Annals of Internal Medicine | Review

# Initial Drug Resistance and Tuberculosis Treatment Outcomes: Systematic Review and Meta-analysis

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**Background:** Despite the increasing prevalence of drug-resistant tuberculosis, most low- and middle-income countries use standardized regimens, without assessment of drug susceptibility.

**Purpose:** To perform a systematic review and meta-analysis of the effect of initial drug resistance and treatment regimen on tuberculosis treatment outcomes.

**Data Sources:** PubMed, the Cochrane Central Database of Clinical Trials, and EMBASE were searched for studies published in English from 1965 to June 2007. Additional studies were identified from cited references.

**Study Selection:** Randomized, controlled trials and cohort studies of standardized treatment of previously untreated patients with culture-confirmed pulmonary tuberculosis. Drug-susceptibility testing was done on pretreatment isolates from all patients and from patients with treatment failure or relapse.

**Data Extraction:** Two authors reviewed the studies for methods, initial drug resistance, treatment regimens, and outcomes.

**Data Synthesis:** Pooled cumulative incidences were computed with random-effects meta-analyses. Association between risk factors and outcomes were determined by using stratified analyses. The cumulative incidence of acquired drug resistance with initially pan-sensitive strains was 0.8% (95% CI, 0.5% to 1.0%) compared with 6% (CI, 4% to 8%) with initially single drug–resistant strains and 14% (CI, 9% to 20%) with initially polydrug-resistant strains. Failure and relapse were most strongly associated with initial drug resistance. Failure was also associated with shorter duration of rifampin therapy and nonuse of streptomycin, whereas the rate of relapse was higher with shorter duration of rifampin therapy and nonuse of pyrazinamide.

**Limitations:** Few studies included HIV-infected persons, and treatment outcomes were pooled despite considerable heterogeneity.

**Conclusion:** Treatment outcomes were substantially worse in the presence of initial drug resistance, which has important implications in resource-limited settings in which drug resistance is prevalent.

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Resistance to antituberculosis drugs was first described soon after the introduction of streptomycin (1) and is currently one of the most important threats to global tuberculosis control (2). In 2004, the World Health Organization estimated that among patients who had never received treatment before (new cases), the prevalence of drug resistance to any of the standard first-line tuberculosis drugs ranged from less than 5% to more than 30% in different countries (3). The World Health Organization also estimated that more than 240 000 cases of multidrug-resistant tuberculosis (defined as resistance to at least isoniazid and rifampin) occurred, which represented 2.7% of all new cases. An additional 181 000 cases of multidrug-resistant tuberculosis occurred among previously treated patients (representing 18.5% of re-treatment cases) (4). The threat of drug resistance has been underscored by recent reports of extensively drug-resistant strains (5). Drug-resistant strains cause much higher rates of mortality, failure, and relapse (6), and treatment is more toxic, expensive, and lengthy (7).

In addition to the ongoing HIV epidemic, the emergence of multidrug-resistant and extensively drug-resistant tuberculosis underscores the importance of preventing drug resistance (8, 9), especially in settings without the resources to do drug-sensitivity testing or purchase the second-line drugs for treatment. Selecting a strategy to prevent drug resistance should be based on strong evidence, such as the results a systematic review can provide. Therefore, we planned a systematic review and meta-analysis (if appropriate) among previously untreated patients (new cases) with active pulmonary tuberculosis to determine the association among tuberculosis treatment outcomes (failure, relapse, and acquired drug resistance) and initial drug resistance (that is, before treatment); duration of rifampin therapy; use of pyrazinamide; use of streptomycin; and the number of drugs used in therapy.

## Methods

### Data Sources

We searched PubMed, EMBASE, and the Cochrane Central Database of Clinical Trials for original articles and reviews from 1965 to June 2007. Our keywords included *tuberculosis* or *TB* and *treatment* or *therapy* and *resistance* or *MDR-TB* or *sensitivity* or *susceptibility*. We limited the

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**Context**

Identifying strategies to optimize tuberculosis treatment outcomes is important in light of the increasing occurrence of drug-resistant tuberculosis.

**Contribution**

This systematic review of 22 trials and 7 cohort studies involved 14 333 new tuberculosis cases. Findings showed that poor outcomes were associated with initial drug resistance and that treatment was not based on susceptibility testing. Estimated rates of failure or relapse were 35% to 40% for patients who received rifampin for 2 months and 20% for those who received rifampin for 6 months.

**Implication**

These findings suggest that poor outcomes can be anticipated in settings that, because of limited resources, do not do susceptibility testing before initiation of tuberculosis treatment.

—*The Editors*

search to studies published in English for treatment of active disease caused by *Mycobacterium tuberculosis* in humans. We searched reference lists of identified original articles and reviews for other relevant articles. We did not include abstracts, chapters of books, conference proceedings, or correspondence.

### Study Selection

We reviewed cohort studies or randomized, controlled trials (RCTs) that reported treatment outcomes of failure or relapse. In selected studies, all patients had active pulmonary disease, without previous treatment, that was confirmed by mycobacterial culture. Drug-susceptibility testing was done in all patients before treatment and among all failures or relapses by using standard methods (10, 11). Treatment was standardized (not individualized), was directly supervised or observed, and included isoniazid and rifampin. We reported the number of patients starting treatment and developing treatment outcomes by each treatment regimen and initial drug-susceptibility testing pattern. We excluded studies or groups that included rifapentine or rifabutine therapy, nondrug therapy (for example, vaccines), or therapies that would be considered inadequate by current standards (12–14).

Two investigators independently conducted the electronic search. The selection of articles for review was done in 3 stages: titles alone, then abstracts, and then full-text articles. Disagreements about study selection were resolved by consensus.

### Data Extraction and Quality Assessment

We reviewed selected studies by using standardized forms to abstract data about study design; treatment regimens; pretreatment drug-susceptibility testing; supervision of treatment; use of fixed-dose combinations; funding source; and numbers of patients who started treatment, defaulted, died, had treatment failure, were lost to follow-up, or had relapse. Two independent reviewers extracted the data, and disagreements were resolved by consensus.

We selected only high-quality studies for diagnosis, treatment, and outcome assessment. Studies were considered high quality if they lost fewer than 10% of patients during treatment, fewer than 10% during follow-up of 30 months or less, or fewer than 20% of patients during follow-up of 30 to 60 months. Randomized, controlled trials were considered high quality if they were double-blind and concealed allocation by using central randomization or numbered opaque, sealed envelopes; sealed envelopes from a closed bag; numbered or coded bottles or containers; or drugs prepared by a central pharmacy.

### Data Synthesis and Analysis

In accordance with the World Health Organization's definitions for tuberculosis control (15), treatment failure was defined as cultures that were consistently positive or positive and required treatment after 5 months of treatment. Relapse was defined as recurrence of positive cultures that required therapy after apparent cure. Initial drug resistance was defined as pretreatment resistance and categorized as pan-sensitive, single drug resistance (resistance to 1 first-line antituberculosis drug other than rifampin), or polydrug resistance (resistance to $\geq$2 drugs). If patients with initial rifampin resistance (and multidrug resistance) were identified in the report, they were excluded from analysis. Acquired drug resistance was defined as new resistance to 1 or more of the tuberculosis drugs received among patients with treatment failure and those with relapse.

Patients treated in different groups of the same RCT were analyzed as separate cohorts if the regimens differed in initial drug resistance, duration of rifampin, use of pyrazinamide or streptomycin, or number of drugs in the initial or continuation phase. The initial phase was defined as the initial period when more drugs were used—typically the first 1 to 3 months. The continuation phase was the remainder of therapy, when the number of drugs was reduced. For each cohort, we calculated cumulative incidence (and 95% CIs) of failure, relapse, and acquired drug resistance. We used forest plots to summarize these results. A random-effects meta-analysis was done by using the DerSimonian–Laird method (Meta-Disc software, version 1.2, Madrid, Spain [16]), with studies weighted by total sample size to pool incidence of all outcomes (17). We corrected for overdispersion to account for variability among studies. To account for heterogeneity, we did subgroup analyses and stratified study results by predefined covariates of interest. We assessed heterogeneity by using the chi-square test (statistical significance was set at $P < 0.05$) and evaluated the presence of a statistically significant degree of variability among studies.

### Role of the Funding Source

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## RESULTS

### Qualitative Assessment of Studies

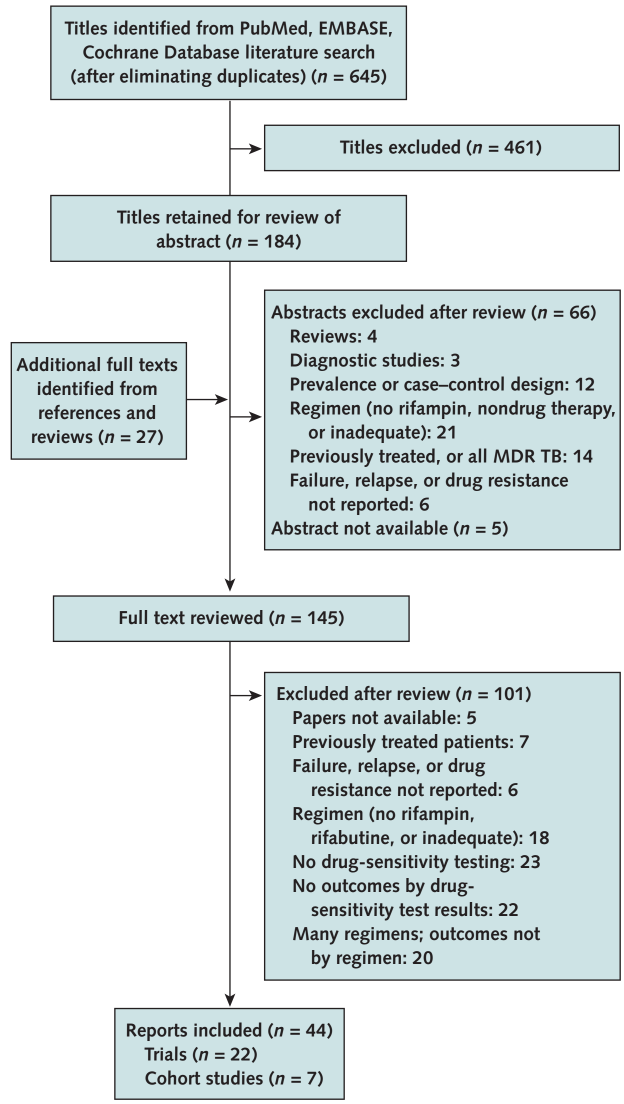
We identified 645 citations through the electronic database search. **Figure 1** summarizes the results of these searches, appraisals, and reasons for exclusion of studies. In brief, 44 of 145 full-text articles were reviewed and selected (22 RCTs and 7 cohort studies). We identified 39 articles describing 25 studies from the PubMed search, then an additional 3 articles describing 2 studies from the Cochrane database search and 2 further articles by using EMBASE. Failure and relapse were reported in 28 and 25 studies, respectively. Only 1 study received operating funds from a pharmaceutical company.

**Appendix Table 1** summarizes cohort studies, and **Appendix Table 2** summarizes the RCTs (both available at www.annals.org). Half of the trials were initiated from 1969 to 1979, compared with only 3 trials and 6 cohorts initiated since 1990. Because of the study selection criteria, all studies were considered to be of high quality in terms of diagnostic criteria, treatment administration, and outcome assessment. Of the studies assessing relapse, 23 (91%) were considered high quality because the dropout rate during follow-up was less than 10%. Half the studies reported methods of randomization, and all were considered adequate. Only 9% of studies were double-blind because of differences between groups in number of drugs, use of streptomycin, different lengths, or different frequency of administration. Only 5 studies included known HIV-positive patients, for a total of 712 HIV-infected patients in our review. Compared with those in RCTs, relapse rates in the cohort studies were the same, whereas rates of treatment failure and acquired drug resistance were somewhat higher (although not statistically significant).

### Incidence and Correlates of Treatment Outcomes

In total, treatment therapy failed in 235 of 13 048 patients (pooled incidence, 1.8% [95% CI, 1% to 3%]), and 591 of 9476 patients had relapse (pooled incidence, 6.2% [CI, 5% to 7%]). Failure and relapse were measured in 12 813 participants; of whom, 178 (1.4% [CI 1.0% to 1.7%]) had acquired drug resistance. Cumulative incidence was consistently low in all cohorts with initially pan-sensitive strains (**Figure 2**) but was much higher and more variable in cohorts with initial drug resistance (**Figures 3** and **4** [18–60]).

*Figure 1.* **Summary of literature search and study selection.**

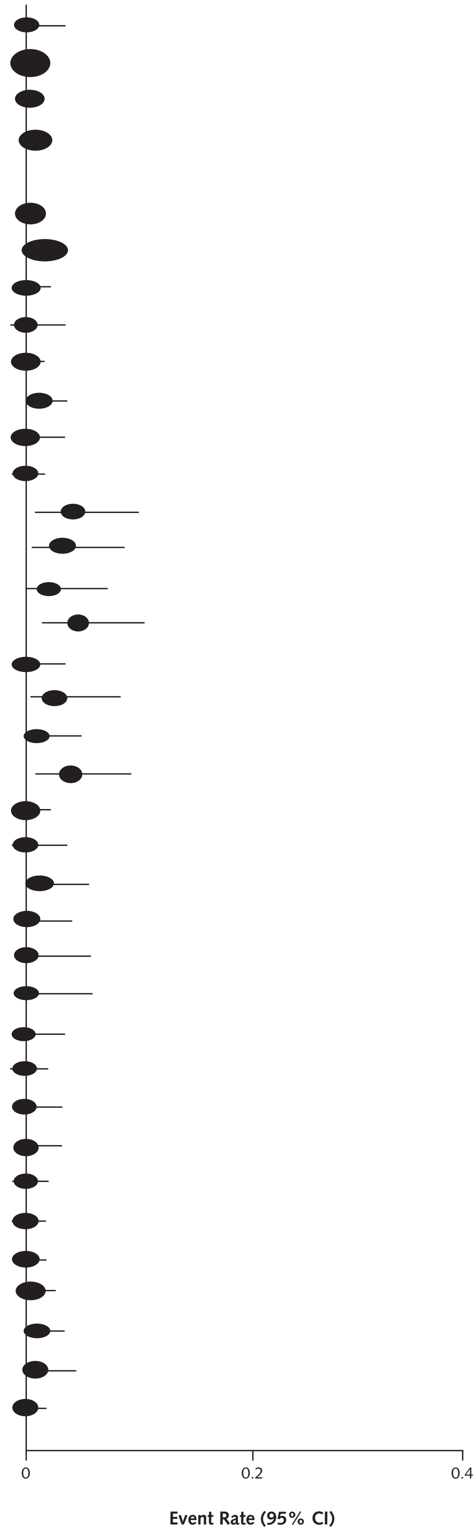



MDR TB = multidrug-resistant tuberculosis.

**Table 1** shows that treatment failure was very strongly associated with initial drug resistance: The cumulative incidence of failure in new cases with preexisting resistance to 1 drug (single drug resistance) was 8% (6% to 11%), and resistance to 2 drugs (polydrug resistance) was 21% (CI, 13% to 29%). The failure rate was also higher if streptomycin was not used or if only 2 drugs were used in the continuation phase of therapy. The cumulative incidence of failure in patients with initial drug resistance who received rifampin for 1 to 4 months was more than double that of patients with the same resistance who received rifampin for 5 months or more (**Figure 5**). Relapse was also strongly associated with initial drug resistance, and the rate was somewhat higher if pyrazinamide was not administered (**Table 2**). The relapse rate in patients who received ri-

*Figure 2.* **Forest plots of acquired drug resistance during treatment among cohorts with initially pan-sensitive strains.**

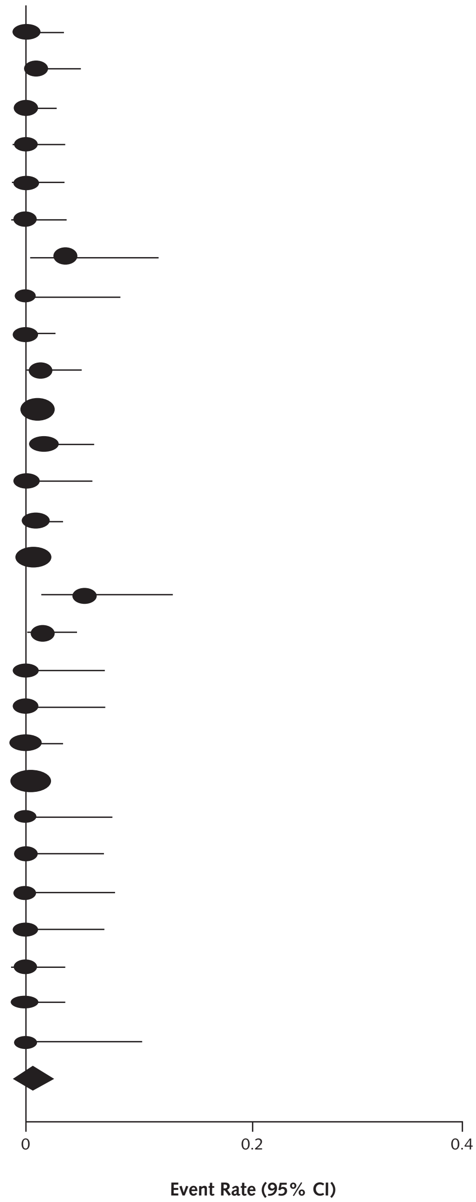
| Study (Reference) | Events, *n* | Patients Treated, *n* | Incidence (95% CI) |
|---|---|---|---|
| Cohn et al. (18) | 0 | 99 | 0.000 (0.000–0.037) |
| Churchyard et al. (21) | 5 | 1308 | 0.004 (0.001–0.009) |
| Churchyard et al. (21) | 1 | 306 | 0.003 (0.000–0.018) |
| Nettles et al. (24) | 3 | 407 | 0.007 (0.002–0.021) |
| Murray et al. (19) and Sonnenberg et al. (20) | 1 | 268 | 0.004 (0.000–0.021) |
| Seung et al. (22) | 21 | 1174 | 0.018 (0.011–0.027) |
| Jasmer et al. (23) | 0 | 135 | 0.000 (0.000–0.027) |
| E Africa/BMRC (26–28) | 0 | 99 | 0.000 (0.000–0.037) |
| E Africa/BMRC (29, 30) | 0 | 181 | 0.000 (0.000–0.020) |
| E Africa/BMRC (29, 30) | 2 | 183 | 0.011 (0.001–0.039) |
| E Africa/BMRC (29, 30) | 0 | 191 | 0.000 (0.000–0.019) |
| E Africa/BMRC (29, 30) | 0 | 179 | 0.000 (0.000–0.020) |
| E Africa/BMRC (33, 34) | 4 | 89 | 0.045 (0.012–0.111) |
| E Africa/BMRC (33, 34) | 3 | 88 | 0.034 (0.007–0.096) |
| E Africa/BMRC (33, 34) | 2 | 91 | 0.022 (0.003–0.077) |
| E Africa/BMRC (33, 34) | 5 | 99 | 0.051 (0.017–0.114) |
| E Africa/BMRC (33, 34) | 0 | 95 | 0.000 (0.000–0.038) |
| E Africa/BMRC (33, 34) | 2 | 77 | 0.026 (0.003–0.091) |
| E Africa/BMRC (33, 34) | 1 | 104 | 0.010 (0.000–0.052) |
| E Africa/BMRC (33, 34) | 4 | 97 | 0.041 (0.011–0.102) |
| HK/BMRC (31, 32) | 0 | 155 | 0.000 (0.000–0.024) |
| HK/BMRC (31, 32) | 0 | 92 | 0.000 (0.000–0.039) |
| HK/BMRC (31, 32) | 1 | 89 | 0.011 (0.000–0.061) |
| HK/BMRC (31, 32) | 0 | 77 | 0.000 (0.000–0.047) |
| HK/BMRC (31, 32) | 0 | 88 | 0.000 (0.000–0.041) |
| HK/BMRC (31, 32) | 0 | 87 | 0.000 (0.000–0.042) |
| HK/BMRC (31, 32) | 0 | 92 | 0.000 (0.000–0.039) |
| Singapore/BMRC (35–37) | 0 | 169 | 0.000 (0.000–0.022) |
| HK/BMRC (40–42) | 0 | 160 | 0.000 (0.000–0.023) |
| HK/BMRC (40–42) | 0 | 161 | 0.000 (0.000–0.023) |
| HK/BMRC (40–42) | 0 | 170 | 0.000 (0.000–0.021) |
| HK/BMRC (40–42) | 0 | 174 | 0.000 (0.000–0.021) |
| HK/BMRC (40–42) | 0 | 168 | 0.000 (0.000–0.023) |
| E&C Africa/BMRC (43, 44) | 1 | 197 | 0.005 (0.000–0.019) |
| E&C Africa/BMRC (43, 44) | 2 | 191 | 0.010 (0.001–0.037) |
| Tanzania/BMRC (48) | 1 | 113 | 0.009 (0.000–0.048) |
| HK/Madras BMRC (53) | 0 | 177 | 0.000 (0.000–0.021) |




*(continued)*

*Figure 2*—Continued.

| Study (Reference) *(continued)* | Events, *n* | Patients Treated, *n* | Incidence (95% CI) |
|---|---|---|---|
| Singapore BMRC (49, 50) | 0 | 103 | 0.000 (0.000–0.035) |
| Singapore BMRC (49, 50) | 1 | 103 | 0.010 (0.000–0.053) |
| Singapore BMRC (49, 50) | 0 | 113 | 0.000 (0.000–0.032) |
| Zierski et al. (38, 39) | 0 | 93 | 0.000 (0.000–0039) |
| Zierski et al. (38, 39) | 0 | 90 | 0.000 (0.000–0.040) |
| Zierski et al. (38, 39) | 0 | 91 | 0.000 (0.000–0.040) |
| HK/Madras/BMRC (55) | 2 | 53 | 0.038 (0.005–0.130) |
| HK/Madras/BMRC (55) | 0 | 38 | 0.000 (0.000–0.093) |
| TBRC Madras (45, 46) | 0 | 129 | 0.000 (0.000–0.028) |
| TBRC Madras (45, 46) | 2 | 132 | 0.015 (0.002–0.054) |
| Kenya/Zambia/BMRC (54) | 6 | 504 | 0.012 (0.004–0.026) |
| Snider et al. (47) | 2 | 112 | 0.018 (0.002–0.063) |
| Snider et al. (47) | 0 | 53 | 0.000 (0.000–0.067) |
| HK/BMRC (56) | 2 | 209 | 0.010 (0.001–0.034) |
| HK/BMRC (56) | 3 | 424 | 0.007 (0.001–0.021) |
| HK/BMRC (56) | 4 | 70 | 0.057 (0.016–0.140) |
| HK/BMRC (56) | 2 | 139 | 0.014 (0.002–0.051) |
| HK/Singapore BMRC (57) | 0 | 46 | 0.000 (0.000–0.077) |
| HK/Singapore/BMRC (57) | 0 | 47 | 0.000 (0.000–0.075) |
| TBRC Madras (51, 52) | 0 | 228 | 0.000 (0.000–0.016) |
| TBRC Chennai (60) | 5 | 867 | 0.006 (0.002–0.013) |
| HK/Singapore/BMRC (57) | 0 | 42 | 0.000 (0.000–0.084) |
| HK/Singapore/BMRC (57) | 0 | 46 | 0.000 (0.000–0.077) |
| HK/Singapore/BMRC (57) | 0 | 41 | 0.000 (0.000–0.086) |
| HK/Singapore/BMRC (57) | 0 | 47 | 0.000 (0.000–0.075) |
| Zhang et al. (58) | 0 | 94 | 0.000 (0.000–0.038) |
| Zhang et al. (58) | 0 | 95 | 0.000 (0.000–0.038) |
| TBTC/CDC (59) | 0 | 31 | 0.000 (0.000–0.112) |
| | | | 0.008 (0.005–0.01)* |




BMRC = British Medical Research Council; E Africa = East Africa; E&C Africa = East and Central Africa; HK = Hong Kong; TBRC = Tuberculosis Research Centre; TBTC/CDC = Tuberculosis Trials Consortium/Centers for Disease Control and Prevention.
*Pooled event rate (95% CI).

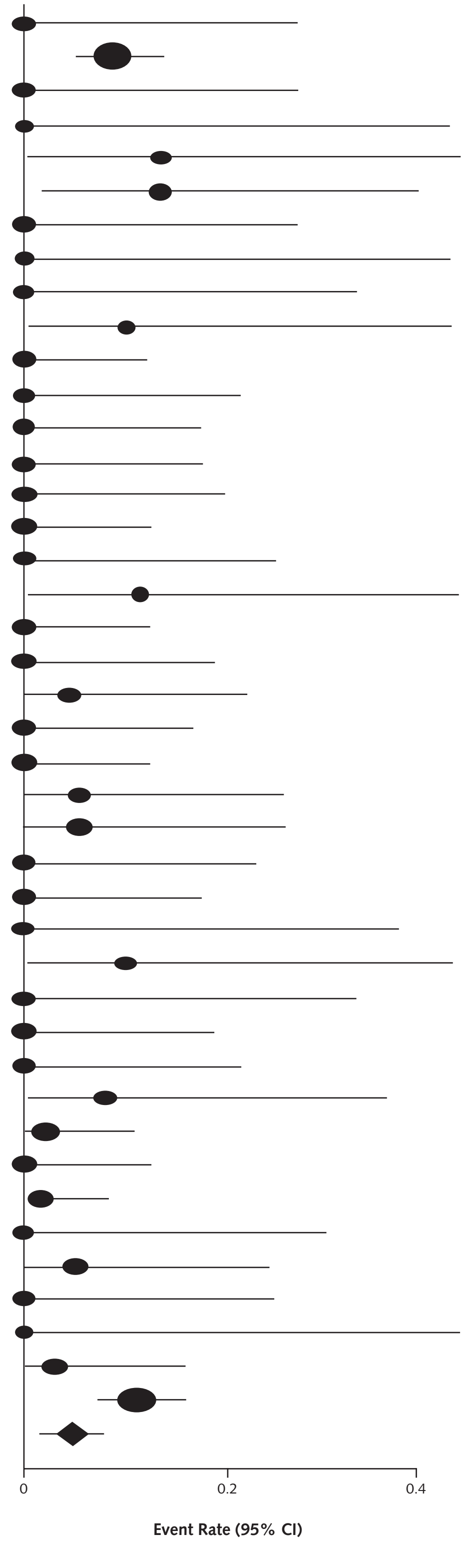
fampin for 4 months or less was more than twice as high in the presence of initial drug resistance (**Figure 5**). Acquired drug resistance was very strongly associated with initial drug resistance (**Table 3**) but only weakly associated with other treatment factors. Acquired drug resistance was more frequent in patients with initial polydrug resistance if a patient received rifampin for a longer duration (**Figure 5**). Pyrazinamide was associated with lower relapse rates in patients with initial drug resistance; however, failure and acquired drug resistance rates did not differ if pyrazinamide was used (data not shown).

## Discussion

In our analysis of 22 RCTs and 7 cohort studies involving 14 333 new tuberculosis cases, the incidence of failure, relapse, and acquired drug resistance were substantially increased in patients with initial drug resistance who

*Figure 3.* **Forest plot of acquired drug resistance during treatment among cohorts with initially single drug–resistant strains.**

| Study (Reference) | Events, *n* | Patients Treated, *n* | Incidence (95% CI) |
|---|---|---|---|
| Cohn et al. (18) | 0 | 9 | 0.000 (0.000–0.336) |
| Seung et al. (22) | 16 | 147 | 0.109 (0.064–0.171) |
| E Africa/BMRC (33, 34) | 0 | 9 | 0.000 (0.000–0.336) |
| E Africa/BMRC (33, 34) | 0 | 5 | 0.000 (0.000–0.522) |
| E Africa/BMRC (33, 34) | 1 | 6 | 0.167 (0.004–0.641) |
| E Africa/BMRC (33, 34) | 2 | 12 | 0.167 (0.021–0.484) |
| E Africa/BMRC (33, 34) | 0 | 9 | 0.000 (0.000–0.336) |
| E Africa/BMRC (33, 34) | 0 | 5 | 0.000 (0.000–0.522) |
| E Africa/BMRC (33, 34) | 0 | 7 | 0.000 (0.000–0.410) |
| E Africa/BMRC (33, 34) | 1 | 8 | 0.125 (0.003–0.527) |
| HK/BMRC (31, 32) | 0 | 23 | 0.000 (0.000–0.148) |
| HK/BMRC (31, 32) | 0 | 12 | 0.000 (0.000–0.265) |
| HK/BMRC (31, 32) | 0 | 15 | 0.000 (0.000–0.218) |
| HK/BMRC (31, 32) | 0 | 15 | 0.000 (0.000–0.218) |
| HK/BMRC (31, 32) | 0 | 13 | 0.000 (0.000–0.247) |
| HK/BMRC (31, 32) | 0 | 22 | 0.000 (0.000–0.154) |
| HK/BMRC (31, 32) | 0 | 10 | 0.000 (0.000–0.308) |
| Singapore/BMRC (35–37) | 1 | 7 | 0.143 (0.004–0.579) |
| HK/BMRC (40–42) | 0 | 22 | 0.000 (0.000–0.154) |
| HK/BMRC (40–42) | 0 | 14 | 0.000 (0.000–0.232) |
| HK/BMRC (40–42) | 1 | 18 | 0.056 (0.001–0.273) |
| HK/BMRC (40–42) | 0 | 16 | 0.000 (0.000–0.206) |
| HK/BMRC (40–42) | 0 | 22 | 0.000 (0.000–0.154) |
| E&C Africa/BMRC (43, 44) | 1 | 15 | 0.067 (0.002–0.319) |
| E&C Africa/BMRC (43, 44) | 1 | 15 | 0.067 (0.002–0.319) |
| Tanzania/BMRC (48) | 0 | 11 | 0.000 (0.000–0.285) |
| HK/Madras BMRC (53) | 0 | 15 | 0.000 (0.000–0.218) |
| Singapore BMRC (49, 50) | 0 | 6 | 0.000 (0.000–0.459) |
| Singapore BMRC (49, 50) | 1 | 8 | 0.125 (0.003–0.527) |
| Singapore BMRC (49, 50) | 0 | 7 | 0.000 (0.000–0.410) |
| Zierski et al. (38, 39) | 0 | 14 | 0.000 (0.000–0.232) |
| HK/Madras/BMRC (55) | 0 | 12 | 0.000 (0.000–0.265) |
| HK/Madras/BMRC (55) | 1 | 10 | 0.100 (0.003–0.445) |
| Kenya/Zambia/BMRC (54) | 1 | 38 | 0.026 (0.001–0.138) |
| HK/BMRC (56) | 0 | 22 | 0.000 (0.000–0.154) |
| HK/BMRC (56) | 1 | 53 | 0.019 (0.000–0.101) |
| HK/BMRC (56) | 0 | 8 | 0.000 (0.000–0.369) |
| HK/BMRC (56) | 1 | 16 | 0.063 (0.002–0.302) |
| HK/Singapore/BMRC (57) | 0 | 10 | 0.000 (0.000–0.308) |
| HK/Singapore/BMRC (57) | 0 | 4 | 0.000 (0.000–0.602) |
| TBRC Madras (51, 52) | 1 | 26 | 0.038 (0.001–0.196) |
| TBRC Chennai (60) | 23 | 167 | 0.138 (0.089–0.199) |
| | | | 0.060 (0.04–0.8)* |



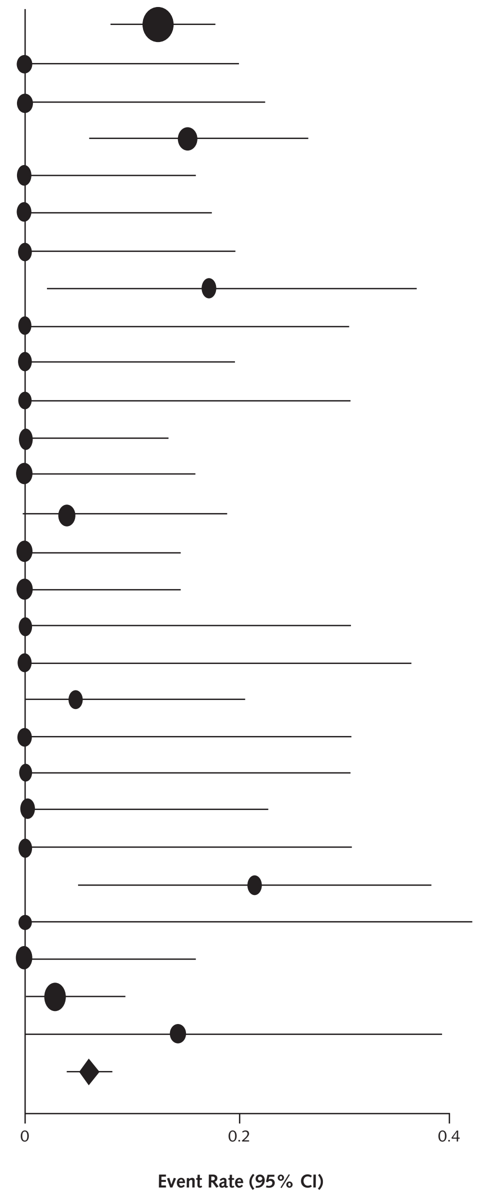

BMRC = British Medical Research Council; E Africa = East Africa; E&C Africa = East and Central Africa; HK = Hong Kong; TBRC = Tuberculosis Research Centre.
*Pooled event rate (95% CI).

were treated with standardized regimens that were not based on susceptibility testing results. Patients with resistance to 2 or more drugs had worse treatment outcomes than patients with single drug–resistant strains. These findings have important implications for global tuberculosis control.

The most consistent finding in our review is that initial drug resistance was associated with substantially increased cumulative incidence of failure, relapse, and acquired drug resistance. This is consistent with recent reports documenting the development of multidrug-resistant tuberculosis in patients with unrecognized initial resistance who received standardized regimens (61, 62). In the studies reviewed, patients received standardized regimens, regardless of drug-susceptibility testing results. Hence, the findings are directly relevant to most low- and middle-income countries, in which patients with newly diagnosed tuberculosis receive standardized therapy (12, 63) without performance of drug-sensitivity testing because it is considered too costly and complex. By using the results of our review, rates of failure and relapse can be predicted

*Figure 4.* **Forest plots of acquired drug resistance during treatment among cohorts with initially polydrug-resistant strains.**

| Study (Reference) | Events, *n* | Patients Treated, *n* | Incidence (95% CI) |
|---|---|---|---|
| Seung et al. (22) | 21 | 72 | 0.292 (0.190–0.411) |
| E Africa/BMRC (33, 34) | 0 | 6 | 0.000 (0.000–0.459) |
| E Africa/BMRC (33, 34) | 0 | 5 | 0.000 (0.000–0.522) |
| HK/BMRC (31, 32) | 6 | 17 | 0.353 (0.142–0.617) |
| HK/BMRC (31, 32) | 0 | 8 | 0.000 (0.000–0.369) |
| HK/BMRC (31, 32) | 0 | 7 | 0.000 (0.000–0.410) |
| HK/BMRC (31, 32) | 0 | 6 | 0.000 (0.000–0.459) |
| HK/BMRC (31, 32) | 2 | 5 | 0.400 (0.053–0.853) |
| HK/BMRC (31, 32) | 0 | 3 | 0.000 (0.000–0.708) |
| HK/BMRC (31, 32) | 0 | 6 | 0.000 (0.000–0.459) |
| Singapore/BMRC (35–37) | 0 | 3 | 0.000 (0.000–0.708) |
| HK/BMRC (40–42) | 0 | 10 | 0.000 (0.000–0.308) |
| HK/BMRC (40–42) | 0 | 8 | 0.000 (0.000–0.369) |
| HK/BMRC (40–42) | 1 | 10 | 0.100 (0.003–0.445) |
| HK/BMRC (40–42) | 0 | 9 | 0.000 (0.000–0.336) |
| HK/BMRC (40–42) | 0 | 9 | 0.000 (0.000–0.336) |
| E&C Africa/BMRC (43, 44) | 0 | 3 | 0.000 (0.000–0.708) |
| Tanzania/BMRC (48) | 0 | 2 | 0.000 (0.000–0.842) |
| HK/Madras BMRC (53) | 1 | 9 | 0.111 (0.003–0.482) |
| Singapore BMRC (49, 50) | 0 | 3 | 0.000 (0.000–0.708) |
| Singapore BMRC (49, 50) | 0 | 3 | 0.000 (0.000–0.708) |
| Singapore BMRC (49, 50) | 0 | 5 | 0.000 (0.000–0.522) |
| HK/Madras/BMRC (55) | 0 | 3 | 0.000 (0.000–0.708) |
| HK/Madras/BMRC (55) | 3 | 6 | 0.500 (0.118–0.882) |
| Kenya/Zambia/BMRC (54) | 0 | 1 | 0.000 (0.000–0.975) |
| HK/BMRC (56) | 0 | 8 | 0.000 (0.000–0.369) |
| HK/BMRC (56) | 2 | 30 | 0.067 (0.008–0.221) |
| HK/Singapore/BMRC (57) | 1 | 3 | 0.333 (0.008–0.906) |
| | | | 0.140 (0.09–0.20)* |




BMRC = British Medical Research Council; E Africa = East Africa; E&C Africa = East and Central Africa; HK = Hong Kong.
*Pooled event rate (95% CI).

*Table 1.* **Pooled Estimates of Treatment Failure, Stratified by Initial Drug Resistance and Treatment Regimen Variables**

| Factor | Cohorts, *n* | Events/Participants, *n/n* | Pooled Cumulative Incidence (95% CI) | *P* Value* |
|---|---|---|---|---|
| **Initial drug resistance** | | | | |
| Sensitive to all tuberculosis drugs | 66 | 108/11 905 | 0.9 (0.6–1.2) | <0.001 |
| Single drug resistance | 42 | 73/883 | 8 (6–11) | <0.001 |
| Polydrug resistance | 28 | 54/260 | 21 (13–29) | <0.001 |
| **Duration of rifampin therapy** | | | | |
| 1–4 mo | 52 | 43/3457 | 1.2 (0.4–3) | <0.001 |
| ≥5 mo | 85 | 192/9591 | 2 (1–3) | <0.001 |
| **Use of streptomycin** | | | | |
| Not used | 32 | 173/6079 | 3 (1–3) | <0.001 |
| Used (0.5–12 mo) | 104 | 62/6969 | 1 (0–2) | <0.001 |
| **Use of pyrazinamide** | | | | |
| Not used | 20 | 11/1385 | 1 (0–3) | <0.001 |
| Used (1–8 mo) | 117 | 224/11 663 | 2 (1–3) | <0.001 |
| **Drugs used** | | | | |
| Initial phase | | | | |
| 2–3 drugs | 31 | 36/3244 | 1 (0–2.5) | <0.001 |
| ≥4 drugs | 105 | 199/9804 | 2 (1–3) | <0.001 |
| Continuation phase | | | | |
| 2 drugs | 65 | 196/8031 | 2 (1–4) | <0.001 |
| ≥3 drugs | 71 | 39/5017 | 0.8 (0–2) | <0.001 |

* Chi-square *P* value for heterogeneity of stratification variable across cohorts.

among patients with newly diagnosed tuberculosis with initial drug resistance who receive internationally recommended standardized regimens, that is, 2 or 6 months of rifampin treatment (12, 63). Therapy will fail or relapse will occur in 35% to 40% of patients with newly diagnosed tuberculosis, who receive the standardized regimen of 2 months of rifampin treatment. Therapy will fail or relapse will occur in 20% of those who receive the standardized regimen of rifampin for 6 months.

These poor outcomes will result in greater morbidity and mortality for patients and, through amplification of drug resistance, greater harm for the community in the long term. Improved capacity to detect initial drug resistance is urgently needed. This could be achieved through greater use of existing technologies for drug-sensitivity testing (64) or through adoption of recently developed rapid tests for drug resistance (65).

There is considerable interest in the development of new diagnostic tests (65), drugs (66), and regimens (67) for the management of multidrug-resistant tuberculosis. We suggest that better detection of initial drug resistance and development of appropriate treatment regimens in countries in which the prevalence of all forms of drug resistance is already high should be an immediate priority for the prevention of multidrug-resistant tuberculosis. Better supervision of currently recommended standardized regimens may prevent multidrug resistance (2). However, our results suggest that greater application of these regimens may actually create more cases of multidrug-resistant tuberculosis, by amplification of resistance in patients with unrecognized initial drug resistance.

Our findings further imply that all outcomes were worse if patients received rifampin for 4 months or less. This is relevant for countries now treating all patients with newly diagnosed tuberculosis with standardized regimens that include rifampin for the first 2 months only (63), and reexamination of these regimens may be warranted, particularly because of the low cost of rifampin when purchased through the Global Drug Facility (68).

Our review has limitations, despite the large number of studies and study participants. The most important is that we compared different groups of RCTs with groups from other trials. Bias could have been introduced if nontreatment covariates, such as age, severity of disease, or other comorbid conditions, were associated with certain regimens. For example, comparison of patients who received rifampin for 2 months with patients in different trials who received rifampin for 6 months could have been problematic if there were baseline differences in the 2 study samples. Pooling results only from trials with identical regimens (and balance of covariates among groups within each trial) would protect against this type of confounding but would have severely restricted this review. We chose to compare several different treatment regimens across studies to allow pooling of the larger study samples that we needed to analyze the relatively uncommon outcome of acquired drug resistance. We were able to analyze multiple treatment factors because the patients with initial drug resistance were treated with many different regimens. To minimize differences among studies, we restricted the review to trials of adequate treatment (those with regimens containing at least isoniazid and rifampin [14, 63, 69]) of previously untreated adults with microbiologically confirmed, active pulmonary tuberculosis and microbiologically confirmed outcomes. Although settings differed, all samples were measured from the general population—not subpopulations (for example, homeless persons or users of illicit drugs)—to enhance comparability.

The original trials were not explicitly designed for patients with drug-resistant strains. In total, 883 patients with single drug resistance were treated in 42 different cohorts, and 260 patients in 28 cohorts had polydrug-resistant strains. The heterogeneity of results in these cohorts with initial drug resistance may have reflected the small numbers in each group; differences in the actual drug resistance patterns or regimens used; and other differences in age, comorbid conditions, disease severity, and health system factors. Thus, the striking results for drug-resistant strains must be viewed with some caution. However, a review of these older trials, in which patients with initial drug resistance were treated with standard regimens, is valuable because these trials will not likely be repeated. Information from RCTs of the treatment of drug-resistant tuberculosis is urgently needed (67).

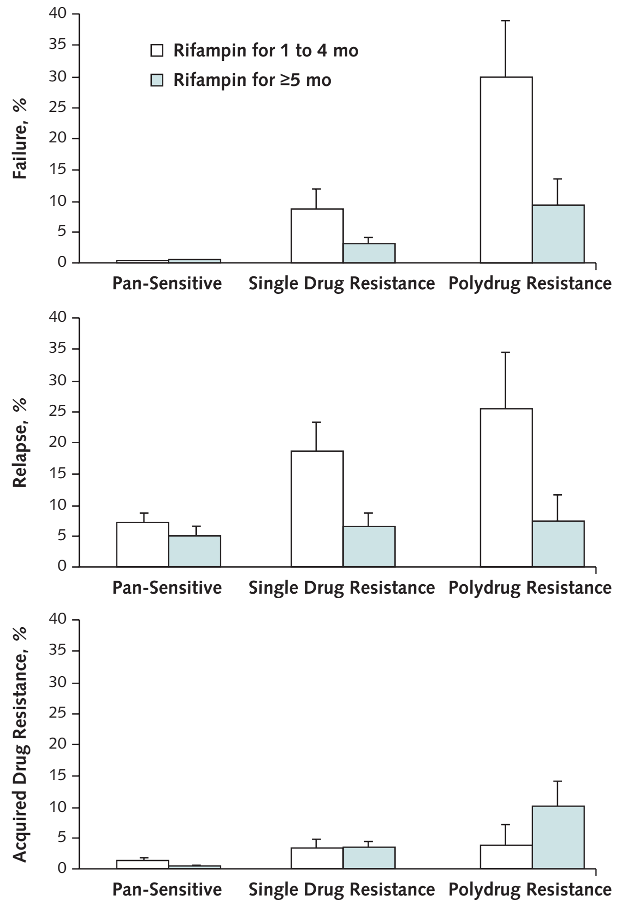
Relatively few studies included HIV-infected patients. Only 712 HIV-infected participants were studied, limiting power to detect effects associated with this covariate. In addition, this information was available only as an overall average prevalence in the study sample, which is inevitably less accurate than individual-level data. Nonetheless, HIV infection was statistically significantly associated with failure, as others have reported (70). We did not assess the effect of other covariates, such as age or sex.

The large number and sample sizes, diverse treatment regimens, and wide range of settings of the trials contributed to the heterogeneity of results. However, this factor, along with the inclusion of cohort studies that better reflect typical practice conditions, should enhance the generalizability of the review. The somewhat worse treatment outcomes in the cohort studies suggest that rates of failure, relapse, and acquired drug resistance may be higher in field conditions than estimated in this review, which predominantly includes results from RCTs. Dropout rates, participant selection, and outcome measures determined that most studies were of high quality. Concealment of treatment allocation was adequate when stated (but was not stated in half of the studies). Although very few trials were double-blind, the use of objective, microbiologically confirmed outcomes should have limited bias. The analysis of results from multiple trials included patients with pan-sensitive and drug-resistant strains, allowing the assessment of the relative effect of different treatment-related variables on tuberculosis treatment outcomes in all patients.

Our findings suggest an urgent need for RCTs to evaluate improved standardized tuberculosis treatment regimens. These trials should be conducted in low- and middle-income countries with limited access to drug-susceptibility testing and moderate to high prevalence of initial drug resistance. Studies in resource-limited settings of the feasibility, cost, and impact of new methods of drug-susceptibility testing are also urgently needed. These studies should assess inexpensive, simple, and rapid methods that have already been developed for these settings (65).

In conclusion, initial drug resistance was very strongly associated with treatment failure, relapse, and acquired drug resistance in previously untreated patients receiving standardized treatment. In the presence of initial drug resistance, treatment outcomes were statistically significantly worse if patients received rifampin for less than 5 months. Prompt action is needed to improve the detection and treatment of patients with underlying initial drug resistance. This is particularly urgent in settings with limited resources—places in which rates of initial drug resistance are high and the current approach may be amplifying drug resistance and worsening prospects for tuberculosis control in the long term.

*Figure 5.* **Association of duration of rifampin therapy and initial drug resistance with failure, relapse, and acquired drug resistance.**




Mean cumulative incidences and standard errors are shown for each estimate in which there were ≥2 studies. *Single drug resistance* is resistance to any 1 drug other than rifampin. *Polydrug resistance* is resistance to ≥2 drugs.

*Table 2.* **Pooled Estimates of Relapse, Stratified by Initial Drug Resistance and Treatment Regimen Variables**

| Factor | Cohorts, *n* | Events/Participants, *n/n* | Pooled Cumulative Incidence (95% CI) | *P* Value* |
|---|---|---|---|---|
| **Initial drug resistance** | | | | |
| Sensitive to all tuberculosis drugs | 63 | 492/8665 | 6 (5–7) | <0.001 |
| Single drug resistance | 41 | 82/661 | 12 (8–17) | <0.001 |
| Polydrug resistance | 27 | 17/150 | 11 (5–18) | NS |
| **Duration of rifampin therapy** | | | | |
| 1–4 mo | 52 | 249/3084 | 8 (6–10) | <0.001 |
| ≥5 mo | 79 | 342/6392 | 5 (4–6) | <0.001 |
| **Use of streptomycin** | | | | |
| Not used | 28 | 215/3404 | 6 (5–8) | <0.001 |
| Used (0.5–12 mo) | 103 | 376/6072 | 6 (5–8) | <0.001 |
| **Use of pyrazinamide** | | | | |
| Not used | 20 | 135/1290 | 11 (6–15) | <0.001 |
| Used (1–8 mo) | 111 | 456/8186 | 6 (5–7) | <0.001 |
| **Drugs used** | | | | |
| Initial phase | | | | |
| 2–3 drugs | 30 | 116/1811 | 6 (4–9) | <0.001 |
| ≥4 drugs | 101 | 475/7665 | 6 (5–7) | <0.001 |
| Continuation phase | | | | |
| 2 drugs | 61 | 352/5129 | 7 (5–8) | <0.001 |
| ≥3 drugs | 70 | 239/4347 | 5.5 (4–7) | <0.001 |
| **Dropouts in follow-up** | | | | |
| ≥10% | 37 | 87/1286 | 7 (4–11) | <0.001 |
| <10% | 94 | 504/8190 | 6 (5–7) | <0.001 |

NS = not significant.
* Chi-square *P* value for heterogeneity of stratification variable across cohorts.

*Table 3.* **Pooled Estimates of Acquired Drug Resistance in Treatment Failure and Relapse, Stratified by Initial Drug Resistance and Treatment Regimen Variables**

| Factor | Cohorts, *n* | Events/Participants, *n/n* | Pooled Cumulative incidence (95% CI) | *P* Value* |
|---|---|---|---|---|
| **Initial drug resistance** | | | | |
| Sensitive to all tuberculosis drugs | 65 | 88/11 670 | 0.8 (0.5–1) | <0.001 |
| Single drug resistance | 42 | 53/883 | 6 (4–8) | <0.001 |
| Polydrug resistance | 28 | 37/260 | 14 (9–20) | <0.001 |
| **Duration of rifampin therapy** | | | | |
| 1–4 mo | 51 | 42/3222 | 1.3 (0.6–2) | 0.007 |
| ≥5 mo | 84 | 136/9591 | 1.4 (0.6–2) | <0.001 |
| **Use of streptomycin** | | | | |
| Not used | 32 | 106/6079 | 1.7 (0–3) | <0.001 |
| Used (0.5–12 mo) | 103 | 72/6734 | 1.1 (0.5–2) | <0.001 |
| **Use of pyrazinamide** | | | | |
| Not used | 20 | 21/1385 | 1.5 (0–4) | <0.001 |
| Used (1–8 mo) | 115 | 157/11 428 | 1.4 (1–2) | <0.001 |
| **Drugs used** | | | | |
| Initial phase | | | | |
| 3 drugs | 31 | 35/3244 | 1.5 (1–2) | <0.001 |
| ≥4 drugs | 104 | 143/9569 | 1.1 (0–2) | <0.001 |
| Continuation phase | | | | |
| 2 drugs | 65 | 136/8031 | 0.9 (0–2) | <0.001 |
| ≥3 drugs | 70 | 42/4782 | 1.7 (1–3) | <0.001 |
| **Dropouts in follow-up** | | | | |
| ≥10% | 43 | 84/4772 | 1.8 (0.3–3) | <0.001 |
| <10% | 92 | 94/8041 | 1.2 (0.6–2) | <0.001 |

* Chi-square *P* value for heterogeneity of stratification variable across cohorts.

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## References

1. **Pyle MM.** Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. Proc Staff Meet Mayo Clin. 1947;22:465-73.
2. **Dye C, Williams BG, Espinal MA, Raviglione MC.** Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. Science. 2002;295: 2042-6. [PMID: 11896268]
3. **Aziz MA, Wright A, Laszlo A, De MA, Portaels F, Van DA et al. WHO/ International Union Against Tuberculosis And Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance.** Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet. 2006;368:2142-54. [PMID: 17174706]
4. **Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al.** Global incidence of multidrug-resistant tuberculosis. J Infect Dis. 2006;194: 479-85. [PMID: 16845631]
5. **Centers for Disease Control and Prevention (CDC).** Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000-2004. MMWR Morb Mortal Wkly Rep. 2006;55:301-5. [PMID: 16557213]
6. **Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al.** Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368: 1575-80. [PMID: 17084757]
7. **Caminero JA, World Health Organization, American Thoracic Society, British Thoracic Society.** Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis. 2006;10:829-37. [PMID: 16898365]
8. **Espinal M, Frieden TR.** What are the causes of drug-resistant tuberculosis? In: Frieden TR, ed. Toman's Tuberculosis: Case Detection, Treatment, and Monitoring. Questions and Answers. 2nd ed. Geneva: World Health Organization; 2004:207-8.
9. **Toman K.** How does drug resistance develop? In: Frieden TR, ed. Toman's Tuberculosis: Case Detection, Treatment, and Monitoring. Questions and Answers. 2nd ed. Geneva: World Health Organization; 2004:193-94.
10. **Boulahbal F, Heifets L.** Bacteriology of tuberculosis. In: Raviglione M, ed. Reichman and Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed. New York: Informa Healthcare USA; 2006:29-46.
11. **Canetti G, Fox W, Khomenko A, Mahler HT, Menon NK, Mitchison DA, et al.** Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organ. 1969;41:21-43. [PMID: 5309084]
12. **World Health Organization.** Treatment of Tuberculosis: Guidelines for National Programmes. Geneva: World Health Organization; 2003:1-108.
13. **Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC.** International standards for tuberculosis care. Lancet Infect Dis. 2006;6:710-25. [PMID: 17067920]
14. American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167:603-62. [PMID: 12588714]
15. **World Health Organization.** Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis. 2001;5:213-5. [PMID: 11326818]
16. **Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A.** Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006; 6:31. [PMID: 16836745]
17. **Normand SL.** Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med. 1999;18:321-59. [PMID: 10070677]
18. **Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA.** A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. Ann Intern Med. 1990;112: 407-15. [PMID: 2106816]
19. **Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P.** Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. Am J Respir Crit Care Med. 1999;159:733-40. [PMID: 10051244]
20. **Sonnenberg P, Murray J, Shearer S, Glynn JR, Kambashi B, Godfrey-Faussett P.** Tuberculosis treatment failure and drug resistance—same strain or reinfection? Trans R Soc Trop Med Hyg. 2000;94:603-7. [PMID: 11198641]
21. **Churchyard GJ, Corbett EL, Kleinschmidt I, Mulder D, De Cock KM.** Drug-resistant tuberculosis in South African gold miners: incidence and associated factors. Int J Tuberc Lung Dis. 2000;4:433-40. [PMID: 10815737]
22. **Seung KJ, Gelmanova IE, Peremitin GG, Golubchikova VT, Pavlova VE, Sirotkina OB, et al.** The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. Clin Infect Dis. 2004;39:1321-8. [PMID: 15494909]
23. **Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL.** Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. Am J Respir Crit Care Med. 2004;170:561-6. [PMID: 15184210]
24. **Nettles RE, Mazo D, Alwood K, Gachuhi R, Maltas G, Wendel K, et al.** Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. Clin Infect Dis. 2004;38:731-6. [PMID: 14986259]
25. Results at 5 years of a controlled comparison of a 6-month and a standard 18-month regimen of chemotherapy for pulmonary tuberculosis. Am Rev Respir Dis. 1977;116:3-8. [PMID: 69411]
26. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. East African-British Medical Research Councils. Lancet. 1974;2:237-40. [PMID: 4135686]
27. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Second report. Lancet. 1973;1: 1331-8. [PMID: 4122738]
28. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet. 1972;1:1079-85. [PMID: 4112569]
29. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet. 1974;2:1100-6. [PMID: 4139405]
30. Controlled clinical trial of four 6-month regimens of chemotherapy for pulmonary tuberculosis. Second report. Second East African/British Medical Research Council Study. Am Rev Respir Dis. 1976;114:471-5. [PMID: 788570]
31. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. First report. Am Rev Respir Dis. 1978;118:219-28. [PMID: 100029]
32. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. Tubercle. 1979;60:201-10. [PMID: 396701]
33. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis. Second report. Third East African/British Medical Research Council Study. Tubercle. 1980;61:59-69. [PMID: 6159711]
34. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis: first report: Third East African/British Medical Research Councils study. Am Rev Respir Dis. 1978;118:

39-48. [PMID: 79319]
35. Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis. 1986;133:779-83. [PMID: 2871788]
36. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis: the results up to 30 months. Tubercle. 1981;62:95-102. [PMID: 7029838]
37. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Am Rev Respir Dis. 1979;119:579-85. [PMID: 375787]
38. **Zierski M, Bek E, Long MW, Snider DE Jr.** Short-course (6-month) cooperative tuberculosis study in Poland: results 30 months after completion of treatment. Am Rev Respir Dis. 1981;124:249-51. [PMID: 7283257]
39. **Zierski M, Bek E, Long MW, Snider DE Jr.** Short-course (6 month) cooperative tuberculosis study in Poland: results 18 months after completion of treatment. Am Rev Respir Dis. 1980;122:879-89. [PMID: 7006476]
40. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis. 1987;136:1339-42. [PMID: 2891333]
41. Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Hong Kong Chest Service/British Medical Research Council. Tubercle. 1982;63:89-98. [PMID: 6758252]
42. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet. 1981;1:171-4. [PMID: 6109855]
43. Controlled clinical trial of 4 short-couse regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis. Tubercle. 1983;64:153-66. [PMID: 6356538]
44. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis: final report. East and Central African/British Medical Research Council Fifth Collaborative Study. Tubercle. 1986;67:5-15. [PMID: 3521015]
45. **Santha T, Nazareth O, Krishnamurthy MS, Balasubramanian R, Vijayan VK, Janardhanam B, et al.** Treatment of pulmonary tuberculosis with short course chemotherapy in south India—5-year follow up. Tubercle. 1989;70:229-34. [PMID: 2516669]
46. Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. Tubercle. 1983;64:73-91. [PMID: 6351390]
47. **Snider DE, Graczyk J, Bek E, Rogowski J.** Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin, and pyrazinamide with and without streptomycin. Am Rev Respir Dis. 1984;130:1091-4. [PMID: 6508006]
48. Controlled clinical trial of two 6-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Tanzania/British Medical Research Council Study. Am Rev Respir Dis. 1985;131:727-31. [PMID: 3890640]
49. Clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis. 1985;132:374-8. [PMID: 2862820]
50. Five-year follow-up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis. 1988;137:1147-50. [PMID: 2904237]
51. **Balasubramanian R, Sivasubramanian S, Vijayan VK, Ramachandran R, Jawahar MS, Paramasivan CN, et al.** Five year results of a 3-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in south India. Tubercle. 1990;71:253-8. [PMID: 2125153]
52. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. Am Rev Respir Dis. 1986;134:27-33. [PMID: 3524334]
53. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1989;139:871-6. [PMID: 2648911]
54. Controlled clinical trial of levamisole in short-course chemotherapy for pulmonary tuberculosis. A Kenyan/Zambian/British Medical Research Council Collaborative Study. Am Rev Respir Dis. 1989;140:990-5. [PMID: 2508527]
55. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. Hong Kong Chest Service/tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1991;143:262-7. [PMID: 1990938]
56. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis. 1991;143:700-6. [PMID: 1901199]
57. Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis. 1991;143:707-12. [PMID: 1901200]
58. **Zhang LX, Kan G, Tu DH, Wan LY, Faruqi AR.** Fixed-dose combination chemotherapy versus multiple, single-drug chemotherapy for tuberculosis. Current Therapeutic Research. 1996;57:849-56.
59. **Vernon A, Burman W, Benator D, Khan A, Bozeman L.** Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet. 1999;353:1843-7. [PMID: 10359410]
60. **Santha T, Rehman F, Mitchison DA, Sarma GR, Reetha AM, Prabhaker R. Tuberculosis Research Centre, Indian Council of Medical Research.** Split-drug regimens for the treatment of patients with sputum smear-positive pulmonary tuberculosis—a unique approach. Trop Med Int Health. 2004;9:551-8. [PMID: 15117298]
61. **Quy HT, Lan NT, Borgdorff MW, Grosset J, Linh PD, Tung LB, et al.** Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? Int J Tuberc Lung Dis. 2003;7:631-6. [PMID: 12870683]
62. **Yoshiyama T, Yanai H, Rhiengtong D, Palittapongarnpim P, Nampaisan O, Supawitkul S, et al.** Development of acquired drug resistance in recurrent tuberculosis patients with various previous treatment outcomes. Int J Tuberc Lung Dis. 2004;8:31-8. [PMID: 14974743]
63. **Enarson DA, Rieder HL, Arnadottir T, Trebucq A.** Tuberculosis Guide for Low Income Countries. 5th ed. Paris: International Union Against Tuberculosis and Lung Disease; 2000.
64. **Brodie D, Schluger NW.** The diagnosis of tuberculosis. Clin Chest Med. 2005;26:247-71, vi. [PMID: 15837109]
65. **Palomino JC.** Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field. Eur Respir J. 2005;26:339-50. [PMID: 16055883]
66. **Sacchettini JC, Rubin EJ, Freundlich JS.** Drugs versus bugs: in pursuit of the persistent predator Mycobacterium tuberculosis. Nat Rev Microbiol. 2008;6:41-52. [PMID: 18079742]
67. **Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W.** Randomized trials to optimize treatment of multidrug-resistant tuberculosis. PLoS Med. 2007;4:e292. [PMID: 17988168]
68. **Global Drug Facility.** First-line tuberculosis drugs & formulations currently supplied/to be supplied by the global TB drug facility. World Health Organization. 2003. Accessed at http://stoptb.org/GDF/drugsupply/drugs.available.html on 3 January 2007.
69. **Platt SD, Martin CJ, Hunt SM, Lewis CW.** Damp housing, mould growth, and symptomatic health state. BMJ. 1989;298:1673-8. [PMID: 2503174]
70. **Li J, Munsiff SS, Driver CR, Sackoff J.** Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. Clin Infect Dis. 2005;41:83-91. [PMID: 15937767]
71. **Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, et al.** Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis. 2005;9:556-61. [PMID: 15875929]
72. **Tripathy SP.** [Controlled clinical trial of a 3-month regimen and 2 5-month regimens in the treatment of pulmonary tuberculosis. 2d study of the short-term treatment administered in Madras]. Bull Int Union Tuberc. 1983;58:97-101. [PMID: 6360263]

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*Appendix Table 1.* **Methods and Quality Assessment of Cohort Studies**

| Study (Reference) | Country | Initial Drug Resistance | Groups Analyzed (Cohorts), *n* | Patients | | | | Treatment Duration, *mo* | | | Follow-up, *mo* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Treated, *n* | Defaulted During Therapy, % | Followed for Relapse, *n* | Lost to Follow-up, % | Rifampin | Pyrazinamide | Streptomycin | |
| Cohn et al. (18) | United States | Pan-sensitive, single drug resistance | 2 | 128 | 14 | 101 | 7 | 6 | 6 | 6 | 56 |
| Murray et al. (19); Sonnenberg et al. (20) | South Africa | Pan-sensitive | 1 | 298 | 4 | 0 | –* | 6 | 2 | 0 | 0 |
| Churchyard et al. (21) | South Africa | Pan-sensitive | 2 | 1876 | 10 | 0 | –* | 6 or 8 | 2 or 3 | 0 or 2 | 0 |
| Seung et al. (22) | Russia | Pan-sensitive, single drug resistance, multidrug resistance | 3 | 1681 | 10 | – | –* | 6 | 2 | 0 | 0 |
| Jasmer et al. (23) | United States | Pan-sensitive | 1 | 372 | 7 | 269 | 13 | 6 | 2 | 0 | 12–24 |
| Nettles et al. (24) | United States | Pan-sensitive | 1 | 575 | 7 | 407 | 0 | 6 | 2 | 0 | 24 |
| Thomas et al. (71) | India | Pan-sensitive | 1 | –* | –* | 485 | 5 | 6 | 2 | 0 | 18 |

* Values missing for those treated or followed for relapse indicate that failure or relapse was not reported.

*Appendix Table 2.* **Methods and Quality Assessment of Randomized, Controlled Trials**

| Study (Reference) | Country | Initial Drug Resistance | Groups Analyzed (Cohorts), *n**† | Patients | | | | Treatment Duration, *mo* | | | Follow-up, *mo* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Treated, *n*‡ | Defaulted During Therapy, % | Followed for Relapse, *n* | Lost to Follow-up, % | Rifampin | Pyrazinamide | Streptomycin | |
| BMRC (25–28) | East Africa | Pan-sensitive | 1 | 742 | 2 | 677 | 4 | 6 | 0 or 6 | 6 | 24 |
| BMRC (29, 30) | East Africa | Pan-sensitive | 4 | 742 | 0 | 677 | 4 | 2, 6 | 0, 2, or 6 | 0, 2, or 6 | 24 |
| BMRC (31, 32) | Hong Kong | Pan-sensitive, single drug resistance, multidrug resistance | 21 | 877 | 3 | 778 | 10 | 2, 4, or 6 | 0, 6, or 8 | 6 or 8 | 18 |
| BMRC (33, 34) | East Africa | Pan-sensitive, single drug resistance, multidrug resistance | 18 | 826 | 2 | 652 | 6 | 1 or 2 | 0, 1, 2, 6, or 8 | 1, 2, 6, or 8 | 42 |
| BMRC (35–37) | Singapore | Pan-sensitive, single drug resistance, multidrug resistance | 3 | 192 | 6 | 166 | 7 | 6 | 2 | 2 | 24 |
| Zierski et al. (38, 39) | Poland | Pan-sensitive, single drug resistance | 4 | 318 | 9 | 278 | 4 | 6 | 0 | 0 | 18 |
| BMRC (40–42) | Hong Kong | Pan-sensitive, single drug resistance, multidrug resistance | 15 | 1055 | 5 | 848 | 16 | 6 | 0, 2, or 6 | 0 or 6 | 60 |
| BMRC (43, 44) | Africa | Pan-sensitive, single drug resistance, multidrug resistance | 5 | 430 | 1 | 359 | 16 | 2 or 6 | 2 | 2 | 24 |
| Tripathy (72) | India | Pan-sensitive | 1 | 521 | 7 | 474 | 1 | 3 | 5 | 5 | 16 |
| Santha et al. (45); TBRC (46) | India | Pan-sensitive | 2 | 550 | 2 | 503 | 5 | 2 | 5 or 7 | 5 or 7 | 24 |
| BMRC (49, 50) | Singapore | Pan-sensitive, single drug resistance, multidrug resistance | 9 | 357 | 1 | 328 | 7 | 6 | 1 or 2 | 1 or 2 | 54 |
| Balasubramanian et al. (51); TBRC (52) | India | Pan-sensitive, single drug resistance | 2 | 561 | 8 | 443 | 18 | 3 | 5 | 5 | 19 |
| BMRC (53) | Hong Kong; Madras | Pan-sensitive, single drug resistance, multidrug resistance | 3 | 213 | 5 | 190 | 9 | 6 | 6 | 6 | 54 |
| BMRC (54) | Kenya; Zambia | Pan-sensitive, single drug resistance, multidrug resistance | 3 | 602 | 9 | 492 | 9 | 2 | 2 | 2 | 24 |
| BMRC (55) | Hong Kong; Madras | Pan-sensitive, single drug resistance, multidrug resistance | 6 | 153 | 19 | 98 | 19 | 6 or 8 | 6 or 8 | 6 or 8 | 36 |
| BMRC (56) | Hong Kong | Pan-sensitive, single drug resistance, multidrug resistance | 10 | 1065 | 7 | 955 | 2 | 6 | 4 or 6 | 0 or 4 | 30 |
| BMRC (57) | Hong Kong; Singapore | Pan-sensitive, single drug resistance, multidrug resistance | 9 | 290 | 1 | 281 | 1 | 6 | 1 or 2 | 0, 1, or 2 | 18 |
| Zhang et al. (58) | China | Pan-sensitive | 2 | 197 | 2 | 186 | 2 | 6 | 2 | 0 | 24 |
| Vernon et al. (59) | United States; Canada | Pan-sensitive | 1 | 35 | 11 | 31 | 0 | 6 | 2 | 0 | 20 |
| Santha et al. (60) | India | Pan-sensitive, single drug resistance | 2 | 1058 | 2 | 989 | 0 | 6 | 2 | 0 | 54 |
| Snider et al. (47) | Poland | Pan-sensitive | 2 | 187 | 11 | 148 | 10 | 6 | 2 | 0 or 2 | 21 |
| BMRC (48) | Tanzania | Pan-sensitive, single drug resistance, multidrug resistance | 3 | 137 | 3 | 115 | 8 | 2 | 2 | 2 | 18 |

BMRC = British Medical Research Council; TBRC = Tuberculosis Research Centre.
* For some randomized, controlled trials, results from only 1 treatment group are shown. These studies had other groups, but these groups used rifapentine, therapy was of inadequate duration (<5 mo), or therapy contained insufficient drugs (such as only 1 in the continuation phase).
† Groups were analyzed separately if results (pan-sensitive, single drug resistance, or multidrug resistance) were reported separately, even if patients were treated with the same experimental regimen.
‡ Patients treated include those who completed treatment successfully or those whose treatment failed, those who died during treatment, or those who defaulted. Patients who were ineligible or discontinued therapy because of side effects were excluded.