The Opti-Q Trial

A randomized controlled trial to identify the optimal dose of levofloxacin for the treatment of rifampicin-resistant TB

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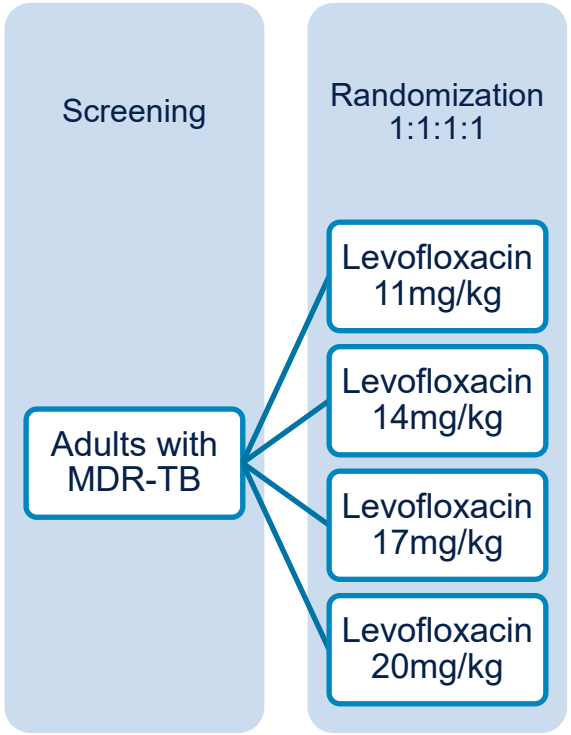
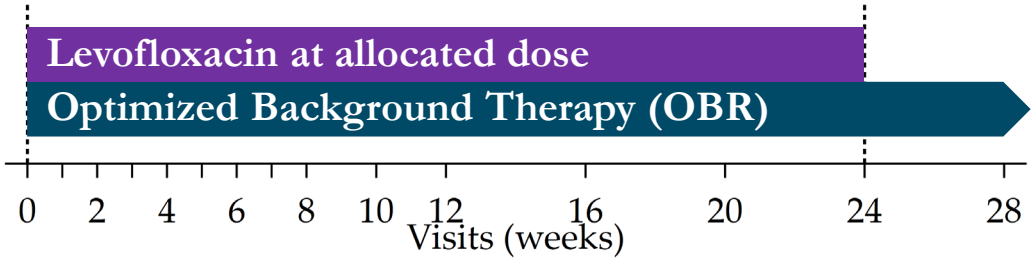
Opti-Q Study Design

- Primary objectives:
  1. Determine the levofloxacin AUC/MIC that provides the shortest time to sputum culture conversion on solid medium.
  2. Determine the highest levofloxacin AUC that is both safe and associated with fewer than 25% of patients discontinuing or reducing their dose of levofloxacin.
  3. Develop a dosing algorithm to achieve the AUC associated with maximal efficacy and acceptable safety and tolerability.
- Target sample size: 120 (assuming 33% loss to follow-up)
- Sites: Lima (2 sites), Cape Town (1 site).
- Participants recruited Jan 2015 – Dec 2016
- Last patient visit: Jul 2017





Background Characteristics

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total randomised				
	48	24	39	**111**
Prior TB diagnoses				
None	24 (50%)	24 (100%)	27 (69%)	**75 (68%)**
Treatment for DS-TB only	22 (46%)	0	8 (21%)	**30 (27%)**
Treatment for MDR-TB	2 (4%)	0	4 (10%)	**6 (5%)**
HIV status				
Negative	26 (54%)	24 (100%)	39 (100%)	**89 (80%)**
Positive	22 (46%)	0	0	**22 (20%)**
Cavitation on chest X-ray				
Absent	11 (23%)	4 (17%)	13 (33%)	**28 (25%)**
Present, <4cm	7 (15%)	11 (46%)	22 (56%)	**40 (36%)**
Present, ≥4cm	30 (63%)	9 (38%)	4 (10%)	**43 (39%)**
Smear grading				
Negative	1 (2%)	1 (4%)	0	**2 (2%)**
Scanty	5 (10%)	1 (4%)	0	**6 (5%)**
1+	10 (21%)	5 (21%)	14 (36%)	**29 (26%)**
2+	8 (17%)	5 (21%)	6 (15%)	**19 (17%)**
3+	24 (50%)	12 (50%)	19 (49%)	**55 (50%)**
Days to positivity in MGIT				
Median (IQR)	10.1 (7.8, 14.2)	9.1 (7.3, 11.0)	6.8 (5.5, 8.6)	**8.4 (6.7, 11.1)**
Sex				
Female	18 (38%)	8 (33%)	17 (44%)	**43 (39%)**
Male	30 (63%)	16 (67%)	22 (56%)	**68 (61%)**
BMI				
Median (IQR)	18.9 (17.6, 20.4)	21.5 (20.5, 24.2)	21.0 (18.7, 23.8)	**20.4 (18.2, 22.6)**
Minimum, Maximum	12.9, 26.0	17.8, 27.8	15.3, 29.8	**12.9, 29.8**

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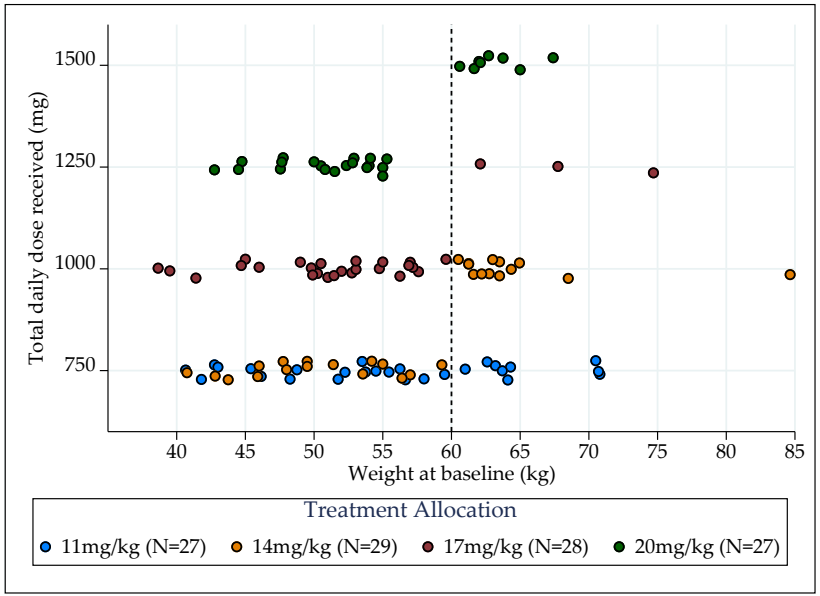
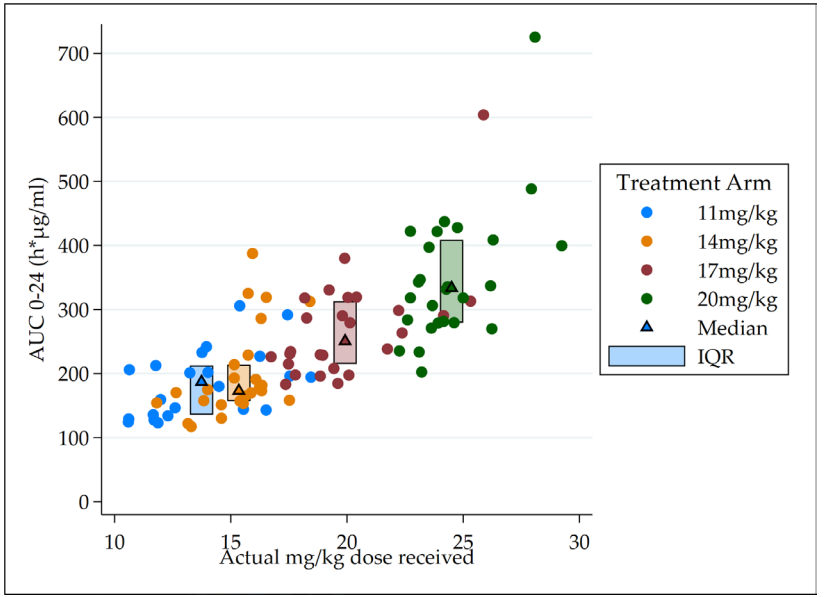
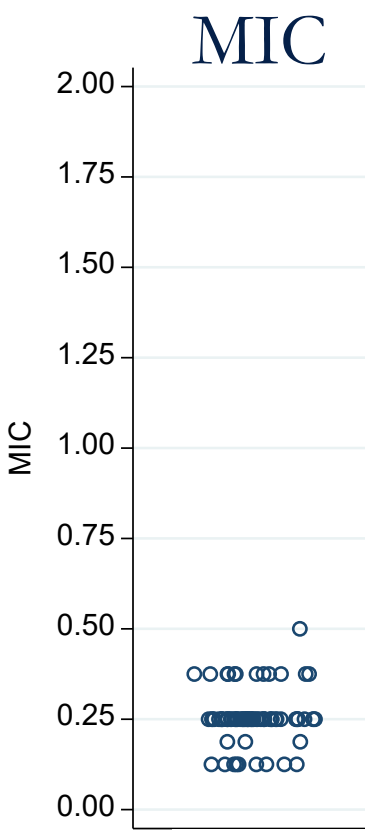
Levofloxacin exposure

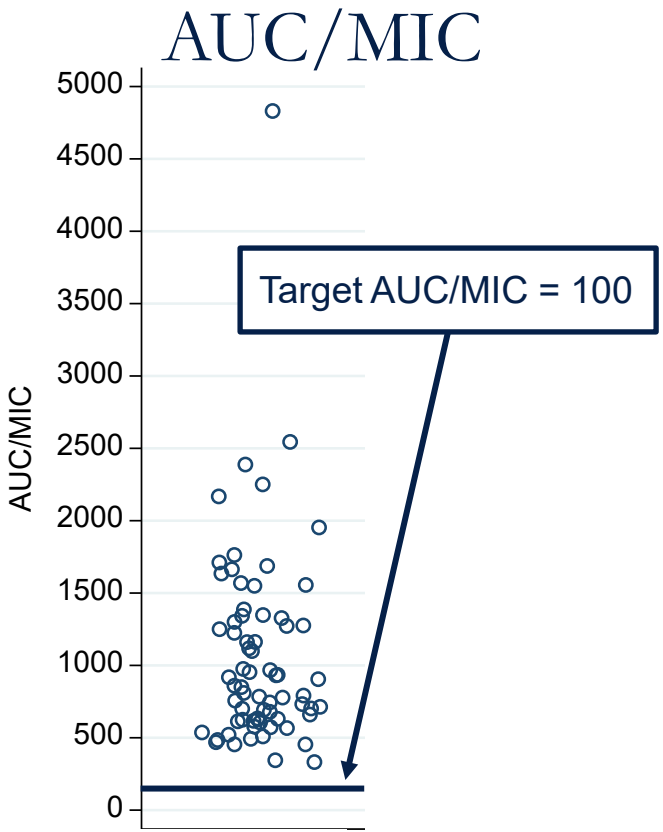
Total daily dose received (mg)



AUC 0-24 (h*µg/ml)







MICs using Agar plate

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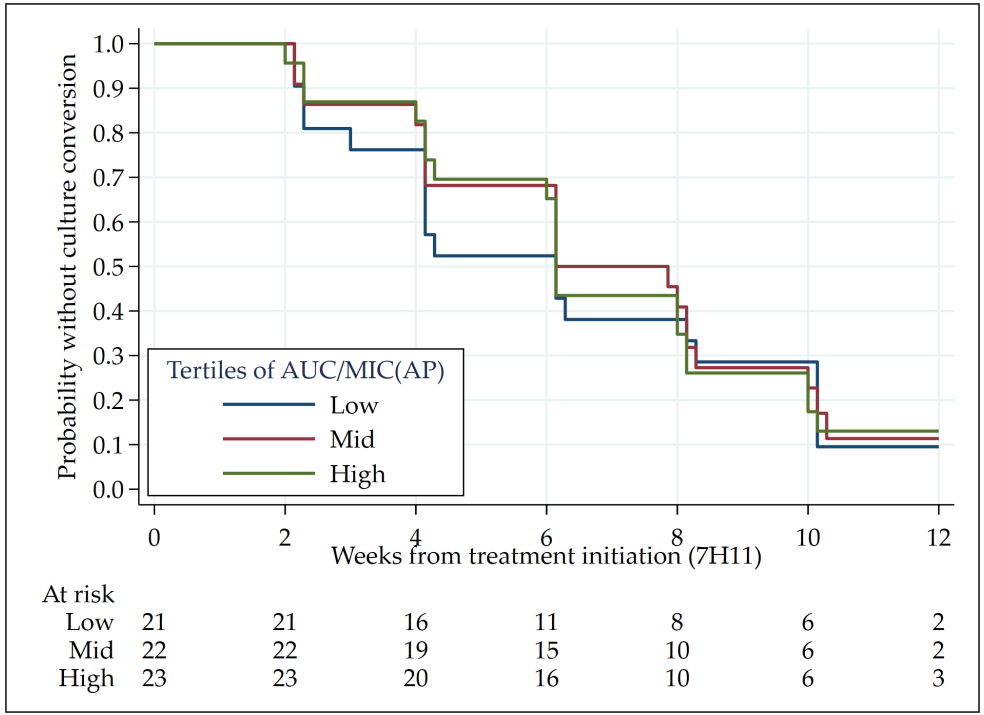
Time to culture conversion (7H11) by AUC/MIC tertile

Efficacy



Time to culture conversion did not differ by AUC/MIC (solid or liquid media)

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Safety outcome by treatment arm and tertile of AUC

Safety

Treatment arm	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total participants	**25**	**28**	**28**	**27**	**108**
Any AE	24 (96.0%)	28 (100.0%)	28 (100.0%)	27 (100.0%)	**107 (99.1%)**
Any Grade 3-5 AE	4 (16.0%)	4 (14.3%)	7 (25.0%)	10 (37.0%)	**25 (23.1%)**
Any SAE	2 (8.0%)	1 (3.6%)	4 (14.3%)	3 (11.1%)	**10 (9.3%)**
Death	0	0	1 (3.6%)	0	**1 (0.9%)**

p = 0.04, trend

Levofloxacin AUC	Lower tertile	Middle tertile	Upper tertile	Total
Total participants	**33**	**33**	**33**	**99**
Any AE	33 (100.0%)	33 (100.0%)	33 (100.0%)	**99 (100.0%)**
Any Grade 3-5 AE	4 (12.1%)	8 (24.2%)	12 (36.4%)	**24 (24.2%)**
Any SAE	0	3 (9.1%)	6 (18.2%)	**9 (9.1%)**
Death	0	0	1 (3.0%)	**1 (1.0%)**

p = 0.02, trend

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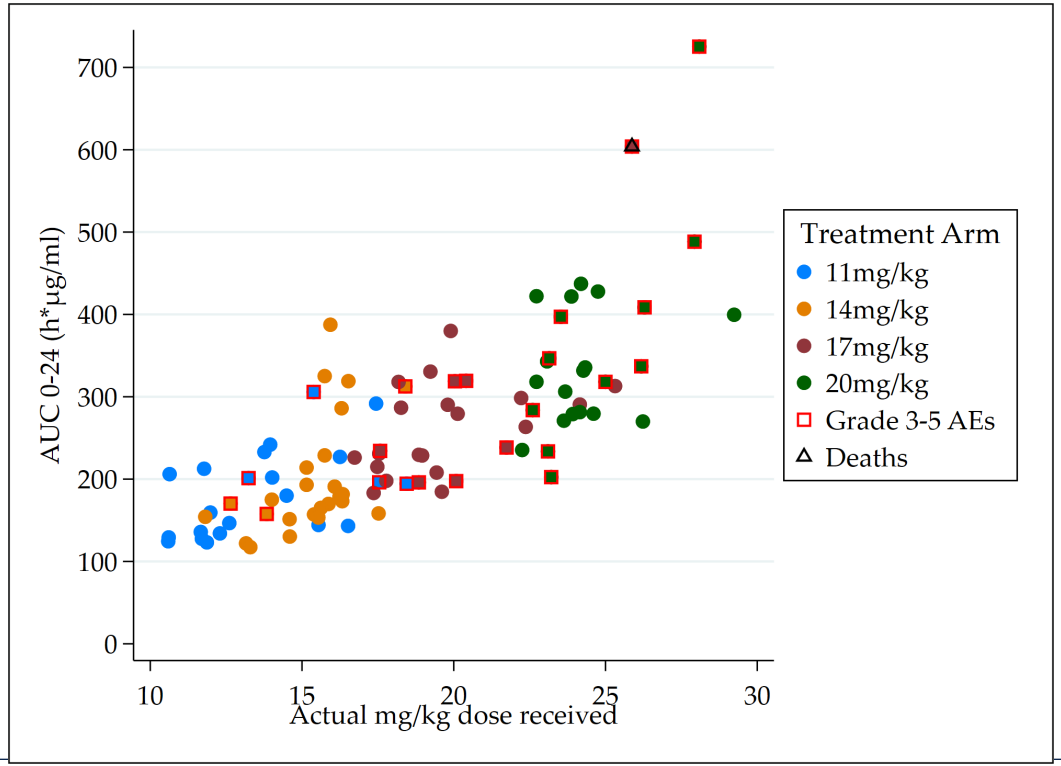
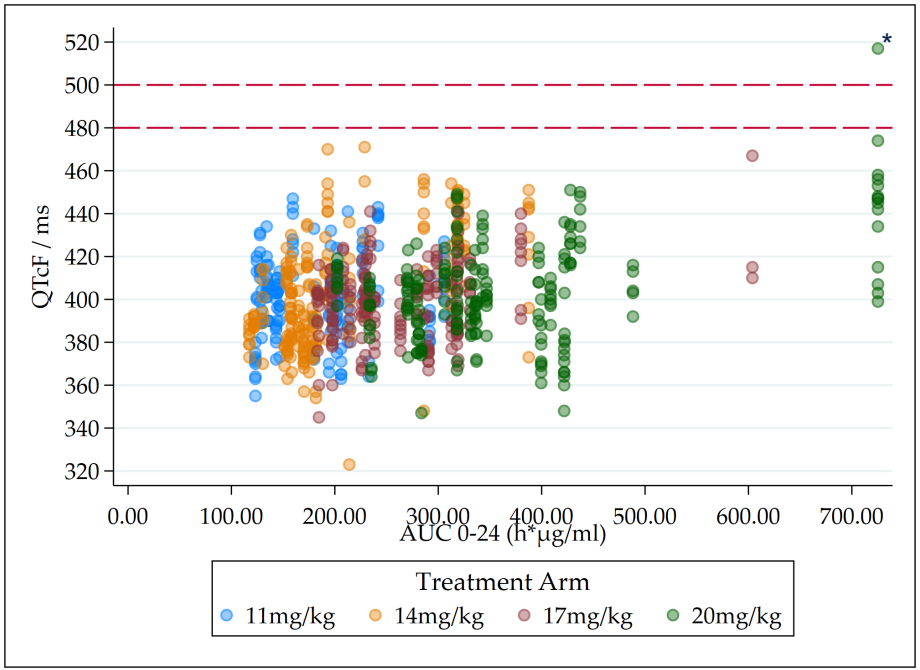
Safety outcomes by AUC and weight-adjusted dose

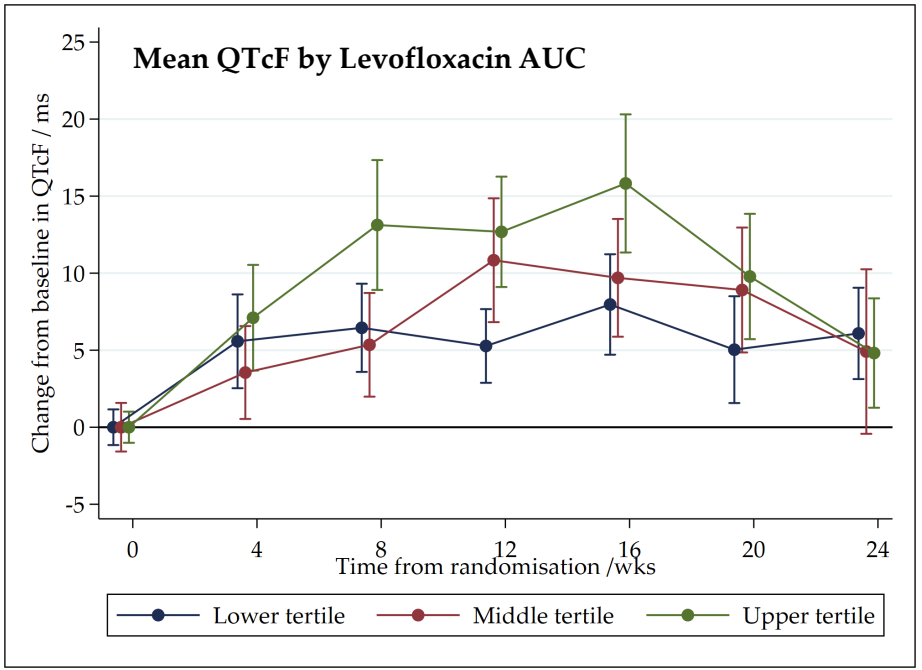
Safety



QTcF Prolongation

Safety





*517ms considered attributable to concomitant use of azithromycin

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Conclusions

1. Levofloxacin AUC increases with increasing dose, but substantial dose overlap at lower doses.

2. AUC/MIC pre-specified target (>100 on Agar Plate) reached for all participants.
3. No relationship between AUC/MIC and culture conversion, even after controlling for other predictors.
4. Higher doses and exposures were associated with more severe adverse events.

Doses of 750-1000mg of levofloxacin are efficacious and safe and are adequate to achieve target exposures.

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Study Team

- ***C. Robert Horsburgh Jr.***
- *Debra Benator*
- *Donna Butler*
- *Lee-Ann Davids*
- *Andreas Diacon*
- *Nancy Dianis*
- *Kathleen Eisenach*
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- *Carlos Seas*
- *Alvaro Schwald*
- *David Sikes*
- *Tim Sterling*
- *Dante Vargas*
- *Florian von Groote-Bidlingmaier*
- *Rob Warren*

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Extra slides

Optimized background regimen at baseline

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total	48 (100.0%)	24 (100.0%)	39 (100.0%)	111 (100.0%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Cycloserine	0	13 (54.2%)	16 (41.0%)	29 (26.1%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone, Isoniazid	27 (56.3%)	0	0	27 (24.3%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Cycloserine	0	9 (37.5%)	17 (43.6%)	26 (23.4%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone	8 (16.7%)	0	0	8 (7.2%)
Pyrazinamide, Ethambutol, Kanamycin, Terizidone, Isoniazid	6 (12.5%)	0	0	6 (5.4%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone, Isoniazid	2 (4.2%)	0	0	2 (1.8%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone	2 (4.2%)	0	0	2 (1.8%)
Pyrazinamide, Ethambutol, Ethionamide, Capreomycin, Cycloserine	0	0	2 (5.1%)	2 (1.8%)
Pyrazinamide, Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid	0	1 (4.2%)	0	1 (0.9%)
Pyrazinamide, Ethionamide, Amikacin, Cycloserine	0	0	1 (2.6%)	1 (0.9%)
Pyrazinamide, Ethambutol, Terizidone, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Terizidone, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Kanamycin, Cycloserine	0	1 (4.2%)	0	1 (0.9%)
Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid, Amoxicillin/clavulanic acid	0	0	1 (2.6%)	1 (0.9%)
Ethambutol, Ethionamide, Kanamycin, Cycloserine, P-aminosalicylic acid	0	0	1 (2.6%)	1 (0.9%)
Not recorded	0	0	1 (2.6%)	1 (0.9%)

Predictors of time to culture conversion (7H11)

- Univariable predictors (not adjusted for other factors)
  - Smear grading ($p < 0.001$)
  - 7H11 colony count ($p < 0.001$)
  - Ethambutol resistance ($p < 0.001$)
  - Resistance to capreomycin ($p < 0.001$)
  - Resistance to pyrazinamide ($p = 0.034$)
  - Age ($p = 0.024$)

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  - Resistance to pyrazinamide ($p = 0.034$)
  - Age ($p = 0.024$)
- Multivariable model (adjusted for other factors, in progress)
  - Smear ($p < 0.001$)
  - Ethambutol resistance ($p = 0.007$)
  - Age ($p = 0.038$)

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