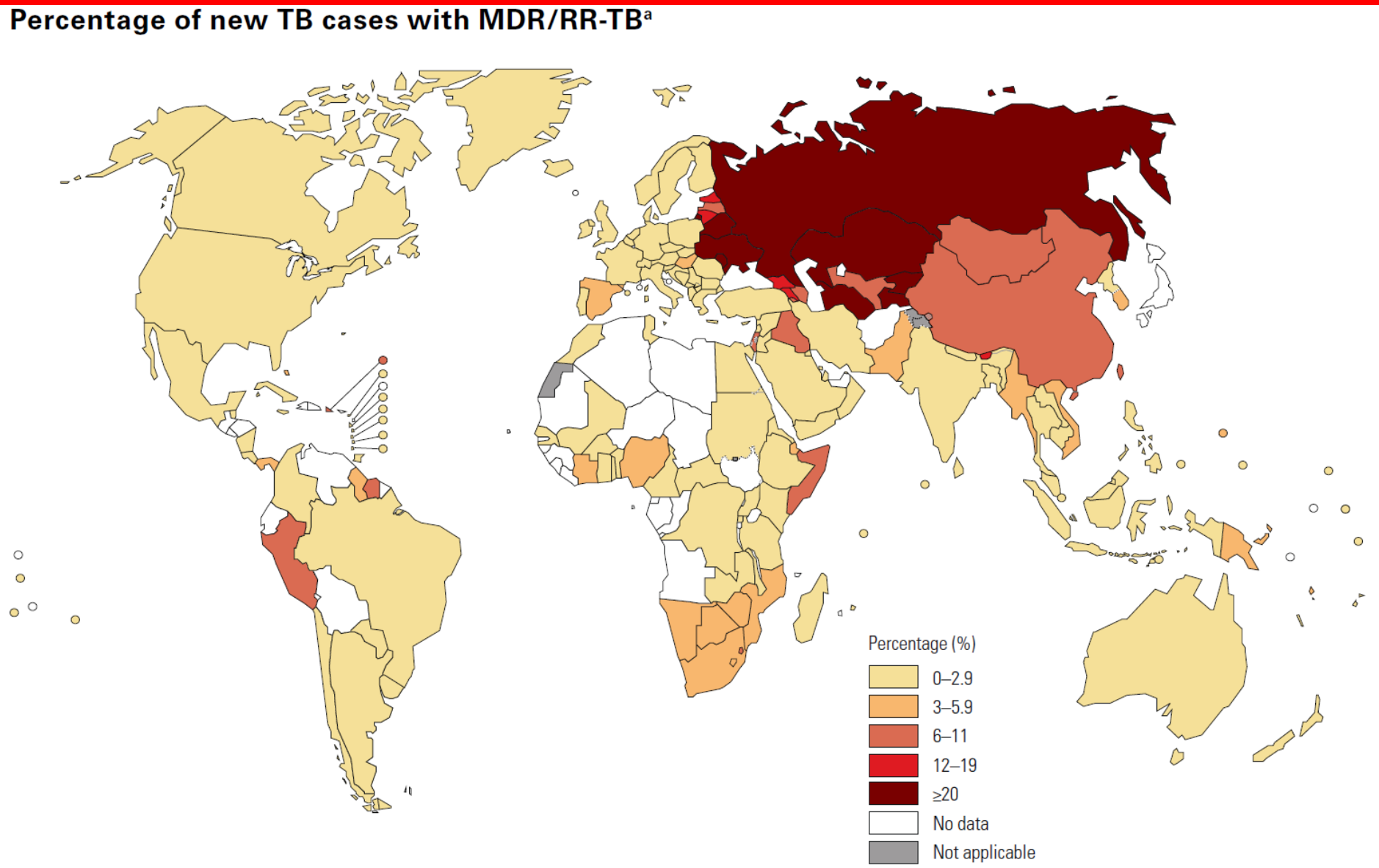


Références: Mondaldi VA: Rev Tuberc 1941, Matarese A, Arch for Chest Disease 2020, Graham 1933, Freelander 1935

Epidemiologie Tuberculose (2020)



Epidemiologie: MDR tuberculose (2020)



Chirurgie pour la tuberculose en 2021

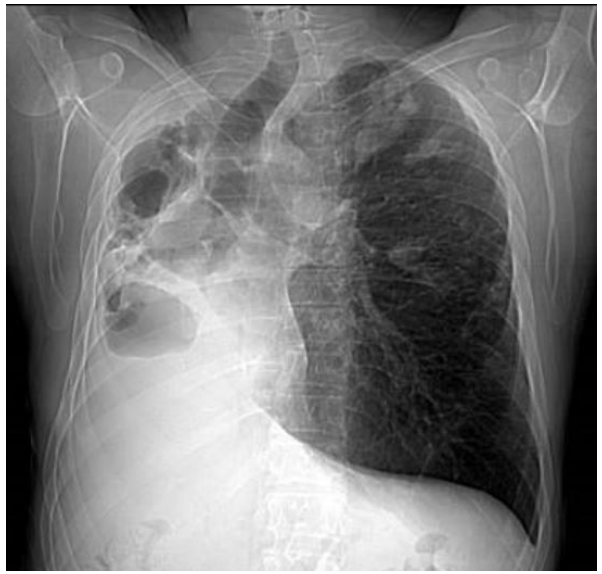
- Tuberculose → prise en charge médicale avant tout!

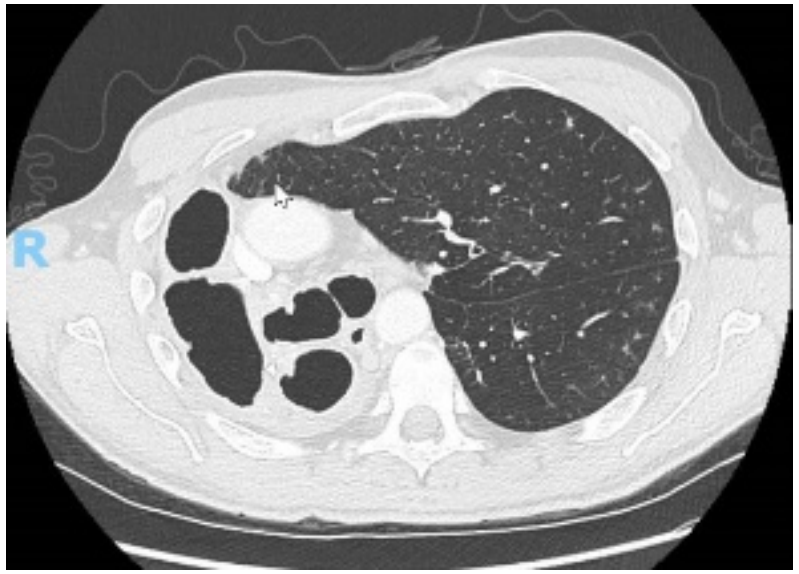
- MAIS:
  - Diagnostique (adénopathies/cultures/plèvre)
  - Contrôle de foyers responsables de résistance/récidive
  - Gestion des complications pleurales/bronchiques/vasculaires

Références: Subotic D et al, JTD 2016

Contrôle de foyers responsables de résistance/récidive

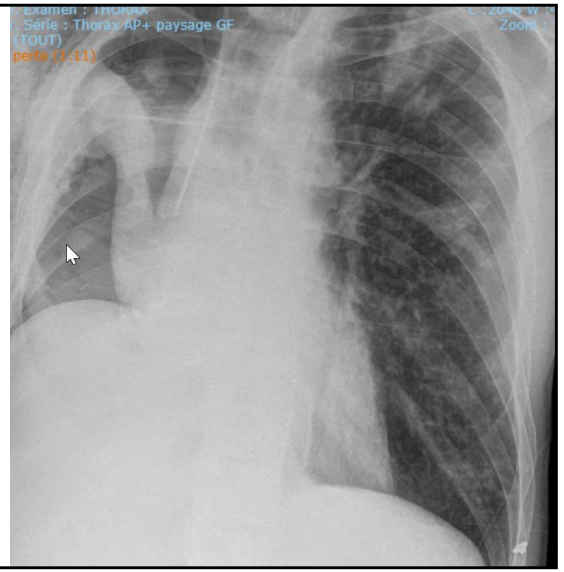
Contrôle d’un réservoir tuberculeux





Patient 49 ans ATCD TBC ttt
Arrivée en Suisse: tuberculose bacillaire XDR
TTT antibiotique de 2 mois initié (Linézolide, Clofazamine, Delamanide, Bédaquiline, Amikacine et Cyclosérine)

Pneumonectomie droite, transposition d’un grand dorsal dans la cavité thoracique sur le moignon bronchique.



Chirurgie dans la tuberculose XDR/MDR

- Pas d'études prospectives randomisées pour évaluer le rôle de la chirurgie
- Dans contexte MDR/XDR→ rôle pour la chirurgie conjointement avec le traitement médical chez de bons candidats

Quelles évidences?

Chirurgie: Elimination d'un réservoir MDR/XDR

Table 2 Surgical series of mutlidrug-resistant (MDR-) and extensively drug-resistant (XDR-) tuberculosis patients surgically treated and described in observational studies

First author	Year	Sample size/M/XDR	Culture positive, %	Sputum conversion rate, %	Morbidity/mortality, %	Success rate, %
Pomerantz *et al.* (51)	2001	172/172/NR	50	98	12/3.3	90
Park *et al.* (100)	2002	49/49/NR	63	94	16/0	90
Kim *et al.* (101)	2007	79/61/18	98	72	23/1.2	72
Naidoo *et al.* (98)	2007	27/27/NR	41	93	26/0	93
Orki *et al.* (102)	2009	55/NR	115	95	29/1.8	95
Park *et al.* (17)	2009	19/17/2	53	95	NR/0	79
Dravniece *et al.* (103)	2009	17/0/17	94	47	18/0	47
Kang *et al.* (59)	2010	72/46/26	81	78	15/1.4	90

NR, not reported.

Références: Subotic D et al, JTD 2016

Chirurgie: Elimination d'un réservoir MDR/XDR

Table 3 Surgical series of MDR- XDR-TB enrolled in cohort studies, comparing medical therapy + surgery *vs.* medical therapy alone

First author	Year	Sample size/% of surgery	Resistence pattern	Overall success rate, %	Surgery superior to medical therapy
Chan *et al.* (104)	2004	205/63	MDR	73	Yes
Torun *et al.*(105)	2007	252/26	MDR	77	Yes
Kim *et al.* (101)	2007	211/30	MDR, XDR	63	No
Keshavjee *et al.* (106)	2008	608/9	MDR, XDR	66	Yes
Kwon *et al.* (107)	2008	155/23	MDR, XDR	66	Yes

MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

→La chirurgie peut être un bon complément à la prise en charge médicale du patient tuberculeux

Références: Subotic D et al, JTD 2016

Chirurgie: pour quels patients

Table 1
Definitions of each component of the LTB-S classification system for surgery of MDR/XDR-TB.

L	Lesion(s): 3 types defined by radiology imaging	
	L1	Stable, localized, unilateral/bilateral lesions.
	L2	Diffused, progressive unilateral lesion(s), with or without stable lesions on the other lobe.
	L3	Diffuse
T	Treatment hist	
	T1	A stan
	T2	More t
	T3	A stan
B	Body: 3 classe	
	tuberculosis in	
	B1 Well gener	
	B2 Permissible	
	which can be	
	B3 Poor gener	
S	Surgery: 2 typ	
	S0	Radical surgery: no tuberculosis foci in other locations are left after resection of localized and stable primary lesions.
	S1	Palliative operation: lesions are present at multiple sites. Stable lesions remain after resection.

Chi-square test of whether individual type affects postoperative efficacy.

Type	Total number	Cure/success	Failure/death	χ^2 value	*Df*	*p*-value
Total	134[a]	121(90.3%)	13(9.7%)	30.074	2	< 0.001
Type I	66	63(95.5%)	3(4.5%)			
Type II	57	55(96.5%)	2(3.5%)			
Type III	11	3(27.3%)	8(72.7%)			

T3/L3/B3→ Facteurs prédictifs d'échec du traitement chirurgical.

Références: Wang L et al, Int J Infect Disease 2020

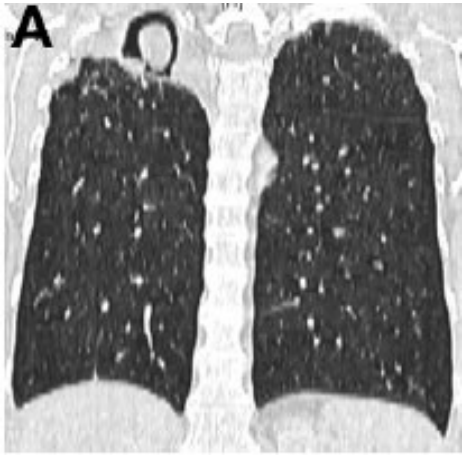
Chirurgie: concepts pour la résection

- Lésion localisée et persistante après traitement bien conduit
- MDR/XDR profile
- Patient opérable!
- Préservation d'un maximum de poumon (résection complète minimale)
- Antibiothérapie post chirurgie: 12 mois MDR, 24 mois XDR
- Attention aux espaces résiduels

Références: Subotic D et al, JTD 2016, Sihoe AD et al, Respirology 2009

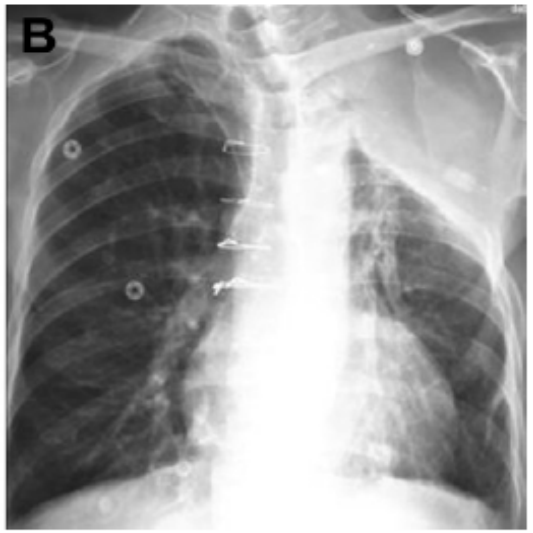
Chirurgie et espace résiduel

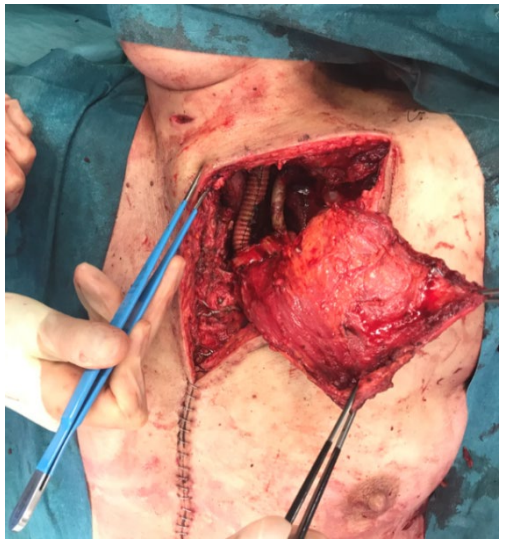
- Espace résiduel: réservoir MDR/XDR ou autre
- Résection pulmonaire + parenchyme pulmonaire pathologique



Contrôle espace

- Transposition grand dorsal
- Anesthésie nerf phrénique
- Mobilisation diaphragme
- Thoracomyoplastie





Chirurgie et espace résiduel

- Peu d'études dans le contexte TBC
- Thoracoplastie limitée→ bonne option chez patients multi-morbides

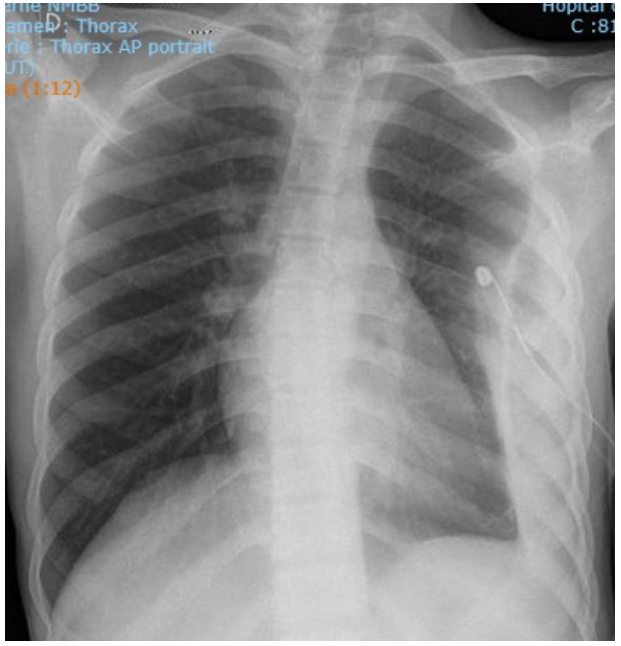
Sex	Age (y)	Cause of Lobectomy	Pleural Microbiology	Time Interval[a] (days)	Resected Ribs (number)	LOS (days)
M	64	Abscess LUL	*Aspergillus*	360	I–V	15
M	46	Abscess LUL	Polymicrobial	30	II–VI	25
M	61	NSCLC LUL	Negative	60	II–IV	11
M	63	NSCLC RUL	Negative	28	II–V	24
M	69	LVRS RUL	*Streptococcus*	30	I–IV	20
M	68	NSCLC LUL	*Staphylococcus* MRSA	90	I–IV	18
F	76	NSCLC LUL	*Streptococcus*	40	I–IV	35
M	51	Bronchiectasis LUL	*Staphylococcus* MRSA	30	I–IV	23
M	40	Sarcoidosis LUL	*Aspergillus*	40	I–VII	14
M	69	NSCLC RUL	*Enterococcus*	30	I–V	45
M	77	Bronchiectasis RUL	*Aspergillus*	28	I–VI	60
F	53	Bronchiectasis LUL	*Aspergillus*	1440	I–VI	14
F	69	Abscess LUL	*Aspergillus*	1445	I–VI	50
M	74	NSCLC RUL	*Staphylococcus* MRSA 46		I–V	90
M	61	NSCLC RUL	*Pseudomonas*	1080	II–VI	18
F	67	NSCLC RUL+ML	*Aspergillus*	1448	II–VI	25
F	59	NSCLC RUL+ML	*Aspergillus*	730	II–IV	21

17 patients
Espace post résection
Contrôle de l'espace pleural: 100%
Morbidité: 40%

Références: Fournier et al, 2015 Ann thor surg 2012

Gestion des complications pleurales/bronchiques

Chirurgie pour corriger des problèmes restrictifs

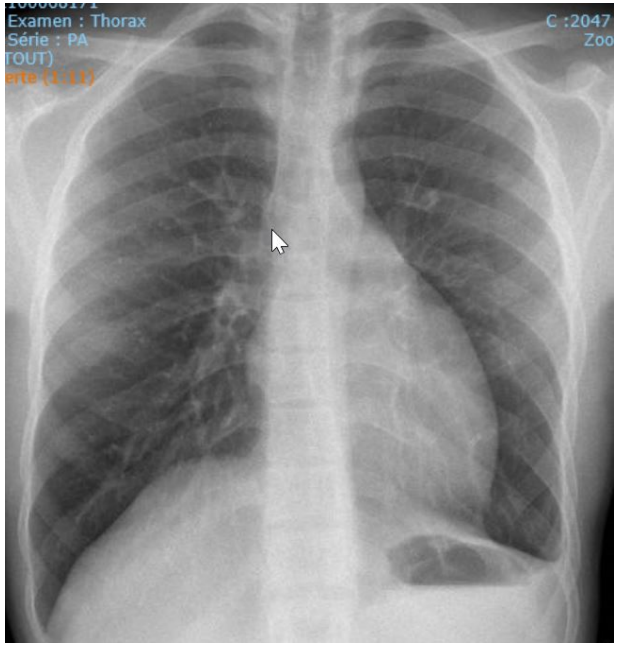


14 ans
Tuberculose pleurale sans atteinte parenchymateuse
TTT (Isoniazid, Rifampicine, Pirazinamide)
9 mois

Développe une dyspnée
Cultures plèvre négatives

→Décortication pleurale thoracoscopie

- Reprise sport
- Bonne amélioration symptomatique



Chirurgie pour corriger des problèmes restrictifs

Outcomes of Video-Assisted Thoracic Surgical Decortication in 274 Patients with Tuberculous Empyema

Baofu Chen, MS, Jian Zhang, MS, Zhongrui Ye, BS, Minhua Ye, MS, Dehua Ma, MS, Chunguo Wang, BS, and Chengchu Zhu, BS

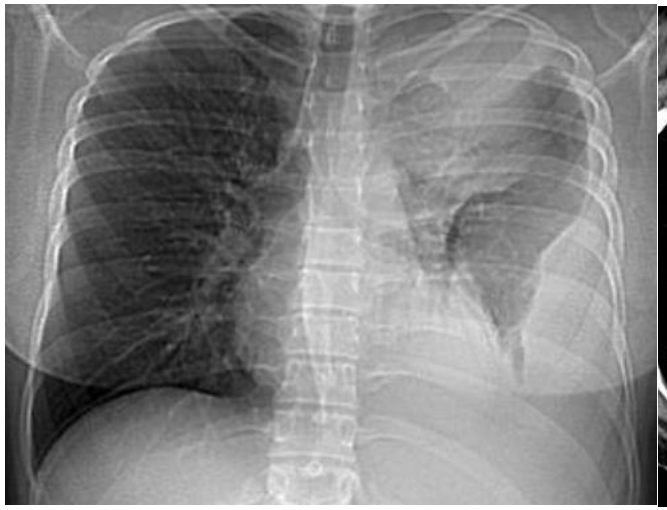
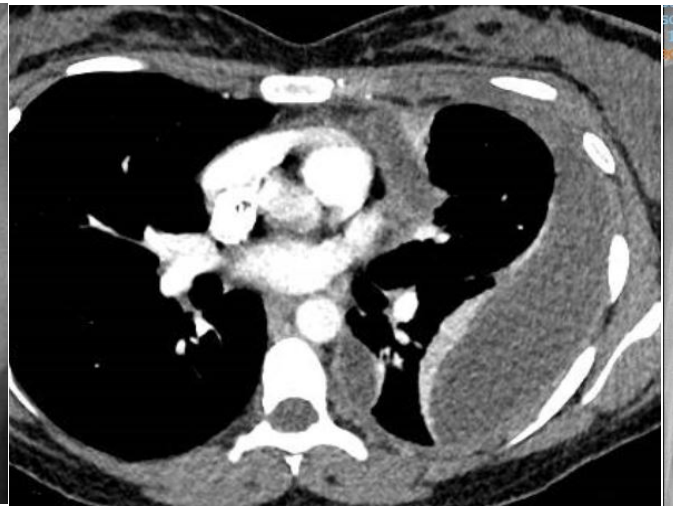
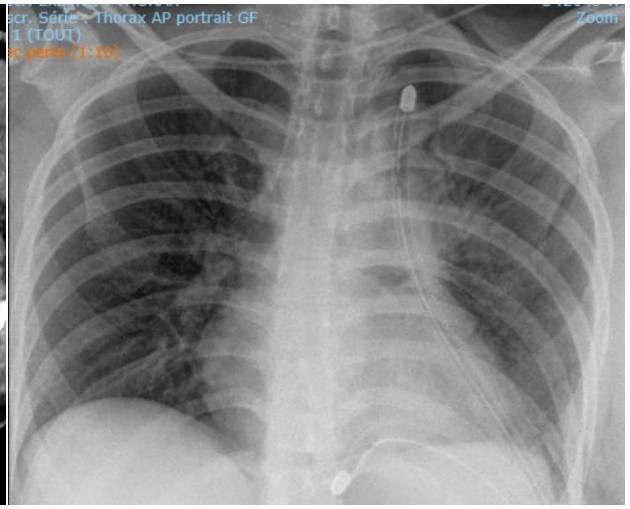
Table 3 Patient data at one year follow-up

		Number of cases	Percentage
Recovery		236	90.1
Complication		26	9.9
Incomplete lung reexpansion		11	4.2
Persistent air leak (>5 d)		6	2.3
Relapse	Early recurrence	3	1.1
	Delay recurrence	6	2.3

Opérations possible en minimal invasif
Bonne récupération des patients et bon pronostic

Références: Chen B et al, Ann Thorac Cardiovasc Surg 2015

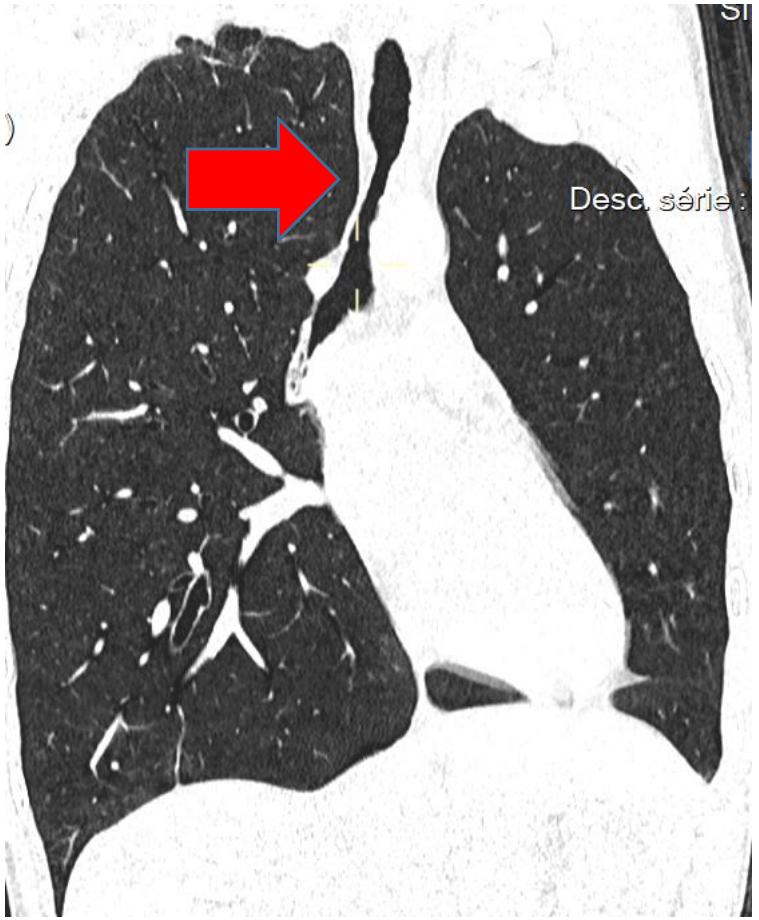
Attention aux situations banales…

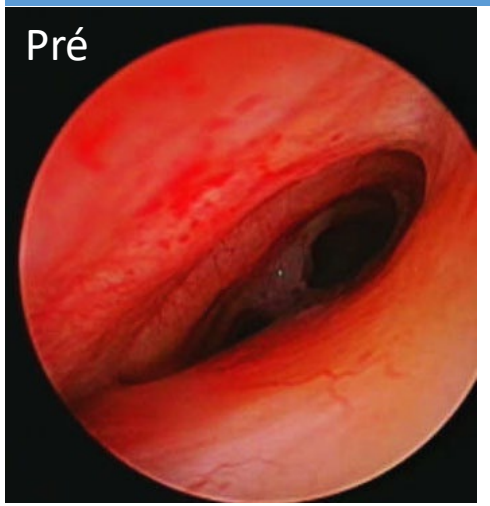
16 ans
Pas d'antécédents
BEG, toux, fièvre
Ponction plèvre: (exsudat)
Fast track: décortication pleurale

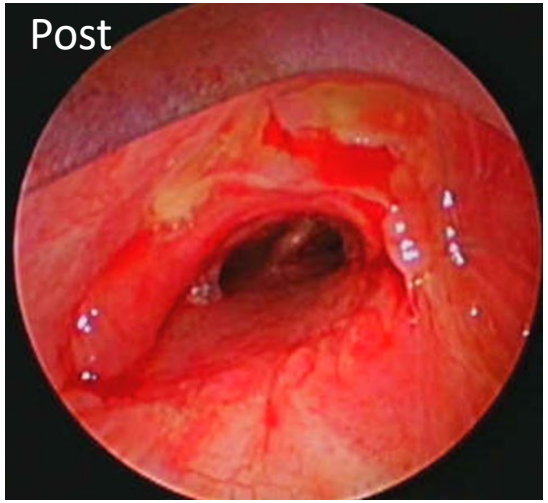
→ Empyème tuberculeux!!!

Stenoses trachéo-bronchiques



30 ans
Tuberculose traitée en 2010
Dyspnée d'éffort
Stenose de 4cm au niveau des voies aériennes proximales





Résection 5 anneaux trachéaux (cervico/sterno)
Amélioration de la symptomatologie

Stenoses trachéo-bronchiques

- Selon les régions: 18% de tuberculose concernant les voies aérienne proximales (Asie) → Risque de stricture/stenoses
- Approches chirurgicales ou endoscopiques: dilatations/stents selon expertise des centres

Table 1—*Clinical Features, Interventions, and Outcomes in Tuberculous Tracheobronchial Stenosis

Patient/Sex/Age, yr	Symptoms	Sites of Lesions	Intervention	Outcome
1/F/59	Dyspnea	Trachea, carina, LMB	Balloon, Dumon Y, EBUS	Improved
2/F/29	Dyspnea	LMB	Balloon, Dumon, EBUS	Improved
3/M/59	Dyspnea	LMB	Balloon, Dumon, EBUS	Improved
4/M/65	Dyspnea	Trachea	Balloon, Dumon Y, EBUS	Improved
5/F/48	Dyspnea	Trachea, carina, RMB	Balloon, APC, cryotherapy, Ultraflex, Dumon Y	Improved
6/F/56	Dyspnea	Trachea	Balloon, APC, cryotherapy, Ultraflex, Dumon	Improved
7/F/77	Dyspnea	RMB	Balloon	Improved
8/F/18	Dyspnea	LMB	Balloon	Improved
9/F/38	Dyspnea	LMB	Balloon	Unchanged
10/F/53	Dyspnea	LMB	Balloon	Unchanged
11/F/31	Cough	LMB	Balloon	Unchanged
12/F/19	Dyspnea	LMB	Left pneumonectomy	Improved

*RMB = right main bronchus; LMB = left main bronchus; F = female; M = male.

Références: Iwamoto et al, CHEST 2004

Conclusion

- L’évolution de l’épidemiologie de la tuberculose redonne une place à la chirurgie
- Importance de la prise en charge multidisciplinaire de ces patients
- Avancées chirurgicales→ plus de malades peuvent qualifier pour des interventions
- Etat général, état nutritionnel, état cardiovasculaire et pulmonaire
- Bons résultats si bonne sélection

Merci pour votre attention

29e Symposium Tuberculose virtuel Formation continue en ligne du Centre de compétence tuberculose pour médecins, personnel des Ligues pulmonaires et autres intéressé(e)s

Tuberculose pulmonaire et COVID-19

Jesica Mazza-Stalder

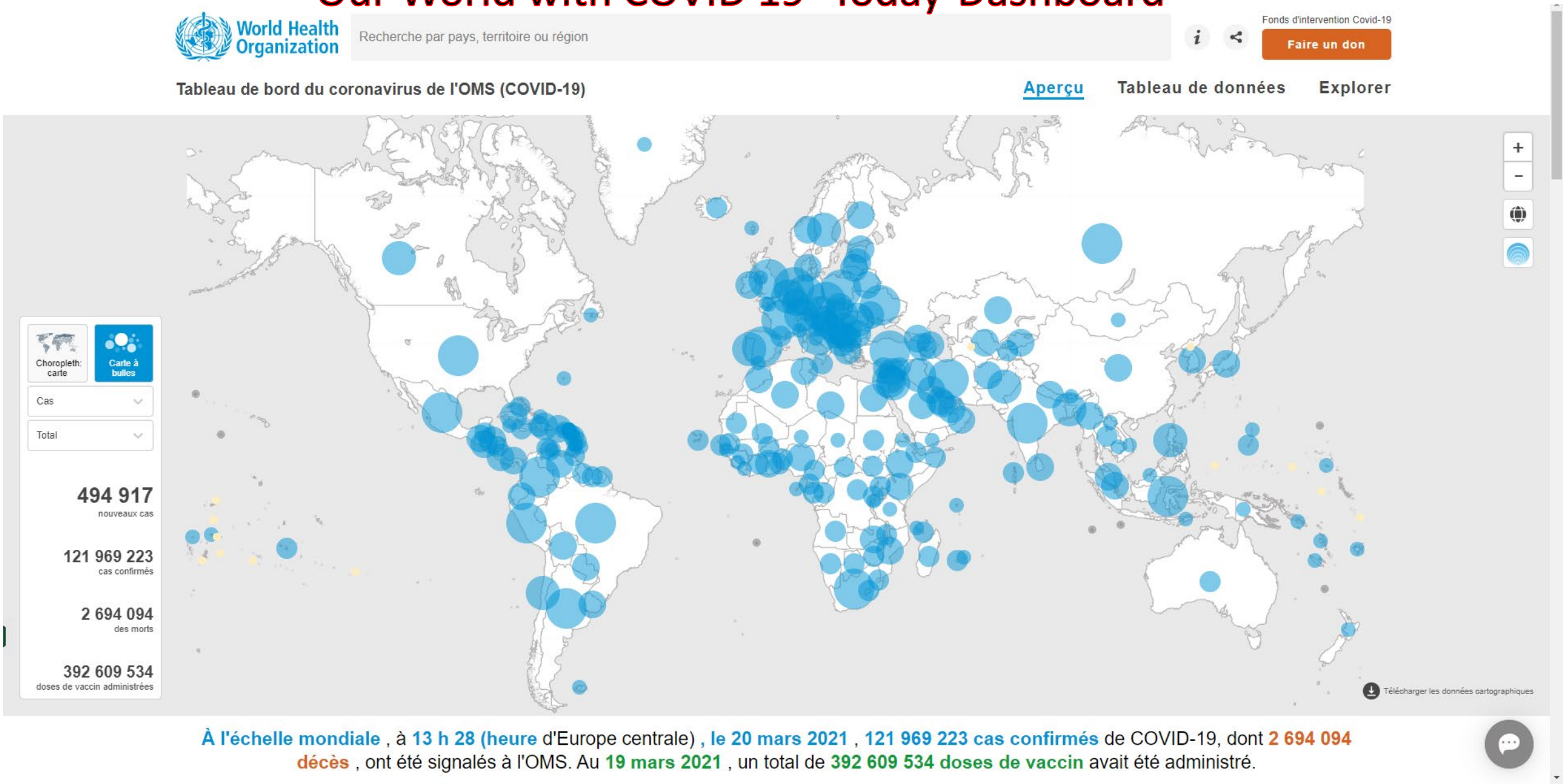
Service de Pneumologie

CHUV, Lausanne

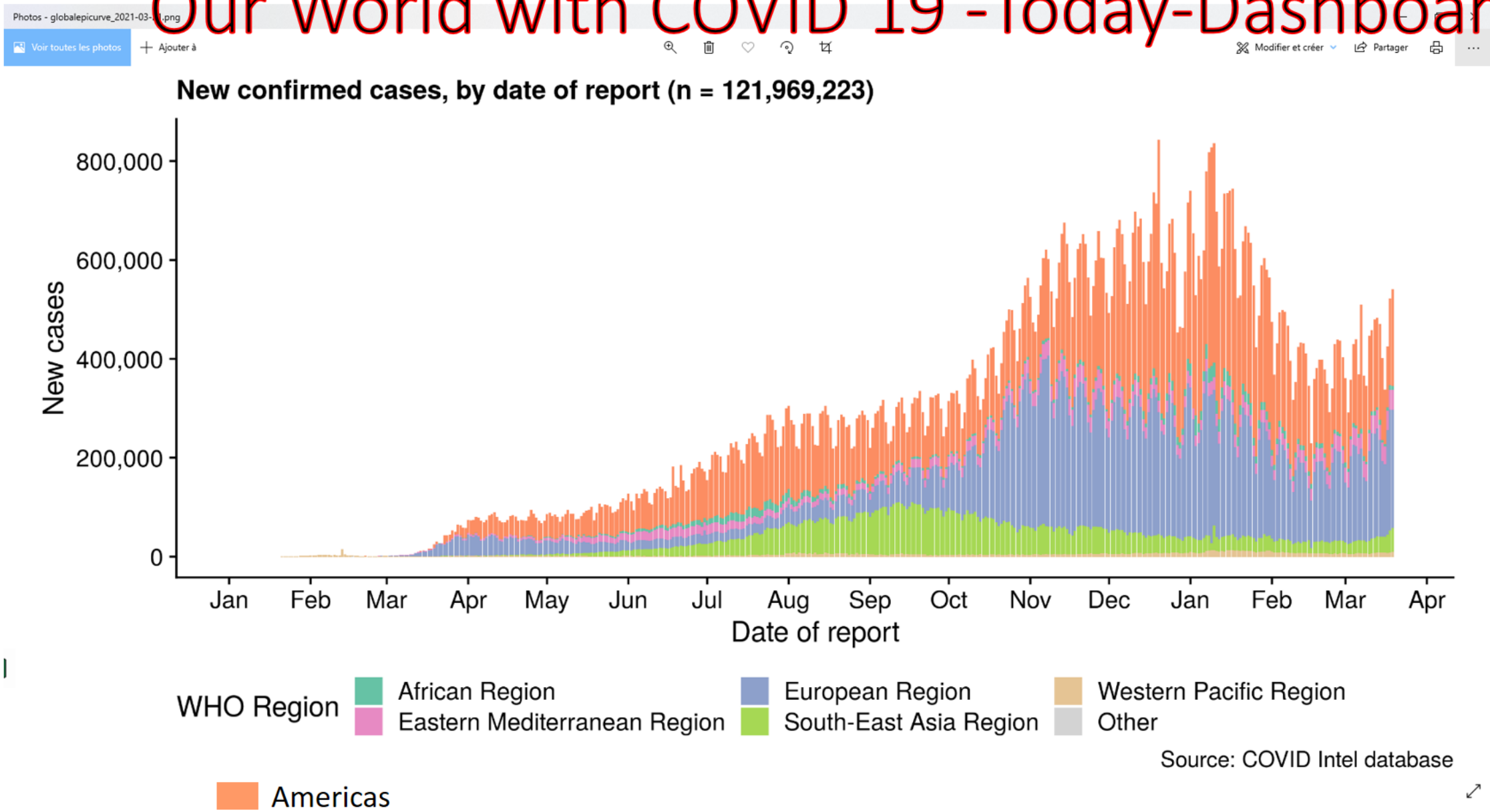
Jeudi 25 mars 2021

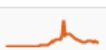
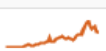
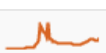

Efficacité de transmission sans précédents
Asymptomatiques et pré-symptomatiques transmets le virus
Réplication viral maximal et contagiosité après le 2 eme jour de Symptômes

Our World with COVID 19 -Today-Dashboard



Our World with COVID 19 -Today-Dashboard



	Country/Area/Territory	Case Trend	New Cases: past 7 days	New Cases per 1M Pop: past 7 days	7-day % Change (cases)	Total Cases	Death Trend	New Deaths: past 7 days	New Deaths per 1M Pop: past 7 days	7-day % Change (deaths)	Total Deaths
1	Brazil		503,103	2,367	4	11,780,820		14,610	69	23	287,499
2	United States of America		375,827	1,135	-29	29,376,388		7,416	22	-38	534,484
3	India		221,556	161	56	11,555,284		1,112	1	41	159,558
4	France		164,372	2,518	6	4,111,105		1,530	23	-18	91,162
5	Italy		156,611	2,590	3	3,332,418		2,677	44	17	104,241
6	Poland		147,340	3,893	20	2,036,700		2,091	55	-3	49,159
7	Turkey		120,703	1,431	29	2,971,633		508	6	12	29,864
8	Germany		87,328	1,042	32	2,645,783		1,264	15	-16	74,565
9	Ukraine		83,474	1,909	45	1,535,218		1,617	37	31	29,775
10	Czechia		67,298	6,284	-16	1,459,406		1,447	135	-5	24,530
11	Russian Federation		67,045	459	-2	4,447,570		2,964	20	0	94,659
12	Jordan		56,605	5,548	21	521,461		477	47	32	5,701
13	Iran (Islamic Republic of)		54,707	651	-6	1,786,265		580	7	4	61,649
14	Hungary		53,344	5,522	12	560,971		1,278	132	25	18,068
15	Peru		48,950	1,485	9	1,443,521		1,222	37	4	49,706
16	Netherlands		42,380	2,473	22	1,186,987		222	13	-15	16,244
17	Argentina		41,006	907	-7	2,226,753		808	18	2	54,386
18	Indonesia		39,998	146	-5	1,450,132		1,110	4	-8	39,339
19	Chile		38,568	2,018	13	918,053		636	33	22	22,087
20	The United Kingdom		37,398	551	-9	4,285,688		683	10	-37	126,026
21	Philippines		36,448	333	52	648,066		206	2	-24	12,900
22	Romania		36.390	1.892	24	886.752		660	34	15	22.020

COVID-19 sets back TB progress by a decade, shows WHO report

Reviewed by Emily Henderson, B.Sc. Mar 24 2021

Plus de 500 000 ont décédé l'année passé
1.4 million de personnes n'ont pas reçu les soins de TB à cause de la pandémie COVID
Données provisoires de 84 pays
4,9 Millions de cas de TB déclarées contre 6,9 mio en 2019
Diminution de 22% globalement
Indonésie (42%), Afrique du Sud (41%), Philippines (37%, Inde (25%)

> *"The effects of COVID-19 go far beyond the death and disease caused by the virus itself. The disruption to essential services for people with TB is just one tragic example of the ways the pandemic is disproportionately affecting some of the world's poorest people, who were already at higher risk for TB."*
>
> *Tedros Adhanom Ghebreyesus, Director-General, World Health Organization*

Challenges de la poursuite de prise en charge de TB pendant la pandémie COVID

- Diminution de diagnostique de nouveau cas (diminution de declarations)
- Complexité de la prise en charge ambulatoire avec difficulté d'arriver au sites de consultation
- Problèmes dans la comunuté avec peur d'aller vers les structures de soins par peur de se contaminer avec COVID
- Contac tracing et difficulté à accede aux personnes
- Monitoring et acquisition des medicaments ant Tb
- Testing de COVID et TB ensemble dans les mêmes structures
- Effects liées au confinement (lockdown)
- Diminution de l 'Equipment de protection pour le personnel
- Interruptions DOT avec plus de risqué de TB-MDR
- Effects de la pandémie COVID-19 sur le programme de immunization
- Consequences économiques de la pandémie

Consequences sociales du COVID et son impact dans la prise en charge de la TB

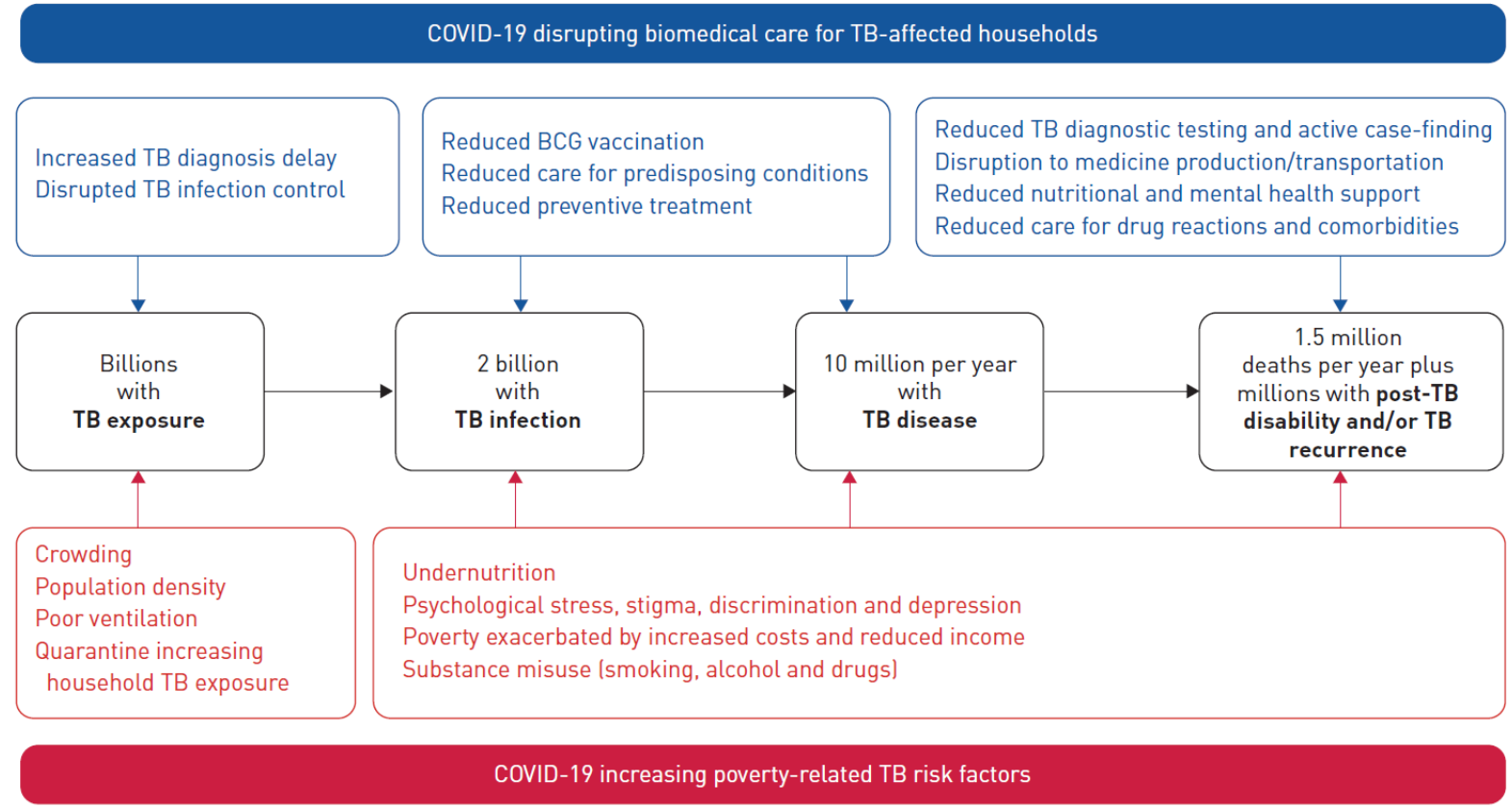
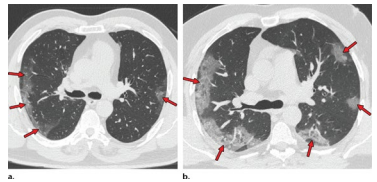
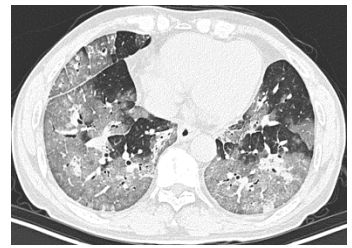


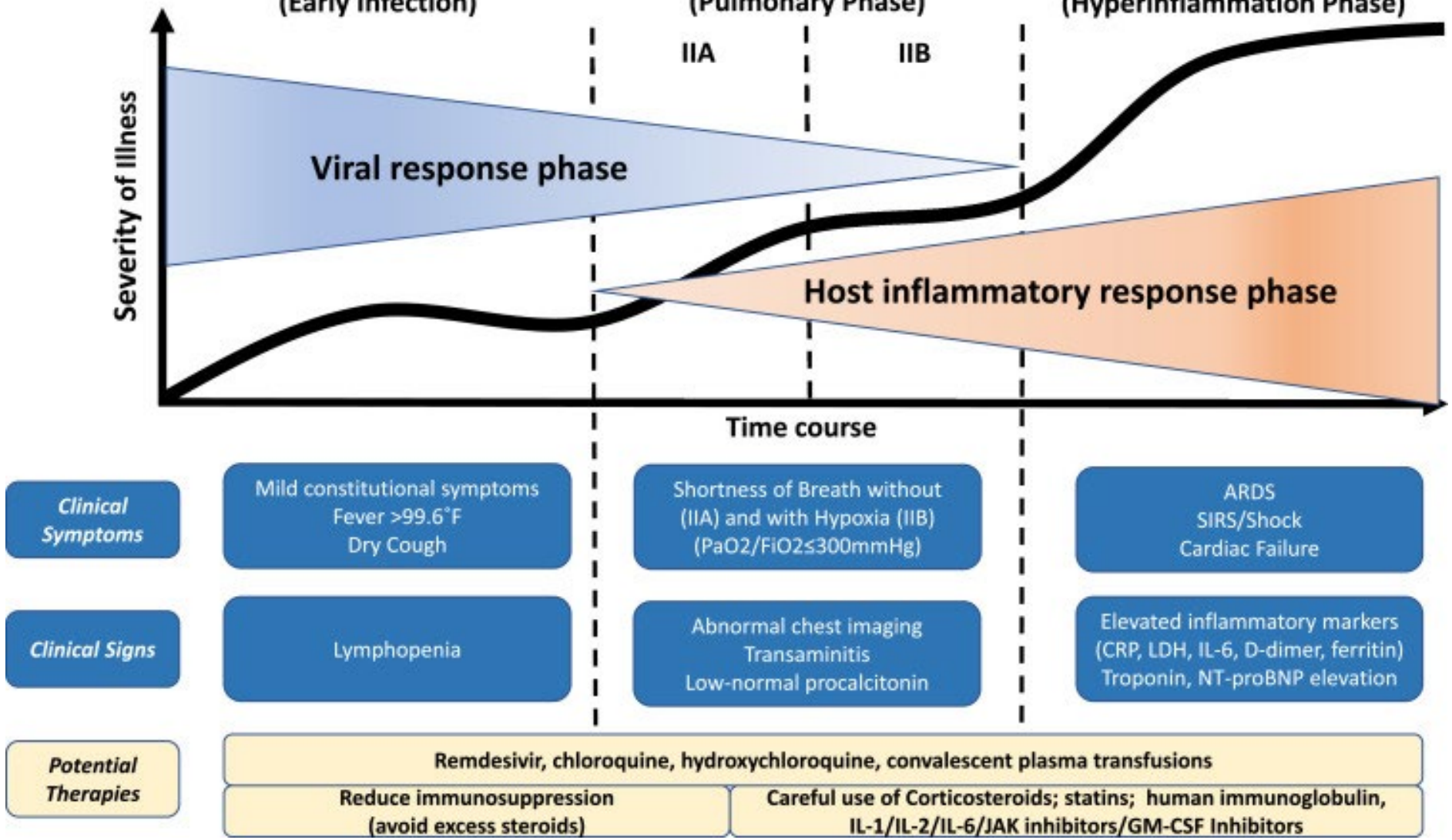
FIGURE 1 Mechanisms by which the COVID-19 pandemic is expected to worsen the tuberculosis (TB) pandemic.

Saunders, ERJ 2020

SARS-CoV2







Siddiqui et al JHLT may 2020

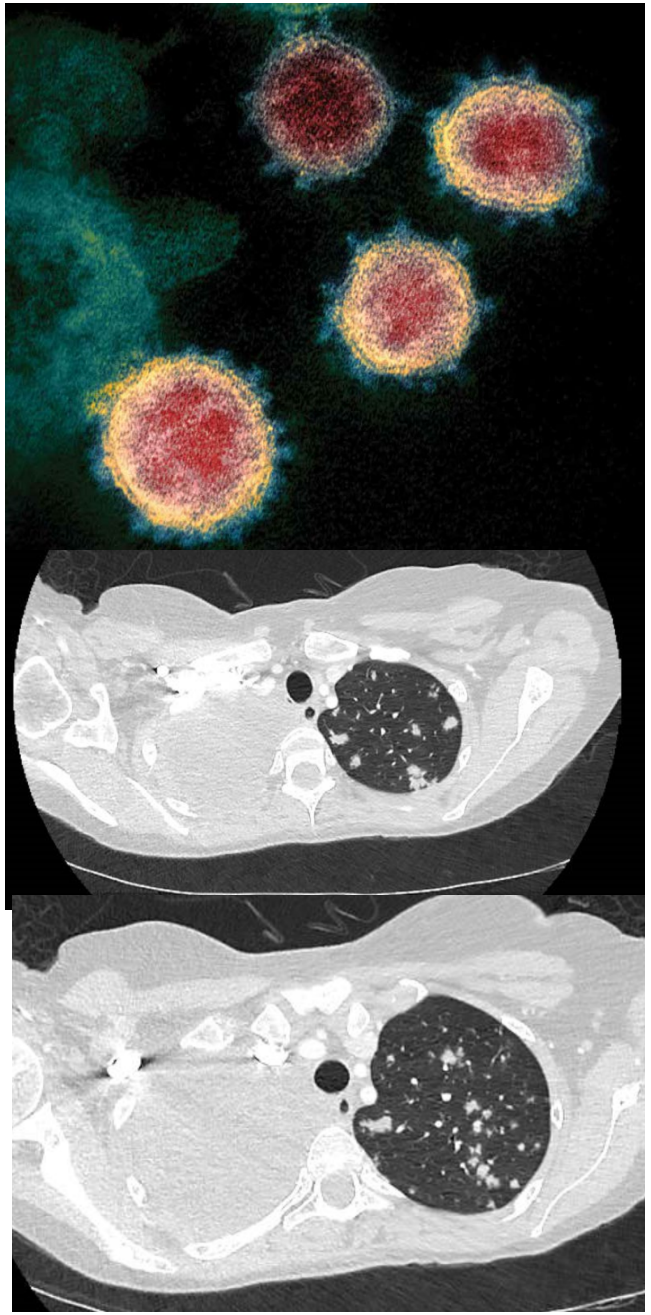
43 Ans

Patiente d’origine Moldave
Toux fièvre et dyspnée
Frottis nasopharingienne SARS-**COV-2 + 02.02.21**

Consulte son médecin traitant par téléphone

Est mise sous Azythromicine, pas d’imagerie à ce moment là.

Perte de contacte avec son médecin traitant

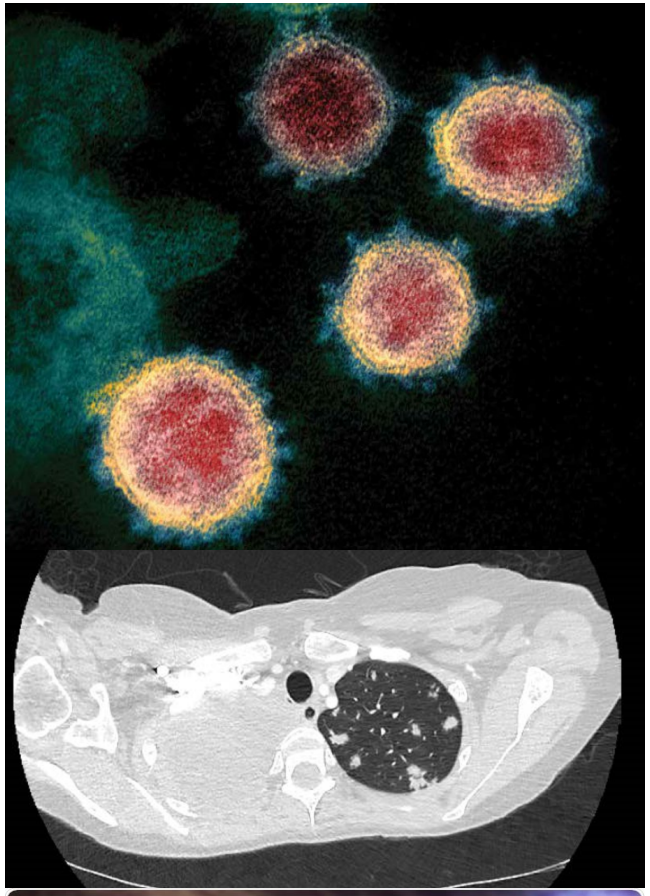


Persistance de état fébrile à 38,5 fluctuant
1 mois et demie.

Aggravation de la dyspnée plus tard consulte aux urgence le 15.03.21

43 Ans
Origine Moldave
Test IGRA au préalable inconnu

Connu pour une maladie de Crohn Sous anti-TNF depuis le mois de novembre

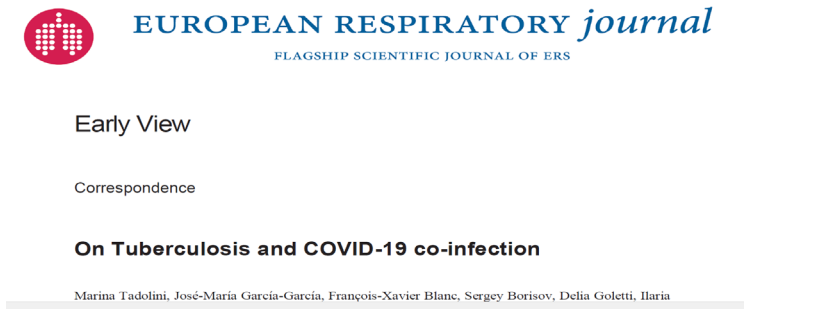


Epanchement Pleural Lymphocytaire à droite 90%
drainage de plus de 3 lt et lésions pulmonaires nodulaires multiples

Expectorations
Genexpert Positive
MTBC-Rif sensible

Un tt de Rimstar est initié

Interaction TB et covid-19



- La première étude 49 patients ayant de cas de TB active ou séquelles et COVID dans 18 pays 5 continents
- Taux de mortalité dans l'ensemble de la cohorte faible (10%)
- Plus de la moitié de cas été des jeunes (âge moyen 33 ans)
- Deuxième cohorte mortalité similaire 11% (plus de migrants)
- La plus part de décès surviennent chez de personnes âgées de >70 ans dans cette deuxième cohorte

Tadolini et al ERJ 2020
Mota et al Pulmonology 2020

COVID et risque de Décès TB

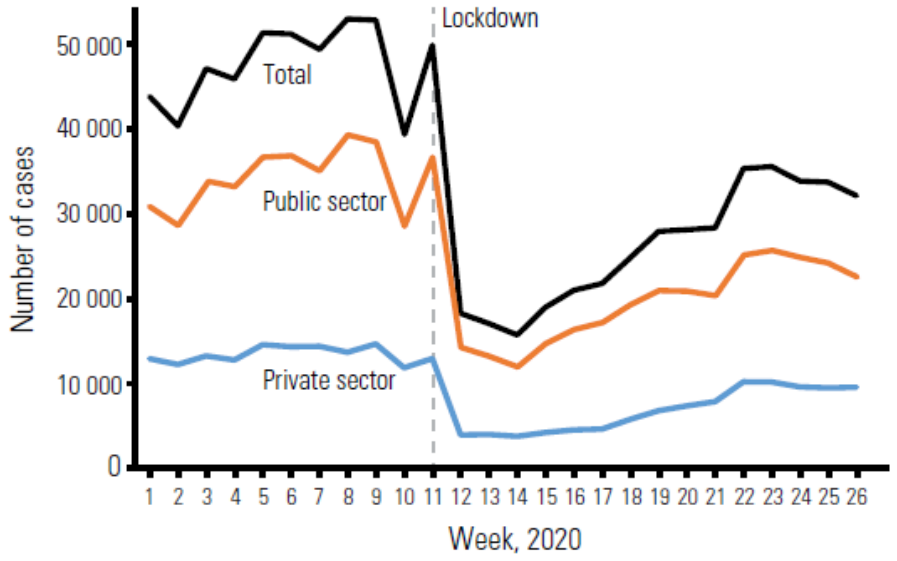
- Plusieurs études de modélisation
- Inde: Prédiction d'un excès de cas de TB non diagnostiqué de /et/ou non traité de 232 665 cas de TB et 11 663 cas de TB-MDR ainsi que de 71290 cas de décès
- Accroissement globale de mortalité pour TB dans de pays à revenu faible ou moyen par un retard du diagnostique 36% pour le Malaria et 10% pour le HIV)
- Chaque effet bénéfique sur la mortalité pour la TB grâce a diminution de la transmission par la distanciation sociale était mis en défaut à cause du manque d'acces au soin

Lancet 2020 Hogan et al

Diminution de cas de TB déclaré en Inde
Prédiction de l'Impact sur mortalité TB (who)

FIG. 3.2

Trends in weekly TB case notifications in India in 2020, before and after lockdown



Source: https://reports.nikshay.in/Reports/TBNotification, accessed 31 July 2020

Nikshay et al

Estimated impact of the COVID-19 pandemic on the global number of TB deaths in 2020, for different combinations of decreases in case detection and the duration of these decreases

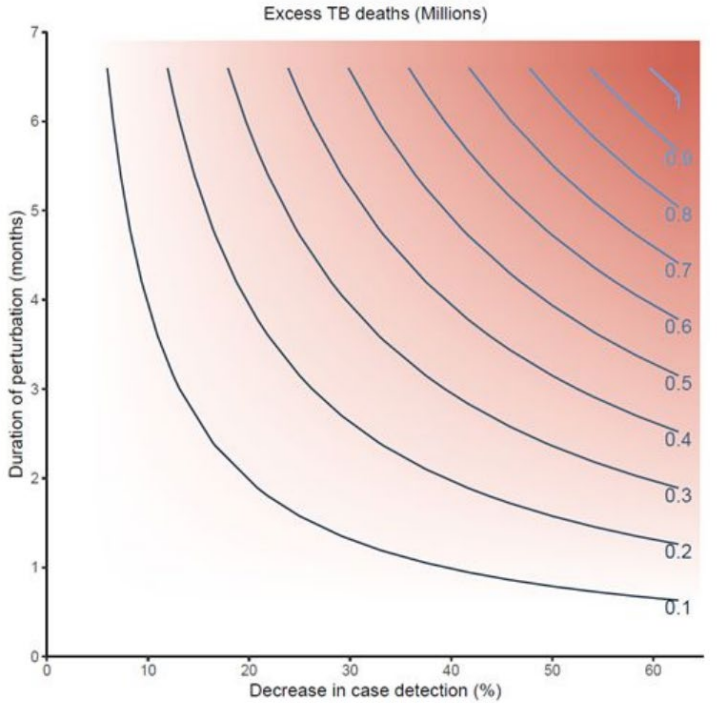
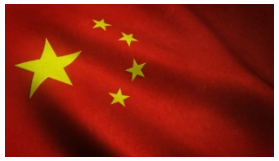


Figure 2. Predicted excess in TB deaths in 2020 in relation to the duration and extent of a temporary average reduction in TB case detection

Impact de nombre de déclarations TB pendant le début de la pandémie / Chine 2020



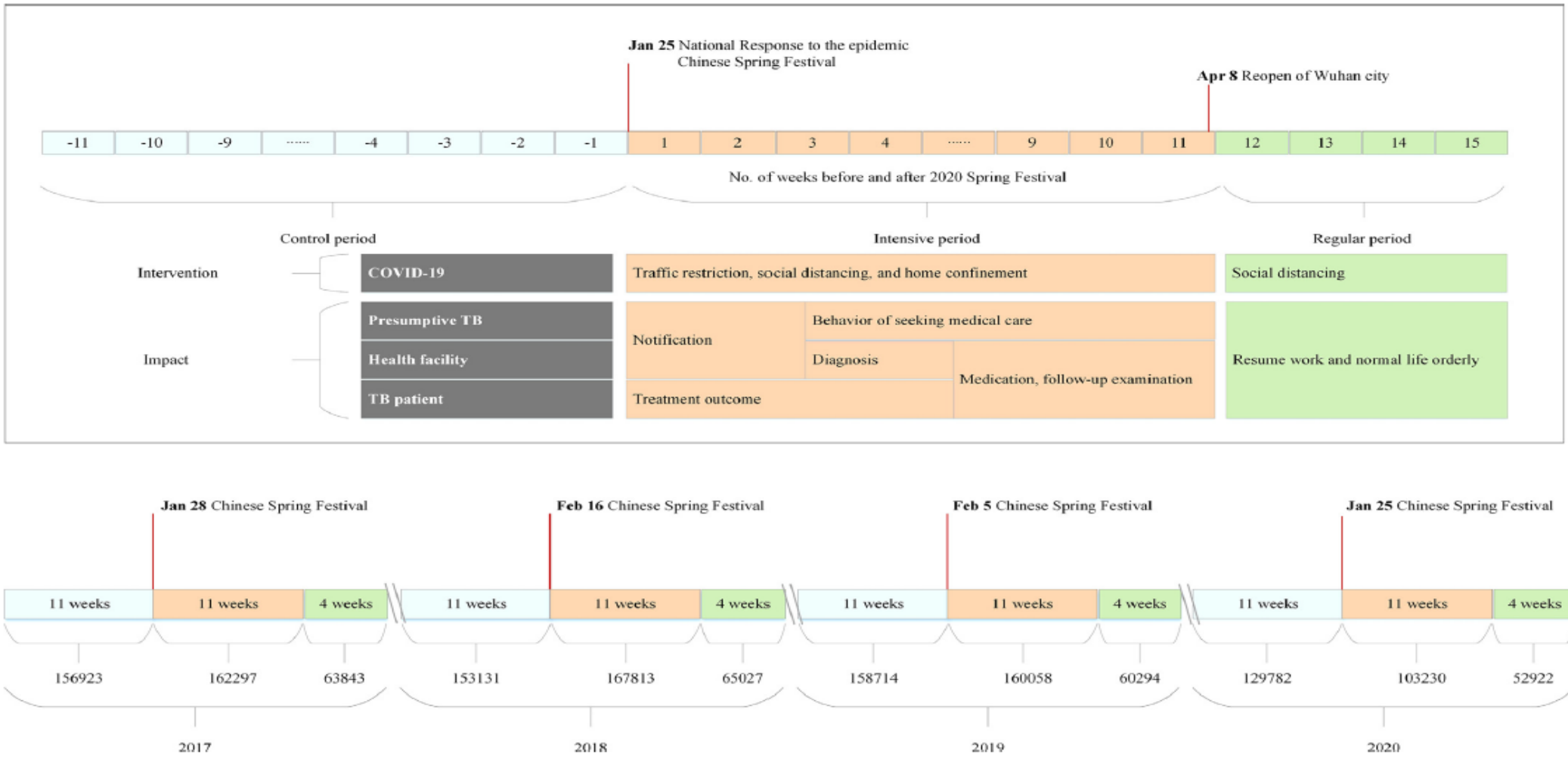
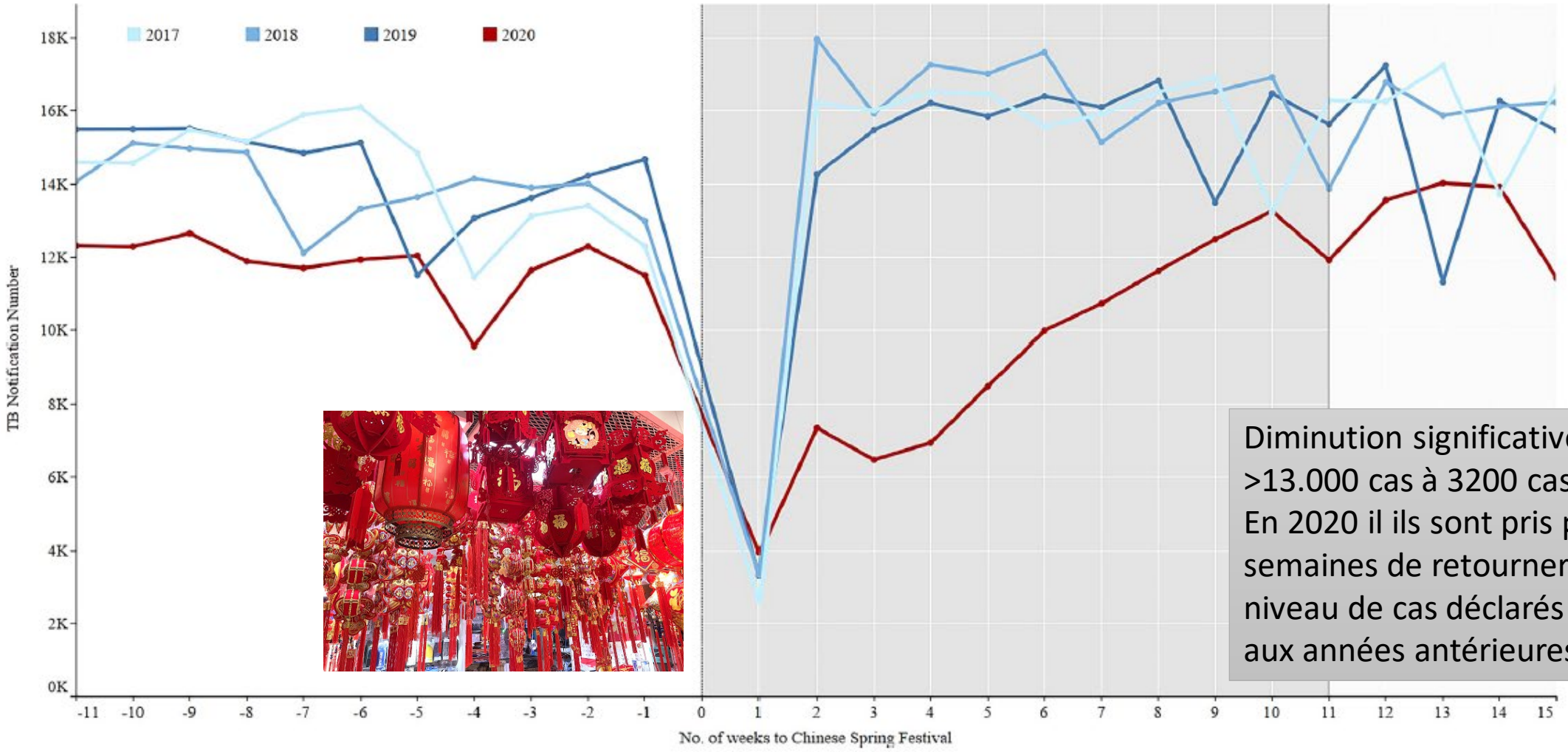


Fig. 1. TB notification breakdown by three time periods, 2017-2020. TB Notification refers to TB cases newly diagnosed by health facilities. The lower part of the figure

Diminution de cas de TB déclarés en Chine

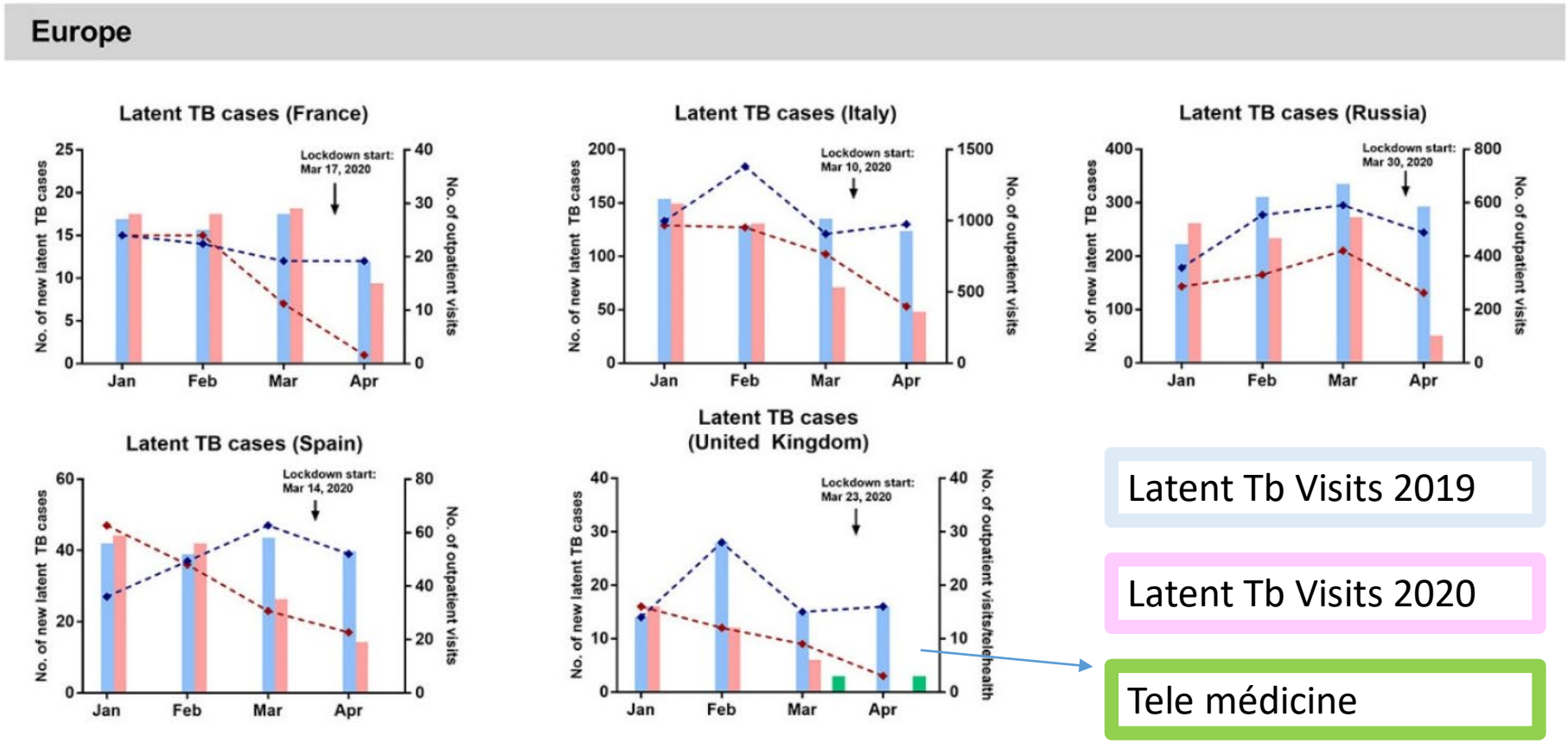


Diminution significative en 2020 de >13.000 cas à 3200 cas
En 2020 il ils sont pris plus de 10 semaines de retourner au même niveau de cas déclarés comparé aux années antérieures

Fig. 2. TB notification in 11 weeks before and 15 weeks after the Chinese Spring Festival, 2017–2020 in China.

FEI et al Lancet 2020

Diminution de suivi de cas de ITBL 2020



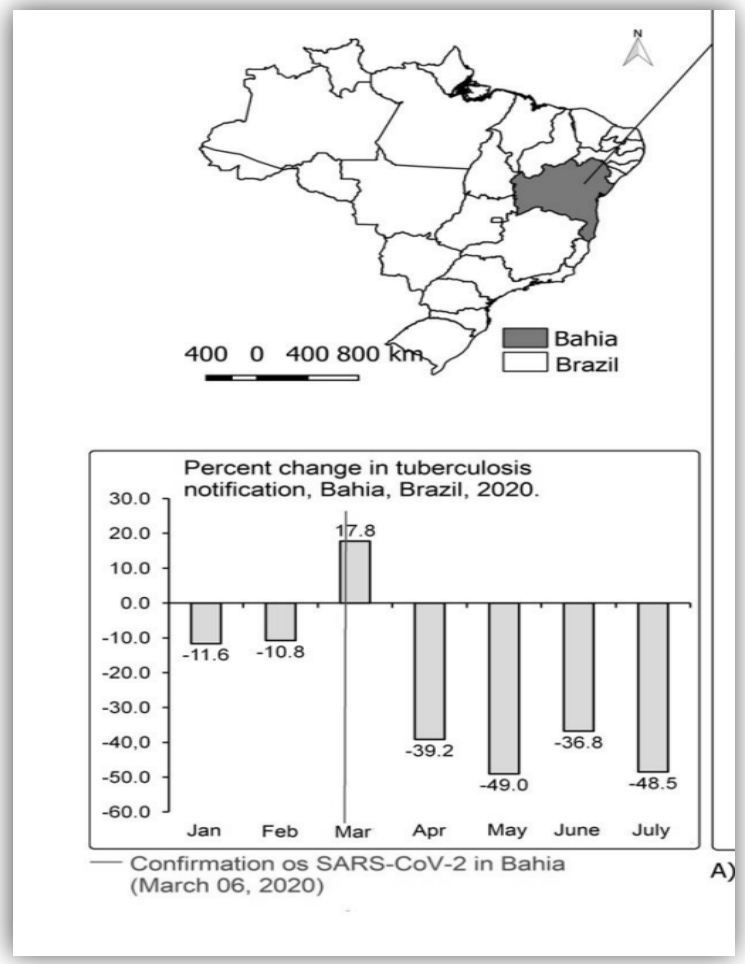
Migliori, Emer Inf Dis 2020;26

Diminution de cas de TB déclarés Bahia Brésil

COVID-19 aggrave la vulnerabilité- Précarité

Au **Brésil** record de nouveaux cas de COVID mars 2021
11.700.000 cas, 285.000 morts

TB
71,000 cas sont diagnostiqué par année et environs 4,500 personnes sont morts chaque année



Most families have decided that the fear of not earning a living is greater than the fear of the virus.

And that is a big problem in countries where the pandemic meets highly vulnerable social conditions, such as in Brazil.

De Souza, IJTLD 2020:24(11):1220

Lien entre Pandémie et précarité

- Travail informel dans les pays moins industrialisées précarise d'avantage leur déjà fragile situation

'No-work-No-pay'

- Absence de revenus augmentation de risque de malnutrition et pauvreté
- Plus de risque de haut niveau de stress et refuge des activités compensatoires (abus de alcool, toxicomanie)
- Conditions de vie et hygiène qui favorisent la transmission de TB et COVID aggravées avec plus de exposition potentielle a des endroits mal ventilées au sein du domicilie
- Pour beaucoup perte de travail signifie perte de accès aux soins aussi

Bacille-Calmette Guerin (BCG) vaccination as a potential intervention against COVID-19

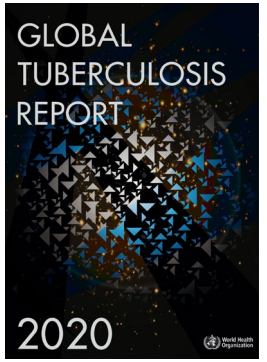
- Effet protector du BCG?
- Etude placebo control Néderlandais en cours
- 2000 travailleurs de la santé
- Personnes vaccinés versus non vaccinés
- Nombre d'infections qui surviennent chez les persones vaccinés versus Non BCG vaccine

Mesures pour assurer prise en charge de TB pendant la pandemie

- Patient centered care
- Prévention et Mesures de contrôle d'infection (mesures simples, triage, cough etiquette , utilization de masques)
- WHO recommande pour MDR passer tout tt en per os
- Pour ITBL utilizer des régimes courts
- Livrer medicaments à la maison
- Utilisation de technologie digital pour monitorer reactions adverses
- Diagnosis: Test pour TB et COVID doit être disponible facilemnet

Conclusions

- Le décès liés au COVID vont beaucoup plus loins que le décès produits par le virus lui même
- Consequences catastrophiques dans la prise en charge de la TB dans le pays moins industrialisées
- Prise en charge assuré pour tous les patients TB Y/C ceux avec COVID
- Planification pour éviter interruption de tt anti-tuberculeux
- Intensification de technologe digital une vraie opportunité
- Opportunités pour synergies diagnostiques et de contact tracing (tester pour le deux, pister les deux maladies au sein de la communauté)



29e symposium Tuberculose

jeudi 25 mars 2021

Therapeutic Drug Monitoring (TDM) in tuberculosis treatment: A pharmacological point of view

Pascal ANDRE (PharmD/PhD)

Pharmacien responsable TDM

Service de Pharmacologie Clinique,
CHUV – Lausanne

Université de Lausanne

Plan

- **TDM levels of interest**
  - all drugs
  - antituberculosis drugs
- **How to perform a TDM interpretation?**
- **1st TDM clinical case :**

  pyrazinamide, ethambutol, rifampicin and isoniazid
- **2nd TDM clinical case :**

  clofazimine
- **Conclusion**

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- **Conclusion**

TDM: levels of interest (CHUV classification)

- «A» TDM highly recommended (especially toxicity)
  + well-defined reference interval + pharmacodynamics
  ex: cefepime, voriconazole,….
- «B» well-defined reference interval
  + pharmacodynamics
  ex: β-lactam antibiotics (meropenem,…)
- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
  ex: new antiepileptics (lamotrigine,…)
- «D» plausibility of the blood level ↔ dosage + patient
  + pharmacodynamics?
  ex: TMP/SMX (BACTRIM®)

TDM: levels of interest (CHUV classification)
+ number of molecules followed by TDM

- «A» TDM highly recommended (especially toxicity)
  + well-defined reference interval + pharmacodynamics
  ex: cefepime, voriconazole,…. → 12% (n = 20)
- «B» well-defined reference interval
  + pharmacodynamics
  ex: β-lactam antibiotics (meropenem,…) → 19% (n = 32)
- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
  ex: new antiepileptics (lamotrigine,…) → 56% (n = 94)
- «D» plausibility of the blood level ↔ dosage + patient
  + pharmacodynamics?
  ex: TMP/SMX (BACTRIM®) → 13% (n = 21)

TDM levels of interest of antituberculosis drugs

- «A» TDM highly recommended (especially toxicity)
  + well-defined reference interval + pharmacodynamics

- «B» well-defined reference interval
  + pharmacodynamics
    ex: pyrazinamide, ethambutol, rifapicin, isoniazid
- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
    ex: others (clofazimine, bedaquiline,…)
- «D» plausibility of the blood level ↔ dosage + patient
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TDM levels of interest of antituberculosis drugs
+ number of molecules followed by TDM

- «A» TDM highly recommended (especially toxicity)
  + well-defined reference interval + pharmacodynamics

- «B» well-defined reference interval
  + pharmacodynamics
  ex: pyrazinamide, ethambutol, rifapicin, isoniazid → 25% (n = 4)

- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
  ex: others (clofazimine, bedaquiline,…) → 75% (n = 12)

- «D» plausibility of the blood level ↔ dosage + patient
  + pharmacodynamics?

TDM levels of interest of antituberculosis drugs
+ number of TDM performed (01.2019 → now)

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- «B» well-defined reference interval
  + pharmacodynamics
  ex: pyrazinamide, ethambutol, rifapicin, isoniazid → 75% (n ≈ 120)

- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
  ex: others (clofazimine, bedaquiline,…) → 25% (n ≈ 40)

- «D» plausibility of the blood level ↔ dosage + patient
  + pharmacodynamics?

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- Conclusion

How to perform a TDM interpretation ?

1. Evaluate chronology :
   - treatment at **steady-state?**
   - samples taken at **trough / peak?**
2. Evaluate blood level **expectedness** considering:
   - **drug dosis**
   - **patient's clinical condition**

   Otherwise **bias suspicion**
   (other dosage, drug interaction, contamination, ….)
3. Evaluate blood level **suitability** (in the **targeted range** of concentration) and **otherwise** perform a **dosage adjustment**

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[ ]

hepatic metabolic activity

altered → maintened

	altered	maintened
total bilirubin	↑↑↑	usual range
factor V	↓↓↓	usual range

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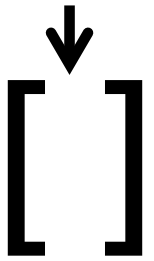

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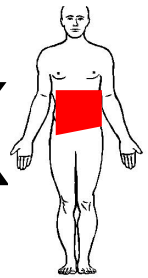

hepatic metabolic activity

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total bilirubin	↑↑↑	usual range
factor V	↓↓↓	usual range

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1st TDM clinical case :

pyrazinamide, ethambutol, rifampicin and isoniazid

A simple and typical clinical case

TDM levels of interest of antituberculosis drugs
+ number of TDM performed (01.2019 → now)

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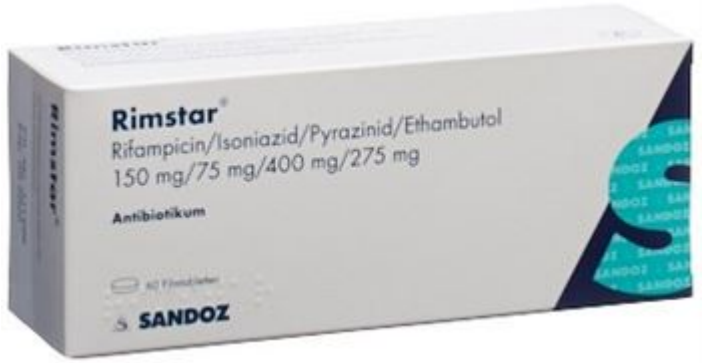
1st clinical case

- ♀ / 22 years old / 174 cm / 51.8 kg
- born in Switzerland but ethiopian family with many visits
- dry cough since november 2019
- clinical exam
  ⇒ sputum culture + mycobacterium

antibiogram		
pyrazinamide	100 mg/L	sensitive
ethambutol	5 mg/L	sensitive
rifampicin	1 mg/L	sensitive
isoniazid	0,1 mg/L	sensitive

- treatment **RIMSTAR® 3 coated tablets / day**
- End 2019, epigastralgia, nausea and vomiting
  H. Pylori gastritis → **pantozol 40 mg 2x/d**
- **TDM at the beginning 2020**

1st clinical case



Daily dose:

number of coated tablets	patient body weight (kg)
2 coated tablets	30-37*
3 coated tablets	38-54
4 coated tablets	55-70
5 coated tablets	≥71

*Rimstar is not suitable for patients weighing less than 30 kg

1st clinical case

	pyrazinamide	ethambutol	rifampicin	isoniazid
doses	1200 mg 1x/d	825 mg 1x/d	450 mg 1x/d	225 mg 1x/d
peak blood level (≈2 h)	29.1 mg/L	3.1 mg/L	3.8 mg/L	3.95 mg/L (acetyl 1.13 mg/L)

1st clinical case

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1st clinical case

- source for targets ?

Therapeutic Drug Monitoring

Principles and Application in Mycobacterial Infections

Charles A. Peloquin, PharmD

P&T/September 1992

Table 3 *NJCIRM Proposed Normal Range for Antimycobacterial Drugs*

Drug	Usual Dose	Proposed 2-Hour Range (μg/mL)
Aminosalicylate (PAS)	4,000 mg	40–70
Ciprofloxacin	750–1,000 mg	4–6
Cycloserine	250–500 mg	20–35
Ethionamide	250–500 mg	1–5
Ethambutol	15 mg/kg	4–6
Isoniazid	300–450 mg	3–5
Pyrazinamide	1,000–2,000 mg	20–60
Ofloxacin	800–1,000 mg	8–12
Rifampin	600–750	8–24
Capreomycin and the aminoglycosides (amikacin, kanamycin, streptomycin)		
conventional*	15 mg/kg	35–45
high dose†	25 mg/kg	65–80

*Conventional dose given five times weekly.
†High dose given three times weekly under experimental protocol.

1st clinical case

	pyrazinamide	ethambutol	rifampicin	isoniazid
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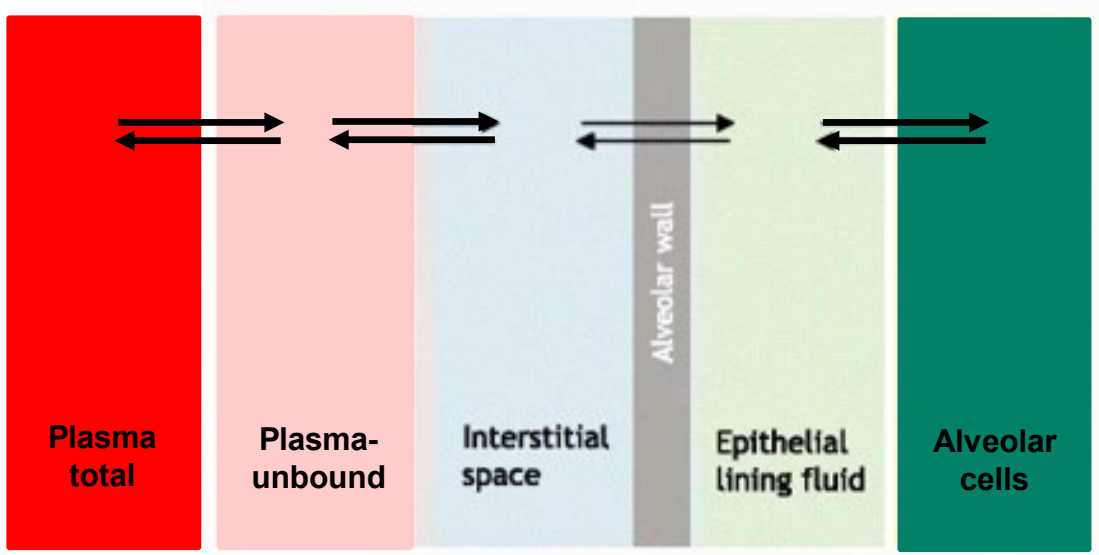
limits for adaptation	< 15 mg/L	< 2 mg/L	< 6 mg/L	< 2 mg/L
antibiogram	< 100 mg/L	< 5 mg/L	< 1 mg/L	< 0.1 mg/L
antibiogram corrected for protein binding	< 200 mg/L	< 6.5 mg/L	< 5-10 mg/L	< 0.15 mg/L

1st TDM clinical case :

pyrazinamide, ethambutol, rifampicin and isoniazid

a simple and typical clinical case



Structure-Based Prediction of Anti-infective Drug Concentrations in the Human Lung Epithelial Lining Fluid

Adapted from Välitalo PAJ et al. *Pharm Res* 33:856-867, 2016

1st TDM clinical case :

pyrazinamide, ethambutol, rifampicin and isoniazid

a simple and typical clinical case

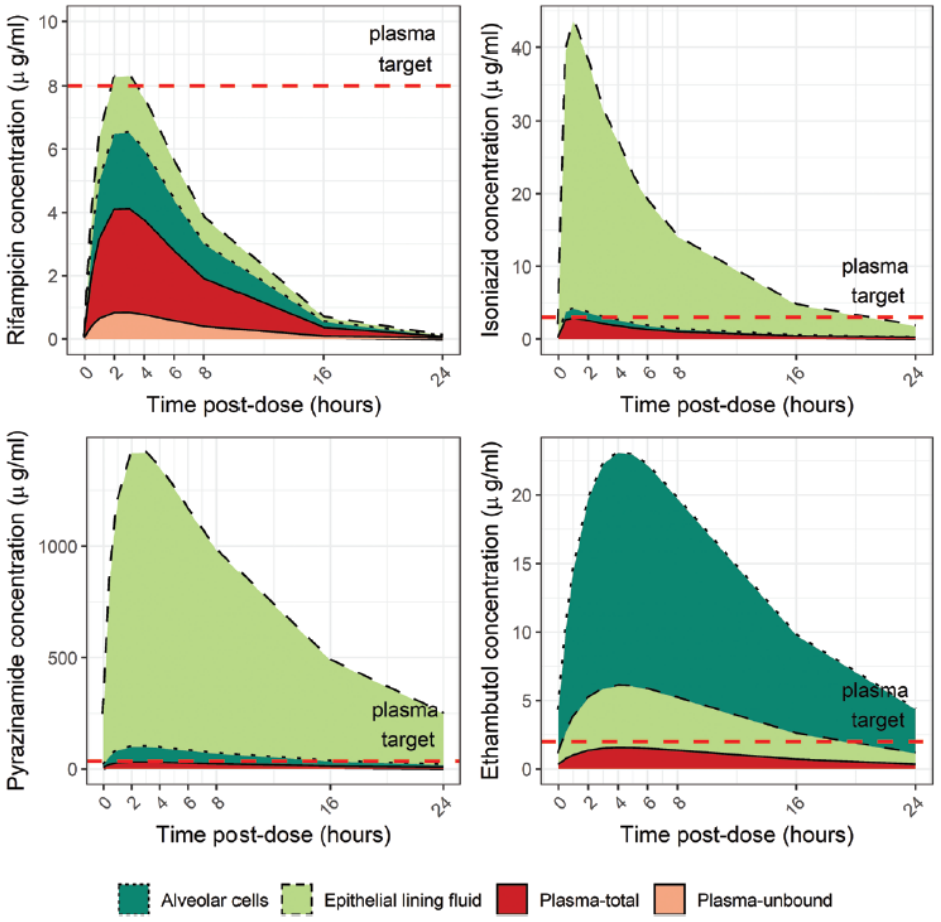


Figure 1. Summary concentration-time plots for rifampicin, isoniazid, pyrazinamide, and ethambutol in plasma, epithelial lining fluid, and alveolar cells from population means at steady state. To account for rifampicin protein binding, the red/pink-shaded area in the top-left panel illustrates plasma drug exposure for total drug (top line) or unbound drug (bottom line), assuming 80% protein binding in plasma and negligible protein binding in epithelial lining fluid. Plasma concentrations for isoniazid, pyrazinamide, and ethambutol are shown as total drug only. Concentrations at the different time points were calculated using the Bayesian posterior pharmacokinetic parameter value estimates and epithelial lining fluid to plasma (R_{ELF}) and alveolar cells to plasma (R_{AC}) ratios. The horizontal dotted line represents the plasma targets for therapeutic drug monitoring [29].

Intrapulmonary Pharmacokinetics of First-line Anti-tuberculosis Drugs in Malawian Patients With Tuberculosis

Andrew D. McCallum,[1,2,3,©] Henry E. Pertinez,[3] Laura J. Else,[3] Sujan Dilly-Penchala,[3] Aaron P. Chirambo,[1] Irene Sheha,[1] Madalitso Chasweka,[1] Alex Chitani,[1] Rose D. Malamba,[1] Jamilah Z. Meghji,[1,2] Stephen B. Gordon,[1,2] Geraint R. Davies,[3] Saye H. Khoo,[3] Derek J. Sloan,[4,a] and Henry C. Mwandumba[1,2,a]

Intrapulmonary PK of Anti-TB Drugs • CID 2020:XX (XX XXXX)

Clinical Infectious Diseases

MAJOR ARTICLE

active transport probably through alveolar wall, still few characterized

⇒ individual variability ?

1st TDM clinical case :

pyrazinamide, ethambutol, rifampicin and isoniazid

a simple and typical clinical case

Drug and Pharmacokinetic Index	Plasma Therapeutic Drug-monitoring Target [29]	Matrix, Median (IQR)		
		Plasma	Epithelial Lining Fluid	Alveolar Cells
Rifampicin				
AUC, µg · h/mL	…	6.6 [5.6–7.5][a]	65.7 [52.4–77.1]	46.0 [36.4–55.1]
AUC. µg · h/mL	…	30.6 [27.3–36.7][b]	…	…
C_{max}, µg/mL	…	0.8 [0.3–1.0][a]	7.8 [6.4–10.0]	5.3 [4.4–7.6]
C_{max}, µg/mL	≥8	4.0 [3.5–4.8][b]	…	…
Isoniazid				
AUC, µg · h/mL	…	19.0 [11.9–25.9]	277.8 [154.9–382.4]	24.4 [14.1–34.8]
C_{max}, µg/mL	≥3	2.6 [2.4–3.0]	38.9 [32.8–46.2]	3.5 [2.9–4.2]
Pyrazinamide				
AUC, µg · h/mL	…	319.5 [292.0–384.3]	16 062 [14 096–19 403]	1036 [899–1272]
C_{max}, µg/mL	≥20[c]	24.0 [22.2–26.3]	1195 [1062–1361]	78 [68–94]
Ethambutol				
AUC, µg · h/mL	…	5.4 [2.9–7.4]	22.6 [11.7–29.2]	83.0 [48.0–110.1]
C_{max}, µg/mL	≥2	1.3 [1.1–1.6]	5.2 [4.2–6.6]	20.0 [15.4–25.3]

[a]Estimated unbound fraction of rifampicin in plasma, assuming typical 80% rifampicin protein binding.

[b]Total rifampicin in plasma.

1st TDM clinical case :

pyrazinamide, ethambutol, rifampicin and isoniazid

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1st clinical case

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antibiogram corrected for protein binding	< 200 mg/L	< 6.5 mg/L	< 5-10 mg/L	< 0.15 mg/L

- AUC/MIC targets are available but need
  - many blood levels (not only 2)
  - many approximations

1st clinical case

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- low rifampicine blood level. Cause(s)?
  1. weight used to calculate daily dose
  2. drugs interactions
  3. insufficient usual dosage + intrinsic variability

1st clinical case

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  1. weight used to calculate daily dose
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1st clinical case

- 174 cm / 51,8 kg → BMI ≈ 17 kg/m^2
- Ideal body weight

  ≈ 65 kg

Daily dose:

number of coated tablets	patient body weight (kg)
2 coated tablets	30-37*
3 coated tablets	38-54
4 coated tablets	55-70
5 coated tablets	≥71

*Rimstar is not suitable for patients weighing less than 30 kg

1st clinical case

- dose adaptation for obese patients (using IBW)

Clinical Infectious Diseases Advance Access published August 10, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[9]

[a] Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses.

Current Pharmaceutical Design, 2015, *21*, 000-000 1

Evolving Larger: Dosing Anti-Tuberculosis (TB) Drugs in an Obese World

Ronald G. Hall II

	Maximum Guideline / Recommended Daily dose
Pyrazinamide	2 g / 15-30 mg/kg (IBW)
Ethambutol	1.6 g / 15-20 mg/kg (IBW)
Rifampicine	600 mg / 10 mg/kg (IBW)
Isoniazide	300 mg / 5 mg/kg (IBW)

1st clinical case

- also for undernourished/low body weight patients?

Low Antituberculosis Drug Concentrations in HIV-Tuberculosis-Coinfected Adults with Low Body Weight: Is It Time To Update Dosing Guidelines?

June 2019 Volume 63 Issue 6 e02174-18 Antimicrobial Agents and Chemotherapy

Christine Sekaggya-Wiltshire,[a] Maxwell Chirehwa,[b] Joseph Musaazi,[a] Amrei von Braun,[c] Allan Buzibye,[a] Daniel Muller,[d] Ursula Gutteck,[d] Ilaria Motta,[a] Andrea Calcagno,[a] Jan S. Fehr,[c] Andrew Kambugu,[a] Barbara Castelnuovo,[a] Mohammed Lamorde,[a] Paolo Denti[b]

Population pharmacokinetic modeling was used to interpret the data and revealed that patients weighing ≤55 kg achieved lower concentrations than those in higher weight bands for all drugs in the regimen. The models predicted that this imbalance could be solved with a dose increment of one fixed-dose combination (FDC) tablet for the weight bands of 30 to 37 and 38 to 54 kg.

→ **until now, only for HIV coinfected patients**

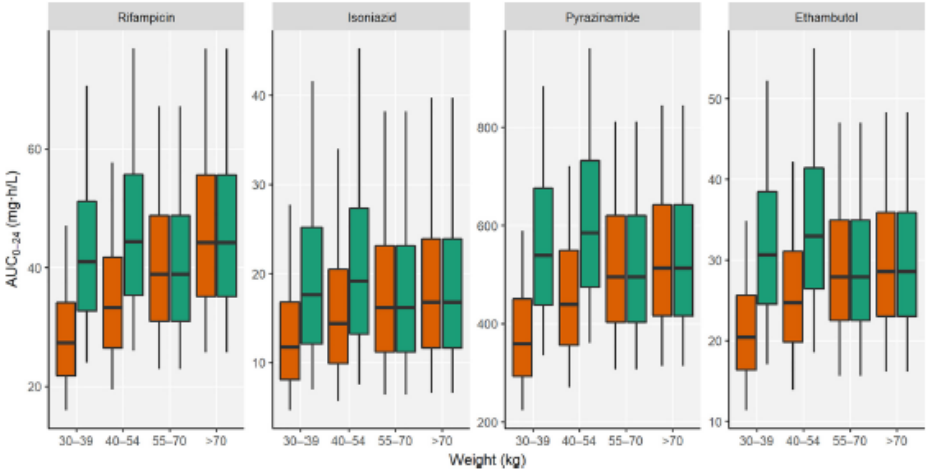

FIG 2 Comparison of simulated exposures using the current dosing strategy versus the suggested dose increment. Shown are box plots of simulated AUC_{0-24} values using the final models for rifampin, isoniazid, pyrazinamide, and ethambutol stratified by weight band. The orange boxes represent the exposure achieved with the currently WHO-recommended dose, while the green ones represent the adjusted dose. The box represents median (central line) and interquartile ranges (box boundaries), while the whiskers are the 2.5th and 97.5th percentiles.

1st clinical case

	pyrazinamide	ethambutol	rifampicin	isoniazid
doses	1200 mg 1x/d	825 mg 1x/d	450 mg 1x/d	225 mg 1x/d
peak blood level (≈2 h)	29.1 mg/L	3.1 mg/L	3.8 mg/L	3.95 mg/L (acetyl 1.13 mg/L)
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- low rifampicine blood level. Cause(s)?
  1. weight used to calculate daily dose
  2. drugs interactions
  3. insufficient usual dosage + intrinsic variability

1st clinical case

- ♀ / 22 years old / 174 cm / 51.8 kg
- born in Switzerland but ethiopian family with multiple stays
- dry cough since november 2019
- clinical exam

  ⇒ sputum culture + mycobacterium

antibiogramme		
pyrazinamide	100 mg/L	sensitive
ethambutol	5 mg/L	sensitive
rifampicin	1 mg/L	sensitive
isoniazid	0,1 mg/L	sensitive

- treatment **RIMSTAR® 3 coated tablets / day**
- End 2019, epigastralgia, nausea and vomiting
  H. Pylori gastritis → **pantozol 40 mg 2x/d**
- **TDM at the beginning 2020**

Cas clinique N°1

- 0 interactions described between rifampicin and proton-pump inhibitors
- but

Effect of antacids on oral absorption of rifampicin

Saleh A.H. Khalil, Labiba K. El-Khordagui and Zeinab A. El-Gholmy

International Journal of Pharmaceutics, 20 (1984) 99–106

A study has been carried out on the effect of concomitant administration of aluminium hydroxide gel (15 ml), magnesium trisilicate (2 g) and sodium bicarbonate (2 g) on the bioavailability of rifampicin in healthy male volunteers.

The results obtained are interpreted in the light of the effect of gastric pH elevation on the solubility and dissolution rate of rifampicin, chelation of the drug with aluminium ions and binding by magnesium trisilicate.

→ possible contribution finally

1st clinical case

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- low rifampicine blood level. Cause(s)?
  1. weight used to calculate daily dose
  2. drugs interactions
  3. insufficient usual dosage + intrinsic variability

1st clinical case

- insufficient usual dosage

Pharmacokinetics and Tolerability of a Higher Rifampin Dose versus the Standard Dose in Pulmonary Tuberculosis Patients[▽]

Rovina Ruslami,[1]† Hanneke M. J. Nijland,[2]† Bachti Alisjahbana,[3] Ida Parwati,[4] Reinout van Crevel,[5] and Rob E. Aarnoutse[2]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2007, p. 2546–2551

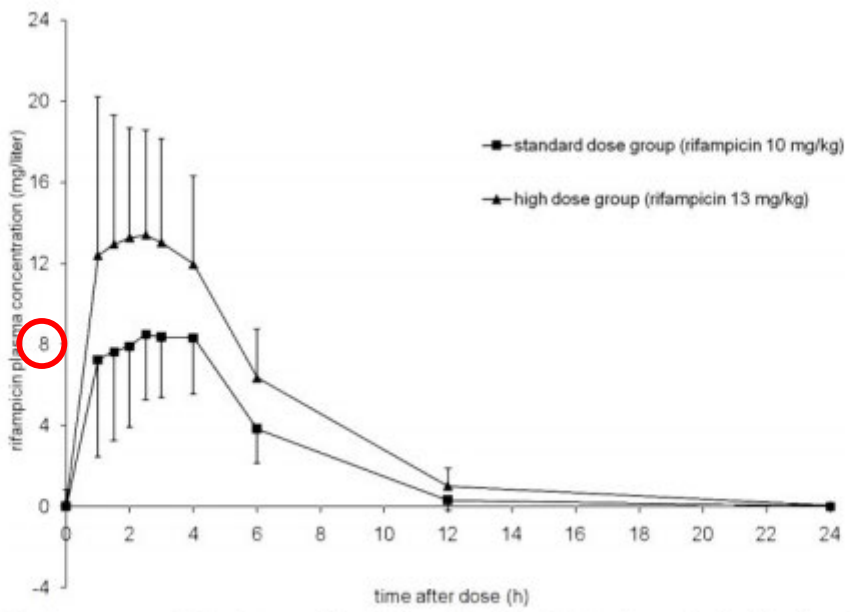

FIG. 1. Mean steady-state plasma concentration-time profiles of rifampin in TB patients who received a high dose (600 mg; 13 mg/kg; $n = 23$) or a standard dose (450 mg; 10 mg/kg; $n = 24$) of rifampin, with standard deviations.

→ confirms this hypothesis

1st clinical case

	pyrazinamide	ethambutol	rifampicin	isoniazid
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     → impossible to exclude one of them

1st clinical case

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- low rifampicine blood level. Cause(s)?
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  3. insufficient usual dosage + intrinsic variability

     → impossible to exclude one of them
- acetylator's type

1st clinical case

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2001; **10**: 127–134
DOI: 10.1002/pds.570

ORIGINAL REPORT

Population screening for isoniazid acetylator phenotype

Heiner I. Seifart[1], Donald P. Parkin[1], Frederik J. H. Botha[1], Peter R. Donald[2] and Ben J. Van Der Walt*[1]

[1]*Department of Pharmacology, University of Stellenbasch, Republic of South Africa*
[2]*Department of Paediatrics and Child Health, University of Stellenbosch, Republic of South Africa*

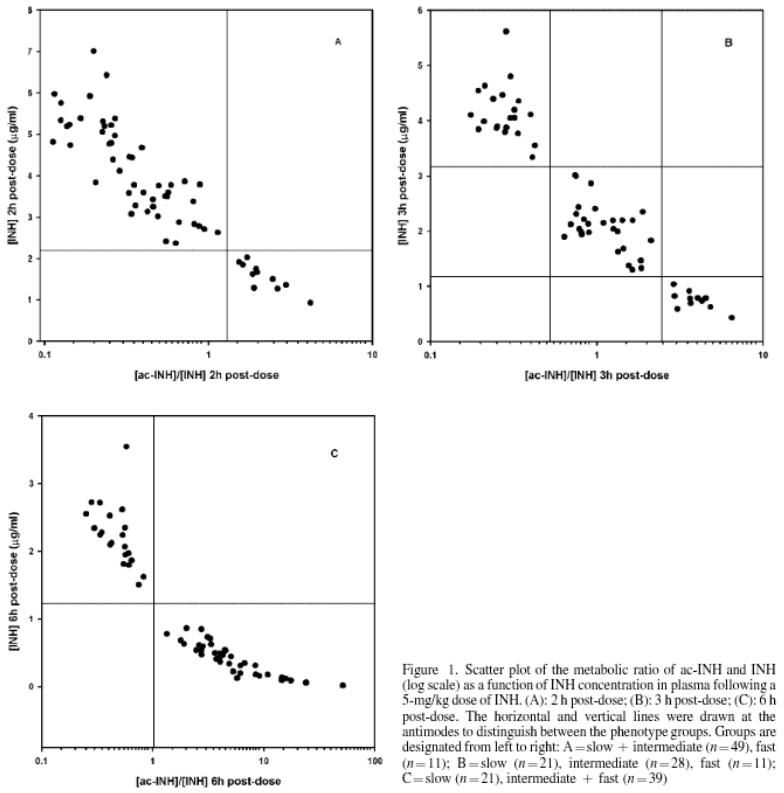
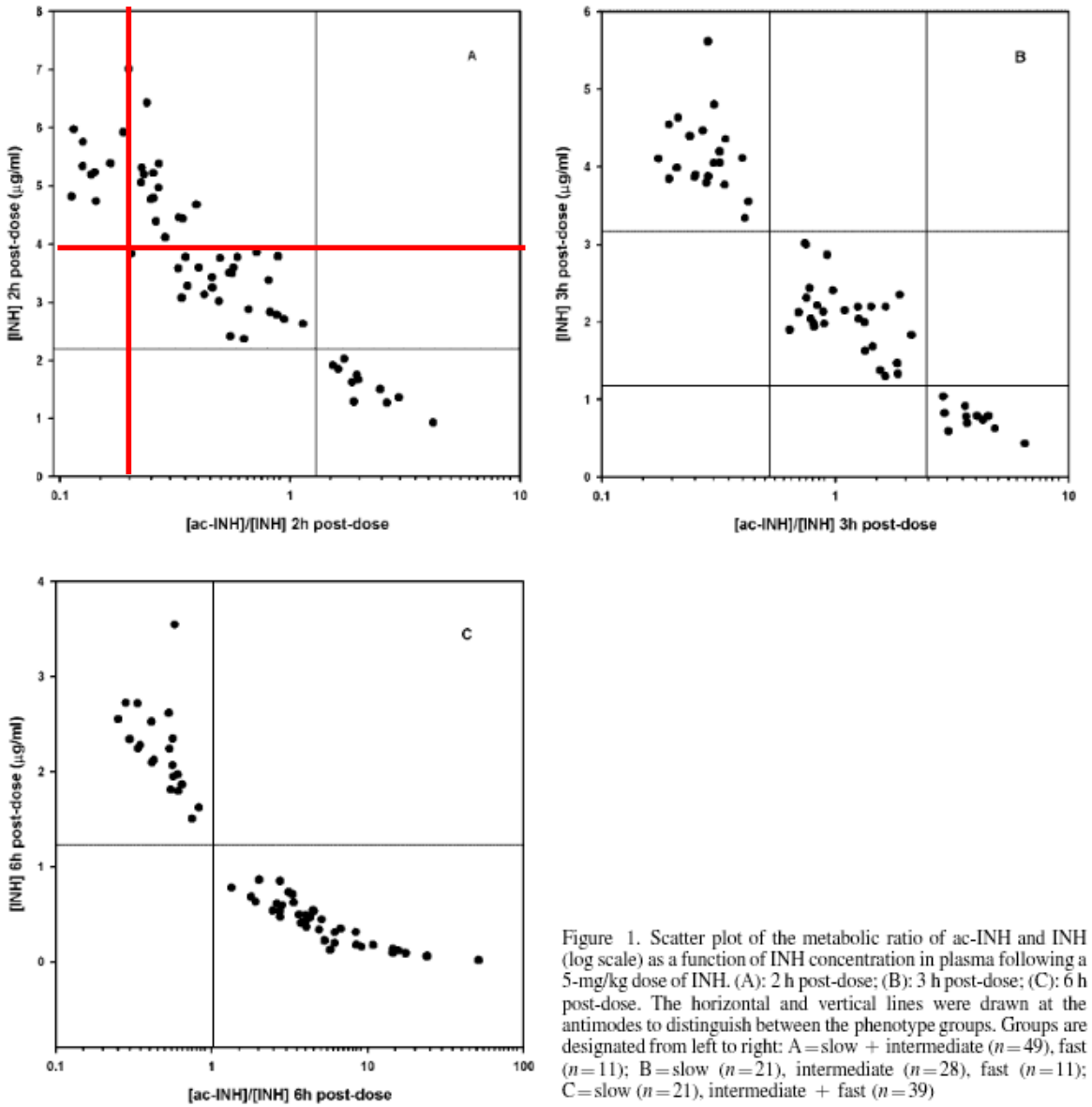


Figure 1. Scatter plot of the metabolic ratio of ac-INH and INH (log scale) as a function of INH concentration in plasma following a 5-mg/kg dose of INH. (A): 2 h post-dose; (B): 3 h post-dose; (C): 6 h post-dose. The horizontal and vertical lines were drawn at the antimodes to distinguish between the phenotype groups. Groups are designated from left to right: A = slow + intermediate ($n = 49$), fast ($n = 11$); B = slow ($n = 21$), intermediate ($n = 28$), fast ($n = 11$); C = slow ($n = 21$), intermediate + fast ($n = 39$)

1st clinical case



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1st clinical case

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- low rifampicine blood level. Cause(s)?
  1. weight used to calculate daily dose
  2. drugs interactions
  3. insufficient usual dosage + intrinsic variability

     → impossible to exclude one of them
- acetylator's type → slow or intermediate with higher hepatotoxicity risk (≈ 25% versus 10%)

Plan

- TDM levels of interest
  - all drugs
  - antituberculosis drugs
- How to perform a TDM interpretation?
- 1st TDM clinical case :

  pyrazinamide, ethambutol, rifampicin and isoniazid
- **2nd TDM clinical case :**

  clofazimine
- Conclusion

2nd TDM clinical case :
clofazimine
a TDM still in development

TDM levels of interest of antituberculosis drugs
+ number of TDM performed (01.2019 → now)

- «C» range of concentrations expected at usual dosages
  + pharmacodynamics
  ex: others (clofazimine, bedaquiline,…) → 25% (n ≈ 40)
- «D» plausibility of the blood level ↔ dosage + patient
  + pharmacodynamics?

How to perform a TDM interpretation ?

1. Evaluate chronology :
   - treatment at **steady-state?** 
   - samples taken at **trough / peak?** 

2. Evaluate blood level **expectedness** considering:
   - **drug dosis**
   - **patient's clinical condition** 

   Otherwise **bias suspicion**
   (other dosage, drug interaction, contamination, ….)

3. Evaluate blood level **suitability** (in the **targeted range** of concentration) and **otherwise** perform a **dosage adjustment**

2nd clinical case

- ♂ / 18 years-old / 189 cm / 76 kg
- MDR-TB + R to streptomycin diagnosed
- treatment started end of july 2019
  bedaquiline, cycloserin, clofazimine, moxifloxacin, linezolid
- cycloserin stopped 27.02.2020 (for simplification after 6 months)
- TDM performed 12.06.2020, clofazimine peak (5h post dose) and trough blood level
  - trough : 0,3 mg/L
  - peak : 0,3 mg/L

2nd clinical case

- expected blood levels under 100 mg 2x/d
  - trough : 0,4 mg/L
  - peak : 0,5 mg/L (≈ 8h)

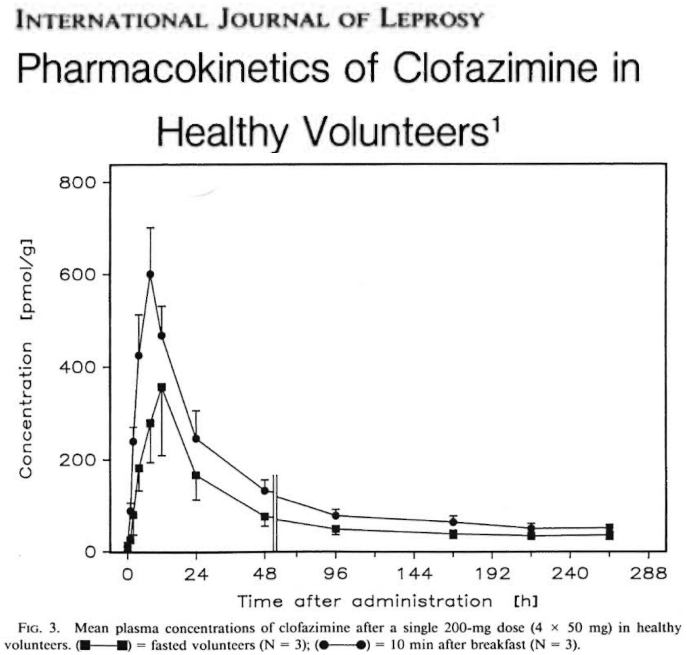


FIG. 3. Mean plasma concentrations of clofazimine after a single 200-mg dose (4 × 50 mg) in healthy volunteers. (■——■) = fasted volunteers (N = 3); (●——●) = 10 min after breakfast (N = 3).

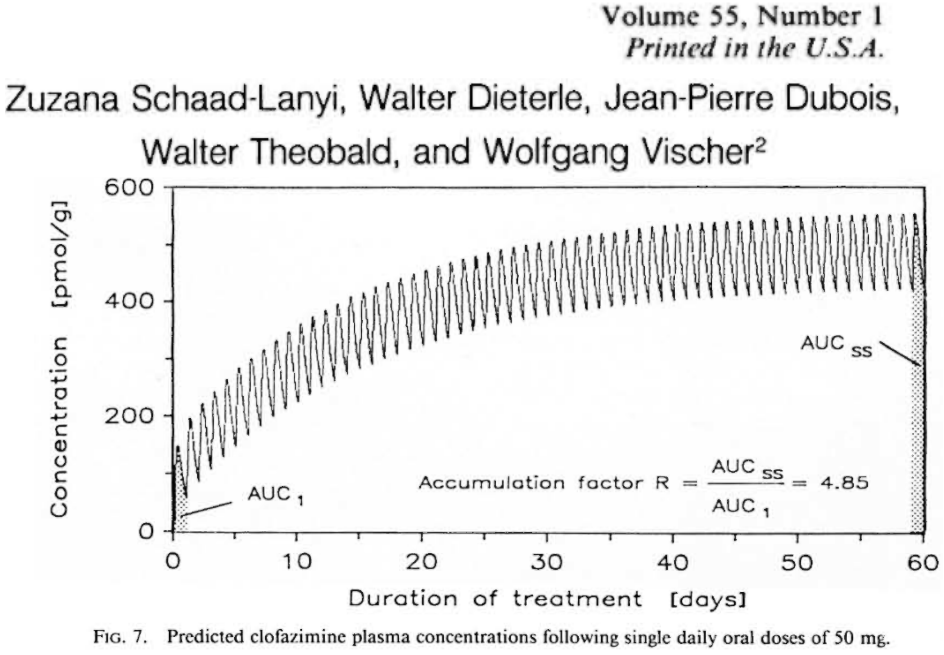


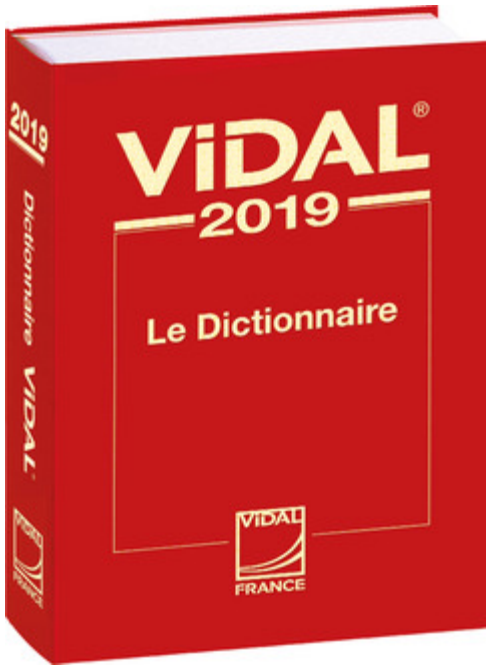
FIG. 7. Predicted clofazimine plasma concentrations following single daily oral doses of 50 mg.

- 50 mg once daily with MW 473.4 g/mol
  - trough : 0,19 mg/L
  - peak : 0,26 mg/L

2nd clinical case

- expected blood levels under 100 mg 2x/d
  - trough : 0,4 mg/L
  - peak : 0,5 mg/L (≈ 8h)

LAMPRENE 50 mg, capsule molle, 2012/11/23



5.2. Propriétés pharmacocinétiques

Absorption

La clofazimine est absorbée relativement lentement.

Après une prise orale unique sous forme de capsule le pic plasmatique de la forme inchangée de clofazimine est atteint en 8 à 12 heures. La biodisponibilité de la clofazimine sous forme cristalline en suspension dans une cire huileuse est supérieur à 70 % après une prise de 100 mg et diminue avec des doses supérieures.

L'ingestion simultanée d'aliments augmente la biodisponibilité en termes d'aire sous la courbe de 60 % et tend à augmenter le taux d'absorption. Après l'administration d'une dose unique de 200 mg au petit-déjeuner, les concentrations plasmatiques moyennes mesurées chez les sujets sains sont de 861 (± 289) pmol/g. Quand la clofazimine est administrée à jeun, le pic de concentration plasmatique diminue approximativement de 20 %.

Lors d'administrations répétées de 50 et 100 mg de clofazimine une fois par jour, les concentrations plasmatiques minimales (avant la prise quotidienne) mesurées chez des patients après 42 jours de traitement ont été respectivement de 580 et 910 pmol/g.

L'état d'équilibre de ces concentrations n'est pas atteint pendant cette période.

100 mg once daily
with MW 473.4 g/mol
→ trough : 0,43 mg/L

http://document-rcp.vidal.fr/71/7eabd0dc641f4cf7994d62c67208f071.pdf

2nd clinical case

- expected blood levels under 100 mg 2x/d
  - trough : 0,4 mg/L
  - peak : 0,5 mg/L (≈ 8h)

Drugs (2014) 74:839–854 CURRENT OPINION

Therapeutic Drug Monitoring in the Treatment of Tuberculosis: An Update

Abdullah Alsultan · Charles A. Peloquin

Table 1 Pharmacokinetic parameters of the anti-tuberculosis drugs

Drug	Normal adult dose	Normal C_{max} (μg/mL)	Normal T_{max} (h)	Normal $t_{½}$ (h)
Clofazimine	100 mg daily	0.5–2.0	2–7	Biphasic: several days, then many weeks

Information in the table is from the following references: [78, 114, 115, 121, 134, 139, 143, 145, 149, 150, 162, 172]

- much higher exposure?

2nd clinical case

- TDM performed 12.06.2020, clofazimine peak (5h post dose) and trough blood level (under 100 mg 2x/d)
  - trough : 0,3 mg/L
  - peak : 0,3 mg/L
- No correlation between :
  - blood level and pharmacological effect
  - blood level and toxicity
- Expected blood levels under 100 mg 2x/d
  - trough : 0,4 mg/L
  - peak : 0,5 mg/L (≈ 8h)
- Risk of concentration dependent toxicity?
- Risk of insufficient exposure?
- Typical of «C» («D»?) drugs (PD not well known)

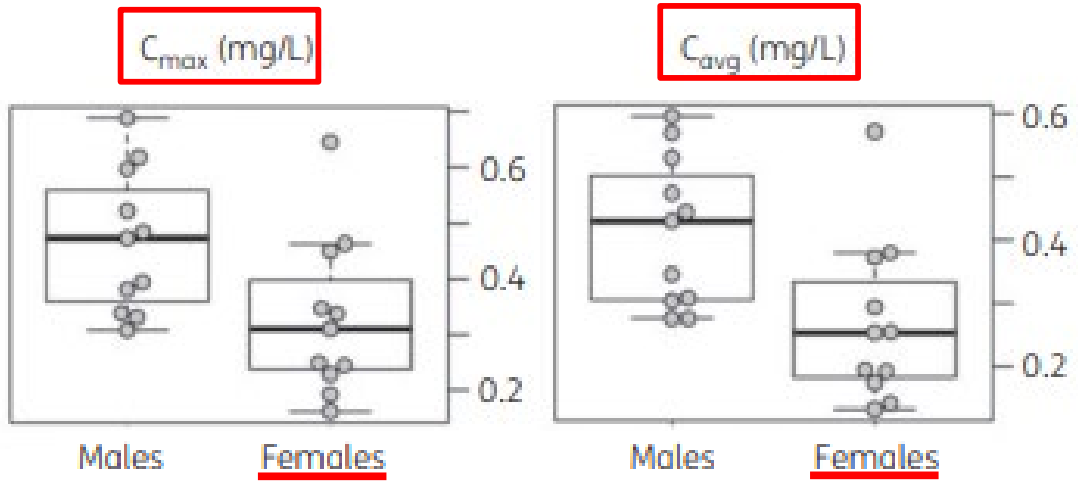
2nd clinical case

- expected blood levels under 100 mg 2x/d
  - trough : 0,4 mg/L
  - peak : 0,5 mg/L (≈ 8h)

Clofazimine pharmacokinetics in patients with TB: dosing implications

Mahmoud Tareq Abdelwahab [1]†, Sean Wasserman [2,3]*†, James C. M. Brust[4], Neel R. Gandhi[5,6], Graeme Meintjes[2,3], Daniel Everitt[7], Andreas Diacon[8], Rodney Dawson[9], Lubbe Wiesner [1], Elin M. Svensson[10,11], Gary Maartens[1,3] and Paolo Denti [1]

J Antimicrob Chemother 2020; **75**: 3269–3277



- strong sex effect on pharmacokinetics?
- exposure finally possible

Plan

- TDM levels of interest
  - all drugs
  - antituberculosis drugs
- How to perform a TDM interpretation?
- 1st TDM clinical case :

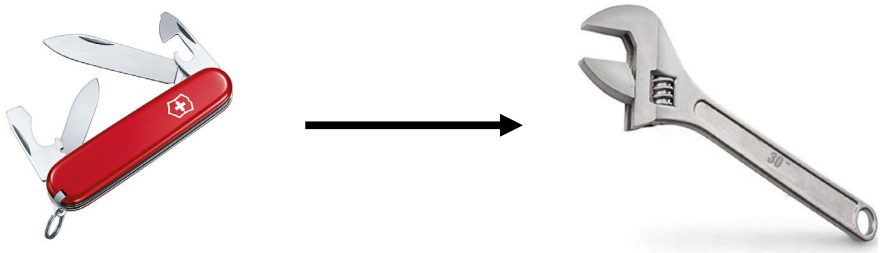
  pyrazinamide, ethambutol, rifampicin and isoniazid
- 2nd TDM clinical case :

  clofazimine
- **Conclusion**

Conclusion

TDM:

- is a tool to adapt anti-tuberculosis drugs but still limited by our current knowledge

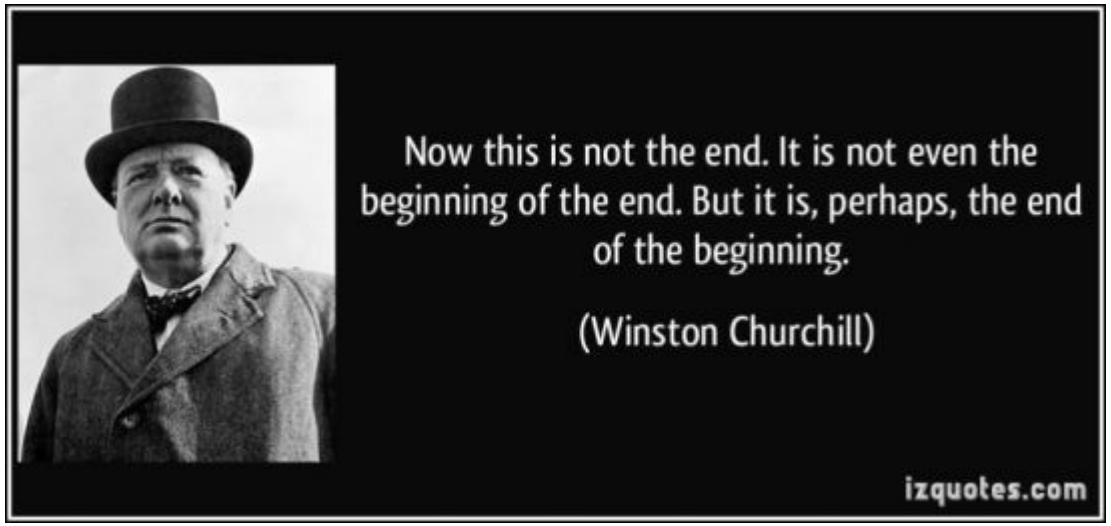


→ to explain some insufficient clinical answer
(lack of therapeutic adhesion, particular metaboliser profil,….)

→ to adapt treatment doses on patients with:

- specific comorbidities (renal and/or hepatic failure, HIV infection,….)
- drugs interactions (even if well described, effect can vary between patients/doses,…)

- cannot replace clinical follow-up


Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.
(Winston Churchill)
izquotes.com

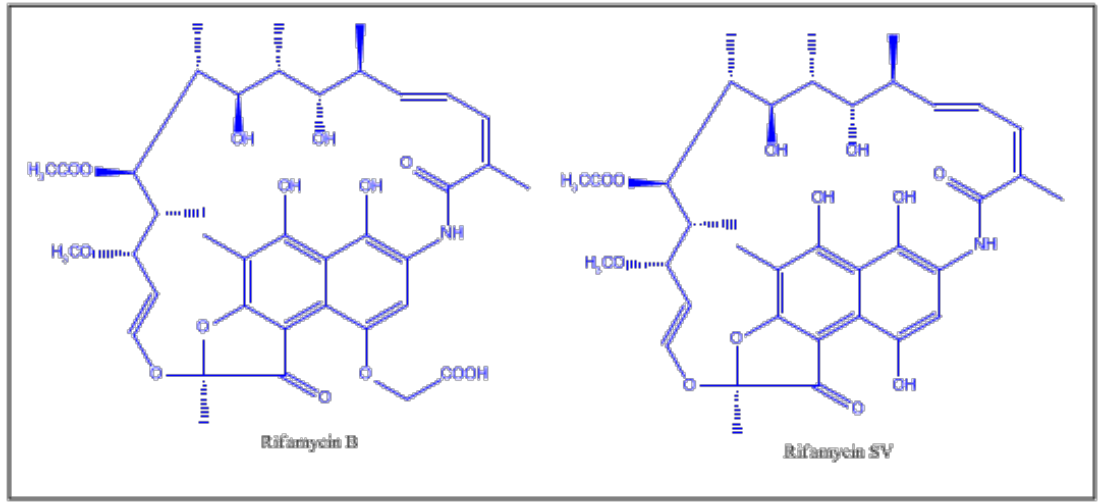
Treatment of tuberculosis with rifampicin: are we using the correct doses?

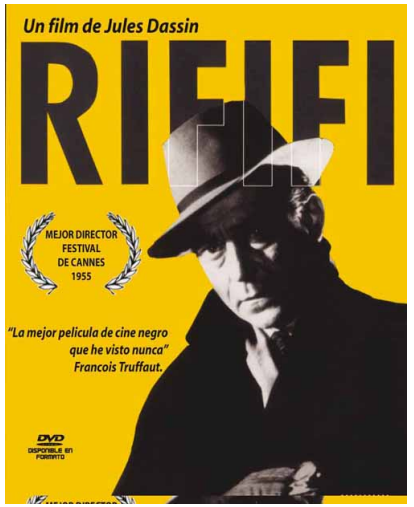
Martin Boeree, MD, PhD, FRCP (Edin)
Professor in Clinical Tuberculosis and other Mycobacterial Diseases
Radboudumc Nijmegen

Virtual Switzerland TB symposium, March 25, 2021

History of the rifamycins

- 1957: Piero Sensi et al. at Lepetit Laboratories in Milan
- Isolated from fermentation cultures of *Streptomyces mediterranei* (currently *Amycolatopsis rifamycinica)*
- Rifamycins: A,B,C,D,E, S and SV





The first clinical trial of rifampicin: Wow!

The Lancet · Saturday 20 May 1972

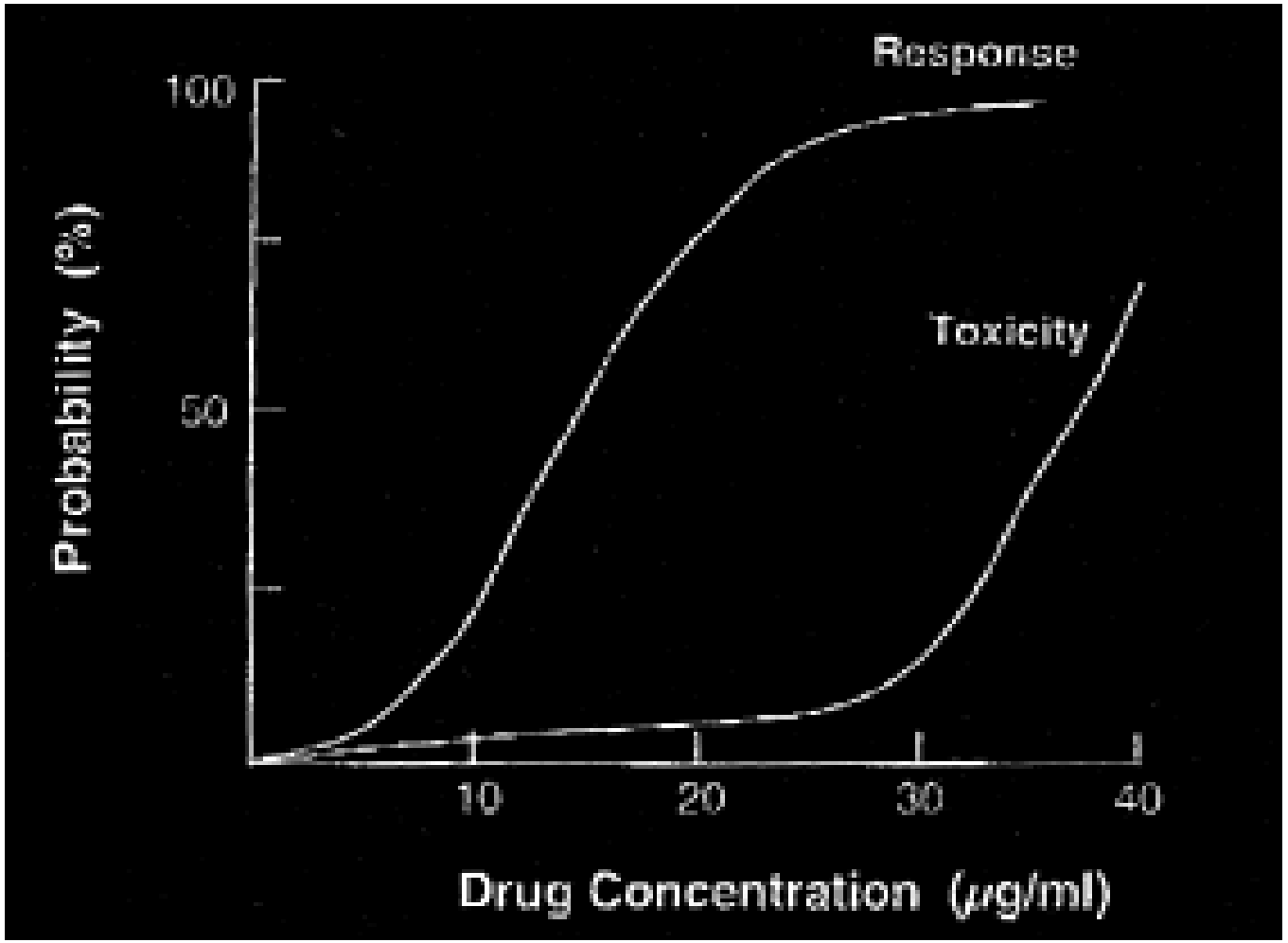
CONTROLLED CLINICAL TRIAL OF SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS

EAST AFRICAN/BRITISH MEDICAL RESEARCH COUNCILS

Dose of rifampin:
450 mg (<50kg)
600 mg (>50kg)
7 days/week

Summary A comparison has been made between four 6-month daily regimens, all containing streptomycin plus isoniazid, and 3 of them a third drug—rifampicin, pyrazinamide, or thiacetazone—and a standard 18-month regimen in the treatment of newly diagnosed extensive smear-positive pulmonary tuberculosis. At 6 months all except 2 of 450 patients (both of them on streptomycin plus isoniazid) had a favourable response. There was also very little drug toxicity. The bacteriological relapse-rates between 6 and 12 months were 18% of 94 patients on the two-drug combination, 4% of 99 on the rifampicin, 6% of 88 on the pyrazinamide, 21% of 84 on the thiacetazone, and 2% of 83 patients on the standard regimen. Most of the relapses occurred by 9 months and nearly every patient who relapsed did so with drug-sensitive organisms. It is concluded that both the rifampicin-containing and pyrazinamide-containing 6-month regimens are highly effective, especially considering the very severe disease under study, and that the prospects of developing effective and practicable short-course regimens are excellent.

Where are we in the dose response curve?



Hypothesis

- Higher doses of rifamycines have increased efficacy resulting in
  - Potential decrease in relapses
  - Potential treatment shortening
  - Potential reduction in morbidity and mortality
  - Potential benefit in subpopulations: children, HIV, TBM, diabetes mellitus
  - Potential decrease of emergence of resistance
  - Potential role in treatment of not very prevalent intermediate resistance to rifampicin

Everyone does fine– or do they?

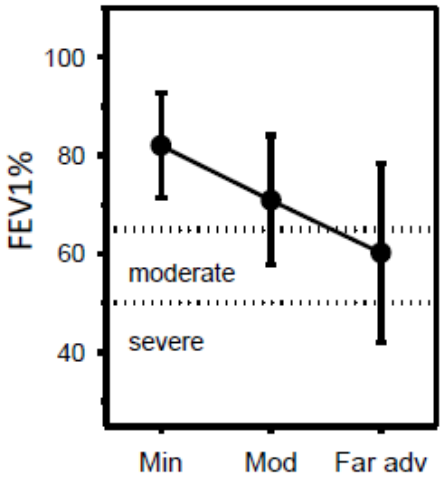
Category	Total	Year 1
Recurrent cases, No. (%)	203	67 (33)
Recurrent cases with DNA fingerprint data, No. (%)	130	44 (34)
Due to relapse	64	35 (55)
Due to reinfection	66	9 (14)
Incidence risk of recurrence[a]	. . .	3584
Incidence risk of relapse[a] (95% CI)	. . .	2836 (2131–3693)
Incidence risk of reinfection tuberculosis[a] (95% CI)	. . .	733 (410-1253)

Among successfully treated patients with TB, incidence risk of relapse is 2,836/100,000 in first year following treatment

Marx et al CID (2014) 58:1676

Relapses cause permanent disability and death

- Each TB episode causes permanent disability
  - Permanent reduction in lung function in relation to initial X-ray extent of disease (Willcox 1989)
  - Lung damage accumulates with each relapse (Hnizdo 2000)
- Survival is shortened despite TB cure
  - 22% dead in 10yrs, 3.6 yrs longevity loss (Hoger 2014)
  - 12% dead in 10yrs, SMR=3.7 (Shuldiner 2016)
  - Deaths not attributable to HIV, and not directly due to TB
    - 1/3 of post-TB deaths were due to pneumonia, influenza, or sepsis (*vs* 4% in general population)
  - Recurrences are likely to further shorten survival



Radiographic extent of disease

Willcox, ***Respir Med*** 1989

Slide from Bob Wallis

What happens when drug concentrations are too low?

Serum Drug Concentrations Predictive of Pulmonary Tuberculosis Outcomes

Jotam G. Pasipanodya,[1] Helen McIlleron,[2] André Burger,[3] Peter A. Wash,[3] Peter Smith,[3] and Tawanda Gumbo[1,4]

[1]Office of Global Health, University of Texas Southwestern Medical Center, Dallas, Texas; [2]Division of Pharmacology, Department of Medicine, University of Cape Town, Observatory; and [3]The Brewelskloof Hospital, Worcester, South Africa; and [4]Department of Medicine, University of Texas Southwestern Medical Center, Dallas

Results. Drug concentrations and pharmacokinetics varied widely between patients. Poor long-term outcomes were encountered in 35 (25%) patients. The 3 top predictors of poor long-term outcome, by rank of importance, were a pyrazinamide 24-hour area under the concentration–time curve (AUC) ≤ 363 mg·h/L, rifampin AUC ≤ 13 mg·h/L, and isoniazid AUC ≤ 52 mg·h/L. Poor outcomes were encountered in 32/78 patients with the AUC of at least 1 drug below the identified threshold vs 3/64 without (odds ratio = 14.14; 95% confidence interval, 4.08–49.08). Low rifampin and isoniazid peak and AUC concentrations preceded all cases of acquired drug resistance.

Conclusions. Low drug AUCs are predictive of clinical outcomes in tuberculosis patients.

JID, 2013

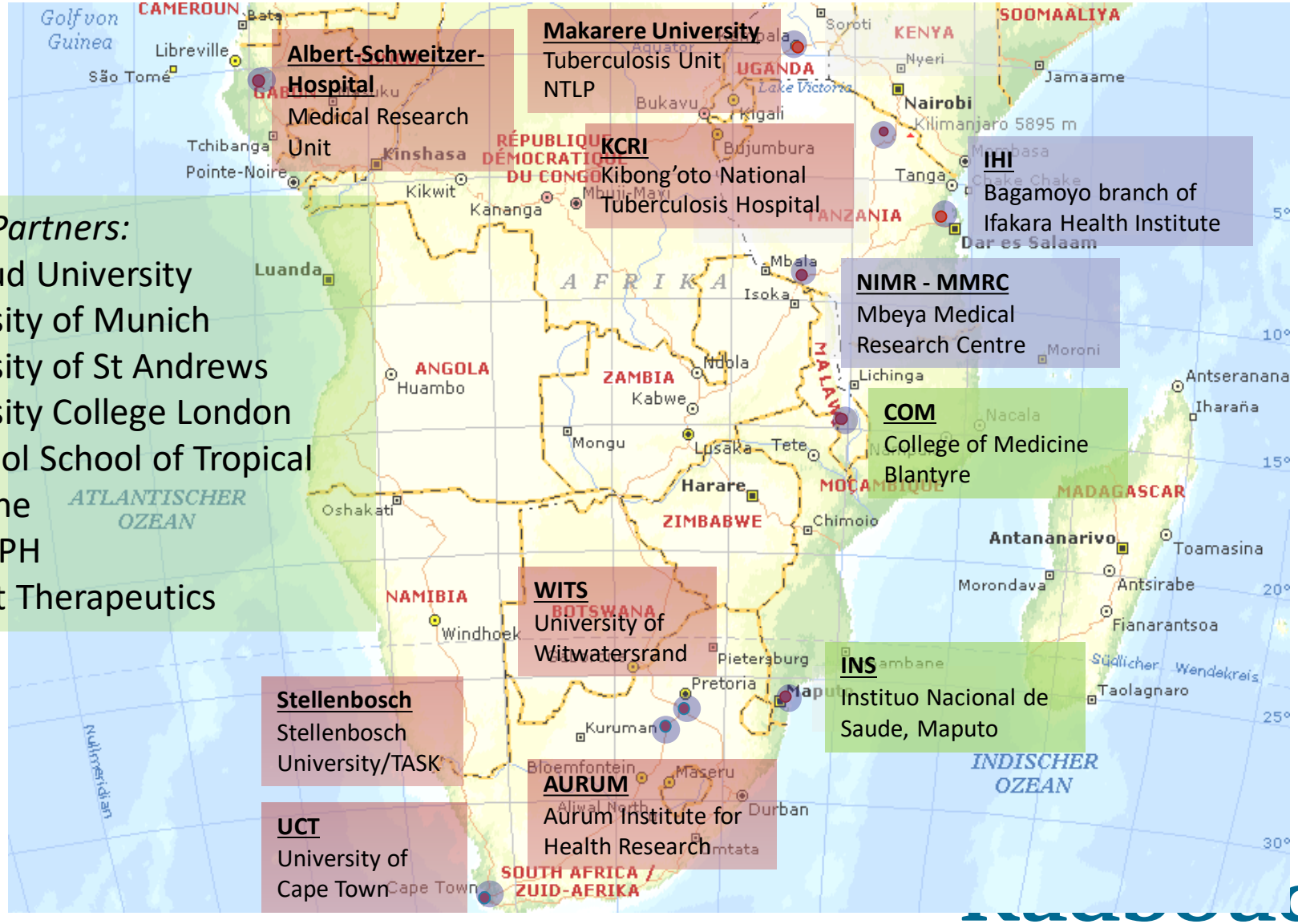
- So, **if** higher dosages of RIF are more efficient, what is the right dose to use?

- We have to identify:
  - Maximum tolerated dose mono-treatment
  - Maximum tolerated dose with other TB drugs for a longer period
  - Efficacy in phase II, III

PanACEA: who we are

Northern Partners:

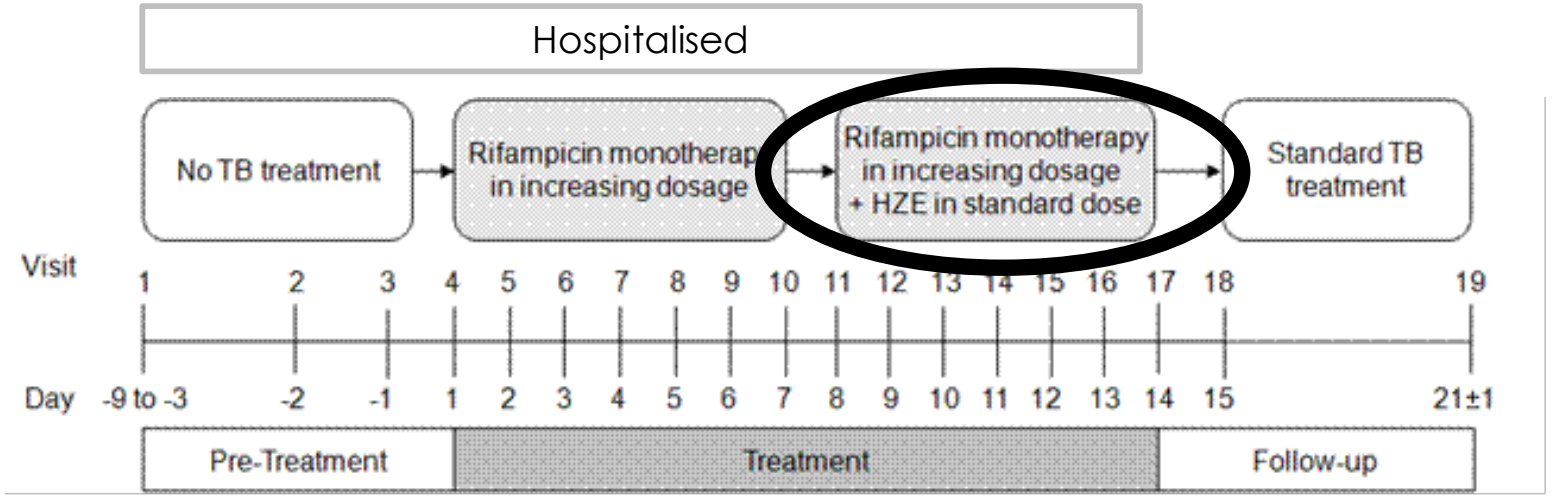
- Radboud University
- University of Munich
- University of St Andrews
- University College London
- Liverpool School of Tropical Medicine
- Swiss TPH
- Qurient Therapeutics



The game plan for the evaluation of high dose rifampicin in PanACEA

- HR1
- HR2
- MAMS 1
- STEP 2C
- HR Phase III

HR1 Trial design



IC procedure, baseline data, baseline sputum (at least two overnight samples)

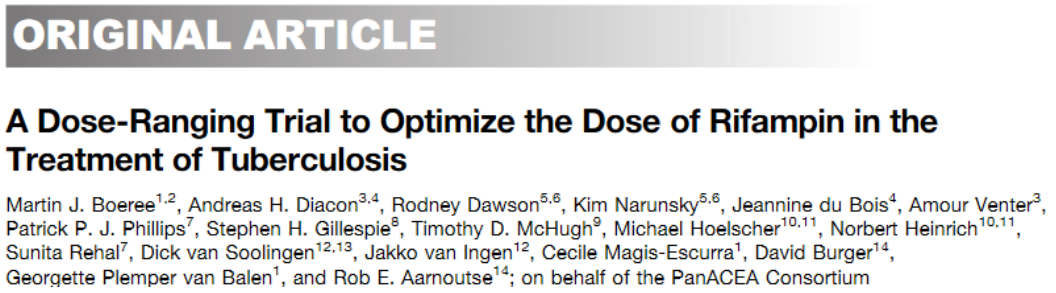
- Daily sputum collection and safety/AE check
- Day 7 and 14 include PK assessments

Additional safety/AE check

→ Not blinded and not randomised

Safety

- One control group with standard 10 mg/kg RIF (N=8)
- 5 consecutive arms of each 15 patients:
  - 20 mg RIF/kg
  - 25 mg RIF/kg
  - 30 mg RIF/kg
  - 35 mg RIF/kg



ORIGINAL ARTICLE

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree[1,2], Andreas H. Diacon[3,4], Rodney Dawson[5,6], Kim Narunsky[5,6], Jeannine du Bois[4], Amour Venter[3], Patrick P. J. Phillips[7], Stephen H. Gillespie[8], Timothy D. McHugh[9], Michael Hoelscher[10,11], Norbert Heinrich[10,11], Sunita Rehal[7], Dick van Soolingen[12,13], Jakko van Ingen[12], Cecile Magis-Escurra[1], David Burger[14], Georgette Plemper van Balen[1], and Rob E. Aarnoutse[14]; on behalf of the PanACEA Consortium

Boeree et al, AJRCCM, 191, 1058-65, 2015

- **All safe and well tolerated**

Recently, just published!

- 40 mg RIF/kg
- 50 mg RIF/kg

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

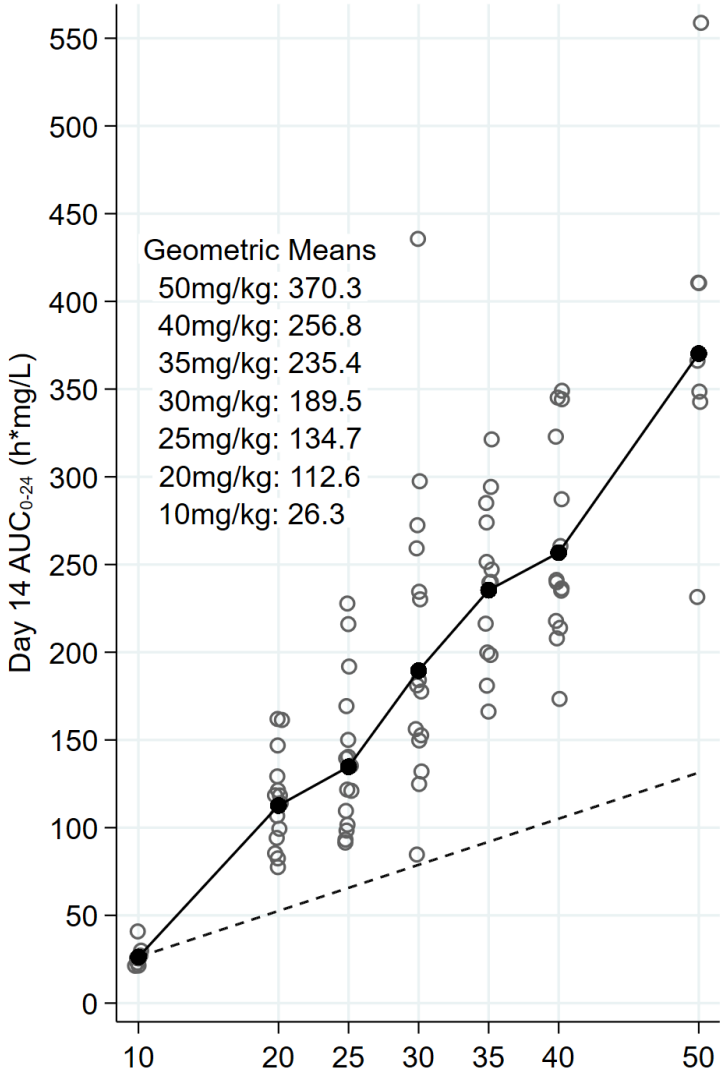
Increased bactericidal activity but dose-limiting intolerability at 50 mg·kg^{-1} rifampicin

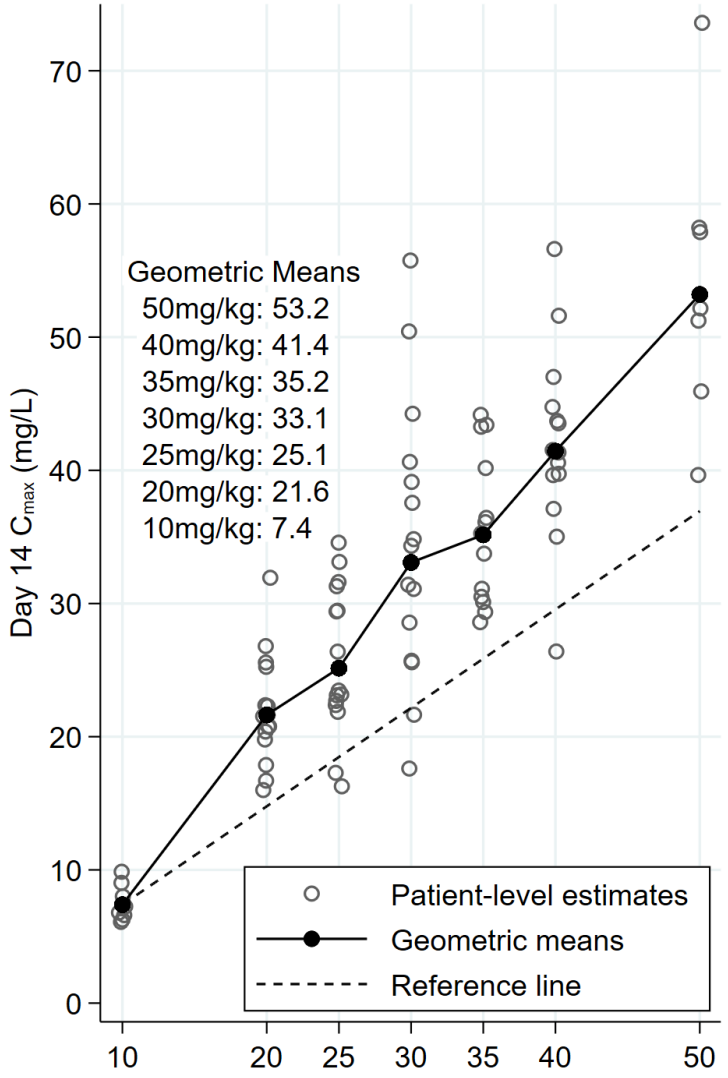
Lindsey H.M. te Brake, Veronique de Jager, Kim Narunsky, Naadira Vanker, Elin M. Svensson, Patrick P.J. Phillips, Stephen H. Gillespie, Norbert Heinrich, Michael Hoelscher, Rodney Dawson, Andreas H. Diacon, Rob E. Aarnoutse, Martin J. Boeree

Please cite this article as: te Brake LHM, de Jager V, Narunsky K, *et al*. Increased bactericidal activity but dose-limiting intolerability at 50 mg·kg^{-1} rifampicin. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00955-2020).

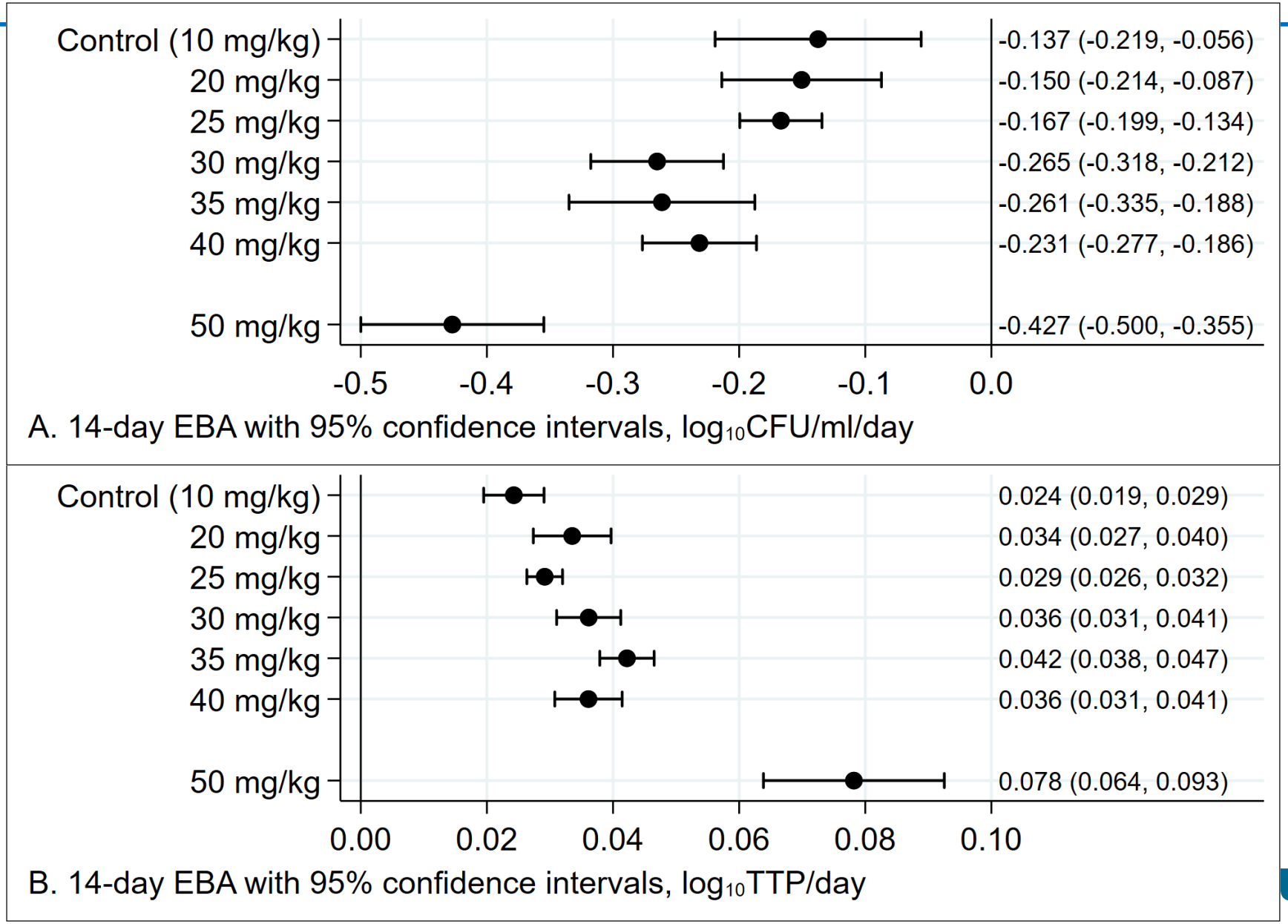
Safety

- 40 mg/kg:
  - 15 patients, no serious adverse events, no withdrawals
- 50 mg/kg:
  - 17 patients, 11 withdrawals
  - Grade 1 (n=60), grade 2 (n=21) or grade 3 (n=1)
  - Generally: “these were not happy patients”

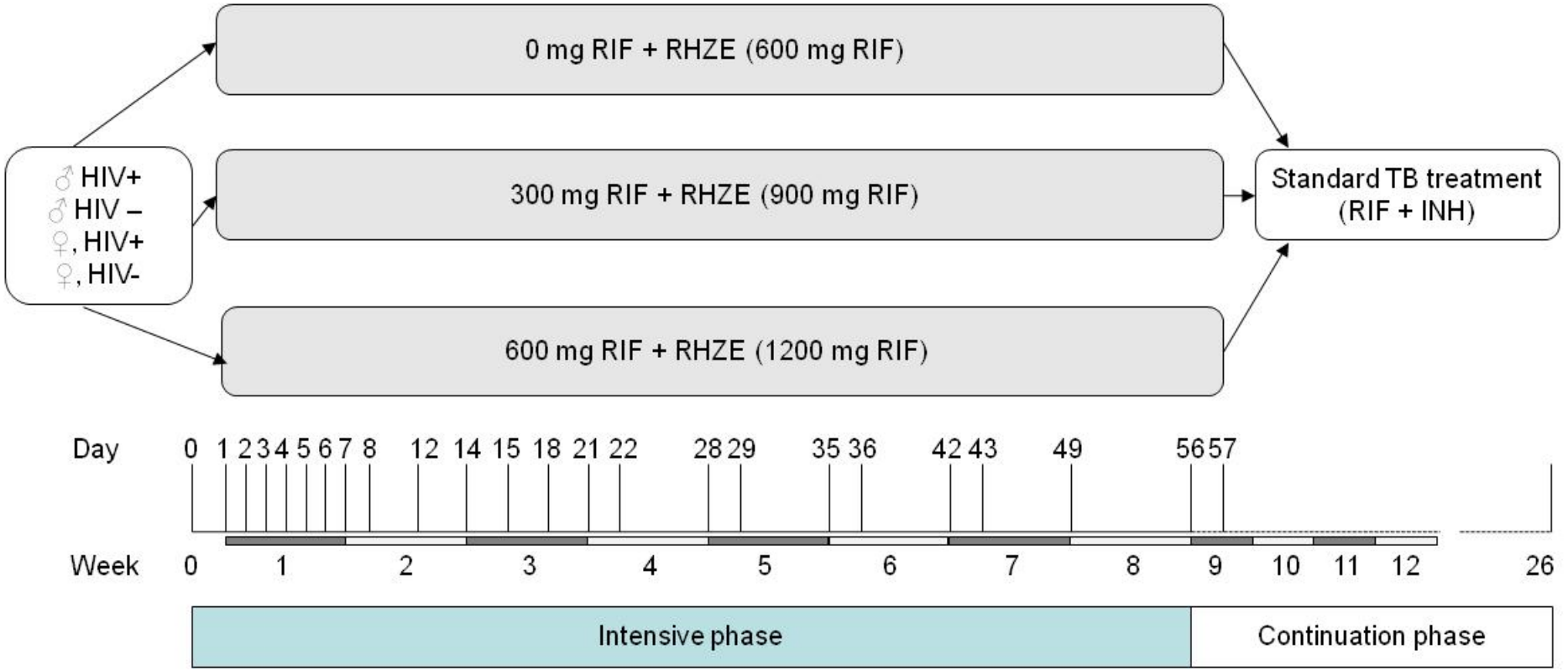

Geometric Means
50mg/kg: 370.3
40mg/kg: 256.8
35mg/kg: 235.4
30mg/kg: 189.5
25mg/kg: 134.7
20mg/kg: 112.6
10mg/kg: 26.3
Day 14 AUC0-24 (h*mg/L)
0
50
100
150
200
250
300
350
400
450
500
550
10
20
25
30
35
40
50


Geometric Means
50mg/kg: 53.2
40mg/kg: 41.4
35mg/kg: 35.2
30mg/kg: 33.1
25mg/kg: 25.1
20mg/kg: 21.6
10mg/kg: 7.4
Day 14 Cmax (mg/L)
0
10
20
30
40
50
60
70
10
20
25
30
35
40
50
Patient-level estimates
Geometric means
Reference line

Early bactericidal activity



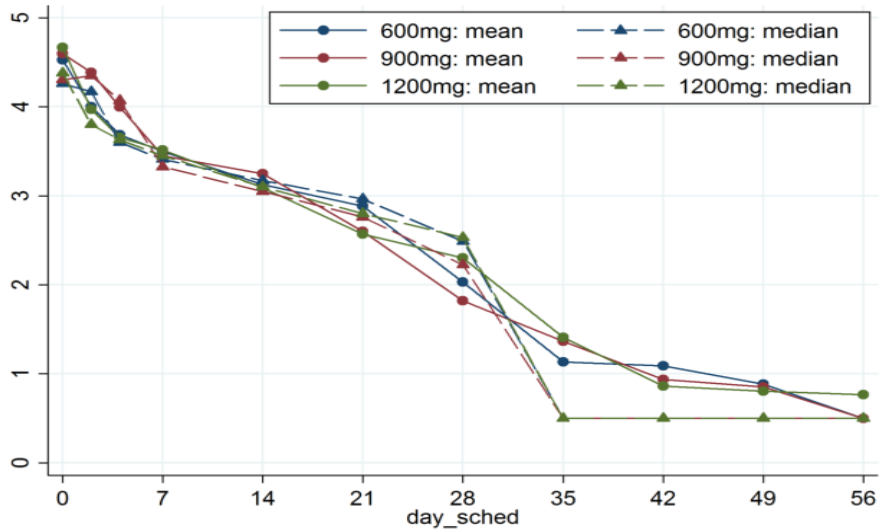
HighRIF2 – study design, N= 50 patients per arm



Results

- No differences in safety and tolerability in the three groups 600, 900, 1200 mg

- 600, 900, 1200 mg do not increase bacteriological response



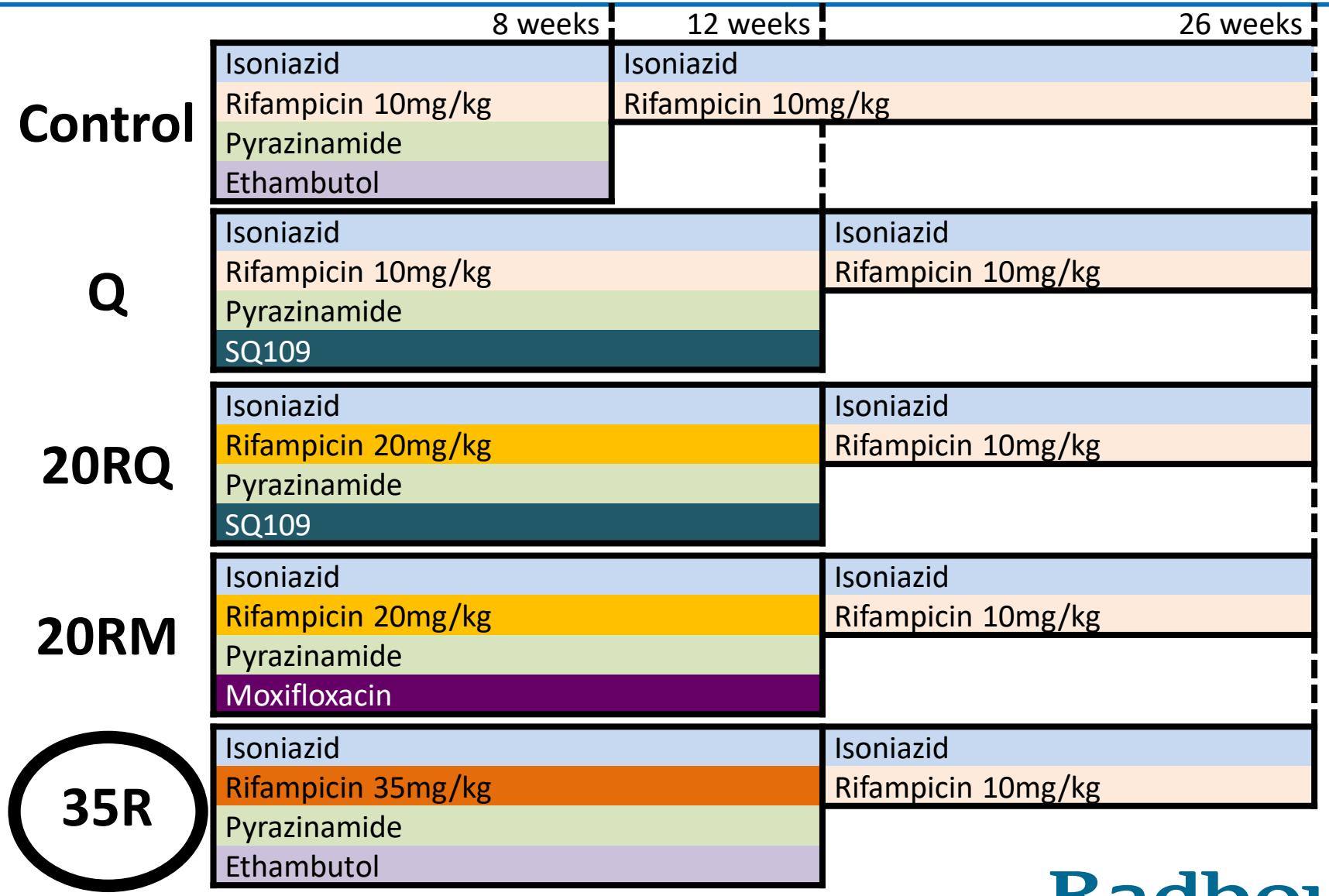
Other high dose rifampicin trials, not in PanACEA

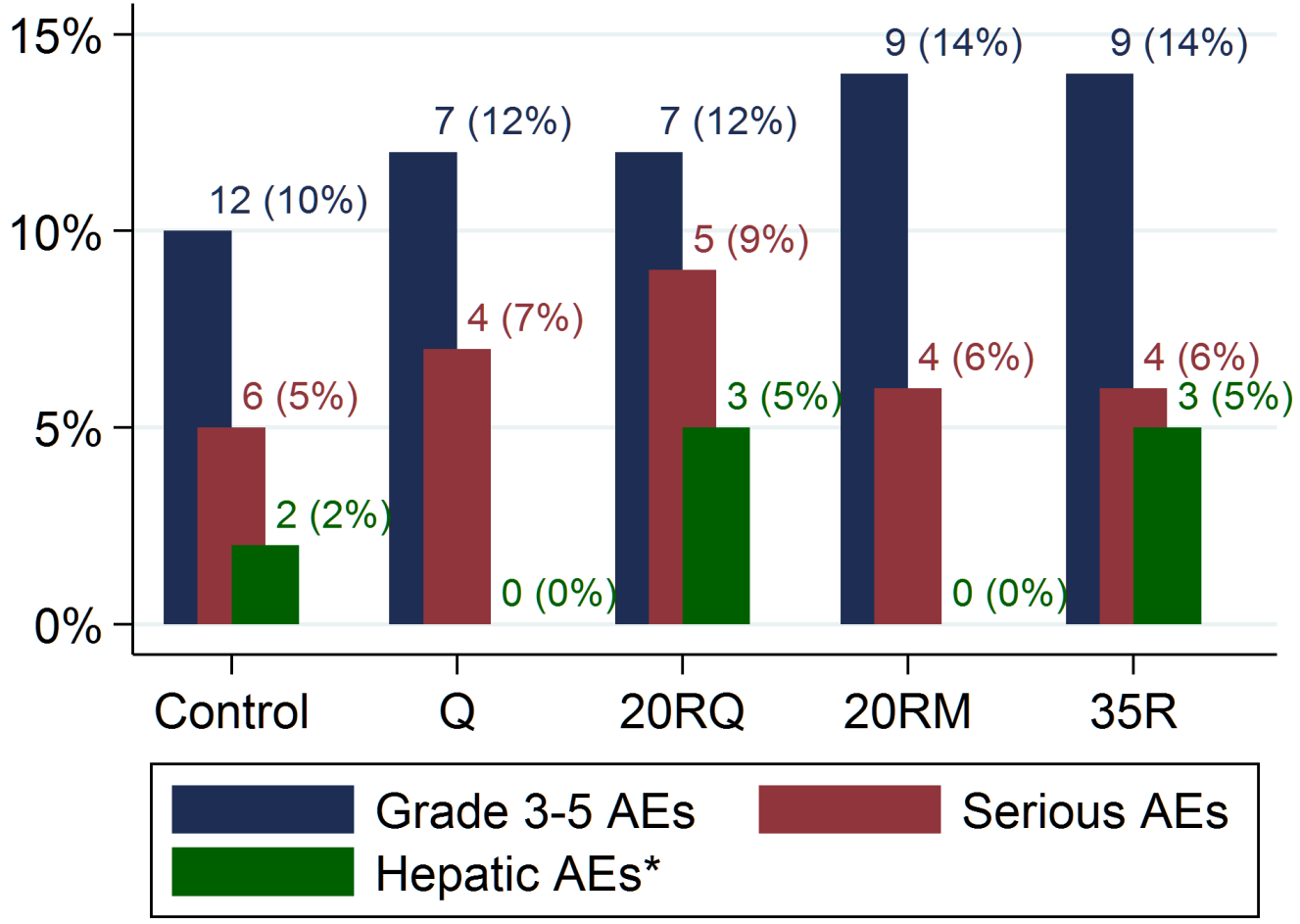
- RIFATOX (St George's University of London):
  - 261 eligible patients 10,15 and 20 mg RIF/kg for 4 months and 2 months standard continuation, looking at safety (Nepal, Bolivia, Uganda). No serious safety problems, especially no hepatic event differences

- **Efficacy and Safety of High-Dose Rifampin in Pulmonary Tuberculosis**
  A Randomized Controlled Trial
  - Same design as HR2; N=180 (Peru, Brazil) from Harvard University
  - Same result, slightly better with trend in increased culture conversion

Vélasques et al, AJRCCM, 2017

PanACEA-MAMS-TB-01




15%
10%
5%
0%
12 (10%)
6 (5%)
2 (2%)
7 (12%)
4 (7%)
0 (0%)
7 (12%)
5 (9%)
3 (5%)
9 (14%)
4 (6%)
0 (0%)
9 (14%)
4 (6%)
3 (5%)
Control
Q
20RQ
20RM
35R
Grade 3-5 AEs
Serious AEs
Hepatic AEs*

Time to stable culture conversion on MGIT liquid media over 12 weeks

	Control	Q	20RQ	20RM	35R
Included in analysis	123	58	56	63	63
Median time	62 days	63 days	66 days	55 days	48 days
Adj. HR[1] (95% CI)		0.82 (0.55 - 1.24)	0.73 (0.48 - 1.13)	1.42 (0.98 - 2.05)	**1.75 (1.21 - 2.55)**
		p=0.35	p=0.16	p=0.07	**p=0.003**
Censoring data at 8 weeks (to mimic previous TB phase II trials)					
Adj. HR (95% CI)[1]		1.05 (0.60 - 1.83)	0.91 (0.50 - 1.68)	**1.69 (1.02 - 2.80)**	**1.99 (1.21 - 3.29)**
		p=0.88	p=0.78	**p=0.04**	**p=0.007**

[1] Analysis has been adjusted for: HIV status; baseline GeneXpert CT; centre; baseline culture (using TTP).

Boeree, Heinrich, Lancet Infect Dis 2017

PanACEA- MAMS

- Rifampicin 35 mg/kg
- No problems in safety
- Increased efficacy in culture conversion

High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial

Martin J Boeree, Norbert Heinrich*, Rob Aarnoutse, Andreas H Diacon, Rodney Dawson, Sunita Rehal, Gibson S Kibiki, Gavin Churchyard, Ian Sanne, Nyanda E Ntinginya, Lilian T Minja, Robert D Hunt, Salome Charalambous, Madeleine Hanekom, Hadija H Semvua, Stellah G Mpagama, Christina Manyama, Bariki Mtafya, Klaus Reither, Robert S Wallis, Amour Venter, Kim Narunsky, Anka Mekota, Sonja Henne, Angela Colbers, Georgette Plemper van Balen, Stephen H Gillespie, Patrick P J Phillips, Michael Hoelscher, on behalf of the PanACEA consortium‡*

Lancet Infect Dis 2016

Published Online
October 26, 2016

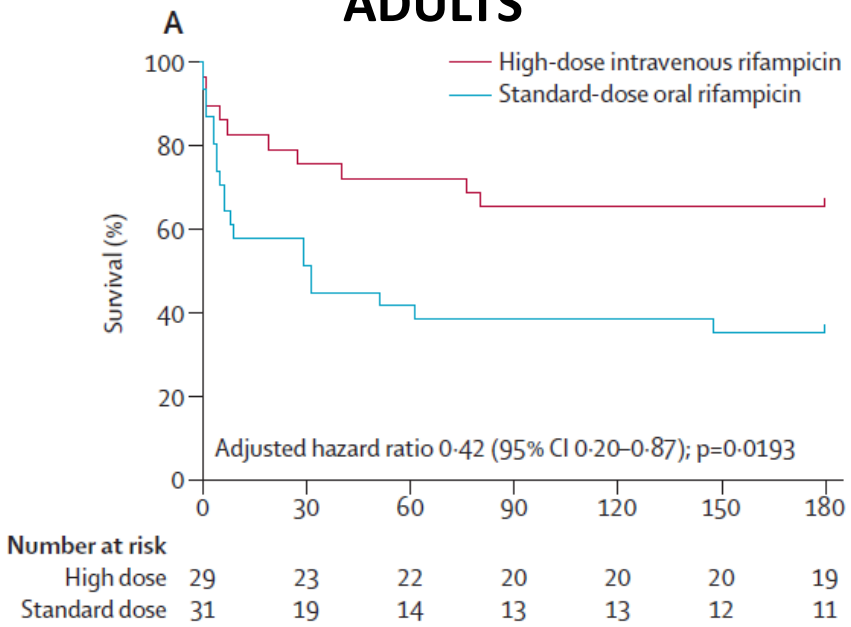
Next steps

- STEP2C with 2100 mg (phase 2B with relapse as endpoint) flat dose for 3 months
- Phase 3
- Pragmatic trial in Europe
- Already phase 3 trial ongoing: RIFASHORT comparing 600, 1200 and 1800 mg by Amina Jindani (St George's University of London)

- Mind you: already successful treatment shortening to 4 months with rifapentin and moxifloxacin (TBTC 31)

Rifampicin in TBM

ADULTS



Ruslami *et al.* (2013) Lancet ID 13: 27.

	Deaths	Univariable	Multivariable
Oral rifampicin 450 mg (n=31)	20 (65%)	1·00	1·00
Intravenous rifampicin 600 mg (n=29)	10 (34%)	0·42 (0·20–0·91)†	0·42 (0·20–0·91)†
No moxifloxacin (n=22)	10 (45%)	1·00	1·00
Moxifloxacin 400 mg (n=19)	8 (42%)	0·74 (0·29–1·89)§	0·76 (0·30–1·94)§
Moxifloxacin 800 mg (n=19)	12 (63%)	1·40 (0·60–3·25)§	1·27 (0·53–3·02)§
HIV positive (n=7)	4 (57%)	..	1·80 (0·59–5·53)
Glasgow Coma Scale at baseline	..	..	0·82 (0·68–0·99)

	600 mg, intravenous (n=26)	450 mg, oral (n=26)
Plasma		
AUC_{0-6} (mg.h/L)	78·7 (71·0–87·3)	26·0 (19·0–35·6)
C_{max} (mg/L)	22·1 (19·9–24·6)	6·3 (4·9–8·3)
C_{max} (≥8 mg/L)	26 (100%)	13 (50%)
T_{max} (h; median, range)	2 (1– 2)	2 (1–6)
CSF		
C_{max} (mg/L)§	0·60 (0·46–0·78)	0·21 (0·16–0·27)

Rx for 14 days

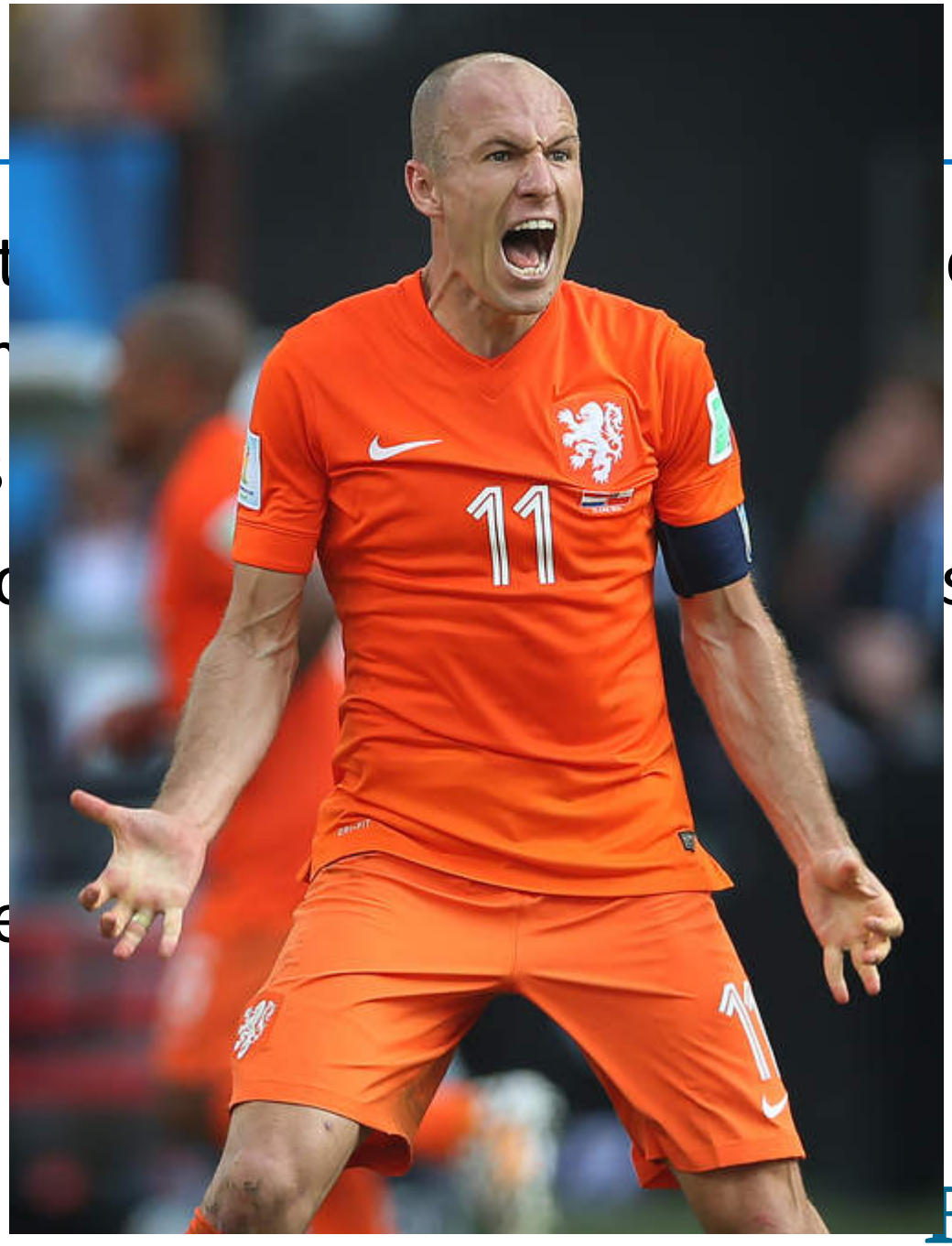
For now

- We use optimized dose of 35 mg/kg rifampicin already in
  - Severe PTB
  - TBM
  - TB and HIV
  - Severe EPTB
  - TB and diabetes mellitus

Conclusion

- Best dose of opt cin probably 2100 mg or 40 r
- HD rifampicin is
- Will possibly sho s
- Already used in

- Rifampicin make



PanACEA
Pan African Consortium for the Evaluation of Antituberculosis Antibiotics

Radboudumc


THANK YOU

Intensive tuberculosis treatment to reduce the high mortality of tuberculous meningitis in HIV-infected and uninfected patients

INTENSE TBM

26th March 2021

Alexandra Calmy (for the Intense TBM team)

Partnering for better care in TB Meningitis

The INTENSE-TBM project is part of the EDCTP2 Programme supported by the European Union (grant RIA2017T-2019) and is sponsored by Inserm-ANRS (ANRS 12398 INTENSE-TBM)

INTENSE-TBM Project

Funder: EDCTP

Sponsor: National Agency on AIDS and Viral Hepatitis (ANRS-MIE), France

Objective: To reduce mortality and neurological complications of TBM in adults with or without HIV co-infection

INTENSE-TBM project is part of the EDCTP2 Programme supported by the European Union


Guinée
Bénin
Nigeria
Sierra Leone
Côte d'
Togo
Ghana
Libéria
Lagos
Accra
Golfe de Guinée
Cameroun
République centrafricaine
Soudan du Sud
Éthiopie
Somalie
Guinée équatoriale
Gabon
Kenya
Nairobi
Rwanda
Burundi
RD Congo
Kinshasa
Tanzanie
Dar es Salam
Luanda
Angola
Zambie
Malawi
Mozambique
Zimbabwe
Madagascar
Namibie
Botswana
Pretoria
Eswatini
Lesotho
Durban
Afrique du S
Océan Atlantique Sud

Background

- Tuberculosis meningitis (TBM): TBM mortality (30% in HIV-negative patients and up to 70% in HIV-positive individuals) mostly occurring in the first 2 weeks
- The reversibility and long-term impact of neurological complications is unknown
- Poor efficacy of the current WHO recommended 1st line, unchanged for decades
- Inadequate CNS drug penetration may contribute to the high early mortality in TBM
- New AntiTB drugs such asbedaquiline (TMC207), delamanid and pretomanid (PA-824) are highly protein-bound and thus unlikely to have free penetration into cerebrospinal fluid (CSF).

Need of a new improved treatment as proposed here in INTENSE-TBM
(Thwaites GE & al. 2013, Donald PR & al. 2016)

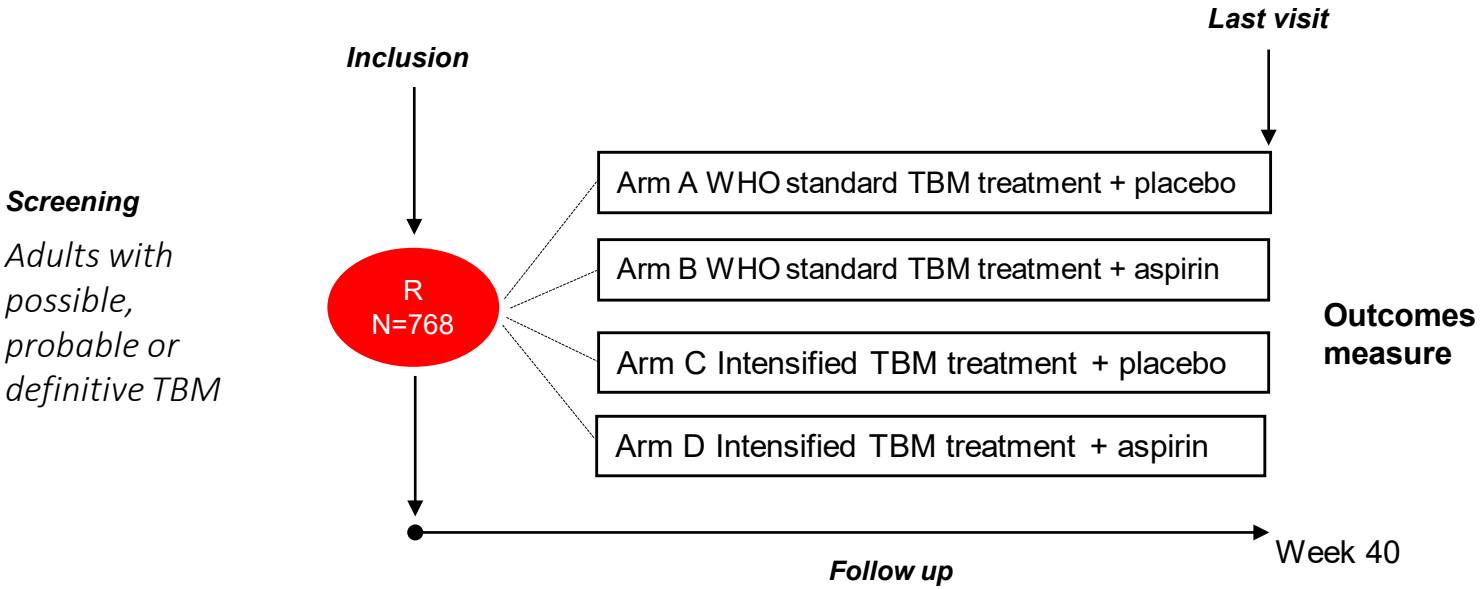
Hypothesis and Primary Objective

1. The trial hypothesis is that an intensified TBM treatment during the first 8-weeks with and without addition of aspirin will reduce the incidence of death compared with the standard of care.

2. The primary objective of the trial is to compare mortality of any cause at W40 : (i) between an intensified TBM treatment and a standard WHO treatment ; (ii) between aspirin and placebo during the first 8 weeks of treatment

Study design

- Factorial plan 2 x 2 Multicentre Phase III Randomized Controlled Superiority Trial
- Randomization (R) in a 1:1:1:1 ratio/ 192 patients per trial arm



Study population

- Sample size: *768 patients*

- Inclusion criteria:
  - ✓ Age > 15 years
  - ✓ TBM defined as “probable” or “definite” classified as per the Marais’s published consensus, and TBM defined as “possible” according to revised Marais criteria

  – Definitive TBM: acid-fast bacilli (AFB) seen in CSF microscopy, positive CSF M. tuberculosis culture, or positive CSF M. tuberculosis commercial nucleic acid amplification test in the setting of symptoms suggestive of meningitis
  – Probable TBM: total Marais’s score (1) of ≥12 when neuroimaging available or total score of ≥10 when neuroimaging unavailable. At least 2 points should either come from CSF or cerebral imaging criteria.
  – Revised possible TBM: total Marais’s score (1) score of 6-11 when neuroimaging available, or total score of 6-9 when neuroimaging unavailable, including LAM and Xpert Ultra and restricting miliary TB for suggestive chest X-ray in the “evidence of TB elsewhere” criteria .

The standard WHO TBM treatment (arms 1 and 2)

- Isoniazid 5 mg/kg/d + rifampicin 10 mg/kg/d + ethambutol 20 mg/kg/d + pyrazinamide 30 mg/kg/d (2 months)
- Isoniazid 5 mg/kg/d + rifampicin 10 mg/kg/d (7 months)
  - orally once a day or intravenously (IV) if clinically indicated.

- Corticosteroids:
  - D0-D7: 0.4 mg/kg eq. dexamethasone
  - D7-D14: 0.3 mg/kg eq. dexamethasone
  - D15-D21: 0.2 mg/kg eq. dexamethasone
  - D22-D60: 0.1 mg/kg eq. dexamethasone
  - IV or orally (depending on the patients' ability to take oral drugs and local practice) once a day.

The intensified TBM treatment (arms 3 and 4)

- Intensified regimen (doses for oral administration):
  - rifampicin 35 mg/kg/d during 8 weeks,
  - linezolid 1200 mg/d 4 weeks, followed by linezolid 600 mg/d 4 weeks
  - isoniazid 5 mg/kg/d, ethambutol 20 mg/kg/d and pyrazinamide 30 mg/kg/d

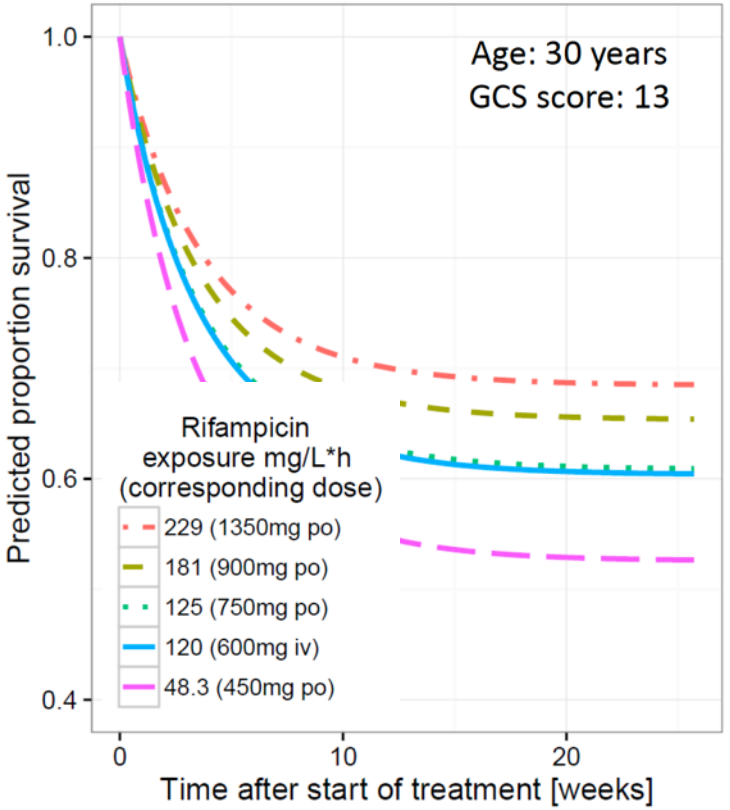
- *IV regimen only if clinically indicated:*
  - *high dose IV rifampicin 20 mg/kg/d*
  - *IV linezolid 1200 mg/d*
  - *IV isoniazid 5 mg/kg/d*
  - *oral pyrazinamide 30 mg/kg/d*

- M3–M9: oral rifampicin 10 mg/kg/d and isoniazid 5 mg/kg/d

- Corticosteroids: similar to standard TBM WHO treatment

INTENSE-TBM Rifampicin-1

1. High-dose Rifampicin in INTENSE-TBM: pulmonary TB example (Svensson et al, CID 2018)
   - Relationship between rifampicin plasma exposure and treatment response over 6 months (n=336, 97 with PK data)
   - Higher rifampicin exposures increased the probability of early culture conversion
   - The effect did not plateau



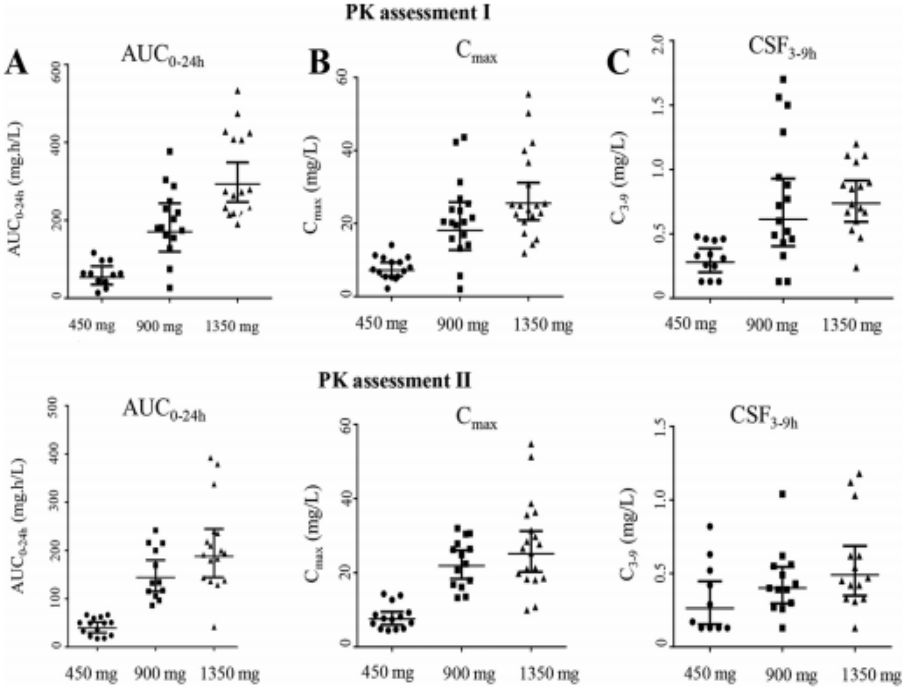
INTENSE-TBM Rifampicin-2

1. High-dose Rifampicin in INTENSE-TBM: PK

- Large increase rifampicine exposure in plasma and CSF and safe of tripling the standard dose of rifampicin (Dian S and al. 2018, Scott KE and al. 2018)

- Concentration–effect relationship on TB culture conversion

- good hepatic tolerance of higher dose of rifampicin (up to 35 mg/kg orally) *(Boeree MJ and al. 2017; Aarnoutse RE and al. 2017).*

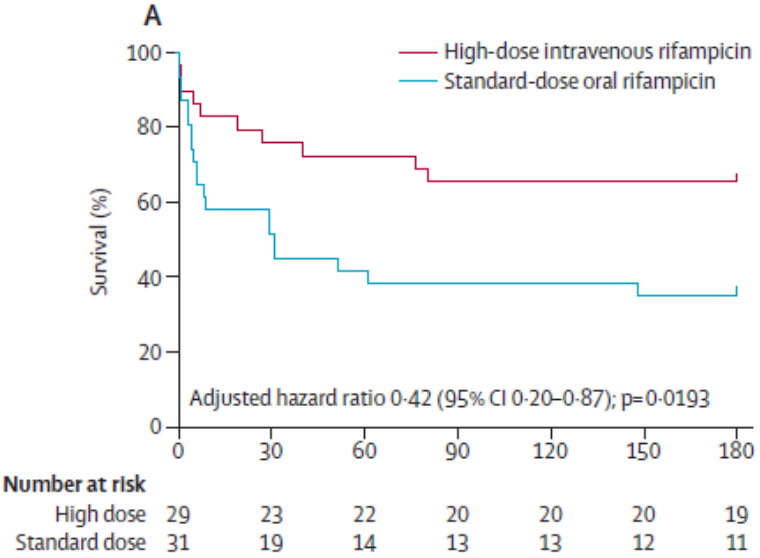


High dose Rifampicin-3

1. High dose Rifampicin in TBM: effect on mortality (phase 2 studies)
   (Ruslami, Lancet ID 2013, Dian, AAC 2018)

ıtive mortality per time point

	All TBM patients				Bacteriologically confirmed (definite) TBM[a]			
n (%)				p				p
	450 mg (10 mg/kg)	900 mg[b] (20 mg/kg)	1350 mg (30 mg/kg)		450 mg (10 mg/kg)	900 mg[b] (20 mg/kg)	1350 mg (30 mg/kg)	
All (n=60)	n=20	n=20	n=20		n=14	n=14	n=15	
13 (22)	5 (25)	5 (25)	3 (15)		3 (21)	4 (29)	1 (7)	
14 (23)	5 (25)	6 (30)	3 (15)		3 (21)	4 (29)	1 (7)	
15 (25)	5 (25)	7 (35)	3 (15)		3 (21)	5 (36)	1 (7)	
15 (25)	5 (25)	7 (35)	3 (15)		3 (21)	5 (36)	1 (7)	
19 (32)	7 (35)	9 (45)	3 (15)	0.116[b]	5 (36)	6 (43)	1 (7)	0.069[b]



High dose Rifampicin-4

1. High dose Rifampicin in TBM: a phase II open-label randomized controlled trial – 61 adults, 92% HIV+, median CD4 cell count 50 cells/µL

   Cresswell et al, CID 2021 (in press)

«Rifampicin is undetectable in the CSF of the majority of TB meningitis patients at standard dosing. High-dose rifampicin administered intravenously 20mg/kg and orally 35mg/kg resulted in therapeutic CSF rifampicin concentrations with no excess toxicity in a predominantly HIV- positive population. «

Achieving CSF concentrations above rifampicin minimal inhibitory concentration (MIC) occurred in 11% (2/18) of standard-of-care, 93% (14/15) of IV-20, and 95% (18/19) of PO-35 participants.

High dose Rifampicin-4

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- ✓ 11% (2/18) of standard-of-care,
- ✓ 93% (14/15) of IV-20, and
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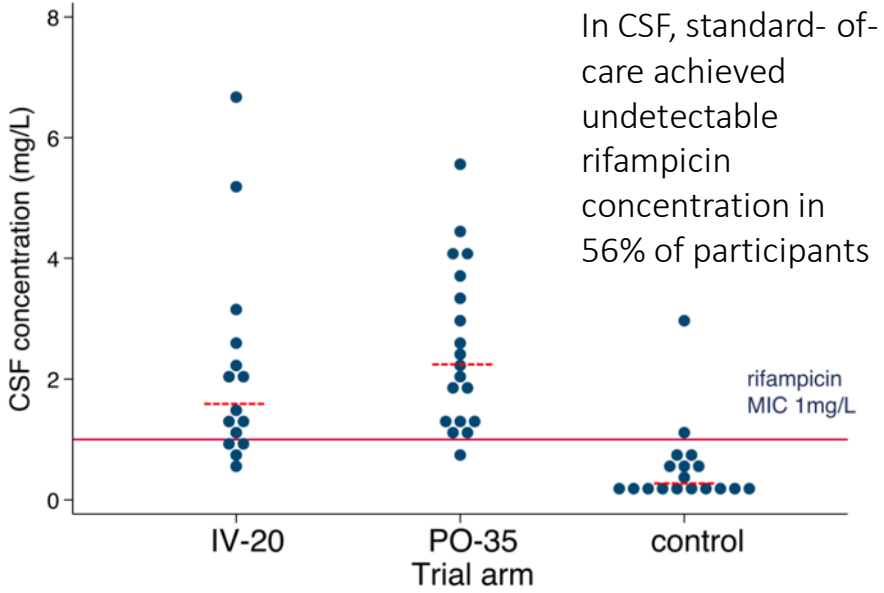


In CSF, standard- of-care achieved undetectable rifampicin concentration in 56% of participants

High dose Linezolid in Intense-TBM

2. Linezolid in INTENSE-TBM (hypothesis for improved efficacy)

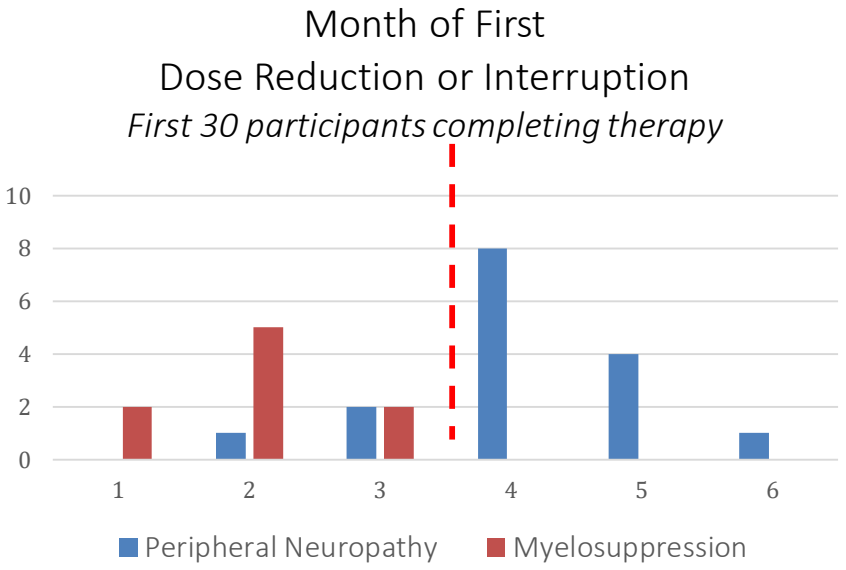
- Recommended by the WHO for the treatment of MDR-TB (March 2017)
- Excellent meningeal diffusion: AUC meningeal / plasma= 0.9 - 1 (un-inflamed or mildly inflamed meninges) *Nau Clin Microbiol Rev 2010*
- MIC against M. tuberculosis = 0.125 - 1 mg/L *Alcala Antimicrob Agents Chemother 2003*
- AUC/MIC ratio= predictive of linezolid in vivo anti-TB activity *Deshpande Clin Infect Dis 2016*
- Rifampicin lead a 40% reduction in linezolid AUC *Pea J Antimicrob Chemother 2012*
- 2-fold increasing of linezolid dose (1,200 mg daily), in combination with rifampicin, will be needed to reach the target AUC/MIC ratio

High Dose Linezolid in Intense-TBM (2)

2. Linezolid in INTENSE-TBM (safety assessment)

- ✓ 1200 mg/d the first 4 weeks to increase anti-TB activity in presence with a drug-drug interaction between LZD and RIF (WHO 2015; Nuermberger E. 2016)

- ✓ Linezolid 1,200 mg daily was evaluated
  - In 15 MDR-TB: After a median period of 375 days, linezolid caused major AE in 6% MDR-TB patients Villar Eur Respir J 2011
  - In 72 XDR-TB: 71% participants had at least 1 dose interruption during the 6 month treatment (myelosuppression= 22% ; peripheral neuropathy= 28%) Conradie NIX-TB trail CROI 2017



Slide courtesy of Francesca Conradie(NIXtb)/provided by Sean Wasserman

Aspirin in Intense-TBM

Reference	ASA dose	Duration	Population	Complications	Conclusion	Place
Misra Journal of Neurological Science 2010	150 mg/d Placebo	3 months	118 HIV-uninfected	28 vomiting 1 epigastric discomfort 4 rashes 28 altered liver function No difference	ASA 150 mg resulted in insignificantly lesser strokes (24 vs 43%) and significantly reduced 3 months mortality (22% vs. 43% in placebo group p=0.02)	India
Schoeman Journal of Child Neurology 2011	75 mg/d 100 mg/kg Placebo	1 month	146 children	1 hematemesis 1 death (intracranial bleeding)	ASA irrespective of dose did not show any significant benefit regarding morbidity and mortality in children	South Africa
Mai Elife 2018	81 mg/d 1000 mg/d Placebo	2 months	120 HIV-uninfected	Cerebral (MRI proven) or gastrointestinal bleeding: Placebo= 14% ASA 81mg= 23% ASA 1000mg= 20% No difference	Potential reduction in new infarcts and deaths by days 60 in the ASA treated participants with microbiologically confirmed TBM : 34% events in placebo 15% in aspirin 81mg/d 11% in aspirin 1000 mg/d (p=0.06)	Vietnam

Aspirin-placebo

ANRS 12398 INTENSE TBM

ASPIRINE 100 mg or/ou PLACEBO (*tablets, oral use* – comprimés, voie orale)

Dosage: 2 tablets per day
Posologie: 2 comprimés par jour

Drug code
Code du médicament **XXX – 1**

Participant Code
Code du participant |___|___|___| - |___|___| - |___|___|___|

Date of first use
Date de première utilisation __ __ 202_

Batch number
Numéro de lot XXXXXXXX

Expiration date
Date d'expiration XX / XX / XXXX

Principal Investigator of the center
Investigateur Principal du centre _____

For clinical research only.
Do not leave within the reach of children.
Keep in the original box.
Store at a temperature not exceeding 25°C.
Return the box to the pharmacy at each visit.

Pour recherche clinique uniquement.
Ne pas laisser à la portée des enfants.
Conserver dans la boite d'origine.
Conserver à une température ne dépassant pas 25°C.
Rapporter la boite à la pharmacie à chaque visite.

Dolutegravir interaction with high dose RIF

1. WHO recommends DTG double dose when associated with RIF
   - A recent study from Uganda presented at CROI (March 2021) showed no concerns relative to the increased dose of RIF (phase 2b trial, 120 patients, median age 36)
   - Sputum concersion 86% in RIF high dose versus 62% in RIF standard dose

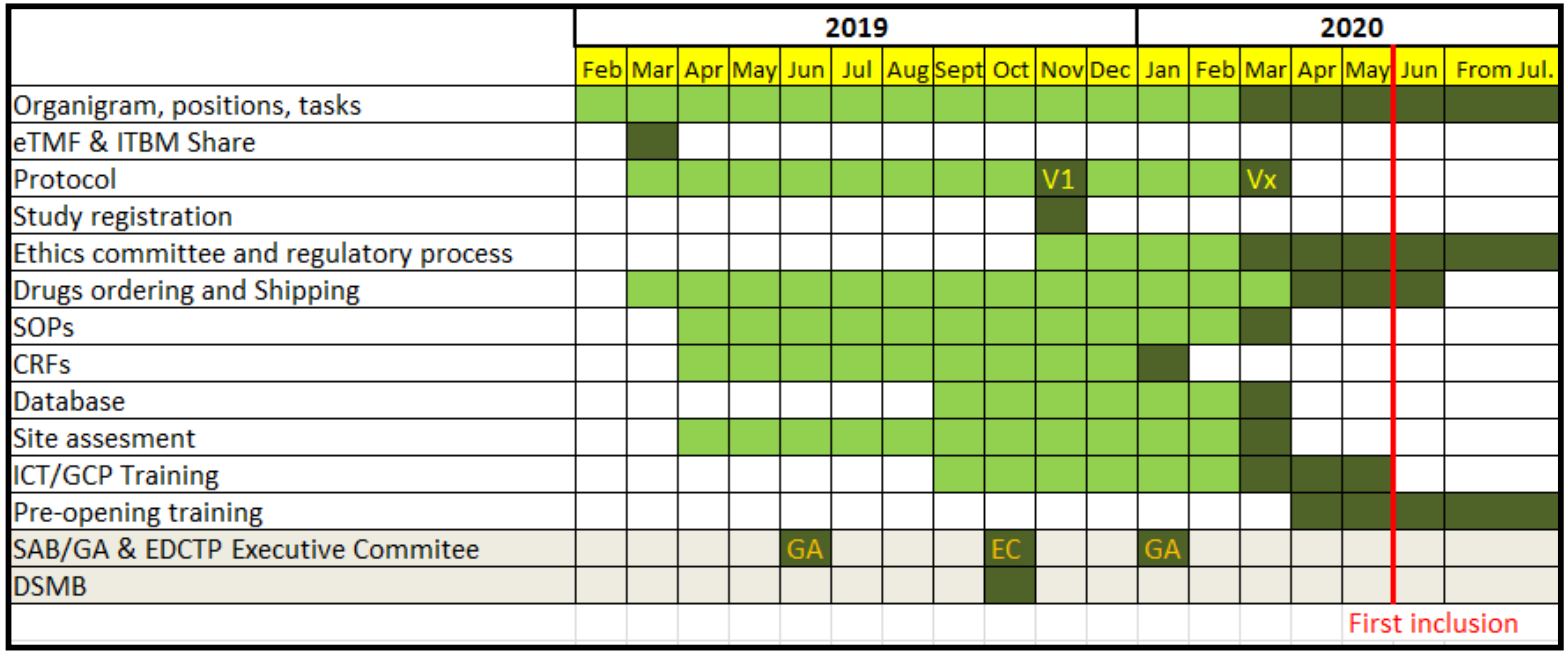
Table 1: Dolutegravir (DTG) trough and Efavirenz (EFV) mid-dose concentration in patients on high dose vs standard dose rifampicin.

	DTG group		EFV group	
	Arm 1A High dose (RIF 35 mg/kg)	**Arm 1B Standard dose (RIF 10 mg/kg)**	**Arm 2A High dose (RIF 35 mg/kg)**	**Arm 2B Regular dose (RIF 10 mg/kg)**
Number randomized, n	30	34	25	29
PK concentrations				
Geometric Mean	0.32	0.30	0.33	0.60
95% Confidence Interval*	0.11 – 0.95	0.11 – 0.82	0.02 – 4.87	0.06 – 6.02
P-value	0.918		0.72	

RIF – Rifampicin, DTG – Dolutegravir, CI = Confidence interval
DTG concentrations represented as trough drug concentration (C_{trough}) and EFV as mid-dose

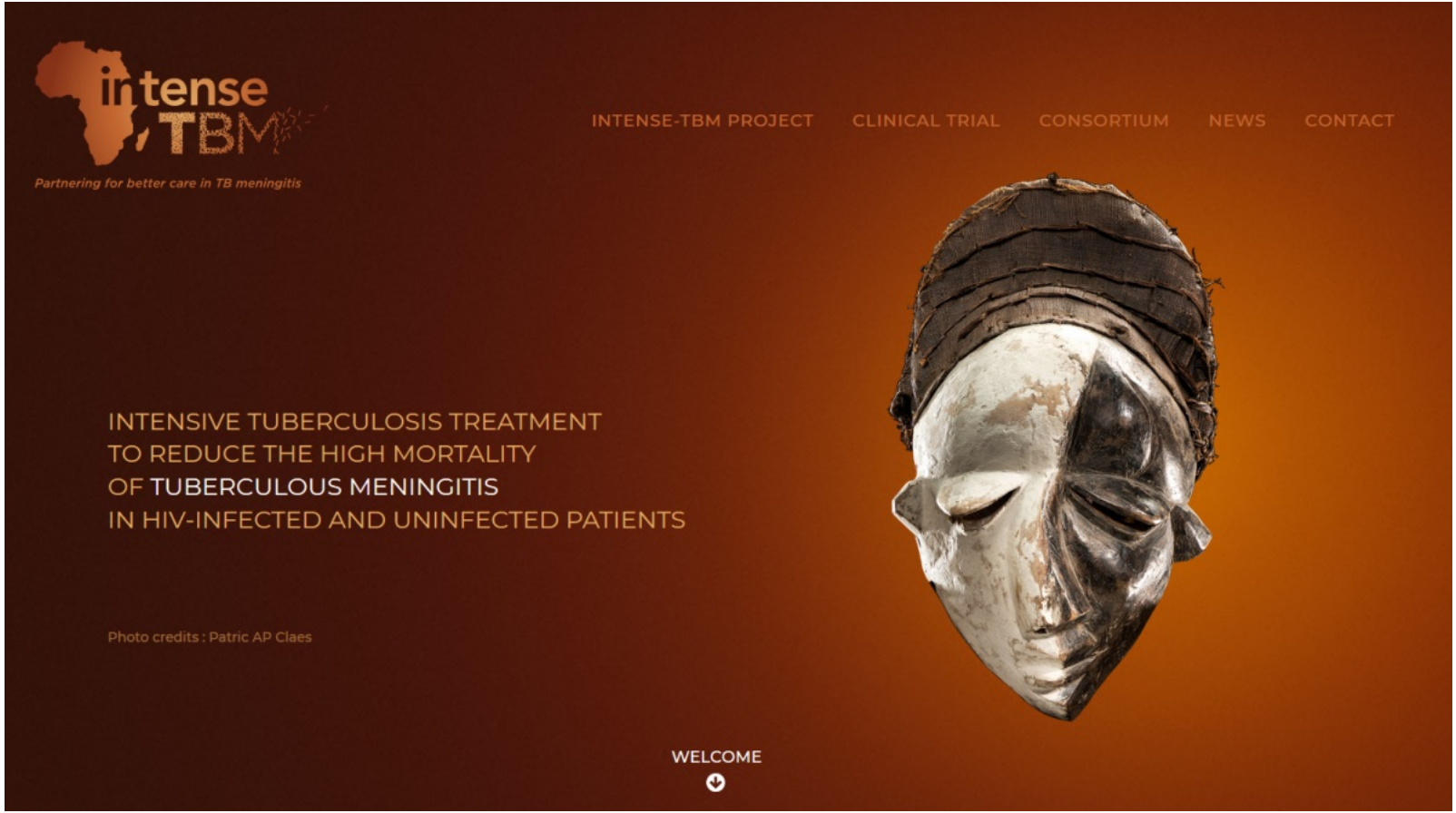
Sekaggya-Wiltshire et al, CROI 2021, abstract 90

Schedule



First inclusion: January 2021 (Madagascar, Ivory Coast

https://intense-tbm.org/



Trial team, Abidjan, 2019

The study is planned to start in April 2020

Submission to Ethics: Nov 2019

https://intense-tbm.org/

PRO-CON Debate:

Measuring serum levels of antituberculosis drugs: Waste of money or necessary for effective individualized treatment?

29. Tuberculosis-Symposium 25th March 2021

PD Dr. med. Gunar Günther

Leitender Arzt

Klinik für Pneumologie

Inselspital Bern

Prof. Dr. med. Jan Fehr

Departementsleiter Public & Global Health

Zentrum für Reisemedizin & Übertragbare Krankheiten

Institut für Epidemiologie, Biostatistik und Prävention, Universität Zürich

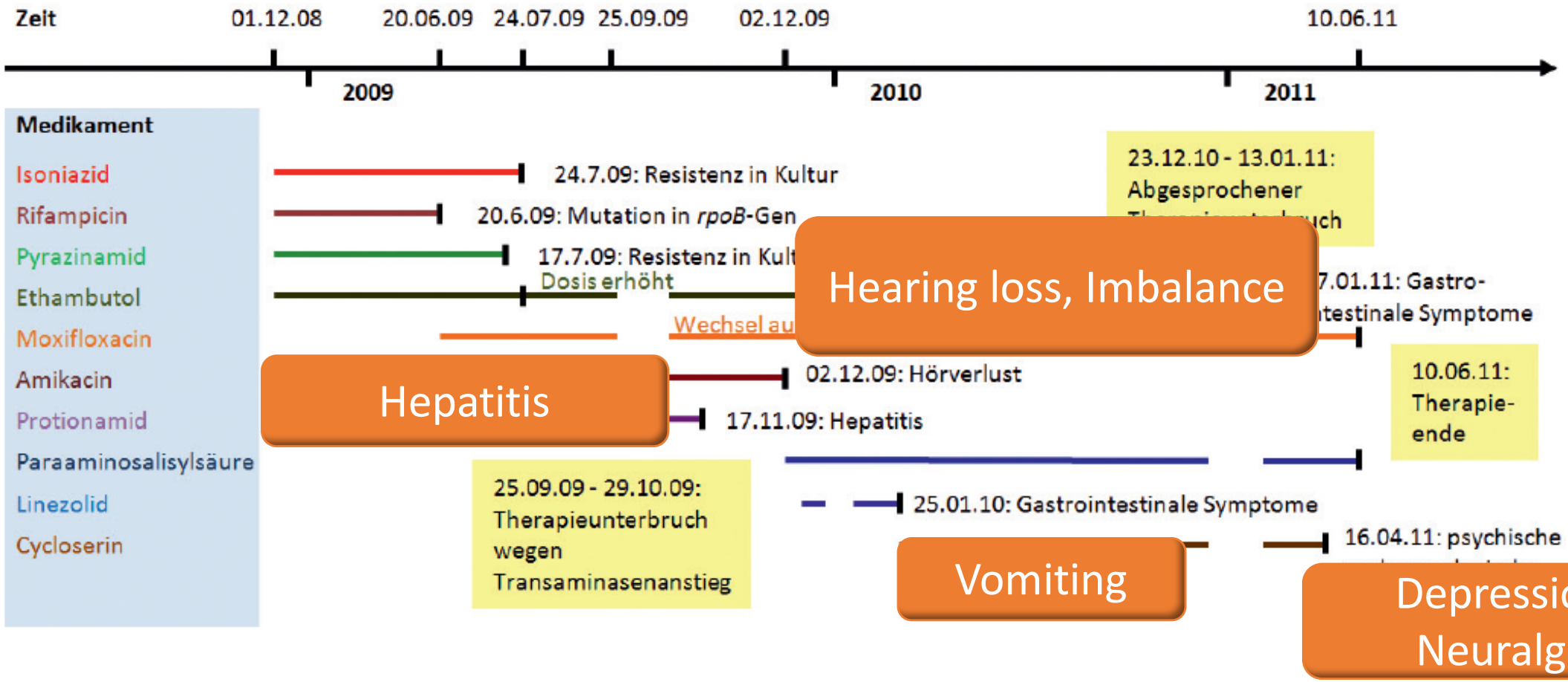
Universität Zürich[UZH]

UniversitätsSpital Zürich

UNIVERSITÄT BERN

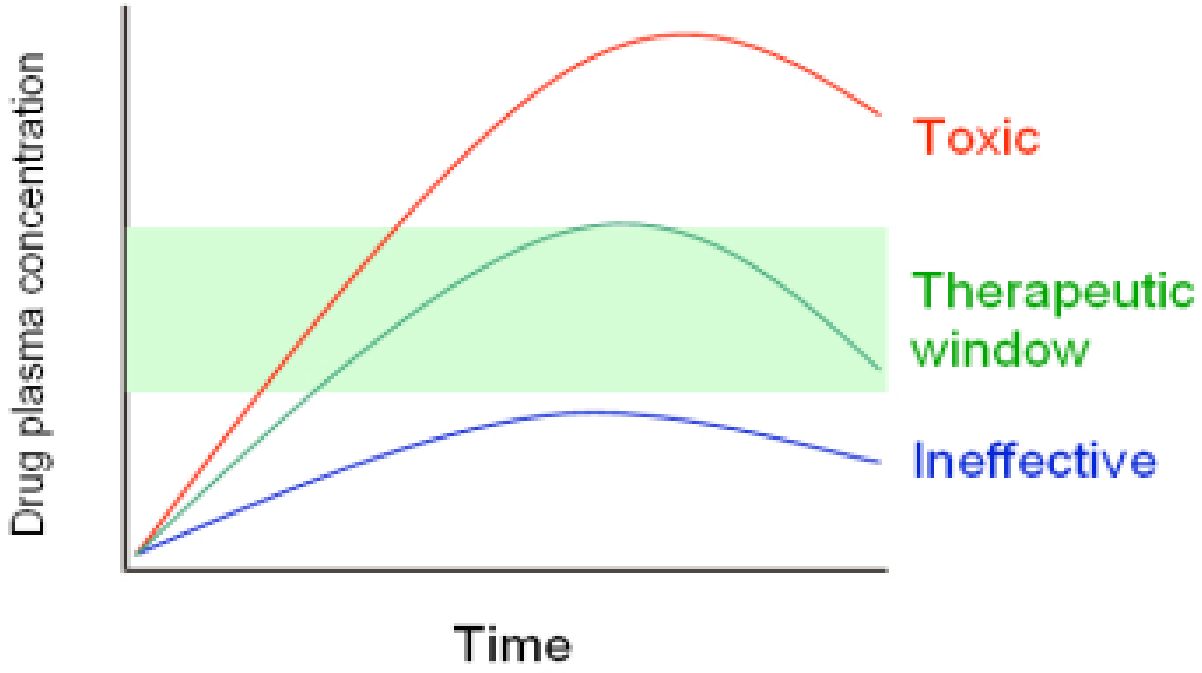
INSELSPITAL UNIVERSITÄTSSPITAL BERN HÔPITAL UNIVERSITAIRE DE BERNE

‘Cured from TB but suffering from side effects for ever’ (40 years old patient)



[1]Verena Schärer, [1]Roland Hafner, [3]Adrian Ciurea, [1]Lars Henning, [2]Akos Somoskövi, [1]Rainer Weber, [1]Jan Fehr

The pitfall of ‚one size fits all‘



Risk for interruption

Optimize e.g. shorter treatment

Risk for failure & resistance

Toxicity matters

Artist Pathy Tshindele

Toxicity matters

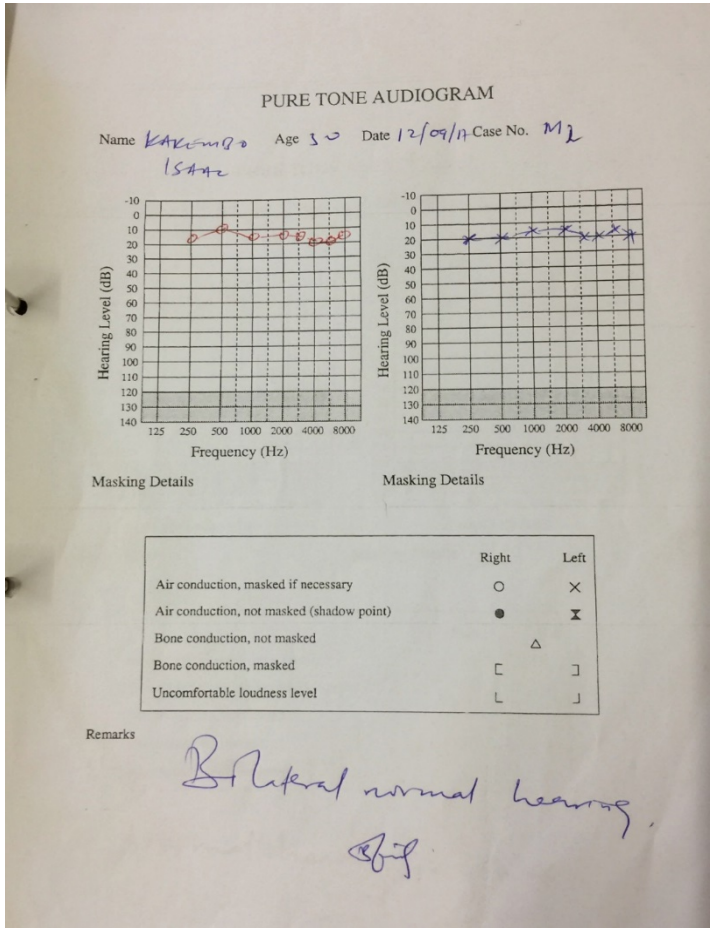
High efavirenz serum concentrations in TB/HIV-coinfected Ugandan adults with a *CYP2B6* 516 TT genotype on anti-TB treatment

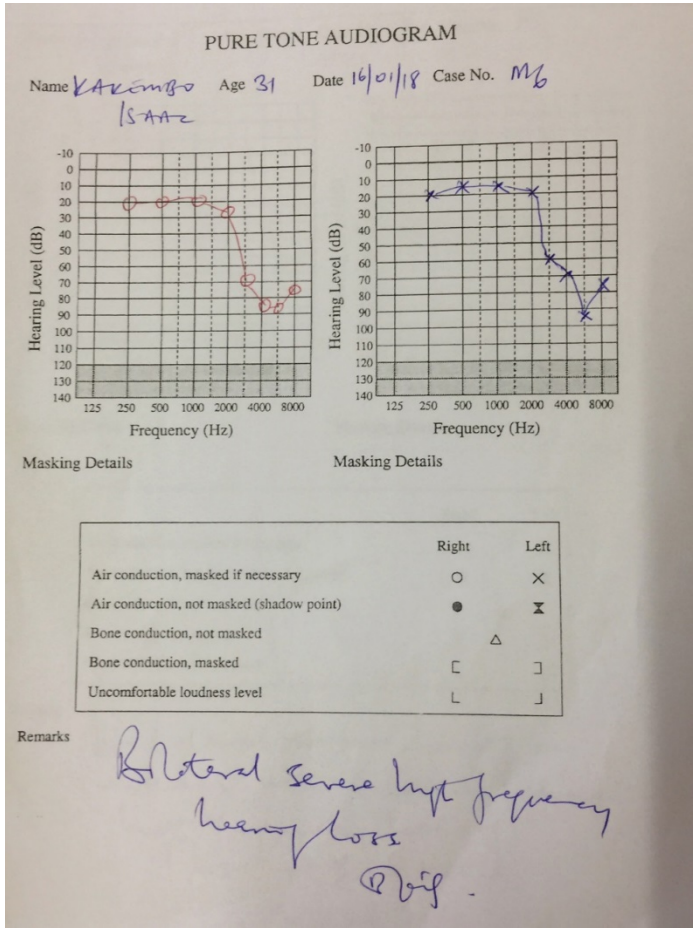
Amrei von Braun[1,2]*, Barbara Castelnuovo[1], Bruno Ledergerber[2], Jessica Cusato[3], Allan Buzibye[1], Andrew Kambugu[1], Jan Fehr[2,4], Andrea Calcagno [3], Mohammed Lamorde[1] and Christine Sekaggya-Wiltshire[1]

Conclusions: A large proportion of our study participants had at least one efavirenz serum concentration >4 mg/L. The *CYP2B6* 516 TT genotype was the strongest predictor of high concentration. Physicians should be vigilant that efavirenz serum concentrations may be elevated in patients on concomitant anti-TB treatment and that individualized care is warranted whenever possible.

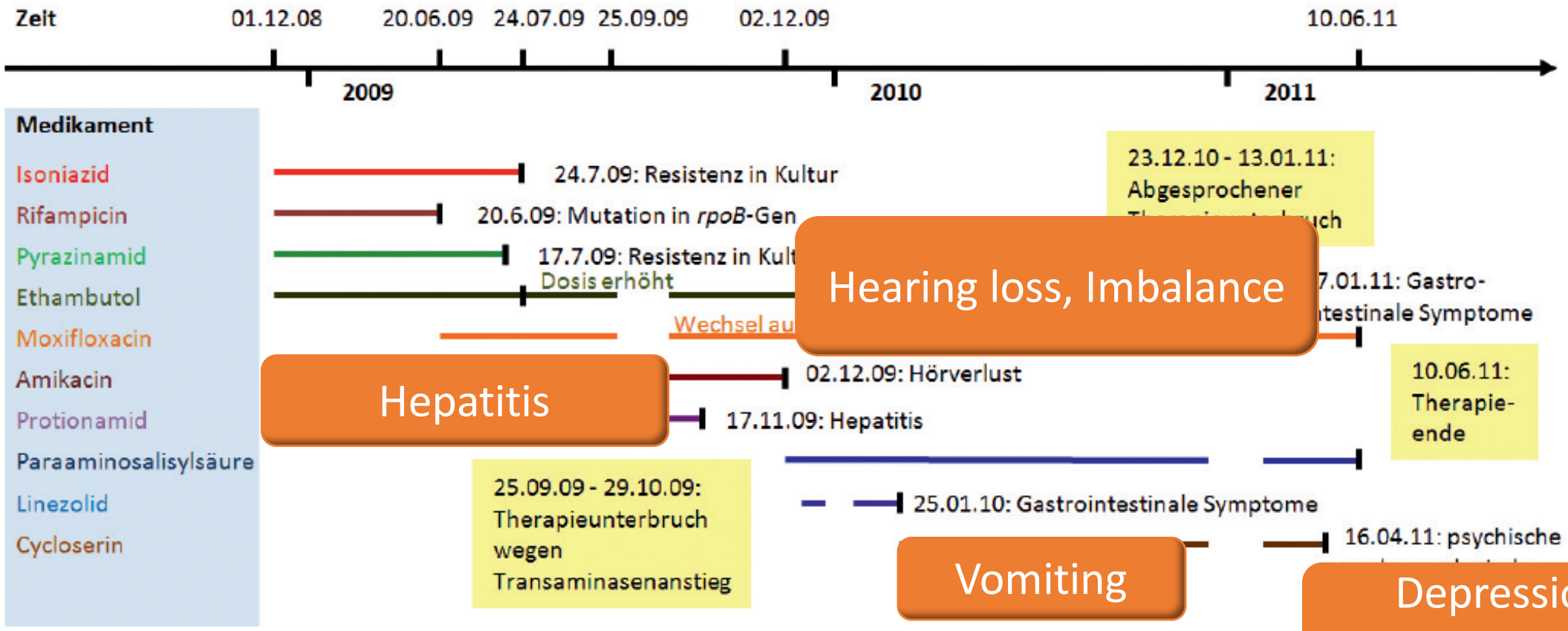
J Antimicrob Chemother 2019; **74**: 135–138

Toxicity matters: MDR-TB treatment in Kampala, Uganda



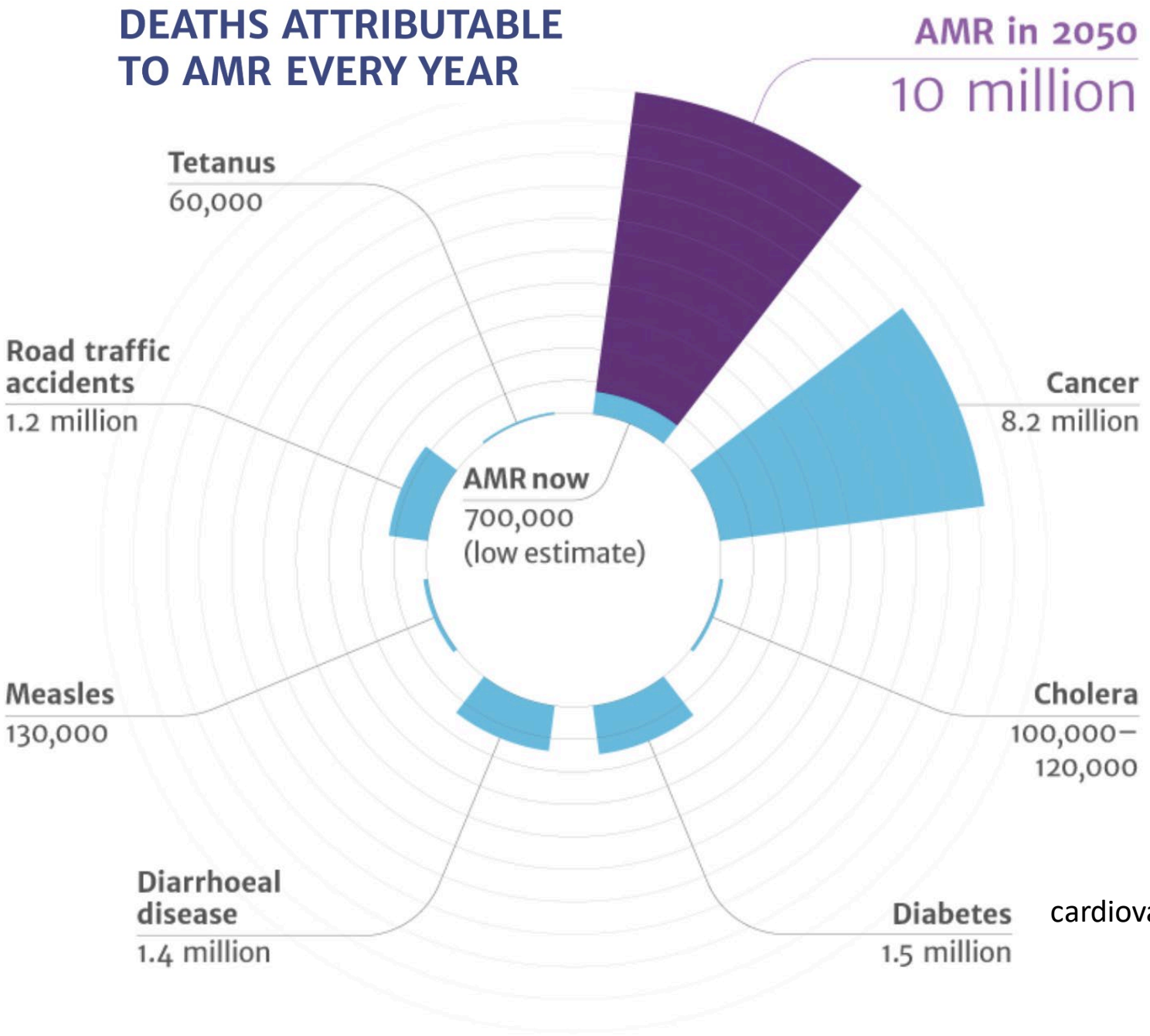


‘Cured from TB but suffering from side effects for ever’ (40y old patient)



[1]Verena Schärer, [1]Roland Hafner, [3]Adrian Ciurea, [1]Lars Henning, [2]Akos Somoskövi, [1]Rainer Weber, [1]Jan Fehr

2050 –
Anti-Microbial Resistance (AMR) – A major threat



cardiovascular

O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations 2016. https://amr-review.org/

Multiresistente Tuberkulose

Dr. med. Marisa Kaelin[a,b], Dr. med. Peter M. Keller[c], Prof. Dr. med. Otto D. Schoch[d,e],
PD Dr. med. Gunar Günther[f,g], Prof. Dr. med. Jan Fehr[a,b]

- Further increase of MDR/XDR TB by 2040 (Sharma et al)
- Globally only 56% of all MDR-TB cases are treated successfully - XDR-TB only 40%
- **50% of all TB-treatment costs** are spent for MDR-TB

***The Lancet Respiratory Medicine* Commission: 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis**

www.thelancet.com/respiratory Vol 7 September 2019

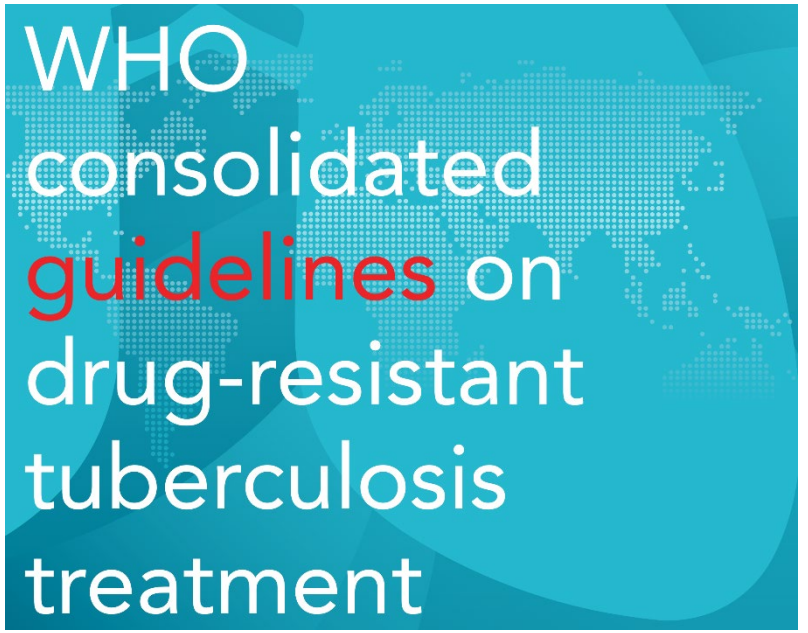
New insights postulate that **PK-PD**, individually different penetration to infect-focus might be a **more important driver than suspected…** (Dheda et al)

What do tell Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis
An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

be helpful (11, 231, 241, 242, 244). Although it is clearly possible to cure patients without TDM and even in the setting of lower serum drug concentrations, the available data suggest that the probability of cure decreases with decreasing drug concentrations (231–241). Given the incomplete information



TDM is advised when the dose is at the *upper and lower ends* of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid, fluoroquinolones)

TDM in drug resistant TB – potential twofold use

Prevent resistance

Achieve cure
in case of resistance

…but how useful in daily practice?
-> is there a correlation of drug concentrations with the outcome?
-> back to square 1

THE UTILITY OF PHARMACOKINETIC STUDIES FOR THE EVALUATION OF EXPOSURE-RESPONSE RELATIONSHIPS FOR STANDARD DOSE ANTI-TUBERCULOSIS DRUGS

Christine Sekaggya-Wiltshire[1], **Mohammed Lamorde**[1], **Agnes N Kiragga**[1], **Kelly E Dooley**[3], **Moses R Kamya**[4], **Andrew Kambugu**[1], **Jan Fehr**[2], **Yukari C Manabe**[3], and **Barbara Castelnuovo**[1]

There is insufficient evidence to suggest that achieving current anti-TB drug targets correlates with a higher chance of favorable treatment outcomes or two-month sputum culture conversion in patients on the standard dose anti-TB treatment. Our main finding was the paucity of studies linking PK to TB treatment outcomes, despite the existence of PK target concentrations that are used commonly by TB programs around the world. We

Tuberculosis (Edinb). 2018 January ; 108: 77–82.

Study on outcomes related to Tuberculosis and HIV drug concentrations in Uganda (SOUTH)

Christine Sekaggya-Wiltshire,[1,a] Amrei von Braun,[2,a] Mohammed Lamorde,[1] Bruno Ledergerber,[2] Allan Buzibye,[1] Lars Henning,[2,3] Joseph Musaazi,[1] Ursula Gutteck,[4] Paolo Denti,[5] Miné de Kock,[5] Alexander Jetter,[6] Pauline Byakika-Kibwika,[1,7] Nadia Eberhard,[2] Joshua Matovu,[1] Moses Joloba,[8] Daniel Muller,[4] Yukari C. Manabe,[9] Moses R. Kamya,[7] Natascia Corti,[6] Andrew Kambugu,[1] Barbara Castelnuovo,[1,b] and Jan S. Fehr[2,10,b]

CID 2018:67 (1 September)

Design

Baseline	Week 2	Week 8	Week 24
Baseline labs CXR Sputum analysis DST Initiate antiTB	Initiate ART Safety labs Sputum analysis PK: antiTB	CXR Safety labs Sputum analysis PK: ART, antiTB	CXR Safety labs Sputum analysis PK: ART, antiTB
		0 hr	0 hr
Observed drug intake			
	1 hr	1 hr	1 hr
	2 hr	2 hr	2 hr
	4 hr	4 hr	4 hr

Results

Despite low drug concentrations:

Isoniazid: 190/227 (84%)

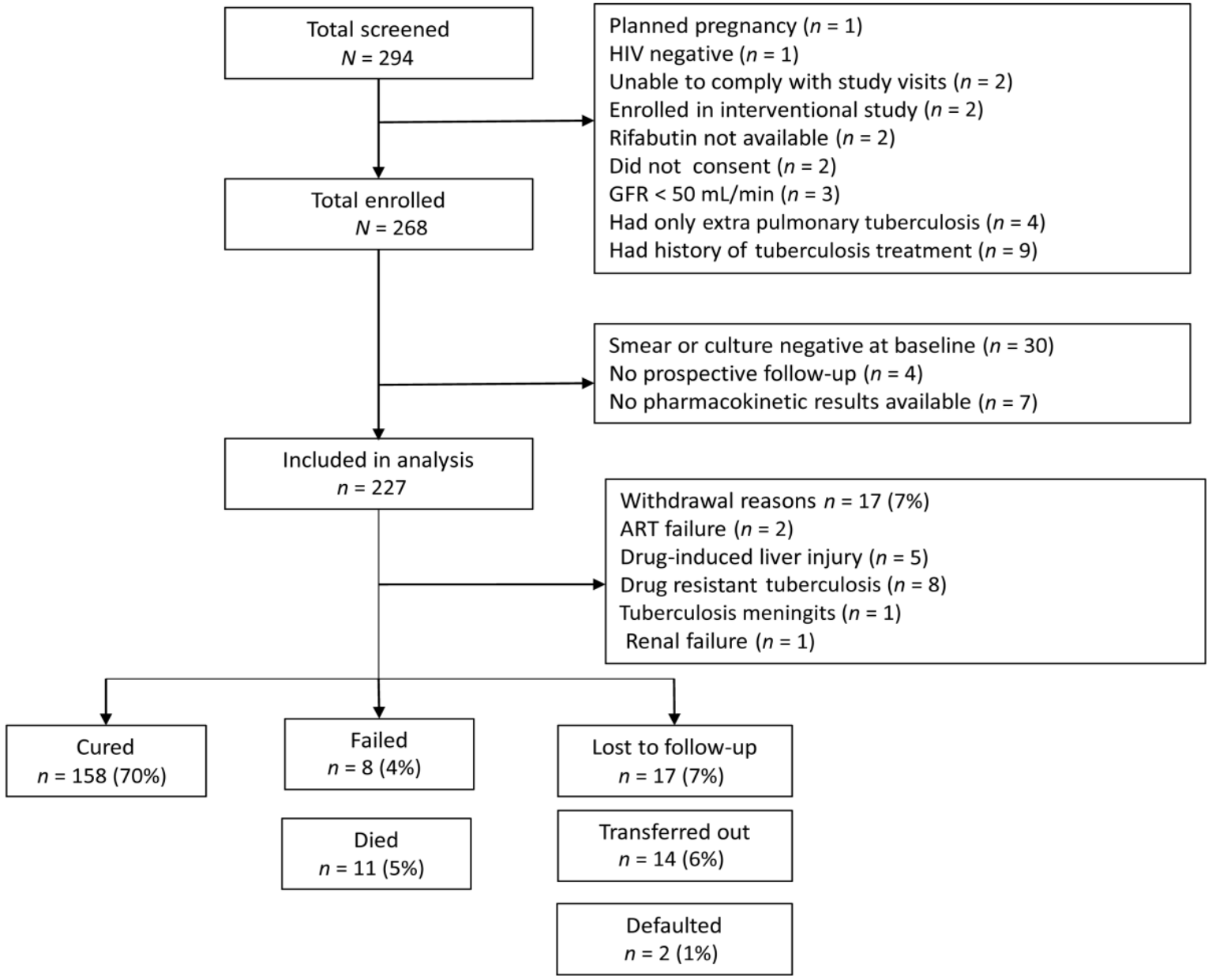
Rifampicin: 176/227 (78%)

Pyrazinamide: 6/227 (3%)

Ethambutol: 70/227 (31%)

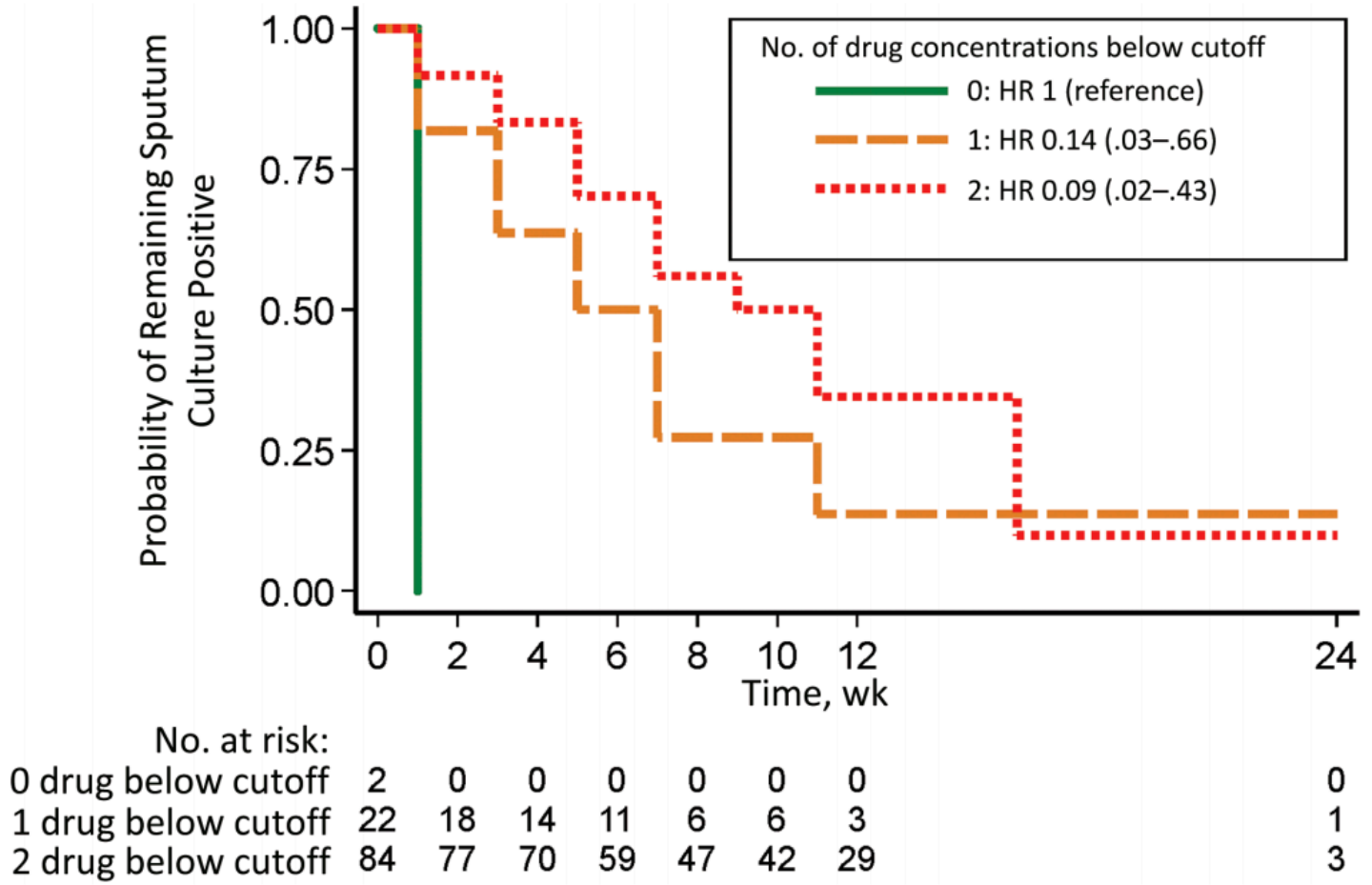
-> only 4% failures

But:
low INH or RIF concentrations less likely to undergo sputum conversion



Higher probability of remaining culture/smear positive

Implication for transmission



The New York Times

GLOBAL HEALTH

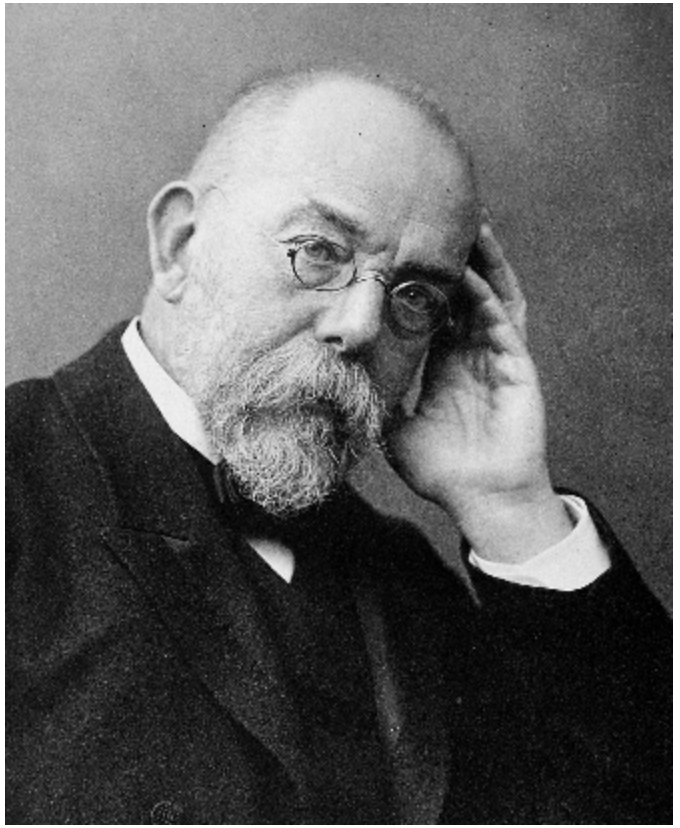
TB Treatment May Leave Some Patients Contagious

April 2018

…hold on…

'Let's imagine Robert Koch *would be with us right now – he would be shocked - he would be shocked by airplanes, cars, computers, smartphones – but he would not be shocked by TB; because it's all the same as it was at his time.'*

Lucica Ditiu



Historical context: The MRC East Africa studies and efficacy of short course treatment

Table 1.7 Short-course chemotherapy studies in East and Central Africa. Results in patients who had drug-sensitive cultures initially.

Study no.	Date of start	Regimen	Duration (months)	Patients assessed for relapse	Relapse rate in 2-year follow-up (%)	Sputum culture negative at 2 months (%)	Reference
1	1970	a) SHR	6	152	3	69	2
		b) SHZ	6	153	8	66	166
		c) SHT	6	104	22	42	167
		d) SH	6	112	29	49	168
		e) 2STH/TH	18	133	3	56	
2	1972	a) SHR	6	171	2	70	169
		b) HR	6	164	7	64	170
		c) 2SHRZ/TH	6	179	7	83	
		d) 2SHRZ/$S_2H_2Z_2$*	6	159	4	80	
3	1974	a1) 2SHRZ/TH	6	75	13	87	171
		a2) 2SHRZ/TH	8	81	0		172
		b1) 1SHRZ/TH	6	79	18	67	
		b2) 1SHRZ/TH	8	58	7		
		c1) 1SHRZ/$S_2H_2Z_2$	6	75	9	68	
		c2) 1SHRZ/$S_2H_2Z_2$	8	88	2		
		d1) 2SHR/TH	6	82	18	75	
		d2) 2SHR/TH	6	77	6		
4	1976	a) 2SHRZ/HRZ	4	104	16	85	173
		b) 2SHRZ/HR	4	104	11		174
		c) 2SHRZ/HZ	4	98	32		
		d) 2SHRZ/H	4	105	30		
		e) 2HRZ/H	4	100	40	79	
5	1978	a) 2SHRZ/HR	6	166	3	84	175
		b) 2SHRZ/HZ	6	164	8		176
		c) 2SHRZ/H	6	156	10		
		d) 2SHRZ/H	8	123	3		
6	1978	a) 2SHRZ/TH	6	105	3	94	177
		b) 2SHRZ/H	6	100	11		
7	1981	2SHRZ/TH+L†	6	456	7	82	178
8	1982	a) 1.5SHRZ/H	7	113	10	85	179
		b) 1.5SHRZ/H+(SRZ)	7	114	5		

* $S_2H_2Z_2$. See footnote for Table 1.5.
† The results of the three regimens with levamisole added for 4 or 8 weeks or not at all have been amalgamated, as there were no differences between them.

Fox et al, IJTLD 1999

Impact of low RIF / INH / PZA levels on treatment outcome in DS – TB in Uganda

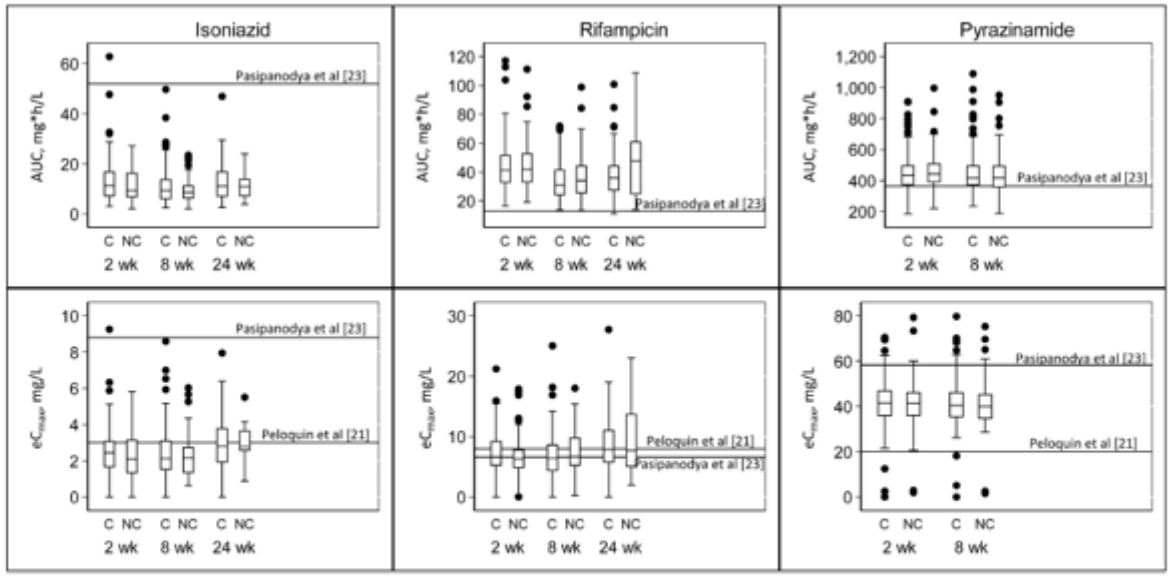


Figure 2. Association between concentrations of rifampicin, isoniazid, and pyrazinamide and tuberculosis treatment outcome. Box plots demonstrating area under the concentration-time curve (AUC) and estimated maximum concentrations (eC_{max}) for isoniazid, rifampicin, and pyrazinamide at weeks 2, 8 and 24 and stratified by tuberculosis treatment outcome: cured (C) and not cured (NC). The top of each box represents the 75th percentile (Q3); the bottom, the 25th percentile (Q1); and the horizontal line within each box, the 50th percentile (median) concentration. The top whisker represents Q3 + (1.5 × the interquartile range [IQR]), and the bottom whisker, Q1 – (1.5 × IQR); dots represent outliers.

In conclusion, *although low isoniazid and rifampicin concentrations in this HIV-tuberculosis–coinfected population did **not** translate into high proportions of patients with treatment failure,* the association between low concentrations of isoniazid and rifampicin and prolonged sputum culture positivity has implications for tuberculosis transmission and warrants further investigation.

Sekkaggya – Whiltshire et al. CID 2018

PK of first line anti TB drugs in HIV positive and negative patients

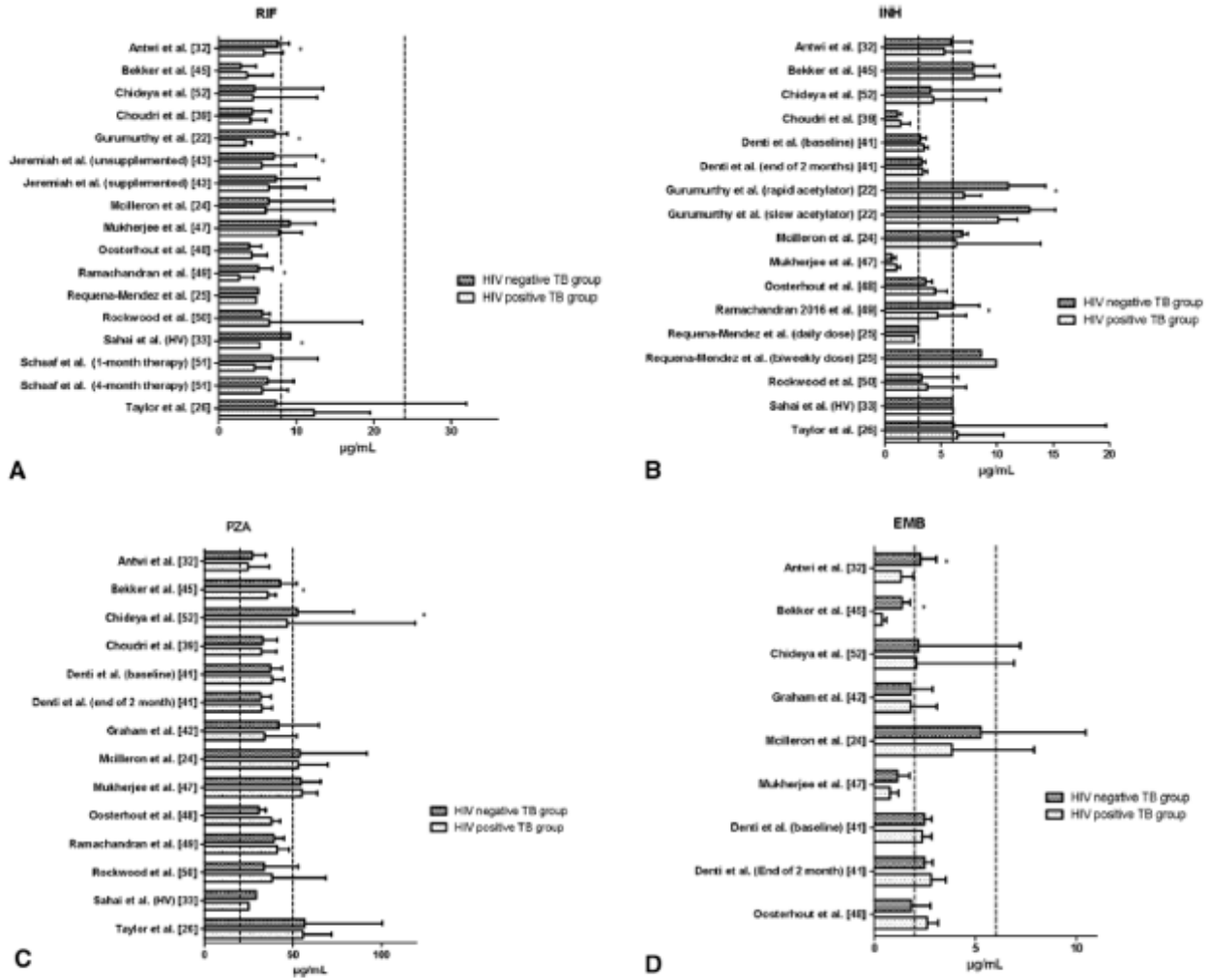


Fig. 3 Histograms of the mean or median peak drug concentration for the HIV-negative and HIV-positive TB groups per study for **a** rifampicin, **b** isoniazid, **c** pyrazinamide and **d** ethambutol. Asterisk indicates statistical significance. The dashed lines represent the generally cited reference ranges by Peloquin [27]: rifampicin 8–24 µg/mL; isoniazid 3–6 µg/mL; pyrazinamide 20–50 µg/mL; ethambutol 2–6 µg/mL. The study by Sahai et al. [33] compared HIV-infected individuals without TB with healthy HIV-uninfected volunteers (healthy volunteers). *INH* isoniazid, *RIF* rifampicin, *PZA* pyrazinamide, *EMB* ethambutol, *TB* tuberculosis

Conclusion: HIV infection may be one of several factors that reduce FLD exposure. We could not make general recommendations with respect of the role of dosing, There is a need for consistant and hoemgeneous studies to be conducted.

Daskapan et al. J Pharmacokin 2018

INT J TUBERC LUNG DIS 24(1):48–64

http://dx.doi.org/10.5588/ijtld.19.0025

A systematic review and meta-analysis of first-line tuberculosis drug concentrations and treatment outcomes

R. Perumal,[1,2,3] K. Naidoo,[1,3] A. Naidoo,[1] G. Ramachandran,[4] A. Requena-Mendez,[5]
C. Sekaggya-Wiltshire,[6] S. G. Mpagama,[7] A. Matteelli,[8] J. Fehr,[9] S. K. Heysell,[10] N. Padayatchi[1,3]

Only metaanalysis of outcomes related to first line drug TDM

- 15 studies
- low PZA concentration appears to **increase** the risk of poor outcomes (RR 1.73, 95%CI 1.10–2.72)
- low RMP concentrations may **slightly increase** the risk of poor outcomes (RR 1.40, 95%CI 0.91–2.16)
- low concentrations of INH (RR 1.32, 95%CI 0.66–2.63) and EMB (RR 1.12, 95%CI 0.41–3.05) appear to make **no difference**
- INH activity more than RMP, PZA and EMB is best defined by AUC/MIC rather than the Cmax /MIC

Problematic: 2nd line TB drugs….

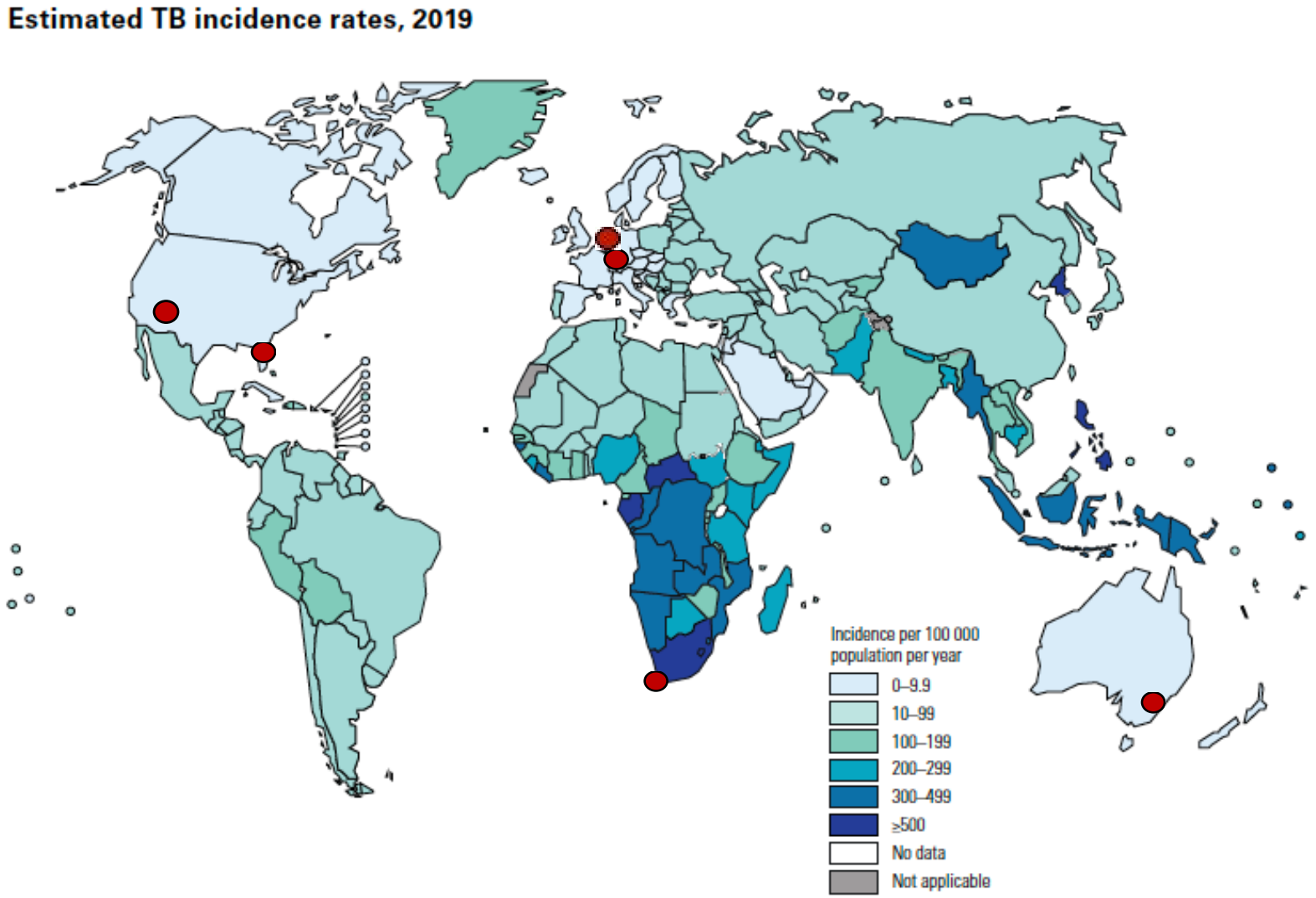
WHO expert meeting – consensus document on PK/PD in MDR- TB 2018

Clinical question 14:
For which TB patients, regimens or medicines is the monitoring of blood or urine levels useful to assess therapeutic and/or toxic effects?

Conclusion: Therapeutic drug monitoring (TDM) is likely to help in the case of medicines with a narrow therapeutic index and for which it is difficult to develop a dosing regimen that applies universally owing to individual variations in PK/PD (e.g. injectable agents, cycloserine, linezolid).
Studies quantifying the value that TDM adds to clinical outcomes - efficacy, safety, quality and cost-effectiveness - are lacking. Likewise the best-suited methods to test and optimal sampling strategies still need to be determined.

Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. WHO 2018

Where are people based, demanding TDM for TB…..

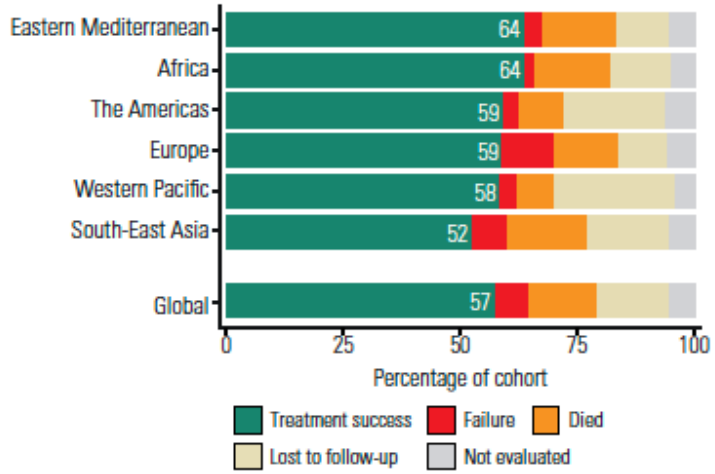


Global TB Report 2020

Good tools available??... Bangladesh regimen in Central Africa and in STREAM I trial

Variable	Modified Intention-to-Treat Population			Per-Protocol Population		
	Long Regimen	Short Regimen	Total	Long Regimen	Short Regimen	Total
Disposition of the participants						
Underwent randomization — no.	142	282	424	142	282	424
Were included in the population — no.	130	253	383	87	234	321
Were considered not able to be assessed — no.						
Had reinfection with a different strain	1	7	8	1	6	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1	6	3	1	4
Were included in primary outcome analysis — no.	124	245	369	83	227	310
Outcome						
Attained favorable status — no. (%)†	99 (79.8)	193 (78.8)	292 (79.1)	67 (80.7)	186 (81.9)	253 (81.6)
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (21.2)	77 (20.9)	16 (19.3)	41 (18.1)	57 (18.4)

STREAM II results expected in 2022



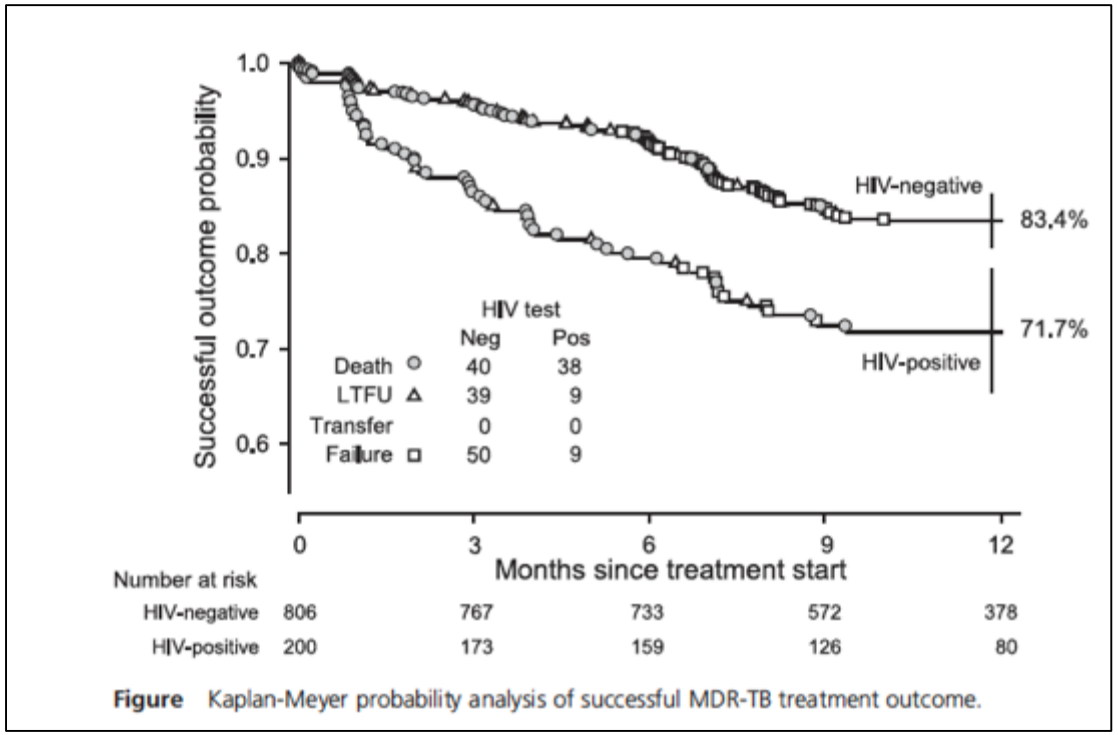
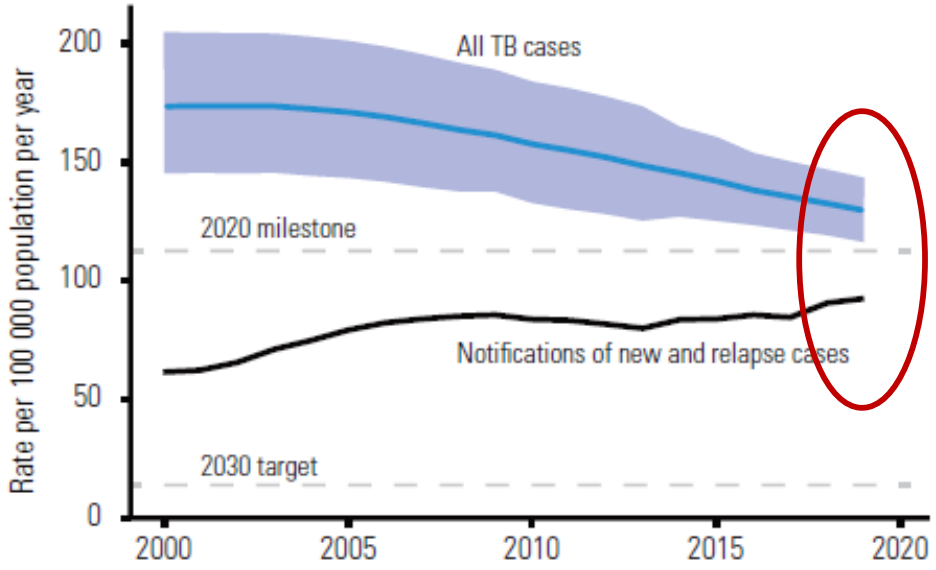
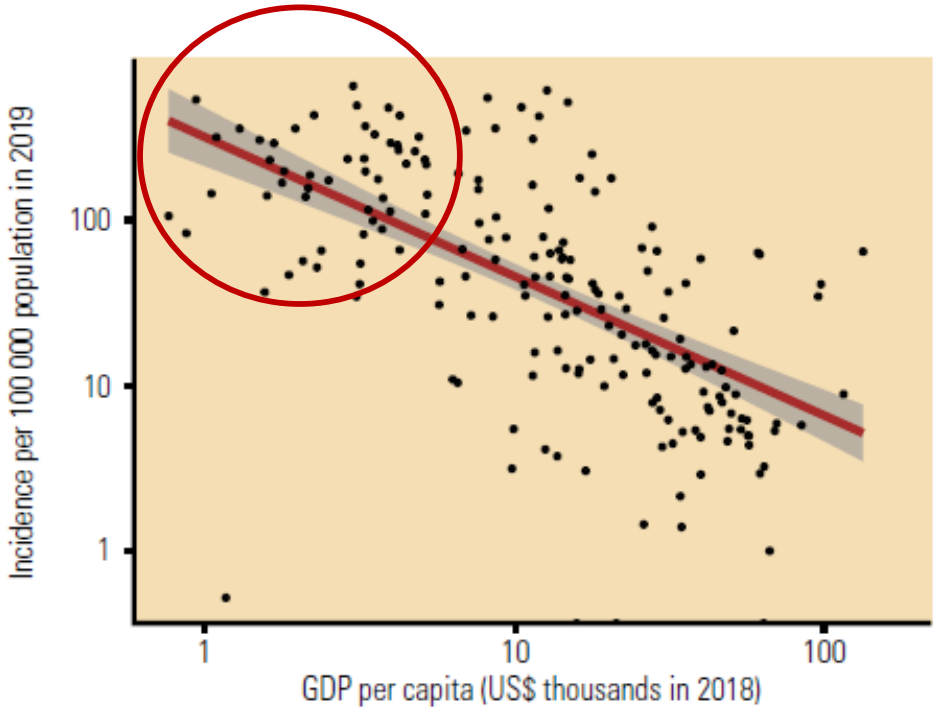


Figure Kaplan-Meyer probability analysis of successful MDR-TB treatment outcome.

Nunn et al; NEJM 2019
Trebucq et al; 2017
Global TB Report 2020

Missing cases…….





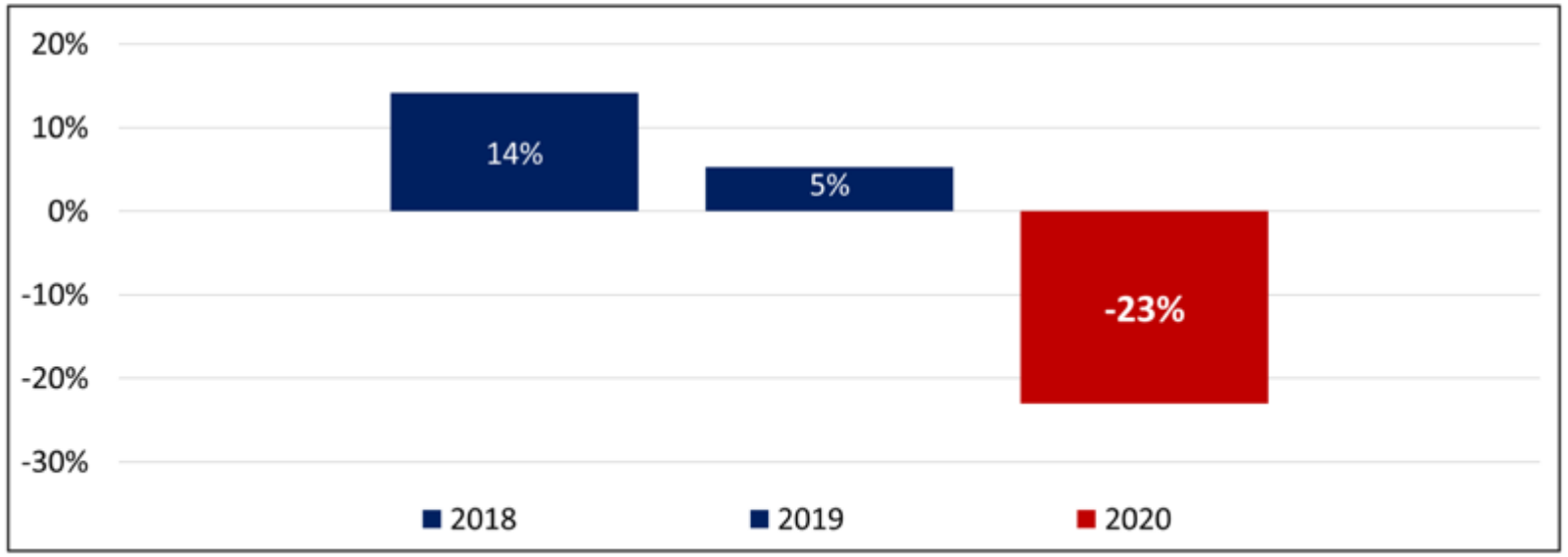
Global TB Report 2020

Impact of COVID 19 on TB notification

Stop TB Partnership

UNDER EMBARGO UNTIL THURSDAY, 18 MARCH, AT 10:00 EDT/14:00 GMT/15:00 CET/19:30 IST

Annual percentage change in TB diagnosis and enrollment for nine high-TB-burden countries

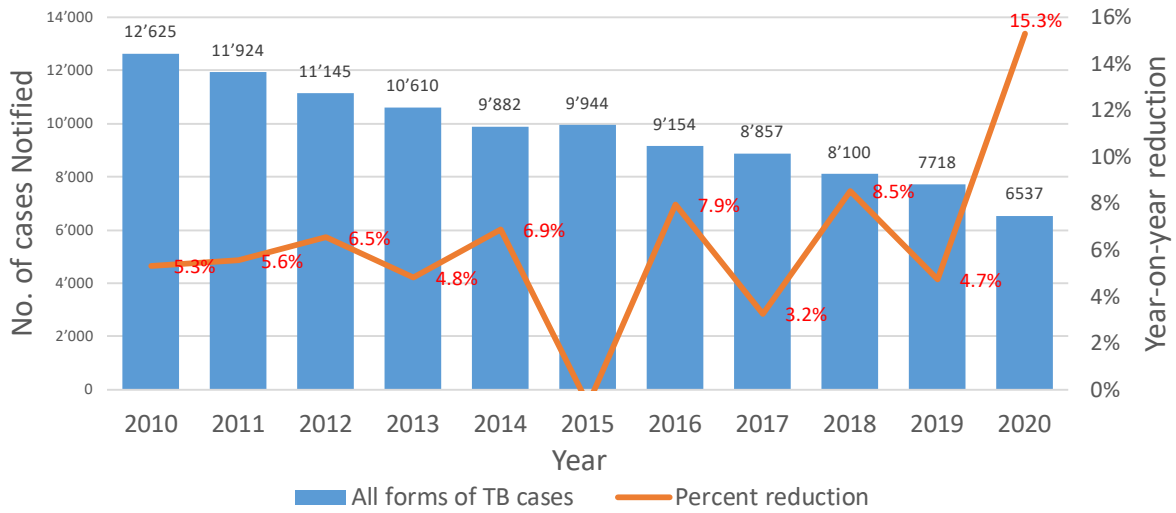


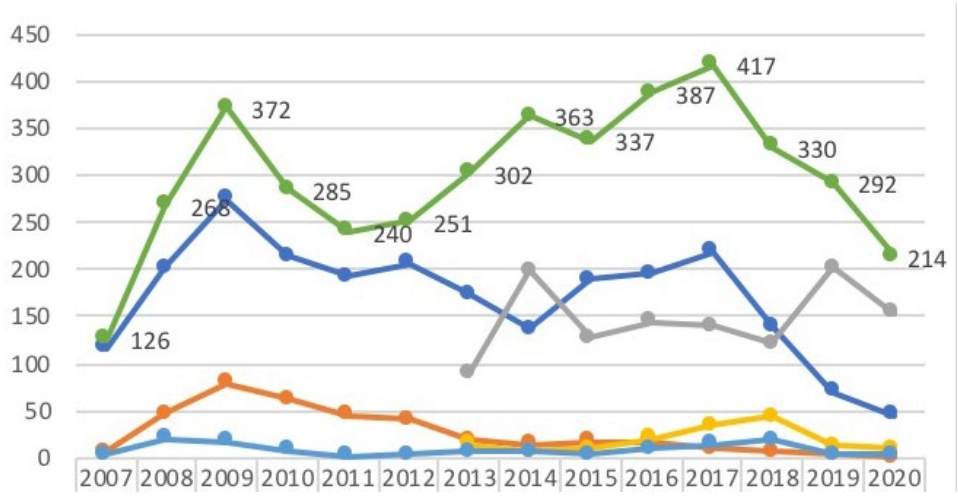
- Stop TB Partnership reports about 1 millions less cases notified in 9 high burden countries
- reflects a 16 – 41% reduction in case notification
- corresponds to the situation in 2008

Stop TB Partnership 2021

Impact of COVID 19 on MDR- TB notification in Namibia

- DR and Prevalance survey 2016 / 2018: 840 cases of RR cases expected per annum
- Estimated incidence 2019: 12000 cases

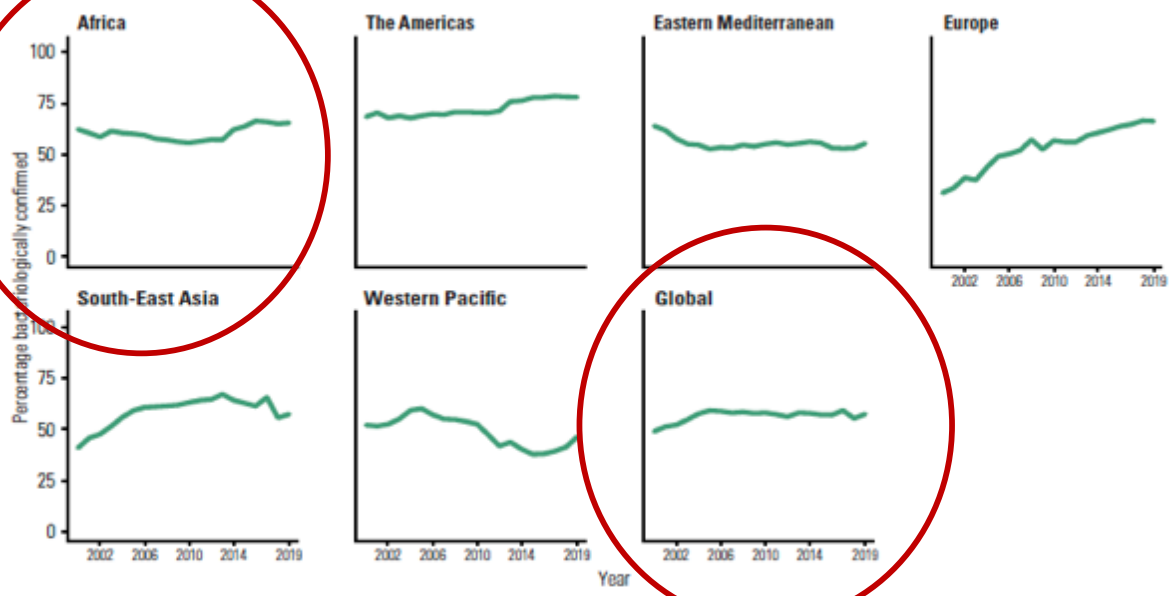




Stop TB Partnership 2021
Dr. Ruswa, NTLP Namibia

What we need more…..bacteriological confirmation of TB

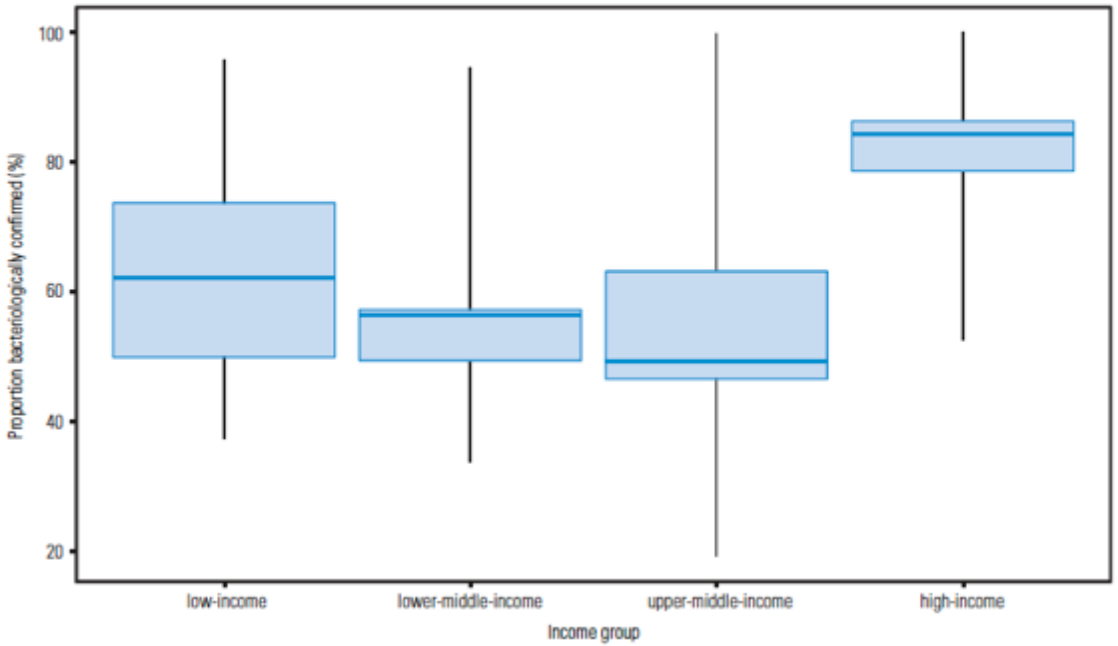
Percentage of new and relapse[a] pulmonary TB cases with bacteriological confirmation, globally and for WHO regions, 2000–2019



[a] The calculation for new and relapse pulmonary cases in years prior to 2013 is based on smear results, except for the European Region where data on confirmation by culture was also available for the period 2002–2012.

Distribution of the proportion of notified pulmonary cases that were bacteriologically confirmed in 2019, by country income group

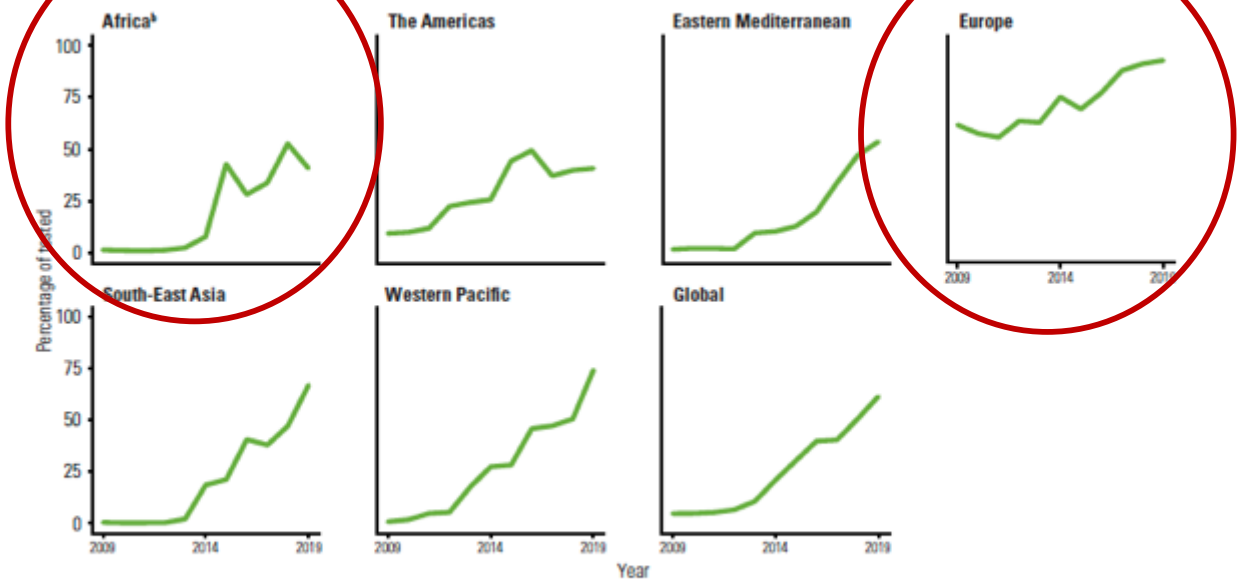
Boxes indicate the first, second (median) and third quartiles weighted by a country's number of pulmonary cases; vertical lines extend to the minimum and maximum values, excluding countries with <10 cases.



Global TB Report 2020

What we need more…..resistance testing for Rifampicin and FQ

Percentage of bacteriologically confirmed TB cases tested for RR-TB,[a] globally and for WHO regions, 2009–2019



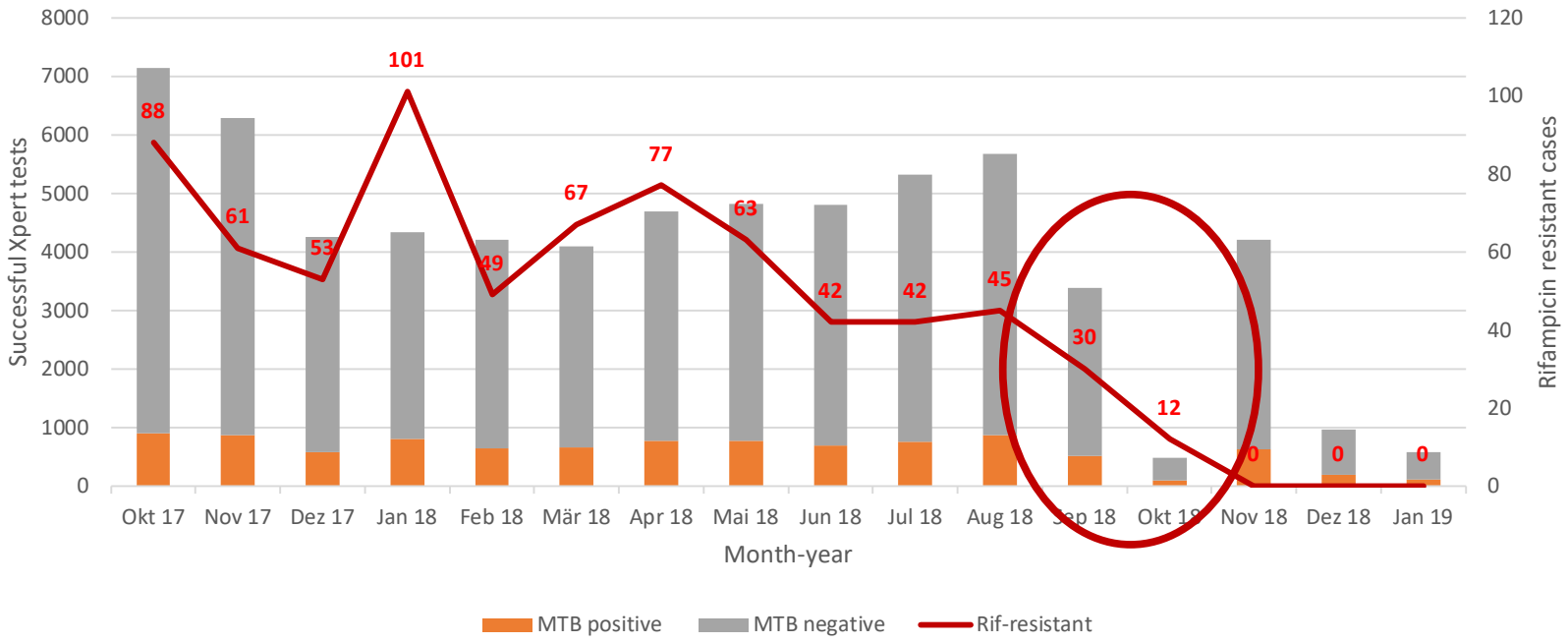
Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones,[a] globally and for WHO regions, 2015–2019

[a] Includes both new and previously treated TB cases; data for 2017 onwards are for pulmonary TB cases only.
[b] The increase in the African Region from 2014 to 2015 was due to a large increase in reporting of laboratory results for cases in South Africa in 2015.

Currently we put only 38% of the estimated MDR- TB cases on treatment……

Global TB Report 2020

Impact of the 1. UN- High level meeting on TB in September 2018 TB (diagnostics) in Namibia



Courtesy Dr. Ruswa NTLP

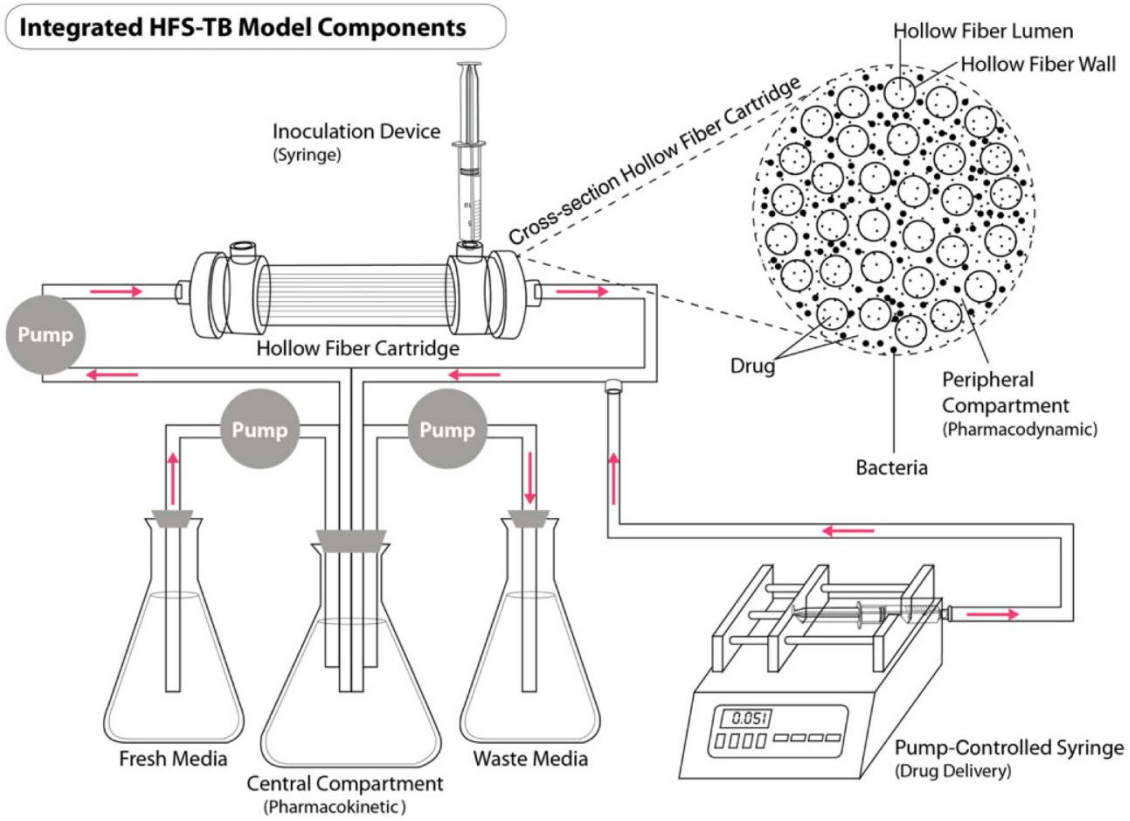
Role of TDM in TB – questions:

- What should be measured: best correlation with toxicity / outcome
  - Cmax?, AUC, *f*AUC (unbound) – combined AUC/MIC, Cmax/MIC
- When should it be measured (time)
- Which drugs are best candidates for TDM?
  - Concentration related toxicity
  - Narrow therapeutic window

- Where plasma/ cite of infection?
- How feasible in resource limited settings?
- How about cost-effectiveness?

‚mimicking human PK/PD‘ to answer: what, when, which?

Groups & steps	Medicine	
Group A: Include all three medicines	Levofloxacin *OR* *Moxifloxacin*	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *OR* Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin *OR* *Meropenem*	Ipm-Cln Mpm
	Amikacin (*OR* streptomycin)	AM (s)
	Ethionamide *OR* Prothionamide	Eto Pto
	P-aminosalicylic acid	PAS



Correlations Between the Hollow Fiber Model of Tuberculosis and Therapeutic Events in Tuberculosis Patients: Learn and Confirm

Tawanda Gumbo,[1,2] Jotam G. Pasipanodya,[1] Eric Nuermberger,[3] Klaus Romero,[4] and Debra Hanna[4]

Table 3. Correlation of Rifampin, Ethambutol, and Pyrazinamide Hollow Fiber System Model of Tuberculosis Findings With Clinical Studies

Pharmacodynamic Parameter	HFS-TB Estimate [Reference]	Clinical Estimate in Sputum [Reference]
Rifampin		
Standard-dose early bactericidal effect, $\log_{10}$ CFU/mL/day (95% CI)	0.28 [39]	0.25 (–.08 to .57) [18]
Sterilizing effect rate, $\log_{10}$ CFU/mL/day (95% CI)	0.28 [39]	0.27 (.06–.47) [21, 22]
PK/PD parameter associated with optimal effect	Peak/MIC; AUC/MIC [39]	Peak/MIC [3, 28]
Ethambutol		
Maximal early bactericidal activity, $\log_{10}$ CFU/mL/day (95% CI or ±SD)	0.22 (.14–.29) [40]	0.26 ± 0.12 [21, 22]
Sterilizing effect rate, $\log_{10}$ CFU/mL/day	0.04–0.10 [40]	0.1 [21, 22]
PK/PD parameter associated with optimal effect	AUC/MIC; peak/MIC [40]	AUC/MIC [3, 29]
Pyrazinamide		
Early bactericidal effect rate, $\log_{10}$ CFU/mL/day	–0.1 [9]	–0.1 ± 0.2 [21, 22]
Sterilizing effect kill rate, $\log_{10}$ CFU/mL/day	0.09–0.01 [9]	0.12 ± 0.05 [21, 22]
Time to emergence of resistance in monotherapy, wk[a]	2–3 [9]	2–3 [20]
PK/PD parameter associated with optimal effect	AUC/MIC [9]	AUC/MIC [3, 30]

Abbreviations: AUC, area under the concentration-time curve; CFU, colony-forming units; CI, confidence interval; HFS-TB, hollow fiber system model of tuberculosis; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetics/pharmacodynamics; SD, standard deviation.

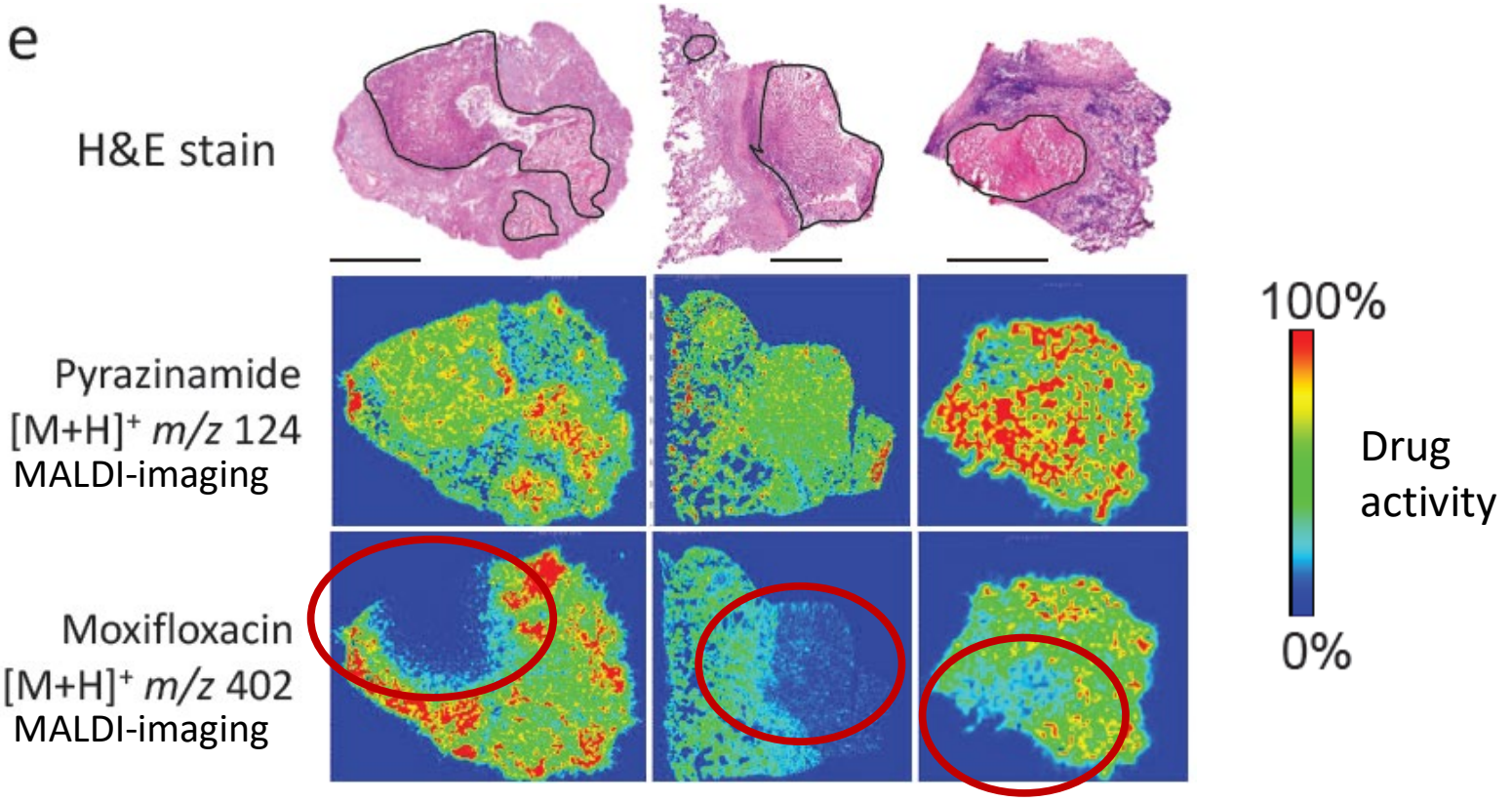
[a] Established by culture methods.

Where –

Penetration into cite of infection

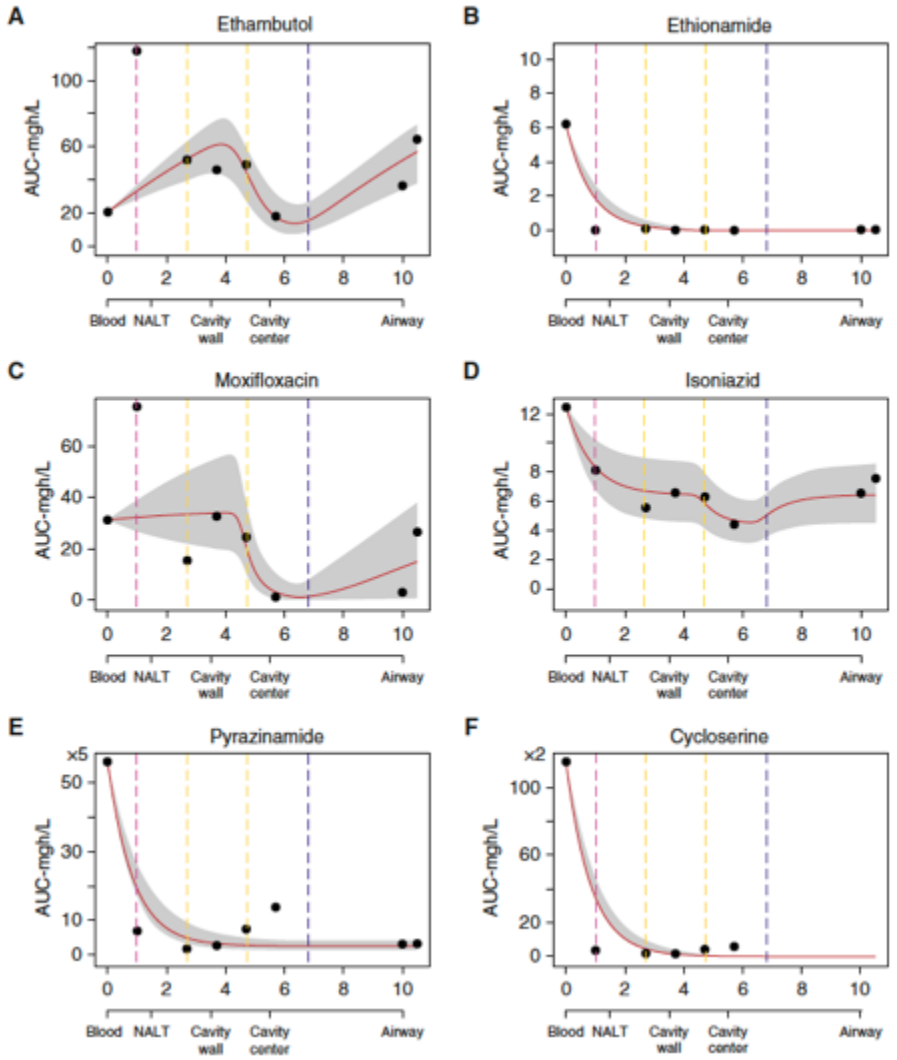
The association between sterilizing activity and drug distribution into tuberculosis lesions

Brendan Prideaux

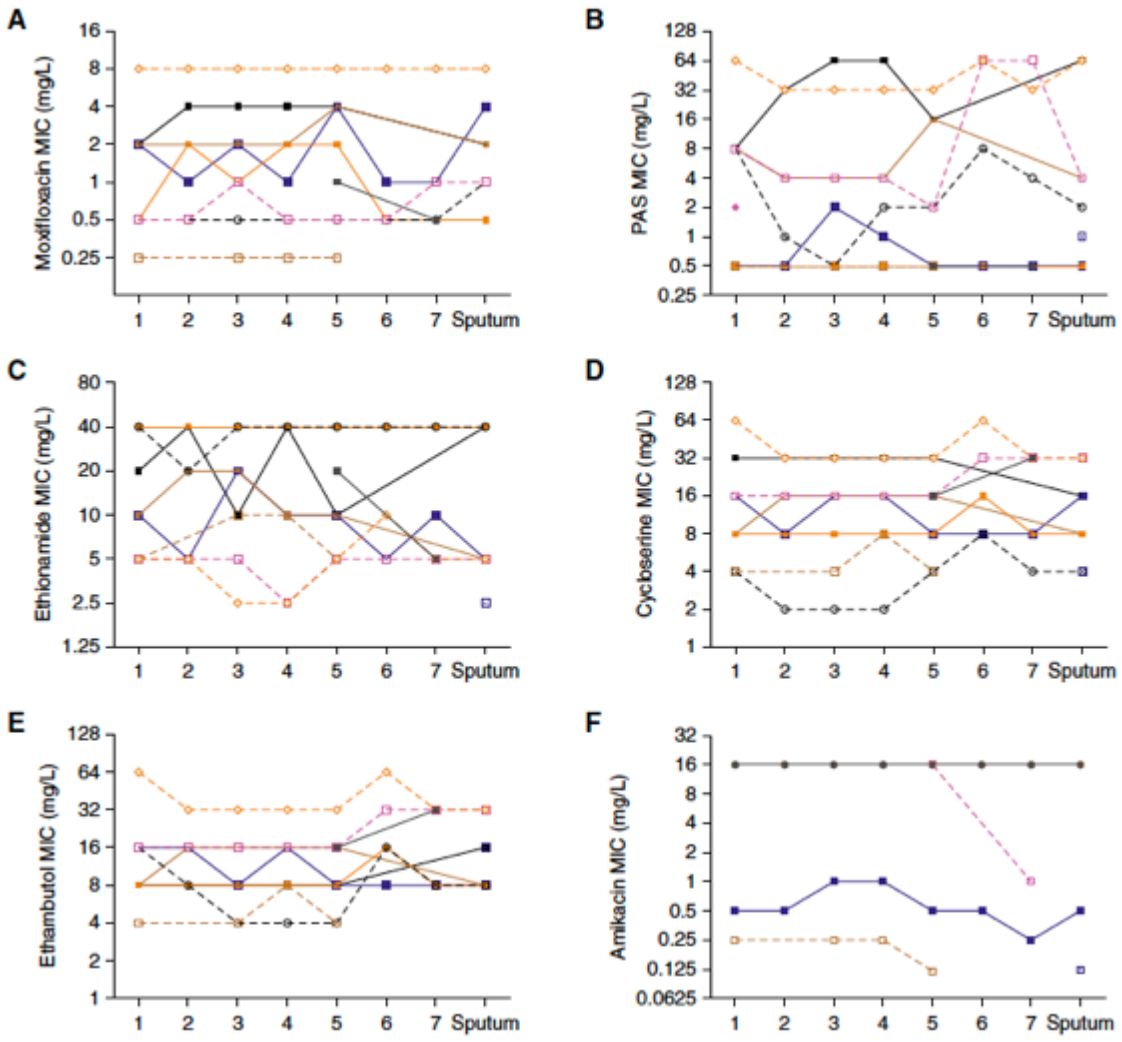


NATURE MEDICINE VOLUME 21 | NUMBER 10 | OCTOBER 2015

Are we measuring the right "thing".....AUC and MIC in differnt tissue compartments



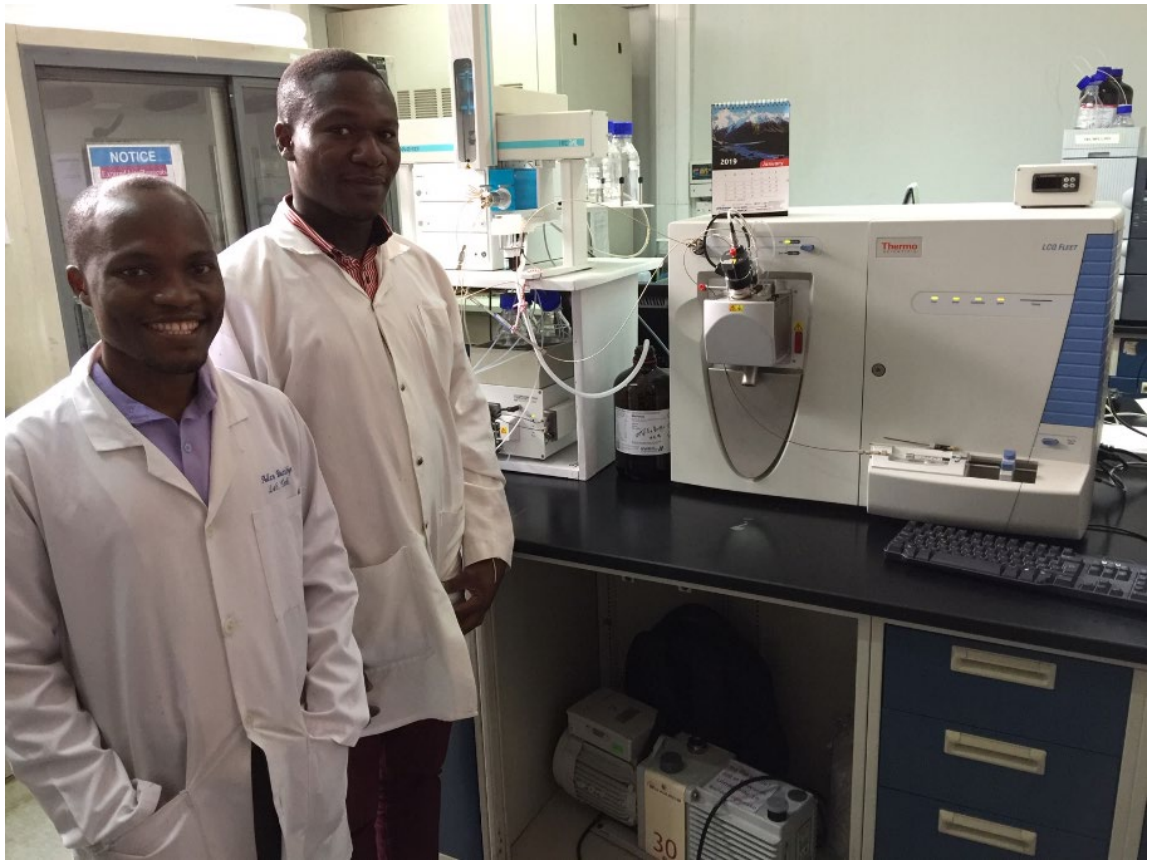
AUC in different pulmonary tissues



MIC at different locations in the lung

Dheda et al, AJRCCM 2018

How feasible – especialle in endemic area?



Infectious Diseases Institute, Kampala
-> reference lab for Uganda

PK analysis using **liquid chromatography coupled with mass spectrometry ("Mass Spec")** at the Infectious Diseases Institute in Kampala

-> reference lab for Uganda

…and: new approaches

How about cost-effectivness?

Review > Ther Drug Monit. 2005 Feb;27(1):10-7. doi: 10.1097/00007691-200502000-00004.

Cost-effectiveness of therapeutic drug monitoring: a systematic review

D J Touw [1], C Neef, A H Thomson, A A Vinks,
Cost-Effectiveness of Therapeutic Drug Monitoring Committee of the International Association for Therapeutic Drug Monitoring and Clinical Toxicology

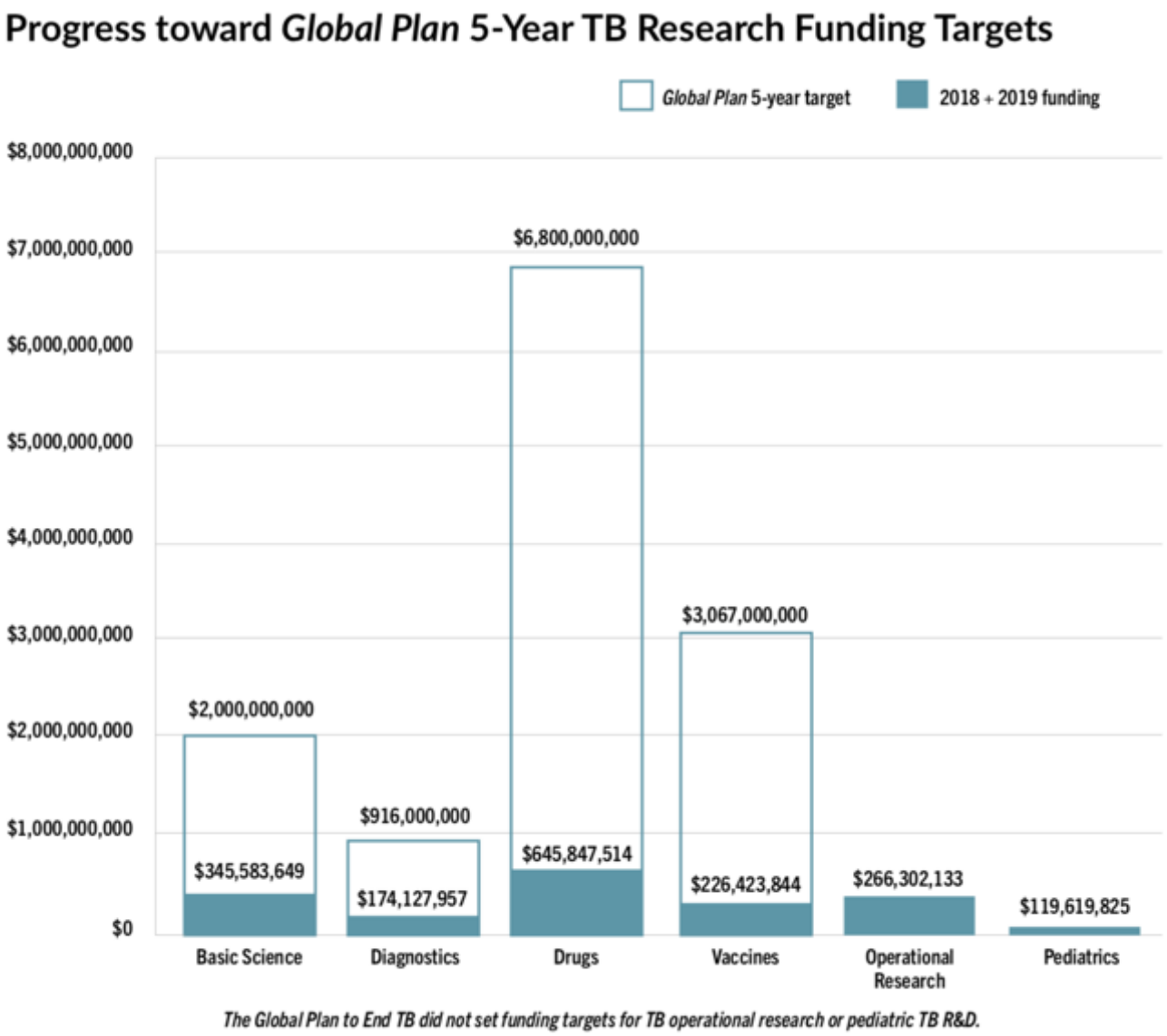
Affiliations + expand

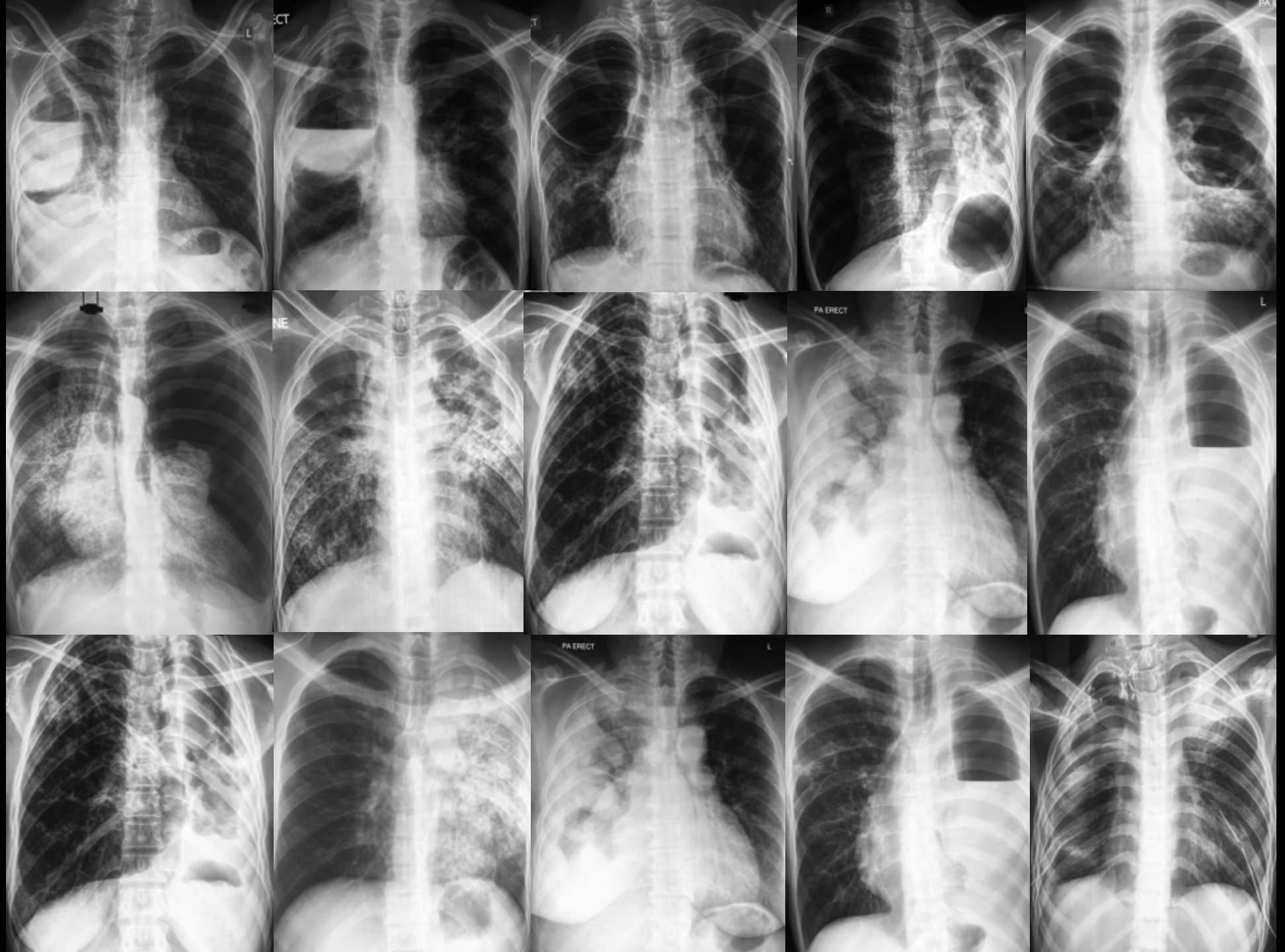
PMID: 15665740 DOI: 10.1097/00007691-200502000-00004

Abstract

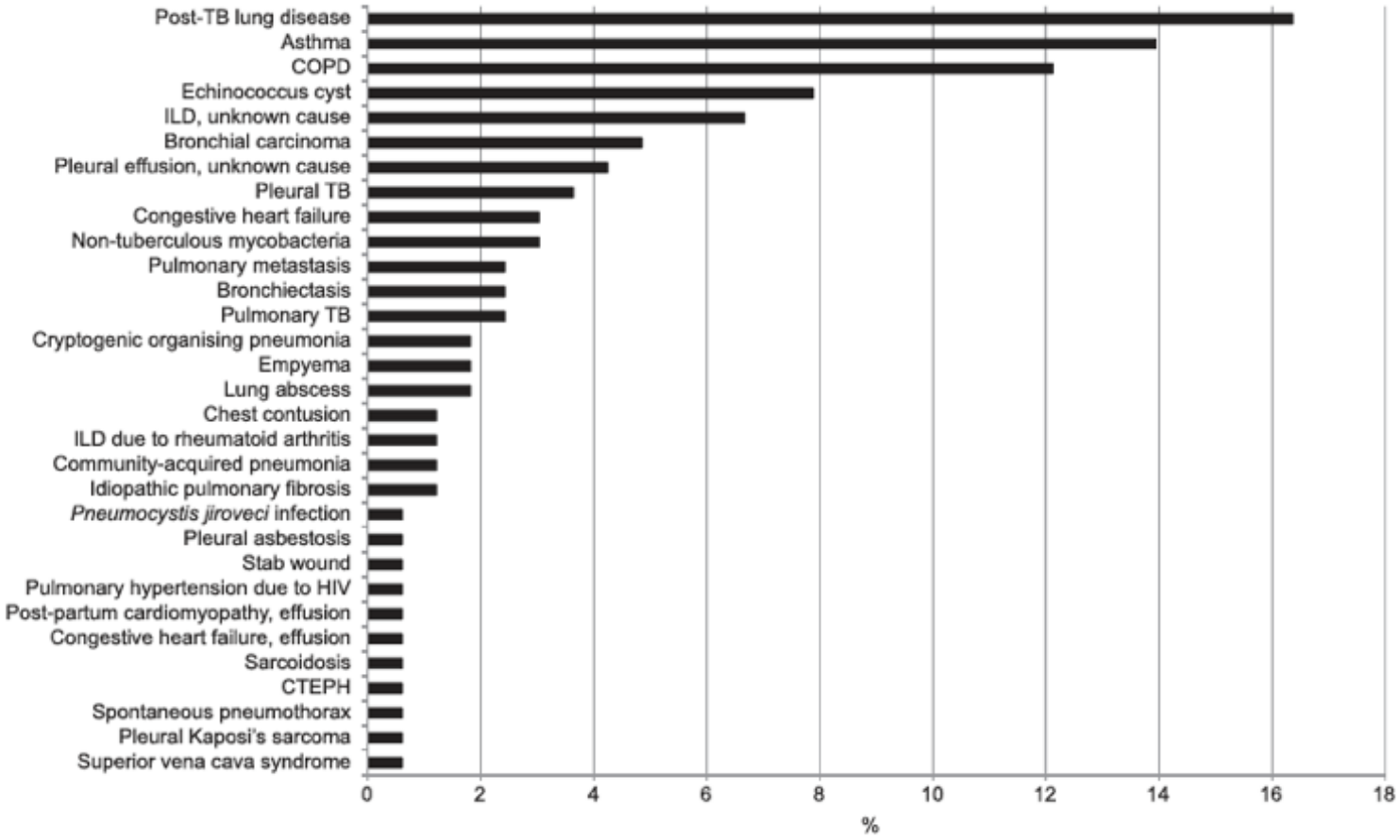
There are a number of effective but highly toxic drugs that exhibit a narrow therapeutic index and marked interpatient pharmacokinetic variability. Individualized therapy with such drugs requires therapeutic drug monitoring (TDM) to obtain the desired clinical effects safely. Cost-effectiveness analysis in health care is still at an early stage of development, especially for TDM. A systematic review was carried out to document studies that have addressed the cost-effectiveness of TDM. The Cochrane database and Medline were searched. References identified by this approach were then searched manually for relevant articles. Very few studies have been performed that document the cost-effectiveness of TDM, and TDM has been demonstrated to be cost-effective only for aminoglycosides. For the other classes of drugs that are monitored, the rationale for TDM has been supported, but appropriate cost-effectiveness analyses have not been performed. Because the use of many of these drugs without TDM would increase the risk of under- or overdosing, emphasis should not be placed solely on cost-effectiveness but rather on how such interventions can be applied in the most cost-effective and clinically useful manner.

TB funding falls short of all targets……



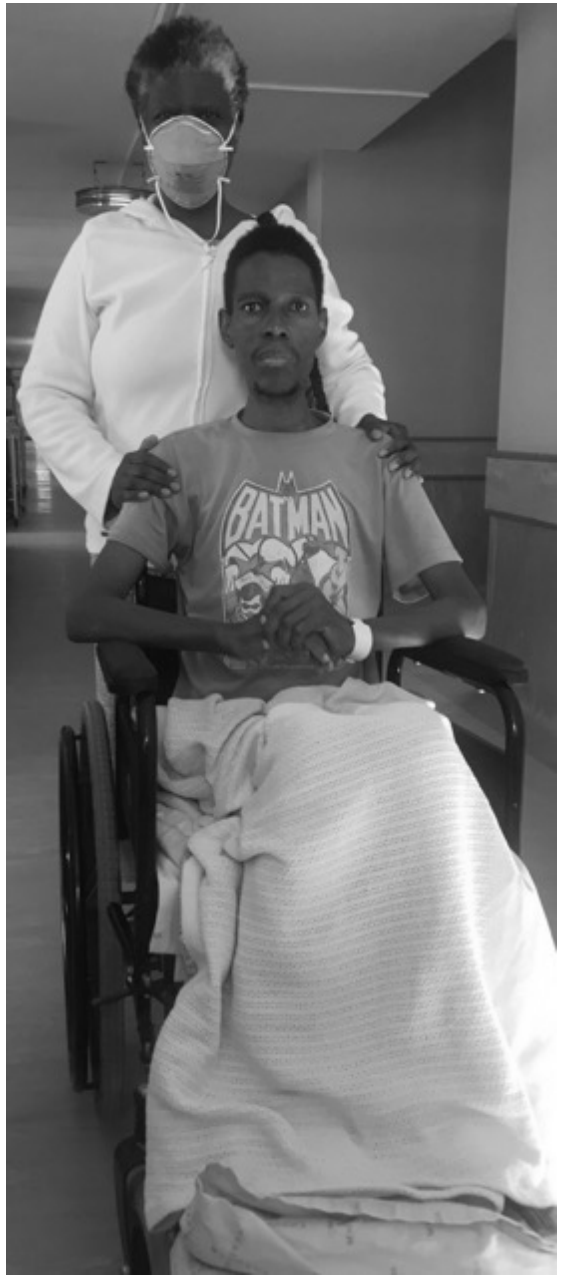

PA ERECT
PA ERECT

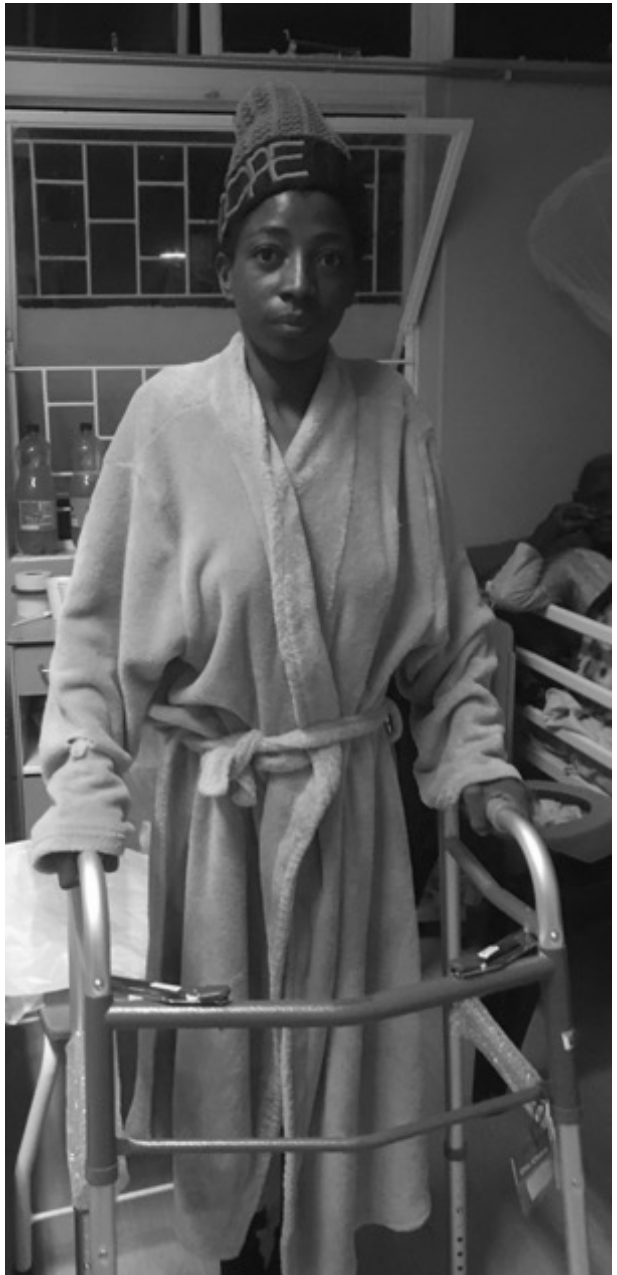
Reasons for consultation in a specialist respiratory service in Namibia



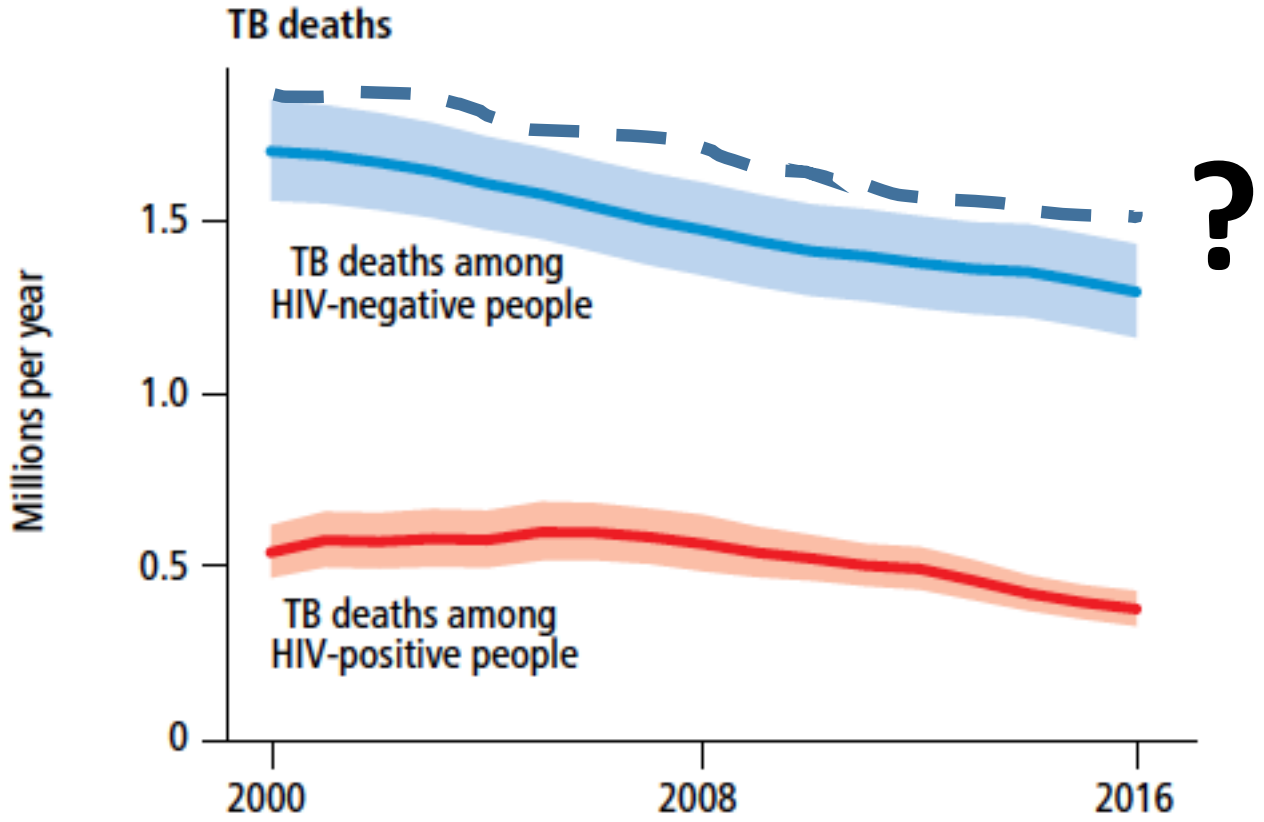
Günther & Ithete, IJTLD 2021

Missing support: physiotherapy, occupational therapy, etc.



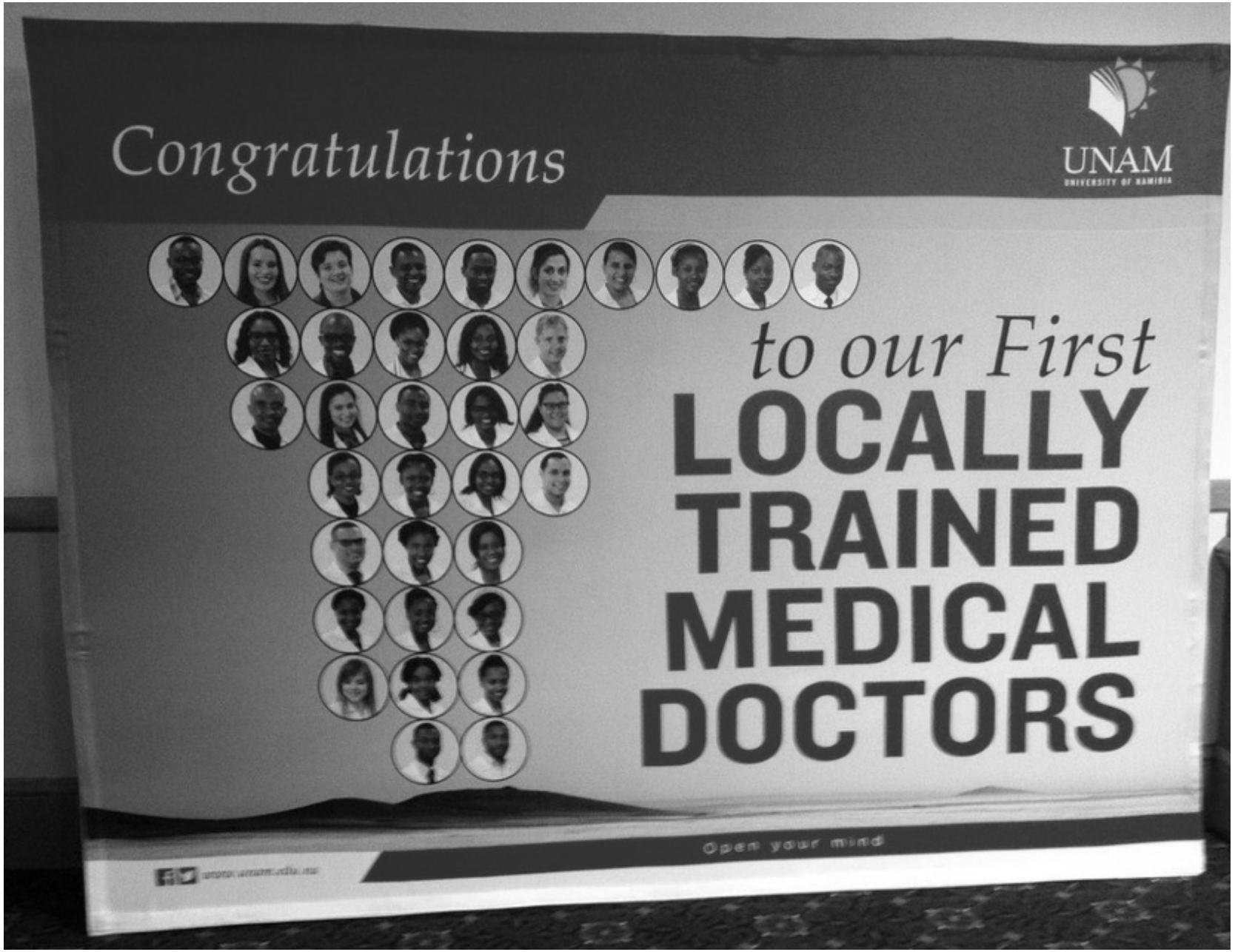


Impact of post TB lung disease on global TB mortality

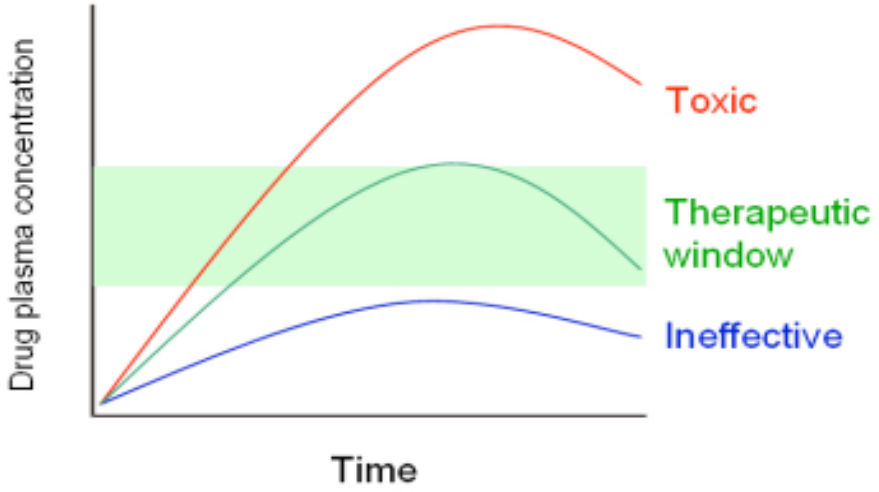


Global TB Report 2018 - adapted

Training of medical practioners



The role of TDM – a balanced view…..



- Special situations
- Special populations
- Sentinella system e.g. hairanalysis

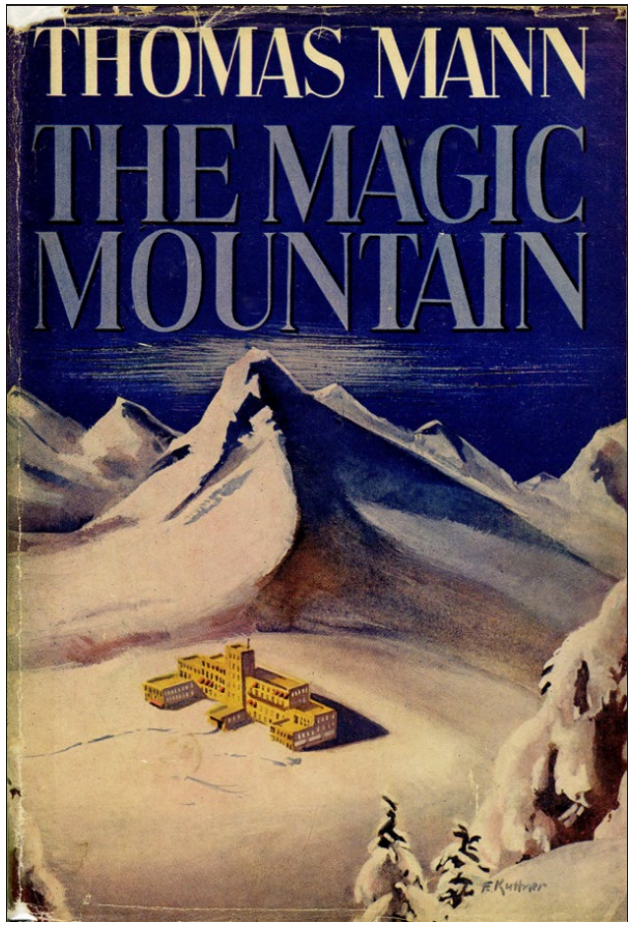
Pro TDM

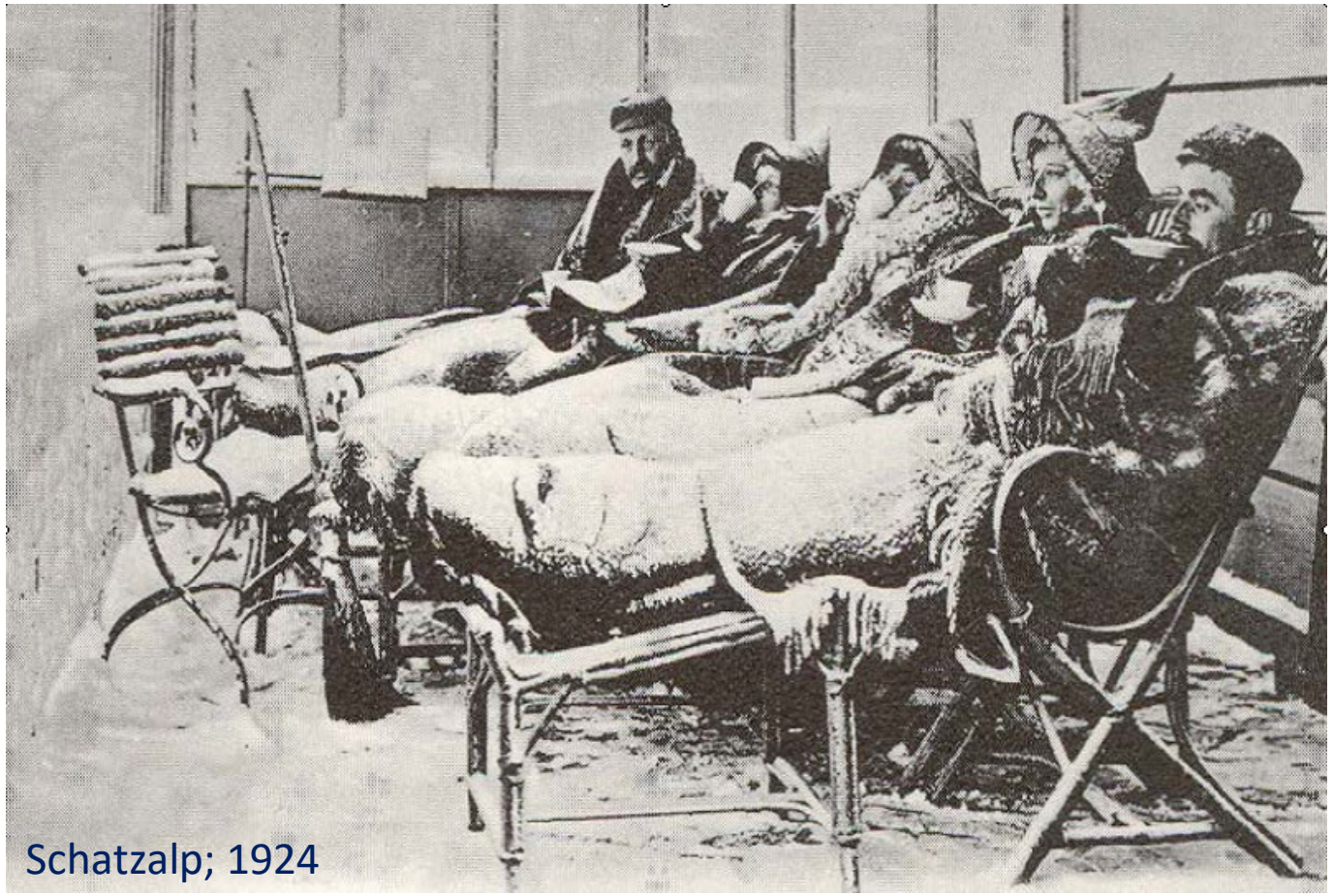
- possibility to reduce toxicity
- likely tool to reduce drug resistance due pharmocokinetic variability
- could improve adherence
- might improve outcome – in DR – TB?

Con TDM

- trials missing to show real outcome benefit
- High end technology - not possible as point of care in high burden settings currently
- costly
- competing public health priorities in TB control

-> There is a role – but we need more to learn and smarter approaches

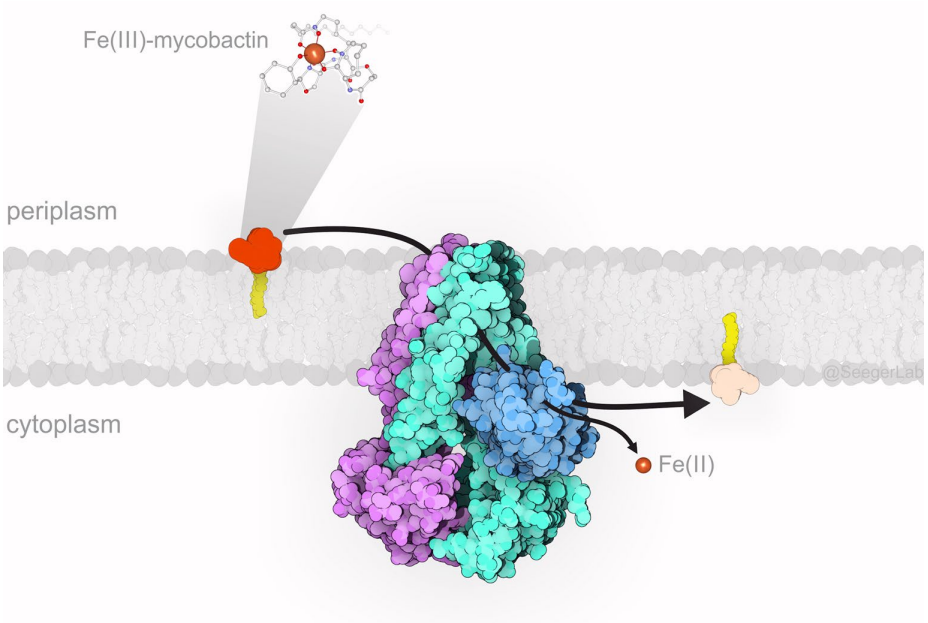




Schatzalp; 1924

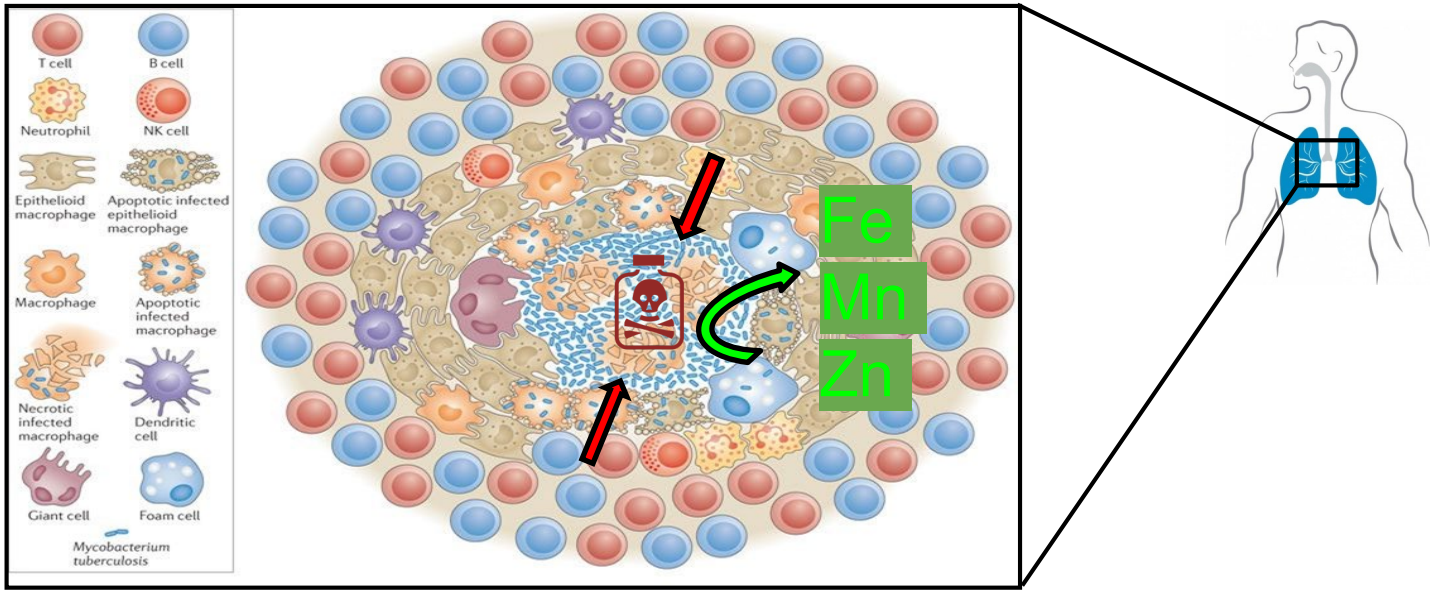
‚…schlaff, fiebrig und innerlich wurmstichig…‘ - Thanks

The ABC exporter IrtAB imports and reduces mycobacterial siderophores



Fabian Arnold, Miriam Weber, Imre Gonda
Tuberkulose Symposium
25. März 2021

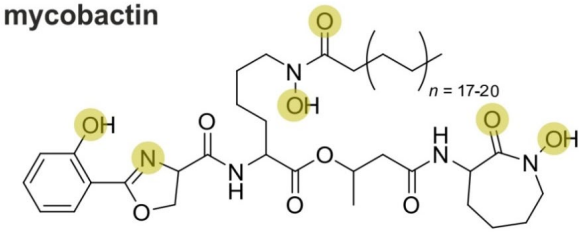
Why does *M. tuberculosis* need siderophores?



- «Nutritional Immunity» present in the human host
- Decreased virulence in *M. tuberculosis* strains with impaired siderophore synthesis/transport

The Mycobactins

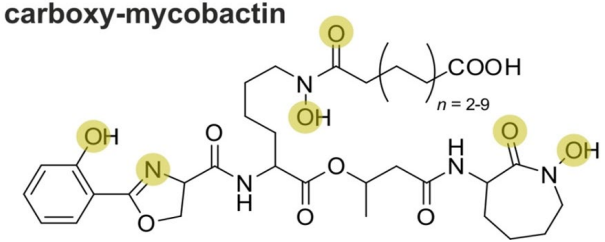
- *M. tuberculosis* produces two types of siderophores, collectively called «mycobactins»
- Synthesized by a series of enzymes MbtA - MbtK

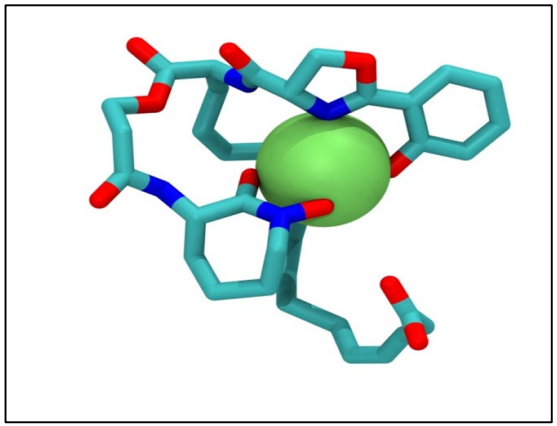


mycobactin

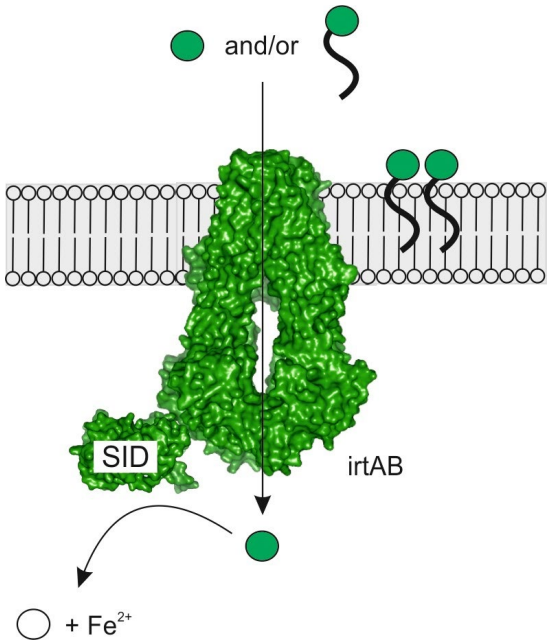
MW ~ 900 Da

(MBT)





IrtAB working model

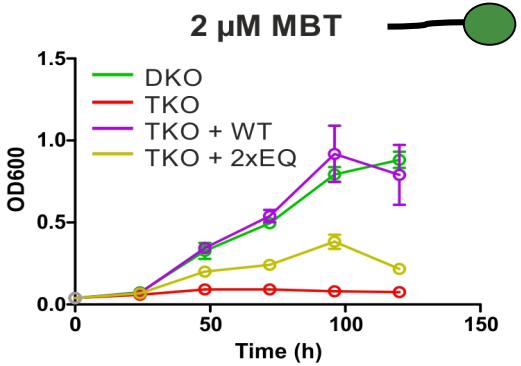


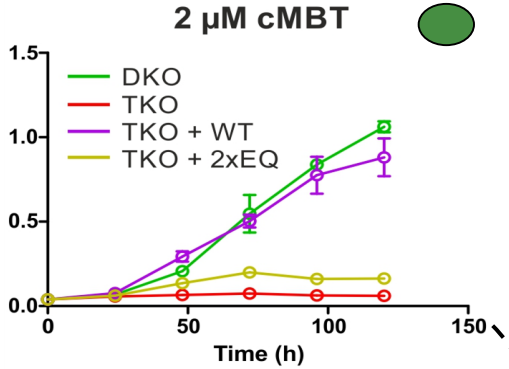
IrtAB was postulated (*in vivo* evidence) to be involved in siderophore trafficking and contribute to virulence in *M. tuberculosis*

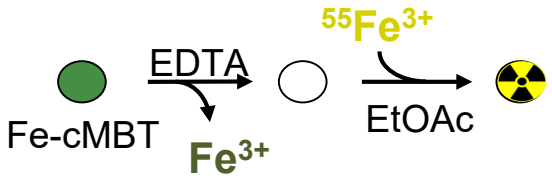
Open questions...

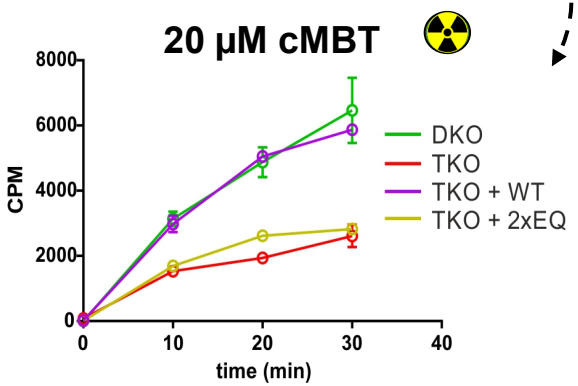
- What is the substrate of IrtAB?
- Is IrtAB importing or exporting siderophores? (ABC Type I exporter fold)
- Is the siderophore interacting domain (SID) involved in siderophore reduction?

Siderophore-dependant growth assay in *M. smegmatis*

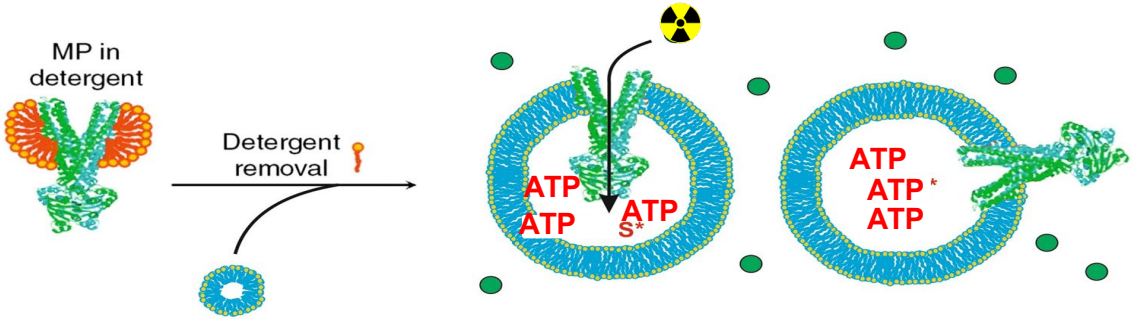






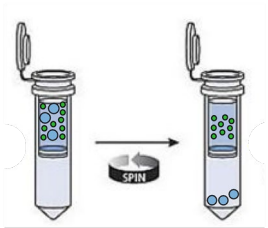


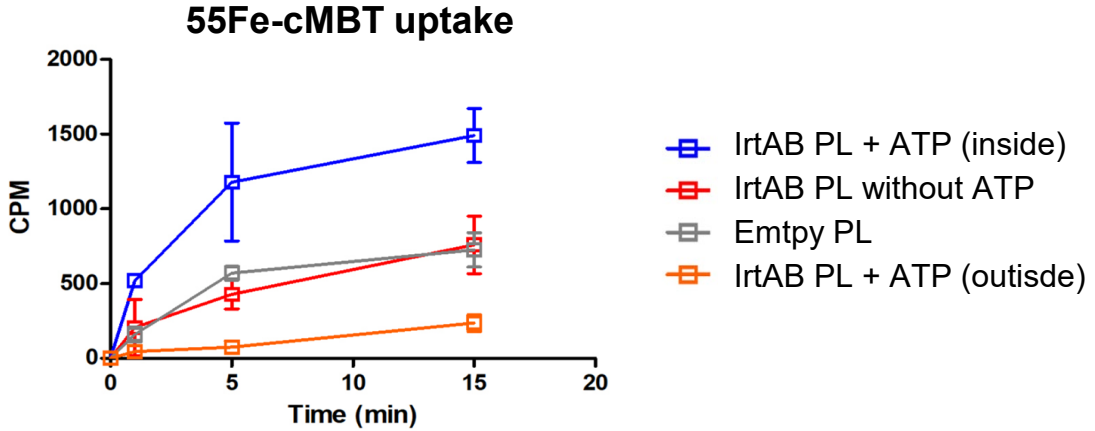
Siderophore import in proteoliposomes



- Reconstitution in proteliposomes with ARS
- Monitor the transport directionality

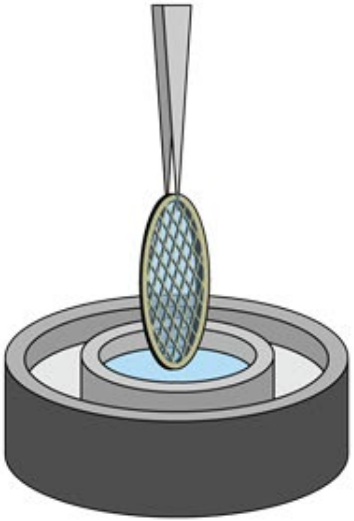
At given timepoints:





Cryo-EM sample preparation and data collection

Purified IrtAB sample



Plunge freezing of sample on EM-grid

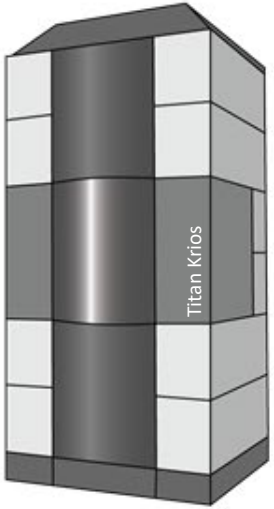


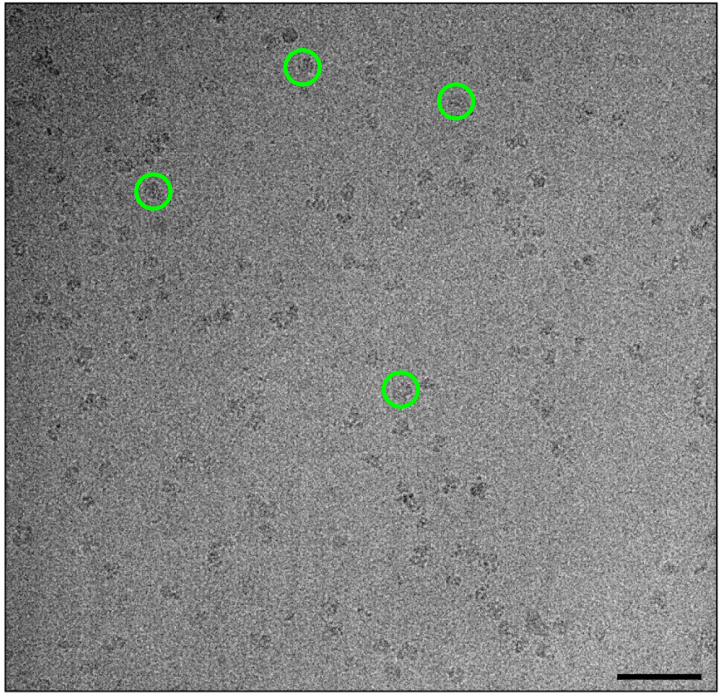
Image acquisition at the electron microscope

Data processing in RELION

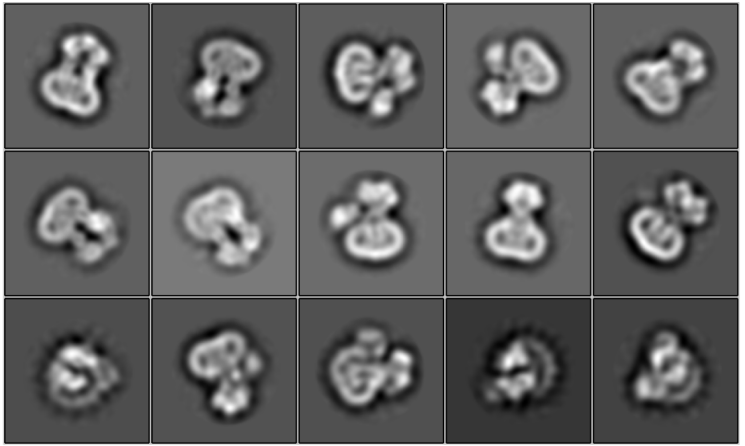
Structure determination with Cryo-EM

- Electron micrographs
- Particle picking
- 2D classification
- 3D classification
- Structure refinement

2 168 micrographs → Picked 335 045 particles



Classified particles in 2D to cover different orientations & remove false-positives



Structure determination with Cryo-EM

Electron micrographs

Particle picking

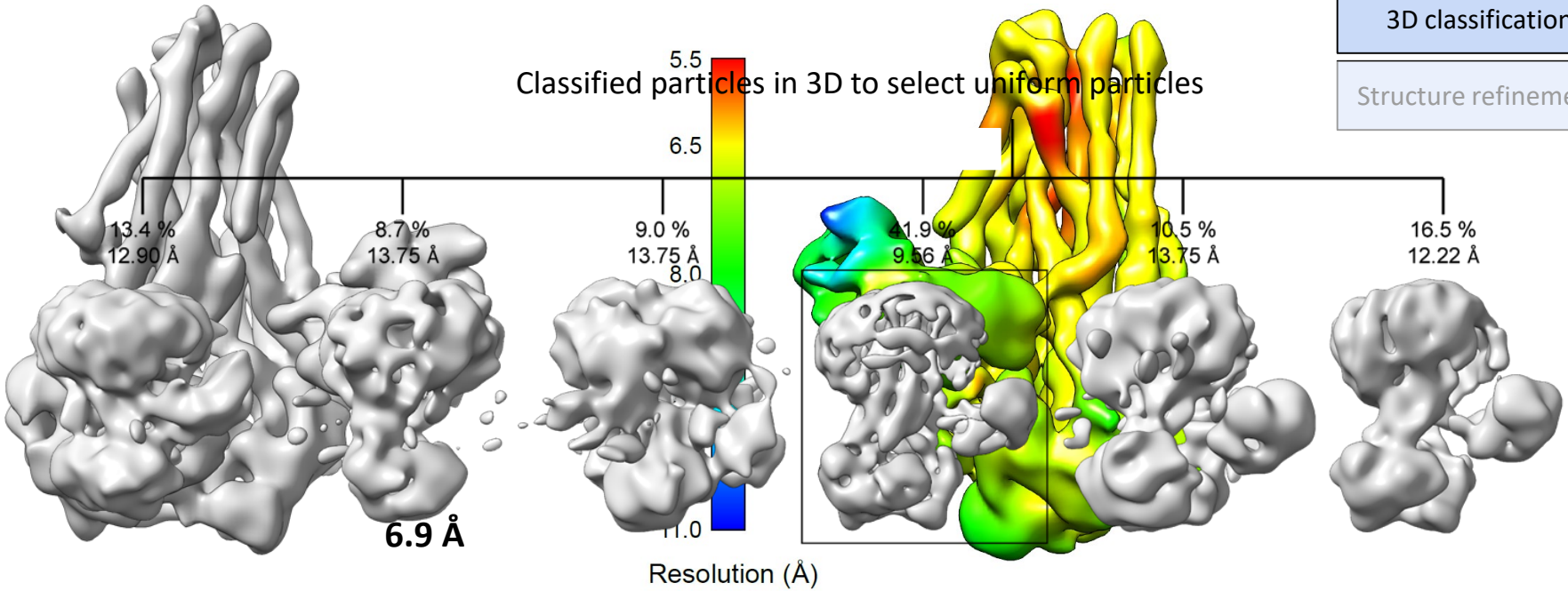
2D classification

3D classification

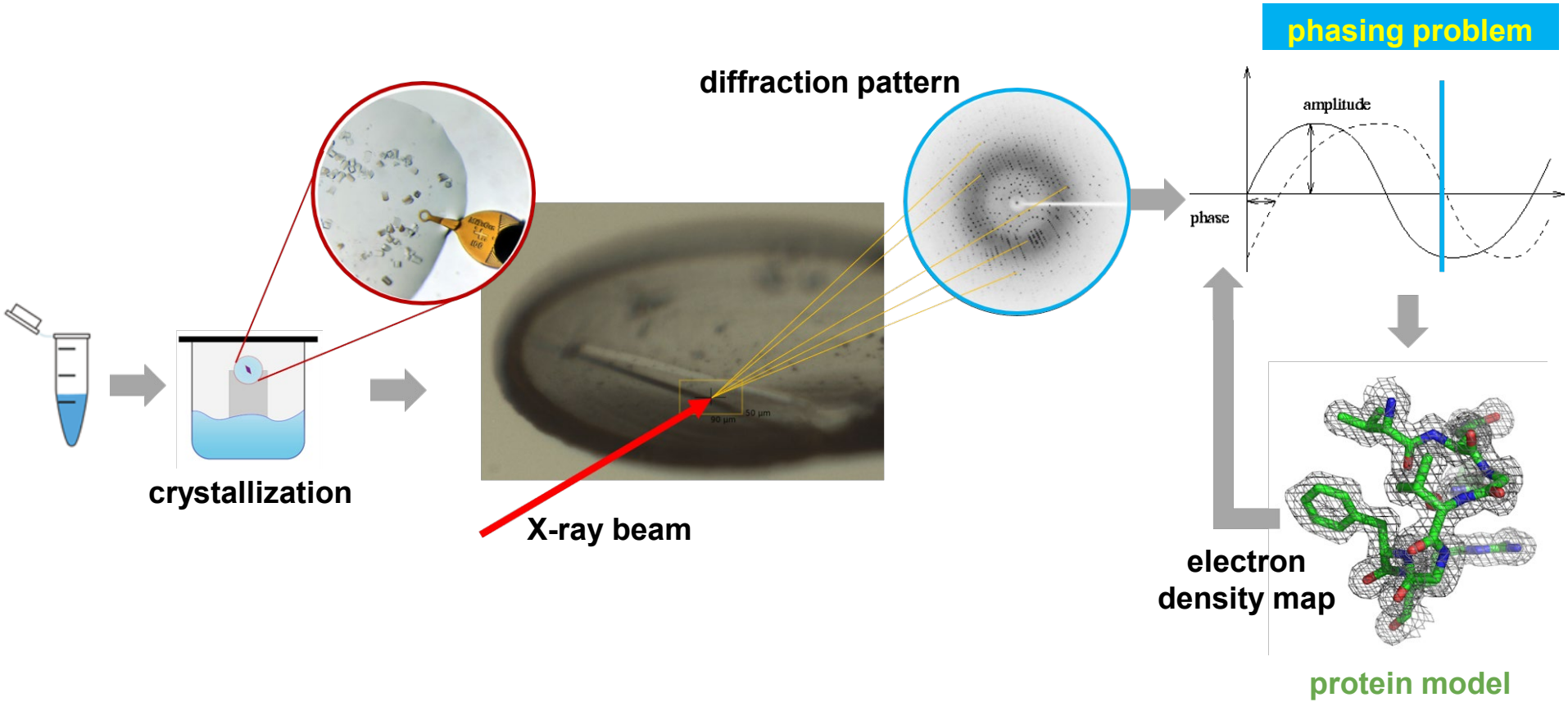
Structure refinement

Refine 3D structure to highest possible resolution

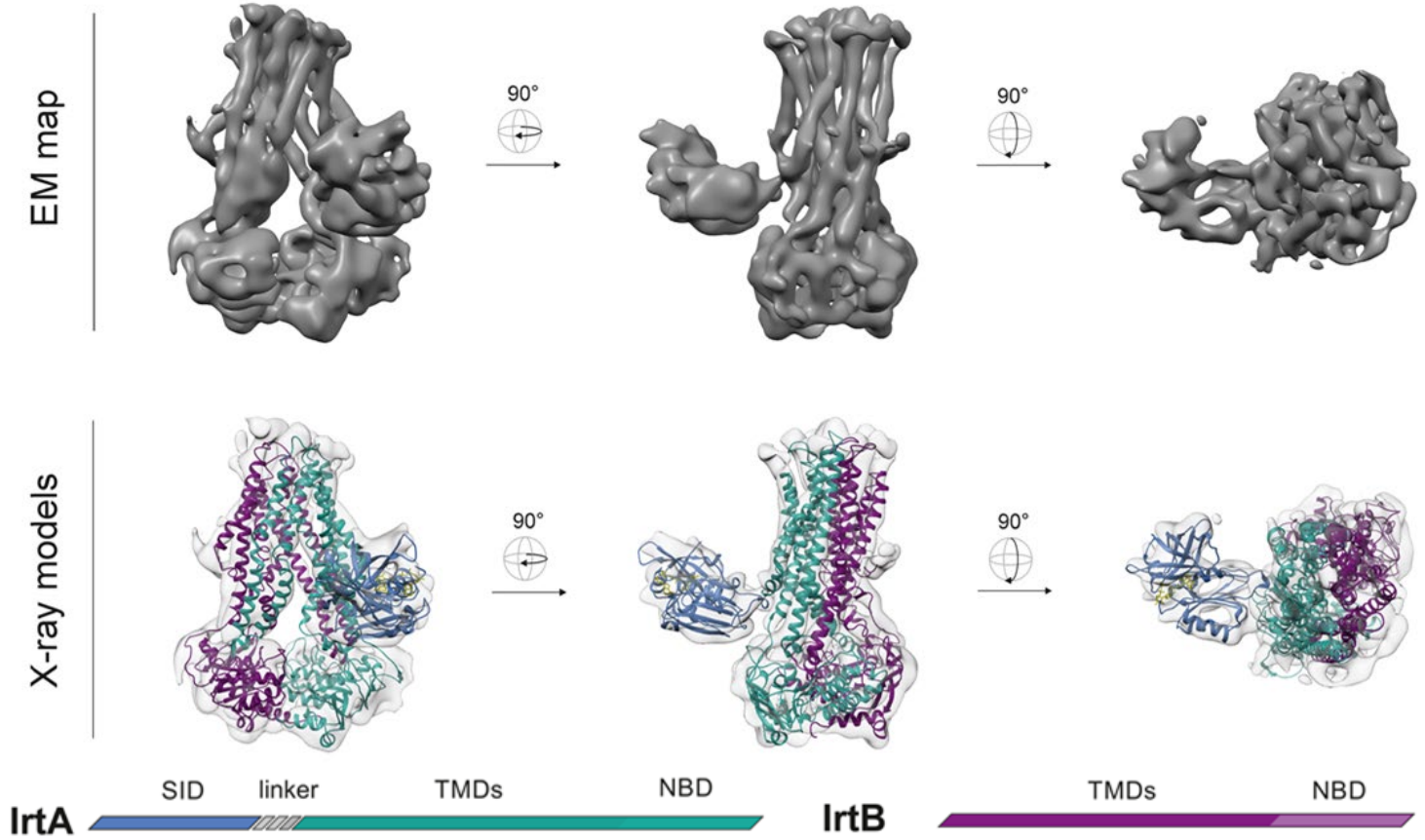
Classified particles in 3D to select uniform particles



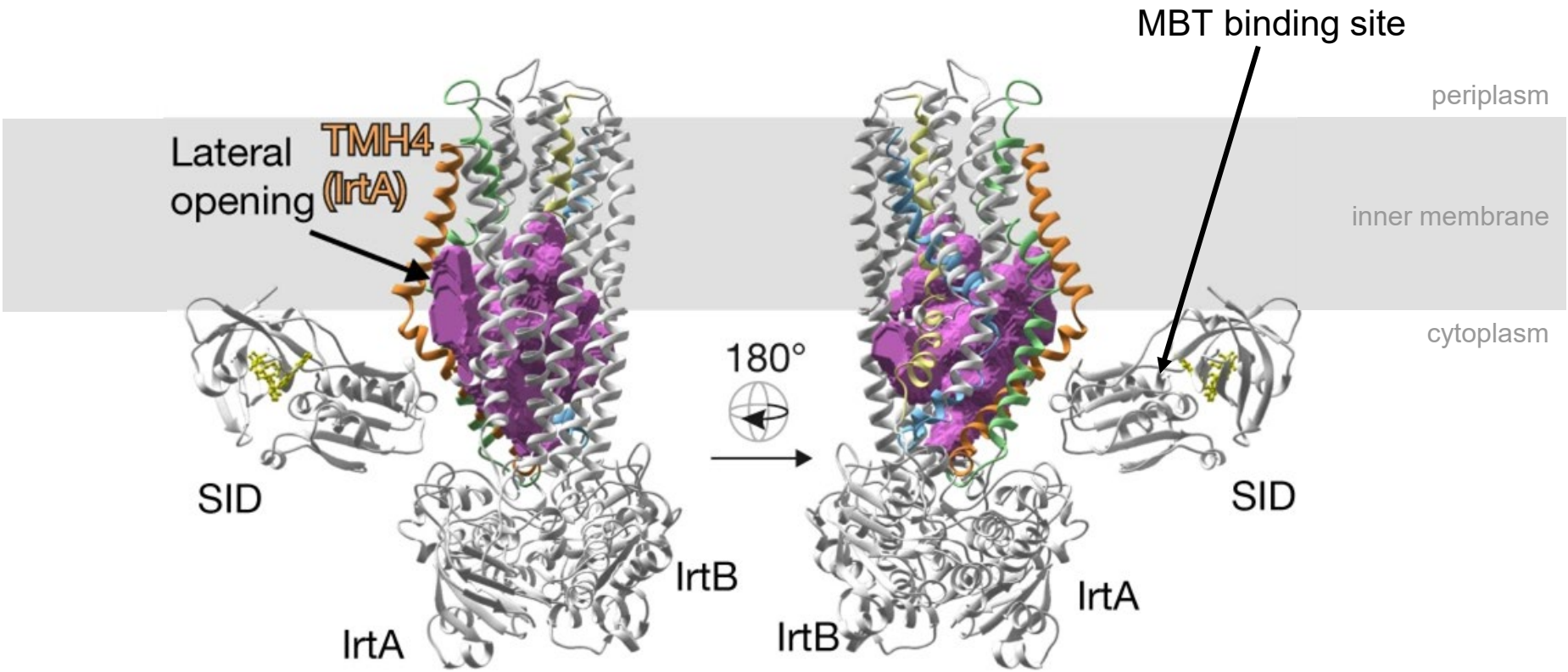
High resolution structures with X-ray crystallography



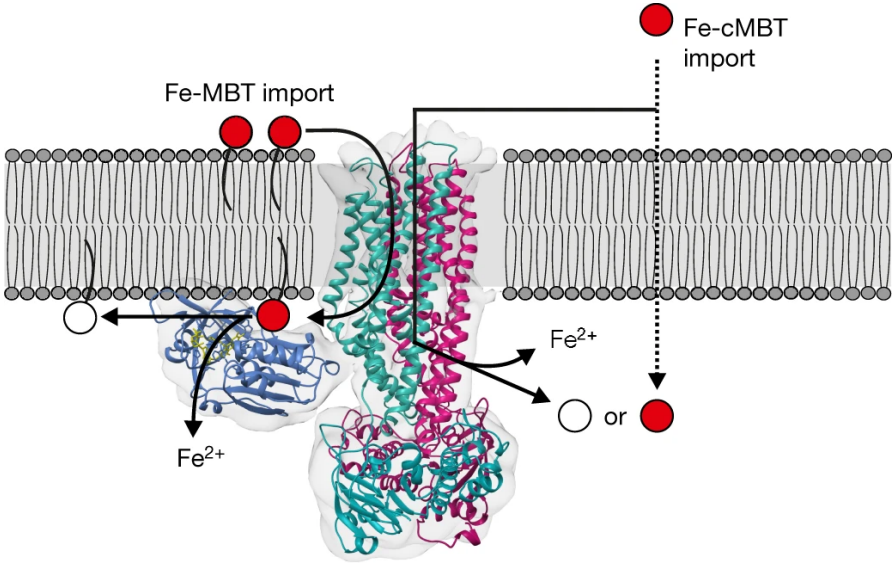
Crystallography and cryo-EM meets



Structural peculiarities of IrtAB



Taking it all together…



- IrtAB is responsible for the **import** of cMBT and MBT
- The main role of IrtAB is the import and reduction of MBT

Open Questions…

→ How does IrtAB **recognize** and **transport** mycobactins?

→ How can we **exploit** IrtAB for antituberculotic drug development?

Acknowledgements

Article

The ABC exporter IrtAB imports and reduces mycobacterial siderophores

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Fabian M. Arnold[1,6], Miriam S. Weber[2,6], Imre Gonda[1,6], Marc J. Gallenito[3], Sophia Adenau[1], Pascal Egloff[1,5], Iwan Zimmermann[1,5], Cedric A. J. Hutter[1], Lea M. Hürlimann[1], Eike E. Peters[4], Jörn Piel[4], Gabriele Meloni[3], Ohad Medalia[2] & Markus A. Seeger[1]✉

Special thanks to:

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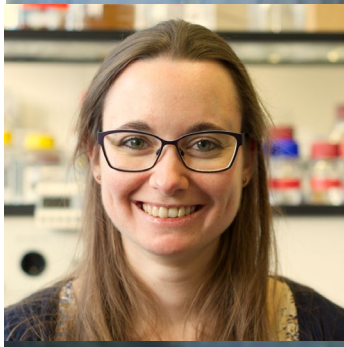
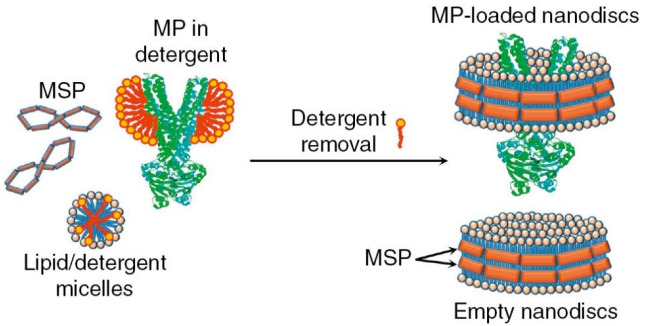
Prof. Ohad Medalia (UZH)
Prof. Jörn Piel (ETH)
Prof. Gabriele Meloni (UT Dallas)

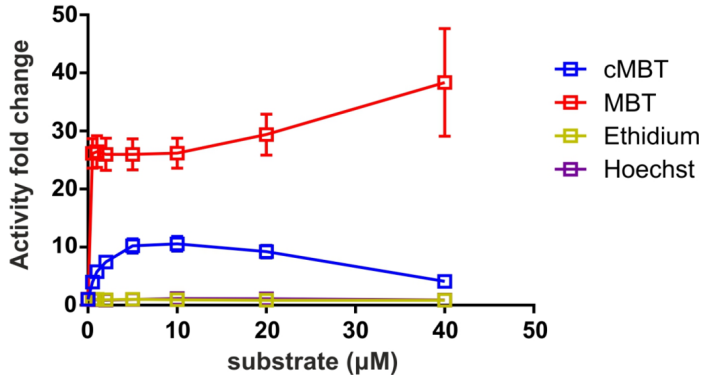


Appendix

ATPase activity is stimulated by siderophores

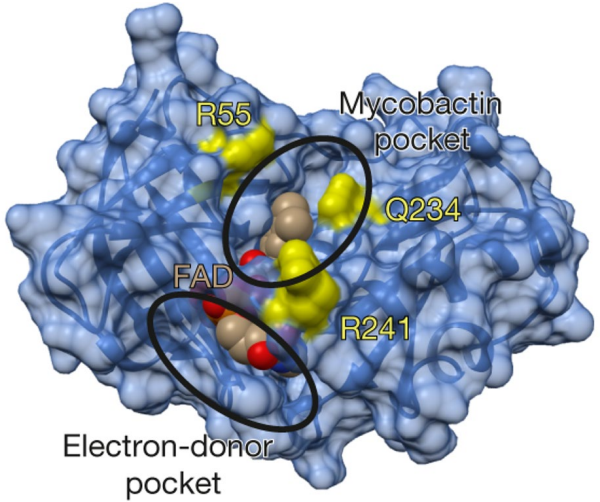


- No ATPase activity with detergent purified IrtAB
- ATPase activity restored after reconstitution in nanodiscs with *E. coli* polar lipids



- Strong ATPase stimulation by the siderophores
- Stimulation by MBT significantly stronger
- Stimulation specific to siderophores

High resolution structures with X-ray crystallography



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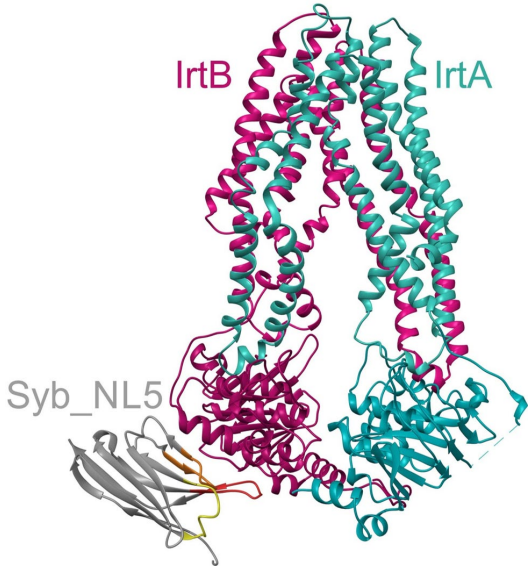
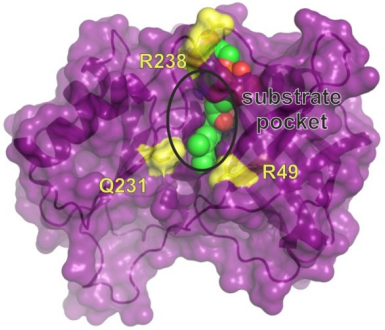


1.8Å resolution crystallographic structure of the SID

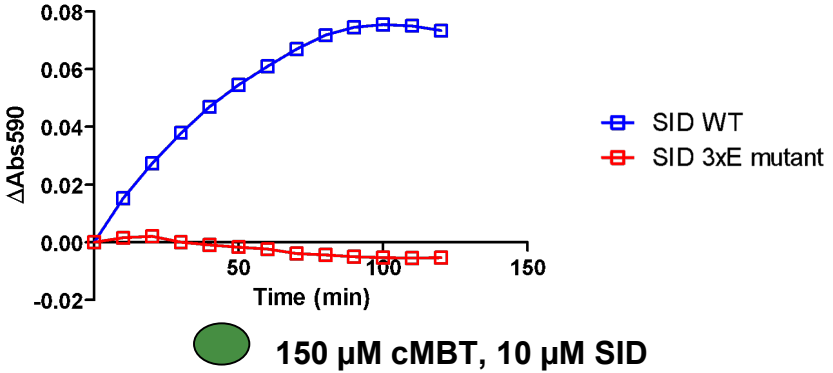
2.7Å resolution crystallographic structure of IrtAB without the SID

Confirming the SID binding pocket



Fe(II)-Ferene

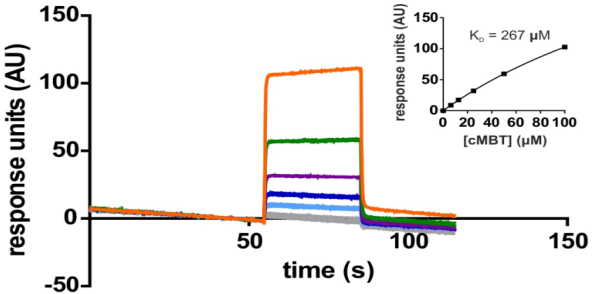
Fe(III)-cMBT + NADPH → cMBT + NADP + Fe(II)



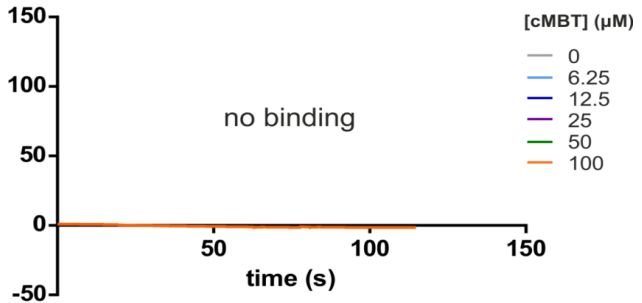
150 µM cMBT, 10 µM SID

SPR

***Msm* SID WT**



***Msm* SID 3xE mutant**



Concluding remarks/Jean-Paul Janssens

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Introduction/ OFSP-BAG/ Andrea Arz de Falco/ Thomas Burgener

29e Symposium Tuberculose virtuel
Jeudi 25 mars 2021

LUNGENLIGA SCHWEIZ
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LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Duration of hospital stay for TB inSwitzerland / Otto Schoch

- 2002-2015: 7726 patients with TB in CH (OFSP). 500-600 /cases/year stable since 2007
- 7395 hospitalizations. ***81% hospitalization rate***; 14% readmission rate
- 76%: TB of airways; mostly male, median age: 40; any resistance: 1.1%; MDR: 0.7%
- Median duration of stay: 14 (IQR: 7-22), longer if > 65 yrs, M, (MD)R, miliary pattern or CNS, co-morbidities (HIV, endocrine, metabolic disorders, malnutrition, lung and liver disorders)
- Wide differences between Cantons: room for improvement by encouraging earlier outpatient care to decrease length of stay

Access to care for vulnerable TB patients / Constantin Bandolfi

Unisanté, Centre universitaire de médecine générale et santé publique, Lausanne

- Concept of vulnerability: *medical & social*; people on the move, poor (8.7% in CH); working poor (4.2% in CH): impact on renouncing to care
- Illustrative clinical case: delayed diagnosis of TB spondylodiscitis in a 46 year old male gambian
- « People on the move »: *systemic* and individual vulnerability; high risk of treatment interruption
- Screening systems (Centres for asylum seakers, prisons, referral in the Cantons to specialized structures: USMI, PSM)
- Importance of correctly identifying situations medically at risk *(« urgent »)* to ensure access to appropriate care and insurance coverage: major role of HCWs
- Among industrialized countries, Switzerland is 4th for equity of care and 8th for access to care

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

What does thoracic surgery bring us today for the treatment of TB?

Jean Y. Perentes, Chirurgie thoracique, CHUV

- Historical perspective: Forlanini (1882), modalities of collapsotherapy, thoracoscopy (1910), thoracoplasty (1920's), pulmonary resection and reexpansion/drainage (as of ≈ 1950); regain of interest with MDR/XDR
- Present role of surgery: 1.Resection of persistent cavitary lesions in MDR/XDR (« reservoir ») added to medical treatment. In MDR/XDR : 47-95% cure rate; combination most often superior to medical treatment alone; mortality rates depend on extension of disease. Treatment after surgery: 12 months for MDR, 24 for XDR
- 2. Importance of treating « residual spaces »; 3. Correction of pleural restrictive sequellae (decortication)
- 4. Treatment of proximal airway stenosis (with endoscopic approach)
- General condition important for prognosis as well as having localized lesions. Multidisciplinary management mandatory.

Pulmonary TB and COVID-19 /Jesica Mazza-Stalder

- TB during the pandemic: > 500'000 deaths; *1.4 M cases may not have received care for TB*. Many countries report *a decrease in case notification* (India, China, Brazil)
- Mortality has increased in emergent countries because of delayed diagnosis: poor access to care?
- Disruption of care for TB because of COVID. ***Worsening economic situation of vulnerable populations***.
- Illustrative case of co-infection with delayed diagnosis of TB in patient under anti-TNF
- Decrease in contact tracing, and management and treatment of LTBI. Marked increase in working poor and precarity
- No positive impact of social distancing.
- Potential positive and helpful contribution of digital technologies , and co-screening (COVID & TB)

Therapeutic drug monitoring (TDM) during treatment for TB /

Pascal André/ Head pharmacist, CHUV

- Indications and modalities of TDM. Available for TB: 4 x 1st-line drugs & 12 x 2nd line drugs
- Reference levels: published in 1992…
- Interpretation: Steady state ?; Trough or peak?; doses and other drugs; clinical condition; suitability of result (or dose adjustment).
- Problem of drug levels in blood versus tissues (i.e. alveolar tissues); free vs linked levels..
- Clinical case: Messages: 1/Use of IBW for drug dosage; 2/drug interactions: no direct role for IPP but effect on gastric pH may affect solubility and dissolution of RIF; 3/Intrinsic variability; 4/ INH acetylor type: slow or intermediate type may have higher hepatotoxicity
- Case 2: CLO: many questions remain ; no correlation between TDM and effect
- THM: *still limited current knowledge*; may be helpful to explain poor clinical response or in case of comorbidities and drug interactions. More important potential for MDR/XDR

Treatment of TB with rifampicin: are we using the right doses?

Martin Boere, Nijmegen, NL

- Background: Relapse rate: 2.8% during 1st year. *Low INH and RIF peak levels and AUC precede acquired drug resistance*. Initially, tests looked for the lowest efficient dose to limit toxicity.
- Higher doses of RIF may decrease relapse rate & emergence of resistance, and decrease TTC
- Many studies in sub-saharan Africa looking at higher doses of RIF (PanACEA): 10 mg/kg vs 20-40 mg/kg: *well tolerated, no withdrawals*
- At 50mg/kg: higher withdrawal rates: « not happy patients »!
- 600-1200 mg RIF in intensive phase: no increase in bacteriological response: up to 20 mg/kg too low!
- ***RIF 35*** vs 10-20 mg/kg: decrease in time to culture conversion (adj HR: 1.99); toxicity stable
- *Team of M Boere uses 35 mg/kg of RIF in severe PTB, TBM, TB and HIV, severe EPTB, TB and diabetes*
- Doses of 40 mg/kg may allow shorter regimens (3-4 months) in the future (2100 mg)

INTENSE TBM: Intensified TB treatment to reduce the mortality of tuberculous meningitis: on-going study / Alexandra Calmy, HUG

- Intense TBM project. Multicentric study in sub-saharan Africa (Ivory Coast, Uganda, Madagascar, South Africa). *Started Jan 2021*. Mortality of TBM: HIV-: 30%; HIV+ : up to 70 %; long term sequellae possible.
- Poor penetration of RIF in CNS.
- Aim: 4 arms (n=192/arm): Mortality: Intense tt for TBM during first 8 weeks vs SOC; 2/ aspirine (8W) vs placebo
- SOC: 2HRZE/7HR + DEX over 60 days; **Intensified REG: RIF 35 mg/kg 8 weeks** then 10mg/kg ; LIN 1200 4 weeks, 600 4 weeks, +HZE. **RIF: 300-750 g vs 1200-2550 mg**
- ***Evidence: High RIF safe, reduces TTC, may decrease mortality (Ph II, 2013); becomes detectable and reaches MIC in CSF at higher doses***
- LIN: interaction with RIF: 2 x increase in dosage; substudies ASP; Dble dose: Dolutegravir

PRO-Con debate: measuring serum levels of anti-TB drugs: Waste of money or effective for individualized treatment?

Jan Fehr, ZH/ Gunar Günther, BE

- Toxicity matters and affects QoL: hearing loss, hepatatis, vomiting, depression , neuralgia
- Risk of MDR/XDR: 50% of all TB-treatment costs for MDR; 56% of MDR and 40% of XDR treated successfully
- Lower serum cc: higher risk of remaining C+
- Possible implications for transmission? Little/no impact on treatment failure.
- Meta-analysis (2020, 15 studies): Low PZA increases poor outcome; low RIF may slightly affect outcome; low EMB and INH: no documented difference
- WHO 2018: no demonstrated added value of TDM except in specific drug regimens (LIN, CYC)
- Many unanswered questions: when, how, what to measure, cost-effectiveness, low income areas…

SwissTB award 2021: and the winners are……..

- Fabian Arnold, ZH, Miriam Weber & Imre Gonda, ZH
- Congratulations! (and thanks to Swiss-TB!)

Mycobacterial siderophores (mycobactins)

Concluding remarks /Jean-Paul Janssens

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LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

- Many thanks to all our excellent speakers
- Many thanks to the organizers and interpreters
- Thank you for your participation
- Stay safe and in good health!
- See you next year hopefully in « real life »:
- Save the date: 24.3.2022

Thank you for participation

Save the Date – 24.3.2022

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