Technical Appendix for "Systematic Review, Meta-Analysis, and Cost Effectiveness of Treatment of Latent Tuberculosis Infection to Reduce Progression to Multidrug-Resistant Tuberculosis"

Additional Methods

Systematic Review

Our population, intervention, comparison, and outcome (PICO) question was: "Among contacts to infectious MDR TB patients with LTBI or presumed LTBI, should LTBI treatment compared with no medical treatment be used?" Populations included all persons with LTBI or presumed LTBI (children < 5 years of age or living with HIV) having contact to infectious MDR TB. Sub-analyses were conducted for children. The intervention was MDR LTBI treatment for 6-12 months with an effective treatment regimen (≥ one medication to which their presumed MDR-LTBI strain was likely susceptible). The comparison was no effective MDR LTBI treatment. Outcomes examined were: TB incidence; MDR LTBI treatment completion; MDR LTBI treatment discontinuation due to adverse effects, overall, by age, by regimen; and cost effectiveness of MDR LTBI treatment regimens.

The systematic review of published studies in English or Spanish was conducted for the period 1/1/1994-12/31/2014 through a search of PubMed, EMBASE, and the Cochrane Library for the key words: tuberculosis, multidrug resistant, contacts, and treatment. We excluded case reports with N < 10 and studies only reporting on the diagnosis or treatment of MDR-TB disease**.** We considered that persons having contact to infectious MDR-TB disease were effectively treated if they received one or more medications to which their MDR-TB strain was likely susceptible.

Cost Effectiveness

To assess incremental cost-effectiveness of individual regimens, we conducted a decision analysis of a hypothetical cohort of contacts of patients with infectious MDR TB who have MDR LTBI over a 40-year (estimated average remaining lifetime) analytic horizon from the societal perspective. A simple decision analysis was chosen because contacts to MDR TB with MDR LTBI are a closed cohort and transitions occur typically once. This analysis uses many of the same inputs that Holland [23] used in his Markov cohort model, and updates them with regimen-specific adverse event rates and treatment completion rates.

We assumed 100 MDR TB patients per year over 40 years for a total cohort of 4000, approximately half of whom have infectious forms of disease (pulmonary sputum smear positive or sputum smear negative culture positive disease) [25]. We estimated approximately 20 contacts per infectious MDR TB patient [26].

We assumed that 100% of MDR TB contacts started MDR LTBI treatment, and applied regimen-specific average completion rates and adverse event discontinuation rates from our review (Table 4 in the main paper). We used regimen-specific efficacy estimates from mouse models published by Nuermberger [27] and Holland [23], since clinical trials of MDR LTBI regimens have not yet been conducted among humans (Table 4 in the main paper). For those who discontinued due to adverse events, we estimated that 0.5% of those

starting treatment were hospitalized, based on historical rates of isoniazid-related hospitalization [28]. We assumed that approximately 7% die from MDR TB [29] and 1% die from all causes [30]. For untreated contacts, we assumed an LTBI progression to TB rate of 3% over 40 years (assuming an average age of LTBI of 39 and 40 years of remaining life with average age of expected death at age 79) from Yeats [31]. We applied a range of remaining lifetime TB incidence of 2.4% to 4.4% (see power calculation details below, incidence in year one of 1.15% from Ferebee, followed by annual reactivation estimates of 0.032% from Walter and 0.084% from Shea.

We applied MDR-TB societal costs in 2014 dollars, excluding lost productivity due to deaths, from Castro [29] ($225,398), along with 9-month MDR LTBI treatment costs, including those of lab monitoring, in 2009 dollars used by Holland [23] (PZA/FQ=$1719, PZA/EMB=$1165, FQ alone=$1261, FQ/EMB=$1634, FQ/ETA=$3635; for no treatment, costs were taken for monitoring for 24 months=$888) updated to 2014 dollars ($1993, $1350, $1461, $1893, $4213, $1029, respectively) using the medical care component of the consumer price index [33] (multiplied by 1.1589). We estimated that patients not completing LTBI treatment would incur one-third of the costs of the full regimen. TB cases and costs were discounted at 3% annually over the 40 year analytic horizon.

We used the following quality-adjusted life year (QALY) estimates from Gao [34] and from Holland [23]: 0.53 alive post MDR TB, 0.90 alive with MDR LTBI, 0.80 alive with MDR LTBI post adverse effect treatment stop, and 0.75 alive with MDR LTBI post hospitalization for adverse effect treatment stop.

One-way sensitivity analyses were conducted to assess the effect of increasing adverse effects by 50% with each regimen. Figure 1 presents the decision tree with state transition probabilities.

Additional Results

TB incidence from Studies Comparing MDR LTBI Treatment with No Effective Treatment

TB incidence from five of six comparison studies (excluding the Attamna registry match) were: 98% (Bamrah [1]), 17% (Denholm [2]), 76% (Schaaf[3], 79% (Adler-Shohet[4]), 47% (Williams [6]).

MDR LTBI TB Incidence Person-months Data							
Study	n	TB	Treatment Tx=0, no Tx=1	Ln(n)	Months	Person months	Ln(person months)
Bamrah	104	0	0	4.6444	36	3744	8.2279
Bamrah	15	3	1	2.7081	36	540	6.2916
Denholm	11	0	0	2.3979	54	594	6.3869
Denholm	38	2	1	3.6376	56.4	2143.2	7.6701
Schaaf	41	2	0	3.7136	30	1230	7.1148
Schaaf	64	13	1	4.1589	30	1920	7.5601
Adler	26	0	0	3.2581	24	624	6.4362
Adler	5	0	1	1.6094	24	120	4.7875
Williams	8	0	0	2.0794	24	192	5.2575
Williams	4	0	1	1.3863	24	96	4.5643

The reduction in MDR TB incidence was found using several methods (a 91%-92% risk reduction controlling for person-time using Poisson regression alone or controlling for zero-inflation and random effects) to analyze count data with multiple zero outcomes. However, the best fit was a negative binomial model that controlled for person-time and over-dispersion that found a 90% risk reduction, but with a very wide confidence interval (9% to 99%). Analysis results using SAS version 9.3 are presented below for each model.

Results of Poisson Regression with Person-time as an Offset

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	8	18.8880	2.3610
Scaled Deviance	8	18.8880	2.3610
Pearson Chi-Square	8	18.9085	2.3636
Scaled Pearson X2	8	18.9085	2.3636
Log Likelihood		9.9688	
Full Log Likelihood		-15.7615	
AIC (smaller is better)		35.5229	
AICC (smaller is better)		37.2372	
BIC (smaller is better)		36.1281	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Likelihood Ratio 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.1116	0.8498	-4.6454	-1.1455	13.41	0.0003
treatment	1	-2.4784	0.7454	-4.3173	-1.2359	11.06	0.0009
Scale	0	1.0000	0.0000	1.0000	1.0000		

NOTE: The scale parameter was held fixed.

Using Poisson regression, the RR of TB incidence, adjusted for study person-time, is 0.0839 with confidence interval (CI) of 0.0133-0.2906.

Results of Zero-Inflation Poisson (ZIP) Regression with Random Intercept and Random Effects and Person-time as an Offset, b0=intercept, b1=treatment, c0=zero inflation, s2u2=random effects

NOTE: GCONV convergence criterion satisfied.

Fit Statistics

-2 Log Likelihood	25.6
AIC (smaller is better)	33.6
AICC (smaller is better)	41.6
BIC (smaller is better)	32.1

Parameter Estimates

Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Gradient
b0	-3.5589	1.0626	4	-3.35	0.0286	0.05	-6.5092	-0.6086	4.357E-6
b1	-2.4396	0.7873	4	-3.10	0.0363	0.05	-4.6255	-0.2537	0.000051
c0	-17.2689	6553.05	4	-0.00	0.9980	0.05	-18211	18177	2.329E-8
s2u2	0.5860	0.6625	4	0.88	0.4263	0.05	-1.2534	2.4254	-0.00005

Using ZIP regression with random effects, the RR of TB incidence, adjusted for study person-time, is 0.0872 with CI of 0.0098-0.7759.

Results of Negative Binomial Regression with Person-time as an Offset

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	8	8.4235	1.0529
Scaled Deviance	8	8.4235	1.0529
Pearson Chi-Square	8	7.7439	0.9680
Scaled Pearson X2	8	7.7439	0.9680
Log Likelihood		12.5474	
Full Log Likelihood		-13.1828	
AIC (smaller is better)		32.3657	
AICC (smaller is better)		36.3657	
BIC (smaller is better)		33.2734	

Algorithm converged.

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Likelihood Ratio 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.3527	1.3052	-6.3542	-0.3696	6.60	0.0102
treatment	1	-2.2734	0.9853	-4.4436	-0.0935	5.32	0.0210
Dispersion	1	0.6560	0.7332	0.0293	5.1318		

NOTE: The negative binomial dispersion parameter was estimated by maximum likelihood.

Using negative binomial regression to account for the dispersion of the data, the RR of TB incidence, adjusted for study person-time, is 0.1030 with CI of 0.0118-0.9107.

TB Incidence in Studies of Treatment-only or No Treatment

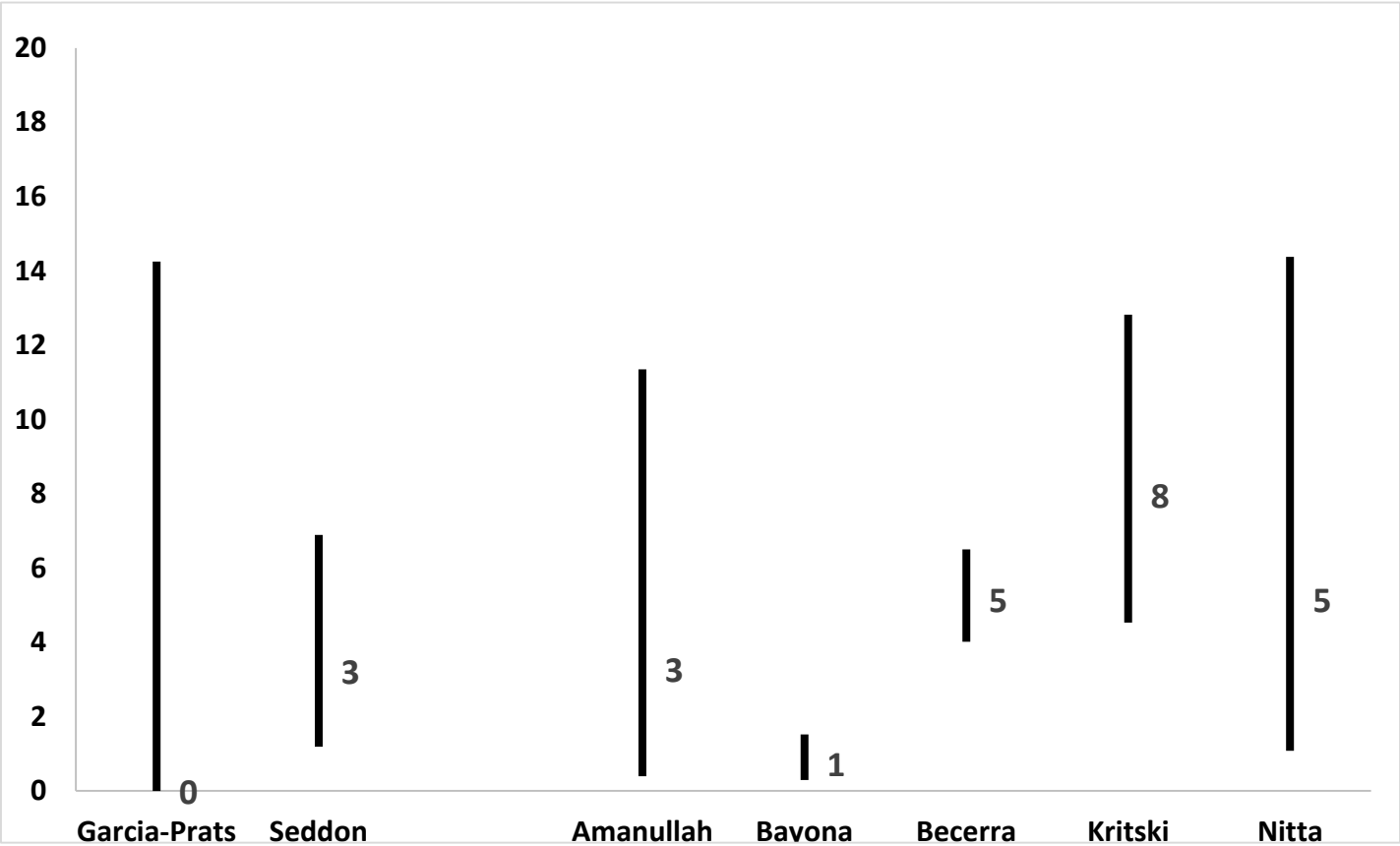
TB incident relative risk reductions from two of 10 treatment-only studies, excluding six studies without data on incidence, the Feja registry match, and Miramontes that didn't describe follow-up procedures and had extensive (48%) lost to follow-up were: Garcia-Prats 0% (0%-14%) [9], Seddon 3% (1%-7%) [15]. Aggregated incidence from the two studies was 6/210 = 3%.

TB incidence in five no-effective-MDR-LTBI-treatment studies were: Amanullah 3% (0.4%-11%) [17], Bayona 1% (0.3%-2%) [18], Becerra 5% (4%-7%) [19], Kritski 8% (5%-13%) [20], Nitta 5% (1%-14%) [21]. Aggregated incidence from the five studies was 94/2554 = 4%.

Limitations of these findings include: There were very few published studies that addressed the PICO question, and there could have been publication bias towards publishing of studies having a treatment effect

- Studies were prospective observational, retrospective reviews, case series N > 10, or registry matches
- In meta-analyses, we excluded registry matches (Attamna, Feja) because their limitations include a much greater likelihood of loss to follow up
- Periods of follow up to identify incident cases varied from 30 months to 6 years in the 3 comparison studies having any TB incidence. In the 2 additional comparison (non-registry match) studies having no TB incidence, follow up was 2 years or less. Power to detect TB incidence was only 1% in these 2 studies (Adler-Shohet and Williams).

Forest Plot of TB Incidence Proportion: 2 Treatment-only Studies and 5 No Treatment Studies



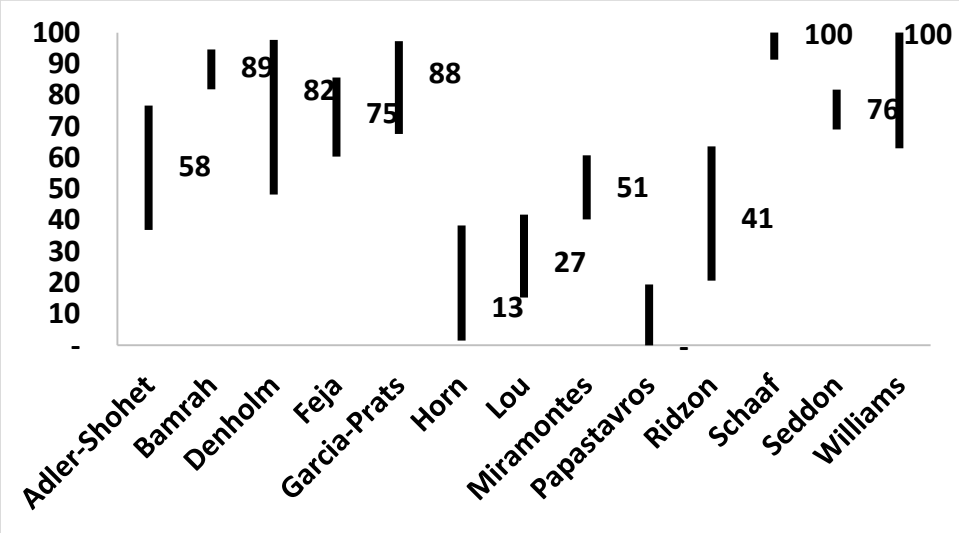
MDR LTBI Treatment Completion

Thirteen studies reported MDR LTBI treatment completion:

- Bamrah [1] 93/104=89% (81.9-94.6)
- Denholm [2] 9/11=82% (48.2-97.7)
- Schaaf [3] 41/41=100% (91.4-100)
- Adler-Shohet [4] 15/26=58% (36.9-76.6)
- Williams [6] 8/8=100% (63.1-100)
- Feja [7] 38/51=75% (60.4-85.7)
- Garcia-Prats [9] 21/24=88% (67.6-97.3)
- Horn [10] 2/16=13% (1.6-38.4)
- Lou [11] 13/48=27% (15.3-41.8)
- Miramontes [12] 44/87=51% (40.3-60.8)
- Papastavros[13] 0/17=0% (0-19.5)
- Ridzon [14] 9/22=41% (20.7-63.6)
- Seddon [15] 141/186=76% (69-81.8)

The pooled average MDR LTBI treatment completion from the 13 studies was 68% (434/641, CI=64.0%-71.2%). However, the studies were too heterogeneous for random effects aggregation. Limitations of these findings were that MDR LTBI treatment completion depended on the regimen, because adverse effects influenced treatment discontinuation.

Forest Plot of MDR TB Treatment Completion Proportions: 13 Studies



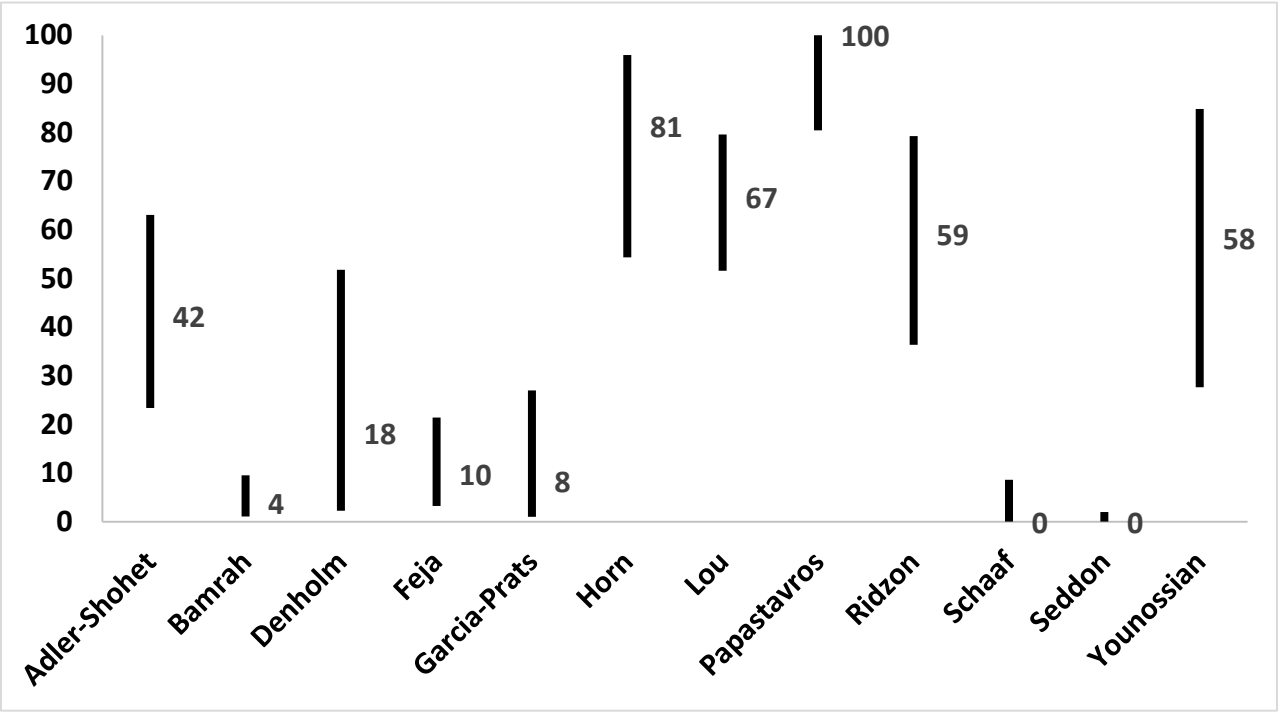
Treatment Discontinuation due to Adverse Effects

Twelve studies reported the overall percentage of persons starting MDR LTBI treatment who discontinued due to adverse effects:

- Adler-Shohet [4] 11/26=42% (23.4-63.1)
- Bamrah [1] 4/104=4% (1.1-9.6)
- Denholm [2] 2/11=18% (2.3-51.8)
- Schaaf [3] 0/41=0% (0-8.6)
- Feja [7] 5/51=10% (3.3-21.4)
- Garcia-Prats [9] 2/24=8% (1.03-27.0)
- Horn [10] 13/16=81% (54.4-96.0)
- Lou [11] 32/48=67% (51.6-79.6)
- Papastavros [13] 17/17=100% (80.5-100.0)
- Ridzon [14] 13/22=59% (36.4-79.3)
- Seddon [15] 0/186=0% (0-2.0)
- Younossian [16] 7/12=58% (27.7-84.8)

The mean percentage of persons experiencing adverse effects resulting in treatment discontinuation (19% [106/558], CI=16%-22%). The studies were too heterogeneous for random effects aggregation.

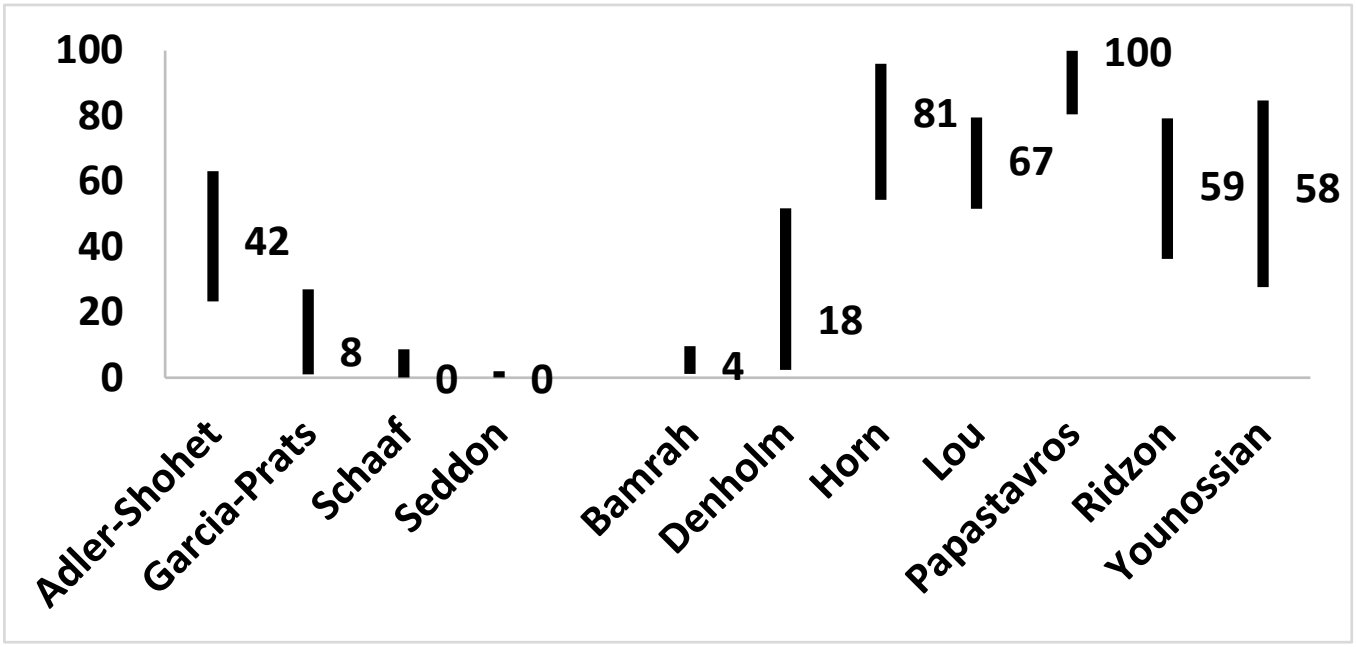
Forest Plot of MDR LTBI TB Treatment Discontinuation due to AE Proportions: 12 Studies



Four studies reported the percentage of persons starting MDR LTBI treatment who discontinued due to adverse effects by age ≤ 15 years:

- Adler-Shohet [4] 11/26=42% (23.4-63.1)
- Garcia-Prats [9] 2/24=8% (1.03-27.0)
- Schaaf [3] 0/41=0% (0-8.6)
- Seddon [15] 0/186=0% (0-2.0)

Forest Plot of MDR LTBI TB Treatment Discontinuation due to AE Proportions in 4 Child and 7 Adult Studies



The percentages for completion and AE stop by regimen were obtained from the studies that reported them, computed by placing the number completing or discontinuing treatment due to AE from a specific regimen over the total number that received the regimen.

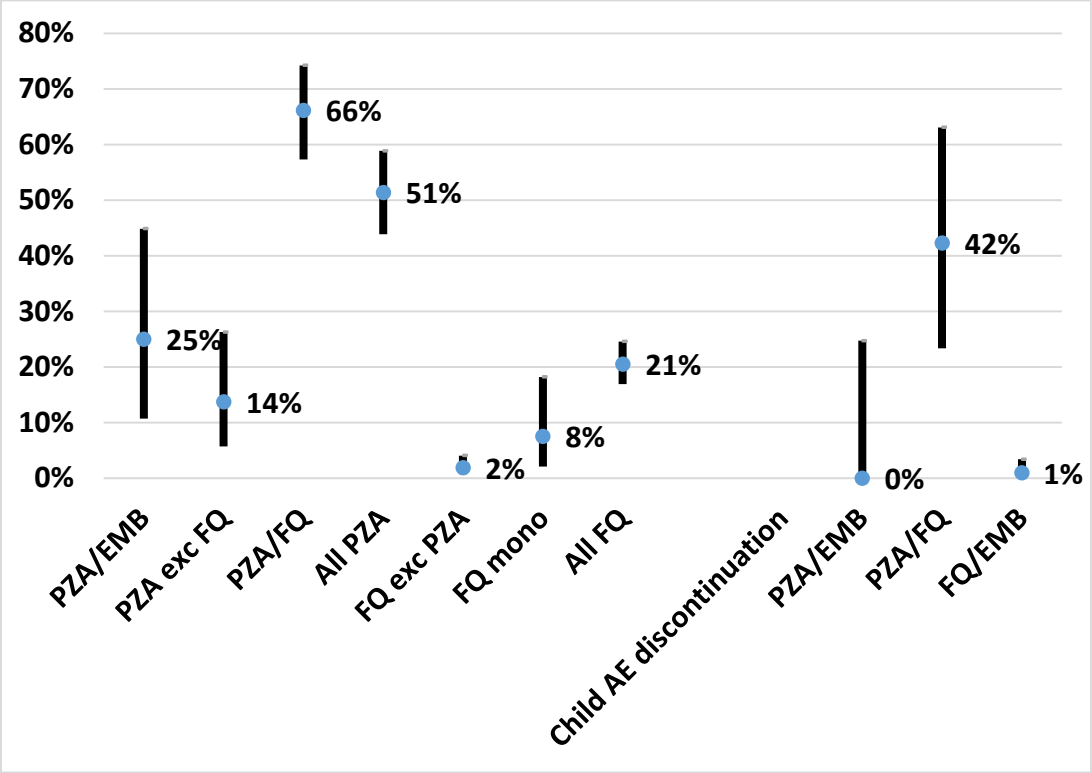
Regimen	Completion by study	Completed	N	% Completed
PZA/EMB	3/3 Denholm, 13/13 Schaaf, 5/12 Younossian	21	28	75% (57-87)
PZA/FQ	15/26 Adler-Shohet, 1/1 Denholm, 2/16 Horn, 13/48 Lou, 0/17 Papastavros, 9/22 Ridzon	40	130	31% (23-39)
FQ mono	41/51 Bamrah, 2/2 Denholm	43	53	81% (69-89)
FQ/EMB	37/41 Bamrah, 2/2 Denholm, 21/24 Garcia-Prats, 141/186 Seddon	201	253	79% (74-84)
FQ/ETA	12/12 Bamrah	12	12	100% (96-100)

For treatment discontinuation due to adverse effects, data were obtained from the following studies:

Regimen	AE stop by study	AE stop	N	% AE stop	Notes
PZA/EMB	0/3 Denholm, 0/13 Schaaf, 7/12 Younossian	7	28	25% (11-45)	4 in Schaaf also received ETA
PZA/FQ	11/26 Adler-Shohet, 0/1 Denholm, 13/16 Horn, 32/48 Lou, 17/17 Papastavros, 13/22 Ridzon	86	130	66% (57-74)	1 in Denholm received ciprofloxacin and PZA
FQ mono	4/51 Bamrah, 0/2 Denholm	4	53	8% (2-18)	

FQ/EMB	0/41 Bamrah, 0/2 Denholm, 2/24 Garcia-Prats, 0/186 Seddon	2	253	1% (0-3)	all in Garcia-Prats also received high dose INH
FQ/ETA	0/12 Bamrah	0	12	0% (0-25)	

Forest Plot of MDR LTBI TB Treatment Discontinuation due to AE Proportions by Regimen



In children ≤ 15 years of age, treatment discontinuation due to adverse effects was low with PZA/EMB (0%, 0%-25%) or FQ/EMB (1%, 0%-3%) , but high with PZA/FQ (42%, 23%-63%). Consistent with drug-susceptible TB LTBI treatment in trials of children, they are less likely to experience or report adverse effects.

In the Adler-Shohet study of 26 children, most AEs were abdominal pain, arthralgias/myalgias, and elevated liver enzymes. Liver enzymes were five times the upper limit of normal in one patient, and 2-4 times the limit in three patients, so 4/8 or half of those with any liver toxicity. While all AEs resolved after withdrawal of the regimen (5/8 with liver toxicity were switched to FQ monotherapy), the authors noted the following: “Children on these regimens should have transaminases checked monthly and be monitored for new gastrointestinal symptoms or other toxicity.” In our paper, the costs are taken from Holland and updated; these costs include monthly lab monitoring and monitoring for AEs.

In Denholm, there was one patient on ciprofloxacin and PZA who initially experienced mild abdominal pain that resolved.

In Horn, the following AEs for the 16 patients on ofloxacin and PZA were common: arthralgias, gastrointestinal distress, hepatitis with elevated ALTs. Of the four with hepatitis, all had taken isoniazid for some period.

In Lou, 48 patients (most having received organ transplants and on immunosuppressive medications) took levofloxacin and PZA and 32 discontinued due to AEs. Two patients discontinued treatment due to elevated transaminase levels. Most other AEs were due to gastrointestinal effects and arthralgias.

In Papastavros, all 17 patients on PZA and levofloxacin discontinued due to AEs. Eight of the 17 discontinued due to elevated liver enzymes. Other common AEs included: gastrointestinal distress, hyperuricemia, CNS issues (dizziness, vertigo, headache, etc.), and arthralgias/myalgias.

In Ridzon, 13/22 patients on PZA and ofloxacin discontinued due to AEs. Seven of the 13 had mild to moderate elevated liver enzymes and two severely elevated levels, as well as two of the nine who completed treatment. One patient developed angioedema resulting in hospitalization.

A FQ/ETA regimen was used in 12 patients less than 18 years of age in Bamrah. Seven experienced AEs (nearly all gastrointestinal), but all continued through completion, so no discontinuations due to AEs. This is a small number of patients from only one study.

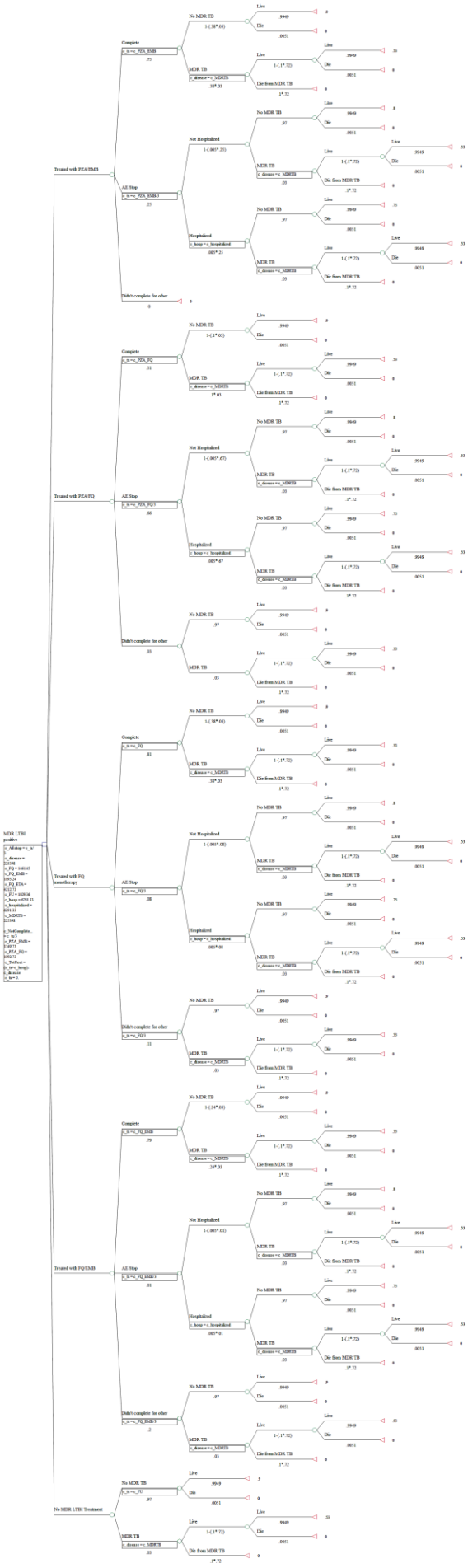
Studies often reported multiple regimens targeted to the drug susceptibility pattern of the index case. Limitations included that there was a wide range of treatment discontinuation by regimen.

Power Calculation to Detect MDR TB Incidence in the United States

In the United States, after the first year a contact was exposed to infectious MDR TB, it would take approximately 3 to 10 years to detect one case of incident MDR-TB disease. Calculations are as follows: Approximately 100 incident MDR TB cases occur per year of which 50 are infectious[35] and have 20 contacts/case[36] = 1000 MDR TB contacts/year, of whom approximately 30%-45% have MDR LTBI.[37, 38, 39] Assume 1.15% of persons with MDR LTBI quickly develop TB within the first year of infection,[40] or about 3 to 5 cases of MDR TB per year that might not be preventable if MDR TB diagnosis of the index case is delayed. The remainder of those with LTBI reactivate to TB at a rate of 0.00032[41] to 0.00084[42] per year for the remaining 39 years of their lives (assuming a normal lifespan of 79 years with 40 remaining years, 1st year of high incidence), then we would expect 0.096-0.378 MDR TB reactivation incident cases per year, or approximately 4 to 15 MDR TB cases over the remaining lives of the 300-450 with MDR LTBI. Average TB incidence per person with LTBI is estimated at:

50 MDR TB cases/year X 20 contacts/case = 1000 MDR TB contacts/year
Low annual estimate of MDR LTBI= 1000 X 0.3 =300
High annual estimate of MDR LTBI =1000 X 0.45 = 450
Low estimate of MDR TB fast incidence = 300 X 0.0115 ~ 3
High estimate of MDR TB fast incidence = 450 X 0.0115 ~ 5
Low estimate of MDR TB reactivation incidence per year = 300 X 0.00032 = .096
High estimate of MDR LTBI reactivation incidence = 450 X .00084 = .378
Low estimate of average MDR TB incidence per year of remaining life = (300 X (0.0115 + 39*(0.00032)))/40 = 0.18
High estimate of average MDR TB incidence per year of remaining life = (450 X (0.0115 + 39*(0.00084)))/40 = 0.50
1/0.50 ~ 2 years for incident MDR TB
1/0.18 ~ 5.5 years for incident MDR TB

Figure 1: Decision Tree


MDR LTBI positive
Treated with PZA/EMB
Complete
AE Stop
Didn't complete for other
No MDR TB
MDR TB
Die from MDR TB
Not Hospitalized
Hospitalized
Live
Die
Treated with PZA/FQ
Treated with FQ monotherapy
Treated with FQ/EMB
No MDR LTBI Treatment

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