Management of Isoniazid-Resistant Tuberculosis
INH抗藥結核的處理

衛生福利部
國立臺灣大學
傳染病防治研究及教育中心
MOHW-NTU Infectious Diseases Research and Education Center



臺大醫院 胸腔內科 李孟叡醫師

2023 07 27

Outline

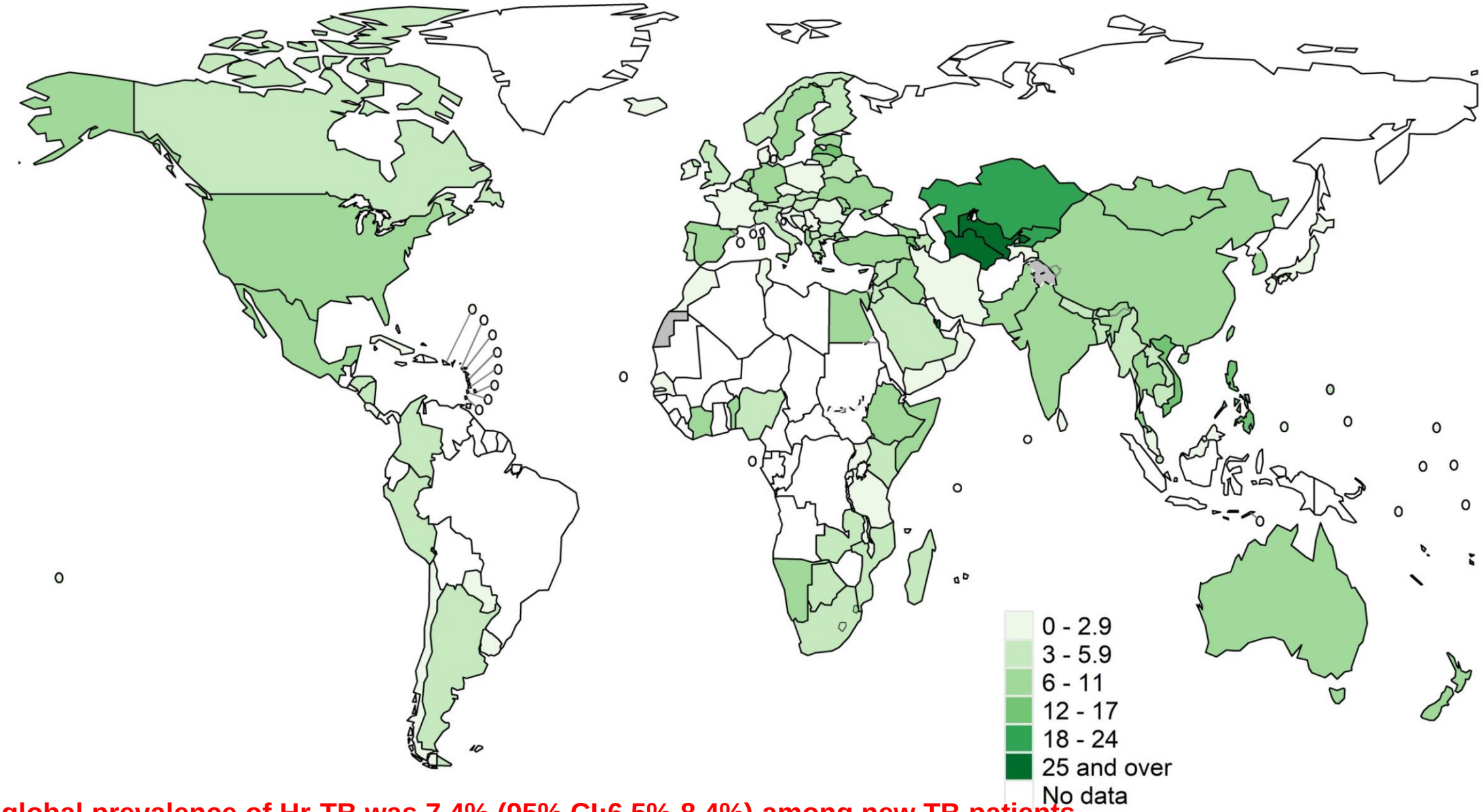
- Epidemiology and Mechanism of Isoniazid Mono-Resistance Tuberculosis (Hr-TB)
- Clinical Impact of Hr-TB
- Treatment of Hr-TB
- Future Perspectives

抗藥性結核的分類

1. 單一抗藥結核 (Mono-resistant TB)：對一種抗結核藥抗藥。

2. 多種抗藥結核 (Poly-resistant TB)：對兩種或兩種以上抗結核藥抗藥，但非同時對isoniazid 及rifampin 抗藥。

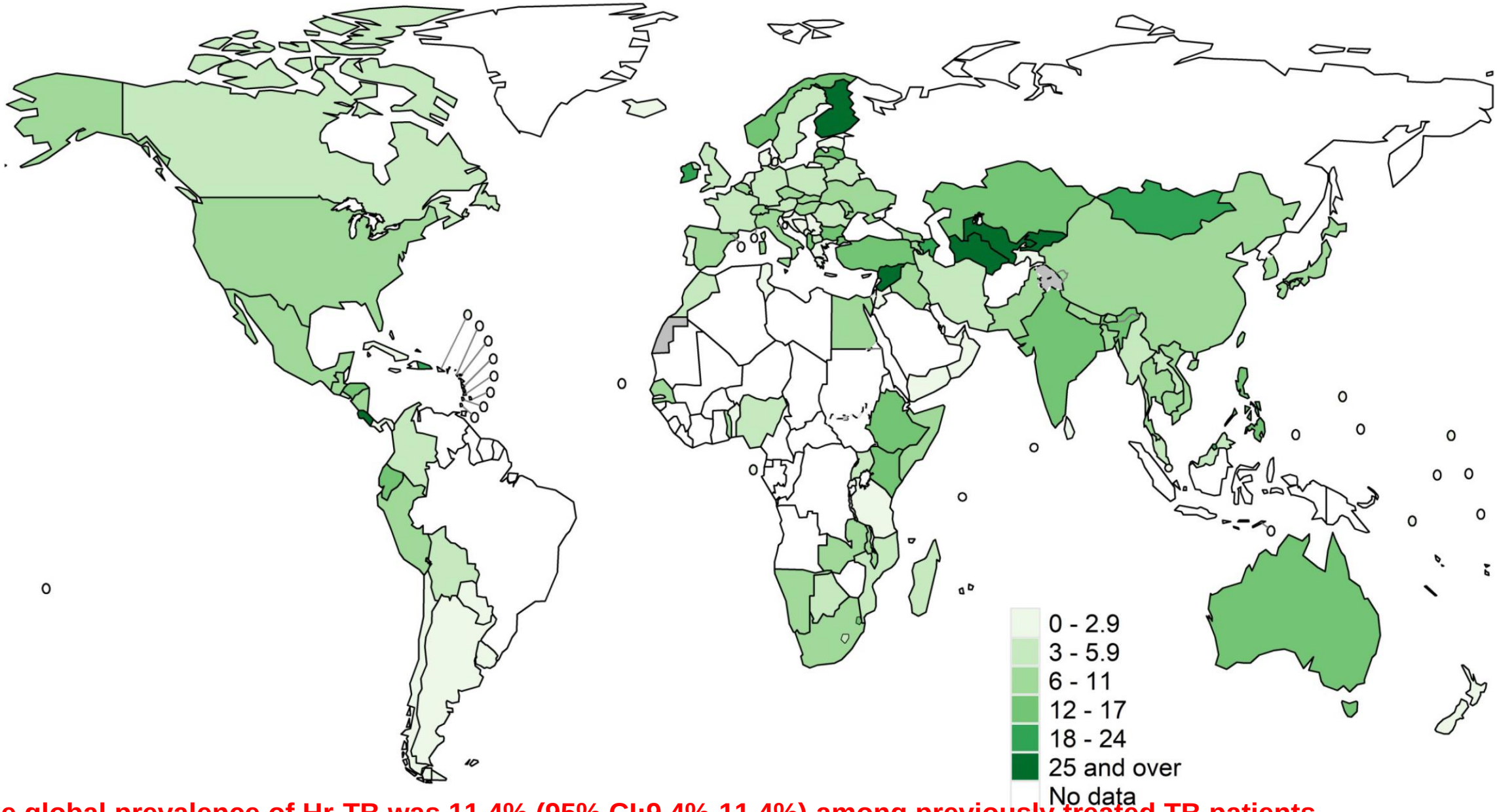
3. 多重抗藥結核（Multidrug-resistant TB, MDR-TB）：至少對 isoniazid 及 rifampin 抗藥。



The global prevalence of Hr-TB was 7.4% (95% CI:6.5%-8.4%) among new TB patients.

Fig 1. Prevalence of Hr-TB among new TB cases. These maps were created using the R package, "whomap." Hr-TB, isoniazid-resistant, rifampicin-susceptible TB; TB, tuberculosis.

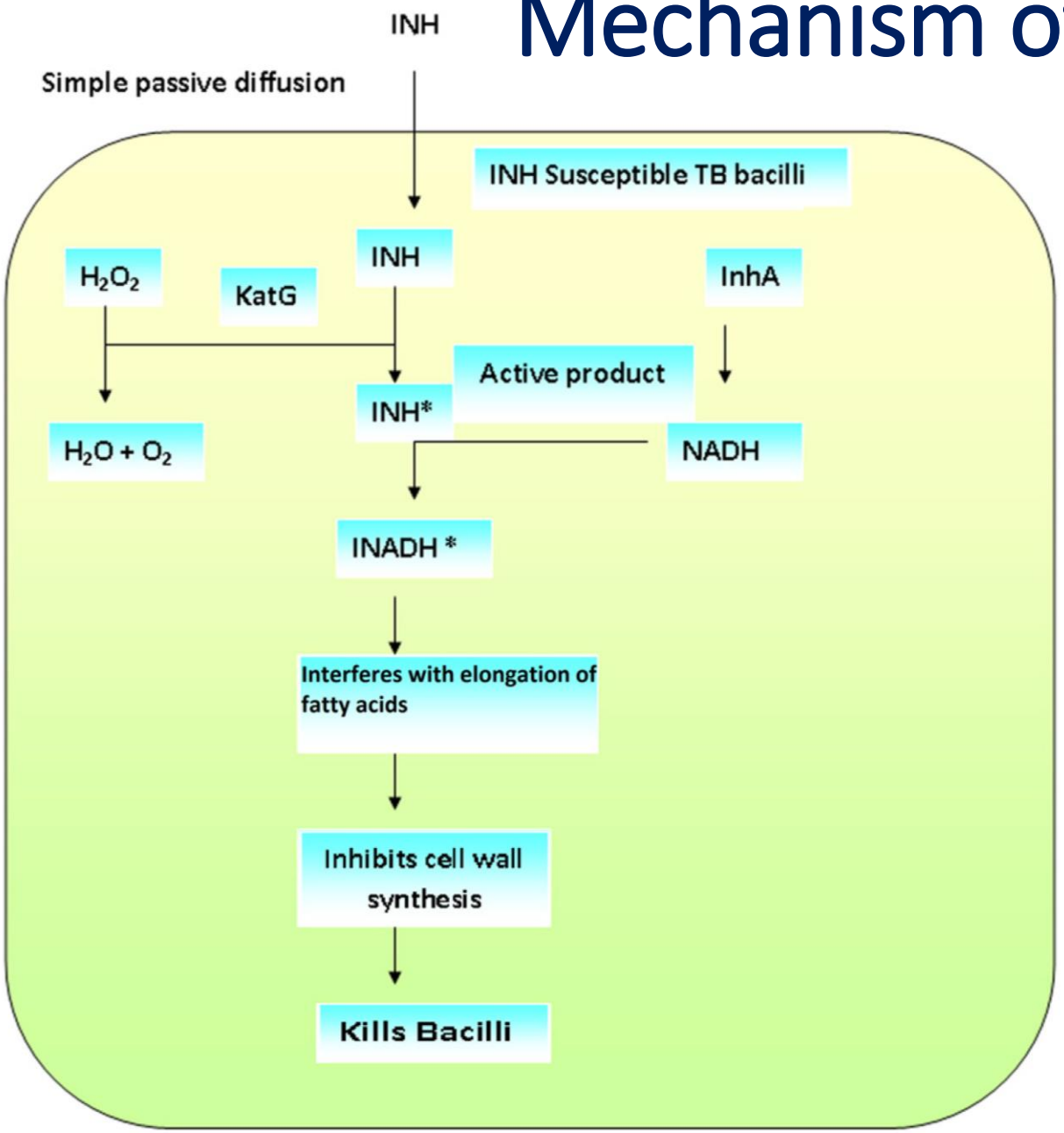
Dean AS et al. PLoS Med 2020



The global prevalence of Hr-TB was 11.4% (95% CI:9.4%-11.4%) among previously treated TB patients.

Fig 2. Prevalence of Hr-TB among previously treated TB cases. These maps were created using the R package, "whomap." Hr-TB, isoniazid-resistant, rifampicin-susceptible TB; TB, tuberculosis.

Mechanism of Isoniazid

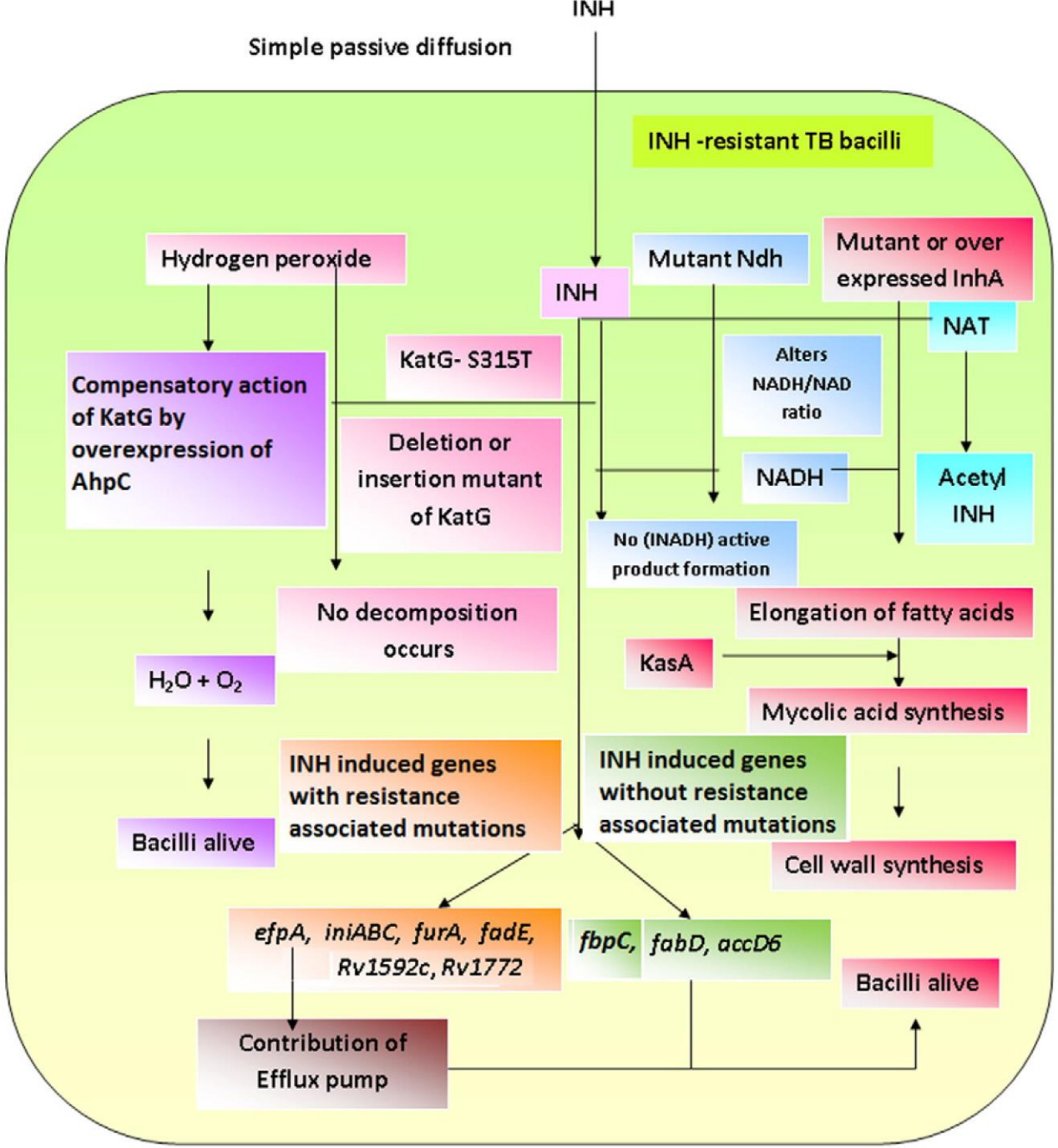


Bactericidal

Act on actively dividing MTB

Inhibit Mycolic Acid- Cell Wall- Acid Fastness

ssa et al. / Infection, Genetics and Evolution 45 (2016) 474–492



Major mechanisms for Resistance

- Loss of the *katG*-encoded catalase peroxidase
- Overexpression or alterations in the INH target *InhA*
- Loss of NADH dehydrogenase II activity (*ndh*)
- Alterations and overexpression of *KasA*

A.N. Unissa et al. / Infection, Genetics and Evolution 45 (2016) 474–492

Low-level and High-Level-Isoniazid Resistance

- High Level Resistance

  >0.4 µg/mL (liquid media), >1.0 µg/mL (solid media)

- Low Level Resistance

  0.1-0.4 µg/mL (liquid media), 0.2-1.0 (solid media)

Riviere E et al. Clin Microbiol Infect 2020

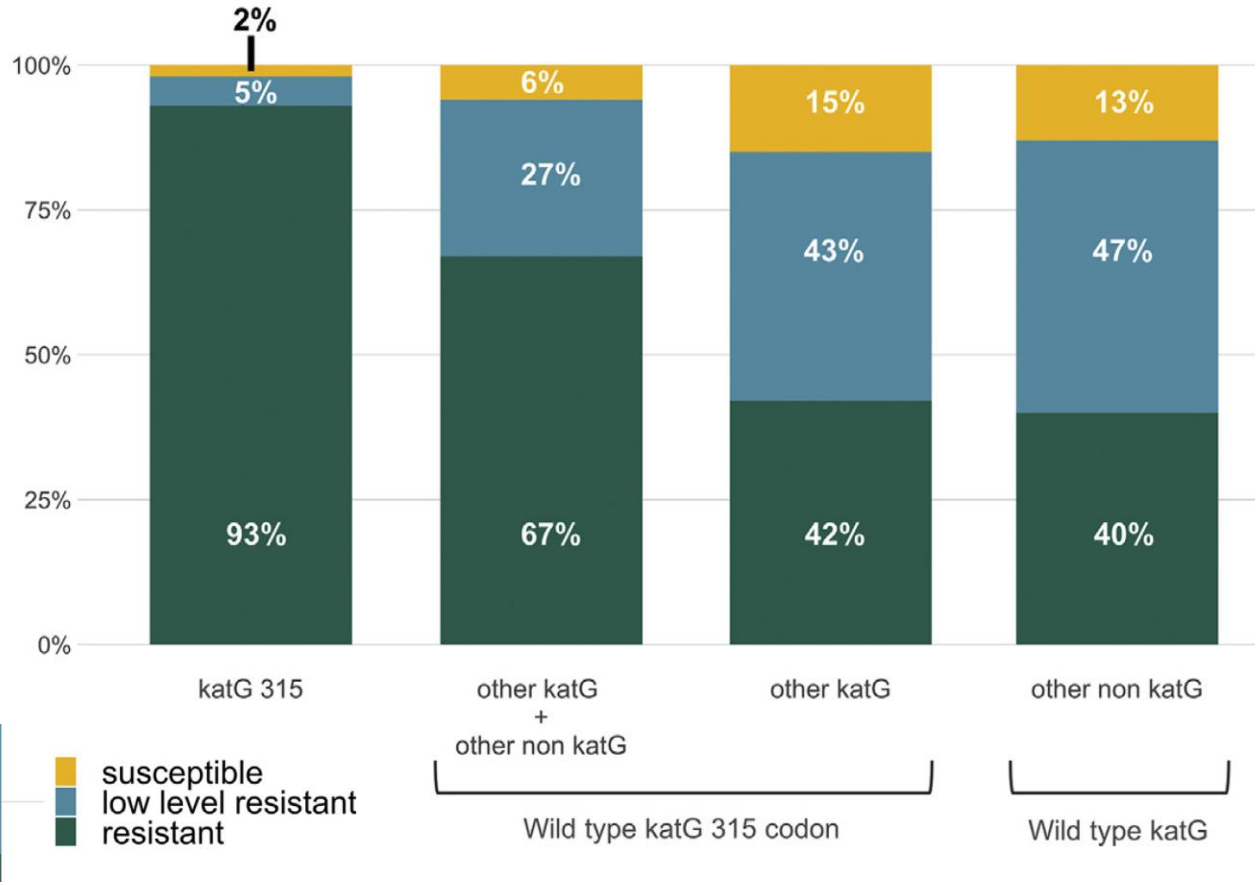
Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis WHO 2018

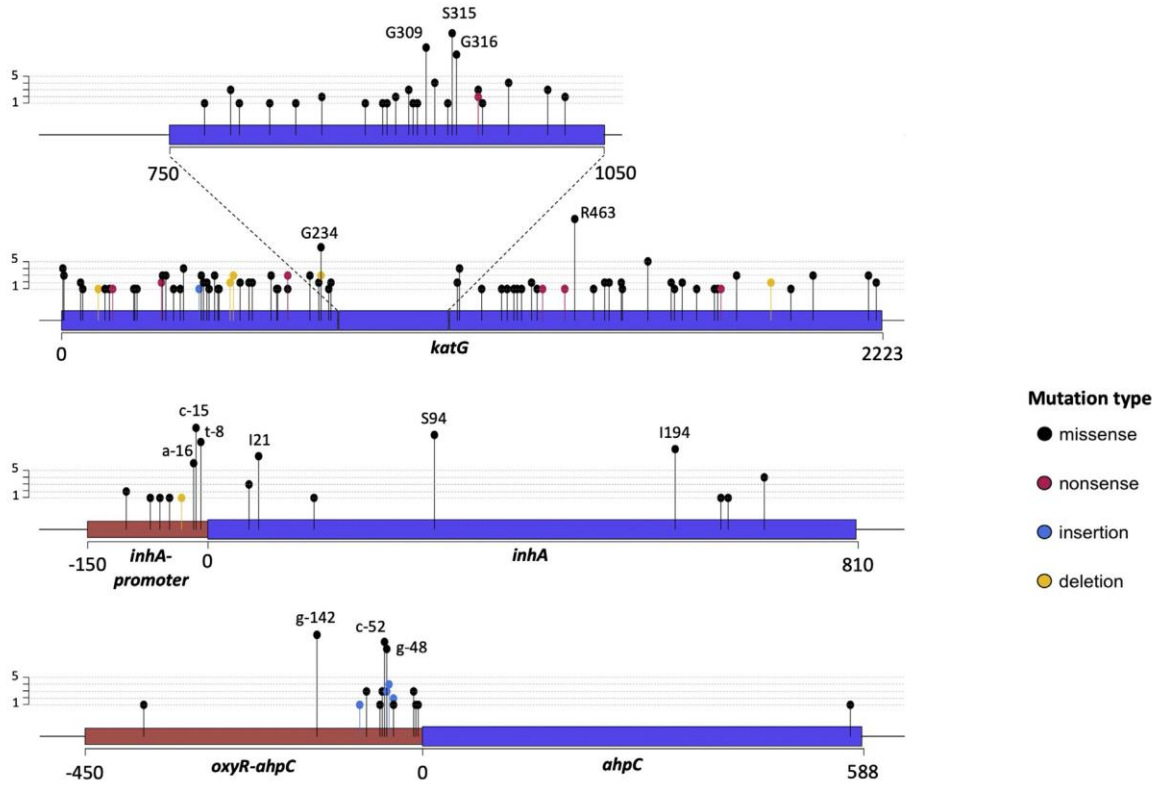
Table 1. Critical concentrations (CC) for first-line medicines recommended for the treatment of drug-susceptible TB.

Medicine	Abbreviation	Critical concentrations (µg/ml) for DST by medium			
		Löwenstein–Jensen[a]	Middlebrook 7H10[a]	Middlebrook 7H11[a]	BACTEC MGIT liquid culture[a]
Rifampicin	RIF	40.0	1.0	1.0	1.0[b]
Isoniazid[c]	INH	0.2	0.2	0.2	0.1
Ethambutol[d]	EMB	2.0	5.0	7.5	5.0
Pyrazinamide[e]	PZA	-	-	-	100

Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis WHO 2018

Genotypic-Phenotypic Association-Not So Clear





Presence of a variant in the katG gene is a good marker of high-level INH resistance only if located in codon 315

Riviere E et al. Clin Microbiol Infect 2020

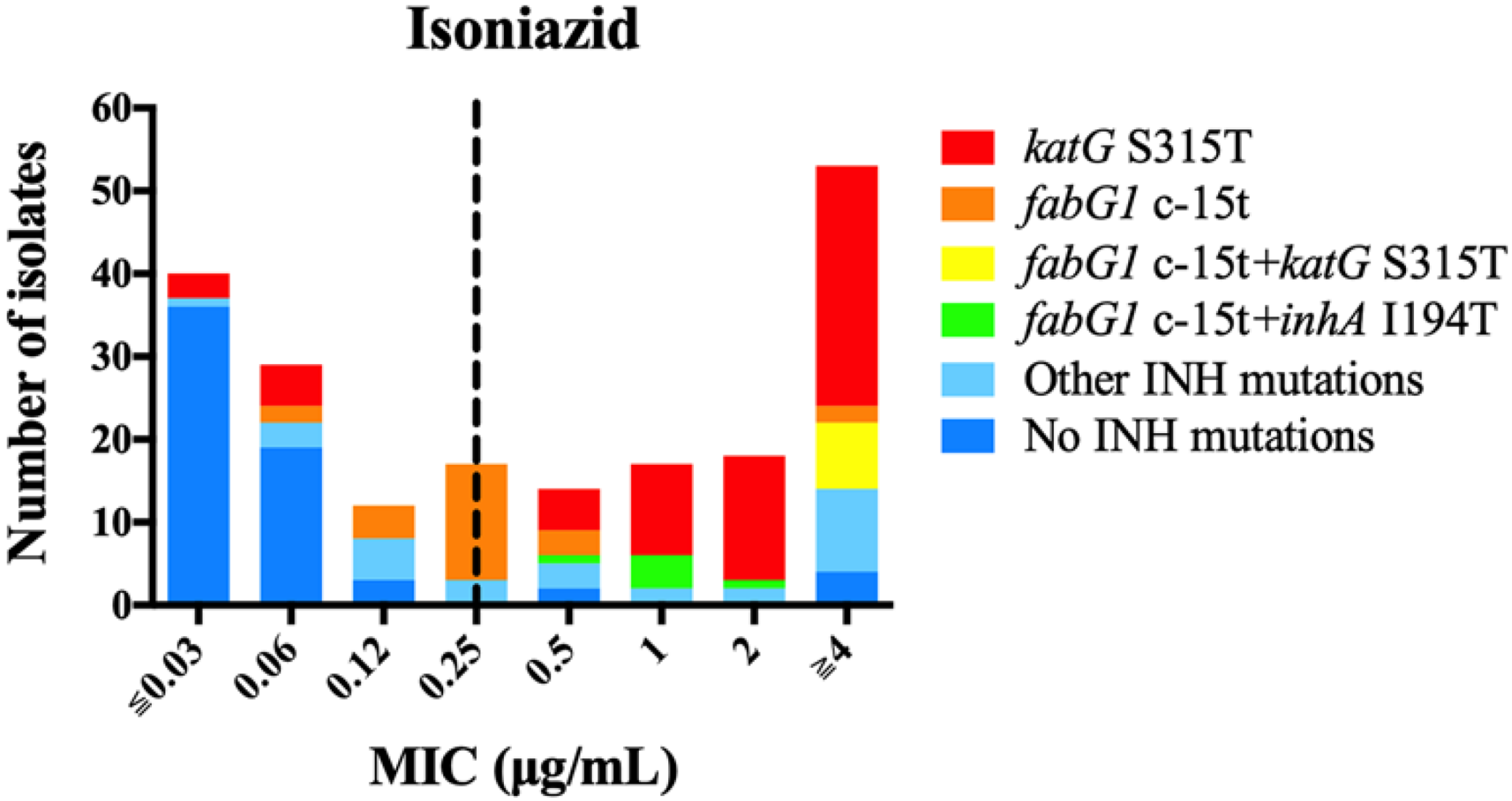
Genotypes Association with Level of Resistance

- Genes Associated with High-Level Resistance

katG Gene, kasA Gene

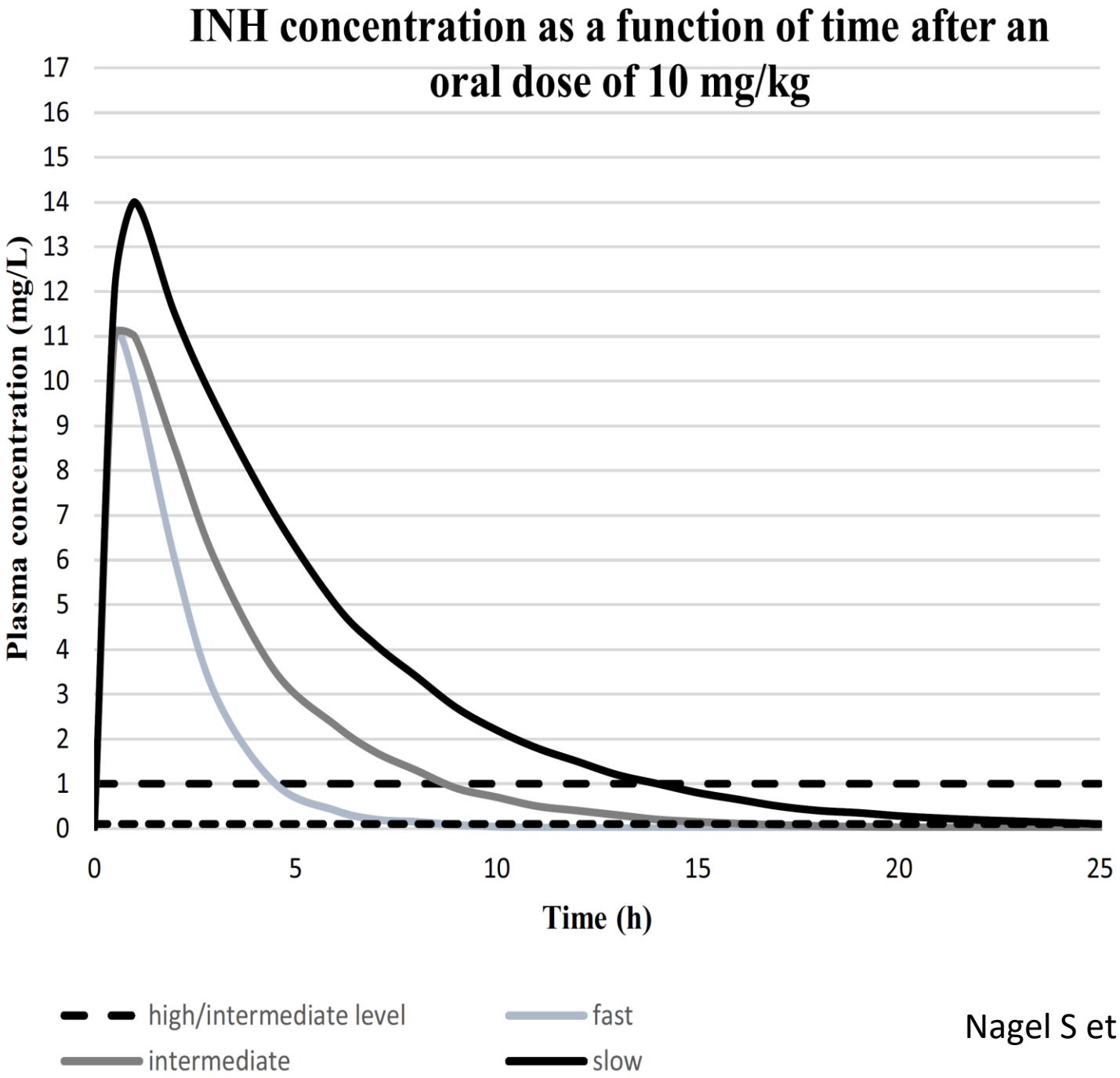
- Genes Associated with low-Level Resistance

inhA (mabA) Promoter, inhA Gene Coding Sequence, ndh Gene



Taiwan Isoniazid Resistance Genotypes

Xiao YX et al. Sci Rep 2023



Metabolism Affects the Area Under Curve of INH for INH-Resistant TB

For Example:
Low level Resistance:
17% time of effective concentration in fast acetylator
60% time in slow acetylator

Nagel S et al. Current Drug Metabolism 2017

Clinical Impact of Hr-TB

Three Key Literatures (Meta-Analysis) to Be Reviewed

- Menzies D et al. PLoS Med. 2009

Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-resistance to Isoniazid: A Systematic Review and Meta-analysis

- Gegia M et al. Lancet Infect Dis. 2017

Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis

- Fregonese F et al. Lancet Respir Med. 2018

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

1

OPEN ACCESS Freely available online

PLoS MEDICINE

Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-resistance to Isoniazid: A Systematic Review and Meta-analysis

Dick Menzies[1]*, Andrea Benedetti[1], Anita Paydar[1], Sarah Royce[2], Madhukar Pai[1], William Burman[3], Andrew Vernon[4], Christian Lienhardt[5]

Literature Searched between 1948-2008

Menzies D et al. PLoS Med. 2009

Table 1. Cohort studies reporting results with standardized retreatment regimen recommended by WHO.

ID	Reference	Regimen[a]	Total Number Treated	Number at Risk for Failure[b]	Number (%) Who Failed	Number at Risk for Acquired Drug Resistance[c]	Number with Acquired Drug Resistance
Pan-sensitive strains							
33	[22]	2HRZES/1HRZE/5HRE	382	306	2 (0.7%)	306	1
34	[23]	2HRZES/1HRZE/5HRE	30	28	0	28	0
340	[25]	2HRZES/1HRZE/5HRE	122	87	5 (6%)	—	—
		2HRZES/1HRZE/5$[HRE]_2$	260	208	13 (6%)	—	—
		2HRZES/1HRZE/5$[HRE]_3$	104	64	17 (27%)	—	—
Mono-resistance to INH							
340	[25]	2HRZES/1HRZE/5HRE	57	39	7 (18%)	—	—
		2HRZES/1HRZE/5$[HRE]_2$	37	31	6 (19%)	—	—
		2HRZES/1HRZE/5$[HRE]_3$	30	18	8 (44%)	—	—
Mixed drug resistance (all forms or unknown)							
324	[24]	2$[HRZES]_3$/1$[HRZE]_3$/5$[HRE]_3$	57	46	4 (9%)	—	—
		2$[HRZES]_3$/2$[HRZE]_3$/5$[HRE]_3$	17	11	5 45%)	—	—
384	[6]	2HRZES/1HRZE/5EHR	210	183	47 (26%)	—	—
415	[26]	2$[HRZES]_3$/1$[HRZE]_3$/5$[HRE]_3$	507	389	52 (13%)	—	—

A single 8-mo ‘‘retreatment’’ regimen (8 mo of isoniazid, rifampin, ethambutol, with pyrazinamide added for the first 3 mo, and streptomycin added for the first 2 mo—2SHRZE/1HRZE/5HRE)

Menzies D et al. PLoS Med. 2009

Insights and Conclusions

- From pooled analysis of 33 trials in 1,907 patients with mono-resistance to isoniazid, lower failure, relapse, and acquired drug resistance rates were associated with longer duration of rifampin, use of streptomycin, daily therapy initially, and treatment with a greater number of effective drugs

- There are few published studies to support use of the current standardized retreatment regimen.

- Randomized trials of treatment of persons with isoniazid mono-resistance and/or a history of previous TB treatment are urgently needed.

表 2各類結核病人的治療建議簡表

病人分類	建議治療方式
新病人	1. 優先：INH + RMP + EMB + PZA 2個月／INH + RMP + EMB 4個月 2. 其次：INH + RMP + EMB 9個月
再治病人 複發、失落、失敗	1. INH+RMP+EMB+PZA+SM 2個月／INH + RMP + EMB +PZA 1個月／INH + RM
藥物抗藥 或已知藥敏試驗結果	・單一藥物抗藥 1. INH不能用：EMB + RMP + PZA 6-9個月（治療2個月時痰培養陽性，治療9個月）

結核病診治指引(第三版) 2008年6月

2

Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis

Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies

Updated a previous systematic review of treatment outcomes associated with use of first-line drugs in patients with tuberculosis resistant to isoniazid but not rifampicin

Updated Review Period 2008-2015

Gegia M et al. Lancet Infect Dis. 2017

	Total arms (arms from cohorts)	Events/ participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Overall				
Isoniazid resistant	124 (30)	640/3744	15% (12–18)*	80% (77–83)
Isoniazid sensitive	89 (13)	1065/19 012	4% (3–5)	84% (81–87)

***Table 2*: Treatment failure or relapse of tuberculosis, or both, by regimen in randomised controlled trials and cohorts**

15% Treatment failure or relapse in Hr-TB and 4% in DS-TB

	Total arms	Events/participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Overall				
Isoniazid resistant	92	205/2024	3·6% (2–5)	5% (0–24)
Isoniazid sensitive	71	167/12 690	0·6% (0·3–0·9)	21% (0–40)

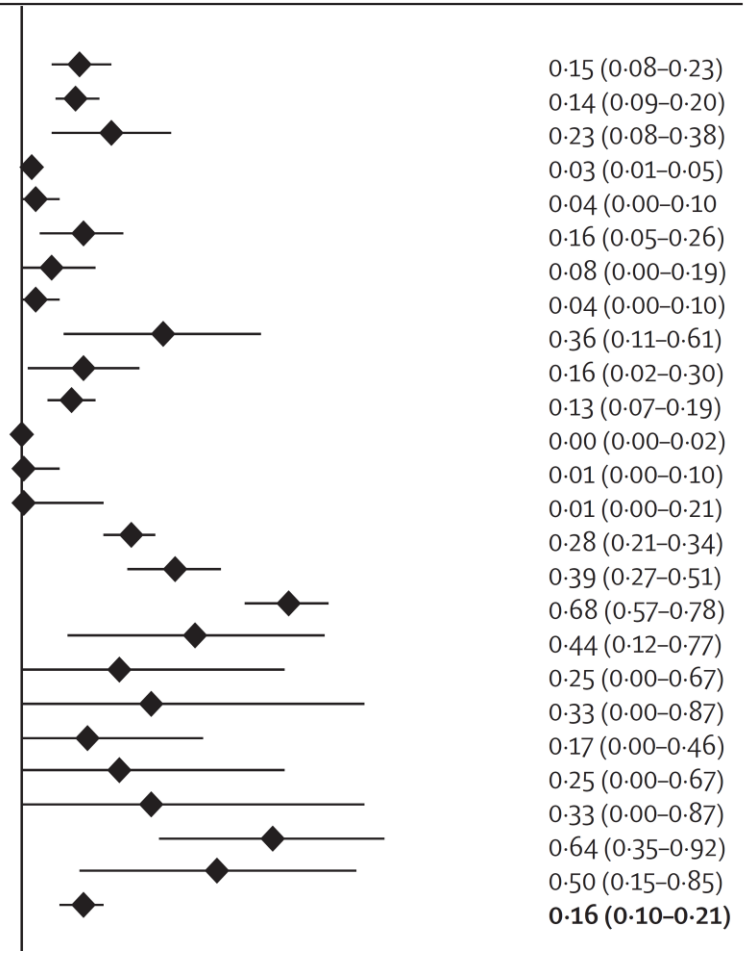
***Table 3*: Acquired drug resistance (among treatment failures or relapses) by regimen in randomised controlled trials and cohorts**

3.6% acquired drug resistance in Hr-TB and 0.6% in DS-TB

Gegia M et al. Lancet Infect Dis. 2017

Different Regimens for Hr-TB- WHO Standard Initial Treatment

	Failure or relapse (n)	N	Design	Effect (95% CI)
WHO–New				
Yoshiyama et al (2004)[50]	14	91	Cohort	0·15 (0·08–0·23)
Seung et al (2004)[49]	21	147	Cohort	0·14 (0·09–0·20)
Thomas et al (2005)[51]	7	30	Cohort	0·23 (0·08–0·38)
Espinal et al (2000)[47]	8	298	Cohort	0·03 (0·01–0·05)
Espinal et al (2000)[47]	2	49	Cohort	0·04 (0·00–0·10
Espinal et al (2000)[47]	7	45	Cohort	0·16 (0·05–0·26)
Davies et al (1999)[46]	2	25	Cohort	0·08 (0·00–0·19)
Bonnet et al (2011)[57]	2	47	Cohort	0·04 (0·00–0·10)
Cox et al (2006)[52]	5	14	Cohort	0·36 (0·11–0·61)
Tabarsi et al (2009)[56]	4	25	Cohort	0·16 (0·02–0·30)
Huyen et al (2013)[61]	18	137	Cohort	0·13 (0·07–0·19)
BMRC (1984)[24]	0	10	RCT	0·00 (0·00–0·02)
STS/BMRC (1985)[26]	0	2	RCT	0·01 (0·00–0·10)
HKCS/BMRC (1991)[39]	0	1	RCT	0·01 (0·00–0·21)
TBRC Chennai (2004)[42]	46	167	RCT	0·28 (0·21–0·34)
TBRC Chennai (1997)[7]	23	59	RCT	0·39 (0·27–0·51)
TBRC Chennai (1997)[7]	50	74	RCT	0·68 (0·57–0·78)
Castelo et al (1989)[32]	4	9	RCT	0·44 (0·12–0·77)
Castelo et al (1989)[32]	1	4	RCT	0·25 (0·00–0·67)
Chaulet et al (1995)[40]	1	3	RCT	0·33 (0·00–0·87)
Chaulet et al (1995)[40]	1	6	RCT	0·17 (0·00–0·46)
Agounitestane et al (1990)[35]	1	4	RCT	0·25 (0·00–0·67)
Agounitestane et al (1990)[35]	1	3	RCT	0·33 (0·00–0·87)
Swaminathan et al (2010)[43]	7	11	RCT	0·64 (0·35–0·92)
Swaminathan et al (2010)[43]	4	8	RCT	0·50 (0·15–0·85)
Summary	**229**	**1269**		**0·16 (0·10–0·21)**

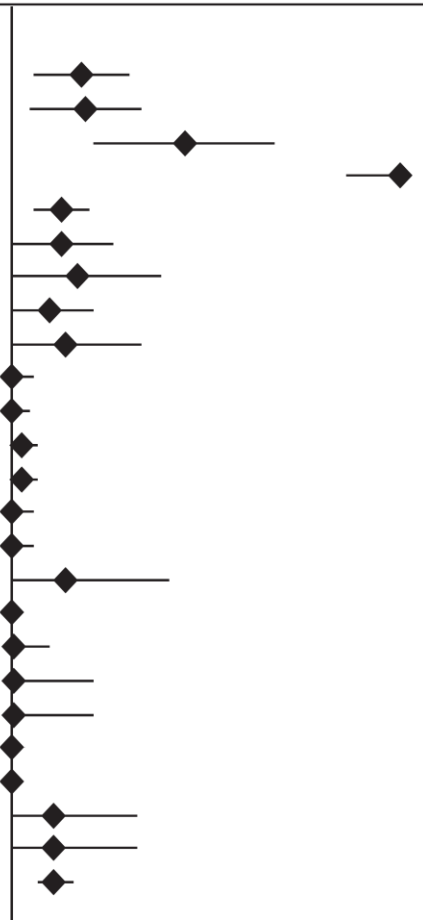


WHO's standard initial treatment regimen for previously untreated patients and consists of
2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin.

Gegia M et al. Lancet Infect Dis. 2017

Different Regimens for Hr-TB- WHO Retreatment

	Failure or relapse (n)	N	Design	Effect (95% CI)
WHO-Retreatment				
Espinal et al (2000)[47]	7	39	Cohort	0·18 (0·06–0·30)
Espinal et al (2000)[47]	6	31	Cohort	0·19 (0·05–0·33)
Espinal et al (2000)[47]	8	18	Cohort	0·44 (0·21–0·67)
Cox et al (2006)[52]	2	2	Cohort	0·99 (0·85–1·00)
Deepa et al (2013)[60]	12	92	Cohort	0·13 (0·06–0·20)
Temple et al (2008)[55]	3	24	Cohort	0·13 (0·00–0·26)
Yoshiyama et al (2010)[58]	2	12	Cohort	0·17 (0·00–0·38)
Huyen et al (2013)[61]	3	30	Cohort	0·10 (0·00–0·21)
ECARC/BMRC (1983)[23]	2	14	RCT	0·14 (0·00–0·33)
STS/BMRC (1985)[26]	0	3	RCT	0·00 (0·00–0·06)
STS/BMRC (1985)[26]	0	4	RCT	0·00 (0·00–0·05)
Babu Swai et al (1988)[30]	3	91	RCT	0·03 (0·00–0·07)
Babu Swai et al (1988)[30]	3	88	RCT	0·03 (0·00–0·07)
HKCS/BMRC (1991)[37]	0	3	RCT	0·00 (0·00–0·06)
HKCS/BMRC (1991)[37]	0	3	RCT	0·00 (0·00–0·06)
HKCS/BMRC (1991)[37]	1	7	RCT	0·14 (0·00–0·40)
HKCS/BMRC (1991)[37]	0	7	RCT	0·00 (0·00–0·02)
STS/BMRC (1991)[39]	0	2	RCT	0·01 (0·00–0·10)
STS/BMRC (1991)[39]	0	1	RCT	0·01 (0·00–0·21)
STS/BMRC (1979)[19]	0	1	RCT	0·01 (0·00–0·21)
STS/BMRC (1979)[19]	0	5	RCT	0·00 (0·00–0·04)
AWG/BMRC (1991)[36]	0	10	RCT	0·00 (0·00–0·02)
AWG/BMRC (1991)[36]	1	9	RCT	0·11 (0·00–0·32)
EAMRC/BMRC (1978)[17]	1	9	RCT	0·11 (0·00–0·32)
Summary	**54**	**505**		**0·11 (0·06–0·17)**

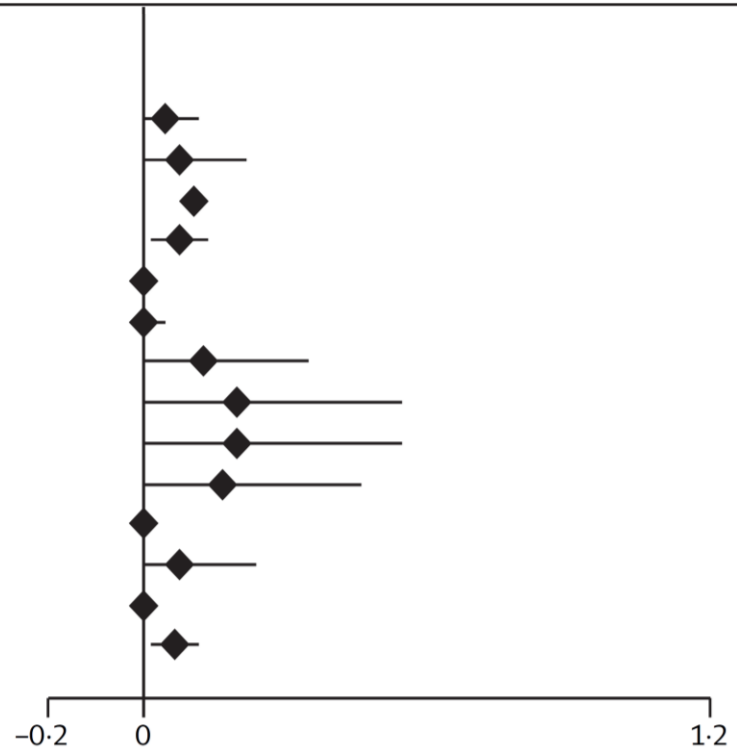


WHO-Retreatment is the standard WHO-recommended regimen for previously treated people and consists of 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol.

Gegia M et al. Lancet Infect Dis. 2017

Different Regimens for Hr-TB- 6-9 mo RZE

	Failure or relapse (n)	N	Design	Effect (95% CI)
6–9 months' rifampicin, pyrazinamide, and ethambutol				
Nolan et al (2002)[48]	2	39	Cohort	0·05 (0·00–0·12)
Kim et al (2008)[54]	1	13	Cohort	0·08 (0·00–0·22)
Gegia et al (2012)[59]	79	710	Cohort	0·11 (0·09–0·13)
Reves et al (2014)[62]	6	74	Cohort	0·08 (0·02–0·14)
Tabarsi et al (2009)[56]	0	16	Cohort	0·00 (0·00–0·02)
HKCS/ BMRC (1991)[37]	0	4	RCT	0·00 (0·00–0·05)
HKCS/ BMRC (1991)[37]	1	8	RCT	0·13 (0·00–0·35)
HKCS/ BMRC (1991)[37]	1	5	RCT	0·20 (0·00–0·55)
STS/BMRC (1979)[19]	1	5	RCT	0·20 (0·00–0·55)
HKCS/BMRC (1981)[22]	1	6	RCT	0·17 (0·00–0·46)
HKCS/BMRC (1981)[22]	0	10	RCT	0·00 (0·00–0·02)
EAMRC/BMRC (1978)[17]	1	12	RCT	0·08 (0·00–0·24)
Abdul Aziz et al (1986)[27]	0	9	RCT	0·00 (0·00–0·02)
Summary	**93**	**911**		**0·07 (0·02–0·12)**



Gegia M et al. Lancet Infect Dis. 2017

	Drug susceptibility	Arms	Events/participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Treatment failure					
WHO-New	Isoniazid resistant	24	170/1239	11% (6–17)*	87% (82–91)
WHO-New	Sensitive	19	241/9792	2% (1–3)	81% (72–88)
WHO-Retreatment	Isoniazid resistant	24	41/505	6% (2–10)*	40% (2–63)
WHO-Retreatment	Sensitive	21	40/2609	1% (0–2)	50% (19–70)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	13	82/911	1% (0–2)*	61% (28–79)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	10	13/1098	1% (0–2)	26% (0–64)
Relapse					
WHO-New	Isoniazid resistant	17	59/482	10% (5–15)	2% (0–45)
WHO-New	Sensitive	15	269/4740	5% (2–7)	79% (69–86)
WHO-Retreatment	Isoniazid resistant	20	13/277	5% (2–8)*	0 (0–44)
WHO-Retreatment	Sensitive	18	115/2205	5% (4–7)	12% (0–47)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	9	11/157	7% (2–11)*	0 (0–55)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	10	55/1010	6% (3–8)	65% (31–82)
Acquired drug resistance					
WHO-New	Isoniazid resistant	18	89/701	8% (3–13)*	14% (0–47)
WHO-New	Sensitive	15	102/5415	1% (0–2)	72% (56–82)
WHO-Retreatment	Isoniazid resistant	17	7/284	3% (0–6)*	23% (0–53)
WHO-Retreatment	Sensitive	16	7/2091	0·3% (0–0·6)	0 (0–47)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	9	3/164	0·3% (0–2)†	0 (0–55)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	8	11/939	0·1% (0–0·4)	0 (0–60)

Table 1: **Outcomes in all studies (randomised controlled trials and cohorts) with the three most commonly used first-line tuberculosis regimens**

Gegia M et al. Lancet Infect Dis. 2017

	Total treated	Any acquired drug resistance	Acquired multidrug resistance	% of acquired drug resistance that is multidrug resistance (95% CI)
All 13 treatment regimens				
Isoniazid sensitive	12 690	167	54	32% (25–40)
Isoniazid resistant	2024	214	205	96% (93–99)
Most commonly used regimens				
Isoniazid sensitive				
WHO-New	5415	102	47	46% (36–57)
WHO-Retreatment	2091	7	2	29% (10–82)
6–9 months of rifampicin, pyrazinamide, and ethambutol	939	11	3	27% (2–52)
Isoniazid resistant				
WHO-New	701	89	87	98% (92–99)
WHO-Retreatment	284	7	5	71% (29–96)
6–9 months of rifampicin, pyrazinamide, and ethambutol	164	3	2	67% (9–99)
Isoniazid critical concentrations overall (resistant strains only)				
High	1203	40	34	85% (70–94)
Low	1864	59	35	59% (46–72)

Data are n unless otherwise specified. WHO-New is WHO's standard initial treatment regimen for previously untreated patients and consists of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. WHO-Retreatment is the standard WHO-recommended regimen for previously treated people and consists of 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol.

***Table 4*: Proportion of patients with multidrug-resistant tuberculosis among all patients with disease with acquired drug resistance**

Gegia M et al. Lancet Infect Dis. 2017

3

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Maryline Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J Garcia-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Sun Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Trieu, Velayutham V Banurekha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

Fregonese F et al. Lancet Respir Med. 2018

Individual Patient Data Meta-Analysis

- Individual patient data were requested for 57 cohort studies and 17 randomised trials including 8089 patients with INH-R tuberculosis

- 33 datasets with 6424 patients, of which 3923 patients in 23 studies received regimens related to the study objectives

Three Important Clinical Questions

1. REZ≥ 6 months vs REZ 6 months
2. Addition of FQ
3. Use of Streptomycin

Fregonese F et al. Lancet Respir Med. 2018

	Regimen	Number of datasets included	Number of events/ number of patients on treatment	I^{2}*	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses in all patients (with or without isoniazid)							
Success	6(H)REZ	15	254/262	NE§	262	2·4 (1·0 to 5·5)	40 (0 to 80)
Success	>6(H)REZ	NA	999/1088	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	6(H)REZ	10	1/168¶	NE§	168	0·2 (0·0 to 1·7)	−10 (−60 to 40)
Acquired rifampicin resistance	>6(H)REZ	NA	43/992¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Success	6REZ	13	136/142	36%	140	2·5 (0·9 to 7·5)	50 (−10 to 100)
Success	>6REZ	NA	701/785	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	6REZ	8	0/84	NE§	84	NE	NE
Acquired rifampicin resistance	>6REZ	NA	43/729	NA	NA	1 (ref)	0 (ref)

Table 1: **Treatment success and acquired rifampicin resistance of different durations of daily regimen of rifampicin, ethambutol, and pyrazinamide, with or without isoniazid**

Compared with a daily regimen of 6 months of (H)REZ (REZ with or without isoniazid), extending the duration to 8–9 months had similar outcomes

Fregonese F et al. Lancet Respir Med. 2018

	Regimen	Number of datasets included	Number of events/number of patients on treatment	I^2*	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ + FQ	15	25/524	12%	522	0·7 (0·4 to 1·1)	−20 (−50 to 0)
Mortality (all durations)	(H)REZ	NA	97/2174	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)REZ + FQ	15	245/251	36%	248	2·8 (1·1 to 7·3)	50 (0 to 90)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ + FQ	15	161/165§	44%	164	2·9 (0·9 to 9·3)	60 (−20 to 140)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)REZ + FQ	10	1/221¶	2%‖	220	0·1 (0·0 to 1·2)	−30 (−60 to 0)
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + FQ	14	8/219	0	205	0·4 (0·2 to 1·1)	−20 (−60 to 20)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	0 (ref)
Success	≥6REZ + FQ	14	131/135	33%	127	5·4 (1·8 to 16·6)	130 (−40 to 230)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6REZ + FQ	9	1/111	NE**	107	0·1 (0·0 to 1·0)	−70 (−140 to 0)
Acquired rifampicin resistance	≥6REZ	NA	43/813	NA	NA	1 (ref)	0 (ref)

Table 2: Association of use of fluoroquinolones with treatment success, mortality, and acquired rifampicin resistance

Addition of a fluoroquinolone to 6 months or more of (H)REZ was associated with significantly greater treatment success (aOR 2.8, 95% CI 1.1–7.3), but no significant effect on mortality (aOR 0.7, 0.4–1.1) or acquired rifampicin resistance (aOR 0.1, 0.0–1.2).

Fregonese F et al. Lancet Respir Med. 2018

	Regimen	Number of datasets included	Number of events/number of patients on treatment	I^{2}*	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses done in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ + SM	23	40/763	14%	756	0·9 (0·6 to 1·3)	–10 (–30 to 20)
Mortality (all durations)	(H)REZ	NA	103/2263	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)RE(1–3)Z + 2SM	23	271/325	0	296	0·4 (0·2 to 0·7)	–120 (–190 to –60)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)RE(1–3)Z + 2SM	14	6/58§	NE¶	..	NE‖	..
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160§	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + SM	14	6/136	NE¶	133	1·2 (0·4 to 4·1)	0 (–50 to 60)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	NA
Success	≥6RE(1–3)Z + 2SM	14	89/107	NE¶	105	0·5 (0·2 to 1·2)	–80 (–170 to 10)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)

Table 4: Association of use of streptomycin with treatment success, mortality, and acquired rifampicin resistance

Compared with 6 months or more of (H)REZ, the standardised retreatment regimen (2 months of streptomycin, 3 months of pyrazinamide, and 8 months of isoniazid, rifampicin, and ethambutol) was associated with significantly worse treatment success (aOR 0.4, 0.2–0.7)

Fregonese F et al. Lancet Respir Med. 2018

Treatment outcome of patients with isoniazid mono-resistant tuberculosis

- Hr-TB, January 2004 to October 2011, recruited in 4 hospitals in Taiwan
- 395 patients with culture-confirmed Hr-TB (high level resistance/low-level resistance:174 (45.9%)/221 (54.1%)
- Treatment success, n=328 (83%)/unfavorable outcomes, n=67 (17%))
- Culture conversion at 2nd month (73.7%)

Chien JY et al. Clin Microbiol Infect 2015

TABLE 3. Factors predicting unfavourable outcomes among patients with isoniazid mono-resistant tuberculosis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Prior TB treatment	1.92	1.06–3.46	0.031	1.50	0.81–2.77	0.194
Age ≥65 years	2.26	1.35–3.79	0.002	1.64	0.95–2.83	0.078
Male	2.54	1.21–5.32	0.013	1.88	0.82–4.27	0.134
Smoker	1.95	1.19–3.22	0.009	1.46	0.84–2.54	0.183
V Cancer	3.55	2.02–6.24	0.000	2.43	1.32–4.48	0.004
Cirrhosis of liver	3.30	1.42–7.66	0.005	2.26	0.90–5.70	0.084
Lower lung involvement	1.68	1.02–2.77	0.042	1.58	0.94–2.64	0.082
V Rifampicin interruption	2.38	1.35–4.17	0.003	1.91	1.07–3.42	0.029
Ethambutol interruption	1.75	1.06–2.89	0.028	1.44	0.85–2.42	0.176

Abbreviations: CI, confidence interval; CXR, chest X-ray; HR, hazard ratio; TB, tuberculosis.

Chien JY et al. Clin Microbiol Infect 2015

Hr-TB in Chang Gung Memorial Hospital During 2006 and 2007
INH low-level resistance (n=44) and INH high-level resistance (n=90)

Table 1. Demographic and clinical characteristics of the patients.

Characteristic	INH low concentration resistance n = 44	INH high concentration resistance n = 90	Odds ratio (95%CI)	p value
Male, n	34(77.3%)	66(73.3%)	1.24(0.53–2.88)	0.623
Age, years	53.2±3.7	58.8±3.0		0.264
Prior tuberculosis treatment	12(27.3%)	29(32.2%)	0.79(0.36–1.25)	0.559
Pulmonary tuberculosis	38(86.4%)	86(95.6%)	0.88(0.16–5.04)	0.889
Positive AFB smear test	30(68.2%)	60(66.7%)	1.50(0.65–3.47)	0.342
Cavitary chest radiograph	10(22.7%)	22(24.4%)	1.03(0.44–2.44)	0.946
Received initial isoniazid	42(95.5%)	88(97.8%)	0.48(0.06–3.51)	0.458
Directly observed therapy	44(100%)	85(93.3%)	5.73(0.31–106)	0.111
Adherence to treatment	43(95.5%)	87(96.7%)	1.48(0.15–14.69)	0.735
Adverse reaction	22(50%)	40(44.4%)	1.25(0.61–2.58)	0.545
Sputum culture conversion at ≤2 months	14(31.8%)	18(20%)	1.87(0.82–4.23)	0.132
Treatment duration, days	297.8±19.0	289.9±14.6		0.750

Wang TY et al. PLoS One 2014

Table 4. Clinical outcomes of the tuberculosis patients with INH monoresistance.

Treatment regimens	INH low concentration resistance, n = 44	INH high concentration resistance, n = 90	Odds ratio (95% CI)	p value
Successful	**36(81.8%)**	**78(86.7%)**		
Cure	35(79.5%)	75(83.3%)	0.78(0.31–1.95)	0.591
Completed	1(2.3%)	3(3.3%)	0.68(0.07–6.68)	0.735
Unsuccessful	**8(18.2%)**	**12(13.3%)**		
Default	1(2.3%)	2(2.2%)	2.07(0.13–33.91)	0.603
Failure	2(4.5%)	2(2.2%)	1.38(0.22–8.58)	0.728
Death	4(9.1%)	7(7.8%)	1.03(0.29–3.61)	0.969

Table 5. Univariable and multivariable associations with unsuccessful treatment outcome.

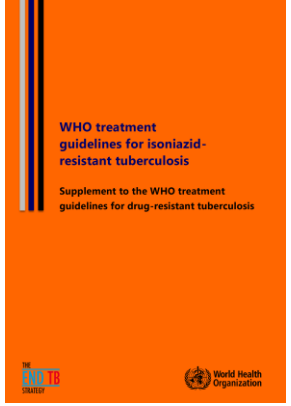
Variables	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% C.I.)	p value	Odds Ratio (95% C.I.)	p value
Age>65 year-old	1.14(0.43–3.02)	0.788	1.24(0.42–3.64)	0.696
Prior tuberculosis treatment	2.68(1.02–3.05)	0.041	2.82(1.02–7.77)	0.045
Positive AFB smear test	1.17(0.42–3.28)	0.770	0.96(0.32–2.95)	0.947
Sputum culture conversion at ≤2 months	1.07(0.36–3.23)	0.899	0.96(0.29–3.18)	0.945
INH high-concentration resistance	0.69(0.26–1.84)	0.459	0.62(0.22–1.72)	0.357

Level of resistance was not associated with outcome

Wang TY et al. PLoS One 2014

Treatment of Hr-TB

WHO treatment guidelines for Hr-TB

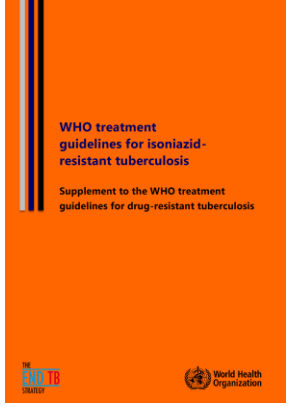


- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months

[Conditional recommendation, very low certainty in the estimates of effects]

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

WHO treatment guidelines for Hr-TB



- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen [Conditional recommendation, very low certainty in the estimates of effects]

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

Scenario One

- Hr-TB is confirmed before TB treatment is started

Treatment with the (H)REZ-Lfx is started immediately.

Strongly presumed Hr-TB (e.g. close contacts of Hr-TB cases with active TB) -> Start (H)REZ-Lfx and wait for drug susceptibility test->INH sensitive-> complete 2HRZE/4HR regimen

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

Scenario Two

- Hr-TB is confirmed after the start of treatment with 2HREZ/4HR regimen

Who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance later while on first-line regimen treatment

Rapid molecular testing for rifampicin resistance must be done (or repeated)

Exclude rifampicin resistance, start (H)REZ-Lfx

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

Important Considerations

- Ahead of starting the (H)REZ-Lfx, it is essential that resistance to rifampicin be excluded

- Preferably, resistance to fluoroquinolones, and if possible to pyrazinamide, is similarly be excluded prior to treatment

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

Contraindications to (H)REZ-Lfx Regimen

- In cases where resistance to rifampicin cannot be excluded
- Known or suspected resistance to levofloxacin
- Known intolerance to fluoroquinolones
- Known or suspected risk for prolonged QTc interval
- Pregnancy or during breastfeeding (not an absolute contraindication).

In Hr-TB cases in whom a FQ cannot be used, the patient may still be treated with 6(H)REZ.

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

Special Considerations

- Where possible, isoniazid resistance testing should also include information on the specific mutations associated with resistance to isoniazid (katG or inhA)

- In addition, knowledge about overall host acetylator status at country or regional level will be useful

Special Considerations

- In vitro evidence seems to suggest that when specific **inhA mutations** are detected (and in the absence of any katG mutations), increasing the dose of isoniazid is likely to be effective; thus, additional isoniazid to a maximum dose of up to **15mg/kg** per day could be considered.

- In the case of katG mutations, which more commonly confer higher-level resistance, the use of isoniazid even at higher-dose is less likely to be effective

WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis

結核診治指引第七版-第十二章

- **WHO建議在臺灣不一定適用**

- 因為大多數病人在治療前沒有DST 結果。通常是在治療1-2 個月後，才知道INH 抗藥。

- 治療1-2 個月後，如果治療反應不佳，不能忽視已產生rifampicin 抗藥(acquired rifampicin resistance)變成MDR-TB 的可能性，再加上fluoroquinolone 有進一步導致fluoroquinolone抗藥的風險， 而fluoroquinolone 是治療MDR-TB 的重要藥物，fluoroquinolone 抗藥的MDR-TB 非常難治療。

- 因此為保護fluoroquinolone，使用fluoroquinolone 前必須經過專家評估，確保不產生fluoroquinolone 抗藥。

結核診治指引第七版-第十二章

- 選項一

每天服用RMP，EMB，PZA，±INH 6 個月。如果一開始開立標準的四種藥物處方，卻得到藥敏結果顯示INH 抗藥時，如果以微生物、臨床及影像學評估，病人反應良好，痰陰轉，則產rifampicin 抗藥的風險及治療失敗的風險低，且對INH、RMP、EMB、PZA耐受良好，可以考慮RMP，EMB，PZA，± INH 6 個月。當病人對INH 沒有不良反應，可以繼續使用INH。

*專家建議可以考慮將INH 劑量增加 (體重>50 公斤600mg，體重≦50kg 400mg)。當病人對INH 有不良反應，可以停用INH。

結核診治指引第七版-第十二章

- **選項二**

每天服用RMP ， EMB ， PZA ， ±INH ， 加上一種近代的fluoroquinolone (FQ)(如moxifloxacin, levofloxacin) ， 和一種針劑(amikacin/kanamycin)。Amikacin/kanamycin 使用至痰陰轉即可考慮停用，RMP，EMB，PZA，FQ ±INH 繼續治療至6-9 個月。

結核診治指引第七版-第十二章

- **選項三**

個人化治療方案。病人如果無法耐受INH、RMP、EMB、PZA 中的某些藥物時，宜慎重調整處方，以病人可以耐受的4 種藥組成個人化治療方案。請謹慎使用FQ，務必將因使用FQ 而導致FQ 抗藥性的可能性降到趨近於零。FQ 需經過專家評估方可使用。

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

FQ+ 6 months of daily rifampin, ethambutol, and pyrazinamide improves treatment success rates

In patients in whom toxicity from pyrazinamide is anticipated or experienced, or in patients with active TB with lower burden of disease (i.e., noncavitary), may consider shortening the duration of pyrazinamide when FQ is included in the regimen

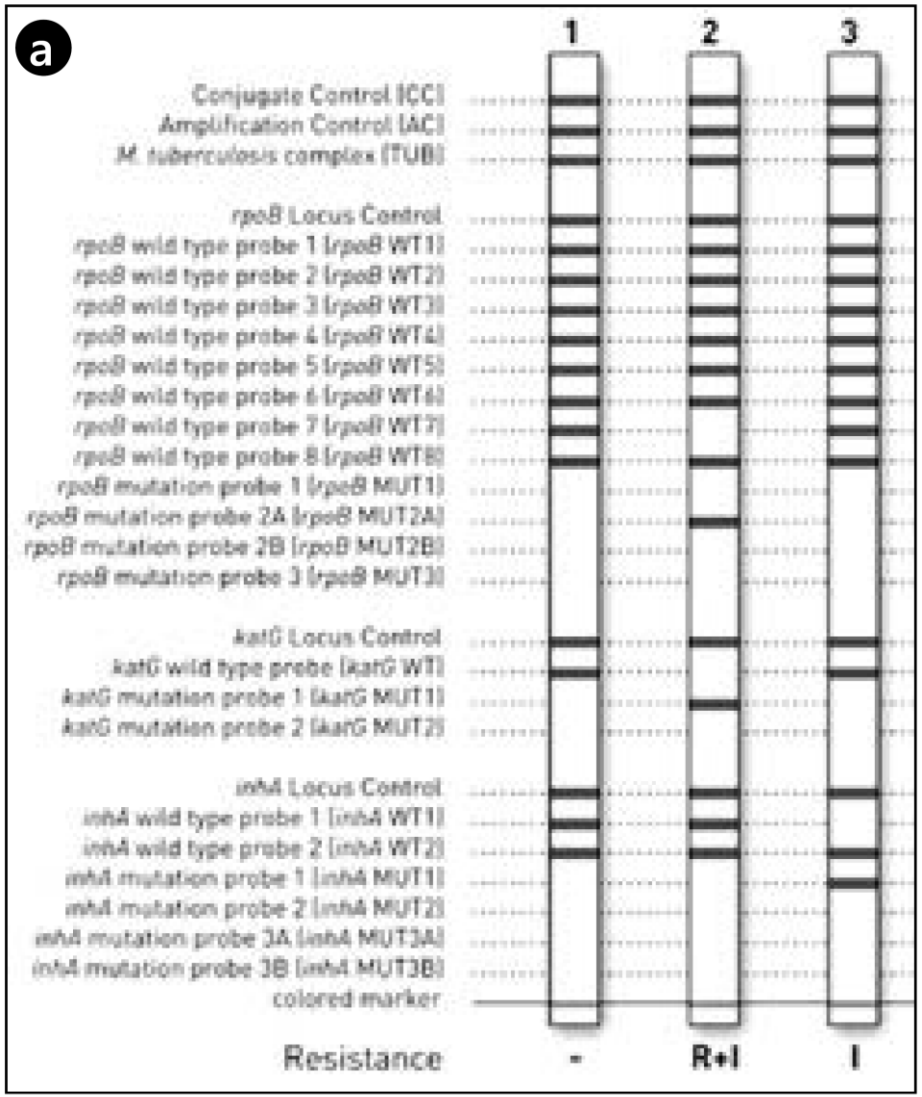
Nahid P et al. Am J Respir Crit Care Med 2019

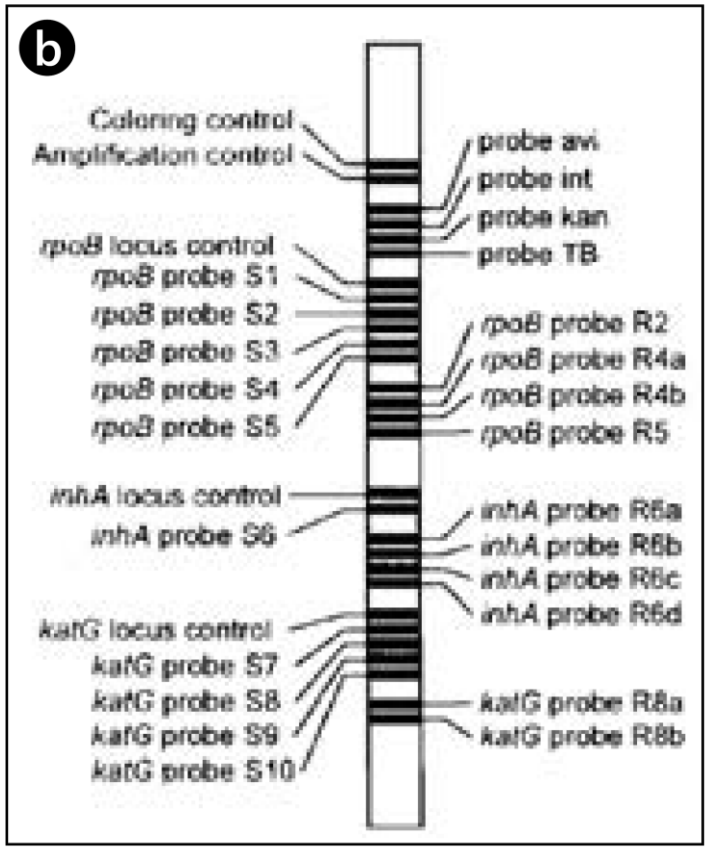
Comparison Between Different Guidelines

	臺灣結核診治指引	WHO	ATS/IDSA/CDC/ERS
一般建議	RMP，EMB，PZA，±INH for 6 months	RMP，EMB，PZA+ Levofloxacin for 6 months	RMP，EMB，PZA，Levofloxacin for 6 months
特別考量點	保護Fluoroquinolone，不建議單獨加上FQ，若要使用FQ，則要加針劑Amikacin/Kanamycin保護	個人資料統合分析顯示加上Levofloxacin對預後有幫助。	可在特定情形下縮短PZA使用的時間。

Fig. 3.1. Examples of different line probe assay strip readouts: (a) Hain GenoType MTBDRplus version 1 and version 2 (Hain Lifescience, Nehren, Germany) and (b) Nipro NTM+MDRTB Detection Kit 2 (Nipro, Tokyo, Japan)

Linear Probe Assays for Isoniazid Resistance Detection





Source: Courtesy of the Foundation for Innovative New Diagnostics (FIND).

WHO consolidated guidelines on tuberculosis Module 3 2020

3.1 Recommendation

3.1 For persons with a sputum smear-positive specimen or a cultured isolate of MTBC, commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid. *(Conditional recommendation, moderate certainty in the evidence for the test's accuracy)*

LPAs are not recommended for the direct testing of sputum smear-negative specimens.

TABLE 4 Diagnostic accuracy of line probe assays for all three assays for *Mycobacterium tuberculosis* (MTB) detection

Reference standard	Test	Direct or indirect	Smear status	Datasets (samples) n	Sensitivity (95% CI)	Specificity (95% CI)
Culture reference	MTB	Direct	All	6 (3451)	85.0% (70.0–93.3)	98.0% (96.2–99.0)
	MTB	Direct	Positive	5 (802)¶	94.4% (89.4–99.4)	#
	MTB	Direct	Negative	5 (961)	44.4% (29.2–71.7)	98.9% (95.4–99.7)
Culture reference	MTB	Direct: fresh	Both	4	83.0% (61.9–93.6)	98.8% (97.2–99.5)
Culture reference	MTB	Direct: frozen	Both	2+	#	#

WHO consolidated guidelines on tuberculosis Module 3 2020

Nathavitharana R et al. Eur Respir J 2017

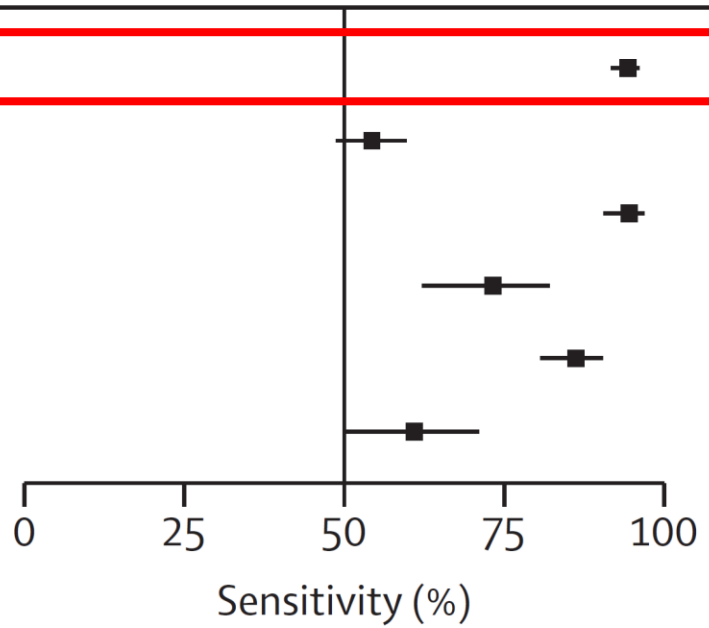
Xpert MTB/XDR

- Individuals presenting with pulmonary tuberculosis symptoms and at least one risk factor for drug resistance in four sites in India, Moldova, and South Africa between 2019 and 2020

- Xpert MTB/XDR assay was used as a reflex test to detect resistance to isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, and capreomycin in adults with positive results for Mycobacterium tuberculosis complex on Xpert MTB/RIF or Ultra (Cepheid).

Penn-Nicholson Adam et al. Lancet Infect Dis 2022

	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
INH	565	460	0	28	77	94 (92–96)	100 (94–100)
ETH	541	178	1	150	212	54 (49–60)	100 (97–100)
FQ	532	222	2	13	295	94 (91–97)	99 (97–100)
AMK	511	60	2	22	427	73 (62–82)	100 (98–100)
KAN	515	181	5	29	300	86 (81–90)	98 (96–99)
CAP	513	53	1	34	425	61 (50–71)	100 (98–100)



	Number*	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Isoniazid resistance							
MTBDR*plus*	575	461	0	36	78	93% (90 to 95)	100% (94 to 100)
Xpert MTB/XDR	575	469	0	28	78	94% (92 to 96)	100% (94 to 100)
Difference	575	..	..	..	..	1·6% (0·2 to 3·4)	0 (−4·7 to 4·7)

Penn-Nicholson Adam et al. Lancet Infect Dis 2022

Take Home Message

- Isoniazid mono-resistance is the most prevalent drug-resistant TB
- Isoniazid resistance is associated with worse treatment outcome and higher risk for acquired drug resistance
- Before adding levofloxacin to regimen, always exclude additional drug resistance (particularly levofloxacin/rifampicin)
- Novel rapid molecular testing may provide more timely diagnosis of isoniazid resistance

Thanks for Your Attention!