Tuberculose
Terug van nooit weggeweest

Eskulaap
7 februari 2023
Inge Muylle

Conflicts of interest

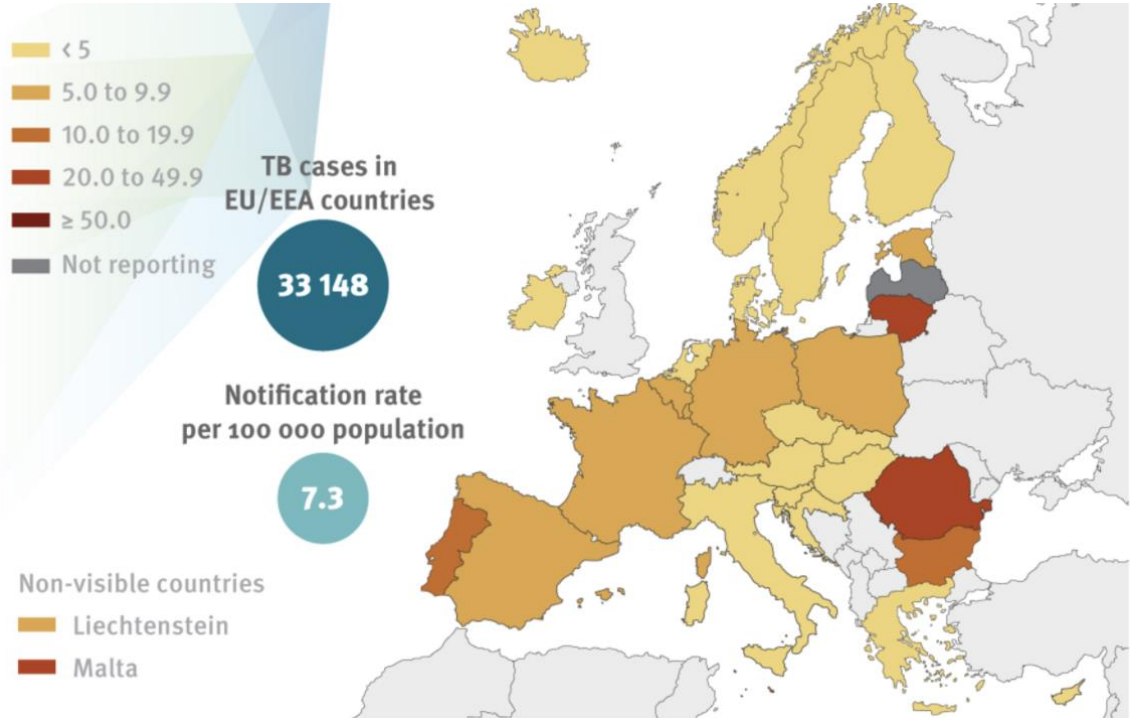
- Speakers fee: J&J
- Advisory Board: J&J
- Lid van Raad van Bestuur VRGT
- Consultancy activiteiten voor VRGT, BELTA-TB & Damiaanactie

Overzicht presentatie

- Epidemiologie & Preventie
- Diagnose ➠ door Dr. van den Wijngaert
- Nieuwe behandelstrategieën
  - Multigevoelige tuberculose
  - Resistente tuberculose
- Praktische aspecten

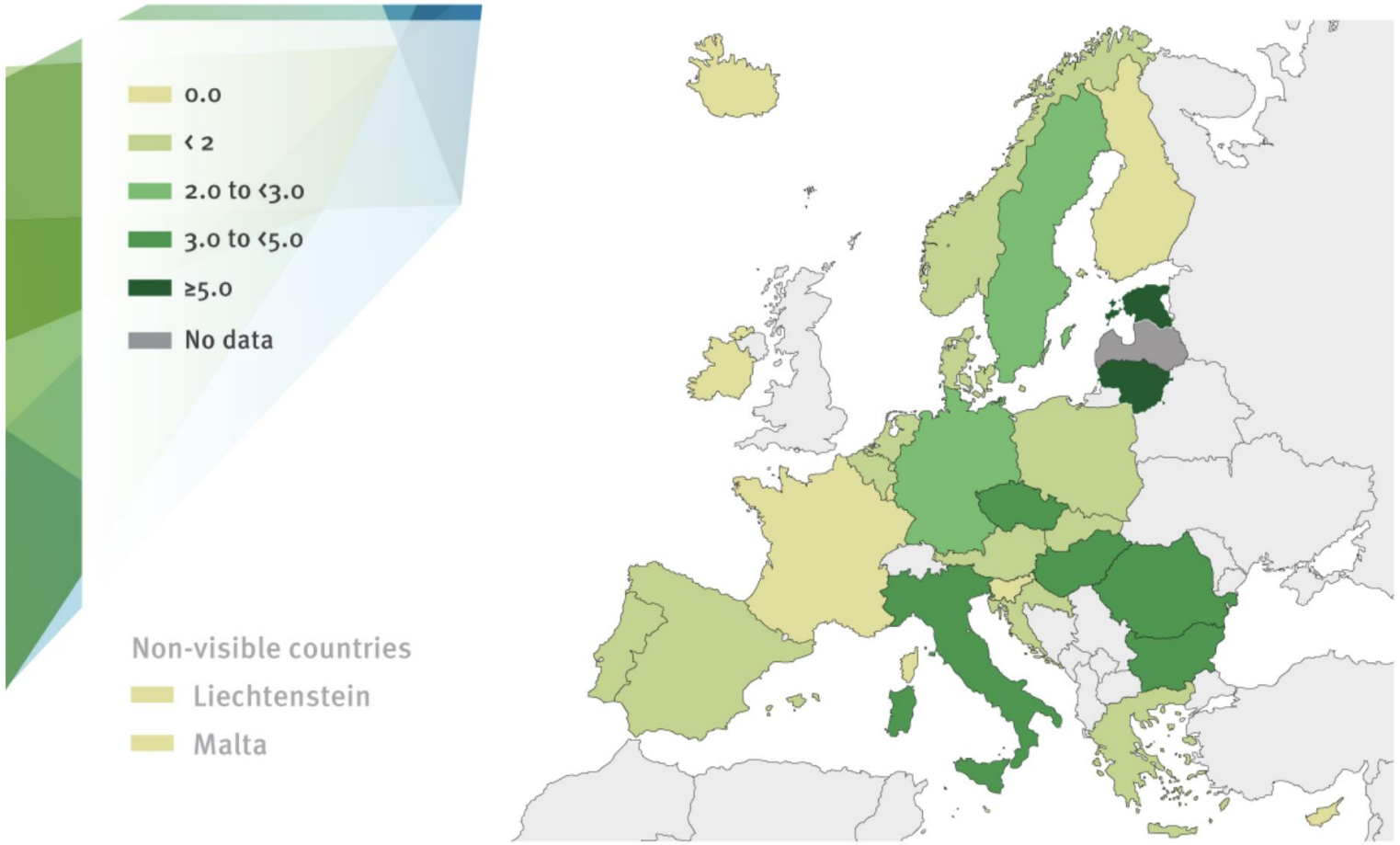
Epidemiologie

Total EU/EEA TB notification rate over time, and the 2030 target: 80% reduction compared with 2015.



https://www.ecdc.europa.eu/en/publications-data/infographic-tuberculosis-eueea-2020 - accessed 08/11/2022

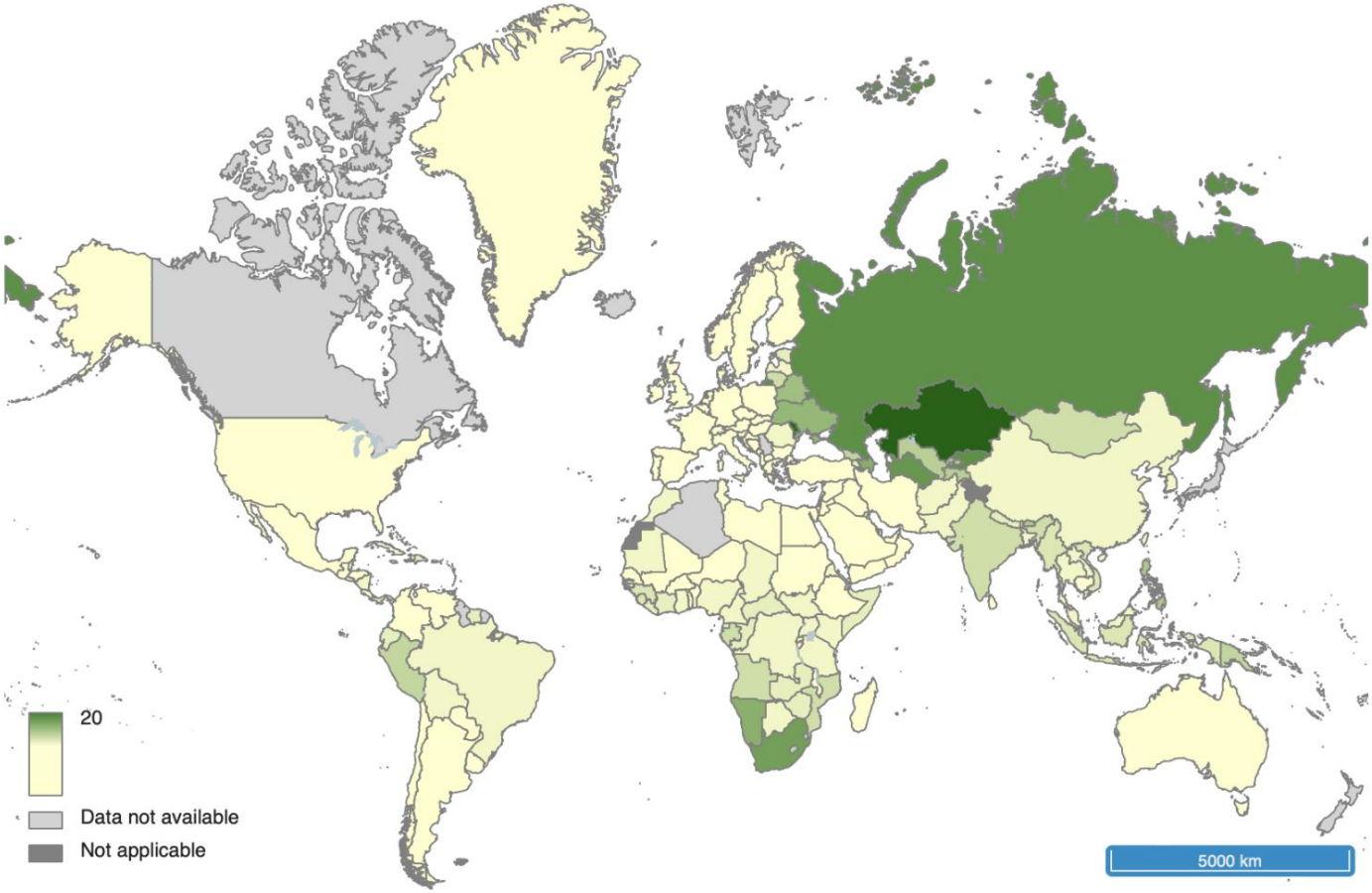
Proportion of TB cases notified as MDR TB in EU/EEA, 2020



https://www.ecdc.europa.eu/en/publications-data/multidrug-resistant-mdr-tuberculosis-eueea-2020 - accessed 08-11-2022

Diagnosis and notification of rifampicin-resistant TB (MDR/RR-TB)

Notified MDR/RR-TB cases (per 100 000 population) | 2021



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

World Health Organization

Generated: 09 November 2022 Source: www.who.int/tb/data

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Epidemiologie - België

Estimates of TB burden*, 2021

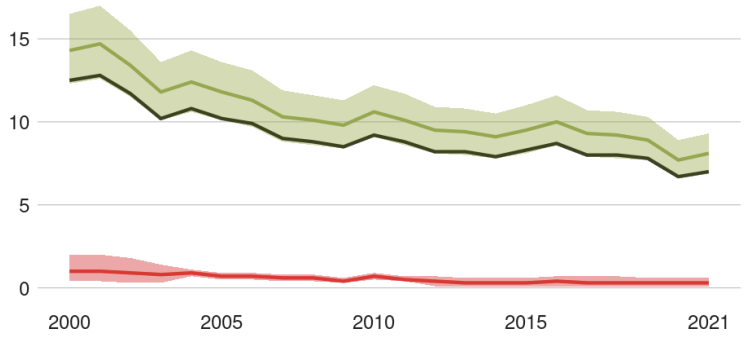
	Number	(Rate per 100 000 population)
Total TB incidence	940 (800-1 100)	8.1 (6.9-9.3)
HIV-positive TB incidence	35 (13-68)	0.3 (0.11-0.58)
MDR/RR-TB incidence**	28 (17-38)	0.24 (0.15-0.33)
HIV-negative TB mortality	33 (32-34)	0.29 (0.27-0.3)
HIV-positive TB mortality	7 (2-14)	0.06 (0.02-0.12)

Estimated proportion of TB cases with MDR/RR-TB*, 2021

New cases	1.9% (1.2-2.7)
Previously treated cases	14% (6.6-24)

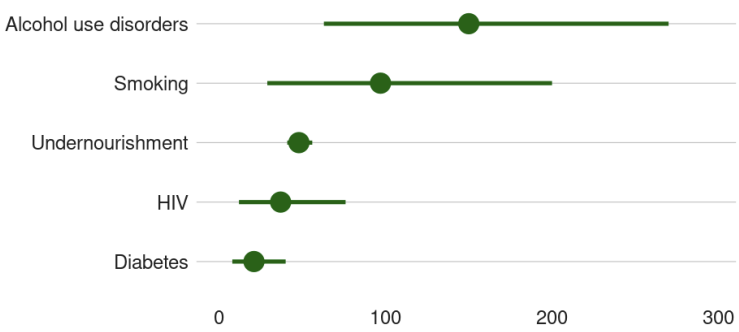
Incidence, New and relapse TB cases notified, HIV-positive TB incidence

(Rate per 100 000 population per year)



Cases attributable to five risk factors, 2021

(Number)



https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type="country"&lan="EN"&iso2="BE" - accessed 08/11/2022

Resistentie? … Hoe zit dat alweer? …

- monoR: resistentie voor 1 1ste lijns tuberculostaticum
- polyR: resistentie voor ≥ 2 1ste lijnsmiddelen (behalve combinatie INH-RMP)

- MDR: resistentie voor INH & RMP
- R-R: resistentie voor minstens RMP

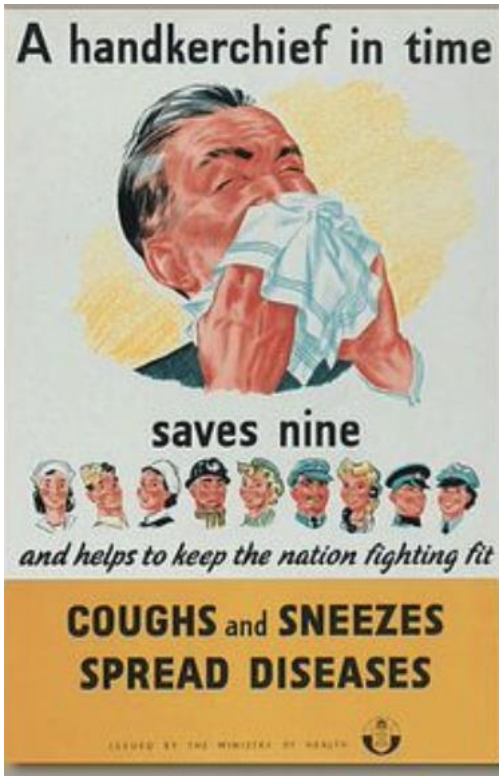
- ~~XDR: MDR met bijkomende resistentie voor quinolones & SLI~~
- ~~preXDR: MDR met ofwel resistentie voor quinolones of minstens 1 SLI~~

—

2021: Nieuwe definities XDR & preXDR

- Pre-XDR-TB:TB veroorzaakt door Mycobacterium tuberculosis (M. tuberculosis) die aan definitie MDR/RR-TB beantwoordt & die tevens resistent is aan een fluoroquinolone
- XDR-TB: TB veroorzaakt door Mycobacterium tuberculosis (M. tuberculosis) die aan definitie MDR/RR-TB beantwoordt & die tevens resistent is aan een fluoroquinolone en minstens nog 1 bijkomend antibioticum uit Groep A (Bedaquiline en/of Linezolid)

Preventie

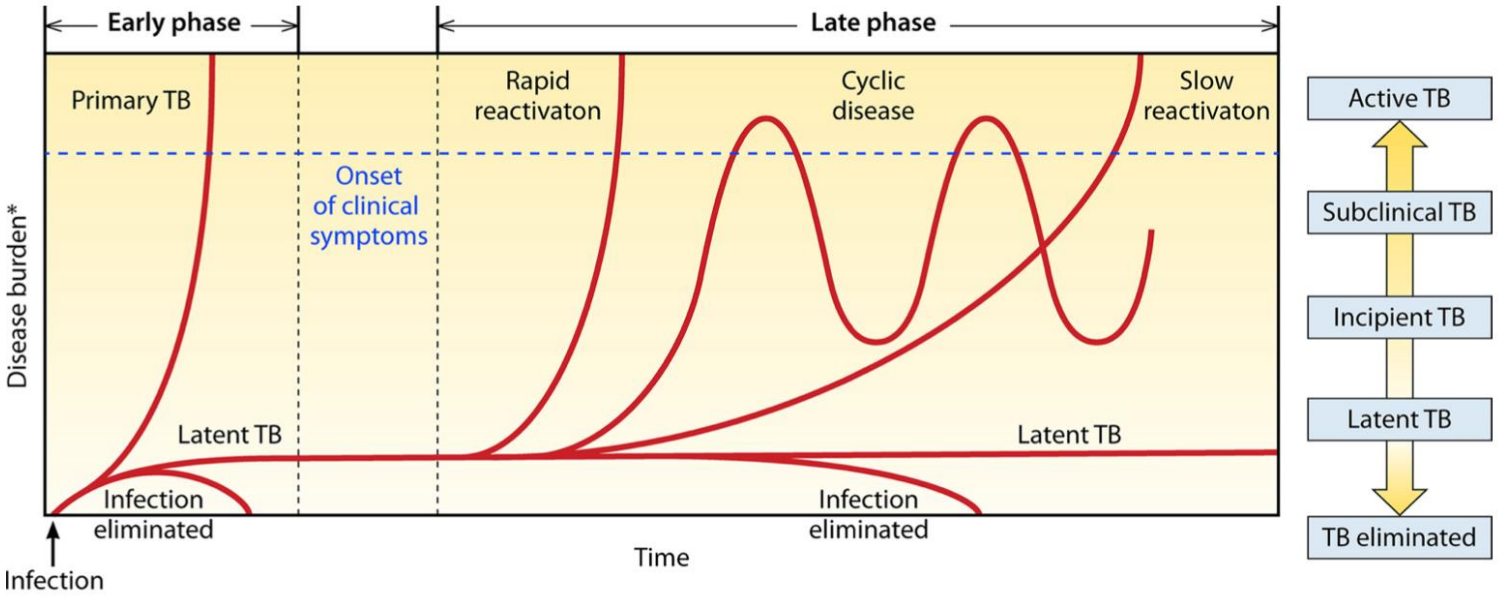

A handkerchief in time
saves nine
and helps to keep the nation fighting fit
COUGHS and SNEEZES
SPREAD DISEASES


VIVRE
1928–1929
COMITÉ NATIONAL
DÉFENSE
CONTRE LA TUBERCULOSE
SEINE-INFÉRIEURE


„ЗДОРОВЫЙ ДУХ ТРЕБУЕТ
ЗДОРОВОГО ТЕЛА.“ К.ВОРОШИЛОВ

Latente TB-infectie … klinkt eenvoudig?

- M.TBC specific immune response in the absence of active disease (Mtb-sir-nodis).



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

Drain et al. Clin Microbiol Rev 31(4):e00021-18. https://doi.org/10 .1128/CMR.00021-18. 2018

Prevalentie LTBI …

Table 1. Proportion of population with latent TB infection.

WHO region	All LTBI		Recent infection prevalence (within 2 y)	
	Prevalence (%)	Proportion of infections in children <15 y (%)	(%)	Proportion with INH-R infection (%)
AFR	22.4 [20.6–24.6]	13.3 [11.8–14.6]	1.5 [1.3–1.7]	7.4 [6.4–8.7]
AMR	11.0 [7.0–20.0]	2.3 [1.3–3.7]	0.2 [0.1–0.2]	7.0 [6.0–8.8]
SEA	30.8 [28.3–34.8]	7.4 [6.3–8.2]	1.2 [0.9–1.6]	9.5 [8.8–10.3]
EMR	16.3 [13.4–20.5]	7.9 [6.0–9.4]	0.7 [0.5–1.0]	13.1 [10.0–15.5]
WPR	27.9 [19.3–40.1]	2.4 [1.7–3.5]	0.5 [0.4–0.7]	14.7 [13.9–15.6]
EUR	13.7 [9.8–19.8]	2.0 [1.3–2.7]	0.3 [0.2–0.3]	29.5 [23.8–45.1]
GLOBAL	23.0 [20.4–26.4]	5.9 [5.1–6.7]	0.8 [0.7–0.9]	10.9 [10.2–11.8]

- **1,7 miljard** mensen wereldwijd
- 4/5 infecties in Zuid-Oost Azië, Western-Pacific & Afrika (WHO regio's)
- Recente infectie 0,8% → 55,5 miljoen met verhoogd risico op TB ziekte
- 10,9% INH-R (globally) but 30% in European WHO region

Houben RMG et al. (2016) PLoS Med 13(10): e1002152. doi:10.1371/journal. pmed.1002152

Schatting ivm MDR-LTBI

	Prevalence (95% uncertainty interval)		Proportion (95% uncertainty interval)	
	Drug-susceptible latent tuberculosis	Multidrug-resistant latent tuberculosis	Latent tuberculosis that is multidrug resistant	Latent tuberculosis that is multidrug resistant in people younger than 15 years
African	22·1% (20·1–25·5)	0·23% (0·19–0·29)	1·0% (0·8–1·3)	2·3% (1·9–2·7)
Americas	10·6% (7·3–19·0)	0·05% (0·04–0·06)	0·5% (0·3–0·8)	3·3% (2·8–4·1)
South-East Asia	30·7% (27·7–34·5)	0·31% (0·23–0·41)	1·0% (0·7–1·3)	2·2% (1·9–2·6)
Eastern Mediterranean	16·4% (13·5–20·9)	0·14% (0·08–0·24)	0·9% (0·5–1·5)	2·9% (1·9–3·8)
Western Pacific	26·8% (17·8–39·2)	0·36% (0·26–0·49)	1·3% (0·7–2·2)	3·7% (3·3–4·1)
European	13·5% (9·9–19·8)	0·38% (0·32–0·44)	2·8% (1·6–3·9)	14·1% (13·1–15·2)
Global	22·9% (20·1–26·1)	0·28% (0·24–0·31)	1·2% (1·0–1·4)	2·9% (2·6–3·1)

Table 1: **Prevalence of latent tuberculosis infection, 2014, by WHO region**

Knight et al. Lancet Infect Dis 2019; 19: 903–12

Schatting ivm MDR-LTBI

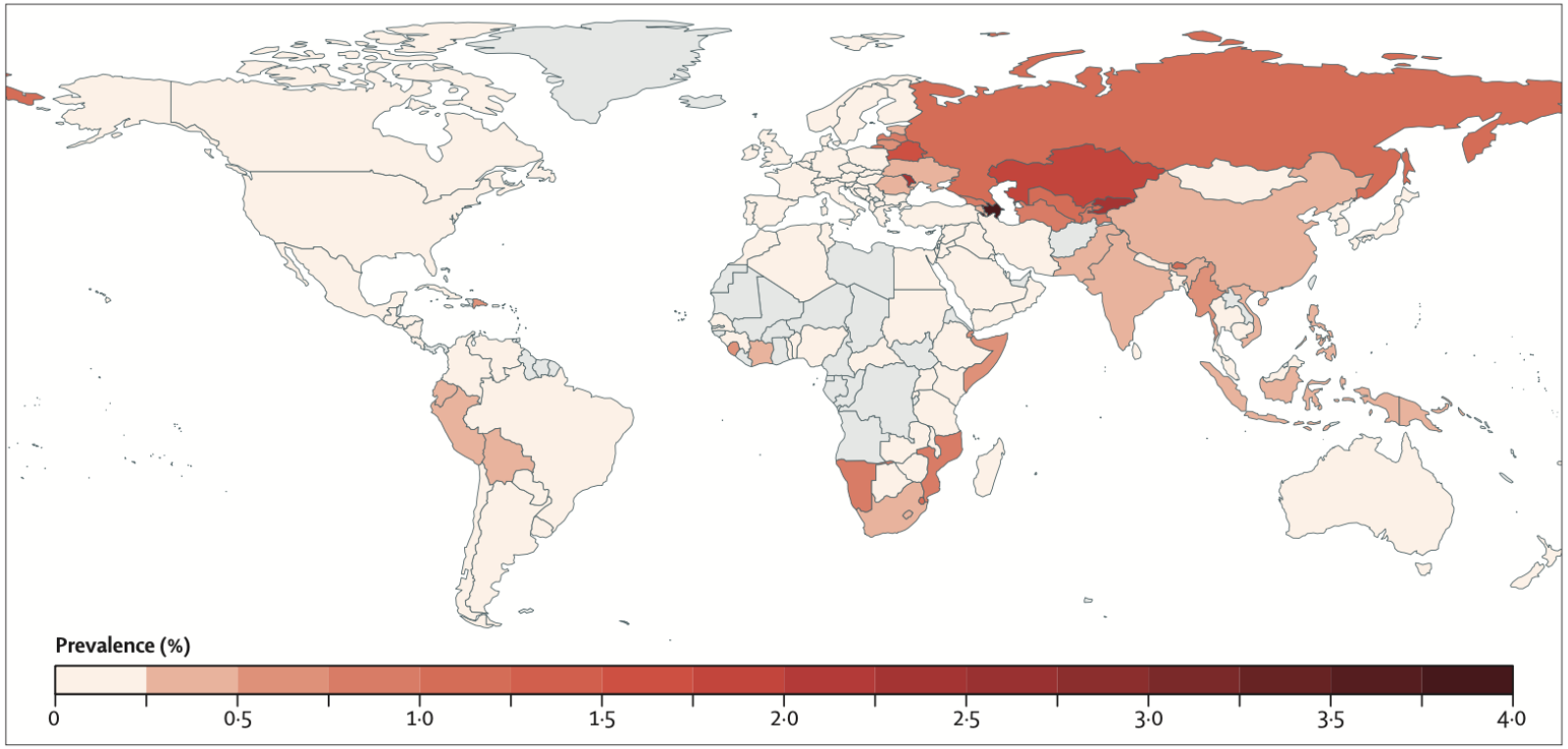


Figure 3: **Estimated worldwide prevalence of latent multidrug-resistant tuberculosis infection**

Knight et al. Lancet Infect Dis 2019; 19: 903–12

Behandeling - LTBI

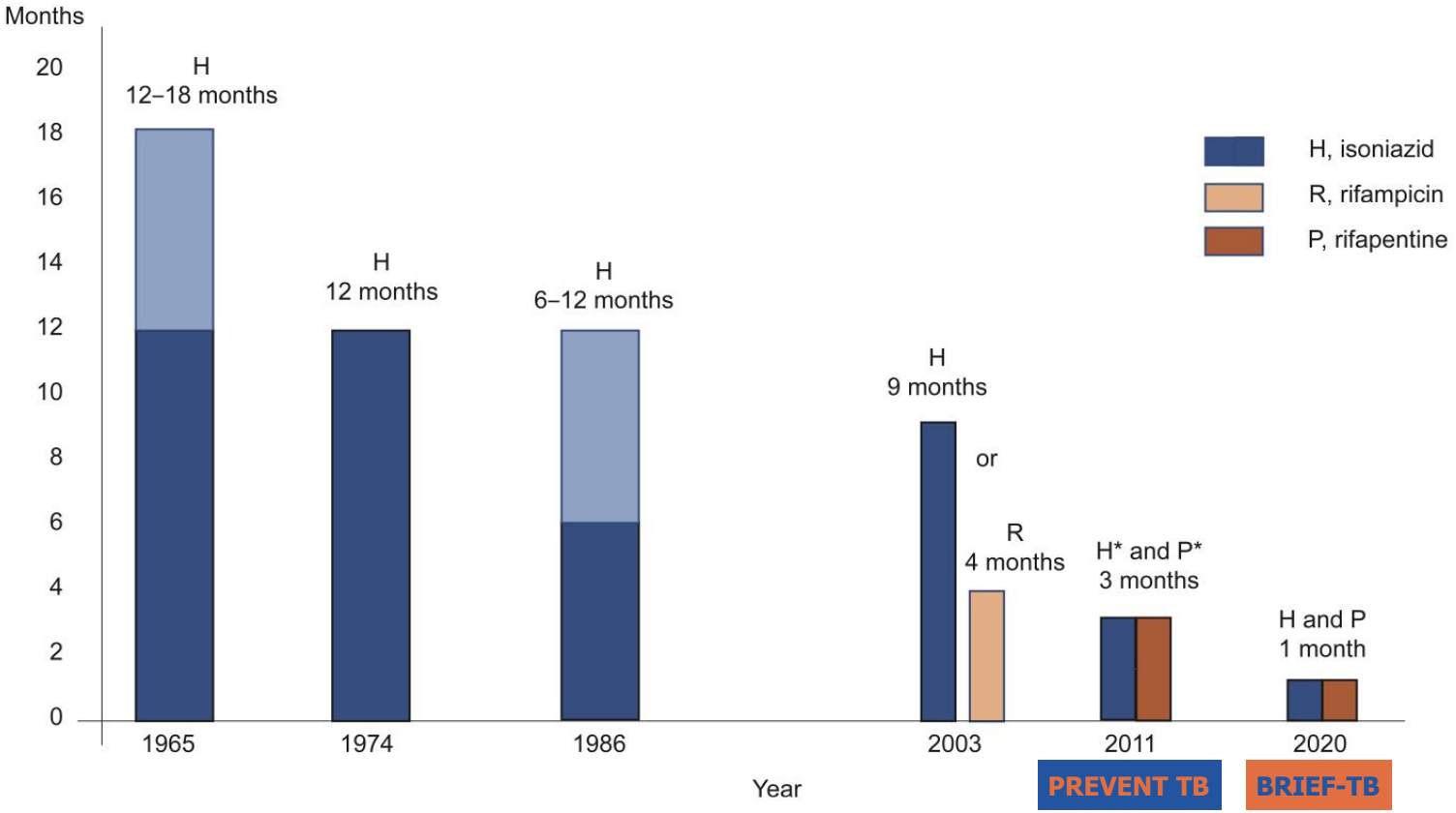


Figure Changes in the recommendation for the duration of preventive therapy between 1965 and 2020. Daily intake of medicines with the exception of *once weekly therapy.

Sterling et al. N Engl J Med 2011; 365:2155-2166
Swindells et al. N Engl J Med 2019;380:1001-11.
Lange et al. Int J Tuberc Lung Dis 2022 26(2):85–88 (2022)

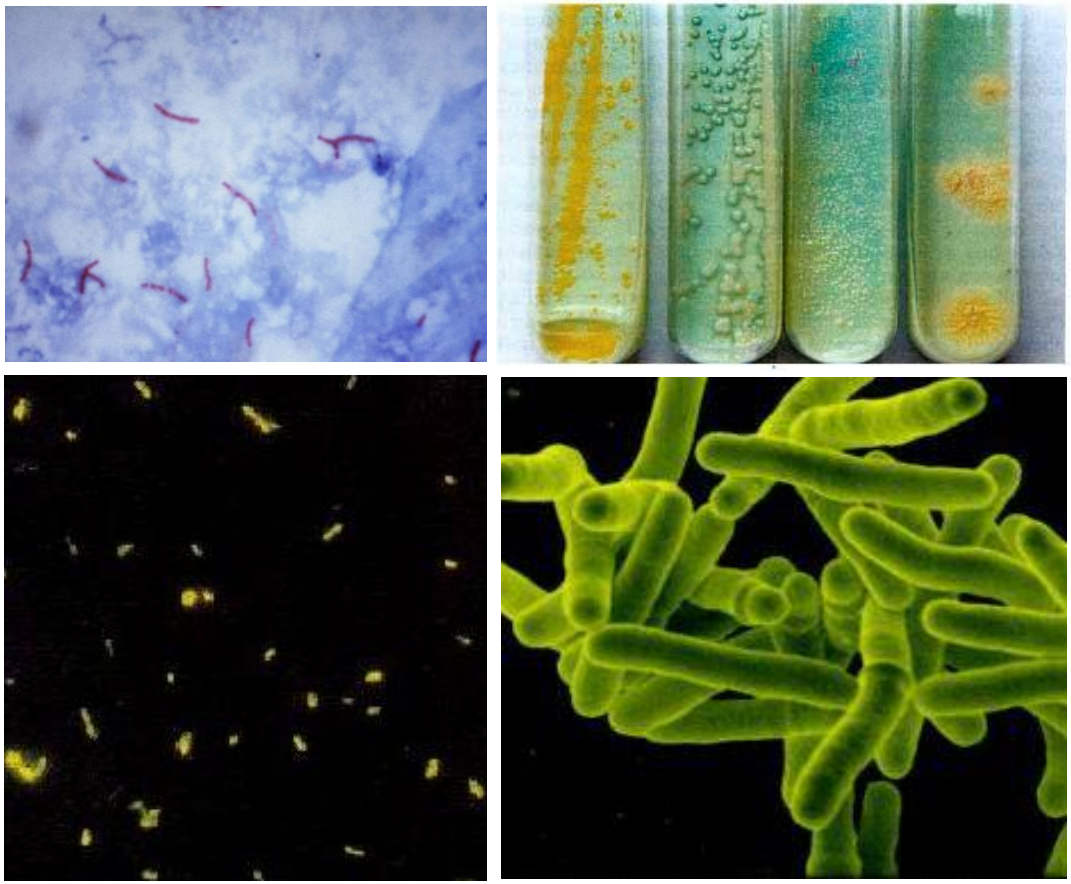
Epidemiologie & Preventie Samenvattend

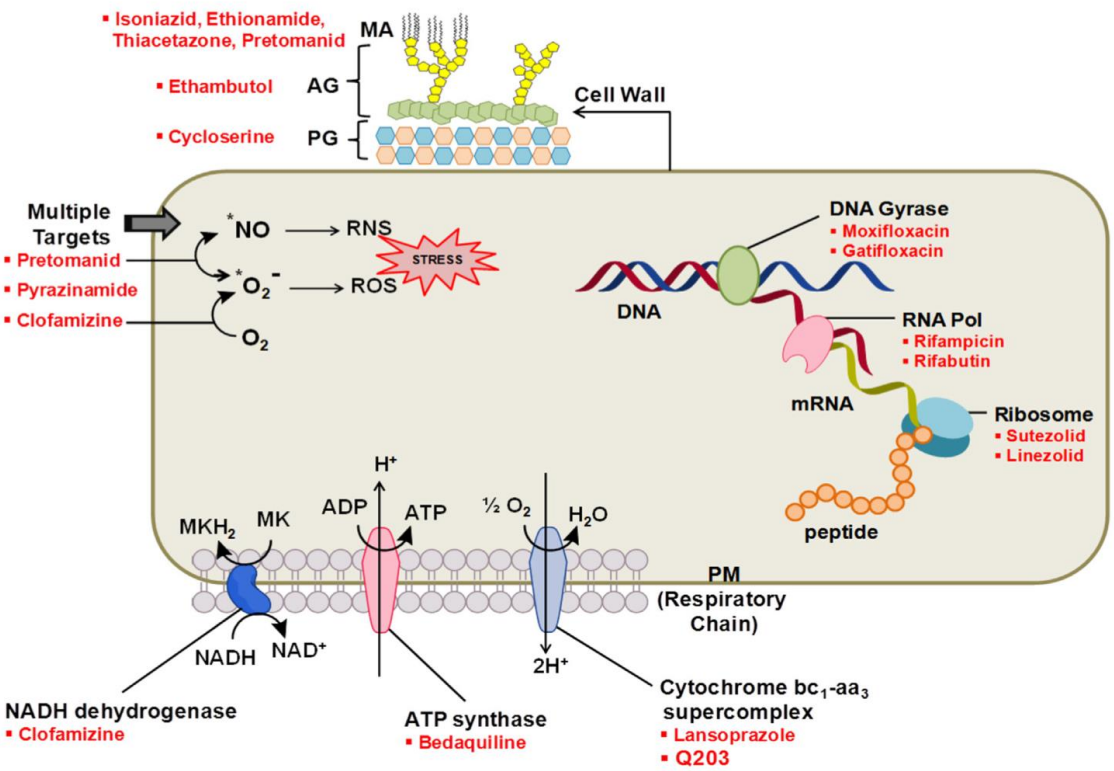
TBC is nog nooit weggeweest (zowel op lokaal vlak als op wereldschaal)

Voorspelling voor de toekomst:
toename in aantal MDR-TB gevallen

Preventieve behandeling
- HP1m
- Rifamycin-gebaseerde therapie te verkiezen vanuit wetenschappelijk oogpunt …
  MAAR … geen toegang tot Rifapentine in Europa & terugbetaling
  Rifadine in België enkel voor actieve TB ziekte.

Diagnostiek





Behandeling

Behandeling - Niet resistente TB

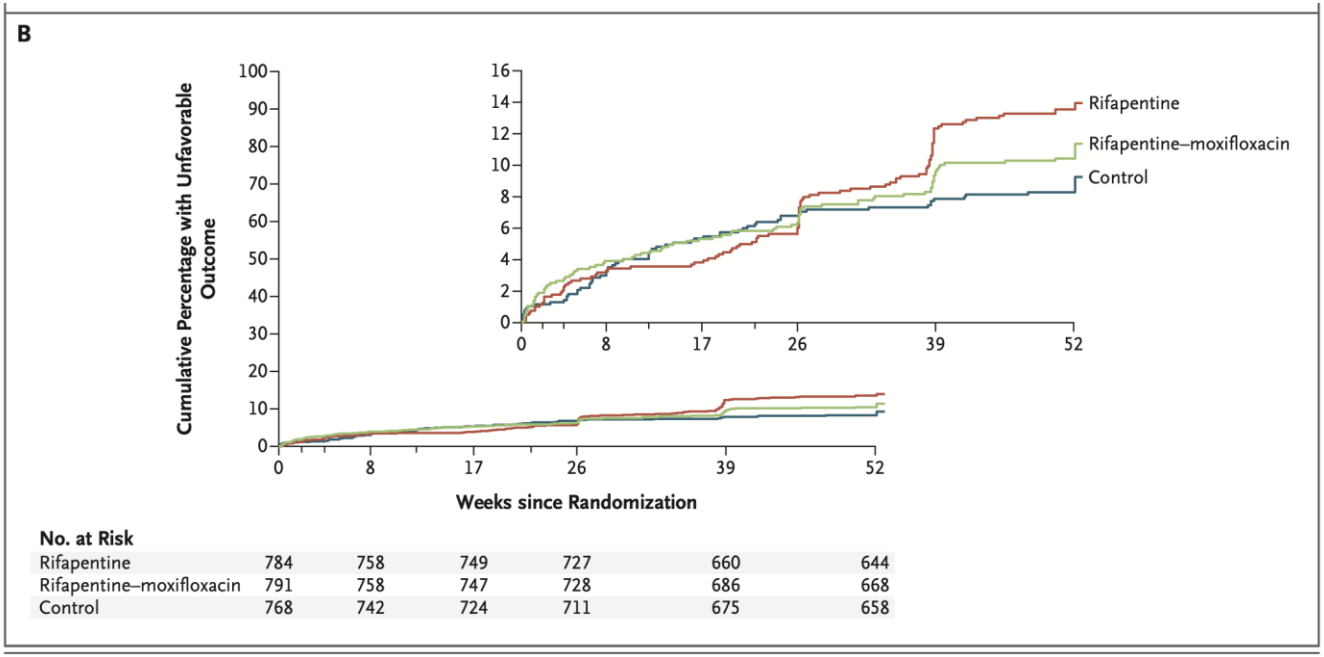
- Duur van behandeling is hinderpaal voor therapietrouw
- Standaard : 2HRZE4HR
- Sinds begin deze eeuw:
  - Onderzoek gefocust op verkorten van therapieschema
  - Fluoroquinolones als deel van 1ste lijn?
    - Moxi vs EMB: meer & snellere sputum conversie
    - REMoxTB trial: non-inferioriteit NIET bewezen

Burman et al Am J Respir Crit Care Med 2006;174:331-8
Conde et al. Lancet 2009 Apr 4;373(9670):1183-9.
Gillespie et al. NEJM 2014 2014;371:1577-87.

Korter ?

Fase 3 studie:

2HRZE4HR vs 2**P**HZE2PH vs 2**P**HZ**M**2**P**H**M**



Dorman et al. N Engl J Med 2021;384:1705-18.

Korter ?

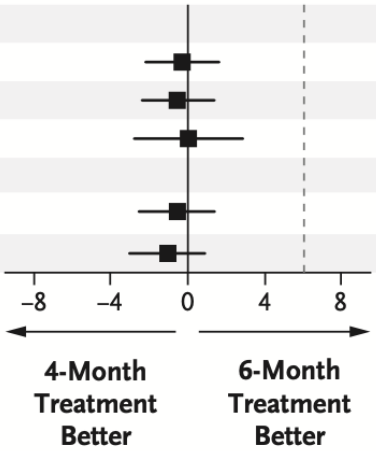
2HRZ ± E
2HR

2HRZ ± E
4HR

SHINE studie bij kinderen

→ Paucibacillaire tuberculos

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)



Turkova et al.N Engl J Med 2022;386:911-22

Recommendation 7.

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – new recommendation.

Remarks:

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern;
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV[16], or of isoniazid resistance[17].

Behandeling - Resistente TB (MDR)

'Bangladesh' behandelschema - 9 - 12 maand

REGIMEN COMPOSITION

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

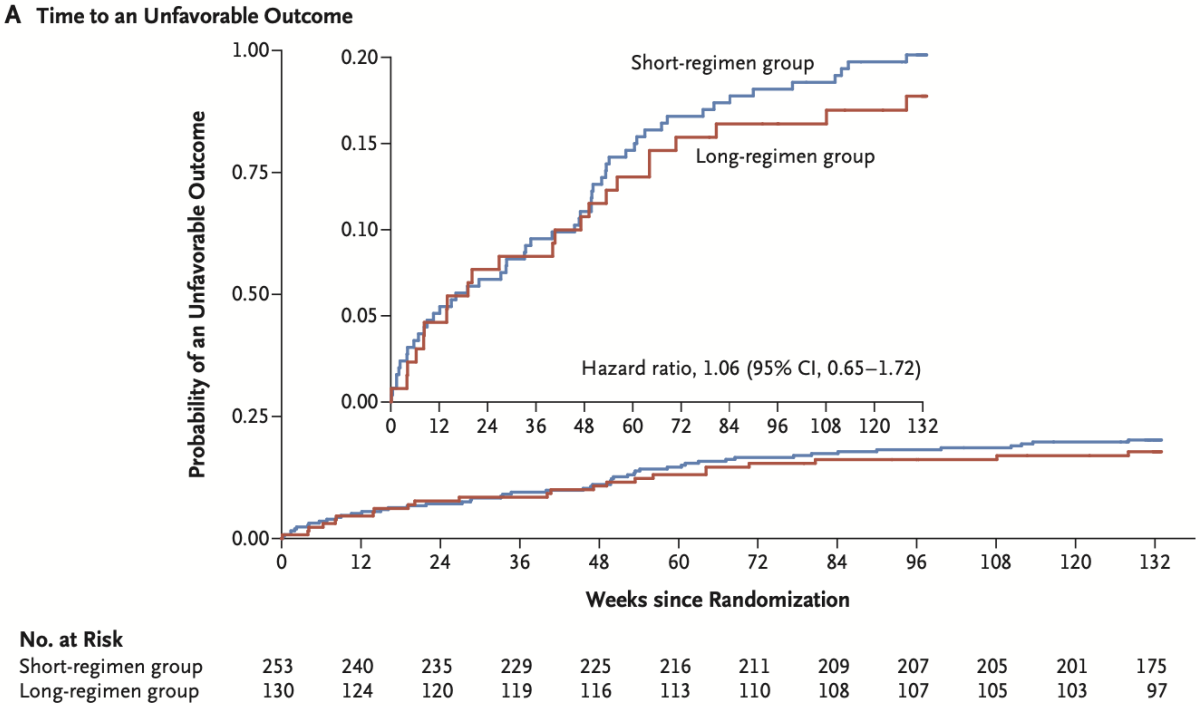
Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

- Observationele studie in Bangladesh bij > 500 MDR- patiënten :
  - 87,9% gunstig resultaat (genezen / zonder herval)
  - Ruimschoots beter dan traditionele behandelschema van 20-24 maand
- Meerdere kleine studies in Afrika met vergelijkbare resultaten (in totaal ± 600 patiënten)
- Kenmerkend voor patiënten binnen deze studies: geen vroegere blootstelling aan 2de lijnsmedicatie & beperkte aantallen met resistentie voor fluoroquinolones

Van Deun et al. Am J Respir Crit Care Med Vol 182. pp 684–692, 2010

STREAM stage 1 - 1st RCT

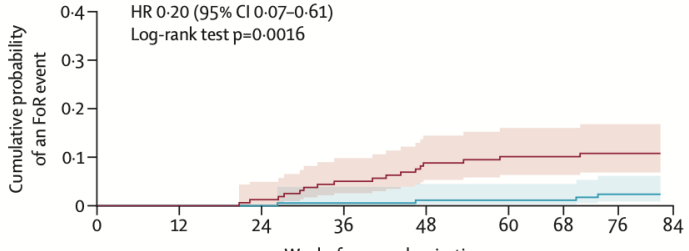
- Gestandaardiseerd kort schema versus Lang schema op maat van antibiogram
  - Geen statistisch verschil in therapiesucces of overlijden; non-inferieur
  - Beduidend minder medicatieblootstelling, lagere medische kost, minder productiviteitsverlies
  - Kanttekening: minder goede resultaten indien PZA & ETH/PTH-R (maar p=NS)



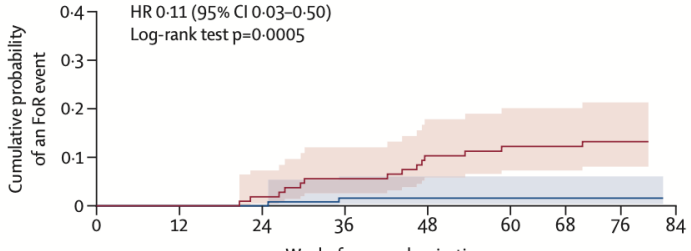
Nunn et al. NEJM 2019 380;13

STREAM stage 2

- RCT met 3 onderzoeksarmen:
  - 9m kort 'Bangladesh'
  - 9m kort met enkel perorale medicatie : BDQ vervangt SLI
  - 6m BDQ-schema (met 2m SLI & hINH)



Oral regimen									
Number at risk	196	182	177	174	172	166	165	136	0
Number censored	0	14	19	21	22	28	29	56	192
Number of events	0	0	0	1	2	2	2	4	4
Control regimen									
Number at risk	187	166	158	150	143	138	138	111	0
Number censored	0	21	27	29	30	33	33	59	170
Number of events	0	0	2	8	14	16	16	17	17



6-month regimen									
Number at risk	134	133	130	126	124	124	123	101	0
Number censored	0	1	4	6	8	8	9	31	132
Number of events	0	0	0	2	2	2	2	2	2
Control regimen									
Number at risk	127	113	105	101	95	91	91	75	0
Number censored	0	14	20	20	21	23	23	38	113
Number of events	0	0	2	6	11	13	13	14	14

Goodall et al. Lancet 2022; 400: 1858–68

Maar … wat als … 2de lijn resistenties?

- NIX-TB : 6m therapie, geen controlegroep
  - BDQ-Pretomanid-Linezolid (= $BPaL_{1200mg}$)
  - 90% gunstig resultaat
- Practecal: RCT (controle 9m met SLI)
  - 6m $BPaL_{600mg}$ + Moxi
  - Genezing 89% in vergelijking met 52% in klassieke WHO-schema
- ZeNix-trial:
  - Evaluatie van dosisreductie LZD

Conradie et al. N Engl J Med 2020;382:893-902
https://msf.org.uk/tb-practecal accessed 2/12/2022
Conradie et al. N Engl J Med 2022; 387:810-823

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase
Oxazolidinones
DnaE1 / Nargenicin analogs

TBD-09, TBD-10 (MK-7762, -3854)
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*

GSK-839*
OTB-658

BVL-GSK098*
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
Telacebec*
Pyrifazimine (TBI-166)
SPR720*
SQ-109*

Results Reported / Expected in 2022/23

TB Practecal
ZeNix
Bedaquiline*
Simplici TB
Delamanid*
(4-month regimen)
Pretomanid*
Truncate TB
(2-month regimens)
STREAM 2

Underline = updates since May 2022

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

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

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

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: November 2022

https://www.newtbdrugs.org/pipeline/clinical accessed 4/12/2022

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Behandeling Samenvattend

!!! KORT - KORT - KORT !!!

- LTBI: INH-Rifapentin (HP) 1 maand
- Niet resistente TB: 2PHZM2PHM
- MDR-TB
  - 6m BPaL(M)
  - 9m BDQ-gebaseerd volledig peroraal
  - BUT don’t try this @ home!!

Struikelblokken:

- Toegang tot medicatie (P, Pa)
- Snelle resistentiebepaling

Praktische aspecten

- TB-diagnose : meldingsplicht
  - Sowieso via labo igv bacteriologische bevestiging
  - Soms geen microbiologisch bewijs, melding belangrijk
- BELTA-TB net:
  - o.m. financiering van diagnostische oppuntstelling & behandeling voor patiënten zonder sociale zekerheid of voor medicatie niet terugbetaald door ziekenfonds.

Wrap-Up

Behalen van TB-doelstellingen is niet evident

Wereldwijd: MDR-TB neemt toe

Belang van moleculaire tests voor diagnose & resistentie bepaling

Nieuwe schema's in verschillende settings, maar problematische toegang tot essentiële medicatie

Met dank aan:

Belta-TBnet

FARES
Fonds des affections respiratoires asbl

VRGT
VLAAMSE VERENIGING VOOR
RESPIRATOIRE GEZONDHEIDSZORG
EN TUBERCULOSEBESTRIJDING VZW

Vragen ?
inge.muylle@olvz-aalst.be

olv
Topline Care.