México Libre de Tuberculosis®

CENAPRECE
Centro Nacional de Programas Preventivos y Control de Enfermedades
SECRETARÍA DE SALUD

80 años de servicio
INER

TRATAMIENTO DE MONO Y POLIRESISTENCIAS

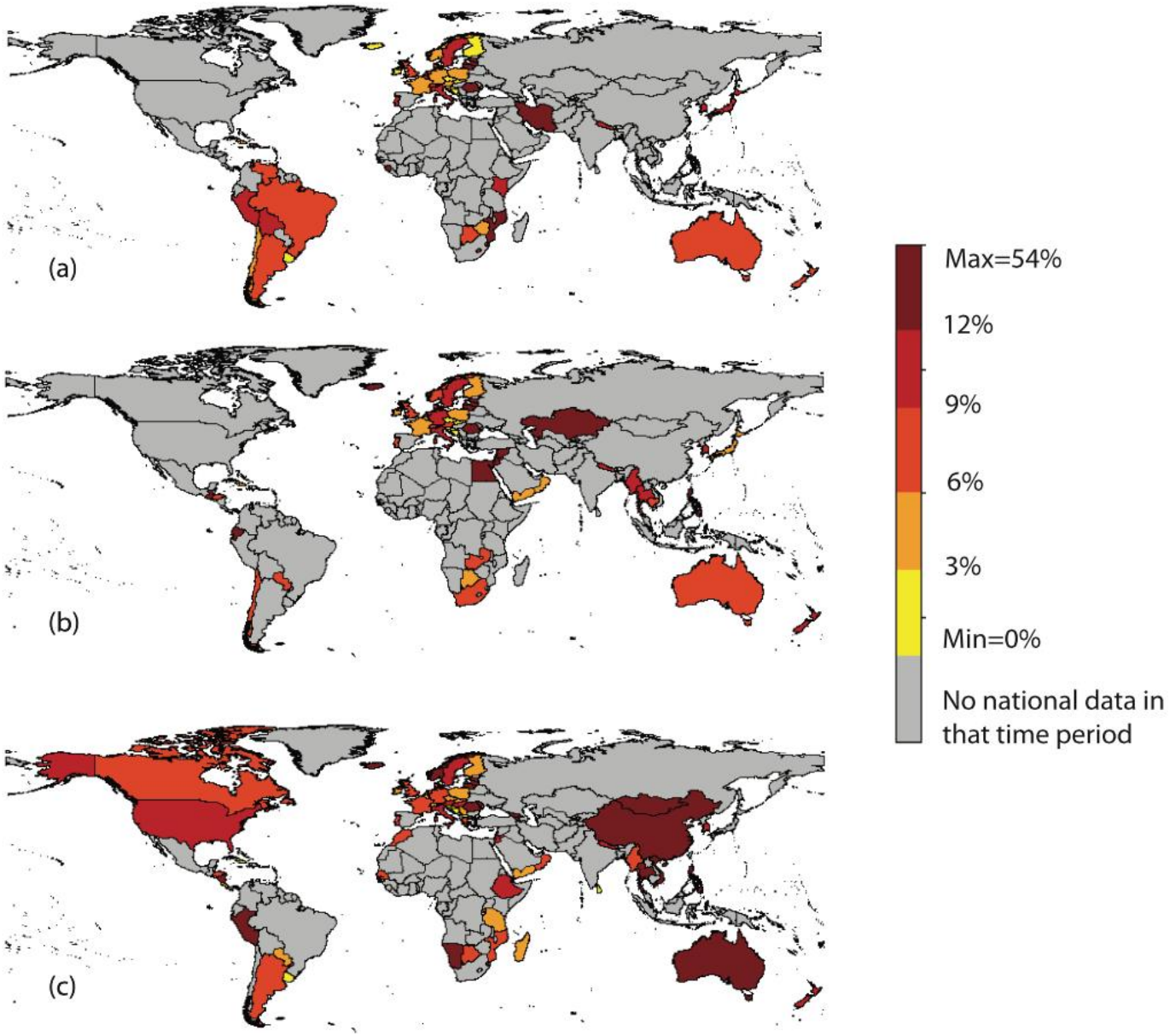
Dra. Marcela Muñoz

Porcentaje de casos incidentes de TB con resistencia a H

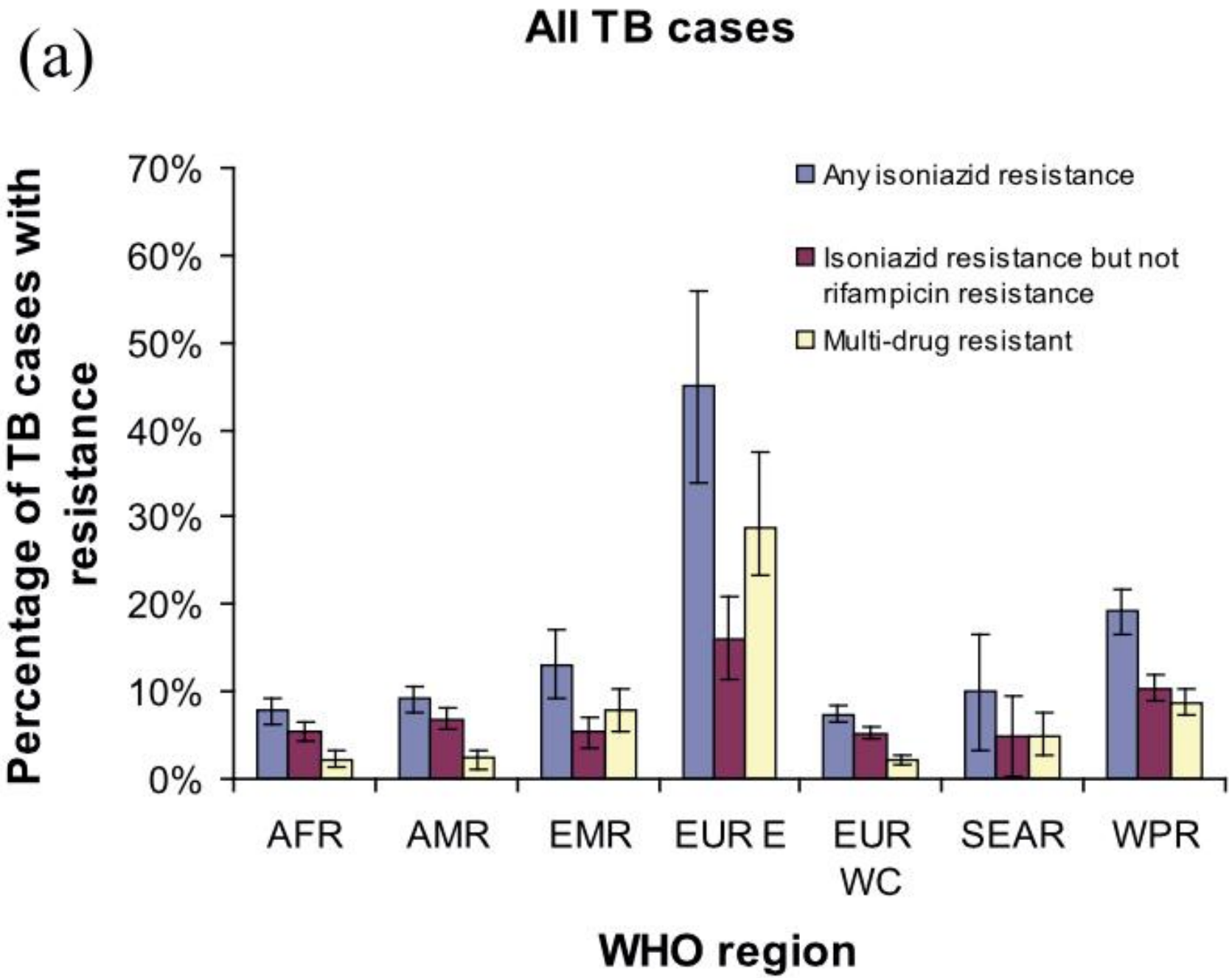
1994 - 1999

2000-2004

2005-2009



(a)


All TB cases
Percentage of TB cases with resistance
70%
60%
50%
40%
30%
20%
10%
0%
Any isoniazid resistance
Isoniazid resistance but not rifampicin resistance
Multi-drug resistant
AFR
AMR
EMR
EUR E
EUR WC
SEAR
WPR
WHO region

Encuesta nacional de TB (ENTB)

- 2,121 muestras
- 9 Estados:
  - Baja California
  - Chihuahua
  - Estado de México
  - Guanajuato
  - Morelos
  - Querétaro
  - San Luis Potosí
  - Sinaloa
  - Yucatán

- 1721 → Pansensibles
- 260 → Monoresistentes
- 96 → Poliresistentes
- 45 → MFR

Int J Tuberc Lung Dis. 2013 Apr;17(4):514-9.

Table 2 Prevalence of patterns of resistance to first-line anti-tuberculosis drugs, ENTB, México, 2008*

	Total % (95%CI)	Previous history of treatment % (95%CI)	No previous history of treatment % (95%CI)
Monoresistance	11.6 (9.6–13.8)	16.8 (8.3–31.2)	11.2 (9.1–13.7)
H	3.7 (2.6–5.1)	6.2 (2.6–14.0)	3.5 (2.4–5.1)
R	0.6 (0.2–1.6)	4.4 (1.3–14.5)	0.1 (2.4–5.1)
E	0.0 (0.0–0.1)	—	0.0 (0.0–0.2)
S	3.9 (2.7–5.7)	3.6 (1.5–8.8)	4.0 (2.8–5.6)
Z	3.4 (2.3–4.8)	2.5 (0.4–14.0)	3.6 (2.4–5.3)
MDR-TB	2.8 (1.9–4.0)	7.2 (3.2–15.3)	2.3 (1.4–3.9)
H+R	0.6 (0.2–1.4)	1.4 (0.5–4.3)	0.5 (0.2–1.6)
H+R+E	0.4 (0.1–1.6)	2.9 (0.5–14.1)	0.1 (0.0–0.5)
H+R+S	0.6 (0.3–1.5)	0.7 (0.2–2.8)	0.7 (0.3–1.9)
H+R+Z	0.2 (0.1–0.4)	0.8 (0.2–2.8)	0.1 (0.0–0.5)
H+R+E+S	0.3 (0.1–0.2)	—	0.4 (0.1–1.5)
H+R+E+Z	0.1 (0.0–0.3)	0.5 (0.1–2.6)	—
H+R+S+Z	0.4 (0.1–1.5)	0.4 (0.1–3.1)	0.4 (0.1–2.2)
H+R+E+S+Z	0.1 (0.0–0.4)	0.4 (0.1–1.7)	0.1 (0.0–0.6)
Polyresistance	3.5 (2.5–4.8)	3.0 (1.5–5.9)	3.3 (2.2–4.8)
H+E	0.0 (0.0–0.2)	—	0.0 (0.0–0.2)
H+S	2.2 (1.4–3.3)	2.0 (0.8–4.8)	1.9 (1.2–3.1)
H+Z	0.7 (0.4–1.4)	0.2 (0.0–1.5)	0.8 (0.4–1.6)
H+E+S	0.1 (0.0–0.3)	0.2 (0.0–1.2)	0.1 (0.0–0.3)
H+E+Z	—	—	—
H+S+Z	0.1 (0.0–0.4)	0.3 (0.0–2.0)	0.1 (0.0–0.5)
R+E	—	—	—
R+S	—	—	—
R+Z	0.0 (0.0–0.1)	0.1 (0.0–1.1)	—
R+E+S	—	—	—
R+E+Z	—	—	—
R+S+Z	0.0 (0.0–0.2)	—	0.0 (0.0–0.2)
R+E+S+Z	0.0 (0.0–0.1)	—	0.0 (0.0–0.1)
E+S	—	—	—
S+Z	0.3 (0.1–0.6)	0.2 (0.0–1.3)	0.3 (0.1–0.7)
Susceptible	82.2 (79.4–84.7)	73.0 (56.8–84.7)	83.2 (80.1–85.9)

Int J Tuberc Lung Dis. 2013 Apr;17(4):514-9.

Clinical Characteristics and Treatment Outcomes of Patients with Isoniazid-Monoresistant Tuberculosis

- Estudio retrospectivo, pareado por tiempo
- Departamento de Salud Pública de San Francisco
- Octubre/1992 a Octubre 2005

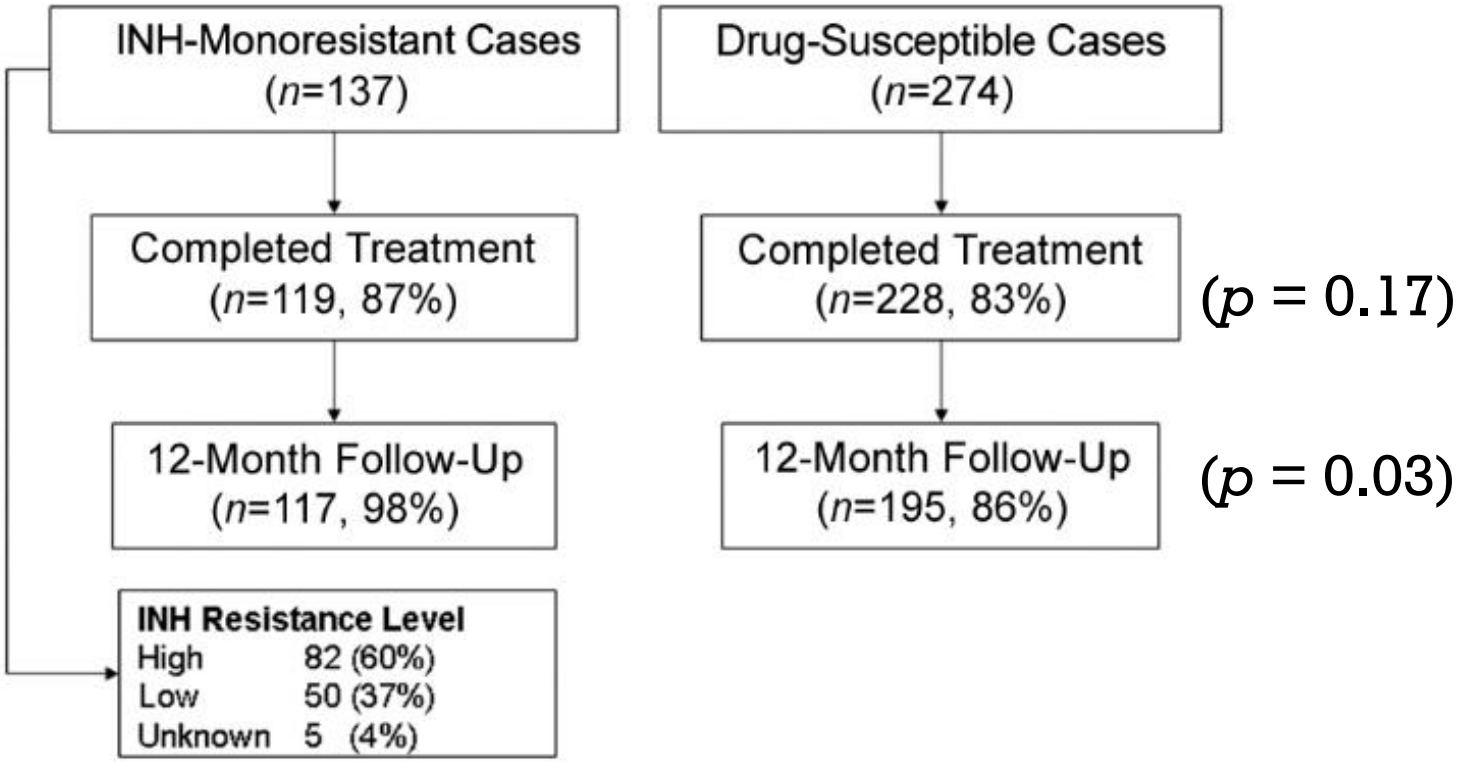


Table 1. Demographic and clinical characteristics of patients.

Characteristic	Patients with INH-resistant tuberculosis ($n = 137$)	Patients with drug-susceptible tuberculosis ($n = 274$)	P
Male	63	70	.12
Age, median years	47	50	.09
Ethnicity			
Non-Hispanic white	8	11	.30
Non-Hispanic black	4	13	.01
Hispanic	9	14	.17
Asian/Pacific Islander	77	60	<.001
Native American	0.7	1.5	.52
Foreign born	85	72	.002
Homeless or SRO resident	8	19	.004
History of drug or alcohol abuse	13	20	.08
HIV infection	7	15	.01
Prior tuberculosis treatment	36	17	<.001
For active tuberculosis	21	9	<.001
For latent tuberculosis	16	8	.01
Pulmonary tuberculosis	88	88	1.00
Positive AFB smear test	47	41	.29
Cavitary chest radiograph	18	14	.26
Tuberculosis diagnosed in hospital	21	29	.10
Directly observed therapy	52	54	.69
Adherent to treatment	84	84	.96
Adverse reaction	31	15	<.001
Sputum culture conversion at ≤2 months	92	91	.70
Treatment duration, median days	306	220	<.001
Treatment at SFDPH Tuberculosis Control Section clinic	82	65	<.001

Table 2. Multivariate analysis of demographic characteristics associated with isoniazid resistance.

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*
Ethnicity			
Non-Hispanic black	0.3 (0.1–0.7)	0.5 (0.2–1.6)	.23
Hispanic	0.6 (0.3–1.2)	1.0 (0.3–3.1)	.96
Asian/Pacific Islander	2.3 (1.4–3.7)	1.6 (0.5–4.6)	.40
Foreign born	2.3 (1.3–2.9)	1.0 (0.4–2.4)	.92
Homeless or SRO resident	0.4 (0.2–0.7)	0.6 (0.2–1.5)	.27
Drug or alcohol abuse	0.6 (0.3–1.1)	1.3 (0.6–3.0)	.48
HIV infection	0.4 (0.2–0.8)	0.5 (0.2–1.2)	.11
Prior tuberculosis treatment			
For active tuberculosis	2.8 (1.6–5.0)	2.7 (1.4–5.0)	.002
For latent tuberculosis	2.2 (1.2–4.1)	3.1 (1.5–6.4)	.003

Risk Factors for Acquired Rifamycin and Isoniazid Resistance: A Systematic Review and Meta-Analysis

- 15 estudios: Casos y controles, cohortes, ensayos clínicos aleatorizados
- Pacientes que hayan recibido al menos un esquema con R
- Desenlace ➔ Resistencia Adquirida (ADR)
  Desenlace Negativo
- Factores de riesgo evaluados:
  - Carga de la enfermedad, factores del patógeno
  - Factores inmunológicos del huésped
  - Factores sociodemográficos
  - Factores programáticos

PLOS ONE, September 25, 2015

La mono – poliresistencia es el camino a la multidrogoresistencia

Guías de Tratamiento

Regímenes de Tratamiento

Perfil de Resistencia	Tx sugerido	Duración
H (±S)	R,Z,E (±Fq)	6-9 m
H, E (±S)	R, Z y Fq	9-12 m
H,E,Z (±S)	R, Fq, Inyectable (2-3m) Pto/Eto (±Z)	18 m
R mono o poli-resistencia	Tx para TB MDR + H	20 m

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014

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

- Se incluyeron 56 publicaciones:

Estudio		Tipo de Tx		Tipo de pacientes
• 6 Cohortes	→	Re-Tx primario	→	Previamente tratados con cultivo y PFS
• 9 ECC	→	Variable	→	Previamente tratados con monoresistencia a H
• 24 ECC	→	Variable	→	Caso nuevo con monoresistencia a H

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%)	—	—

Table 2. Regimens and results in randomized trials in previously treated patients with INH mono-resistance.

ID	Reference	Regimen[a]	Total Number Treated	At Risk for Failure (*N*)[b]	Number (%) who Failed	At Risk for Relapse (*N*)[c]	Number (%) who Relapsed	At Risk for Acquired Drug Resistance (*N*)[b]	Number (%) with Acquired Drug Resistance
14	[27]	2SZRE/4RE	101	91	0	72	3 (4%)	91	0
		2SZRE/7RE	97	88	1 (1%)	72	2 (3%)	88	0
23	[28]	2[HRZE]$_3$/4[HR]$_2$	171	167	32 (19%)	135	14 (10%)	167	23 (14%)
50	[29]	2HRZE/6EH	101	94	16 (17%)	73	6 (8%)	94	3 (3%)
		2[HRZE]$_2$/4[HRE]$_2$	63	59	12 (20%)	44	11 (25%)	59	7 (12%)
		2[HRZ]$_2$/4[HR]$_2$	79	74	46 (62%)	27	4 (15%)	74	13 (18%)
302	[34]	**Subgroup with isoniazid mono-resistance**							
		12RE *(RIF 450)*	83	73	20 (27%)	19	5 (26%)	73	19 (26%)
		12[RE]$_3$ *(RIF 450)*	91	75	22 (29%)	22	6 (27%)	75	21 (28%)
		3[REZ]$_3$/9[RE]$_3$ *(RIF 450)*	89	77	18 (23%)	30	6 (20%)	77	17 (22%)
		3[RE]$_3$/9[RE]$_3$ *(RIF 450)*	94	75	10 (13%)	35	12 (34%)	75	10 (13%)
302	[34]	**Subgroup with isoniazid and ethambutol resistance**							
		12RE *(RIF 450)*	25	15	10 (67%)	5	1 (20%)	—	—
		12[RE]$_3$ *(RIF 450)*	22	12	8 (67%)	4	1 (25%)	—	—
		3[REZ]$_3$/9[RE]$_3$ *(RIF 450)*	20	12	5 (42%)	7	0	—	—
		3[REPt]$_3$/9[RE]$_3$ *(RIF 450)*	16	6	2 (33%)	4	1 (25%)	—	—
326	[31]	12ER *(RIF 450)*	112	106	11 (10%)	—	—	106	9 (8%)
		12[ER]$_2$ *(RIF 450)*	93	87	16 (18%)	—	—	87	15 (17%)
328	[32]	2HRZ/4HR	9	9	3 (33%)	6	1 (17%)	6	0
		2HRZ/4(HR)$_2$	4	4	1 (25%)	3	0	3	0
357	[33]	6HRZ	9	9	0	—	—	—	—
		6HRE	10	10	5 (50%)	—	—	—	—
		6HRZ	15	9	0	—	—	—	—
		6HRE	15	10	5 (50%)	—	—	—	—
400	[30,35,36,38]	3RE/9[RE]$_2$	43	40	2 (5%)	38	2 (5%)	—	—
		3RE/9[RE]$_2$ *(RIF 1200)*	42	39	2 (5%)	37	0	—	—
		3RE/15[RE]$_2$ *(RIF 1200)*	43	40	1 (3%)	40	2 (5%)	—	—
		3RE/21[RE]$_2$ *(RIF 1200)*	42	39	1 (3%)	38	0	—	—
416	[37]	1.5RE/10.5[RE]$_3$	34	30	2 (7%)	23	0	—	—
		12[RE]$_3$	38	33	4 (12%)	25	0	—	—

Table 3. Stratified analysis of covariates associated with TB treatment outcomes in RCT of patients with INH resistance in new or previously treated cases: Failure in isoniazid mono-resistance.

Factor	Arms (*N*)	Events/Patients (*N*)	Pooled Event Rate	95% CI	I^2 (95% CI)
Rifampin use					
Rifampin 1–2 mo	19	30/256	6.2	0–12.8	0 (0–0.48)
Rifampin 3–5 mo	10	2/88	0.9	0–2.9	0 (0–0.60)
Rifampin 6–7 mo	46	108/645	4.8	0.8–8.8	0.76 (0.69–0.82)
Rifampin 8+ mo	19	136/858	7.4	0–15.1	0.87 (0.82–0.91)
Frequency of therapy in the initial intensive phase[a]					
Daily	65	99/1,062	5.1	2.2–8.0	0.50 (0.33–0.62)
Thrice weekly	25	102/559	5.2	0–10.5	0.44 (0.10–0.65)
Twice weekly	4	75/226	25.5	0–52.8	0.93 (0.86–0.97)
Duration of PZA					
No PZA	28	123/769	**11.4**	**4.0–18.8**	0.74 (0.63, 0.82)
1–3 mo	39	147/871	6.6	2.3–10.9	0.83 (0.77–0.87)
4 mo or more	27	6/207	1.7	0–3.6	0 (0–0.42)
Duration of streptomycin					
No streptomycin	43	258/1,294	**13.6**	**7.8–19.3**	0.80 (0.73–0.85)
1–3 mo	28	13/383	2.8	0.6–5.0	0 (0–0.41)
4 mo or more	23	5/170	2.1	0–4.5	0 (0–0.46)
Number of drugs to which strains susceptible (effective drugs)					
Initial phase[b]					
1 drugs	3	22/39	**50.8**	**6.1–9.6**	0.52 (0–0.86)
2 drugs	31	99/628	11.3	0.3–19	0.58 (0.37–0.72)
3 drugs	55	148/932	3.8	0.9–6.7	0.58 (0.43–0.69)
4 or more drugs	3	1/185	0.4	0–1.5	0 (0–0.73)
Continuation phase					
0–1 drugs	44	153/688	**9.1**	**3.0–15.2**	0.71 (0.61–0.79)
2 drugs	35	116/998	**6.0**	**1.6–10.5**	0.72 (0.61–0.80)
3 or more drugs	11	1/92	0.5	0–1.6	0 (0–0.58)
Supervision of therapy					
All doses fully supervised	69	148/1,341	3.8	1.2–6.3	0.59 (0.46–0.68)
None/partial supervision	25	128/506	13.8	4.7–22.8	0.80 (0.71–0.86)
Completion of treatment					
≥90%	55	187/1,353	6.0	2.0–9.9	0.78 (0.71–0.83)
<90%	39	89/494	6.5	0.7–12.4	0.50 (0.28–0.66)

Table 4. Stratified analysis of covariates associated with TB treatment outcomes in RCT of patients with INH resistance in new or previously treated cases: Relapse in isoniazid mono-resistance.

Factor	Arms (*N*)	Events/Patients (*N*)	Pooled Event Rate	(95% CI)	I^2 (95% CI)
Rifampin use					
Rifampin 1–2 mo	18	43/196	**23.8**	**11.6–36.0**	**0.44 (0.02–0.68)**
Rifampin 3–5 mo	10	10/83	9.2	0.9–17.5	0 (0–0.60)
Rifampin 6–7 mo	43	46/479	7.1	3.4–10.9	0 (0–0.35)
Rifampin 8+ mo	17	38/409	4.6	0.6–8.6	0.58 (0.29–0.76)
Frequency of therapy in the initial intensive phase[a]					
Daily throughout	60	76/738	9.3	5.2–13.5	0.25 (0–0.47)
Thrice weekly throughout	25	46/353	7.3	1.5–13.1	0.07 (0–0.39)
Twice weekly throughout	3	15/76	13.4	0–33.3	0 (0–0.73)
Duration of PZA					
No PZA	25	45/365	10.9	3.6–18.2	0.53 (0.26–0.70)
1–3 mo	38	78/641	10.1	5.1–15.2	0.28 (0–0.53)
4 mo or more	25	14/161	6.4	1.4–11.3	0 (0–0.43)
Duration of streptomycin					
No streptomycin	38	77/705	7.5	3.3–11.7	0.41 (0.13–0.60)
1–3 mo	28	46/328	13.2	6.4–20.0	0.43 (0.11–0.64)
4 mo or more	22	14/134	6.9	1.1–12.8	0 (0–0.45)
Number of drugs to which strains susceptible (effective drugs)					
Initial phase[b]					
1 drugs	3	3/17	15.3	0–40.8	0 (0–0.73)
2 drugs	26	24/278	7.7	1.2–14.1	0.11 (0–0.44)
3 drugs	54	105/675	12.2	6.2–18.2	0 (0–0.32)
4 or more drugs	3	5/149	2.6	0–7.9	0 (0–0.73)
Continuation phase					
0–1 drugs	43	71/514	9.3	4.0–14.5	0 (0–0.35)
2 drugs	30	55/516	11.1	4.2–17.9	0.52 (0.28–0.69)
3 or more drugs	11	10/83	8.0	0–16.7	0 (0–0.58)
Supervision of therapy					
All doses fully supervised	66	107/861	12.3	7.7–16.8	0.36 (0.14–0.53)
None or partial supervision	22	30/306	5.8	1.6–10.0	0 (0–0.46)
Completion of treatment					
≥90%	51	97/886	11.1	6.5–15.7	0.40 (0.16–0.57)
<90%	37	40/281	8.2	3.1–13.3	0 (0–0.37)

Table 6. Adjusted incidence rate ratios of failure, relapse, and acquired drug resistance in INH resistant strains.

Factor	Failure	Relapse	Acquired Drug Resistance[a]
Duration of rifampin therapy			
1–2 mo	**4.1 (1.2–13.4)**	**3.8 (1.6–9.0)**	0.7 (0.4–1.3)
3–4 mo	0.8 (0.2–5.0)	1.9 (0.7–5.2)	1.0 (0.3–3.0)
5–7 mo	1.0 (reference)	1.0 (reference)	1.0 (reference)
≥8 mo	1.6 (0.8–2.8)	1.0 (0.5–2.0)	2.1 (0.9–4.9)
Overall significance (*p*-value)[b]	(0.004)	(0.02)	(0.20)
Number of drugs in regimen to which strains sensitive			
Initial intensive phase			
0 or 1 drug	**6.9 (1.4–33)**	**5.9 (1.0–33)**	No obs.
2 drugs	2.7 (0.7–10.0)	1.9 (0.6–6.7)	**18 (1.4–99)**
3 drugs	1.6 (0.4–6.0)	3.1 (0.9–9.9)	9.6 (0.8–99)
4 or more drugs	1.0 (reference)	1.0 (reference)	1.0 (reference)
Overall significance (*p*-value)[b]	(0.06)	(0.12)	(0.25)
Continuation phase			
0 or 1 drug	2.5 (0.7–9.0)	1.0 (0.5–2.3)	1.8 (0.5–6.5)
2 drugs	2.2 (0.6–8.5)	1.2 (0.7–2.5)	1.2 (0.3–5.0)
3 or more drugs	1.0 (reference)	1.0 (reference)	1.0 (reference)
Overall significance (*p*-value)[b]	(0.36)	(0.80)	(0.25)
Frequency of therapy			
Initial daily	1.0 (reference)	1.0 (reference)	1.0 (reference)
Thrice weekly throughout	**3.6 (1.6–7.7)**	2.1 (1.0–4.9)	2.1 (0.9–4.5)
Twice weekly throughout	**3.3 (1.8–6.2)**	**5.8 (1.8–18. 2)**	**1.6 (1.1–2.3)**
Overall significance (*p*-value)[b]	(0.0003)	(0.01)	(0.14)
Streptomycin			
Not used	1.0 (reference)	1.0 (reference)	1.0 (reference)
Used (2 wk or more)	**0.4 (0.2–0.9)**	1.1 (0.5–2.2)	**0.5 (0.2–1.0)**
Overall significance (*p*-value)[b]	(0.007)	(0.80)	(0.003)
Pyrazinamide			
Not used	1.0 (reference)	1.0 (reference)	1.0 (reference)
Used (2 wk or more)	1.2 (0.6–2.0)	**0.5 (0.2–1.0)**	1.5 (0.9–2.3)
Overall significance (*p*-value)[b]	(0.52)	(0.05)	(0.15)

En conclusión.....

- Se requieren esquemas de Tx que:
  - Incluyan Rifampicina
  - Incluyan mas de 2 drogas efectivas
  - No dar tratamientos intermitentes
  - En uso de Z y S podría relacionarse con un mejor desenlace

Actualización al 2016

- 19 cohortes
- 33 ECC

} 3,744 pacientes resistencia H
19,012 pacientes con TB PS } 28 países

- Pacientes con Dx realizado por cultivo y PFS
- Objetivo: Evaluar el desenlace al Tx en pacientes con TB resistente a H tratados con
  - Tx primario (2HREZ/4H_3R_3)
  - Re-Tx primario (2SHREZ/1HREZ/5$H_3R_3E_3$)
  - Tx modificado (R, E, Z por 6-9 meses)

Table 1a: Failure

Regimen[1]	DST	Arms	Events/ Subjects (N/N)	Pooled event rate[2] (%, 95% CI)	I^2 (95% CI)
WHO –New pts (Cat 1)	INH Resistant	24	170/1239	11% (6, 17) ****	87% (82, 91)
WHO – New pts (Cat 1)	Sensitive	19	241/9792	2% (1, 3)	81% (72, 88)
WHO – Retreat (Cat 2)	INH Resistant	24	41/505	6% (2, 10) ****	40% (2, 63)
WHO – Retreat (Cat 2)	Sensitive	21	40/2609	1% (0, 2)	50% (19, 70)
6-9 mos RZE	INH Resistant	13	82/911	1% (0, 2) †	61% (28, 79)
6-9 mos RZE	Sensitive	10	13/1098	1% (0, 2)	26% (0, 64)

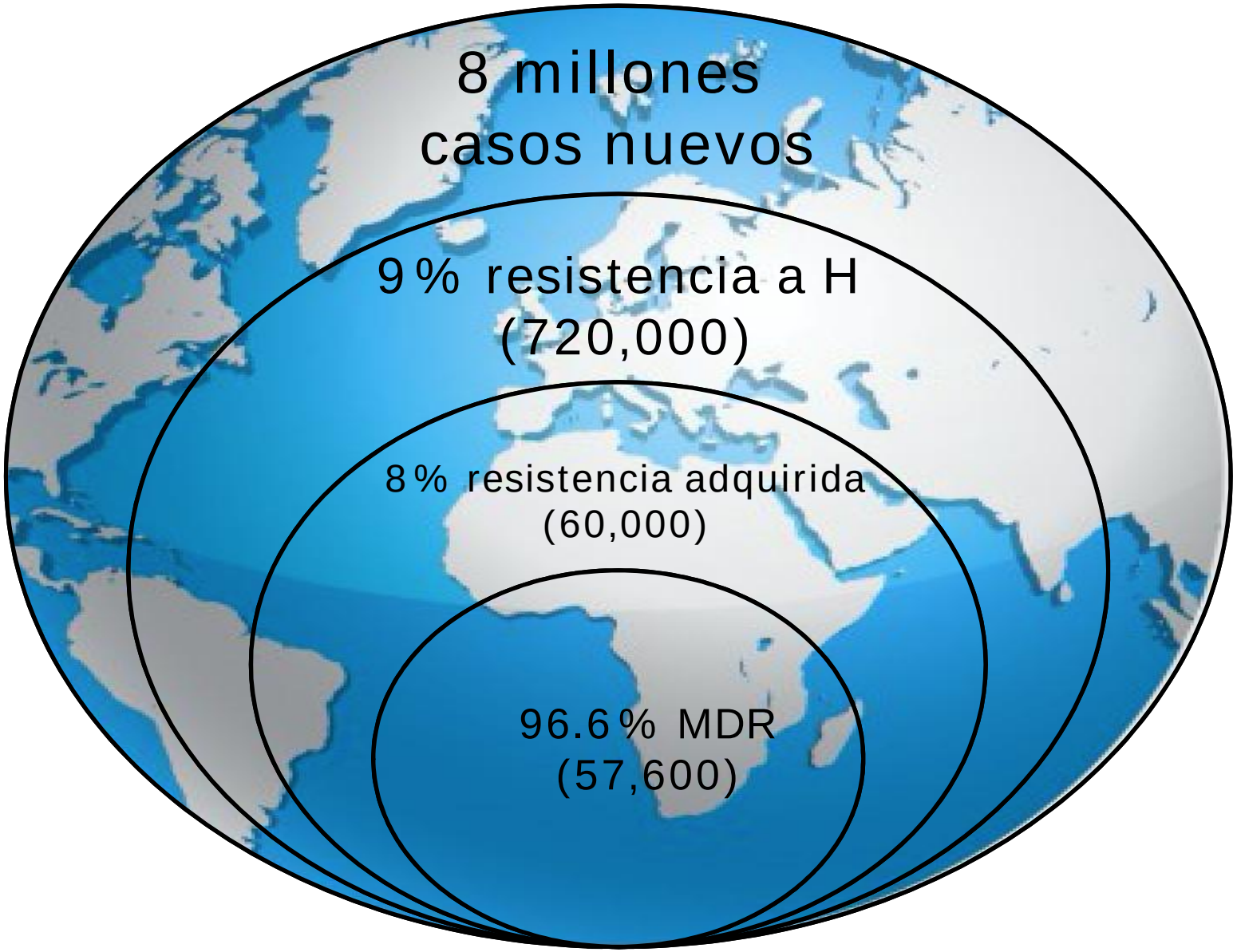
Table 1b Relapse

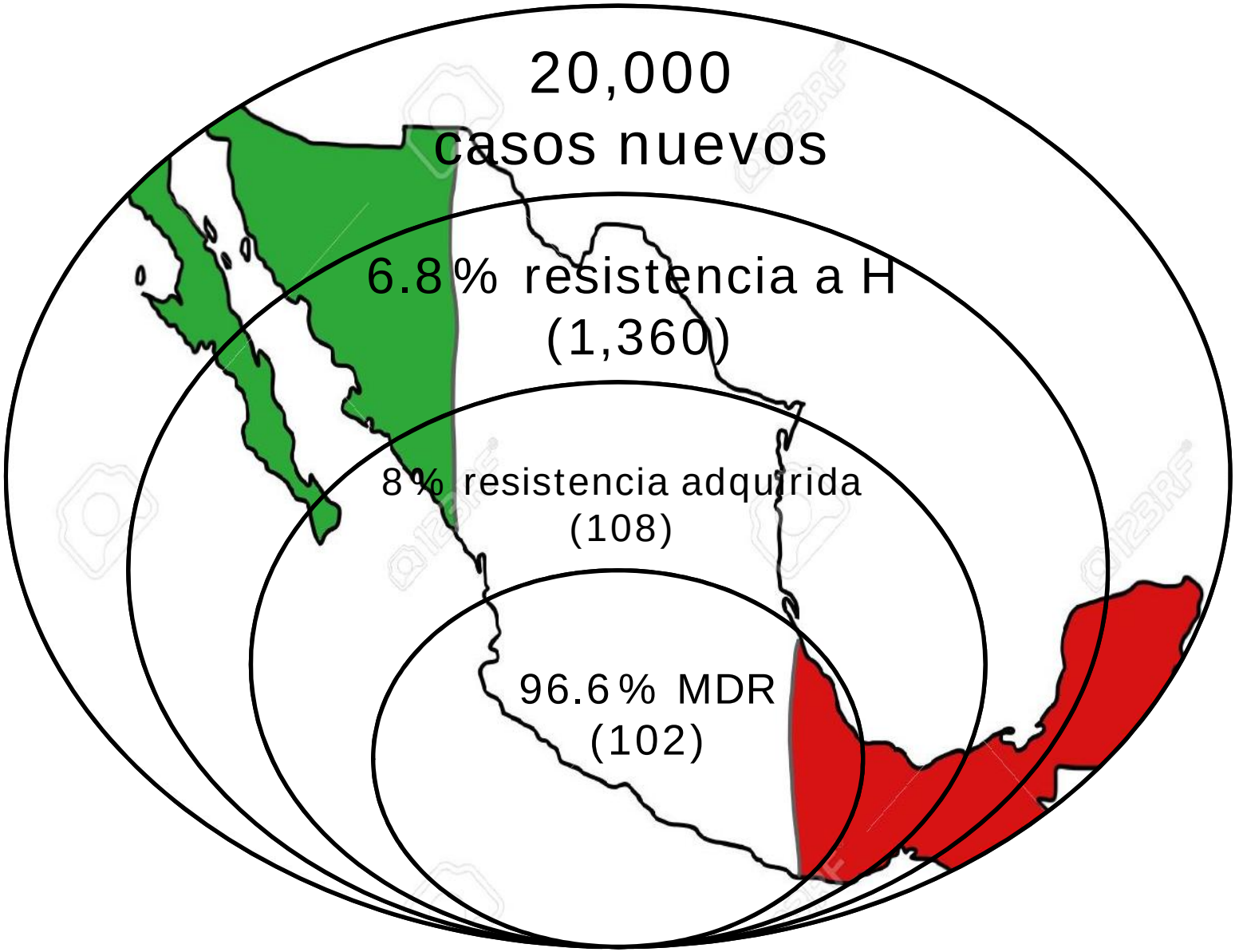
Regimen	DST	Arms	Events/ Subjects (N/N)	Pooled event rate (95% CI)	I^2 (95% CI)
WHO –New pts (Cat 1)	INH Resistant	17	59/482	10% (5, 15)	2% (0, 45)
WHO – New pts (Cat 1)	Sensitive	15	269/4740	5% (2, 7)	79% (69, 86)
WHO – Retreat (Cat 2)	INH Resistant	20	13/277	5% (2, 8) †	0 (0, 44)
WHO – Retreat (Cat 2)	Sensitive	18	115/2205	5% (4, 7)	12% (0, 47)
6-9 mos RZE	INH Resistant	9	11/157	7% (2, 11) †	0 (0, 55)
6-9 mos RZE	Sensitive	10	55/1010	6% (3, 8)	65% (31, 82)

Table 1C: Acquired drug resistance

Regimen	DST	Arms	Events/ Subjects (N/N)	Pooled event rate (95% CI)	I^2 (95% CI)
WHO –New pts (Cat 1)	INH Resistant	18	89/701	8% (3, 13) ****	14% (0, 47)
WHO – New pts (Cat 1)	Sensitive	15	102/5415	1% (0, 2)	72% (56, 82)
WHO – Retreat (Cat 2)	INH Resistant	17	7/284	3% (0, 6) ***	23% (0, 53)
WHO – Retreat (Cat 2)	Sensitive	16	7/2091	0.3% (0, 0.6)	0 (0, 47)
6-9 mos RZE	INH Resistant	9	3/164	0.3% (0, 2) †	0 (0, 55)
6-9 mos RZE	Sensitive	8	11/939	0.1% (0, 0.4)	0 (0, 60)

96.6% con resistencia adquirida a MDR


8 millones
casos nuevos
9% resistencia a H
(720,000)
8% resistencia adquirida
(60,000)
96.6% MDR
(57,600)


20,000
casos nuevos
6.8% resistencia a H
(1,360)
8% resistencia adquirida
(108)
96.6% MDR
(102)

Conclusiones

- El esquema de Tx primario NO es adecuado
- El esquema de Re-Tx primario NO es mejor
- Dx tardío incrementa el riesgo de MDR
- Se requieren mas estudios para tener mejores opciones terapéuticas.

Treatment outcome of patients with isoniazid mono-resistant tuberculosis

- Hospitales del Norte, centro y sur de Taiwán
- Enero 2004 – Octubre 2011
- 8,414 pacientes ➔ 425(5.1%) resistentes a H
- 395 paciente incluidos en el estudio
  - Mediana de edad 64 años
  - 299 (75.7%) Hombres
  - 6 (1.5%) co-infección con VIH
  - 345 (87.3%) casos nuevos

TABLE 1. Characteristics of patients with isoniazid mono-resistant tuberculosis

	All (n = 395)	Treatment success (n = 328)	Unfavourable outcomes (n = 67)	p value
Prior treatment of TB	50 (12.7)	36 (11.0)	14 (20.9)	0.026
Age (years)				<0.001
<44	79 (20.0)	76 (23.2)	3 (4.5)	
45–64	113 (28.6)	95 (29.0)	18 (26.9)	
≥65	203 (51.4)	157 (47.8)	46 (68.6)	
Male	299 (75.7)	240 (73.2)	59 (88.1)	0.010
Smoking history	190 (48.1)	147 (44.8)	43 (64.2)	0.004
Co-morbidity				
Diabetes mellitus	101 (25.6)	82 (25.0)	19 (28.4)	0.566
Cancer	41 (10.4)	25 (7.6)	16 (23.9)	<0.001
Liver cirrhosis	14 (3.5)	8 (2.4)	6 (9.0)	0.019
End-stage renal disease	14 (3.5)	10 (3.0)	4 (6.0)	0.270
Positive AFB smear	201 (50.9)	167 (50.9)	34 (50.7)	0.980
Findings of CXR				
Disease extent				0.114
Mild	237 (60.0)	204 (62.2)	33 (49.3)	
Moderate	118 (29.9)	94 (28.7)	24 (35.8)	
Severe	40 (10.1)	30 (9.1)	10 (14.9)	
Lower lung involvement	100 (25.3)	76 (23.2)	24 (35.8)	0.030
Cavitary lesions	110 (27.8)	90 (27.4)	20 (29.9)	0.688
Cavity size				0.791
<4 cm	77 (19.5)	64 (19.5)	13 (19.4)	
≥4 cm	33 (8.4)	26 (7.9)	7 (10.4)	
Pleural effusion	42 (10.6)	32 (9.8)	10 (14.9)	0.211
High-level isoniazid resistance	174 (45.9)	143 (43.6)	31 (46.3)	0.751
After 2 months treatment				
Smear conversion	334 (84.6)	276 (84.1)	58 (86.6)	0.617
Culture conversion	291 (73.7)	245 (74.7)	46 (68.7)	0.306
Acquired drug resistance	10 (2.5)	5 (1.5)	5 (7.5)	0.015
Drugs throughout the whole treatment course				
Isoniazid	219 (55.4)	182 (55.5)	37 (55.2)	0.968
Rifampicin	349 (88.4)	299 (91.2)	50 (74.6)	<0.001
Ethambutol	298 (75.4)	255 (77.7)	43 (64.2)	0.019
Pyrazinamide	228 (57.7)	185 (56.4)	43 (64.2)	0.240
Fluoroquinolones	105 (26.6)	88 (26.8)	17 (25.4)	0.806
Drugs throughout the initiation phase				
Isoniazid	290 (73.4)	243 (74.1)	47 (70.1)	0.506
Rifampicin	369 (93.4)	314 (95.7)	55 (82.1)	<0.001
Ethambutol	336 (85.1)	286 (87.2)	50 (74.6)	0.009
Pyrazinamide	308 (78.0)	258 (78.7)	50 (74.6)	0.468
Streptomycin	33 (8.4)	28 (8.5)	5 (7.5)	0.772
Fluoroquinolones	111 (28.1)	92 (28.0)	19 (28.4)	0.959
Drugs throughout the continuation phase[a]				
Isoniazid	196 (54.4)	182 (55.5)	14 (43.8)	0.264
Rifampicin	323 (89.7)	299 (91.2)	24 (75.0)	0.010
Ethambutol	276 (76.7)	255 (77.7)	21 (65.6)	0.129
Pyrazinamide	203 (56.4)	185 (56.4)	18 (56.3)	1.000
Fluoroquinolones	102 (28.3)	88 (26.8)	14 (43.8)	0.062

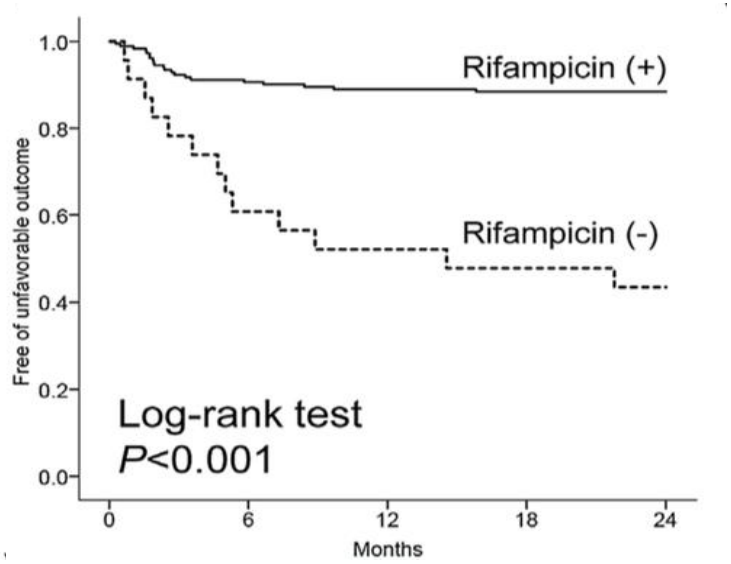
Data are presented as n (%).
AFB, acid-fast bacilli; CXR, chest X-ray; TB, tuberculosis.
[a]Excluding 35 patients who died during the initiation phase, there were 328 and 32 remaining among patients with treatment success and unfavourable outcomes during the continuation phase, respectively.

- Factores asociados a un desenlace negativo (Fracaso, muerte, abandono)
  - Edad (70.7±15.7 vs 59.3±19.2 años, p <0.001)
  - Varones (p 0.010)
  - Tabaquismo (p 0.004)
  - Malignidad asociada (p < 0.001)
  - Enfermedad hepática (p = 0.019)
  - Enfermedad moderada - extensa (p 0.049)
  - Mayor compromiso en lóbulos inferiores (p 0.030)

- Factores asociados a un desenlace positivo (curación, término de Tx)
  - Uso de Rifampicina durante todo el Tx (82.1% versus 95.7%, p <0.001)
  - Etambutol al menos durante la fase intensiva (74.6% versus 87.2%, p 0.009)

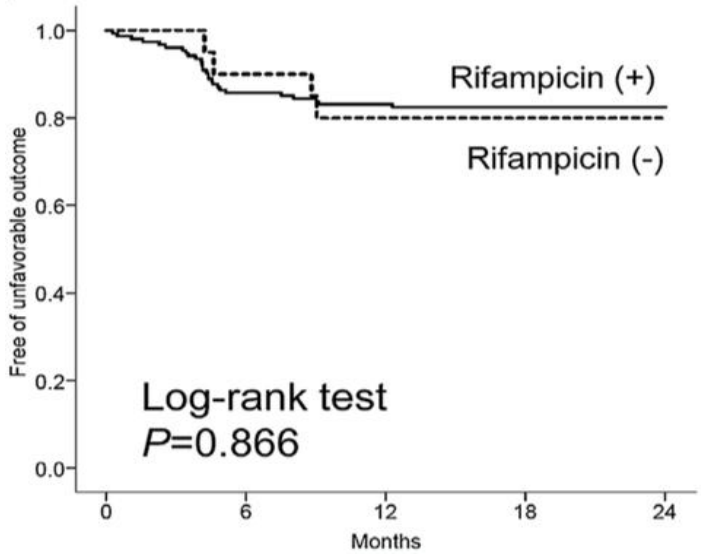
Resistencia a baja concentración H (0.2 µg/mL)

205 (51.9%) pacientes



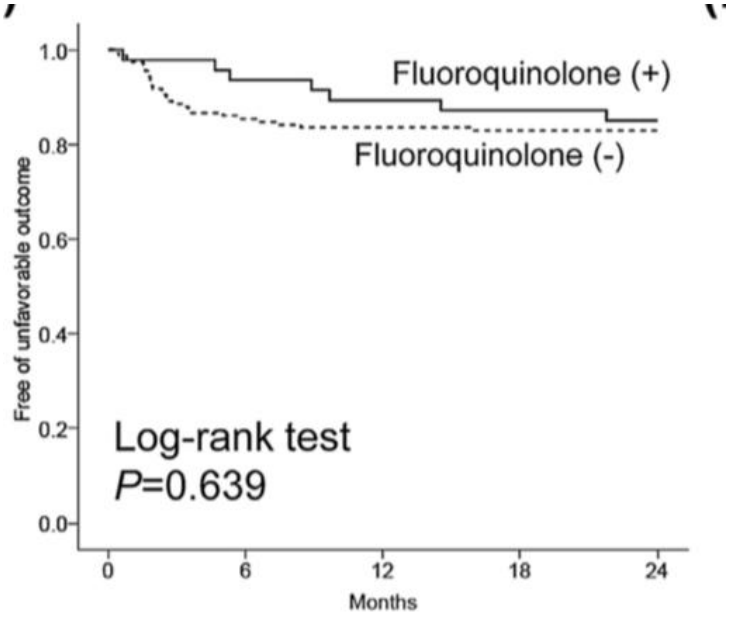
Resistencia a alta concentración H (0.2 µg/mL)

174 (44.1%) pacientes*

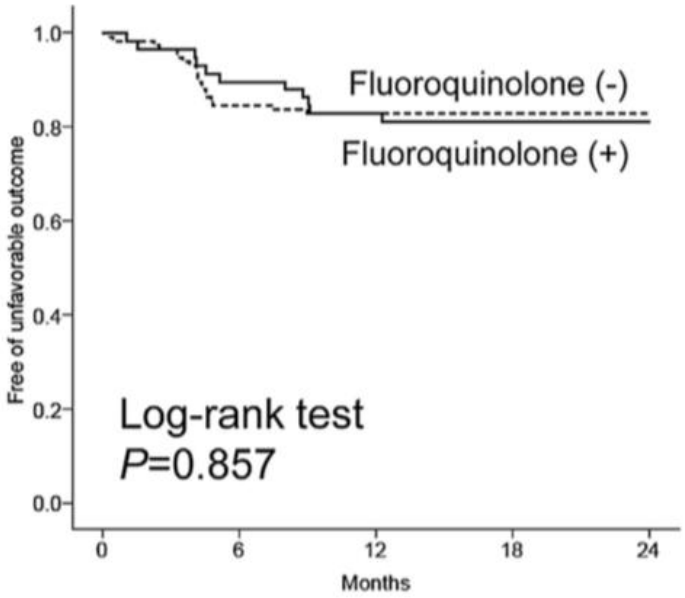


*Resultados faltantes en 16 pacientes

Resistencia a baja concentración H
(0.2 µg/mL)
205 (51.9%) pacientes



Resistencia a alta concentración H
(0.2 µg/mL)
174 (44.1%) pacientes*



23 pacientes NO toleraron la R, se agrego Fq en 15 casos
El uso de una Fq se asocia con una menor probabilidad de un desenlace negativo (6/15, 40.0% vs. 7/8, 87.5%; p 0.003)

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
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
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.

TABLE 4. Detailed clinical information of patients with isoniazid mono-resistant tuberculosis and new acquired drug resistance

Patient	Age (years) /sex	Previous TB Tx	Underlying conditions	Isoniazid resistance level	Initial AFB smear	Sm / Cul result, 2nd month	Disease extent on CXR	Pulmonary cavitary lesions	Regimen, initiation/ continuation phase	Tx duration (months)	Tx outcomes	Acquired resistance	Relapse
1	46/M	no	DM	high	+	− / +	moderate	+	REZS / REZS	>12	failure	E	no
2	65/M	yes	DM, smoking	low	+	− / +	moderate	−	HREZ / HEZ	>12	failure	high-level H	no
3	59/M	no	smoking	high	+	− / −	moderate	+	HRZ / RZQ	>12	failure	HR	no
4	56/M	no	DM, smoking	high	+	+ / +	moderate	+	HRE / REQ	>12	failure	HR	no
6	83/M	no	DM	low	−	+ / +	moderate	+	HREZ	death	death	E	no
5	56/M	no	DM, smoking	low	+	+ / +	moderate	+	HRZS / HRZ	>12	success	S	no
7	26/M	no		high	+	− / −	mild	+	HREZS / HREZ	10–12	success	S	no
8	64/M	yes		low	+	− / +	moderate	+	HREZSQ / REQ	10–12	success	S	no
9	37/M	yes	smoking	high	+	+ / +	mild	+	HRESQ / HREQ	>12	success	S	no
10	74/M	no		high	+	− / −	moderate	+	HRE / HRE	7–9	success	S	no

Abbreviations: AFB, acid-fast bacilli; Cul, culture; CXR, chest x-ray; DM, diabetes mellitus; E, ethambutol; H, isoniazid; M, male; Q, fluoroquinolone; R, rifampicin; S, streptomycin; Sm, smear; TB, tuberculosis; Tx, treatment; Z, pyrazinamide. Patients 3, 7 and 10 were found to acquire new drug resistance at the fifth month, first month and first month of treatment, respectively.

- Resistencia adquirida 10 (2.5%)
  - Mayor en pacientes con desenlace negativo (7.5% versus 1.5%, p 0.019)
  - BK positivos (4.5% versus 0.5%, p 0.020),
  - Enfermedad moderada – severa (5.1% versus 0.8%, p 0.017)
  - Enfermedad cavitaria (8.2% vs. 0.4%, p<0.001)
  - Tx con estreptomicina (15.2% vs. 1.4%, p=0.001).

En conclusión:

- Se requieren:
  - Incluir R durante todo el tiempo de Tx.
  - Considerar el uso de Fq en pacientes que no toleran R.
  - Pacientes con enfermedad cavitaria y/o extensa tienen mayor riesgo de fracaso/recaída

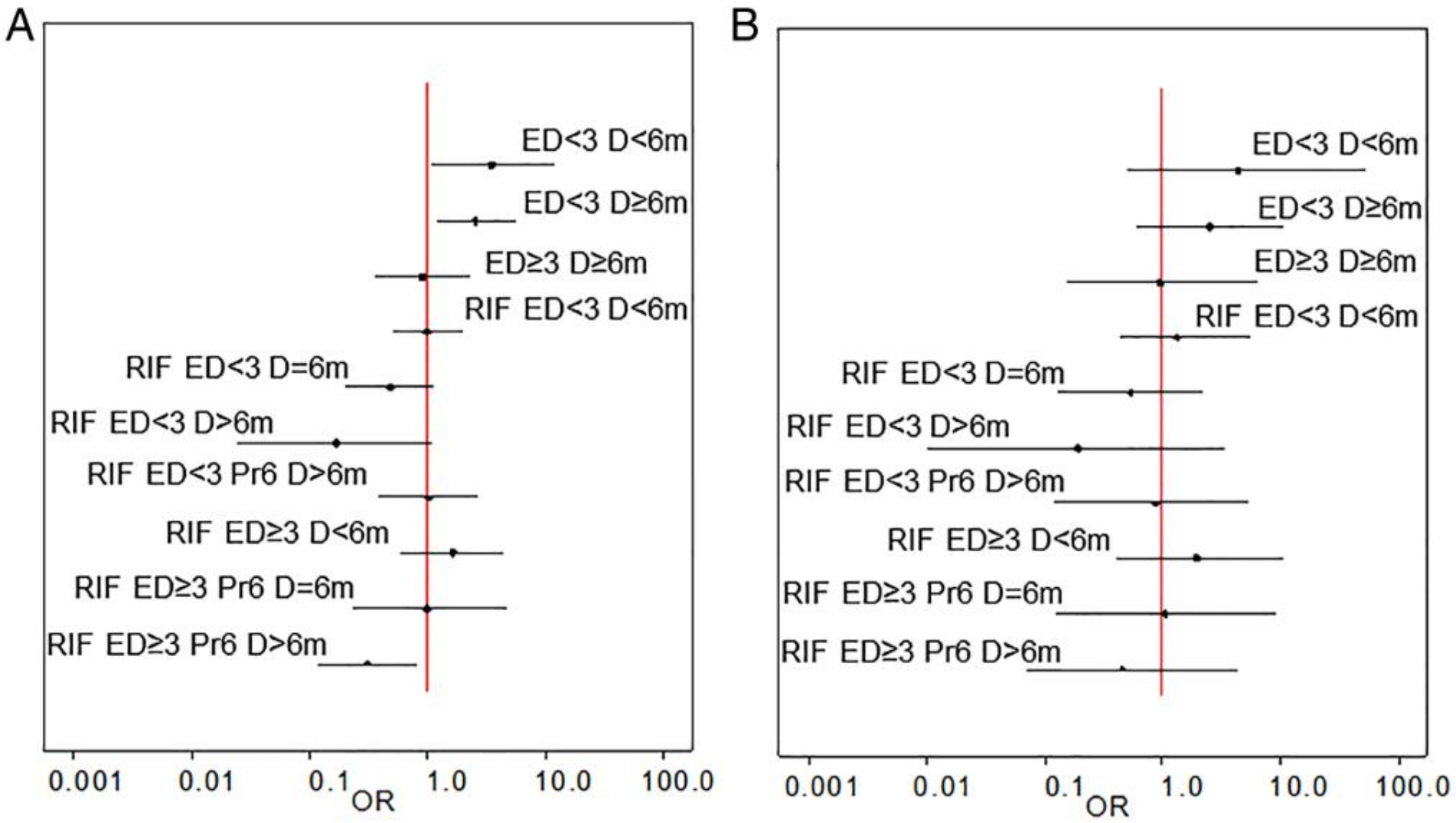
What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis

- ECC registrados al 21 de enero/2015
- ECC con Dx confirmado por cultivo y PFS
- Datos disponibles del desenlace y recaídas de los pacientes con resistencia a H.
- Sin restricción de lenguaje

Table 2 ORs, relative ranks and absolute proportion difference from fixed-effects and random-effects network meta-analyses across all isoniazid resistance profiles

	OR (95% CrI)		Rank (95% CrI)		Proportion difference (95% CrI)	
Treatment	**Fixed effects**	**Random effects**	**Fixed effects**	**Random effects**	**Fixed effects**	**Random effects**
ED<3 D<6m	3.47 (1.08–11.55)	4.38 (0.50–52.41)	11 (8–11)	11 (4–11)	0.26 (0.01–0.52)	0.29 (−0.09–0.74)
ED<3 D≥6m	2.54 (1.19–5.59)	2.50 (0.62–10.36)	10 (8–11)	10 (5–11)	0.18 (0.03–0.34)	0.16 (−0.07–0.43)
ED≥3 D≥6m	0.91 (0.35–2.30)	0.95 (0.15–6.21)	6 (3–9)	6 (2–10)	−0.01 (−0.14–0.14)	−0.01 (−0.20–0.31)
RIF ED<3 D<6m	1.00 (0.52–1.95)	1.32 (0.44–5.52)	6 (4–9)	7 (4–10)	0.00 (−0.11–0.10)	0.04 (−0.13–0.25)
RIF ED<3 D=6m	0.48 (0.20–1.14)	0.53 (0.13–2.20)	3 (2–6)	3 (1–7)	−0.09 (−0.20–0.02)	−0.07 (−0.23–0.09)
RIF ED<3 D>6m	0.17 (0.02–1.07)	0.19 (0.01–3.36)	1 (1–6)	1 (1–9)	−0.15 (−0.26–0.01)	−0.12 (−0.28–0.19)
RIF ED<3 Pr6 D=6m	Baseline	Baseline	6 (3–9)	6 (2–9)	Baseline	Baseline
RIF ED<3 Pr6 D>6m	1.01 (0.39–2.62)	0.85 (0.12–5.25)	6 (3–10)	5 (1–11)	0.00 (−0.13–0.17)	−0.02 (−0.20–0.30)
RIF ED≥3 D<6m	1.60 (0.59–4.35)	1.89 (0.40–10.27)	9 (4–10)	9 (3–11)	0.08 (−0.08–0.28)	0.10 (−0.13–0.43)
RIF ED≥3 Pr6 D=6m	0.98 (0.24–4.57)	1.04 (0.13–9.25)	6 (2–11)	6 (1–11)	0.00 (−−0.16–0.31)	0.01 (−0.19–0.44)
RIF ED≥3 Pr6 D>6m	0.31 (0.12–0.81)	0.45 (0.07–4.32)	2 (1–4)	3 (1–9)	−0.12 (−0.23–0.02)	−0.08 (−0.24–0.23)

Main results from the network depicted in figure 3B. Baseline proportion with a negative outcome 0.19 (95% CrI 0.12–0.29) in the fixed-effects model and 0.16 (95% CrI 0.07–0.31) in the random-effects model.
CrI, credible interval; ED, effective drugs; Pr6, protected at 6 months; RIF, rifampicin.


A
ED<3 D<6m
ED<3 D≥6m
ED≥3 D≥6m
RIF ED<3 D<6m
RIF ED<3 D=6m
RIF ED<3 D>6m
RIF ED<3 Pr6 D>6m
RIF ED≥3 D<6m
RIF ED≥3 Pr6 D=6m
RIF ED≥3 Pr6 D>6m
0.001
0.01
0.1
OR
1.0
10.0
100.0
B
ED<3 D<6m
ED<3 D≥6m
ED≥3 D≥6m
RIF ED<3 D<6m
RIF ED<3 D=6m
RIF ED<3 D>6m
RIF ED<3 Pr6 D>6m
RIF ED≥3 D<6m
RIF ED≥3 Pr6 D=6m
RIF ED≥3 Pr6 D>6m
0.001
0.01
0.1
OR
1.0
10.0
100.0

En conclusión

- Se requieren:
  - Tratamientos prolongados
  - Tratamientos que incluyan R
  - Se requieren mas estudios

Conclusiones

- La monoresistencia a H es muy frecuente en nuestro medio.
- En pacientes con monoresistencia a isoniazida, NO DEBEN pasar a fase de mantenimiento
- NO DEBEN recibir Tx intermitente
- Prolongar Tx en fase intenviso (4 drogas) por al menos 9 -12 m

Conclusiones

- Considerar agregar una Fq en:
  - Pacientes con poli-resistencia (cualquier combinación que no incluya R)
  - En pacientes con enfermedad extensa:
    - Radiológicamente extensa
    - Persisten positivos al segundo mes de Tx.

ANTES DE AGREGAR UNA Fq, SIEMPRE SE DEBE DESCARTAR EXTENSION DE LA RESISTENCIA A RIFAMPICINA

Conclusiones

- TODOS los pacientes con mono o poliresistencia son de seguimiento estrecho durante y después del Tx.
- La identificación tardía INCREMENTA el riesgo de MDR

JUNTOS LO
LOGRAREMOS

Organización
Mundial de la Salud