Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis

Medea Gegia, Nicholas Winters, Andrea Benedetti, Dick van Soolingen, Dick Menzies

Summary

Background The results of some reports have suggested that treatment of isoniazid-resistant tuberculosis with the recommended regimens of first-line drugs might be suboptimal. We updated a previous systematic review of treatment outcomes associated with use of first-line drugs in patients with tuberculosis resistant to isoniazid but not rifampicin.

Methods In this systematic review, we updated the results of a previous review to include randomised trials and cohort studies published in English, French, or Spanish to March 31, 2015, containing results of standardised treatment of patients with bacteriologically confirmed isoniazid-resistant tuberculosis (but not multidrug-resistant tuberculosis—ie, not resistant to rifampicin) in whom failure and relapse were bacteriologically confirmed. Results in patients with drug-sensitive tuberculosis included in the same studies were also analysed. We pooled treatment outcomes with random-effects meta-analysis.

Findings We identified 19 cohort studies and 33 trials with 3744 patients with isoniazid-resistant tuberculosis and 19 012 patients with drug-sensitive disease. The pooled rates of failure or relapse, or both, and acquired drug resistance with all drug regimens were 15% (95% CI 12–18) and 3·6% (2–5), respectively, in patients with isoniazid-resistant tuberculosis and 4% (3–5) and 0·6% (0·3–0·9) in those with drug-sensitive tuberculosis. Of patients with initial isoniazid-resistant tuberculosis with acquired drug resistance, 96% (93–99) had acquired multidrug-resistant disease. Treatment of isoniazid-resistant tuberculosis with the WHO standard regimen for new patients resulted in treatment failure, relapse, and acquired multidrug resistance in 11% (6–17), 10% (5–15) and 8% (3–13), respectively; treatment with the standard WHO regimen for previously treated patients resulted in treatment failure in 6% (2–10), relapse in 5% (2–8), and acquisition of multidrug resistance in 3% (0–6). For patients with drug-sensitive disease treated with the standard retreatment regimen the rates were 1% (0–2), 5% (4–7), and 0·3% (0–0·6).

Interpretation Treatment of isoniazid-resistant tuberculosis with first-line drugs resulted in suboptimal outcomes, supporting the need for better regimens. Standardised empirical treatment of new cases could be contributing substantially to the multidrug-resistant epidemic, particularly in settings where the prevalence of isoniazid resistance is high.

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Introduction

Between 1994 and 2009, isoniazid resistance was detected in 45% of all strains causing active tuberculosis in eastern Europe, and 14% of all strains causing the disease in all other regions.[1] In 2014, among all cases of tuberculosis, the average global frequency of isoniazid resistance without concurrent rifampicin resistance was 9·5% (95% CI 8·0–11·0). In new and previously treated cases, the global averages were 8·1% (6·5–9·7) and 14·0% (11·6–16·3), respectively.[2] In a separate survey, 4·8% of all estimated incident tuberculosis cases were multidrug resistant[3]—suggesting that most cases of isoniazid-resistant tuberculosis are mono-drug or poly-drug resistant.[1,3]

Recommendations for treatment of isoniazid-resistant tuberculosis are to use first line tuberculosis drugs. Specifically, WHO recommends rifampicin, ethambutol, and pyrazinamide for 9 months with the addition of a fluoroquinolone if the strain has concomitant resistance to ethambutol or pyrazinamide.[4] The American Thoracic Society recommendations are similar: rifampicin, pyrazinamide, and ethambutol for 9–12 months; a fluoroquinolone "may be added".[5] In 2008, we did a systematic review of retreatment, and treatment of isoniazid resistance without multidrug resistance.[6] We found no trials and only six cohorts in which WHO's recommended retreatment regimen was assessed, only nine trials focused on isoniazid resistance or retreatment cases, and no two trials made the same pair-wise comparison of regimens, precluding pooling.[6] The last trial specifically of patients with isoniazid-resistant tuberculosis was published almost 20 years ago.[7]

We updated our previous review. Our objective was to review treatment outcomes with use of first-line drugs (including streptomycin) for patients with active pulmonary tuberculosis caused by strains resistant to isoniazid but not to rifampicin.

Methods

Search strategy and selection criteria

In our previous systematic review,[6] which has already been reported in detail, we searched PubMed, Embase, and the Cochrane Library for articles published between Jan 1, 1948,

Research in context

Evidence before this study

Isoniazid-resistant tuberculosis that is not resistant to rifampicin (ie, not multidrug resistant) is a common problem. Prevalence of isoniazid-resistant tuberculosis in previously untreated patients ranges from 2% to more than 20% worldwide; the average prevalence is close to 10% among all new cases. The impact of isoniazid resistance on treatment outcomes is controversial: some experts think that isoniazid resistance does not matter whereas others think of it as a precursor to multidrug resistance. The optimal treatment of isoniazid-resistant disease is unclear because very few randomised trials investigating this condition specifically have been done (the last randomised trial specifically of patients with isoniazid-resistant tuberculosis was published in 1997). Isoniazid resistance is no longer reported by WHO in its annual global tuberculosis report, and the rapid diagnostic test GeneXpert MTB/RIF includes testing for the mutations causing rifampicin resistance, but not for those causing isoniazid resistance. However, in some studies published in the past 5 years poor treatment outcomes have been noted when first-line drugs are used to treat isoniazid-resistant disease.

Added value of the study

In this systematic review and meta-analysis, we searched four electronic databases— the Cochrane databases of systematic reviews and randomised trials, PubMed, Embase, and HealthStar— with the search terms "Tuberculosis" AND "Treatment" or "Therapy" AND "INH" or "isoniazid resistance". From this search, and a previous review that we did in 2008, we identified many cohort studies and randomised trials in which 3744 patients with isoniazid-resistant tuberculosis were treated with a range of regimens comprising first-line drugs. The overall failure and relapse rates ranged from 10% to 20% and acquired drug resistance occurred in 1–10% of patients with isoniazid-resistant disease—significantly higher than the rates in patients with drug-sensitive tuberculosis who were given the same regimens in many of the studies. The finding that treatment with WHO's recommended standardised regimen for previously untreated patients resulted in failure in 11% of patients, relapse in 10%, and acquired multidrug resistance in 8% is particularly important. Treatment of patients with isoniazid-resistant disease with 6–9 months of rifampicin, pyrazinamide, and ethambutol was associated with rates of failure and relapse that were similar to those in patients with drug-sensitive disease who were given the same regimen, but the combination of rifampicin and pyrazinamide is potentially limited by high rates of hepatotoxicity (which has been reported when the combination was used for treatment of latent infection).

Implications of all the available evidence

Treatment of isoniazid-resistant tuberculosis with standardised regimens of first-line drugs resulted in suboptimal treatment outcomes. The high rate of failure, relapse, and acquired multidrug resistance associated with the regimen recommended by WHO for previously untreated patients is particularly worrisome. In settings with a high prevalence of initial isoniazid resistance, empirical use of this regimen without identification of the patients with resistant disease could contribute substantially to the epidemic of multidrug-resistant tuberculosis. There is an urgent need to enhance diagnosis of isoniazid resistance and identify safe and effective treatment regimens.

and June 30, 2008. For this update, we searched the Cochrane database of systematic reviews and randomised trials, PubMed, Embase, and HealthSTAR (using Ovid) with the terms "Tuberculosis" AND "Treatment" or "Therapy" AND "INH" or "isoniazid resistance" (the major difference from the previous review is that in that one we used the term "retreatment" and related synonyms). The update extended from Jan 1, 2008, to March 31, 2015. To identify additional relevant articles we searched reference lists of identified original articles, and reviews or treatment guidelines published since 2008.

We included studies published in English, French, or Spanish in which primary data from prospective or retrospective cohorts or randomised trials were reported. Case-control studies, other designs, and surveillance data for which individual outcomes were not reported were excluded, as were abstracts, conference proceedings, reviews, editorials, and letters.

Further inclusion criteria were that all participants were treated for culture-confirmed active pulmonary tuberculosis, caused by strains that were resistant to isoniazid (either mono-resistant or also resistant to other first-line drugs) but not to rifampicin. Isoniazid resistance was assessed by phenotypic (drug-susceptibility testing) or genotypic (eg, line probe assay) methods. Studies that included patients with drug-susceptible tuberculosis or multidrug-resistant tuberculosis, or both, were included if treatment outcomes were stratified by type of resistance. Treatment regimens had to include at least 2 months of rifampicin and had to be standardised for all patients, and treatment outcomes of cure or completion and bacteriologically confirmed failure or relapse, or both, had to be reported. We excluded studies or study arms in which rifapentine, rifabutin, or non-drug therapy were given, regimens were once weekly, or drug monotherapy was used. We also excluded studies in which therapy was individualised according to patient characteristics or response.

Studies of patients with extrapulmonary disease were excluded because of the difficulty of microbiological confirmation for diagnosis and treatment outcomes. To avoid bias created by small case series reporting unusual

events we excluded cohort studies describing fewer than 20 patients. Randomised trials with subgroups of patients with isoniazid-resistant tuberculosis were included, irrespective of the number of participants with such disease.

We also used these study selection criteria described for our previous search,[6] except that only cohorts in which WHO's standard retreatment was used were included, and trials of patients receiving retreatment were included even if susceptibility testing was not done or study participants were infected with drug-sensitive as well as isoniazid-resistant strains.

Two reviewers (MG and DM) reviewed all titles and abstracts, and then full text articles for the update. They also re-reviewed all full-text of studies included in the previous review. Differences at each step were resolved by consensus.

Data abstraction and assessment of quality

We used standardised forms to extract data from selected studies about patient populations and characteristics (eg, size of population, mean age, gender, country, type of institution [tertiary *vs* primary care centre, local *vs* national programme]), population source (general *vs* institution based), HIV, pretreatment method of drug-susceptibility testing (genotypic, liquid *vs* solid culture), isoniazid critical concentration, genotyping results (*KatG* and *inhA* promoter mutations), treatment regimens, supervision of treatment, and number of patients who started treatment, died, failed, relapsed, stopped therapy early or were otherwise lost to follow-up. We accepted authors' definitions of all outcomes. Authors were contacted to obtain missing information, such as results stratified by treatment regimen, or drug-susceptibility results.

The study selection criteria of microbiological confirmation for initial diagnosis and treatment outcomes meant that selected studies were judged to have high-quality diagnostic and outcome ascertainment methods. Trials were judged to have high-quality methods of randomisation if central randomisation was done and numbered opaque sealed envelopes, sealed envelopes from a closed bag, or numbered or coded bottles or containers were used. We further assessed quality on the basis of losses during treatment. A study was defined as high quality when less than 10% of all patients who started treatment were lost to follow-up, transferred without knowledge of outcomes, or otherwise not accounted for.

Statistical analysis

102 different regimens were reported in the included studies (some varied only by use of fixed-dose combinations or intermittency schedule). Therefore, we grouped regimens on the basis of the use and duration of streptomycin, pyrazinamide, and rifampicin (appendix). The most common regimens were classed as WHO-New (ie, the standard WHO-recommended regimen for new cases: 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin), WHO-Retreatment (ie, the standard WHO-recommended regimen for previously treated people: 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol), and rifampicin, pyrazinamide, and ethambutol together for 6–9 months.

We wanted to understand the efficacy of different regimens in preventing failure, relapse, and acquired drug resistance—endpoints with objective microbiological definitions that were consistent across trials. Therefore, we used a per-protocol analysis, excluding patients who did not complete therapy because they developed serious adverse reactions, died, transferred out, dropped out, or for other reasons. For failures, the denominator was all participants who started treatment minus those who

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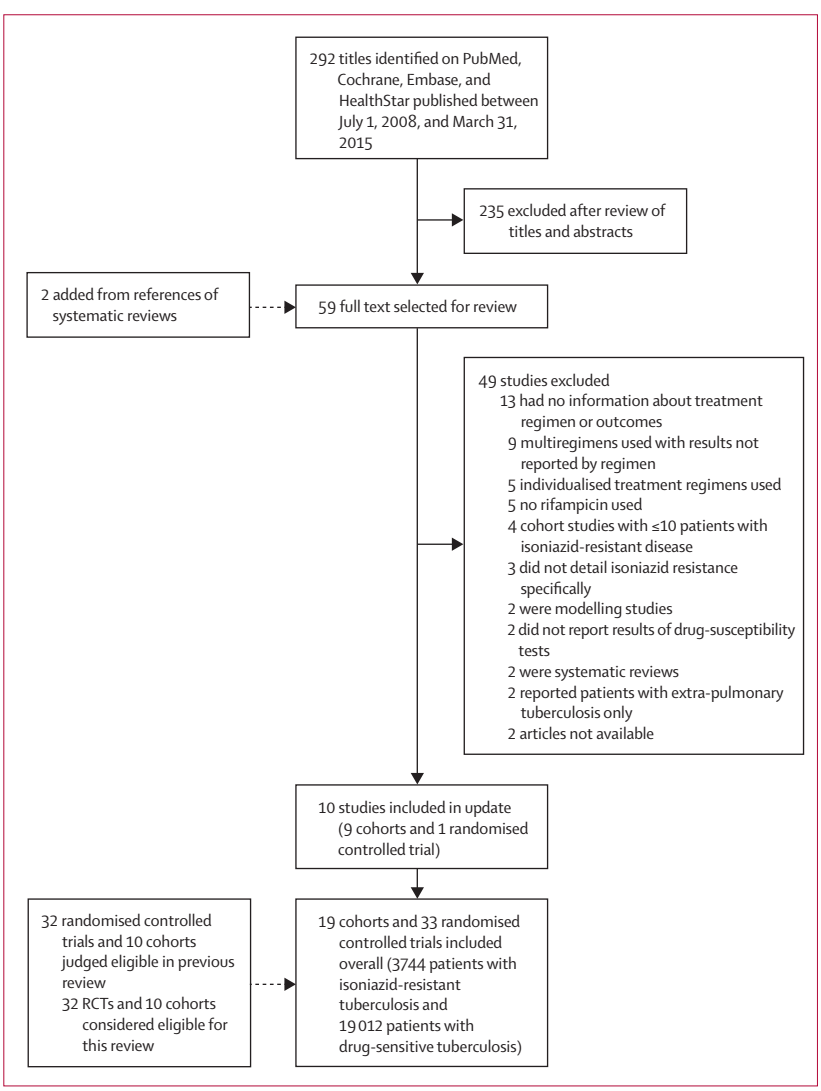

***Figure 1*: Flow diagram of study selection for update**

	Drug susceptibility	Arms	Events/participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Treatment failure					
WHO-New	Isoniazid resistant	24	170/1239	11% (6–17)*	87% (82–91)
WHO-New	Sensitive	19	241/9792	2% (1–3)	81% (72–88)
WHO-Retreatment	Isoniazid resistant	24	41/505	6% (2–10)*	40% (2–63)
WHO-Retreatment	Sensitive	21	40/2609	1% (0–2)	50% (19–70)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	13	82/911	1% (0–2)*	61% (28–79)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	10	13/1098	1% (0–2)	26% (0–64)
Relapse					
WHO-New	Isoniazid resistant	17	59/482	10% (5–15)	2% (0–45)
WHO-New	Sensitive	15	269/4740	5% (2–7)	79% (69–86)
WHO-Retreatment	Isoniazid resistant	20	13/277	5% (2–8)*	0 (0–44)
WHO-Retreatment	Sensitive	18	115/2205	5% (4–7)	12% (0–47)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	9	11/157	7% (2–11)*	0 (0–55)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	10	55/1010	6% (3–8)	65% (31–82)
Acquired drug resistance					
WHO-New	Isoniazid resistant	18	89/701	8% (3–13)*	14% (0–47)
WHO-New	Sensitive	15	102/5415	1% (0–2)	72% (56–82)
WHO-Retreatment	Isoniazid resistant	17	7/284	3% (0–6)*	23% (0–53)
WHO-Retreatment	Sensitive	16	7/2091	0·3% (0–0·6)	0 (0–47)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Isoniazid resistant	9	3/164	0·3% (0–2)†	0 (0–55)
6–9 months of rifampicin, pyrazinamide, and ethambutol	Sensitive	8	11/939	0·1% (0–0·4)	0 (0–60)

WHO-New is WHO's standard initial treatment regimen for previously untreated patients and consists of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. WHO-Retreatment is the standard WHO-recommended regimen for previously treated people and consists of 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol. Pooled event rate is the cumulative percentage associated with the outcome. For treatment failure, pooled event rates among patients with isoniazid-resistant disease did not differ significantly between those given WHO-New and those given WHO-Retreatment, but differed significantly between those given 6–9 months of rifampicin, pyrazinamide, and ethambutol and those given WHO-New (p=0·007). For relapse, pooled event rates among patients with isoniazid-resistant disease differed significantly between those given WHO-New and those given WHO-Retreatment (p=0·02) but did not differ significantly between those given 6–9 months of rifampicin, pyrazinamide, and ethambutol and those given WHO-New. For acquired drug resistance, pooled event rates among patients with isoniazid-resistant disease differed significantly between those given WHO-New and those given WHO-Retreatment (p=0·02) and between those given 6–9 of months rifampicin, pyrazinamide, and ethambutol and those given WHO-New (p=0·02). p values for comparison between patients with isoniazid-resistant disease and those with drug-sensitive disease for each outcome and regimen are indicated by footnote. *p<0·0001. †p=0·004.

Table 1: **Outcomes in all studies (randomised controlled trials and cohorts) with the three most commonly used first-line tuberculosis regimens**

defaulted or died. For relapse, the denominator used was all participants who were cured or completed treatment minus those who died or were lost to follow-up after the end of treatment. The denominator for the combined outcome of failure or relapse, or both, was the denominator for failure. Acquired drug resistance was estimated as the proportion of participants with any amplification of resistance, or the proportion with acquired multidrug resistance from pre-treatment to the time of fail or relapse.

We first compared treatment outcomes in randomised trials with those in cohorts to ascertain if these results could be pooled together. This comparison was restricted to the three most commonly used regimens described previously. In all subsequent analyses we pooled results from cohorts and trials.

In view of the wide variety of regimens, we analysed different arms within each randomised controlled trial as separate cohorts and pooled them across trials, which also allowed us to include the cohort studies. (Within each study, there might have been several arms, because each arm was defined on the basis of drug susceptibility—ie, isoniazid resistant or drug susceptible—and the regimen.)

For comparison, we pooled outcomes in the strata of patients with drug-sensitive tuberculosis who were included in the same studies as patients with isoniazid-resistant disease. For the primary analyses all studies were included, irrespective of study quality. Three sensitivity analyses were done to determine the effect of the region where the study was done (Africa *vs* Asia), the effect of quality of follow-up during therapy, and the effect of isoniazid resistance genotype, or critical concentrations used to define isoniazid resistance.

We used an exact binomial likelihood random effects meta-analysis to estimate the cumulative proportion and

95% CI of failure, relapse, and acquired drug resistance. In this approach,[8] a binomial distribution is used to approximate the distribution of the outcomes, which accounts for study size and includes a random effect to account for between-study heterogeneity. When proportions are the outcome measure, this approach produces less-biased estimates of the pooled effect than the Der Simonian and Laird method.[8]

We assessed heterogeneity of proportions of participants with outcomes, overall, and within subgroups defined by covariates of interest by estimating the I^2 statistic and associated 95% CIs.[9–11] All analyses were done with SAS v9.4.

Role of the funding source

The study sponsor had no role in study design; data collection, analysis, or interpretation; or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our updated search identified 294 titles, of which one trial and nine cohort studies were deemed eligible (figure 1; appendix). We added these newly identified articles to the 32 trials and ten cohorts identified for the previous review. The characteristics of the 33 trials[7,12–43] and 19 cohort studies[44–62] are summarised in the appendix. In seven of the cohort studies and 28 of the trials, data for patients with active drug-susceptible tuberculosis were also reported. 3744 patients with isoniazid-resistant tuberculosis and 19 012 patients with drug-susceptible tuberculosis were analysed. The most commonly reported regimens were WHO-New and WHO-Retreatment, and 6–9 months of rifampicin, pyrazinamide, and ethambutol.

Our comparison of treatment outcomes between cohorts and randomised trials showed that results were not substantially affected by study design (appendix). Hence, we pooled results from cohorts and trials in all subsequent analyses. Use of WHO-New resulted in treatment failure in 11% (95% CI 6–17) of patients with isoniazid-resistant disease compared with 2% (1–3) of drug-susceptible patients (p<0·0001; table 1). Relapse occurred in 10% (5–15) of patients with drug-resistant tuberculosis and 5% (2–7) with drug-susceptible disease, and the rates of acquired drug resistance were 8% (3–13) and 1% (0–2), respectively (p<0·0001 for both comparisons). The frequency of treatment failure and acquired drug resistance differed significantly between patients with isoniazid-resistant disease and those with drug-susceptible disease when treated with the WHO-Retreatment regimen, although no significant differences in outcomes were noted in patients treated with 6–9 months of rifampicin, pyrazinamide, and ethambutol (table 1).

The combined outcome of failure or relapse, or both, occurred in 15% (12–18) of all patients with isoniazid-resistant tuberculosis treated with all 13 categories of regimens, compared with 4% (3–5) of those with drug-susceptible disease (p<0·0001; table 2). This outcome was very heterogeneous between studies for most

	Total arms (arms from cohorts)	Events/ participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Overall				
Isoniazid resistant	124 (30)	640/3744	15% (12–18)*	80% (77–83)
Isoniazid sensitive	89 (13)	1065/19 012	4% (3–5)	84% (81–87)
Rifampicin for 6 months, no streptomycin or pyrazinamide				
Isoniazid resistant	10 (0)	9/55	7% (0–17)†	0 (0–60)
Isoniazid sensitive	10 (0)	53/1254	2% (0–5)	77% (57–87)
Rifampicin for at least 9 months, no streptomycin or pyrazinamide				
Isoniazid resistant	12 (2)	105/479	11% (0–22)‡	92% (87–95)
Isoniazid sensitive	0	..	..	..
WHO-New: full course of rifampicin, initial pyrazinamide, no streptomycin				
Isoniazid resistant	24 (10)	229/1269	16% (10–21)*	92% (89–94)
Isoniazid sensitive	20 (8)	510/10 247	4% (3–6)	92% (89–94)
Rifampicin for at least 9 months, initial pyrazinamide, no streptomycin				
Isoniazid resistant	4 (0)	31/114	20% (1–39)§	61% (0–87)
Isoniazid sensitive	0	..	..	..
Rifampicin, ethambutol, and pyrazinamide for 6–9 months, no streptomycin				
Isoniazid resistant	13 (5)	93/911	7% (2–12)*	0 (0–55)
Isoniazid sensitive	10 (0)	68/1098	7% (4–10)	76% (56–87)
Initial streptomycin and rifampicin, no pyrazinamide				
Isoniazid resistant	2 (0)	6/10	66% (37–96)¶	0 (0–0)
Isoniazid sensitive	2 (0)	21/196	10% (6–14)	76% (0–95)
Initial streptomycin, pyrazinamide, and rifampicin				
Isoniazid resistant	13 (1)	91/235	40% (33–46)†	61% (29–79)
Isoniazid sensitive	9 (1)	132/1798	7% (6–9)	80% (63–89)
WHO-Retreatment: full course of rifampicin, initial streptomycin and pyrazinamide				
Isoniazid resistant	24 (8)	54/505	11% (6–17)*	23% (0–53)
Isoniazid sensitive	21 (4)	155/2609	6% (4–9)	51% (19–70)
Full course of pyrazinamide, initial streptomycin and rifampicin				
Isoniazid resistant	2 (0)	5/24	25% (8–41)‖	0 (0–0)
Isoniazid sensitive	1 (0)	32/106	27% (0–99)	..
Full course of streptomycin, initial rifampicin, no pyrazinamide				
Isoniazid resistant	2 (0)	6/20	29% (11–49)‡	46% (0–99)
Isoniazid sensitive	2 (0)	28/176	15% (11–20)	83% (31– 96)
Full course of streptomycin and rifampicin, initial pyrazinamide				
Isoniazid resistant	2 (0)	3/19	15% (0–31)**	0 (0–0)
Isoniazid sensitive	1 (0)	8/155	5% (2–8)	..
Full course of streptomycin and pyrazinamide, initial rifampicin				
Isoniazid resistant	8 (0)	7/67	8% (2–15)*	0 (0–65)
Isoniazid sensitive	9 (0)	37/1035	4% (3–5)	22% (0–63)
Full course of streptomycin, pyrazinamide, and rifampicin				
Isoniazid resistant	8 (2)	1/36	2% (0–6)‡	0 (0–65)
Isoniazid sensitive	4 (0)	21/338	6% (0–11)	78% (41–92)

Pooled event rates among patients with isoniazid-resistant disease did not differ significantly between those taking WHO-Retreatment and those taking WHO-New but differed significantly between those taking 6–9 months of rifampicin, pyrazinamide, and ethambutol (p=0·03). Pooled event rate is the cumulative percentage associated with the outcome. p values for comparison between patients with isoniazid-resistant disease and those with drug-sensitive disease for each outcome and regimen are indicated by footnote. *p< 0·0001. †p=0·003. ‡p=0·0005. §p=0·03. ¶p=0·31. ‖=0·01. **p=0·006.

***Table 2*: Treatment failure or relapse of tuberculosis, or both, by regimen in randomised controlled trials and cohorts**

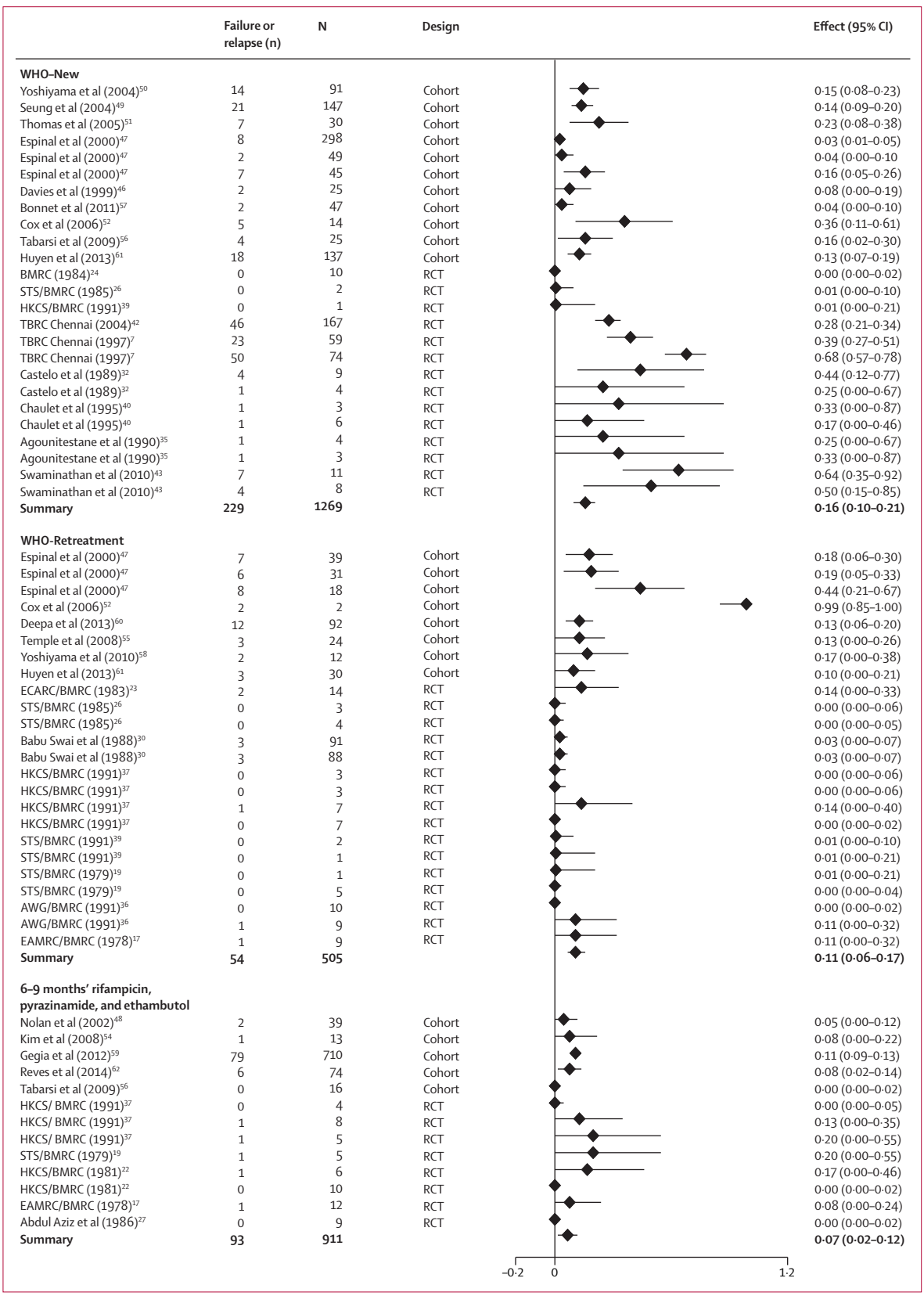

Figure 2: **Forest plot of combined outcome of failure or relapse, or both, in patients treated for isoniazid-resistant tuberculosis given WHO-New, WHO-Retreatment, or 6–9 months of rifampicin, pyrazinamide, and ethambutol**

Weights are from random-effects analyses. WHO-New is WHO's standard initial treatment regimen for previously untreated patients and consists of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. WHO-Retreatment is the standard WHO-recommended regimen for previously treated people and consists of 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol. Regimens within each group might differ slightly. RCT=randomised controlled trial. BMRC=British Medical Research Council. STS=Singapore Tuberculosis Society. HKCS=Hong Kong Chest Service. TBRC=Tuberculosis Research Centre. ECARC=East and Central Africa Research Council. EAMRC=East Africa Medical Research Council.

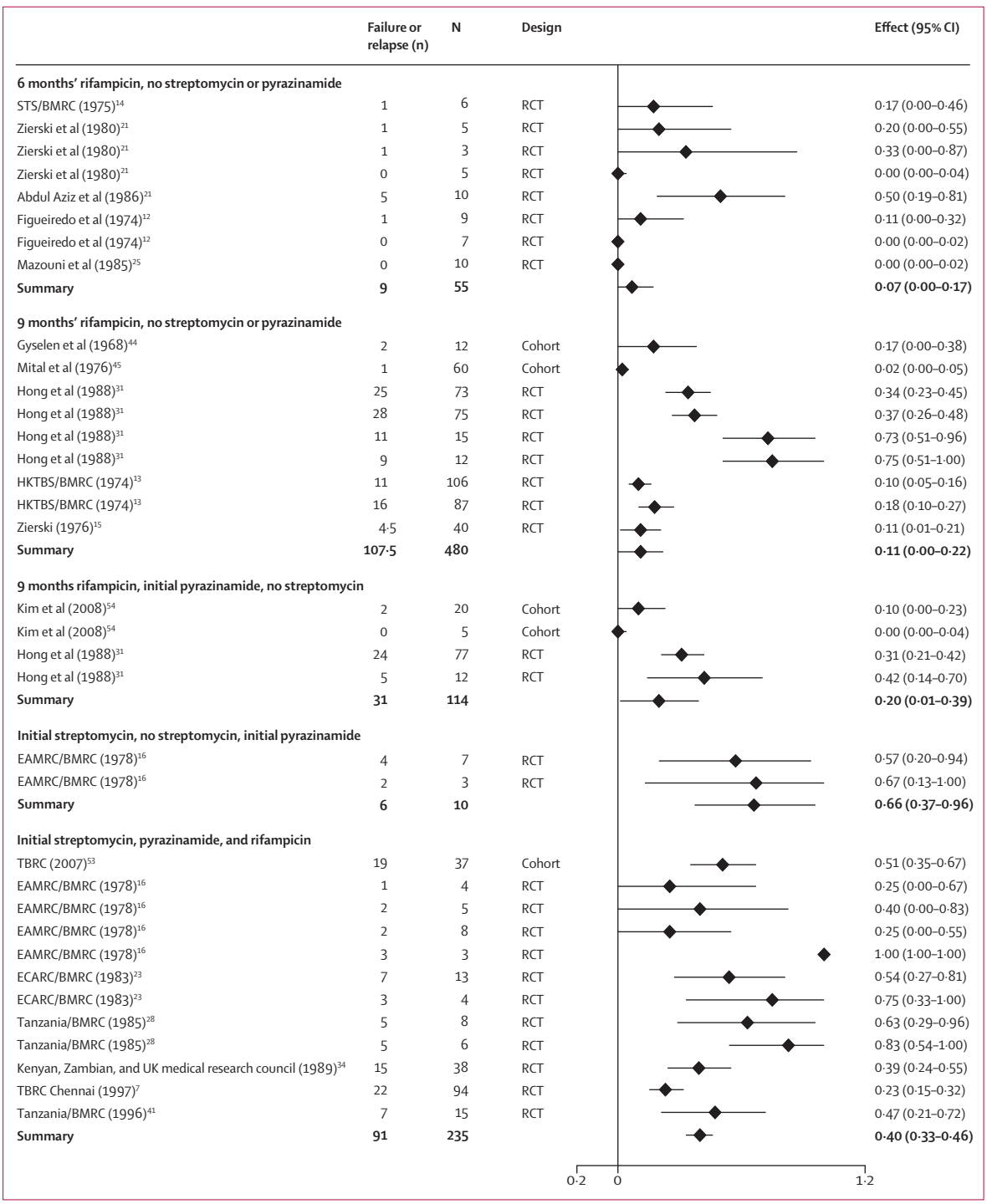

Figure 3: **Forest plot of combined outcome of failure or relapse, or both, in patients treated initially for tuberculosis with regimens without streptomycin or pyrazinamide, or both**

Weights are from random-effects analyses. Regimens within each group might differ slightly. RCT=randomised controlled trial. STS=Singapore Tuberculosis Society. BMRC=British Medical Research Council. HKTBS=Hong Kong Tuberculosis Service. TBRC=Tuberculosis Research Centre. ECARC=East and Central Africa Research Council. EAMRC=East Africa Medical Research Council.

regimens (figures 2–4). Combined rates of failure or relapse, or both, were significantly higher in patients with isoniazid-resistant tuberculosis than in those with drug-susceptible tuberculosis for almost all regimens, except in patients given rifampicin for 6 or more months plus 1–3 months of streptomycin and 1–4 months of

pyrazinamide. Overall, 3·6% (95% CI 2–5) of all patients with isoniazid-resistant disease acquired further drug resistance during treatment compared with 0·6% (0·3–0·9) of participants with drug-susceptible disease (table 3; p<0·0001). The proportion of all treated patients who developed acquired drug resistance was significantly higher in those with isoniazid-resistant strains (table 3). In patients with isoniazid-resistant strains, between 8% and 25% acquired drug resistance when treated with either (or neither, but not both) pyrazinamide or streptomycin only for the first 2 months, but ranged from 0% to 3% with all other regimens.

Of patients who acquired further drug resistance during treatment, 96% (95% CI 93–99) of those with pre-treatment isoniazid-resistant strains developed multidrug-resistant tuberculosis compared with 32% (25–40) of patients with initially drug-susceptible strains (table 4). Patients with isoniazid-resistant disease treated with the WHO-New regimen had proportionally the highest frequency of multidrug resistance (table 4).

Very few of the studies reviewed described methods for measurements of serious adverse events. If described, the methods were not standardised across studies, precluding pooling of this outcome. 27 trials and seven cohort studies were judged to have high-quality follow-up (we judged that 24 trials had high-quality randomisation). In sensitivity analyses, neither follow-up quality nor the region where the study was done significantly affected treatment outcomes (appendix). In the two studies in which a higher critical concentration (1·0 µg/mL) was used to define isoniazid resistance, treatment outcomes were similar to those in which a lower critical

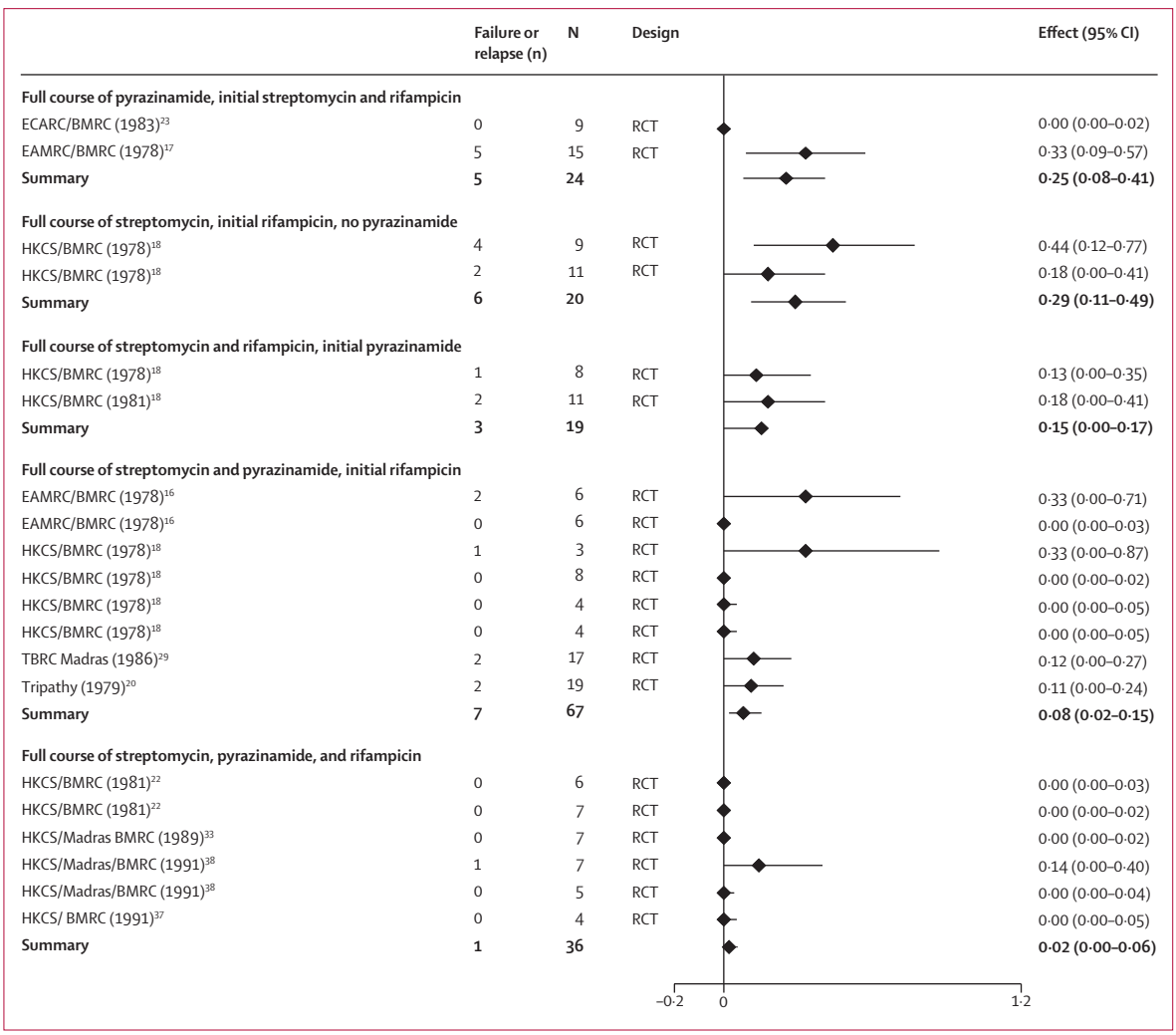

***Figure 4*: Forest plot of combined outcome of failure or relapse, or both, in patients treated for isoniazid-resistant tuberculosis with regimens containing streptomycin or pyrazinamide, or both, throughout**

Weights are from random-effects analyses. Regimens within each group might differ slightly. RCT=randomised controlled trial. ECARC=East and Central Africa Research Council. BMRC=British Medical Research Council. EAMRC=East Africa Medical Research Council. HKCS=Hong Kong Chest Service. TBRC=Tuberculosis Research Centre.

concentration was used (data not shown). In one cohort study, outcomes were not significantly worse in patients with tuberculosis caused by bacteria with *KatG* mutations than in those with disease caused by bacteria with *inhA* promoter mutations, treated with the WHO-New or WHO-Retreatment regimens (appendix).

Discussion

Overall, failure, relapse, and acquired drug resistance were significantly more common in patients with pre-treatment isoniazid-resistant, rifampicin-susceptible tuberculosis than in those infected with fully drug-susceptible organisms when treated with standardised regimens of first-line tuberculosis drugs. Of particular importance is the finding that the frequency of failure, relapse, and acquired multidrug resistance with the widely used WHO-New regimen were 11% (95% CI 6–17), 10% (5–15), and 8% (3–13), respectively, among all patients with isoniazid-resistance disease who were treated.

Our study had several strengths. In total we identified 19 cohort studies and 33 randomised trials, which allowed us to pool results from 3744 patients with isoniazid-resistant tuberculosis who were treated with a wide range of regimens, and also allowed comparison with outcomes among 19 012 patients with drug-susceptible tuberculosis treated at the same centres and with the same regimens. All outcomes were microbiologically confirmed, and acquired drug resistance was assessed in most studies. Despite greater losses to follow-up during treatment, the findings from cohorts were consistent with those from trials, making the results more generalisable to practice under the conditions experienced in many high-burden countries. Studies were done in 28 different countries, further enhancing generalisability.

Nevertheless, our study also had several important limitations. We completed our search in March, 2015, so some more recent studies might not have been included. Because so many different regimens were used, these had to be classified by major ingredients, such as duration of rifampicin, as well as by use and duration of streptomycin or pyrazinamide. Within each group (eg, the WHO-Retreatment category), there were some differences between regimens, which could have been clinically important. We also combined regimens that included similar drugs and duration but had different schedules of administration. Relapse and acquired drug resistance were not reported in some studies, limiting information on these outcomes for some regimens. The combined outcome of failure or relapse, or both, tended to underestimate event rates, because some studies reported only failure, and the denominator for all studies was the number analysed for failure—a larger number than those eligible for relapse. Reporting of genotype was available in only one study, and although critical concentrations were available for 31 studies, higher concentrations were used in only two studies, limiting comparisons. Laboratory methods also varied between studies and with time. Information on tolerability was especially limited; in most studies adverse events were not reported, or were reported but without description of

	Total arms	Events/participants (n/N)	Pooled event rate % (95% CI)	I^2 (95% CI)
Overall				
Isoniazid resistant	92	205/2024	3·6% (2–5)	5% (0–24)
Isoniazid sensitive	71	167/12 690	0·6% (0·3–0·9)	21% (0–40)
Rifampicin for 6 months, no streptomycin or pyrazinamide				
Isoniazid resistant	4	1/19	5% (0–17)*	0 (0–60)
Isoniazid sensitive	7	2/808	0·2% (0–1)	0 (0–60)
Rifampicin for at least 9 months, no streptomycin or pyrazinamide				
Isoniazid resistant	7	83/380	18% (6–31)†	77% (61–87)
Isoniazid sensitive	0	..	..	..
WHO-New: full course of rifampicin, initial pyrazinamide, no streptomycin				
Isoniazid resistant	18	89/701	8% (3–13)‡	14% (0–47)
Isoniazid sensitive	15	102/5415	1% (0–2)	72% (56–82)
Rifampicin for at least 9 months, initial pyrazinamide, no streptomycin				
Isoniazid resistant	4	24/114	16% (3–28) †	37% (0–78)
Isoniazid sensitive	0	..	..	..
Rifampicin and pyrazinamide for 6–9 months, no streptomycin				
Isoniazid resistant	9	3/164	0·3% (0–2)§	0 (0–55)
Isoniazid sensitive	8	11/939	0·1% (0–0·4)	0 (0–60)
Initial streptomycin and rifampicin, no pyrazinamide				
Isoniazid resistant	2	1/10	24% (2–45)¶	0 (0–0)
Isoniazid sensitive	2	7/196	5% (0–15)	0 (0–0)
Initial streptomycin, pyrazinamide, and rifampicin				
Isoniazid resistant	11	6/220	2% (0–5)‡	0 (0–55)
Isoniazid sensitive	9	32/1798	1% (0–2)	0 (0–62)
WHO-Retreatment: full course of rifampicin, initial streptomycin and pyrazinamide				
Isoniazid resistant	17	7/284	3% (0–6)‡	0 (0–44)
Isoniazid sensitive	16	7/2091	0·3% (0–0·6)	0 (0–46)
Full course of pyrazinamide, initial streptomycin and rifampicin				
Isoniazid resistant	1	0/9	0 (NE)†	..
Isoniazid sensitive	0	..	..	..
Full course of streptomycin, initial rifampicin, no pyrazinamide				
Isoniazid resistant	2	0/20	0 (NE)†	0 (0–0)
Isoniazid sensitive	2	1/176	1% (0–4)	0 (0–0)
Full course of streptomycin and rifampicin, initial pyrazinamide				
Isoniazid resistant	2	0/19	0 (NE)†	0 (0–0)
Isoniazid sensitive	1	0/155	0 (NE)	..
Full course of streptomycin and pyrazinamide, initial rifampicin				
Isoniazid resistant	7	1/48	2% (0–6)‖	0 (0–65)
Isoniazid sensitive	7	3/774	0·3% (0–1)	0 (0–62)
Full course of streptomycin, pyrazinamide, and rifampicin				
Isoniazid resistant	8	0/36	0 (NE)**	0 (0–65)
Isoniazid sensitive	4	2/338	0·3% (0–0·1)	0 (0–77)

Pooled event rate is the cumulative percentage associated with the outcome. p values for comparison between patients with isoniazid-resistant disease and those with drug-sensitive disease for each outcome and regimen are indicated by footnote. NE=not estimable. *p=0·03. †p=NE. ‡p<0·0001. §p=0·004. ¶p=0·05. ‖p=0·0007. **p=0·99.

***Table* 3: Acquired drug resistance (among treatment failures or relapses) by regimen in randomised controlled trials and cohorts**

	Total treated	Any acquired drug resistance	Acquired multidrug resistance	% of acquired drug resistance that is multidrug resistance (95% CI)
All 13 treatment regimens				
Isoniazid sensitive	12 690	167	54	32% (25–40)
Isoniazid resistant	2024	214	205	96% (93–99)
Most commonly used regimens				
Isoniazid sensitive				
WHO-New	5415	102	47	46% (36–57)
WHO-Retreatment	2091	7	2	29% (10–82)
6–9 months of rifampicin, pyrazinamide, and ethambutol	939	11	3	27% (2–52)
Isoniazid resistant				
WHO-New	701	89	87	98% (92–99)
WHO-Retreatment	284	7	5	71% (29–96)
6–9 months of rifampicin, pyrazinamide, and ethambutol	164	3	2	67% (9–99)
Isoniazid critical concentrations overall (resistant strains only)				
High	1203	40	34	85% (70–94)
Low	1864	59	35	59% (46–72)

Data are n unless otherwise specified. WHO-New is WHO's standard initial treatment regimen for previously untreated patients and consists of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. WHO-Retreatment is the standard WHO-recommended regimen for previously treated people and consists of 2 months of streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 5 months of isoniazid, rifampicin, and ethambutol.

***Table 4*: Proportion of patients with multidrug-resistant tuberculosis among all patients with disease with acquired drug resistance**

methods of ascertainment, grading of severity, or attribution to specific drugs.

This study has important implications for countries where prevalence of initial isoniazid resistance is more than 5% and WHO-New is used empirically without drug-susceptibility testing. In view of WHO's estimates of global prevalence of isoniazid resistance (without multidrug resistance) of roughly 9%[1] among an estimated 8 million previously untreated people with tuberculosis annually, then 720 000 new patients would be expected to have disease with initial isoniazid resistance. On the basis of the results of this review, if these patients were all treated empirically with the WHO-New regimen, we predict that treatment would be unsuccessful or disease would relapse with multidrug resistance in about 60 000 because of the effective monotherapy with rifampicin in the final 4 months of therapy. This rough estimate suggests that treatment of unrecognised isoniazid resistance might be contributing very substantially to the epidemic of multidrug resistance. The situation will be worse in settings with high prevalence of poly-drug resistance (isoniazid resistance associated with resistance to pyrazinamide or ethambutol, or both), which can cause even higher rates of failure and relapse.

The other implication is that the commonly used WHO-Retreatment regimen was associated with failure and acquired drug resistance rates that were about six and ten times (respectively) higher in patients with isoniazid resistance than in patients with drug-susceptible tuberculosis, although pooled relapse rates were similar. These results support calls for a strengthened retreatment regimen.[63,64] Although the regimen of 6–9 months of rifampicin, pyrazinamide, and ethambutol had reasonable treatment outcomes, it is limited by the well known hepatotoxicity of the combination of rifampicin plus pyrazinamide, demonstrated by numerous reports[65–67] of excessive hepatotoxicity with use of these two drugs for treatment of latent tuberculosis. As an alternative, results of randomised trials of use of fluoroquinolones for 2 months[68,69] or 4 months[70, 71] suggest that such an approach merits consideration for treatment of isoniazid-resistant strains (for at least 6 months' duration).

On the basis of this review, isoniazid resistance is associated with increased treatment failure, relapse, and acquired multidrug resistance in patients treated with regimens containing only first-line tuberculosis drugs. Treatment with the standardised regimen recommended for new patients without drug-susceptibility testing could contribute substantially to the epidemic of multidrug-resistant tuberculosis, particularly in settings with high prevalences of initial isoniazid resistance. Our results suggest that greater priority should be placed on rapid and accurate detection and more effective treatment of isoniazid-resistant tuberculosis.

Contributors

DM conceived the study questions and design and did the search. MG and DM did the review and DvS contributed original data. NW, AB, and DM analysed the data. DM wrote the first draft of the article. All authors revised the Article and approved the final version.

Declaration of interests

We declare no competing interests.

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