The Union

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Union Internationale Contre la Tuberculose et les Maladies Respiratoires

Unión Internacional Contra la Tuberculosis y Enfermedades Respiratorias

Novel Regimen Options for DR-TB Treatment

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International Union Against Tuberculosis and Lung Disease (The Union), Paris, France

Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2007–2012 cohorts

WHO. Global Tuberculosis Report 2015

Unsatisfactory outcome of MDR-TB

- Long duration of treatment
- High frequency of adverse drug reactions
- Mixture of MDR-TB, fluoroquinolone-resistant MDR-TB, and XDR-TB

Short standardized treatment of multidrug-resistant tuberculosis

Intensive phase: GEZC KHP 4 months, extended till sputum conversion	Continuation phase: GEZC 5 months
Kanamycin (K)	
Prothionamide (P)	
Isoniazid (H)*	
Gatifloxacin (G)*	Gatifloxacin (G)*
Clofazimine, C	Clofazimine, C
Ethambutol, E	Ethambutol, E
Pyrazinamide, P	Pyrazinamide, P

*high dose

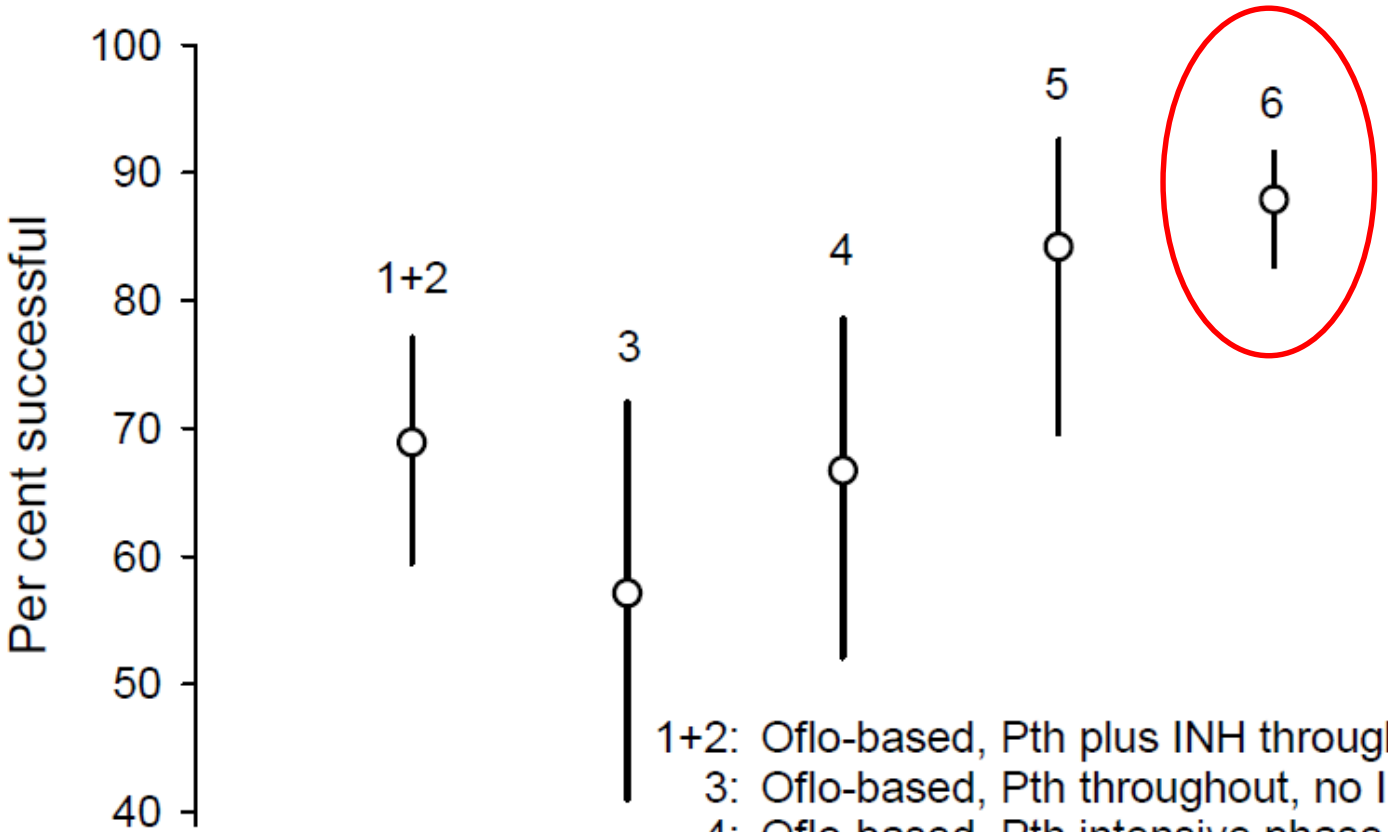
Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684–692

Daily Drug Dosages Used For Standardized Multidrug-resistant Antituberculosis Treatment, Bangladesh Damien Foundation Projects

Drug	Weight group		
	<33 kg	33–50 kg	>50 kg
Kanamycin*	500 mg	750 mg	1,000 mg
Ofloxacin	400 mg	600 mg	800 mg
Gatifloxacin†	400 mg	600 mg	800 mg
Prothionamide‡	250 mg	500 mg	750 mg
Clofazimine	50 mg	100 mg	100 mg
Isoniazid	200 mg	300 mg	300 mg
Isoniazid high dose‡	300 mg	400 mg	600 mg
Ethambutol	800 mg	800 mg	1,200 mg
Pyrazinamide	1,000 mg	1,500 mg	2,000 mg

*KM reduced by 25% for patients aged ≧45, later precisely as 15 mg/kg, 3 times weekly 4th month onward
† Gatifloxacin was used at a lower dosage for the first 50 patients enrolled
‡The high dose of isoniazid was used with the gatifloxacin-based regimen, whereas the normal dose was given in all ofloxacin-based regimens

Proportion of patients with a successful treatment outcome for multidrug-resistant tuberculosis, by regimen, Bangladesh



1+2: Oflo-based, Pth plus INH throughout
3: Oflo-based, Pth throughout, no INH
4: Oflo-based, Pth intensive phase, INH throughout
5: Oflo-based, Pth intensive phase, INH and Clo throughout
6: Gati-based, Pth and INH intensive phase, Clo throughout

Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684–692

MDR-TB, Niger

- 12-month standardised regimen:

  4 Km Gfx Pto H Cfz E Z / 8 Gfx Cfz E Z (Gfx, high dose)
- 65 MDR-TB patients
  - Cure: 58 patients (89.2%, 95%CI 81.7–96.7),
  - died 6
  - Defaulted 1.
- No relapse at the 24-month follow-up after cure (49 patients)

Piubello A, et al. Int J Tuberc Lung Dis 2014;18:1188–1194

High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon

150 MDR-TB patients (20% HIV-positive)

4 Km Gfx Pto H Cfz E Z / 8 Gfx Cfz Pto E Z (Gfx 400 mg)

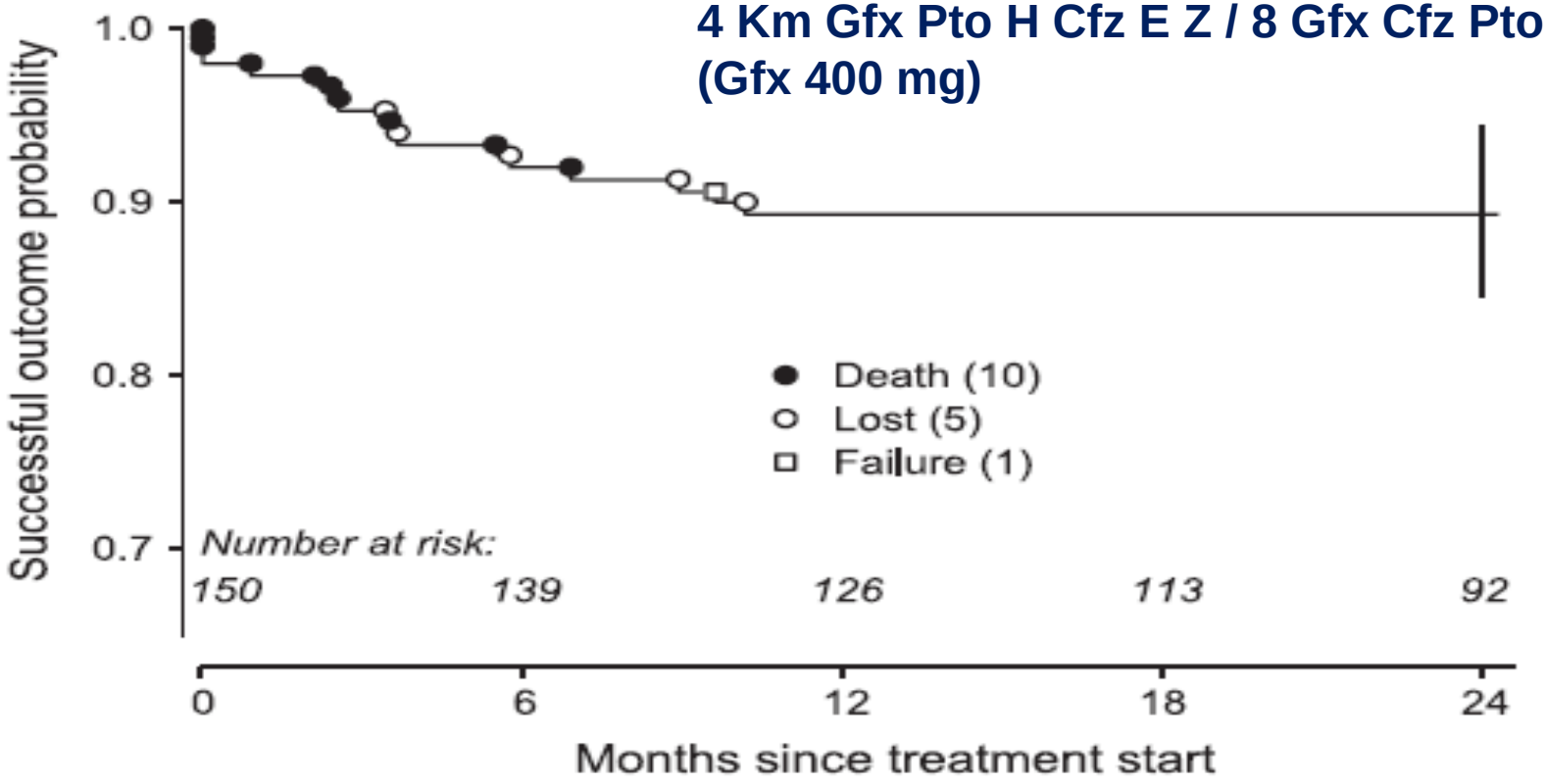


Figure 2 Kaplan-Meier estimate of successful treatment outcome, Cameroon, treatment of patients with MDR. MDR = multidrug resistance.

Kuaban C, et at. Int J Tuberc Lung Dis 2015; 19:517–524

Bangladesh MDR-TB, 2005-2011
4 Km Gfx Pto H Cfz E Z / 5 Gfx Cfz E Z

- relapse-free treatment success 84% (N = 515)
  - cured 423 (82%)
  - completed 12 (2%)
  - defaulted 40 (8%)
  - died 29 (6%)
  - failed 7 (1%)
  - relapsed 4 (0.8%)

Aung KJM *et al.* Int J Tuberc Lung Dis 2014;18:1180–1187

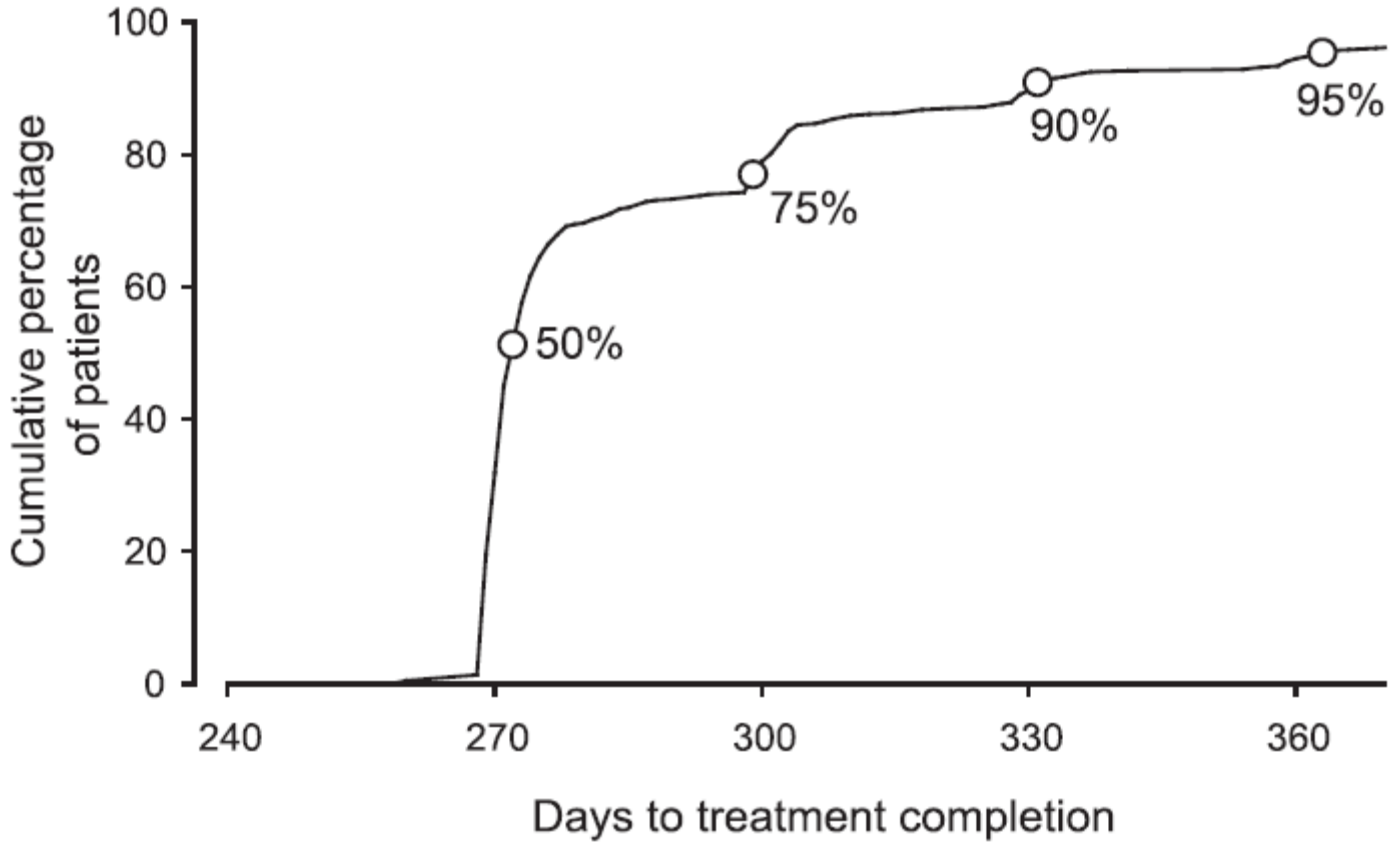


Figure 1 Number of days to treatment completion among the 439 patients who did not end treatment prematurely (due to death, default or treatment failure).

Table 1 Treatment outcome among patients with multidrug-resistant tuberculosis. Treatment success comprises cured and treatment completed; all other standard outcomes together constitute non-success

	n (%)	95%CI
Total ($n = 515$)		
Success ($n = 435$, 84.5%)		
Completion	17 (3.3)	2.1–5.2
Cure, 0 months follow-up	4 (0.8)	0.3–2.0
Cure, 6 months follow-up	7 (1.4)	0.7–2.8
Cure, 12 months follow-up	11 (2.1)	1.2–3.8
Cure, 18 months follow-up	36 (7.0)	5.1– 9.5
Cure, 24 months follow-up	358 (69.5)	65.4–73.3
Cured, reinfection disease	2 (0.4)	0.1–1.4
Non-success ($n = 80$, 15.5%)		
Failure	7 (1.4)	0.7–2.8
Death, first 60 days	14 (2.7)	1.6–4.5
Death, after 60 days	15 (2.9)	1.8–4.7
Default, first 60 days	19 (3.7)	2.4–5.7
Default, after 60 days	21 (4.1)	2.7–6.2
Relapse	4 (0.8)	0.3–2.0

CI = confidence interval.

Successful '9-month Bangladesh regimen' for MDR-TB patients

Of the 515 patients

- Eleven patients failed (n=7) or relapsed (n=4)

- Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to kanamycin and clofazimine

Acquired Resistance to Fluoroquinolones Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Of those without baseline resistance to specific second-line drugs,

- 68 (8.9%) acquired extensively drug-resistant (XDR) tuberculosis,
- 79 (11.2%) acquired fluoroquinolone (FQ) resistance, and
- 56 (7.8%) acquired resistance to second-line injectable drugs

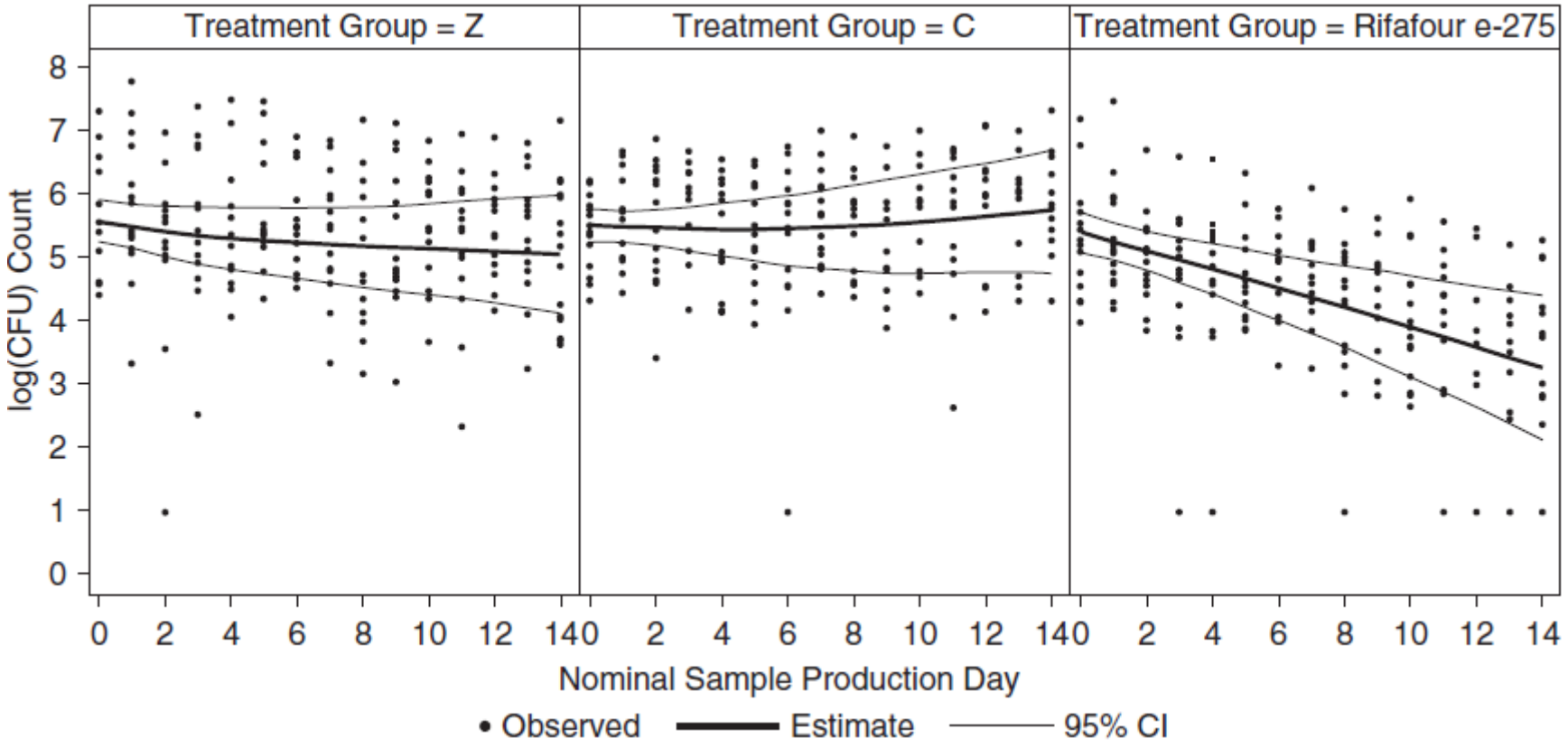
Cegielski JP, et al. Clin Infect Dis 2014;59:1049–63

Acquired Resistance to Fluoroquinolones Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Baseline DST	Acquired FQ resistance	RR (95% CI)
Ethambutol		
Resistance	17.4%	1.86 (1.14–3.05)
susceptible	7.9%	1
kanamycin		
Resistance	36.8%	6.14 (4.08–9.24)
susceptible	6.0%	1
Ethionamide		
Resistance	11.5%	0.95 (.55–1.63)
susceptible	12.1%	1

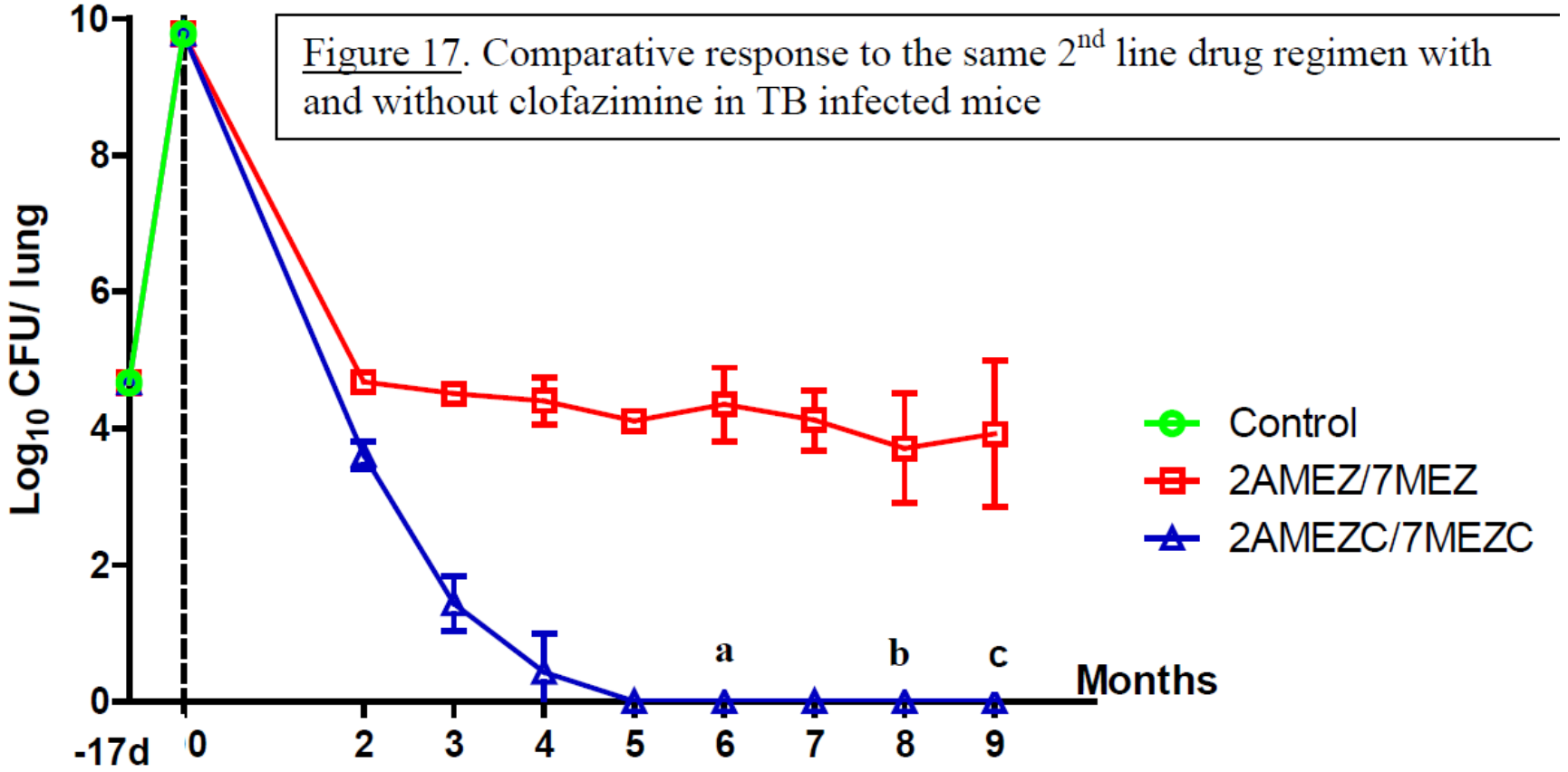
Cegielski JP, et al. Clin Infect Dis 2014;59:1049–63

Mean log_{10}CFU over time. Observed values (dots) and posterior estimates calculated from the joint Bayesian nonlinear mixed-effects regression model with 95% CIs of mean logCFU over time



Diacon AH, et al. Am J Respir Crit Care Med 2015

Clofazimine



Study designed and supervised by: Jacques Grosset, MD
And conducted by: Sandeep Tyagi, BS, Si-yang Li, BS, Deepak Almeida, PhD, Paul Converse, PhD

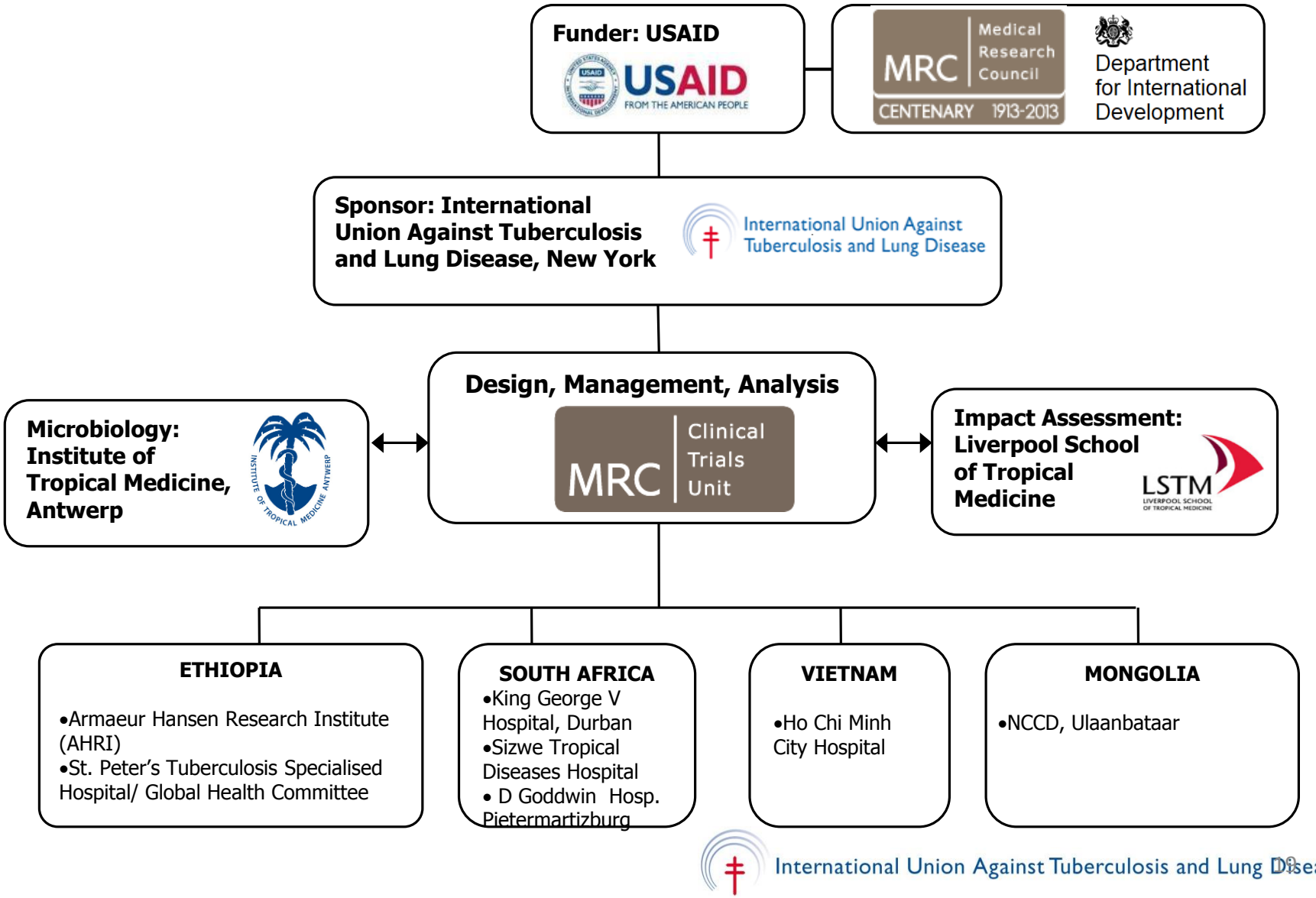
The Bangladesh MDR-TB regimen

- The core drug is likely high-dose gatifloxacin, acting both as bactericidal and sterilizing agent.
- Kanamycin as a powerful companion drug protecting the fluoroquinolone.
- It is likely that clofazimine plays an important yet not fully understood role.
- Not satisfactory for fluoroquinolone-resistant MDR-TB

STREAM

The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB

STREAM Study Partners



STREAM study design

- STREAM is a randomised controlled trial of non-inferiority design
- Study population: MDR-TB patients
  - Patients with resistance to either fluoroquinolone or second line injectables are excluded
- The control regimen is the locally used WHO recommended regimen in the participating countries
- The study regimen is closely similar to the regimen used by Van Deun in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

STREAM Stage 2

- Early in 2013 in recognition of the progress made to date in STREAM and noting the provisional licensing of the first new drug for TB for almost 50 years we were asked to consider:

  - is it possible to include additional regimens to the STREAM trial in its present form?
  - if so, what would be the appropriate regimens to evaluate?

Additional regimens proposed for Stage 2

- After extensive discussions between the study team, the local investigators and other experts it was agreed that the primary interest to patients and programmes would be:
  - a fully oral 9-month regimen
  - a 6-month simplified regimen

- Both of these regimens would include bedaquiline

Regimen C

- In Regimen C, the fully oral regimen, **kanamycin is replaced by bedaquiline** and **moxifloxacin by levofloxacin**

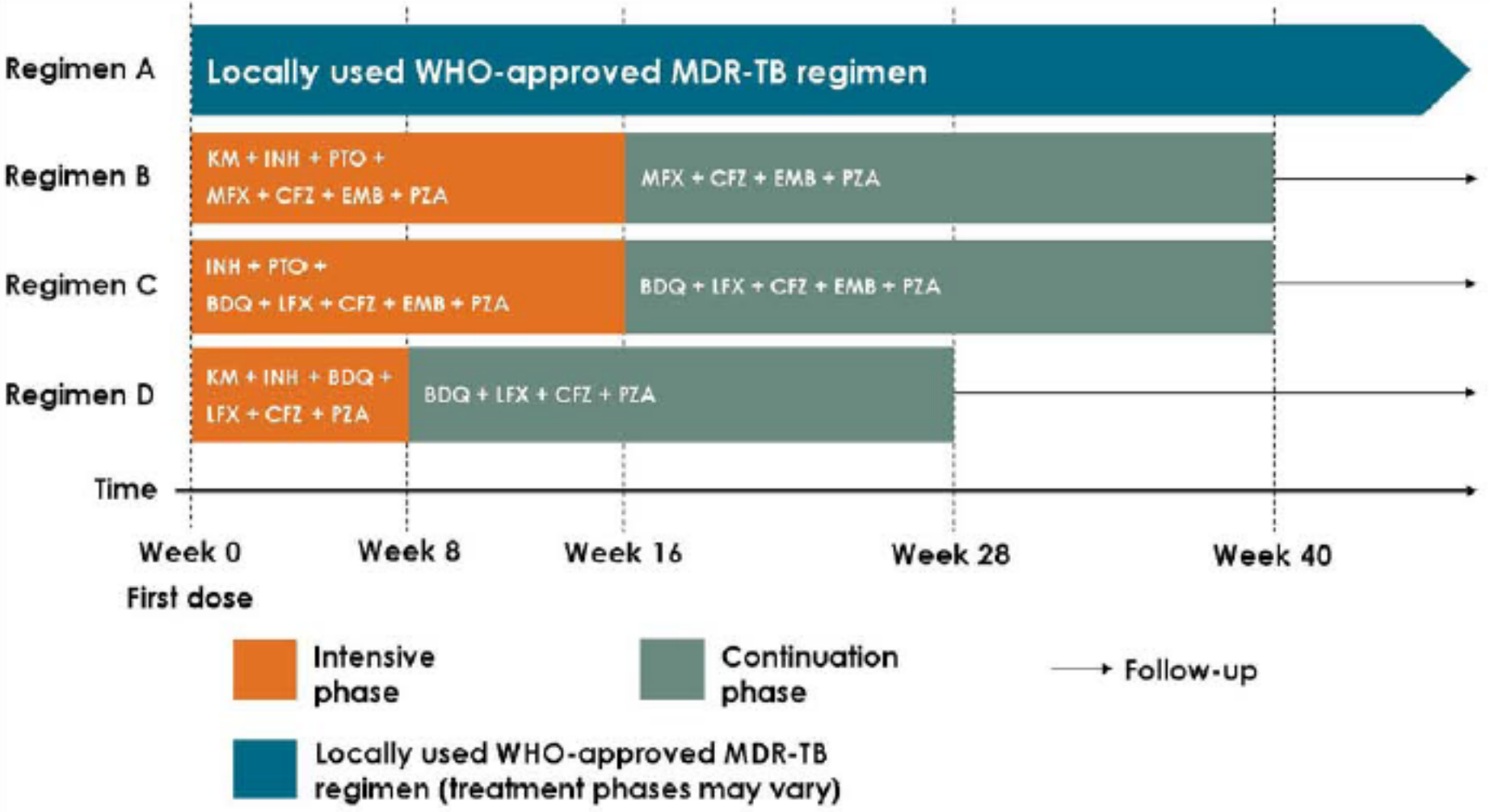
Product	Weeks	**Weight group**		
		Less than 33 kg	**33 kg to 50 kg**	**More than 50 kg**
Bedaquiline	**1 – 40**	**400 mg once daily for first 14 days/200 mg thrice weekly thereafter**		
Levofloxacin	**1 – 40**	**750 mg**	**750mg**	**1000 mg**
Clofazimine	1 – 40	50 mg	100 mg	100 mg
Ethambutol	1 – 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 – 40	1000 mg	1500 mg	2000 mg
Isoniazid	1 – 16	300 mg	400 mg	600 mg
Prothionamide	1 – 16	250 mg	500 mg	750 mg

Regimen D

- In Regimen D prothionamide is replaced by bedaquiline, moxifloxacin is replaced by levofloxacin, ethambutol is removed, the dose of isoniazid is increased and the total duration is reduced from 40 to 28 weeks

Product	Weeks	Weight group				
		Less than 33 kg	33 kg to less than 40 kg	40 kg to less than 50 kg	50 kg to less than 60 kg	More than 60 kg
Bedaquiline	**1 – 28**	**400 mg once daily for first 14 days/200 mg thrice weekly thereafter**				
Levofloxacin	**1 – 28**	**750 mg**	**750 mg**		**1000 mg**	
Clofazimine	**1 – 28**	50 mg	100 mg		100 mg	
Pyrazinamide	**1 - 28**	1000 mg	1500 mg		2000 mg	
Isoniazid	**1 – 8**	**400 mg**	**500 mg**	**600 mg**	**800 mg**	**900 mg**
Kanamycin	**1 – 8**	15 mg per kilogram body weight (maximum 1g)				

Treatment phases of investigational regimens



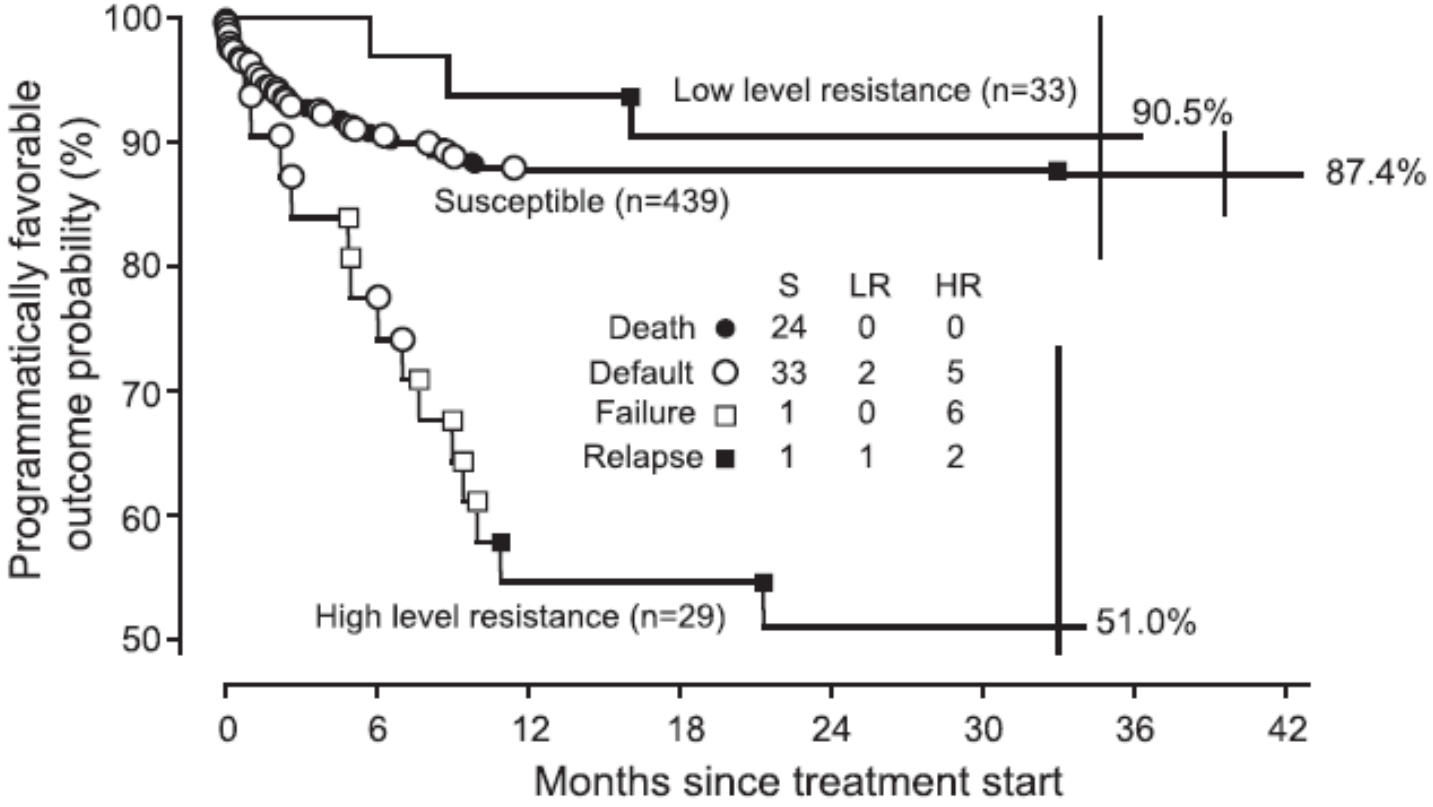


Figure 3 Programmatically favorable treatment outcome probability derived from a Cox's proportional hazard model among 501 patients, stratified by initial fluoroquinolone susceptibility test result, adjusted for age and sex. S = susceptible to ofloxacin and/or GFX at the standard critical concentration; LR = low-level resistance (GFX MIC 0.5–1.0 mg/l); HR = high-level resistance (GFX MIC ⩾2 mg/l); GFX = gatifloxacin; MIC = minimum inhibitory concentration.

INT J TUBERC LUNG DIS 18(10):1180–1187

http://dx.doi.org/10.5588/ijtld.14.0100

Cascade of regimens

Rifampicin	Quinolone	Treatment approach
Susceptible		First line anti-TB treatment
Resistant	Susceptible	Second line anti-TB treatment (9-month regimen)
Resistant	Resistant	New drugs needed