multidrug-resistant tuberculosis Dutch experience

Tjip van der Werf
University of Groningen
University Medical Center Groningen
The Netherlands

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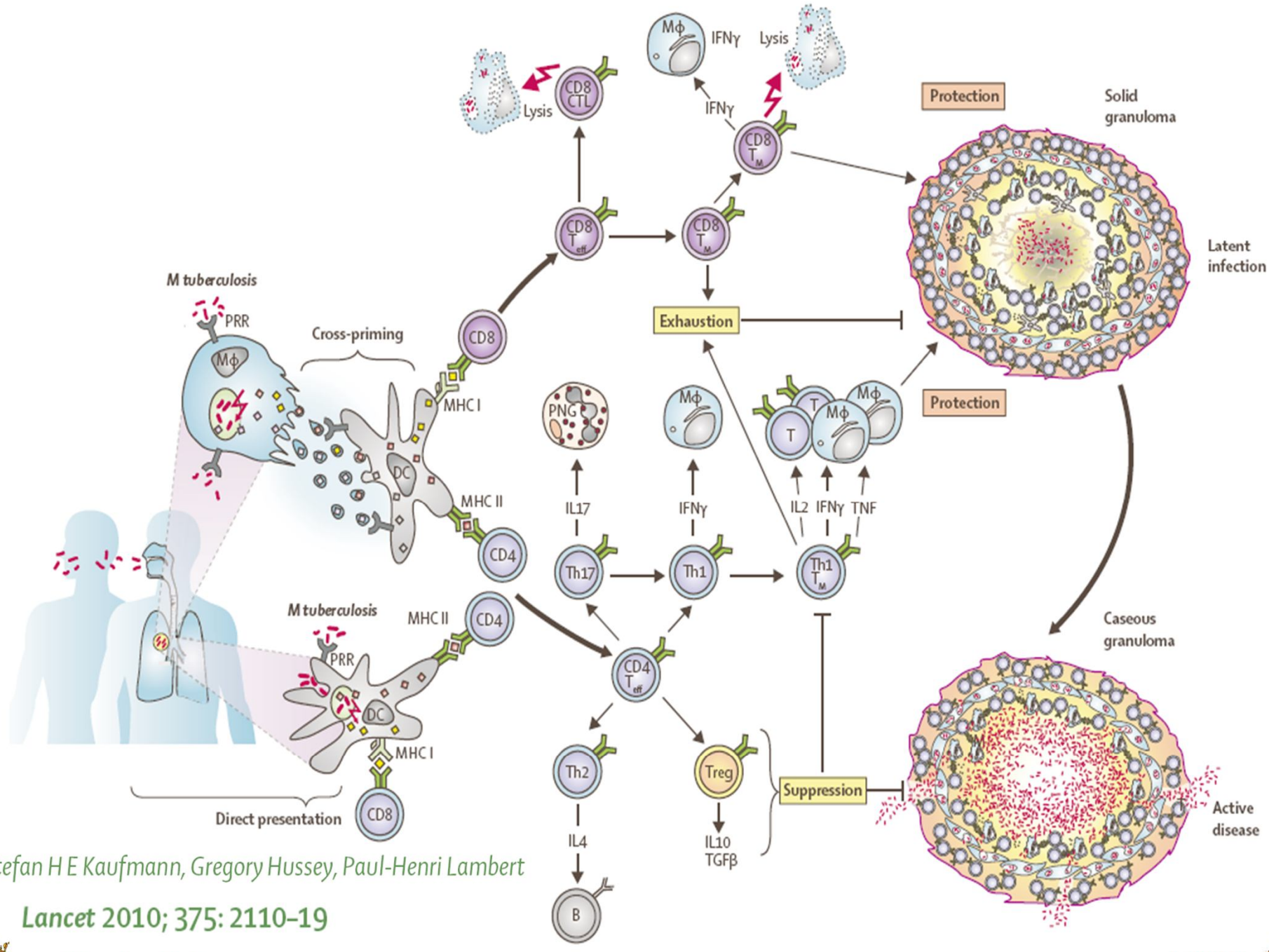

Stefan H E Kaufmann, Gregory Hussey, Paul-Henri Lambert

Lancet 2010; 375: 2110–19

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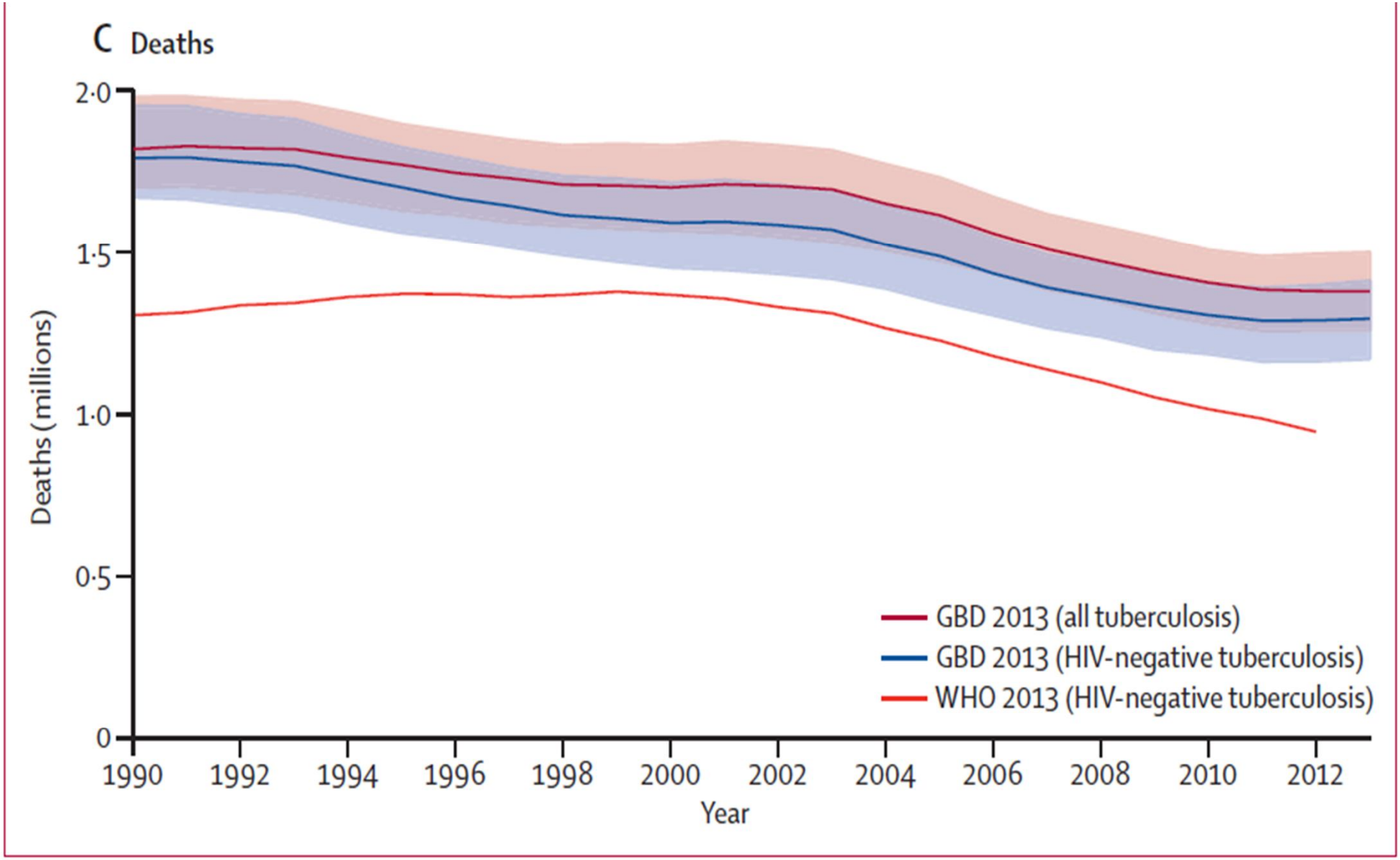
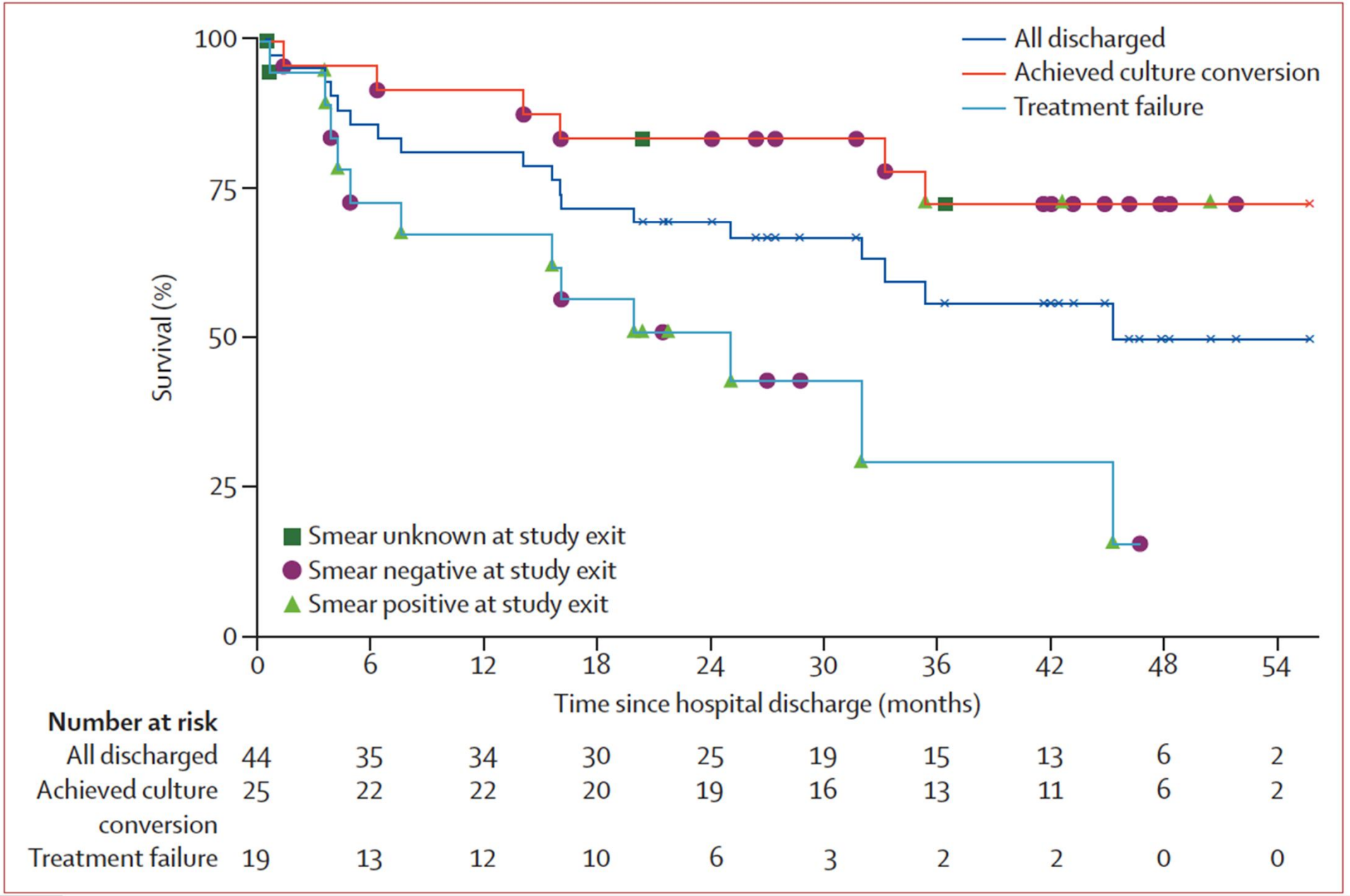
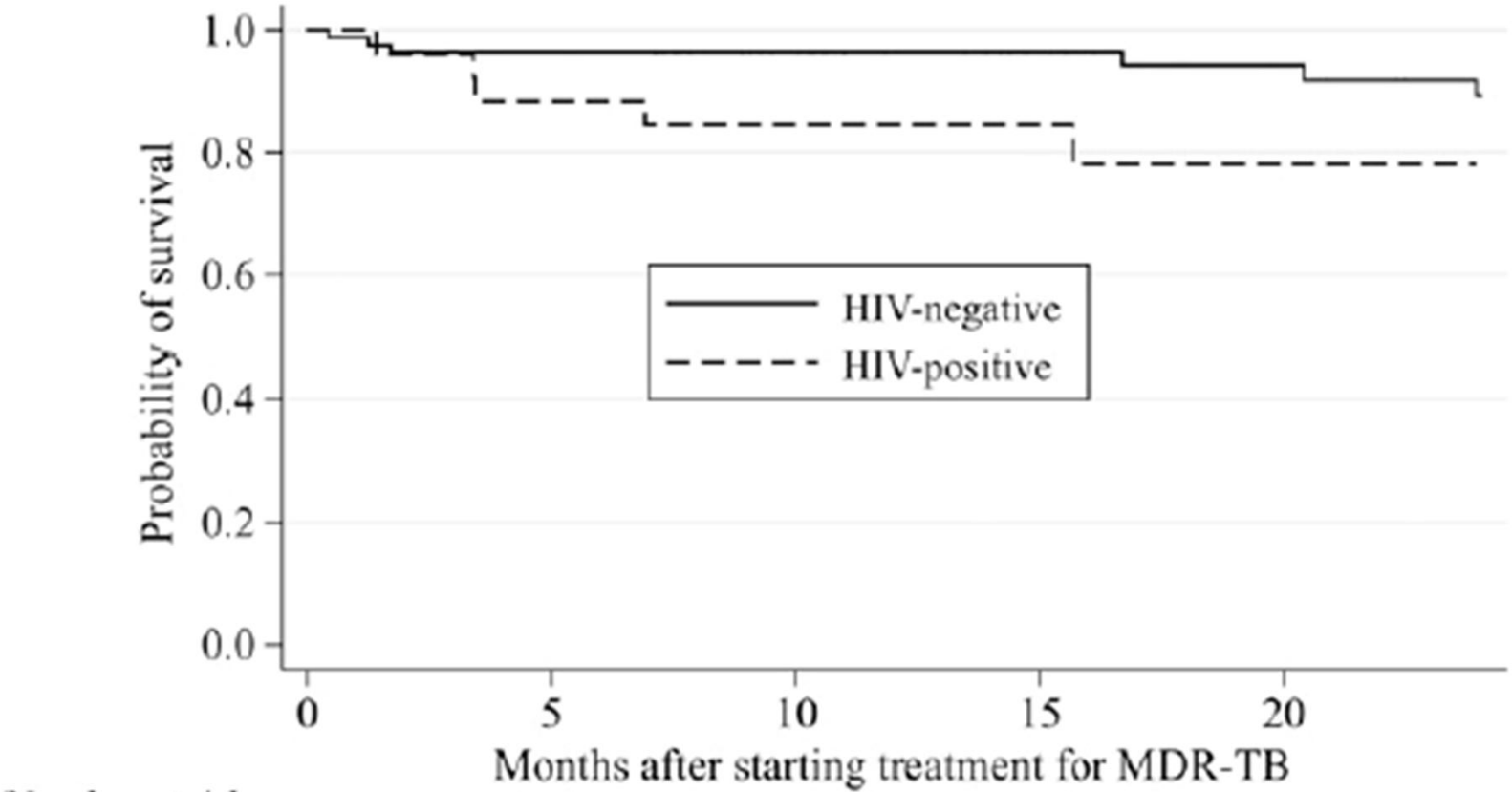


Figure 13: Global tuberculosis incidence (A), prevalence (B), and deaths (C), 1990–2013, for all ages and both sexes combined



Number at risk

All discharged	44	35	34	30	25	19	15	13	6	2
Achieved culture conversion	25	22	22	20	19	16	13	11	6	2
Treatment failure	19	13	12	10	6	3	2	2	0	0

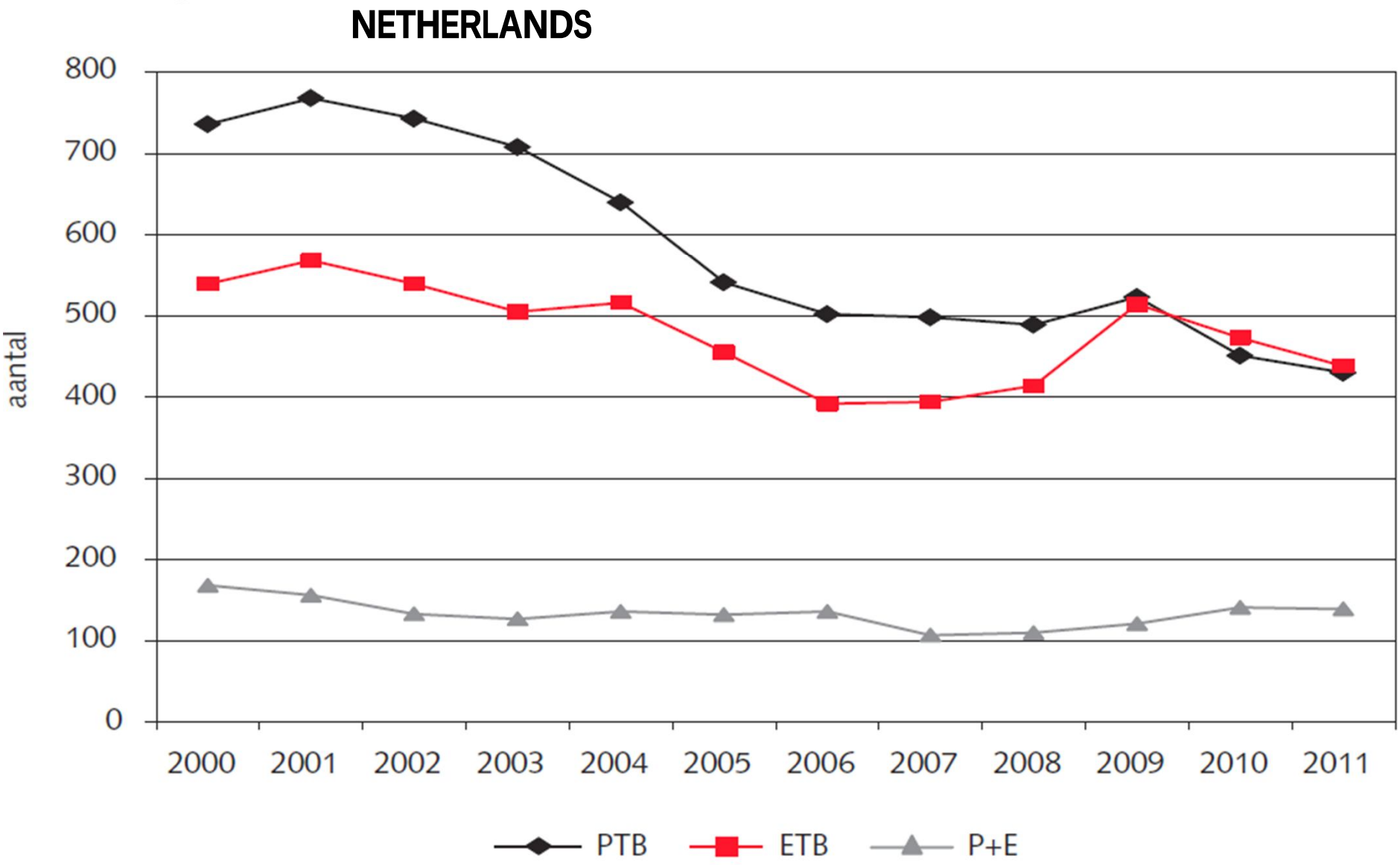


Number at risk					
HIV-negative	83	77	65	49	41
HIV-positive	27	23	18	14	10

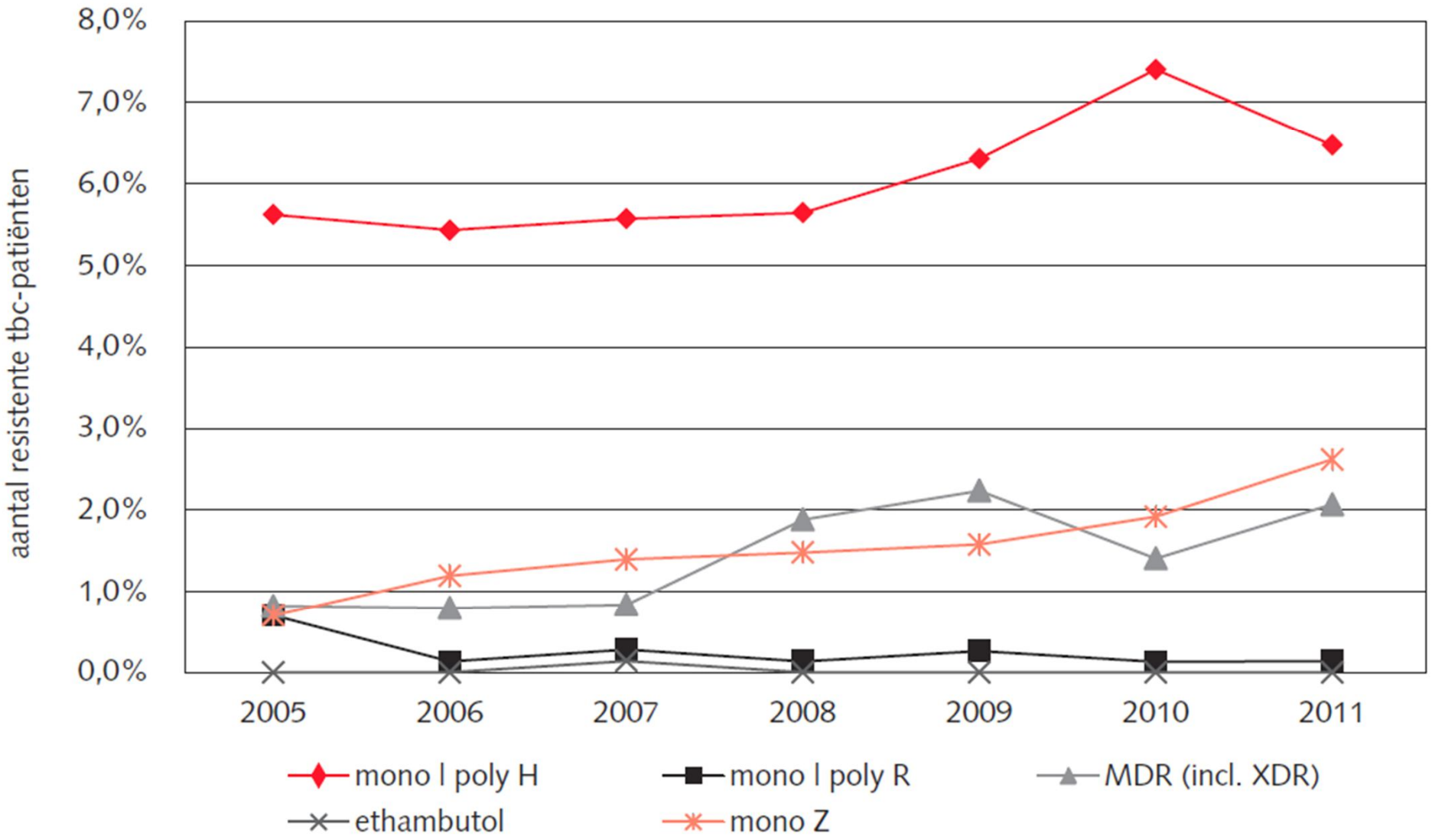
FIGURE 2. Kaplan–Meier estimates of the probability of survival after starting treatment of MDR-TB in HIV-negative and HIV-positive patients.

Figuur 11

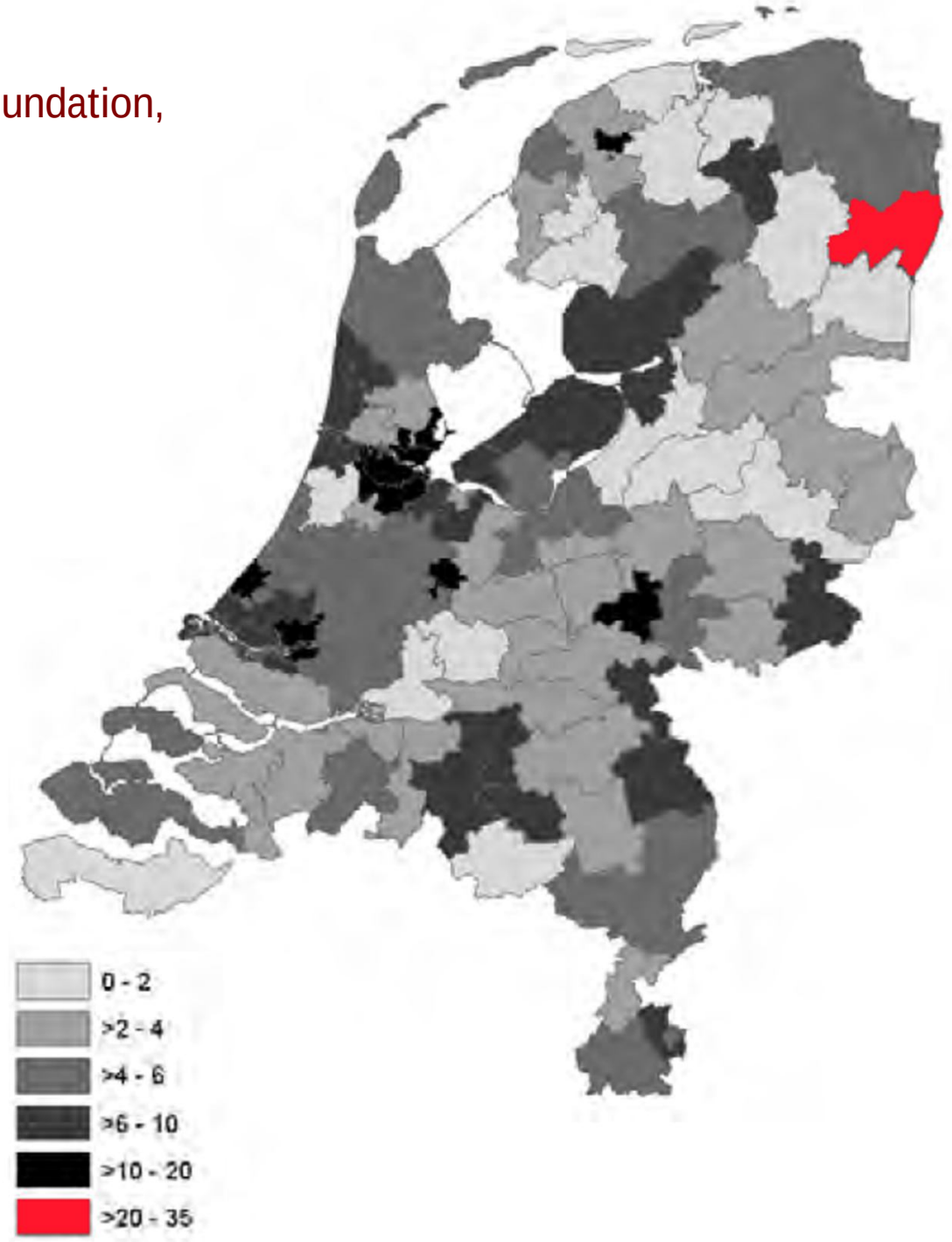
trend van PTB, ETB, PTB/ETB, 2000-2011



Figuur 16 **NETHERLANDS** % resistentie bij kweekpositieve tuberculose, 2005-2011

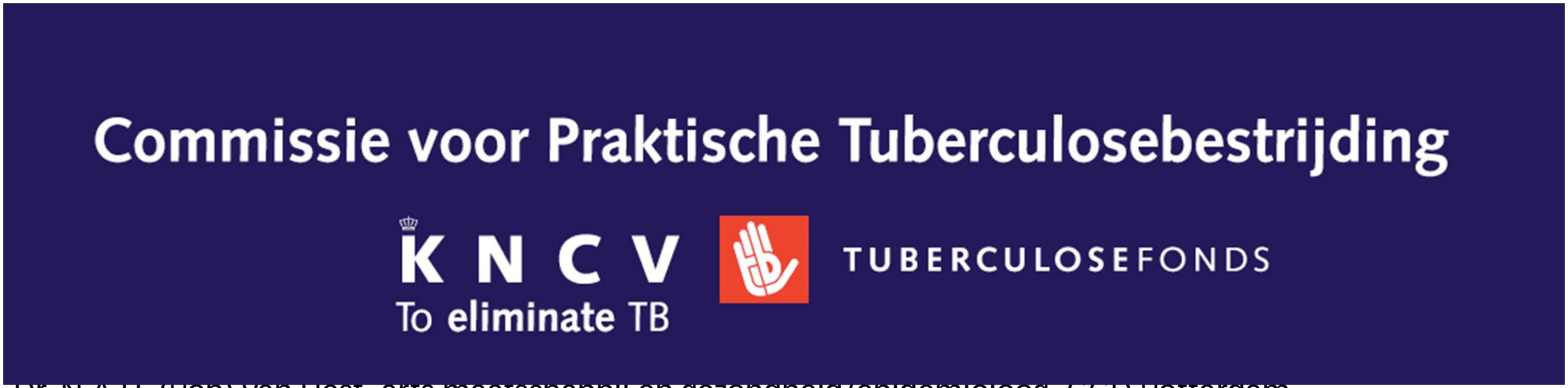


KNCV Tuberculosis Foundation,
The Hague, 2014

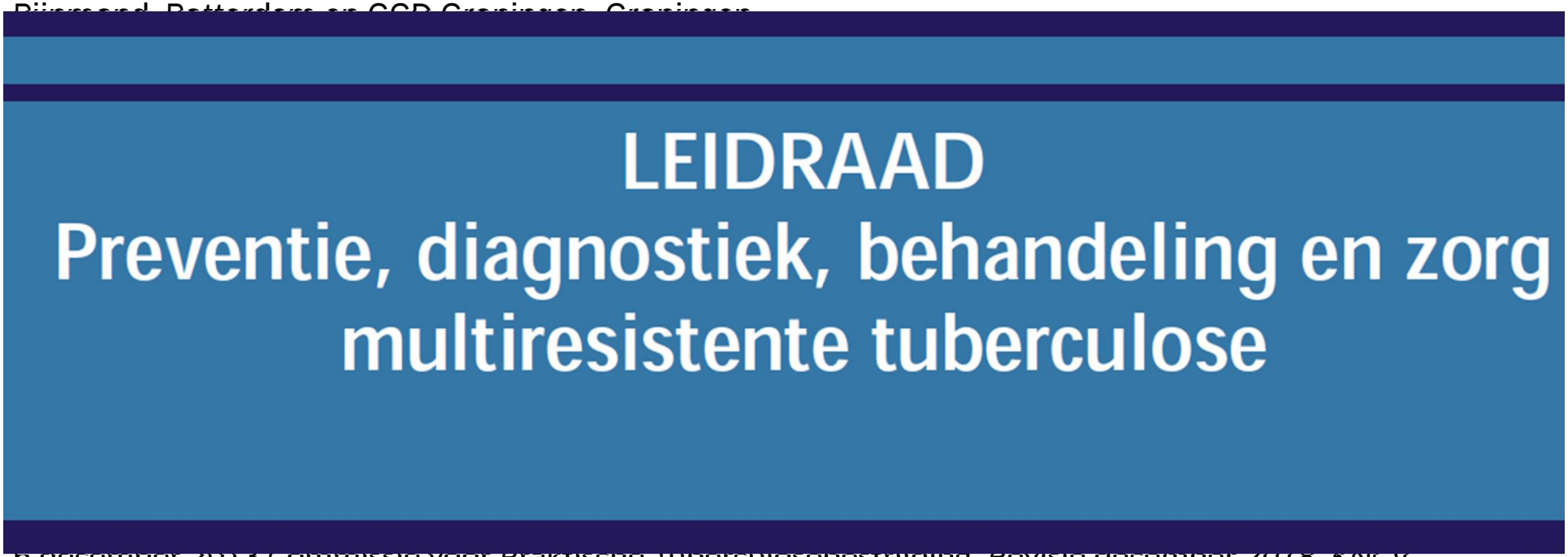


Dutch Polder Model: collaboration between Hospital-based Service and Public Health-based TB Service

- TB: notifiable disease; GGD (Municipal Health Authority) with TB Department perform contact- and source investigations
- CPT: KNCV Tuberculosis Foundation provides platform for ongoing training and guideline development & revisions
- Mtb strains from >40 labs all submitted for DST in the National Mycobacteriological Reference Lab
- MDRTB: all cases referred to dedicated TB centers



Dr. N.A.H. (Rob) van Hest, arts maatschappij en gezondheid/epidemioloog, GGD Rotterdam-Rijnmond, Rotterdam en GGD Groningen, Groningen



6 december 2013 Commissie voor Praktische Tuberculosebestrijding. Revisie december 2018. KNCV Tuberculosefonds Den Haag, december 2013

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founded in 1614 - top 100 university
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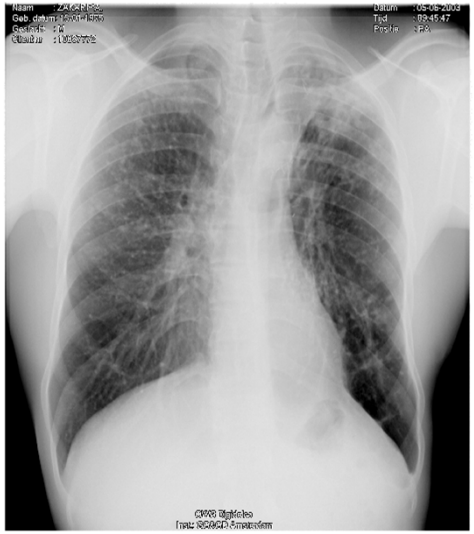
Was- & strijkruimte
opp: 10.28 m²
Sluis
opp: 14.03 m²
Sluis
opp: 5.82 m²
Badkamer
opp: 5.18 m²
Kamer gelsoleerd
opp: 16.25 m²
Kamer gelsoleerd
opp: 21.86 m²
Recreatieruimte
Voedingskeuken
opp: 14.07 m²
Dagverblijf Isolatiedeel
58.77 m² opp:
Dagverblijf NIET isolatiedeel
opp: 30.81 m²
Afvalberging
opp: 5.51 m²
Kantoor teamcoördinator
opp: 16.90 m²
Diëtist & regieverpleegkundige
opp: 12.22 m²
Spreekkamer
opp: 12.44 m²
Teohniek of berging
opp: 1.80 m²
Medicijnkamer & magazijn
opp:10.07 m²
Magazijn, rollators, infuuspalen
opp: 7.04 m²
Kamer ongelsoleerd
opp: 20.34 m²
Schoon linnen
opp: 3.81 m²
Vuil linnen
opp: 3.81 m²
Opslag schoonmaak
opp: 3.81 m²
Teohniek - Verdeelinrichting E
opp: 3.81 m²
Kamer ongelsoleerd
opp: 20.34 m²
Teohniek - Bevelliging en communicatie
opp: 6.69 m²
Toilet bezoek
opp: 4.68 m²
Kantoor longartsen
opp: 23.25 m²
Secretariaat & ontvangst
opp: 16.25 m²
Kantoor maatschappelijk werk
opp: 16.25 m²
Teohniek - CV, warm tapwater, klimaatregeling en WKO

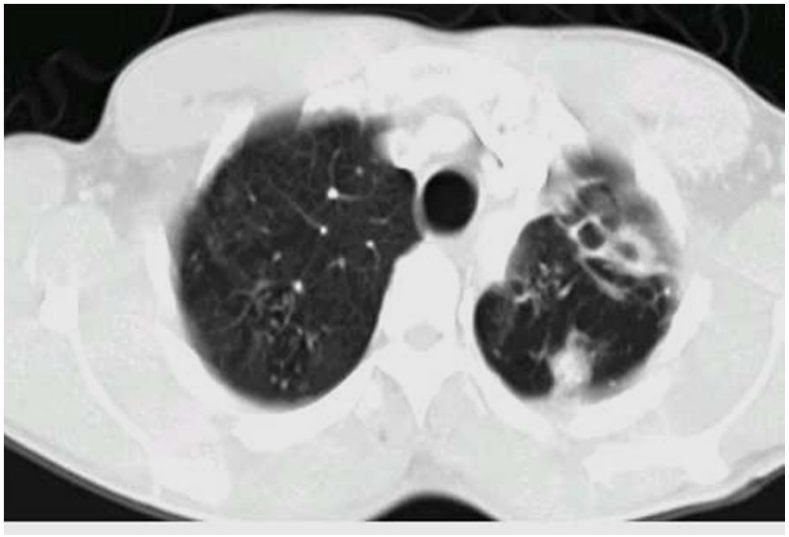
- Beatrixoord: Rehabilitation Centre
- TB Unit, >25 (30) beds
- > 140 admissions annually
- >80% of patients are foreign born
- All Multi-Drug Resistant TB is referred – 17M population


umco


104

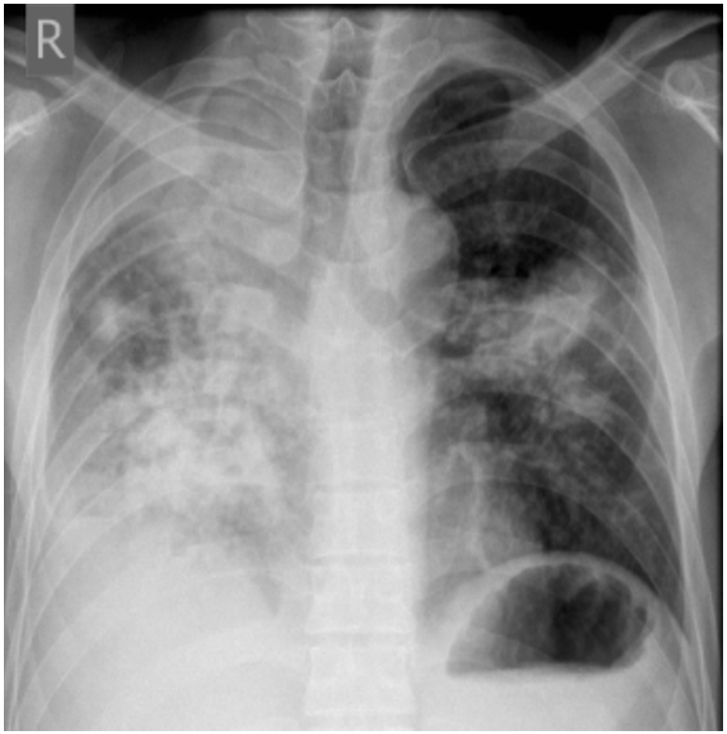
MDR-TB - role of surgery





Beatrixoord	**NL**	**10**	**33 y 6 M**	**8**	**1**	**1**	**2 (0)**	**8**	**all survivors did well**
Total of all reported patients		**499**	**Mean, 36.4 yrs 291 M (64%)**	**287 (57.5%)**	**10 (2%)**	**15 (3%)**	**85 (17%) BPF: 17 (3%)**	**251 / 287 = 87.5%**	

41-yr old Chinese man, XDR-TB



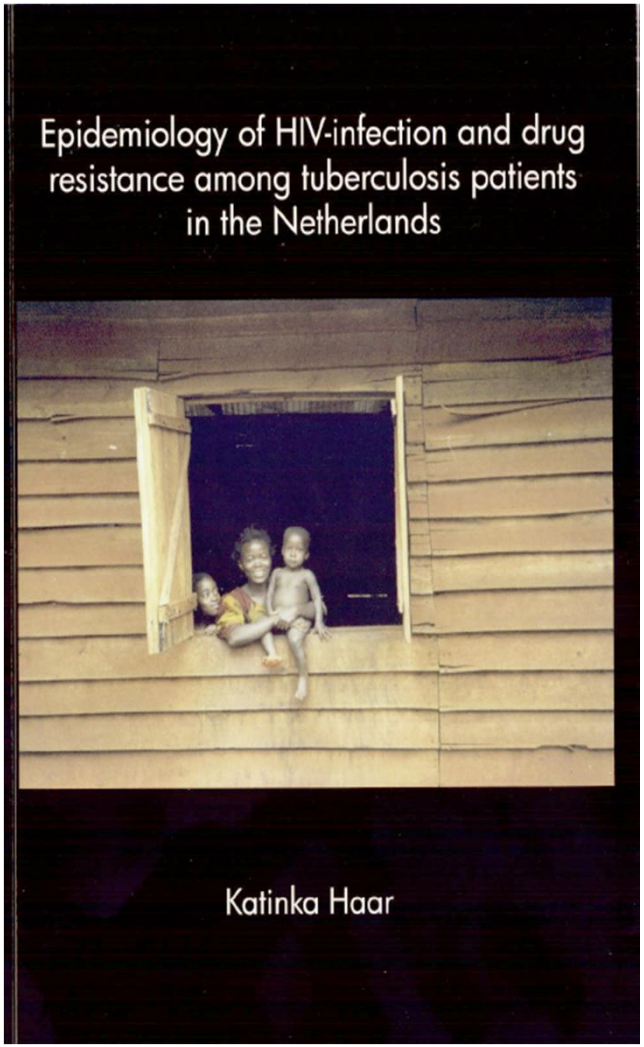
Microbiologisch onderzoek:

Resistentiebepaling RIVM — **Mycobacterium tuberculosis complex**

Antibiogram	Gev.	MIC (mg/l)
Amikacine	R	>20
Ciprofloxacine	R	4
Isoniazide (INH)	R	0.1
Rifampicine	R	1
Pyrazinamide	R	100
Ethambutol	R	5
Streptomycine	R	1
Cycloserine	S	20
Protionamide	S	<1
Clofazimine	S	<0.5
Claritromycine	S	4
Rifabutine	S	2

Table 3. Treatment Outcome for 76 patients with MDR-TB in the Netherlands

Treatment outcome	n	%
Cured	35	46.0
Completed treatment	29	38.2
Favourable outcome	**64**	**84.2**
Died		
Cause, TB	4	5.3
Cause other than TB	4	5.3
Defaulted	2	2.6
Failure	1	1.3
Transferred out	1	1.3
Unfavourable outcome	**12**	**15.8**



British Journal of Nutrition (2011), **105**, 400–408
doi:10.1017/S0007114510003636

Weight loss during tuberculosis treatment is an important risk factor for drug-induced hepatotoxicity

Ina Warmelink[1]*, Nick H. ten Hacken[2], Tjip S. van der Werf[2,3] and Richard van Altena[1]

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[2]*Department of Pulmonary Diseases and Tuberculosis, University Medical Center Groningen (UMCG), PO Box 30001, 9700 RB Groningen, The Netherlands*
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(Received 23 April 2010 – Revised 20 July 2010 – Accepted 26 July 2010 – First published online 28 September 2010)

Abstract

The objective of this study was to determine the association between weight loss and drug-induced hepatotoxicity (DIH). A retrospective observational study of 192 active tuberculosis (TB) patients consecutively admitted in a tertiary referral TB centre in the Netherlands was conducted. The outcome measure for DIH was defined as hepatotoxicity necessitating interruption of anti-TB drugs. Multivariate logistic regression analysis on interruption of anti-TB drugs was performed, with age, sex, nutritional status, TB disease severity, drug resistance, comorbidity including baseline liver function tests, anti-TB drug regimen, co-medication and addictions as independent risk factors. Anti-TB drugs were interrupted in thirty-one patients (16·1 %). The most important risk factor was weight loss of 2 kg or more within 4 weeks during TB treatment (OR 211, 95 % CI 36·0, 1232). Other independent risk factors were infection with hepatitis C (OR 19·6, 95 % CI 2·4, 164), age over 60 years (OR 18·5, 95 % CI 2·3, 151) and multi-drug-resistant TB (OR 8·2, 95 % CI 1·3, 53·6). This study shows that weight loss during TB treatment was the most important risk factor for DIH necessitating interruption of anti-TB drugs. Causes of weight loss during TB treatment and the association between weight change and hepatotoxicity need further investigation.

Key words: **Malnutrition: Weight loss: Risk factors: Drug-induced hepatotoxicity: Tuberculosis**

Journal of Nutrition

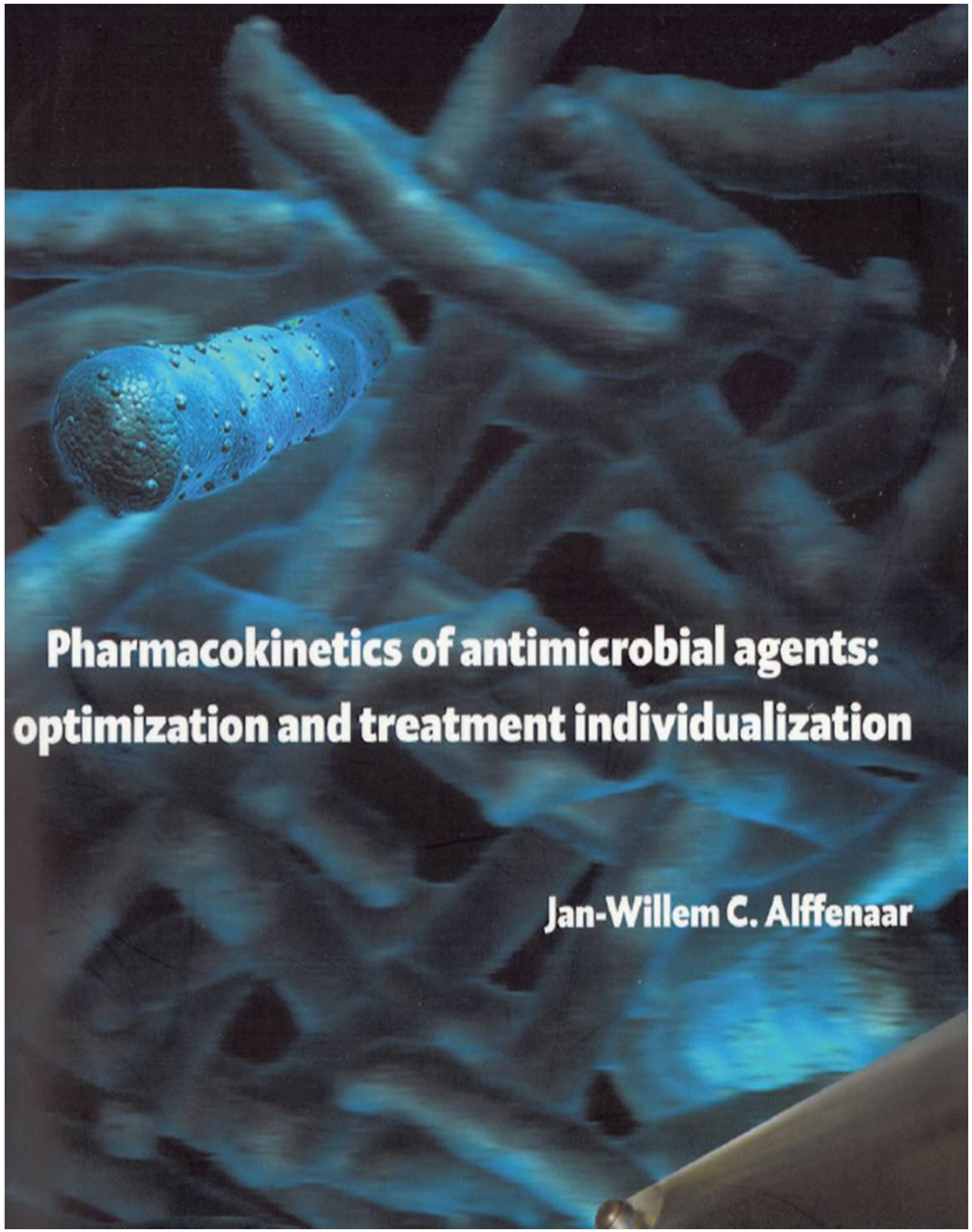
PK studies in MDR-TB

Pharmacokinetics of Moxifloxacin in Cerebrospinal Fluid and Plasma in Patients with Tuberculous Meningitis

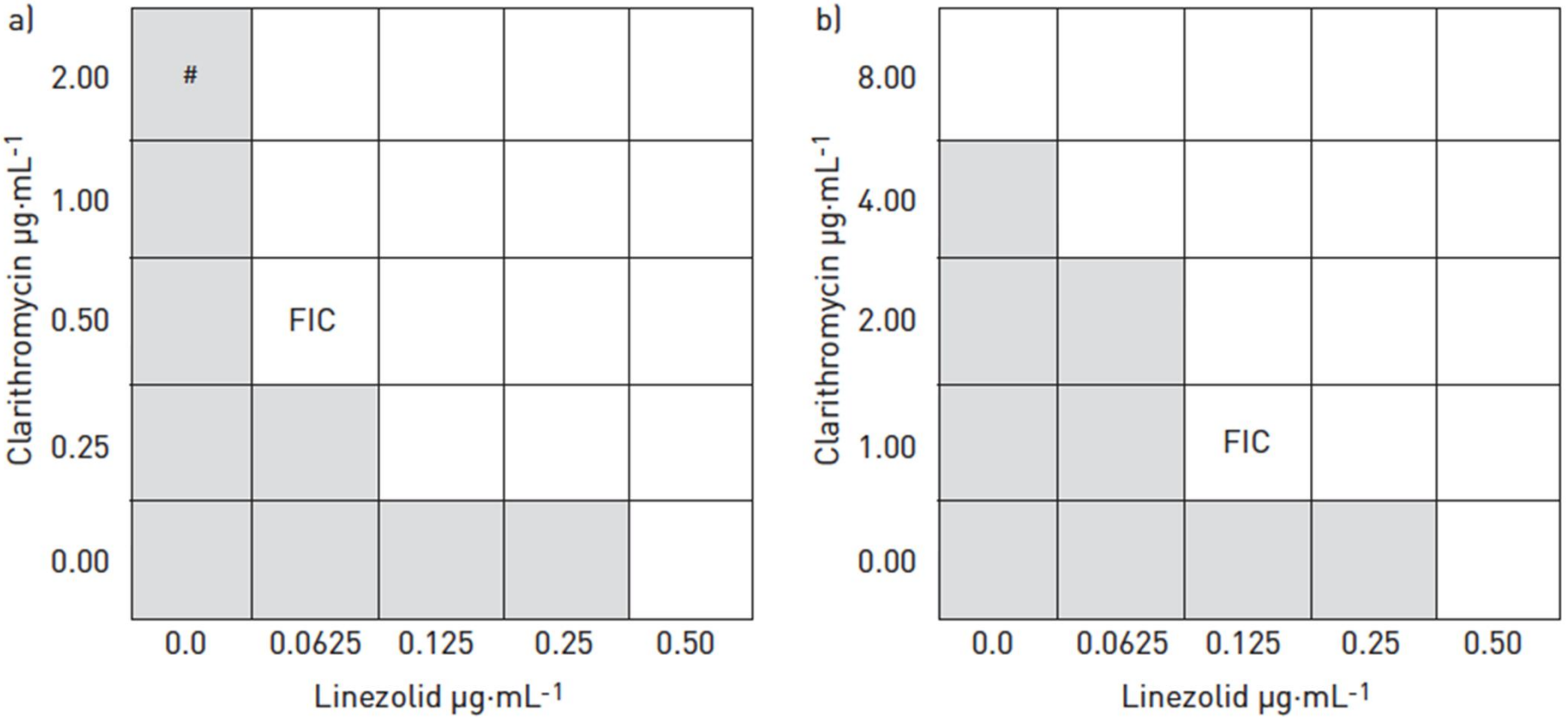
J. W. C. Alffenaar,[1] R. van Altena,[5] H. J. Bökkerink,[2] G. J. Luijckx,[2] D. van Soolingen,[6] R. E. Aarnoutse,[7] and T. S. van der Werf[3,4]

Departments of [1]Hospital and Clinical Pharmacy, [2]Neurology, [3]Internal Medicine, and [4]Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, Groningen, [5]Tuberculosis Centre Beatrixoord, University Medical Center Groningen, University of Groningen, Haren, [6]National Mycobacteria Reference Laboratory, National Institute of Public Health and the Environment, Bilthoven, and [7]Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

1080 • CID 2009:49 (1 October) •




NAME
DATE
Specimen Form


a)
2.00
1.00
0.50
0.25
0.00
#
FIC
Clarithromycin µg·mL-1
0.0
0.0625
0.125
0.25
0.50
Linezolid µg·mL-1
b)
8.00
4.00
2.00
1.00
0.00
FIC
Clarithromycin µg·mL-1
0.0
0.0625
0.125
0.25
0.50
Linezolid µg·mL-1

TUBERCULOSIS | M.S. BOLHUIS ET AL.

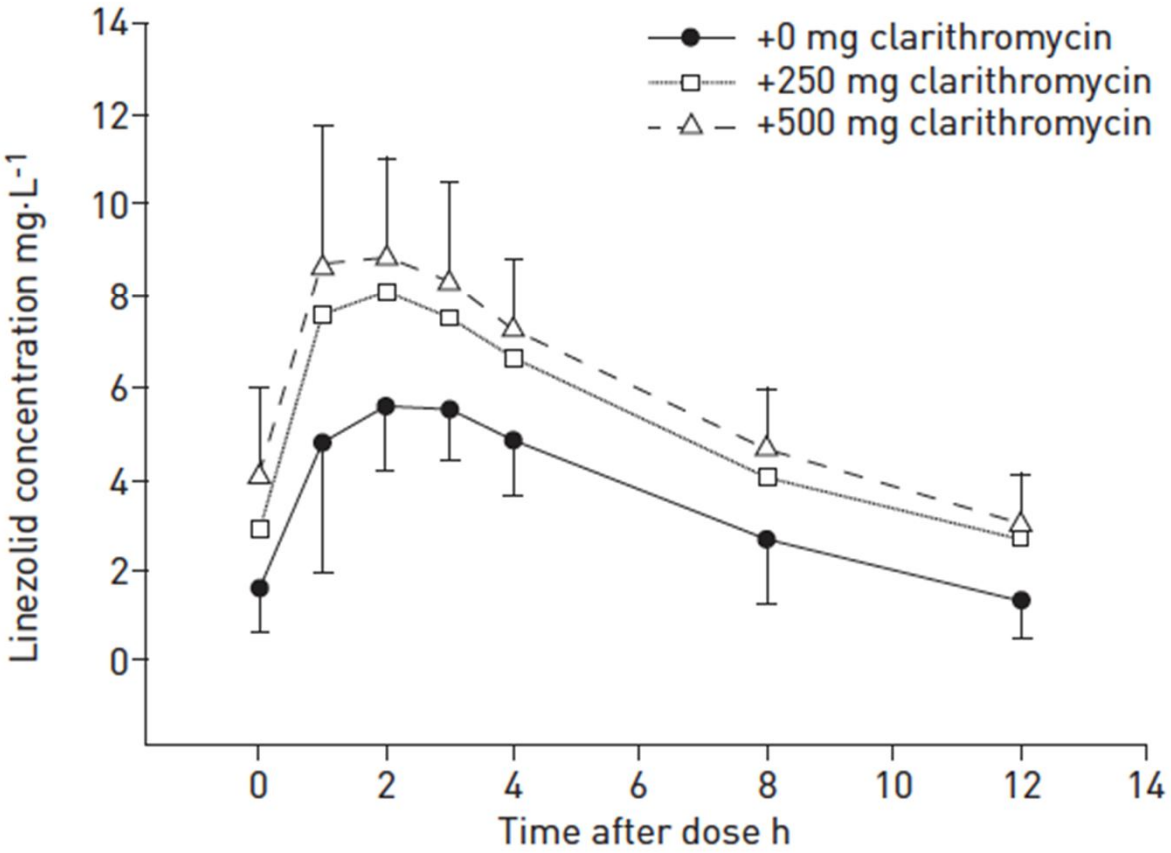


FIGURE 2 Mean linezolid concentration–time curves in serum (n=5) without clarithromycin, with 250 mg clarithromycin and with 500 mg clarithromycin. Error bars: SD. For visual purposes, error bars for linezolid with 250 mg clarithromycin have been omitted.

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Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, Hollm-Delgado MG, Palmero D,

Dekkerswald, Rehabilitation Centre, Radboud University Nijmegen

- 8-bed Unit with isolation facilities
- focus on NTM disease; PK studies
- scientific programs in Africa and Indonesia

INT J TUBERC LUNG DIS 4(8):758–764

Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands

W. A. Geerligs,* R. van Altena,* W. C. M. de Lange,† D. van Soolingen,‡ T. S. van der Werf§

* Tuberculosis Units of Beatrixoord, Haren, and † Dekkerswald, Groesbeek, ‡ National Reference Laboratory for Tuberculosis, National Institute of Public Health and the Environment, Bilthoven, § Intensive and Respiratory Care Unit, Department of Internal Medicine, Groningen University Hospital, the Netherlands

MAJOR ARTICLE

Treatment Outcomes of Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis According to Drug Susceptibility Testing to First- and Second-line Drugs: An Individual Patient Data Meta-analysis

Mayara L. Bastos,[1,2] Hamidah Hussain,[3] Karin Weyer,[4] Lourdes Garcia-Garcia,[5] Vaira Leimane,[6] Chi Chiu Leung,[7] Masahiro Narita,[8] Jose M. Peñã,[9] Alfredo Ponce-de-Leon,[10] Kwonjune J. Seung,[11] Karen Shean,[12] [illegible]ntes-Osornio,[10] Martie Van der Walt,[13] Tjip S. Van der Werf,[14] Wing Wai Yew,[15] and Dick Menzies[16,17]; for [illegible] for Meta-analysis of Individual Patient Data in MDR-TB[a]

[illegible]000; Thorax 2002; NEJM 1998

41/44 (92%) favourable outcome

Geerligs WA, et al. IJTLD 2000; Thorax 2002; NEJM 1998

Table 2 Anti-tuberculosis drug treatment in 44 patients with MDR-TB; duration of treatment and reported side effects

Agents	Patients (*n*)	Duration in days (range)	Total side effects (*n*)	Side effect
Isoniazid	36	471 (20–1684)	3	N, S, L
Rifampin	5	341 (85–534)		
Pyrazinamide	38	461 (18–1001)	5	L, J
Ethambutol	42	526 (44–1474)	4	I, K, V
Aminoglycoside	40	108 (20–383)	6	H, I, N, K
Quinolone	38	504 (31–898)	4	L, I, J, K
Rifabutin	9	276 (14–1474)	1	S
Prothionamide	16	244 (6–617)	6	P, L, I
Thioacetazone	4	511 (415–651)		
Cycloserine	5	193 (16–478)	2	N, P
Gamma interferon	1	21		
Clofazimine	39	533 (75–1474)	2	S, K
Clarithromycin	2	520 (443–596)		
Co-amoxiclav	1	61		

N = neurological disorders; S = itching; L= liver-test abnormalities; J = joint complaints; I = gastro-intestinal complaints; K = renal dysfunction; V = visual disorder; H = acoustic symptoms; P = mental disturbances.

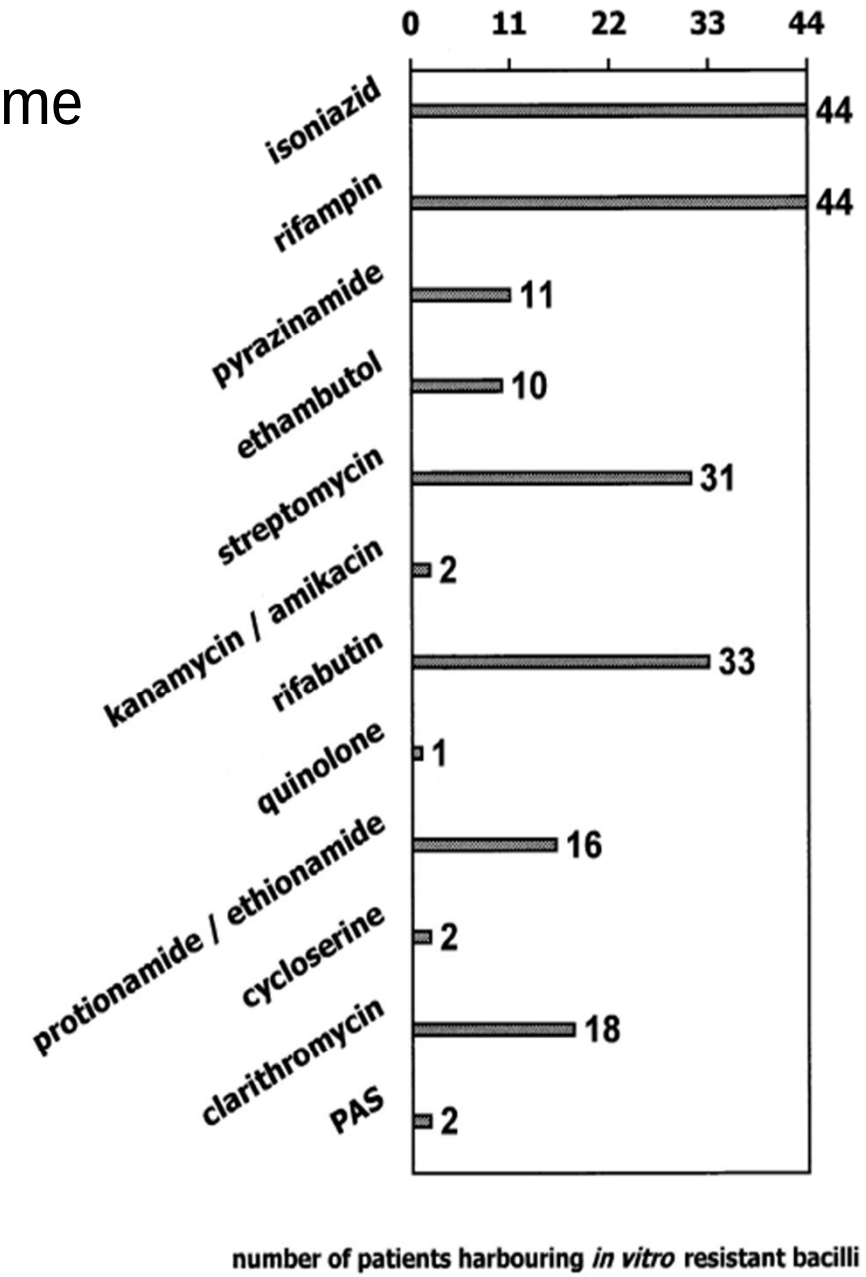
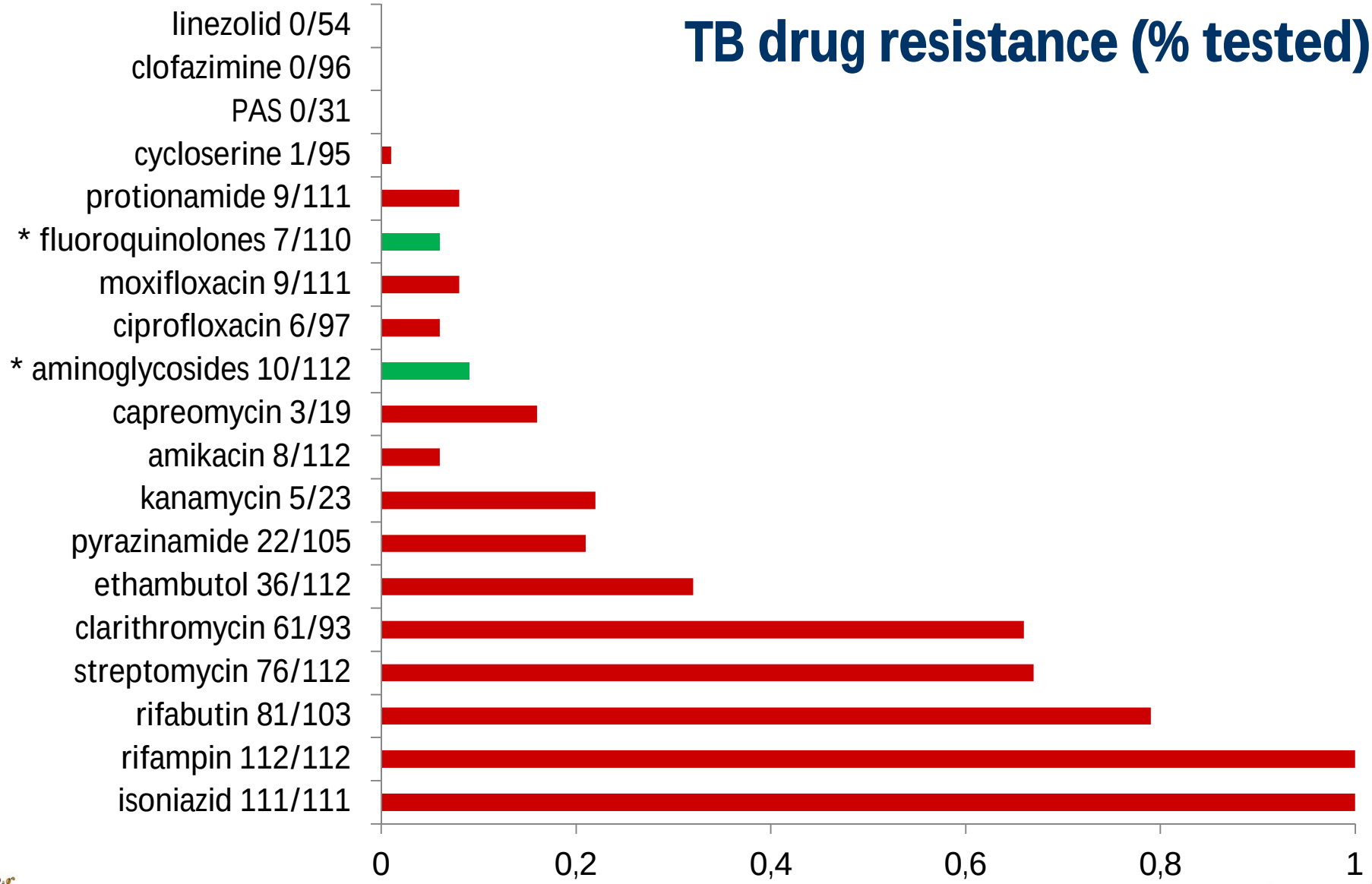


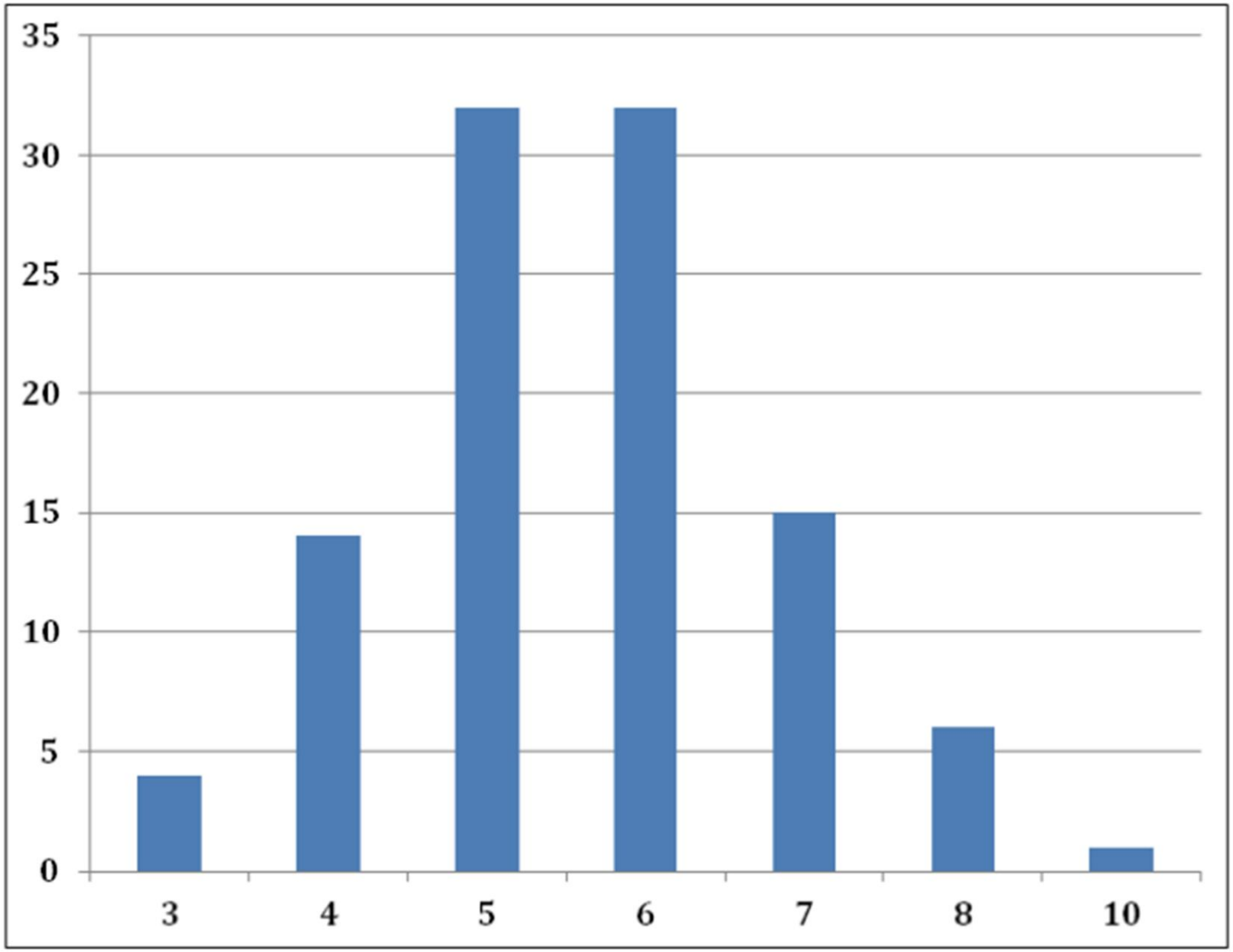
Figure In vitro resistant tubercle bacilli recovered from 44 MDR-TB patients.

MDRTB Netherlands, 2000-2009

- DST results were obtained from the RIVM
- absolute concentration method was used for most second-line TB drugs
- for moxifloxacin and linezolid, three different concentrations were tested to assess the minimal inhibitory concentration (MIC) during the last few years of the study period
- All *Mycobacterium tuberculosis* complex isolates were submitted to the RIVM for identification, DST and genotyping during the study period

TB drug resistance (% tested)





No of drugs to which isolates tested drug-resistant; n=112

Drugs with anti-TB effect used	Patients (n)	Duration in days: mean (min-max)	Duration in days: median, (IQR)	Total side effects (n)	Side effect
Isoniazid	15	400 (37-723)	378 (274-548)		
Rifampicin	0				
Ethambutol	68	405 (6-730)	456 (270-548)	2	V
Pyrazinamide	55	297 (6-730)	209 (62-546)	6	I, J, L
Rifabutin	14	394 (263-617)	364 (328-468)		
Amikacin	64	165 (6-549)	165 (89-193)	3	H
Kanamycin	23	147 (47-394)	113 (92-197)	2	H, K
Capreomycin	3	394 (243-691)	249 (243-243)		
Any injectable	**88**	**172 (6-691)**	**160 (92-209)**		
Ciprofloxacin	4	218 (56-550)	133 (56-465)	1	I
Levofloxacin	43	448 (6-730)	508 (365-549)	1	I
Moxifloxacin	57	400 (37-611)	442 (277-548)	2	N, T
Any fluoroquinolone	**101**	**425 (6-730)**	**485 (364-549)**		
Prothionamide	72	323 (6-638)	348 (146-528)	16	I, L, P
Cycloserin	14	317 (7-598)	360 (129-417)	2	P
PAS	3	354 (12-659)	12 (394-394)	1	I
Clofazimine	74	343 (7-706)	374 (91-547)	2	S, I

Results

- 113 patients with MDR-TB
- M/F ratio 1.57
- 96% foreign born
- age (median) 29 yr
- 95 (84%) had pulmonary TB, 55 (49%) had smear-positive sputum
- 14 (12%) were HIV co-infected

Results (2)

	All MDR TB cases (n=113)*		Cases who started MDR drug treatment in the Netherlands (n=104)	
	n	%	n	%
Cured	47	41.6	47	45.2
Completed	42	37.2	42	40.4
Favourable outcome	**89**	**78.8**	**89**	**85.6**
Died	9*	8.0	6	5.8
Defaulted/stopped	8	7.1	8	7.7
Transferred out	1	0.9	1	1.0
Unknown or no treatment	6*	8.0		
Unfavourable outcome	**24**	**21.2**	**15**	**14.4**

Results (3)

- Of 104 (92%) started on MDR-TB treatment, 86% had favourable outcome using median 6 drugs; 8 had pulmonary surgery
- Multivariable regression: HIV negative status associated with favourable outcome (OR 10.1; $p<0.01$)

Table 2. Classes of Drugs with Antituberculosis Activity in Clinical Studies

Class	Drug(s)	Mechanism of Action
Diarylquinoline	**bedaquiline**	interferes with how bacterial cells make energy by targeting the proton pump adenosine triphosphate synthase[23]
Ethylenediamine	**SQ109**	disrupts bacterial cell-wall construction by disturbing the assembly of mycolic acids, possibly by targeting the MmpL3 protein;[24] in vitro activity has yet to be confirmed in humans
Fluoroquinolone	gatifloxacin, levofloxacin, moxifloxacin, ofloxacin	disrupts bacterial replication by inhibiting the DNA gyrase enzyme, thus preventing bacterial DNA from unwinding and duplicating[25]
Nitroimidazole	**delamanid**, **pretomanid** **TBA354** (preclinical)	destabilizes the bacterial cell membrane by blocking the synthesis of mycolic acids;[26] poisons the bacterial cell by releasing nitric oxide when metabolized[27]
Oxazolidinone	**AZD5847**, linezolid, **sutezolid, tedizolid** (for MRSA)	blocks protein synthesis (translation) by inhibiting the initiation step at the ribosome[28]
Rifamycin	rifabutin, rifampicin, rifapentine	blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase[29]
Riminophenazine	clofazimine	unclear, but it appears that the bacterium's ineffective attempts to metabolize drug lead to cycle (redox cycle), which generates toxic reactive oxygen species within the bacteria; may target the bacterium's outer membrane by inhibiting the bacterial respiratory chain and ion transporters[30]

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  - Dick van Soolingen, Mycobacteriology Lab

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