Correlates of treatment outcomes of Multidrug-Resistant Tuberculosis (MDR-TB): a systematic review and meta-analysis

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Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements of the degree of Master of Science

August 2009

Acknowledgements

I have a number of people to thank for their contributions toward the completion of this thesis. My supervisor Dr. Dick Menzies for his good ideas, guidance and sage advice. My co-supervisor Dr. Madhukar Pai, for his expertise, encouragement, and timely e-mails. Both of my supervisors have shown exceptional dedication to this project, and for that I am grateful. Alice Zwerling, for her contribution as the second reviewer for this systematic review. Dr. John Hanley, Dr. Lawrence Joseph and Dr. Roger Harbord, for their advice on the statistical analysis. Laurence Brunet and Marthe Pelletier, for their generous help with the French translation. To all the principle investigators who answered my e-mails and shared with me additional information about their studies- a great big thank you.

And finally, I would like to thank my family for their incredible support during this process. My brother Osman, for his critical thinking and avid interest in research methods. And my parents, Neriman and Mustafa, for never letting me forget about "the other degree."

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Abbreviations

ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
DST	Drug susceptibility testing
DOT	Directly observed therapy
GLC	Green Light Committee
GNIPC	Gross National Income per capita
MDR-TB	Multidrug-Resistant Tuberculosis
M. tuberculosis	Mycobacterium tuberculosis
PZA	Pyrazinamide
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

Glossary of Terms

Acquired drug resistance:	A patient with initially drug susceptible disease who develops drug resistance caused by non-adherence or inadequate, inappropriate, or irregular drug treatment.
Cumulative success:	Total number who were cured or completed treatment but did not meet the definition of failure, minus those who relapsed during post-treatment follow-up.
Cumulative failure:	Total number of failure during treatment and/or relapse after treatment.
Cure:	Culture negative by the end of the treatment period.
Death:	Death due to any cause during the course of tuberculosis treatment.
Default:	Treatment was interrupted for two consecutive months or more, or patient transferred out and treatment outcome was unknown. In addition, patients whose treatment outcomes were not described in the study were considered to have defaulted.
Failure:	Culture-positive status after five or more months of treatment.
Multi-drug resistant tuberculosis:	Drug resistance to at least both isoniazid and rifampin.
Primary drug resistance:	Drug-resistant tuberculosis in a previously untreated patient.
Relapse:	Recurrence of bacteriological confirmed tuberculosis after treatment success (cure or treatment complete).
Treatment complete:	Completed the prescribed treatment without bacteriological evidence of either cure or failure.

Abstract

Background: Multi-drug resistant tuberculosis **(**MDR-TB) is a major threat to global tuberculosis control. While observational studies have reported outcomes of MDR-TB treatment, there have been no randomized controlled trials for MDR-TB treatment outcomes. We did a systematic review and meta-analysis to examine individual and study-level factors associated with treatment outcomes for MDR-TB in the observational studies.

Method: We searched MEDLINE, EMBASE, BIOSIS, Web of Science from 1970 to July 2008, for publications in any language that described at least one treatment outcome among at least 25 patients with microbiologically proven MDR-TB. Data were extracted and where missing, principle investigators were contacted for more information. Rates of treatment outcomes were pooled using random effects. Subgroup analyses and meta-regression models were used to explore sources of heterogeneity.

Results: After screening 2187 titles and abstracts, 265 articles were identified for retrieval and full-text review, and of these, 72 articles met the inclusion criteria and were included in the meta-analysis. Data analysis was performed using the 64 unique cohorts reported by the 72 articles. The cohorts were quite heterogeneous in characteristics and outcomes. The mean size of the cohorts was 124 patients (range 25 to 1011). The mean age of participants in the cohorts was 39 years with females accounting for about one third. The median length of treatment was 18 months, and the average number of drugs in the regimen was five. The overall pooled rates of cumulative success (successful patients who did not relapse) was 50%, of cumulative failure (failure plus relapse) was 17%, of death was 13% and of default was 18%. These pooled outcome rates, however, must be interpreted with caution because of heterogeneity across studies. Subgroup and meta-regression analyses helped identify several factors associated with improved outcomes. Factors significantly associated with increased treatment success are treatment duration longer than 20 months, use of more than three sensitive drugs, individualized regimen, use of fluoroquinolones, or use of second-line agents in general. Factors that were significantly associated with high treatment mortality were high prevalence of HIV co-infection and use of three or fewer drugs. Low default rate was most strongly associated with shorter treatments and directly observed therapy. Use of second-line drugs was significantly associated with higher default rate. Considerable heterogeneity remained even within subgroups.

Conclusion: Outcomes of MDR-TB appear to vary considerably across studies and populations. The heterogeneity among studies poses a challenge in interpreting the results of this meta-analysis for clinical care, underscoring the need for future research to clarify optimal treatment of MDR-TB.

Résumé

Contexte : La tuberculose multi-résistante (TB-MR) est une menace importante pour le contrôle de la tuberculose dans le monde. Tandis que les études d'observation ont rapporté des résultats de traitements de TB-MR, il n'y a eu aucune étude randomisée. Nous avons fait une revue systématique de la littérature et une méta-analyse afin d'examiner les facteurs liés aux résultats de traitement pour TB-MR, au niveau de l'individu et de l'étude, dans les études d'observation.

Méthode : Nous avons cherché à l'aide de MEDLINE, EMBASE, BIOS, et Web of Science, les publications dans toutes les langues qui décrivent au moins un résultat de traitement parmi au moins 25 patients atteints de TB-MR microbiologiquement prouvée, de 1970 à juillet 2008. Les données ont été extraites et les taux de résultats de traitement ont été mis en commun en utilisant le modèle d'effet au hasard *random effect*. Des analyses de sous-groupes et des modèles de méta régression ont été employés pour explorer les sources d'hétérogénéité.

Résultats : Après avoir répertorié2187 titres et résumés d'articles, 265 articles ont été identifiés et sélectionnées afin de récupérer le texte intégral pour les réviser; 72 de ces articles ont répondu aux critères d'inclusion et ont été inclus dans la méta analyse. L'analyse de données a été exécutée en utilisant les 64 cohortes uniques rapportées par les 72 articles. Les cohortes étaient hétérogènes dans leurs caractéristiques et leurs résultats. La taille moyenne des cohortes était de 124 patients (25 à 1011). L'âge moyen des participants était de 39 ans et les femmes représentaient environ le tiers des participants. La longueur médiane du traitement était de 18 mois et les patients recevaient en moyenne cinq médicaments différents. Le taux global de succès cumulatif (patients guéris qui n'ont pas fait de rechute) était de 50%, d'échec cumulatif (échec plus rechute), 17%, de mort, 13% et d'abandon de traitement, 18%. Toutefois, ces taux doivent être interprétés avec prudence en raison de l'hétérogénéité à travers des études. Avec des analyses de sous-groupes et de méta régression plusieurs facteurs associées à succès de traitement ont été identifier, comme – durée de traitement plus que 20 mois, utilisation de 3 médicaments ou plus, traitement individualise, ou l'utilisation de médicaments de secondes lignes. Facteurs associe avec la mortalité étaient haut prévalence de VIH et utilisation de 3 médicaments ou moins. Un taux élevé de non-adherence etait associe avec traitement plus longue, auto administration de médicaments, et l'utilisation de médicaments de seconde ligne. Une importante hétérogénéité est demeurée même dans les sous-groupes.

Conclusion : Les résultats de TB-MR semblent varier considérablement selon les études et les populations. L'hétérogénéité parmi les études pose un défi dans l'interprétation des résultats de cette méta analyse, soulignant le besoin d'autre recherche afin d'évaluer le traitement optimal pour TB-MR.

Chapter 1 Introduction

1. 1. Epidemiology of tuberculosis and drug-resistant tuberculosis

Tuberculosis (TB) is an infectious disease that remains a serious global public health concern. It is estimated that about one third of the world is infected with tuberculosis, and approximately 5-10% of this infected population will progress to develop active disease. Tuberculosis is globally manifested, but is endemic in developing regions, with over 80% of new cases occurring in Africa, South-East Asia and the Western Pacific.

According to the most recent data from the World Health Organization (WHO), there were 10.4 million cases of tuberculosis reported in 2007, of which 1.2 million had a history of prior tuberculosis disease and treatment [1]; these numbers are impressive, and likely are an under-estimate of the true burden of disease because of the tendency for national public health agencies to under-report their cases. Of these cases, 511 000 had multidrug-resistant tuberculosis (MDR-TB), which is defined as bacteriological proven resistance to the two most potent anti-tuberculosis drugs isoniazid and rifampin.

The proportion of MDR-TB among new TB cases is 3.1%; among previously treated patients, the proportion increases to 19.0%. China and India account for approximately half of the world's MDR-TB burden, while the former Soviet Republics account for about one fifth [1]. MDR-TB is a growing public health problem that is especially troublesome because it is associated with high mortality and poses a major treatment challenge for clinicians.

The risk factors for acquiring MDR-TB differ from risk factors for drug sensitive tuberculosis (DS-TB). The mode of initial transmission by airborne droplets is the same for both MDR-TB and DS-TB. Historically, MDR-TB was thought to be a phenomenon of acquired disease due to poor management of an earlier DS-TB disease; however, WHO data from 2006 indicates that 58% of MDR-TB in the world is primary disease,

highlighting that contact with an MDR-TB positive patient is the most significant risk factor for disease [1]. Nevertheless, risk factors for getting MDR-TB remain specific to each setting and depend on its prevalence in the community and transmission patterns. A systematic review of risk factors for MDR-TB in Europe concluded that previous treatment was the most significant distinguishing feature from DS-TB; in fact, MDR-TB was ten times more likely in individuals previously treated for tuberculosis [2]. Other associated risk factors for MDR-TB diagnosis were: age less than 65 years (pooled odds ratio 2.53), male sex (pooled odds ratio 1.38), and HIV co-morbidity (pooled odds ratio 3.52). The association with HIV was explained by nosocomial infection.

More recently, extensively drug-resistant tuberculosis (XDR-TB) has emerged as a noteworthy consequence of poorly managed drug sensitive and multi drug-resistant TB. XDR-TB is defined as resistance to isoniazid and rifampin plus a fluoroquinolone and a second-line injectable agent (e.g. capreomycin, kanamicin, and amikacin) [3]. Epidemiological data about the prevalence of XDR-TB is limited; however preliminary surveys have shown that the proportion of XDR-TB among MDR-TB in the US, South Korea and Latvia is 4%, 15% and 19%, respectively [3]. Because extensive resistance to both first and second line drugs has shrunk the roster of available drugs for treatment, XDR-TB is even more difficult to manage than MDR-TB, and is associated with greater morbidity and mortality [4]. The growing problem of XDR-TB is an added motivation to address the MDR-TB crisis before it becomes wholly unmanageable.

1. 2. Pathogenesis of drug resistance in Mycobacterium tuberculosis

Patients may acquire MDR-TB through two ways. Primary drug resistance occurs in patients who have never had tuberculosis before, and acquired drug resistance is the result of inappropriate medical management of initially drug-sensitive tuberculosis. Typically in low incidence settings, MDR-TB is considered an outcome of poor regimen compliance, and therefore, acquired. However, in certain regions, such as Eastern Europe and Central Asia, the rate of primary drug resistance exceeds the rate of acquired drug

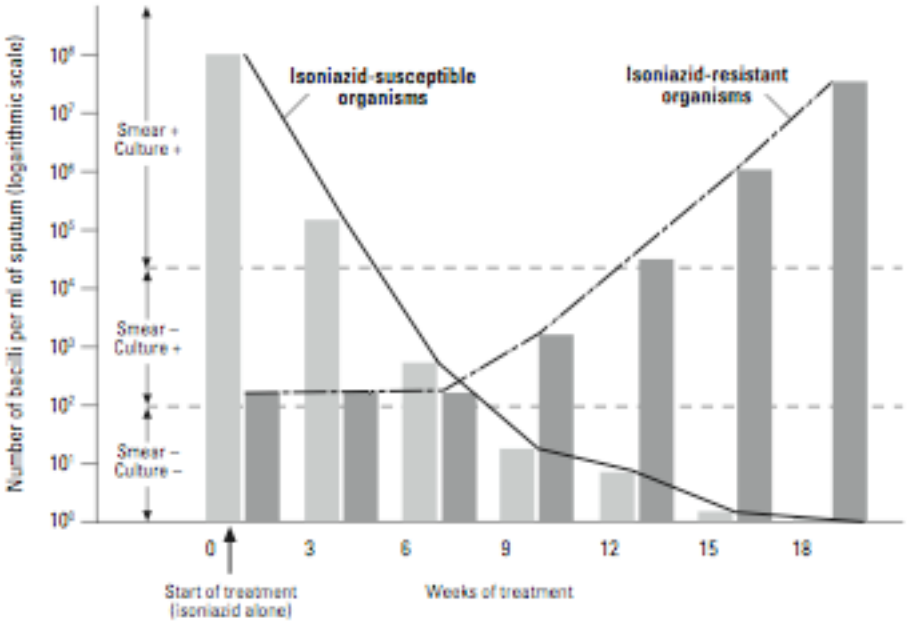
resistance, which is particularly alarming because of its potential to become a disseminated epidemic where MDR-TB is the common infectious strain.

At a microbiological level, drug resistance develops in *Mycobacterium tuberculosis* through two mechanisms: spontaneous mutation and selective pressure that permit naturally drug resistant strains to proliferate in the host. Spontaneous mutation in a wild type population of tubercle bacilli occur at a very low rate; the mutation rate of *M. tuberculosis* strains resistant to isoniazid, streptomycin, ethambutol and rifampin is 2.56 x 10^{-6}, 2.95 x 10^{-8}, 1.00 x 10^{-7}, 2.25 x 10^{-10} mutations per bacterium per generation, respectively[5],[6].

The probability of spontaneously occurring resistance to both isoniazid and rifampin is on the order of 1 in 10^{14}, and is therefore highly unlikely even in a patient with advanced disease, where the bacillary load is in the same order of magnitude. Therefore MDR-TB is generally considered a by-product of inadequate treatment of initially drug-sensitive or mono-resistant TB.

Full bacterial sterilization with multiple drugs is the principle behind modern tuberculosis chemotherapy. Monotherapy (i.e. treatment with a single effective drug) is widely accepted as the main mechanism for the development of drug resistance, which arises if therapy consists of a single drug, there is poor absorption of all but one drug, or the strain is resistant to all but one of the drugs administered. Other causes of effective monotherapy include poor treatment compliance, selective drug intake, irregular drug supply, poor drug quality and inappropriate prescription. Use of just one drug would selectively promote the growth of *M. tuberculosis* strains resistant to it. These resistant populations must be suppressed using other drugs. With monotherapy there is an initial fall in bacilli levels due to the killing of susceptible strains; however the bacilli levels eventually rise again through the propagation of resistant *M. tuberculosis* [7]. The characteristic fall and rise of bacilli levels due to isoniazid monotherapy is illustrated in the following diagram. Within the first six weeks of treatment, the bacterial load falls and

the patient is smear negative; however the patient eventually becomes smear positive again due to the growth of isoniazid-resistant organisms:



(figure copied from *Toman's Tuberculosis*, 2004)

Drug resistance can also arise from inadequate therapy that is not necessarily effective monotherapy, and is recognized as the "sequential regimen" mechanism. Mitchison proposed several mechanisms by which an irregular schedule of taking tuberculosis medication can promote the emergence of drug resistance [8]. These mechanisms are based on the cycles of killing and growth of the bacterial population when patients are on or off of their medications. A regimen taken in fits and starts may, on a break from treatment, promote the selective growth of certain drug resistant strains if the bactericidal rate of each drug were different (i.e. drug A killed strains resistant to drug B faster than drug B killed strains resistant to drug A). Once the patient resumes the normal course of therapy, the medications may no longer adequately kill the bacteria because the ratio of resistant to susceptible strains has increased. Conceptually it is easy to accept that in a population of partially resistant and fully sensitive bacteria, that the fully sensitive ones will be killed more rapidly. Early cessation of treatment would allow re-growth of the organisms left over, which would result in a higher proportion of partially resistant

organisms than at the start of therapy. Repeated cycles of treatment then cessation, such as through multiple defaults from treatment, would lead to selection of completely resistant organisms

It has been shown that resistance to rifampin is far more clinically significant than resistance to isoniazid [9]. Resistance to rifampin is the main reason for the difficulty in treating MDR-TB because no other drug can match its effective activity; therefore alternative therapies using second-line drugs must be of longer duration, and are often more toxic and less successful.

1. 3. Diagnosis of MDR-TB

Laboratory resources, the regional prevalence of disease, and the patient's medical history impact the diagnosis of MDR-TB.

Laboratory based diagnosis of pulmonary tuberculosis requires a sputum sample, which can be spontaneously produced, induced or obtained from methods such as bronchoscopy. The sample can be analyzed through two main methods: smear microscopy or culture growth. For smear microscopy, an acid-fast stain is applied to the specimen, which colours all strains of mycobacterium, including non-tubercular. The number of colony counts corresponds to the bacillary load, and therefore is proportionate to the infectiousness of the patient and is a useful prognostic indicator [10]. Smear microscopy is the mainstay of tuberculosis diagnosis in developing countries because it is inexpensive and quick; however its main disadvantage is its lack of sensitivity [11], and technician-dependent (i.e. experience and training related) sensitivity [12]. Of particular relevance is that smear microscopy cannot differentiate between drug-sensitive and drug-resistant tuberculosis; this information requires the use of culture and sensitivity testing, or molecular approaches.

A diagnostic method with superior sensitivity compared to smear microscopy is solid or liquid cultures. Most mycobacteria can be isolated and regrown for analysis within 21 days using liquid cultures; results with most solid media are slower, taking up to eight weeks [11]. However, cultures require more equipment, technician time and expertise, more materials, and are generally much more expensive and complex to undertake than smear microscopy. They also represent a significant biohazard, while smear microscopy does not. As well, cultures are prone to contamination during laboratory manipulation; therefore false positives can be a significant issue for this diagnostic media [13].

Drug susceptibility testing (DST) is usually done using solid or liquid cultures. In general, DST is an expensive and lengthy process that requires specialized laboratory facilities that are often inaccessible in MDR-TB endemic regions [11]. A typical DST is a two step process: first the *M. tuberculosis* must be cultured on a solid culture, which takes approximately four to eight weeks, followed by a sub-culture that takes about four weeks to see whether or not the cultured *M. tuberculosis* can proliferate in media incubated with standardized concentrations of anti-tuberculosis drugs. To delay treatment until the results of the test return has an increased risk of morbidity and mortality for the patient. Moreover from a public health point of view, the patient will remain infectious during this period.

A number of new techniques are being developed to increase the accuracy and reduce the turnaround time for test results. New tests that use molecular methods (i.e. line probe assays that detect gene mutations associated with drug resistance), simplified culture methods (i.e. MODS - microscopic observation drug susceptibility) or are phage-based show promise [14]. However, many of these diagnostic tools are still novel and have not been sufficiently validated for disseminated use [15].

Due to the high level of technical expertise, DSTs are usually performed under the supervision of a Supranational Reference Laboratory. Approximately 25 of these laboratories exist in the world and are overseen by a centre in Antwerp, Belgium as a part the WHO's Global Project on anti-TB drug resistance surveillance established in 1994

[16]. The laboratories participate in annual proficiency testing and quality assurance of results [17]. Nevertheless, differences exist in the standards used in the different laboratories [18].

The DSTs have variable reliability. The susceptibility tests for the first-line agents isoniazid, rifampin, streptomycin, and ethambutol are robust and have sensitivities of 99%, 97%, 94%, and 94%, respectively [15]. Pyrazinamide resistance testing requires a radiometric or calorimetric method that is not available in most laboratories; therefore it is not frequently tested. Drug susceptibility testing of second-line agents have poor reliability [15] and reproducibility [18], which is understandable given the difficulty in establishing minimum inhibitory concentrations, which varies depending on the distribution of *M. tuberculosis* strains in the population. Moreover differences between laboratories in the critical concentrations of drugs used in the testing limits the ability of cross-laboratory comparisons [18]. In light of this diagnostic challenge, it is recommended to correlate DST findings of second-line agents with the patient's drug treatment history.

1. 4. General principles of tuberculosis treatment

Treatment of tuberculosis consists of two phases: an initial intensive phase, and a continuation phase. The goal, duration and number of drugs used are different for each phase. The purpose of the intensive phase is the bactericidal killing of actively growing and semi-dormant *M. tuberculosis*. This phase is intended to drastically cut the bacillary load, thereby reducing the patient's infectious period. For drug sensitive tuberculosis, the intensive phase lasts approximately two to three months, and generally consists of a minimum of four first-line anti-tuberculosis agents. Four drugs are suggested in order to reduce the probability of promoting the growth of drug resistant tuberculosis, which is a risk if the initial bacillary load of the patient is high. To improve compliance with treatment, it is recommended that patients take their medication under direct health care supervision (i.e. directly observed therapy [DOT]). In addition, the medications can be

used in an intermittent dosing schedule, so that doses can be taken three times per week as opposed to daily in order to facilitate DOT. To reduce the likelihood of monotherapy, several of the drugs are available in fixed-dose combination tablet form. After the initial intensive phase, the continuation phase of treatment lasts from four to six months, uses fewer drugs (two to three) and is designed to kill any remnant bacilli. This basic approach to treatment is recommended by the WHO for all forms of pulmonary and extra-pulmonary tuberculosis except chronic tuberculosis cases and MDR-TB [7].

1. 5. Guidelines for MDR-TB treatment

Treatment of MDR-TB is largely guided by clinical experience and published guidelines by organizations such as the WHO and the American Thoracic Society (ATS). Traditional narrative reviews [19-23] have summarized leading expert opinions in the field. However, these opinions usually reflect clinical experience garnered in tertiary referral centres that manage complex MDR-TB cases [24], which leaves policymakers with a patchy evidence base for proposing universal guidelines for the treatment of MDR-TB, especially in the context of low-income and resource-limited settings. The situation is made especially difficult by the fact that no randomized controlled trials evaluating treatment outcomes of MDR-TB regimens have been published. Nonetheless, some general principles about MDR-TB treatment are accepted based on observational studies and clinical plausibility; using these, an expert committee of the WHO established new guidelines in 2008 for the treatment of MDR-TB [25].

Anti-tuberculosis drugs are classified into tiers, where the levels have progressively lower efficacy and more frequent or severe side effects [26]:

Group	Drugs
1- First-line oral antituberculosis agents	isoniazid, rifampin, ethambutol, rifabutin, pyrazinamide (PZA)
2- Injectable antituberculosis agents	streptomycin, kanamycin, amikacin, capreomycin
3- Fluoroquinolones	ofloxacin, levofloxacin, moxifloxacin, gatifloxacin (ciprofloxacin is no longer recommended as an anti-TB agent)[27]
4- Other bacteriostatic second-line oral antituberculosis agents	ethionamide, prothionamide, cycloserine, para-aminosalicylic acid, terizidone
5- Reinforcement drugs of unclear efficacy	amoxicillin/clavulinic acid, clofazimine, linezolid, clarithromycin, thioacetazone, imipenem, high dose isoniazid

Current WHO guidelines recommend the use of a minimum of four drugs with proven effectiveness, or five to seven drugs if their effectiveness against the strain is uncertain. Drugs should be selected from the highest level possible when designing a treatment regimen that is tailored to the patient's drug susceptibility profile (i.e. individualized). Because of high cross-resistance within the class of drugs, only one drug from groups two and three should be included in the regimen at a time. Group five drugs are used as a last resort because of weak or unproven in vivo activity or frequent adverse events. Each dose of the treatment should be directly observed.

MDR-TB treatment should last a minimum of 18 months past culture conversion; if there is evidence of extensive lung damage, treatment should continue for at least 24 months past culture conversion. MDR-TB treatment has an intensive phase, where the majority of the bactericidal activity is concentrated, and a continuation phase, where fewer drugs are used to suppress the proliferation of the remaining strains. The optimal length of the intensive phase of treatment for MDR-TB is a subject of debate. Since use of injectables is resource-intensive and a burden to patients, minimizing the duration of their use in the intensive phase is an important objective. The WHO recommends injectable drugs be used for at least six months with a minimum of four months past culture conversion.

To determine which drugs should be used for the patient, drug susceptibility testing, national surveillance of drug resistance, national accessibility of second-line agents, and past tuberculosis treatment history should be considered. As previously discussed, the reliability of drug susceptibility testing is dependent on the quality of the laboratory, and the results may not be dependable for second-line drugs. Proxy measurements of the patient's own drug resistance profile can be made using national data, such as drug resistance surveys. In addition, sensitivity to second-line agents may be assumed if they were not historically available in the country. Previous tuberculosis treatment history can also be used to guide current therapy; however, there may be difficulty obtaining official clinical records of this treatment, and the patient's recollection of the treatment specifics could be imperfect. Past treatment history is considered important because it is assumed that the current tuberculosis disease is a relapse of the original strain, and that it has grown resistant to the previously used drugs. Ideally, never-used drugs should be used in MDR-TB treatment regimens.

MDR-TB experts with the International Union Against Tuberculosis and Lung Disease, recommend an MDR-TB treatment strategy based on history of previous treatment [28]. They suggest three categories: patients with no prior TB treatment history (primary MDR-TB), patients who have only received first-line drugs in the past, and patients who have received both first and second line drugs in the past. This method of patient categorization allows for the use of standardized regimens in certain cases, as opposed to the individualized regimens emphasized by the WHO.

Patients with primary MDR-TB should be treated with as many first-line agents as possible, and then one from group two and one from group three for a minimum of four drugs [26]. Treatment of MDR-TB with a standardized regimen that includes isoniazid and rifampin has had variable treatment success in the literature, ranging from 11% to 60% [29], therefore there is insufficient proof of the efficacy of a standardized regimen containing first-line agents. Whether or not patients with primary MDR-TB should be treated with a standardized regimen containing first-line drugs remains controversial. The

second category of patients (who have only received first-line agents in the past) can be treated with a standardised regimen consisting of a minimum of four second-line agents. A standardized regimen would avoid the expense, delay and uncertainty of a DST-reliant regimen. The last category of patients (who have received first and second-line agents in the past) are the most complicated to treat because they have resistance to multiple classes of anti-tuberculosis agents; therefore they should receive individualized regimens. However, it is plausible that a standardised regimen consisting of second-line drugs that are entirely naïve to the country can be successfully used for these patients [28].

Surgery as an adjunct to pharmacologic treatment of MDR-TB is an option that some doctors in specialized tertiary care centres explore with their patients. It is recommended for patients with a localised lesion, adequate pulmonary function, and who are only eligible to take two to three weak-action drugs (i.e. their drug regimen is deemed inadequate) [28].

1. 6. Controversies in MDR-TB treatment

Several leading health policy-influencing institutions generate guidelines for MDR-TB treatment that are regularly updated. However, given the lack of randomized controlled trials for MDR-TB treatment, the guidelines can have conflicting recommendations [24]. This confusion is well illustrated by the recommended number of drugs used in an MDR-TB treatment regimen. The ATS has changed its stance a few times: in 1965 and 1966, it recommended two to three drugs, in 1994, a minimum of three drugs, and 2003, four to six drugs [24]. The WHO recommended a minimum of three drugs in its guidelines published in 1996 and 2003; however in 2006 and 2008, the recommendation was for four drugs [26]. The British Thoracic Society (BTS) recommended three drugs in 1990, which increased to a minimum of five drugs in 1998. The Canadian Tuberculosis Standards currently recommends a minimum of four efficacious drugs, or five second-line drugs if no first-line drugs can be included in the regimen [30]. Some experts argue that these changes in policy were often arbitrary, and if they were supported by peer-

reviewed studies, they were in a highly selected group from whom generalized treatment principles should not be derived. A brief survey of published literature from the pre-rifampin era on tuberculosis treatment demonstrates very high success rates (81-100%) for cohorts treated with a standardized regimen of three drugs: isoniazid, streptomycin and para-aminosalicylic acid [28]. Since such high treatment success is documented with a three-drug regimen not containing rifampin, the validity of some policy recommendations for MDR-TB treatment can be questioned.

Other unsettled questions in MDR-TB treatment are the optimal length of the intensive phase and injectable drug use, the role of standardized drug regimens, and the role of adjunctive surgical resection. Guidelines and expert opinion vary considerably on these questions [28], which leaves many decisions up to the doctor's clinical discretion.

1. 7. Evidence base for MDR-TB treatment

The University of Oxford's Centre for Evidence Based Medicine ranks levels of evidence that should be considered in clinical decision-making [31]:

Level of Evidence	Type of Evidence
1a	Systematic review of randomized controlled trials
1b	Single randomized controlled trial
2a	Systematic review of cohort studies
2b	Single cohort study
3a	Systematic review of case-control studies
3b	Single case-control study
4	Case-series
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

Randomized controlled trials (RCT) are considered the gold standard method to determine the standard of care for a particular disease. To date, there has been one published phase two RCT investigating the efficacy of the new anti-tuberculosis drug TMC207 [32]; however there have been no RCTs investigating optimal treatment excluding novel therapies. A number of factors have discouraged RCT studies for MDR-TB, including the small number of patients at many centres, controversy over the appropriate regimens to be considered for the experimental and control arms, and the methodological challenge of designing such a trial [33]. The only data on optimising MDR-TB treatment outcomes are based on observational studies (levels 2b, 3b and 4) and leading expert opinions (level 5).

1. 8. Study Rationale

In order to appreciate the scope of the literature and summarize the findings across the studies, this systematic review was initiated in June 2007 to produce level 2a evidence for clinical care. Before this research was completed, Orenstein et al published in March 2009 a systematic review and meta-analysis investigating treatment-related prognostic factors for successful MDR-TB treatment outcomes [34]. In September 2009, Johnston et al published a systematic review of patient and disease-related prognostic factors associated with MDR-TB treatment outcomes [35]. Using subgroup analysis, Orenstein et al found that length of treatment greater than 18 months, directly observed therapy, individualized regimens, resistance to more than 4.4 drugs and a drug regimen containing more than five drugs were prognostic indicators (although not statistically significant) for treatment success. Johnston et al found that statistically significant positive correlates of treatment success were adjunctive surgery, no history of previous TB treatment, and fluoroquinolone use. Negative correlates of treatment success were male sex, alcohol abuse, low BMI, smear positivity, Fluoroquinolone resistance, and XDR-TB.

There are some important distinguishing features in the methodologies of the Orenstein and Johnston meta-analyses and this review that makes this current research relevant. For

example, these studies did not investigate relapse as a treatment outcome, which is a shortcoming given the high rates of relapse associated with MDR-TB [36]. In addition, both published studies had comparatively narrow inclusion criteria, such that their sample sizes were nearly half that of this thesis. Johnston excluded articles where data was not presented in an 'appropriate format.' Orenstein's inclusion criteria were limited to studies that exclusively used CDC treatment outcome definitions, and studies that only used regimens with second-line therapy. The stringent definition used for MDR-TB cure (five negative cultures in the final 12 months of treatment) was recently advanced by the CDC, but has not been correlated with a more accurate assessment of long-term treatment outcomes in MDR-TB patients [37]. Applying such stringent testing standards may be a source of bias because studies from low income settings would be less likely to meet these standards, and so would be excluded from the review. Moreover, by excluding studies where first-line agents were used in MDR-TB treatments, important information about these treatments' efficacy is lost. This clinical question is especially important in light of the fact that some leading experts in the field believe that there remains a role for first-line drugs in the management of this disease. In addition to applying narrow inclusion criteria, Orenstein did not contact authors for additional data, despite recognizing the inconsistency in information reported in the studies.

In terms of analysis, the two published studies limited their investigation to prognostic indicators in treatment characteristics (Orenstein) and disease and patient characteristics (Johnston), whereas this thesis analyzed patient, disease, treatment and health setting characteristics. We also included meta-regression analysis in addition to the sub-group analysis, which modelled the data using several characteristics at once. The following is a table comparing the methodologies of all three studies:

Comparison of the methodologies of three systematic reviews exploring correlates of treatment outcomes of MDR-TB

Category	This thesis	Johnston et al [35]	Orenstein et al [34]
Period covered	1970- July 2008	1965- December 2008	1965- December 2008
Inclusion Criteria	- DST confirmed MDR-TB - ≥25 patients in cohort - at least one treatment outcome that met definition: success, failure, relapse, death, default - English, French or Spanish publications only	- DST confirmed MDR-TB in adult population - "reported outcomes presented in a format allowing for comparison with other studies" - >10 patients in cohort - study design had to be: prospective cohort, retrospective consecutive cohort, consecutive case control, or randomized control -treatment ≥ 12 months -reported basic demographic data -less than 1/3rd of cohort defaulted -English publications only	- DST confirmed MDR-TB -treatment outcomes defined by WHO & mycobacterial culture endpoints -treatment regimens used second-line drugs -exclusion of cohorts with exclusively XDR-TB -English publications only
Number of cohorts in final analysis	64	31	33
Investigator Contact	Yes	Yes	No
Method of Analysis	-Random effects meta-analysis (pooling) -meta-regression	-Random effects meta-analysis (pooling)	-Bayesian random effects meta-analysis (pooling)
Treatment Outcomes analyzed	success, failure, relapse, death, default	success, failure, death, default	success, failure, death, default

The strength of our study design is that it is more inclusive of the published literature through broader inclusion criteria and has a more complete dataset through investigator contact. In addition, our treatment outcome definitions factored relapse into the measurement of success and failure, which is important to gain a long-term perspective of treatment efficacy. In summary, our research was better able to assess the scope of MDR-TB treatments (including those just using first-line drugs) and comment on their efficacy, minimize selection bias and more thoroughly explore correlates of treatment outcomes.

Chapter 2 Study Objectives

1. Estimate the rates of treatment outcomes in MDR-TB, including treatment success, death, and default, using meta-analysis to pool rates across all studies.

2. To explore the population, disease, treatment and health setting correlates of these treatment outcomes. Based on narrative reviews and consultation with TB experts, we were particularly interested in confirming the importance of directly observed therapy, type of drug regimen (individualized or standardized), number of drugs in regimen, use of second-line agents, and duration of treatment on treatment outcomes.

Chapter 3 Methods

We performed a systematic review and meta-analysis to summarize MDR-TB treatment outcomes and their correlates.

3. 1. Inclusion criteria

To be eligible for inclusion in the systematic review, studies must have reported treatment outcomes for patients with bacteriological proven resistance to isoniazid and rifampin (i.e. MDR-TB). Studies reporting exclusively on XDR-TB were excluded. Studies reporting exclusively on extra-pulmonary MDR-TB were also excluded. At least one treatment outcome had to meet our definition for success, failure, relapse, death or default (see section 3.3). Studies were not excluded based on any population, disease or treatment characteristics. To minimize bias due to inclusion of atypical case reports and small case series, and to increase the precision of effect measures, only studies with a minimum of 25 subjects were considered for inclusion. Only studies published in peer-reviewed journals in English, French, or Spanish languages were eligible for review. Because rifampin was introduced into clinical use only in 1969, the review was further restricted to studies published after 1970.

3. 2. Literature search

Article citations were found by searching four major electronic health science databases. In addition, the reference list of narrative reviews and published guidelines on MDR-TB were screened to identify additional studies.

MEDLINE (1970- July 2008) and EMBASE (1980- July 2007) were searched using subject headings, whereas BIOSIS (1970- July 2007) and Web of Science (1970- July 2007) were searched using free text. The specificity of the search was improved by the use of subject headings in MEDLINE (MeSH) and EMBASE (EMTREE). The following

search strings relating synonyms of tuberculosis, pulmonary, drug resistance and therapy were used, and were developed with the consultation of TB experts, as well as the librarian staff at the McGill Health Sciences Library.

MeSH headings in MEDLINE

- Antitubercular Agents [Therapeutic Use]
- Tuberculosis, multidrug-resistant
- Tuberculosis, pulmonary

EMTREE terms in EMBASE

- Lung Tuberculosis [Drug resistance]

Free-text search terms in BIOSIS & Web of Science

- MDR
- XDR
- Tuberc* OR TB
- Multi*
- Drug*
- Resist*
- Pulmonary OR lung* OR respirator*

3. 3. Study selection process

The citations retrieved from all sources were merged into one reference library in the software program EndNote (version 11). Duplicate citations were deleted.

The citations underwent an initial screening, and then a full-text review to derive a final set of articles included in the study. During the initial screening, a single reviewer (YA) excluded studies based on a title and abstract review. At this stage, if there was any uncertainty about the article's inclusion in the systematic review, it was included for the next stage of review. This pared down list of citations then underwent a two person (YA

& AZ) full-text review. Full-texts of all articles were retrieved and assigned a unique identification number. A second copy of these full-text articles was made, with each reviewer receiving a copy. The two reviewers independently read the articles and applied the inclusion/exclusion criteria; when applicable, reasons for exclusion were recorded. In order to ensure that both reviewers were correctly interpreting the inclusion criteria, results of the first ten articles were compared to see if there was a reasonable degree of concordance. At the completion of the full-text review, the two sets of results were compared. Articles where both parties agreed on inclusion were included in the systematic review. Discordance between the reviewers was resolved in discussion and consensus between DM & YA.

3. 4. Treatment outcome definitions

The following tuberculosis treatment outcomes (proportions) were used as dependent variables. Their definitions are a modification of the US Centers for Disease Control's (CDC) proposed treatment outcome definitions for MDR-TB [37]:

- Cure: culture converted by the end of the treatment period.
- Treatment complete: completed the prescribed treatment without bacteriological evidence of either cure or failure.
- Default: treatment was interrupted for two consecutive months or more, or patient transferred out and treatment outcome was unknown. In addition, patients whose treatment outcomes were not described in the study were considered to have defaulted.
- Failure: culture-positive status after five or more months of treatment.
- Relapse: recurrence of bacteriological confirmed tuberculosis after treatment success (cure or treatment complete).
- Death: death due to any cause during the course of tuberculosis treatment.

Given the high rates of relapse after apparent cure reported in MDR-TB cohorts, the rates of treatment success and failure are not accurately represented by patients' end of

treatment outcomes. To address this issue, we created two new treatment outcome definitions that accounted for relapse during the post treatment follow-up period (if reported):

- Cumulative success: total number who were cured or completed treatment but did not meet the definition of failure, minus those who relapsed during post-treatment follow-up.
- Cumulative failure: total number of failure during treatment and/or relapse during post-treatment follow-up.

The treatment outcomes used in the final analysis were cumulative success, cumulative failure, default, and death.

3. 5. Data abstraction

Important risk factors and key variables for MDR-TB treatment prognosis were identified through personal communication with expert clinicians and preliminary readings of primary research and narrative reviews on the topic. Data abstraction forms were pilot-tested on a few articles to ensure that the abstracted information was accurately captured, and also that important information was not missed (Appendix 2).

The independent variables (i.e. risk factors) were divided into categories: bacteriological methods, population characteristics, disease characteristics, treatment characteristics, and national data. Average values were recorded when possible for continuous variables; however, if only median values were reported they were recorded instead. Additional information about national MDR-TB prevalence and per capita health care spending was retrieved from the most recent WHO TB reports [38]. National income level data was taken from the World Bank's reports [39].

The following is a list of the variables that were collected, along with the unit of measurement if applicable:

Bacteriological Methods:

- Method of smear microscopy
- Method of culture
- Method of drug susceptibility testing

Population Characteristics:

- Country
- Start year of patient enrolment (year)
- Duration of patient enrolment period (months)
- Total number of MDR-TB patients enrolled in the study
- % of MDR-TB patients with pulmonary disease only
- % of MDR-TB patients with pulmonary and extra-pulmonary disease
- % of MDR-TB patients with extra-pulmonary disease only
- Characteristics reported for the MDR-TB cohort only?
    - Yes
    - No
- % female
- average, or median, age (years)
- % with HIV infection
- % with prior TB treatment history
- % that failed previous TB treatment
- % that relapsed previous TB treatment
- % that returned after default of previous TB treatment

Disease Characteristics:

- % of cohort with positive smear
- % of cohort with cavitary disease
- % of cohort with bilateral pulmonary disease
- Average, or median, number of drugs resistant to <u>in addition</u> to isoniazid and rifampin

- % of cohort resistant to a fluoroquinolone
- % of cohort resistant to pyrazinamide (PZA)

Treatment Characteristics:

- Directly observed treatment (DOT)
    - Yes
    - No
    - Partial
- Type of drug regimen
    - Individualized
    - Standardized
    - Mixed (Individualized & Standardized)
- Institution
    - Specialized Hospital (used first and/or second line drugs)
    - Specialized national/regional TB treatment program (used second-line drugs)
    - National/Regional TB program (used first-line drugs only)
    - Other
- Average, or median, length of treatment (months)
- Average, or median, length of post-treatment follow-up (months)
- Average, or median, number of drugs given in regimen
- Average, or median, number of sensitive drugs given in regimen
- Use of second-line drugs in therapy
    - Yes
    - No
- % of the cohort receiving fluoroquinolones
- % of the cohort receiving pyrazinamide (PZA)
- % of the cohort receiving an injectable drug
- % of the cohort that had adjunctive surgical resection

National Data:

Information about national tuberculosis prevalence levels and health expenditure was collected from the World Health Organization Core Health Indicators database [38]. Data were available for the years 2005 and/or 2008; information was used from whichever year was closest to the midpoint of the patient enrolment period.

- National proportion (%) of primary MDR-TB among all TB cases
- National proportion (%) of secondary MDR-TB among all TB cases
- Per capita government expenditure on health (US dollars)
- Per capita total expenditure on health (US dollars)

Information about national income level was taken from the World Bank website, and based on 2007 data [39]:

- Country Income level
  - High Income
  - Upper Middle Income
  - Lower Middle Income
  - Low Income

The income categories were defined by the World Bank. High income was defined as Gross National Income per capita (GNIPC) greater than $11,456 US dollars. Upper middle income was defined as GNIPC between $3,706- $11,455. Lower middle income was defined as GNIPC between $936- $3,705. Low income was defined as GNIPC less than $936.

For some cohorts there was a large time span between the patient enrolment period and the years for which national health expenditure and income data were available. There was no way to confirm that the available data accurately reflected the cohort's period.

3. 6. Quality assessment of studies

There are no published criteria or validated tools for assessing the quality of tuberculosis treatment research. Study quality was assessed by investigating several study design elements and their influence on the three main types of bias in epidemiologic studies: selection bias, information bias and confounding. Selection bias is a systematic error in selecting patients for inclusion in the study, such that there is a difference in the exposure-disease relationship of study participants versus non-participants. An example of selection bias is found in studies based in tertiary care referral centres: these centres usually have a higher proportion of more complex and treatment-refractory patients. Such patients may not be representative of all MDR-TB patients. Loss to follow-up can also introduce selection bias due to attrition, that is patients with worse prognoses are more likely to drop-out or be lost to follow-up which leaves healthier people to be included in long-term outcome assessment.

Strategies used to evaluate potential selection bias:

- Type of institution where patients were treated (level of healthcare delivery)
- Whether the method of patient sampling was consecutive, convenience or other
- % of eligible patients included in the study
- % successful patients who are followed-up
- Average length of follow-up

Publication bias is a type of selection bias, whereby studies with positive results are more likely to be published than those with null, or negative results. A funnel plot is a graphical representation of study size and treatment effect, and is traditionally used for meta-analyses of RCTs to evaluate the degree of publication bias; however, its validity for observational data is uncertain [40]. Hence publication bias was not evaluated in this study, although we attempted to minimize this type of bias by excluding cohorts of less than 25 patients, because it has been shown that smaller studies disproportionately tend to have greater treatment effects than larger studies [40].

Information bias is a systematic error in measurement of a variable that can result in incorrect classification of a patient's exposure or disease status. In the case of tuberculosis studies, misclassification of MDR-TB status is a concern if drug susceptibility results are not accurate.

Strategies to evaluate potential information bias:

- Quality control for drug susceptibility testing (use of internationally recognized standards)

Lastly, confounding addresses whether the measured exposure is actually causing the outcome, or whether the outcome is the effect of another unmeasured covariate that is related to both the measured exposure and the outcome. Confounding is a complicated topic in epidemiology, and has significant implications in determining causality between exposure and outcome. Several risk factors influence outcomes in MDR-TB and these are often correlated, so it becomes difficult to determine the distinct effect of all potential exposures. Therefore, adjustment for confounding is an important issue to consider when interpreting the results. Confounding in the primary studies cannot be minimized post hoc; it reflects study design and data collection.

Since this review uses only study-level covariates and not individual patient data, we were not able to control for confounding at the individual patient level. Since this meta-analysis makes study-level associations between covariates and treatment outcomes, there is inherently an ecological fallacy, which is the understanding that inferences at the study-level may not hold at the individual-level. Meta-regression methods somewhat overcome this problem, because study-level covariates can be simultaneously entered into regression models, and this addresses confounding at the study level. However, residual confounding in this study is likely because of the observational nature of the data (not randomized).

Subgroup analysis was done to explore potential selection and information biases.

3. 7. Reproducibility of data abstraction

To ensure reproducibility of the data abstraction, a second reviewer (AZ) abstracted data from a randomly selected subset consisting of 15% of the articles included in the systematic review (nine cohorts). Nine key variables were selected a priori to compare across both reviewers, along with an acceptable range of error:

Variable	**Range of Error**
Average number of drugs resistant to (in addition to isoniazid and rifampin)	± 0.5 drug
Directly Observed Therapy	None (categorical variable)
Type of Drug Regimen	None (categorical variable)
Average, or median, number of drugs given in treatment regimen	± 0.5 drug
Cure	± 1 patient
Treatment Complete	± 1 patient
Death (all cause)	± 1 patient
Failure	± 1 patient
Default	± 1 patient

All of the information from the data abstraction forms were entered into an Excel document by YA. To ensure accurate transcription, two articles selected at random were re-entered into the data set, and compared with their original entry to see the amount of agreement. A minimum 98% agreement was defined a priori as an acceptable level of transcription accuracy.

3. 8. Investigator contact

To ensure complete information across studies, principle investigators were contacted for additional information on certain key variables, selected based on a priori knowledge of their prognostic significance for MDR-TB treatment outcomes. To increase the likelihood of a response from the authors, these variables were limited to the ten most important:

- Definition of treatment outcomes (if not already defined in the text)

- Was MDR-TB diagnosis confirmed by drug susceptibility testing for all patients enrolled in the study?
- Drug sensitivity testing with internationally recognized quality control measures (Yes, No, Unknown)
- % female
- Age (mean/median years)
- % HIV infected
- Directly Observed Therapy (Yes, No, Partial)
- Type of drug regimen (Individualized, Standardized, Both)
- Characterization of the degree of specialized MDR-TB medical care offered by the institution(s) in the study
- Length of treatment (mean/median months)

3. 9. Data Analyses

Meta-analysis is done to generate pooled estimates, which are essentially weighted averages, and there are two models that are used for meta-analysis: fixed effects and random effects. Fixed effects assumes that the true value of the parameter measured in each study is the same, whereas random effects assumes that there is a distribution of the true effects reflected in the sample of studies [41]. This latter method is considered more conservative and provides pooled estimates with wider confidence intervals. Given the variation of the characteristics, treatments and outcomes of the cohorts included in the systematic review, we used the random effects model in our meta-analyses. To account for residual heterogeneity, a between-study variance factor was included in the model (τ^2) [42].

The random effects pooling of proportions was done with the "metan" command in STATA using a model proposed by DerSimonian and Laird [41]. To prevent the automatic exclusion of studies with 0% of a certain treatment outcome, a count of 0.1 of that treatment outcome (i.e. 0.1 of a patient) was added to that study to give a percent

outcome that was close to zero. It was not anticipated that this correction factor would artificially inflate the pooled outcome.

The studies were weighted by the inverse of the sum of the standard error for each study and the between-study variance statistic τ^2. This method of calculation provided proportionally greater weight to smaller studies than to larger ones as compared to a conventional fixed effects weighting formula [43].

The calculation of the confidence interval for the pooled estimate factored in the between-study variance statistic τ^2 to reflect the uncertainty in the point estimate and distribution of the random effects model [41]. The prediction interval for the pooled treatment outcome was calculated by the formula:

$$\text{Mean} \pm t_{df}\sqrt{(se^2 + \tau^2)}$$

where t_{df} is the 95th percentile of the t distribution with k-2 degrees of freedom, se^2 is the square of the mean's standard error, and τ^2 is the between-study variance statistic.

The heterogeneity of the studies was assessed by estimating the I^2 index; this statistic is now the preferred tool for assessing heterogeneity in meta-analysis studies. This statistic measures the proportion of total variability in a set of effect sizes due to between-study variability. As a general rule of thumb, if the I^2 index is greater than 50%, this is considered significant between cohort heterogeneity [44].

Descriptive analysis was done for all the independent variables. Continuous variables were analyzed by their distribution, mean (not weighted by study size), standard deviation, median, inter-quartile range, and total range. Categorical variables were analyzed by tabulating the percent breakdown of studies that fell into each category. The percent of cohorts that reported the variable was also noted.

Correlates of treatment outcomes were analyzed using subgroup analysis. The treatment outcomes assessed were cumulative success, death and default; cumulative failure was not separately reported because its results would be complementary to those for cumulative success, and therefore would not add any new information. Studies were separately stratified by each of the covariates. Categorical variables were stratified by category. Continuous variables were stratified by clinically meaningful cut-points. The strata were compared to see if the covariate resolved the heterogeneity, or if there was a trend in the treatment outcome. Statistically significant correlates were those in which the confidence intervals of the pooled outcomes in each stratum did not overlap, and are hereafter called significant associations. Correlates that displayed a trend with the treatment outcomes but were not statistically significant were called associated trends. These associations were labelled weak or strong based on the relative difference in the pooled estimates.

Meta-regression was performed to further explore sources of statistical heterogeneity by investigating correlates of treatment outcomes. Each study was treated as one data point that was represented by study-level aggregate information, in contrast to a multivariate regression where each person is a data point that is described by individual-patient data. Covariates for inclusion in the meta-regression model were selected based on an a priori review of the literature and consultation with TB experts. Traditional strategies of multivariate model building generally do not apply to meta-regression because of the relatively small size of the sample. Meta-regression was done using the command "metareg" in STATA, which uses a model that approximates random effects hierarchical logistic regression, except that the within-cohort data are summarised by an effect estimate and its standard error for each cohort [45].

The relatively small size of the dataset limited the number of covariates that could be included in the model without over fitting; therefore a few multivariate models were built for the treatment outcomes cumulative success, death and default in order to investigate other potential correlates. The health setting was explored using the covariates: institution, government health expenditure, and national proportion of acquired MDR-TB

among all TB cases. The classes of drugs used in the regimens were explored with the covariates: proportion of patients treated with fluoroquinolones, PZA, or injectable drugs. The model investigating modifiable treatment characteristics included the variables: number of drugs given in the regimen, administration of second-line drugs, type of drug regimen, and length of treatment. A final model with all of these covariates was also created in order to control for more confounding. Goodness of fit of the models was ascertained by the R^2 value, which is the proportion of the between-study variance that is explained by the covariates; values closer to 0% indicate that the covariates do not explain much of the variability in the treatment outcome.

Statistical analysis was carried out using STATA software (Stata Corp, Texas, USA), version 10.0.

3. 10. Ethical considerations

No ethics approval for this systematic review was sought because it utilized publicly available, published data.

Chapter 4 Results

4. 1. Study selection process

Figure 1 shows the study selection process. 2149 potentially relevant citations were found by searching the databases MEDLINE, EMBASE, BIOSIS, and Web of Science for the period of 1970 to July 2007. Only date, and not language limits, were placed on the search to have a record of the potentially relevant articles in other languages that would necessarily be excluded, thereby estimating the language bias of our study. The keyword search was repeated in MEDLINE for the period July 2007 to February 2008, resulting in an additional 29 articles to be screened. Nine additional unique citations were found by screening the references of major MDR-TB reviews and treatment guidelines. In total, 2187 article titles and abstracts were screened for inclusion in the next round of full-text review.

Of these 2187 articles, 1917 articles were excluded based on language or title/abstract review, and 265 articles were identified for retrieval and full-text review. Full-text reports of all but seven of the 265 articles were retrieved, and 65 were excluded for being the wrong type of article, or not original research (i.e. conference abstract, review, editorial or commentary, letter to the editor).

193 full-text articles were screened for inclusion in the systematic review by two reviewers. There was 90% concordance between the two independent screenings: 68 included, 105 excluded (see figure 1 for listed reasons), and 20 discordant conclusions. The fate of the 20 discordant studies was resolved through mutual agreement between two reviewers; 16 were excluded, and four included in the final systematic review.

Ultimately, 74 articles met the inclusion criteria for the systematic review and were included in this study.

4. 2. Articles and cohorts included

74 articles met the inclusion criteria for the review. These articles reported on a total of 84 cohorts. However, some of these cohorts were subsets of cohorts reported in other included articles. For example several subsets of the same cohort from Hong Kong were reported on three separate occasions by Yew [46, 47] and Espinal [48]. The difference between them was the start date and duration of the patient enrolment period: start 1990 (duration 131 months), start 1990 (duration 77 months), start 1994 (duration 36 months), respectively. In each case where overlapping cohorts were identified, only the report describing the largest cohort with the longest follow-up period was included in the final analysis. As a result there were 64 unique cohorts analyzed in the final dataset. These are listed in Table 1. Appendix 1 is an account of all the unique and duplicated cohorts from countries with multiple studies.

4. 3. Investigator contact

Corresponding authors were contacted by e-mail if information in their articles needed clarification or supplementation on key variables selected a priori (see section 3.8). Of the 74 articles that met the criteria for inclusion, 17 were not contacted because they were repeated reports of the same cohorts, three were not contacted because there was no deficiency in reported information, five had no known email contact information and 17 were contacted twice with no response (14 corresponding authors were listed as the primary contacts in these 17 articles). In total, 32 completed questionnaires were returned. The response rate for successful investigator contact (excluding the 17 that were repeated reports of the same cohorts) was 32/57= 56%.

4. 4. Reproducibility of data abstraction and transcription

The information abstracted from nine randomly selected articles was compared between the two reviewers. 59 items were the same, and 22 were different (total of 81 “pairs” of

data); most of the discordant pairs were due to no value being entered by one of the reviewers while the other reviewer was able to locate a measurement of the variable in the study.

All the abstracted data from two randomly selected articles was re-entered into an Excel spreadsheet and compared against the original entry for that article. Only two discordances were found out of a total of 108 entries for both articles, making the proportion of correct transcription 106/108 (98.1%).

4. 5. Descriptive statistics of the cohorts

Table 2 summarizes the information about the distribution of the independent variables for the 64 cohorts in the final dataset.

4. 5. 1. Population characteristics

The mean size of the cohorts was 124 patients. The mean age of the cohorts was 39 years. The cohorts were on average 31% female. The mean prevalence of HIV infection was 11%; however the distribution of this variable was not normal, and the median value was 0.2%. The median prevalence of previous tuberculosis treatment was 77%.

4. 5. 2. Health system factors

A very high correlation was noted for the two variables measuring national health care costs: per capita national total health expenditure (US dollars) and per capita government health expenditure (US dollars). Therefore, further analysis of health care costs was done by using the variable per capita government health expenditure: the mean was $603 and the median was $108.

National income level was also used as a measurement for the health care setting. By World Bank categorization, 44% of the cohorts were from high income, 18% upper middle income, 12% lower middle income, and 7% from low income countries.

The mean proportion of MDR-TB among all national TB cases was 4% for primary and 19% for acquired disease.

4. 5. 3. Disease characteristics

The mean percentage of the cohort with exclusively pulmonary tuberculosis with no extra-pulmonary manifestations was 95%. The mean prevalence of a positive sputum smear was 74%; however less than half of the cohorts reported this variable. The mean number of drugs the cohorts were resistant to was two, in addition to isoniazid and rifampin. Less than one third of the cohorts specifically reported the prevalence of resistance to fluoroquinolones and PZA, which was on average 13% and 38% respectively.

4. 5. 4. Treatment Characteristics

The median length of treatment was 18 months; this variable was reported for 54/64 cohorts. The median length of post-treatment follow-up was 24 months; however, less than half of the studies explicitly reported a follow-up period. The mean number of drugs given in the treatment regimen was five. The mean number of sensitive drugs given in the treatment regimen was four. About two thirds of the cohorts reported the total number of drugs given, while only one third reported the number of sensitive drugs given.

Information about the proportion of patients receiving fluoroquinolones, PZA or injectable drugs was available for approximately two thirds of the cohorts, and was on average 61%, 66%, and 80%, respectively. Less than half of the cohorts reported the use of surgery as adjunctive therapy. Four surgical series skewed the mean prevalence of surgical resection to 23%; the median was 7%.

For the variable directly observed treatment, 34% of the cohort had all doses directly observed, 36% had some but not all doses directly observed, and 14% had self-administered therapy. For type of drug regimen, 67% had individualized therapy, and 27% had standardized therapy. For the type of institution where care was provided, 50% of the cohorts were treated in specialized TB hospitals where 25/32 (78%) administered second-line drugs, 19% in a specialized MDR-TB national treatment program where

second-line drugs were administered, and 20% in a national TB treatment program where only first-line agents were administered.

4. 5. 5. Treatment Outcomes

Table 3 summarizes pooled treatment outcomes without stratification, calculated by a random effects model. The Forest Plots in figures 2-5 illustrate the wide range in the treatment outcomes across the studies; this variability is quantified by the I^2 Index, which is over 90% for all treatment outcomes, indicating significant heterogeneity. Therefore, all the pooled outcomes should be interpreted with caution.

The mean cumulative success (successful patients who did not relapse) was 50%. The mean cumulative failure (failure plus relapse) was 17%. The mean death rate during treatment was 13%. The mean treatment default rate was 18%.

Because of the overall high degree of heterogeneity in all the outcomes, we used subgroup analysis as the first approach to exploring sources of heterogeneity.

4. 6. Subgroup Analysis

4. 6. 1. Cumulative Success

Table 4 summarizes all the subgroup analyses for the treatment outcome cumulative success. Most subgroups had significant heterogeneity, with I^2 values in the 90% range.

The mean age and sex distribution of the cohorts were not associated with cumulative success. A high prevalence (>6%) of HIV had an associated trend of lower cumulative success. Notably, a history of prior tuberculosis treatment was not associated with worse cumulative success.

Factors measuring the severity and complexity of the disease were strongly associated with cumulative success. Cohorts with a lower proportion of smear positive pulmonary disease (hence less extensive disease) tended to have higher cumulative success. There

was also a significant association of increased cumulative success with increasing resistance to drugs. This counterintuitive finding is thought to be because most studies in high income countries reported on cohorts treated at tertiary health care institutions, to which more complex patients, with more extensive drug resistance were referred, yet these facilities had excellent resources including access to second-line drugs.

Measurements of the health system factors, such as national income and health expenditure, were not associated with cumulative success. A weak associated trend was found for the national proportion of acquired MDR-TB among all TB cases, where a low prevalence (<14%) was associated with a slightly higher cumulative success than for a high prevalence setting (54% versus 46% cumulative success, respectively).

Numerous treatment characteristics were associated with cumulative success. Cumulative success was significantly higher in national MDR-TB treatment programs where second-line drugs were used (66%), in contrast to the low success rates achieved in tuberculosis treatment programs using only first-line drugs (30%). This finding is corroborated by a separate subgroup analysis for the categorical variable that explored the use of second-line drugs in the regimen; use of second-line drugs was significantly associated with a nearly twofold increase in cumulative success (57% versus 30%). Individualized regimens were also significantly associated with greater cumulative success than standardized regimens. Having at least some doses taken under direct observation had an associated trend of greater cumulative success compared with having a completely self-administered therapy. Longer duration of therapy had a strong associated trend with greater treatment success.

A regimen that contained more drugs, especially second-line drugs, had a strong associated trend with cumulative success. A higher proportion of patients treated with fluoroquinolones (>50%) was significantly associated with almost a twofold increase in cumulative success. High use of injectable drugs (>67%) had an associated trend with higher cumulative success. High use of PZA (>67%) had an associated trend with lower cumulative success.

4. 6. 2. Death

Table 5 summarizes all the subgroup analyses for the treatment outcome death. Most subgroups remained significantly heterogeneous, with I^2 values in the 90% range.

There were no demographic characteristics of the cohorts, such as age and sex, nor disease characteristics, such as smear positivity and degree of drug resistance, that were associated with the death rate. A high prevalence of HIV co-infection was significantly associated with a higher death rate, while a high prevalence of previous tuberculosis treatment had an associated trend with a lower death rate. An increasing national prevalence of MDR-TB was significantly associated with a lower death rate, yet neither national health expenditure, nor national income level, exhibited a clear association with death.

The treatment characteristic that exhibited the strongest trend of a high death rate was the use of three or less drugs, either sensitive or not specified, in the regimen (death rates ranged from 25% to 52% for these sub-groups). Prevalence of specific drug use did not display a trend in association with death. Use of directly observed therapy and longer duration of therapy had an associated trend with higher death rate. Individualized regimens had significantly higher death rates, while the use of second-line drugs in the regimen had a weak associated trend of an increase in death rate.

4. 6. 3. Default

Table 6 summarizes all the subgroup analyses for the treatment outcome default. As with cumulative success and death, most subgroups remained significantly heterogeneous, with I^2 values in the 90% range.

The mean age and sex distribution, and history of prior treatment were not associated with the default rates, although high prevalence of HIV co-infection had a strong significant association with greater default. Disease characteristics, such as smear

positivity and degree of drug resistance were not associated with default. Interestingly, higher per capita total health expenditure was associated with increasing default, yet national income level was not clearly associated with default. An increasing prevalence of MDR-TB was associated with a significant associated decrease in default.

Directly observed therapy, use of more drugs in the regimen, use of fluoroquinolones, PZA or injectable drugs all had associated trends with lower default. On the other hand, individualized and longer therapies plus use of other second-line drugs had associated trends with higher default.

4. 7. Meta-Regression

Because substantial heterogeneity was found even in subgroup analyses, we used meta-regression to simultaneously explore multiple covariates that may explain the heterogeneity. Four multivariate models were built based on an a priori selection of important prognostic factors as well as factors that showed strong associations in the stratified analysis (Table 7).

4. 7. 1. Cumulative Success

The model investigating modifiable treatment characteristics included the variables number of drugs given in the regimen, administration of second-line drugs, type of drug regimen, and length of treatment. Type of drug regimen was dropped from the model due to collinearity. Greater number of drugs given in the regimen, longer duration of treatment, and administration of second-line drugs were all associated with an increase in cumulative success; however, use of second-line drugs in the regimen was the only statistically significant predictor for success in the model. The R^2 value indicates that approximately 40% of the between-study variance remains unexplained by these covariates.

The classes of drugs used in the regimens were explored with the covariates proportion of the cohort using fluoroquinolones, PZA, and injectable drugs. Higher prevalence of fluoroquinolone and injectable drug use, and lower prevalence of PZA use, was associated with increasing success; however fluoroquinolone use was the only statistically significant predictor. A low R^2 for this model indicate that considerable heterogeneity remains unexplained by this model.

The model that explored the health system factors included the variables institution, government health expenditure, and proportion of acquired MDR-TB among all national TB cases. Increased government expenditure on health care and increased prevalence of acquired MDR-TB were associated with a decrease in success. The type of institution providing TB care was a strong statistically significant predictor of successful outcome. Receiving treatment at either a specialized MDR-TB treatment program or a specialized TB hospital was associated with higher success than treatment received at a TB treatment program where only first-line drugs were administered. A low R^2 in this model indicate that considerable variation in the results remains unexplained in this model.

A final model was created using the covariates from all the models, in order to investigate a more realistic algorithm of MDR-TB treatment outcomes, that is, a model that includes both treatment and health setting factors. Neither population nor disease factors were included because the important covariates, such as smear positive status, were poorly reported across the studies, and the other factors were not suspected to be strong treatment outcome correlates. The variables institution, second-line drug use, and type of regimen were dropped due to collinearity. The final model had the variables total health care expenditure, prevalence of acquired MDR-TB, use of fluoroquinolones, use of injectable drugs, use of Pyrazinamide, total number of drugs given in the regimen, and duration of treatment. There were no statistically significant predictors in the model for cumulative success.

4. 7. 2. Death

There were no statistically significant covariates associated with death in the two models exploring treatment regimen and type of drugs used. Use of more drugs, use of second-line agents, and shorter duration of treatment had an associated trend of higher death rates in the model exploring modifiable treatment characteristics.

A higher rate of death had a significant association with greater government health expenditure in the model exploring health system factors. There were no statistically significant predictors in the final model with all factors.

Low R^2 values indicate that none of the models were a good fit.

4. 7. 3. Default

There were no statistically significant predictors of treatment default in any of the four models. Low R^2 values indicated that none of the models were a good fit.

Chapter 5 Discussion

5. 1. Synopsis of main findings for treatment outcomes in MDR-TB

The overall pooled rate of cumulative success was 50%. The overall pooled rates of death and default during treatment were 13% and 18%, respectively.

The modifiable factors that were shown to be important prognostic indicators of treatment success are longer duration of treatment, more drugs used in the regimen, individualized regimens, and directly observed therapy. Treatment for more than 20 months, use of more than three drugs to which the organisms were sensitive to, use of fluoroquinolones, and use of second-line drugs in general were all factors that were associated with higher cumulative success rates.

The modifiable factor most strongly associated with higher death rate was use of less than three drugs in the regimen.

The modifiable treatment factors most strongly associated with lower default was treatment duration of less than 12 months, and direct observation of all doses. Use of second-line drugs was significantly associated with higher default.

It is difficult to compare the results of this study to those of the published systematic reviews on MDR-TB treatment outcomes because the inclusion criteria were considerably different. However, all the studies found significant heterogeneity in subgroup analysis, validating the need for further research in MDR-TB treatment. The following is a chart comparing the main findings in the three studies:

Comparison of the results of three systematic reviews exploring correlates of treatment outcomes of MDR-TB

Results	This thesis	Johnston et al [35]	Orenstein et al [34]
Overall pooled outcomes % (95% Confidence Interval)			
Success	50 % (46 – 59 %)	62 % (57 – 67%)	62% (58 – 67 %)
Failure	16 % (14 – 19 %)	8 % (5 – 11%)	No other pooled outcomes across all studies were reported
Relapse	5 % (3 – 6 %)	Not reported	
Death	13 % (11 – 16 %)	11% (9 – 13%)	
Default	18 % (16 – 19 %)	13 % (7 – 20%)	
Main findings	- patient, disease, treatment and health setting characteristics analyzed -significant heterogeneity found in the subgroup analysis -Statistically significant correlates (in subgroup analysis): -positive correlates of cumulative success rate: low smear positivity, increasing resistance to drugs, use of second-line drugs, individualized regimens, fluoroquinolone use -positive correlates of death rate: high HIV prevalence in the cohort, low national incidence of MDR-TB, use of fewer drugs in regimen -positive correlates of default rate: high HIV prevalence, decreasing national prevalence of MDR-TB	-focus on patient and disease characteristics -significant heterogeneity found in the subgroup analysis -Statistically significant correlates: -Positive correlates of success: surgery, no TB treatment history, fluoroquinolone use - Negative correlates of success: male sex, alcohol abuse, low BMI, smear positivity, fluoroquinolone resistan-TB -positive correlates of death rate: XDR-TB, no fluoroquinolone use	-focus on treatment characteristics -significant heterogeneity found in the subgroup analysis -no single factor was a statistically significant predictor of success -treatment duration ≥ 18 months and all doses directly observed were the two strongest predictors of treatment success (although not statistically significant).

5. 2. Limitations

5. 2. 1. Selection and Publication Biases

Attempts to minimize publication bias were made by extensively searching the literature. Despite this effort, it is impossible to rule out or even quantify publication bias in our

review. Although tests and funnel plots are used to detect publication bias in meta-analyses of randomized controlled trials, such tests do not apply to meta-analyses of proportions [49]. In the absence of any easy method to quantify publication bias, we can only speculate on its impact on our study findings. For example, if MDR-TB cohorts with very poor outcomes were never published, and those with excellent outcomes were preferentially published, then our pooled outcomes are likely to be optimistic. On the other hand, if MDR-TB cohorts with poor outcomes were published because of their serious public health implications, then the reverse is likely to be true.

It is difficult to assess selection bias within each study without knowing the characteristics of the patients who ought to have been included in that study, but were not, for various reasons such as missing records, lack of consent, or loss to follow-up. Base-line information about the patients not included in the cohort was rarely available in the studies, making it difficult to assess the degree of selection bias. The percent of eligible patients included in the cohort was available for less than two thirds of the studies and averaged approximately 88%; however, the eligibility criteria may not have necessarily reflected the population base from which the patients arose. It is probably safe to assume that all cohort studies are affected by selection and attrition bias, and the effect of this may be to inflate the rate of positive outcomes, if individuals with poor prognosis were more likely to drop out or not participate in the study.

We hypothesized that the types of medical institution providing the tuberculosis treatment would be associated with different referral patterns and patient recruitment strategies. This type of selection bias could be associated with a difference in treatment outcomes; however, it is impossible to distinguish whether the difference is due to a true effect of a quality of care in the institution, or due to selection of patients with certain prognostic factors. Highly specialized referral hospitals would be expected to care for more complicated MDR-TB cases with more advanced disease caused by more resistant organisms, and hence may report lower treatment success and higher mortality.

On the other hand, these centres may provide better care because of the availability of medical expertise, diagnostic services, and better access to second-line drugs. Use of second-line drugs was significantly associated with cumulative success (57%); however it was also significantly associated with a higher default rate (19%). Nonetheless, subgroup analysis for the variable "institution" confirmed that the type of treating institution was associated with a statistically significant difference in cumulative success (Table 4d). The pooled rate of cumulative success was much lower in regional TB treatment programs using only first-line drugs (30%) than in specialized hospitals, of which 80% used second-line drugs (53%), or regional MDR-TB treatment programs that consistently used second-line drugs (66%). The default rate was significantly higher for specialized hospitals (19%) compared to national MDR-TB treatment programs (10%), and could explain the difference in cumulative success between these two types of MDR treatment facilities.

Our study is also subject to language bias, which is a type of selection bias. The language expertise in our team included English, French and Spanish only; therefore relevant publications in other languages were necessarily excluded from analysis. Our initial keyword search in the medical databases was not restricted by language, and only 14 out of 268 (5%) articles that were identified for full-text review were not in English, French or Spanish. This small proportion of articles in other languages suggests that language bias should have been minimal; however, publications from India, China and the former Soviet Republics, where there are major MDR-TB hotspots, may not have been well represented in our databases. Electronic journal databases from these regions do not have an English interface and since we had limited language expertise on the team, a hand-search of key foreign-language journals was not feasible; therefore it was difficult to systematically search for relevant articles in these different languages. Since publications from these regions in their native languages were inaccessible to us, it is difficult to know how many relevant articles were missed in order to quantify the degree of language bias.

5. 2. 2. Information Bias

We assumed that information bias in our study would be minimized if quality control measures were enforced for drug susceptibility testing. About one third of the studies did not report whether quality control measures were performed or not; however, of those reporting this information, all but two studies reported having followed internationally recognized quality control guidelines. However, there is evidence that there is reduced reliability of second-line drug susceptibility testing [18], which increases the likelihood of incorrect classification of drug resistance, and thus information bias, for these results.

5. 2. 3. Missing information and confounding

Within-study confounding was unavoidable in this review, and individual studies used various approaches to deal with this issue. There was a significant inconsistency in reporting the values of nearly all variables (Table 2). Additional information was sought from the corresponding authors on certain key variables; however, there was a modest response rate (56%). The true impact of prognostic indicators on treatment outcomes are probably masked due to under-reporting of important variables, leaving room for the potential confounding of results.

5. 2. 4. Lack of post-treatment follow-up

Less than half of the studies reported any post-treatment follow-up for the cohort. When follow-up was reported, the mean duration was for 29 months. The proportion of successfully treated patients who developed disease a second time during follow-up (i.e. who relapsed) was 5% for these studies; however there was a considerable range from 0 to 63%. Since on average 73% of the cohorts had a history of prior tuberculosis treatment, relapse, failure and return after default appear to be significant sources of active MDR-TB disease. It follows that treatment efficacy is best estimated when post-treatment follow-up data are included in the study as well. In general, studies that did not measure relapse after the end of treatment would have overestimated treatment efficacy.

5. 2. 5. Ecological Fallacy

Since this systematic review makes study-level associations between covariates and treatment outcomes, there is inherently an ecological fallacy, which is the problem that inferences at the study-level may not be true at the individual-level. This is to say that prognostic associations for treatment outcomes using aggregate data of continuous (e.g. treatment duration) or dichotomous (e.g. use of a specific drug in the treatment regimen) variables may not necessarily reflect the values for these prognostic factors in individual patients. We attempted to limit the ecological fallacy though subgroup analysis by limiting the range of aggregate exposure data. However, even though the aggregate data fell into more restricted ranges, the within-study variation of the covariates was often considerable, hence the ecological fallacy could have still confounded the results [50].

5. 2. 6. Heterogeneity of results and their generalizability

There was significant heterogeneity in outcomes across studies in nearly all subgroups, which has several implications for the validity and interpretation of results (Tables 4, 5, and 6). Glasziou discusses two main types of heterogeneity: real (due to patient and clinical factors) and artefactual (due to research methodology) [51]. Our study likely has both types of heterogeneity. There were important methodological differences between the studies, such as inconsistent quality control of drug susceptibility testing and different follow-up periods, which contributed to artefactual heterogeneity. There were also a number of clinical sources of heterogeneity, such as severity of disease and type of treatment intervention; these key variables were often underreported and likely contributed to the observed differences in treatment outcomes.

Some would argue that results should only be pooled for a meta-analysis if there is relative homogeneity within and between the cohorts. This condition was not met in this study, yet results were pooled in order to explore the relationships between a number of factors and patient outcomes. While this heterogeneity limits the interpretation of the pooled outcomes, this meta-analysis was justified because of the public health importance of MDR-TB, the current poor treatment outcomes, paucity of high quality data, and

resultant controversy over treatment. No method of analysis in this study was able to resolve the heterogeneity, which suggests that treatment outcomes are influenced by numerous factors that cannot be controlled for because of the limitations of the dataset, such as small size, incomplete information for the variables, and aggregate as opposed to individual data. Subgroup analysis identified prognostic correlates of outcomes; however since there remained considerable heterogeneity within the subgroups, the implications for clinical care should be interpreted with caution. The key message of this study is that outcomes of MDR-TB are influenced by a number of covariates that vary considerably across studies, populations and subgroups.

5. 3. Clinical Implications

Given the limitations of this methodology, the main value of this work is to help clarify questions for future research, and to define treatment outcomes with current standard of care for MDR-TB. These values can be used to benchmark RCTs as the results of standard therapy against which new drugs can be compared.

Unsettled questions about MDR-TB treatment are the optimal duration of the intensive phase and overall treatment, the minimum number of drugs used, and the role of standardized regimens of second-line drugs. However, our study does help to address the other controversial topics, and supports current WHO guidelines. The WHO recommends that treatments last a minimum of 18 months past culture conversion; treatments lasting longer than 20 months had cumulative success of 65%, which is 13% higher than for the 13- 20 month category for treatment length. Standardized regimens were a strong statistically significant predictor of lower cumulative success (38%), and are not recommended for MDR-TB by the WHO. The WHO's recommendation for the minimum number of sensitive drugs used in the regimen changed lately from three to four; however, our subgroup analysis shows that cumulative success is quite high at 59% when more than three and up to and including four drugs are used. Use of more than four drugs has a cumulative success of 63%; therefore there appears to be no demonstrated great

advantage to using more than four sensitive drugs when anything above three seems to provide comparable benefit. However, since this variable is the average number of drugs given during the intensive and continuation phase, we cannot comment on the optimal number of drugs for each period.

When drug sensitivity information is unknown, the WHO suggests a minimum of five to seven drugs in the regimen, a recommendation that is corroborated by our subgroup analysis that shows that more than five overall drugs had a much greater cumulative success than using five or fewer drugs.

Use of second-line drugs was shown to be an important contributor to high cumulative success. Fluoroquinolones and injectable drugs had associated trends with high cumulative success, while high PZA usage had an associated trend with low cumulative success. A study from South Africa demonstrated that PZA resistance was highly correlated to MDR-TB, which is logical since PZA is a staple drug in DOTS and most MDR-TB is due to acquired infection from previous treatment [52]. Given that PZA susceptibility testing is technically challenging and yet it is often used in the treatment of MDR-TB, further research should clarify its therapeutic role for MDR-TB treatment.

The patients' likelihood to default is a particular challenge in MDR-TB care, since non-compliance with original therapy for drug sensitive tuberculosis is considered one of the major pathways of acquired drug resistance. The factors that are most associated with cumulative success, such as long treatment duration and use of second-line drugs, are also associated with high default rates. This effect might be mitigated with a protocol of more vigilant follow-up including directly observed therapy for the full duration of treatment. The greater availability of resources for follow-up close to patients' homes may explain why national MDR-TB treatment programs that used second-line drugs reported a default rate that was only half that of specialized hospitals. Serious adverse events associated with the more toxic second-line agents are also a source of treatment default [53] which calls for the development of new anti-tuberculosis drugs that are not only more efficacious, but have fewer side effects.

Chapter 6 Conclusion

This research was able to address some controversial topics in MDR-TB care, such as the optimal length of treatment, type of regimen and number of drugs. Treatment duration longer than 20 months, use of more than three sensitive drugs, individualized regimen, use of fluoroquinolones, and use of second-line agents in general were associated with an increased rate of cumulative success. A high prevalence of HIV co-infection and use of three or fewer drugs was associated with higher mortality. Low default was most strongly associated with shorter treatments and directly observed therapy. Use of second-line drugs was significantly associated with higher default. Standardized regimens and exclusive use of first-line drugs were associated with much lower rates of treatment success.

These results are interesting, and often confirm published guidelines, but clinical inferences should be made cautiously. In the case where the same factor was associated with both positive and negative outcomes, such as second-line drug use, the reasons for the difference cannot be thoroughly explored due to the limitations of the dataset, which leaves important clinical questions unanswered. The significant heterogeneity observed in the overall pooled outcomes as well as the subgroup analyses also demonstrate the methodological challenges of this research. This heterogeneity signals the complex nature of MDR-TB disease and the many patient-level prognostic indicators that cannot be controlled for in our limited dataset. MDR-TB remains a highly complex disease that would require individual patient data to more fully understand factors, including treatment-related, that affect its course and prognosis.

To advance the evidence base for clinical MDR-TB care an individual patient data meta-analysis would be an excellent next step to explore the prognostic factors of MDR-TB treatment. However, randomized controlled trials are critically needed to resolve many of the treatment controversies as these would best control the problems of bias and confounding that limit inferences from results of this meta-analysis. Indeed, an

international group of experts have called for randomized trials of MDR-TB therapies, and our study supports this call [33].

Figure 1 Process of study selection for systematic review

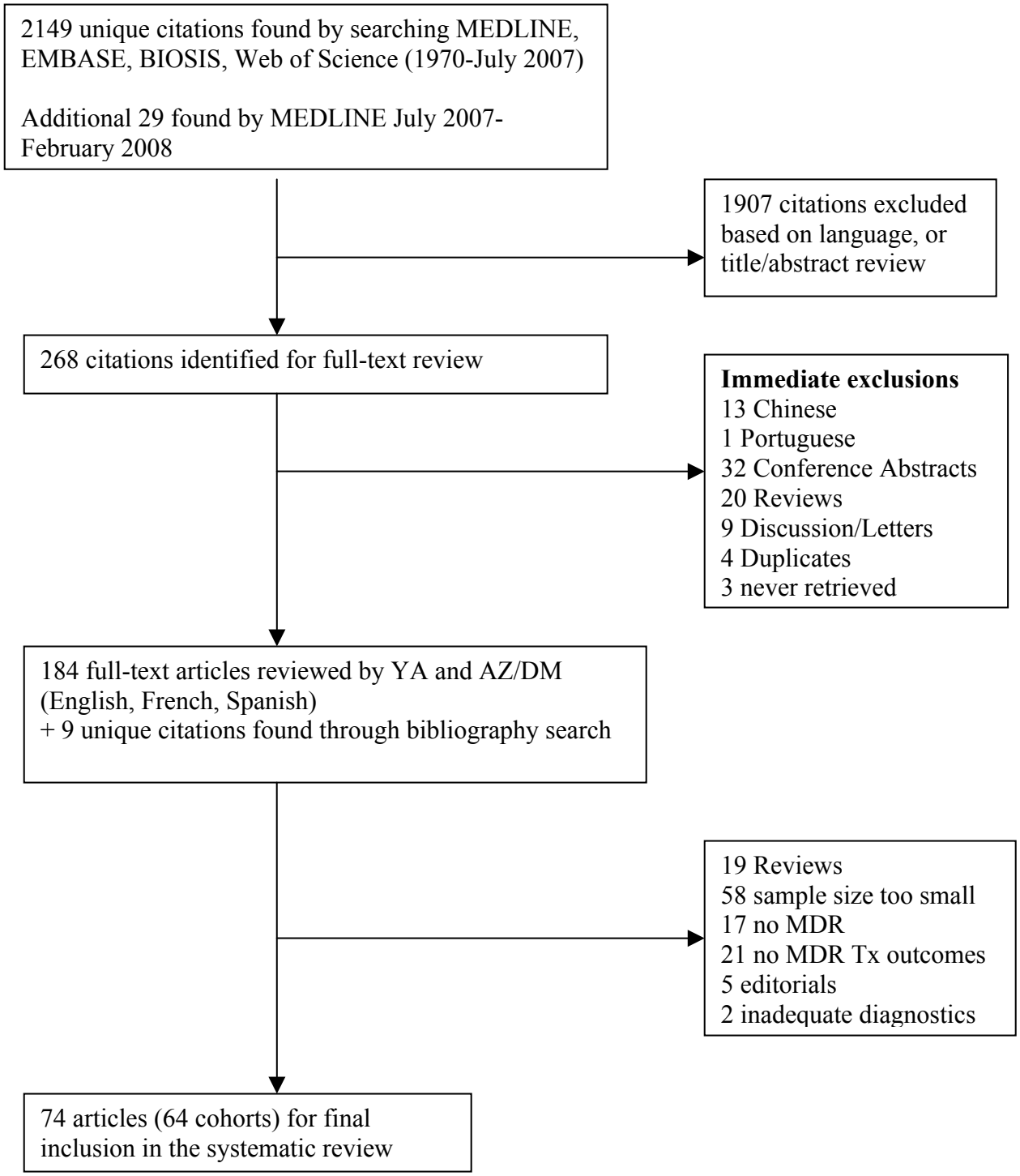
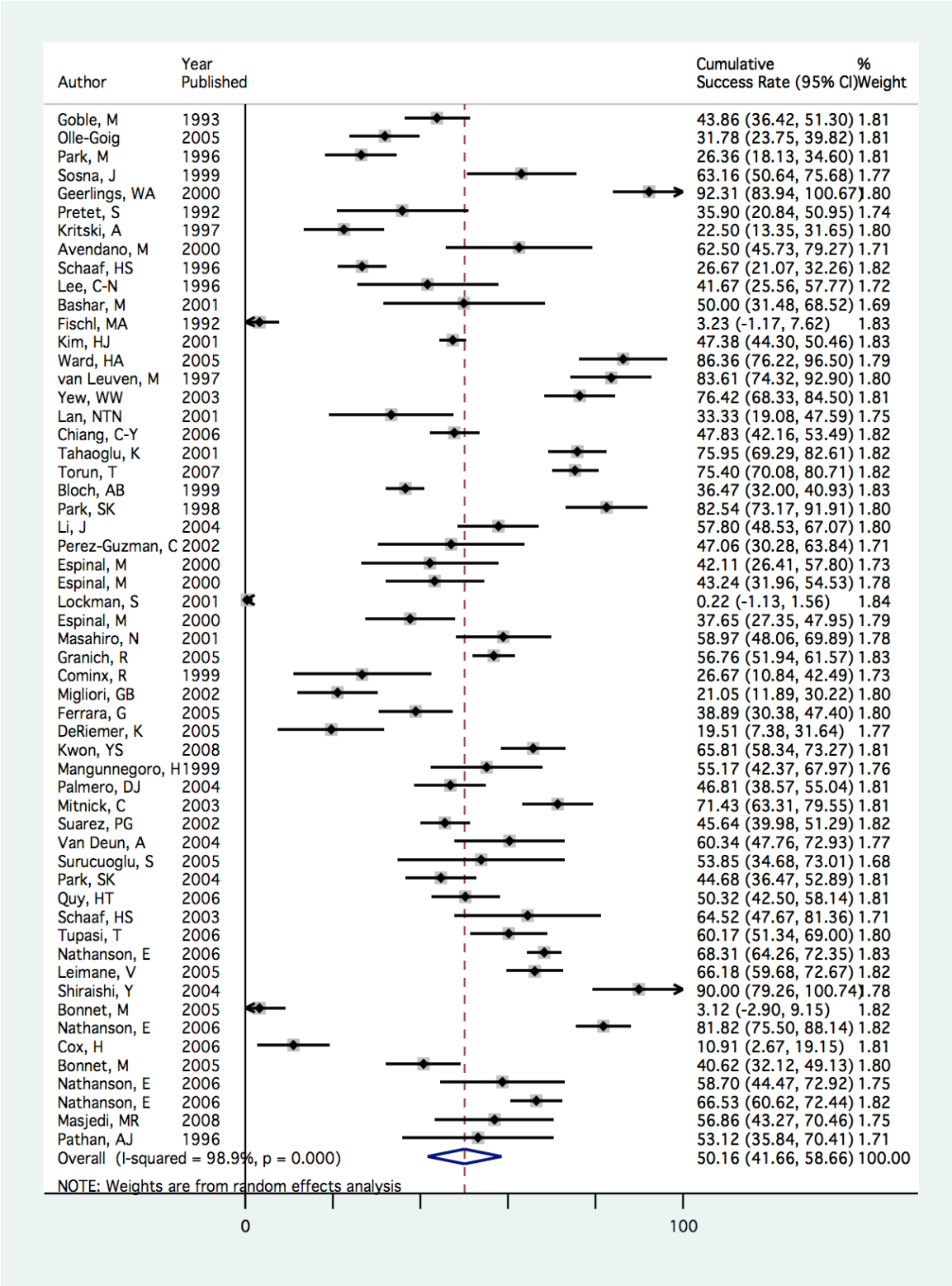
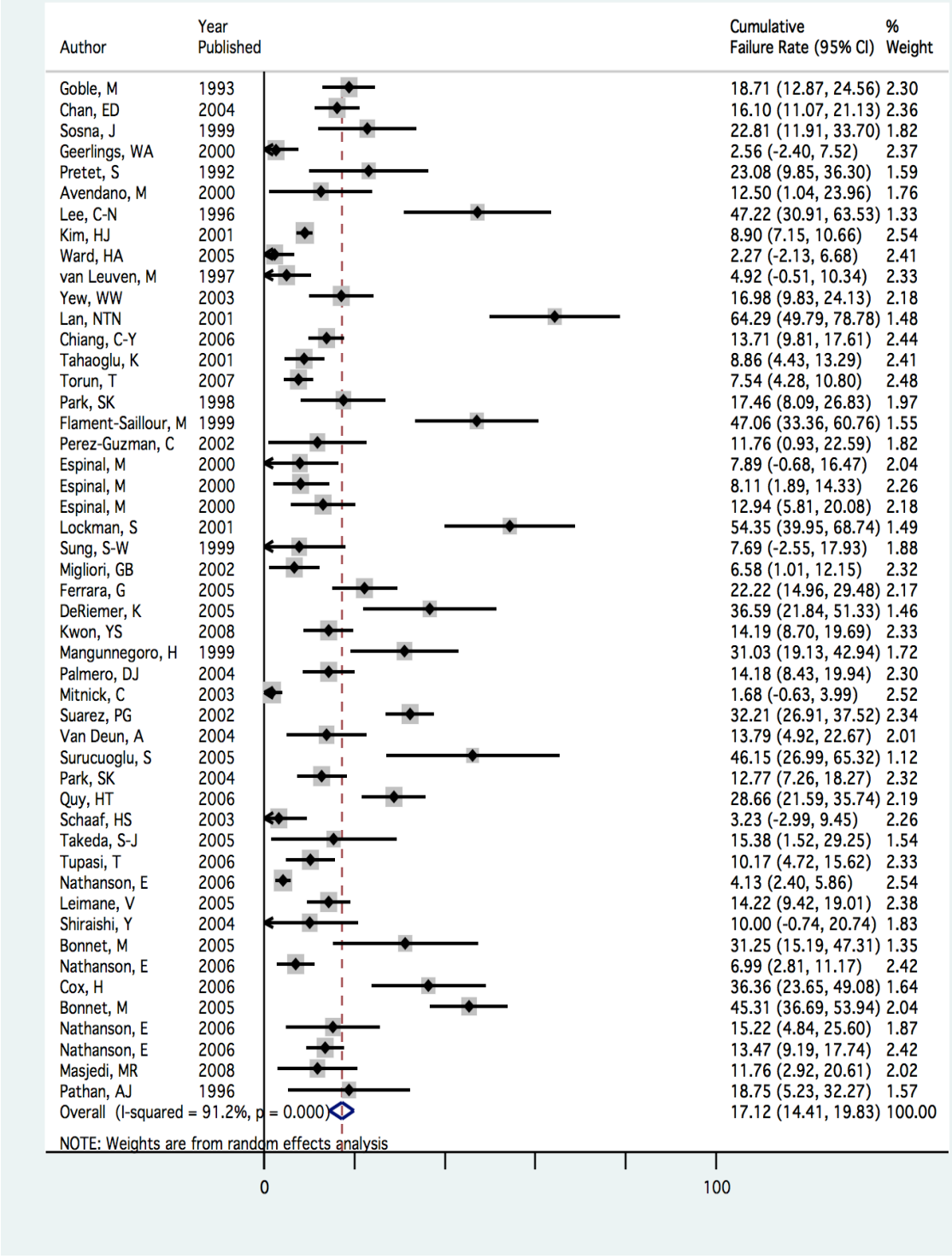


Figure 2 Forest Plot for pooled cumulative success[1]



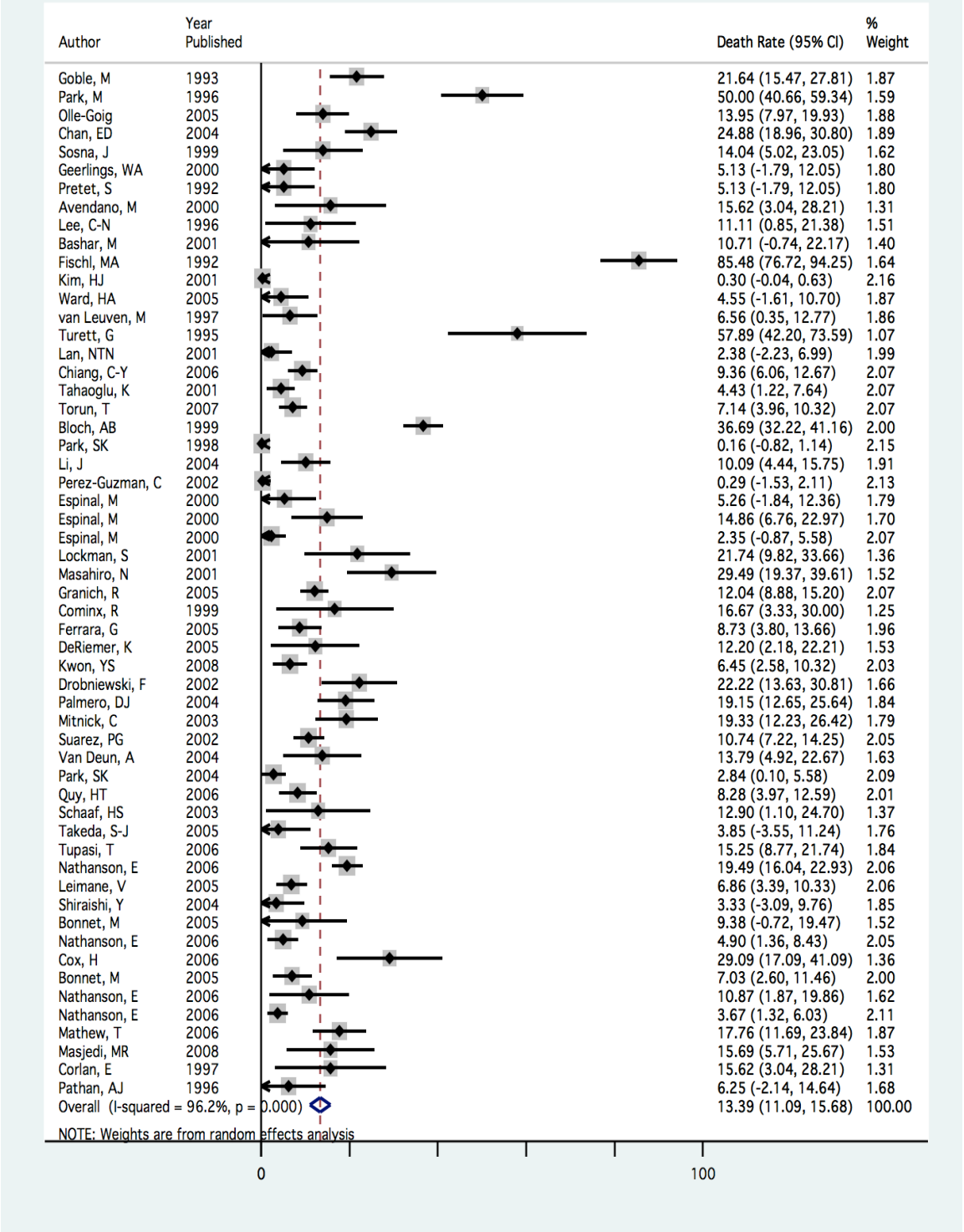
[1] Studies are ordered by the start year of the patient enrolment period and by its duration

Figure 3 Forest Plot for pooled cumulative failure[2]



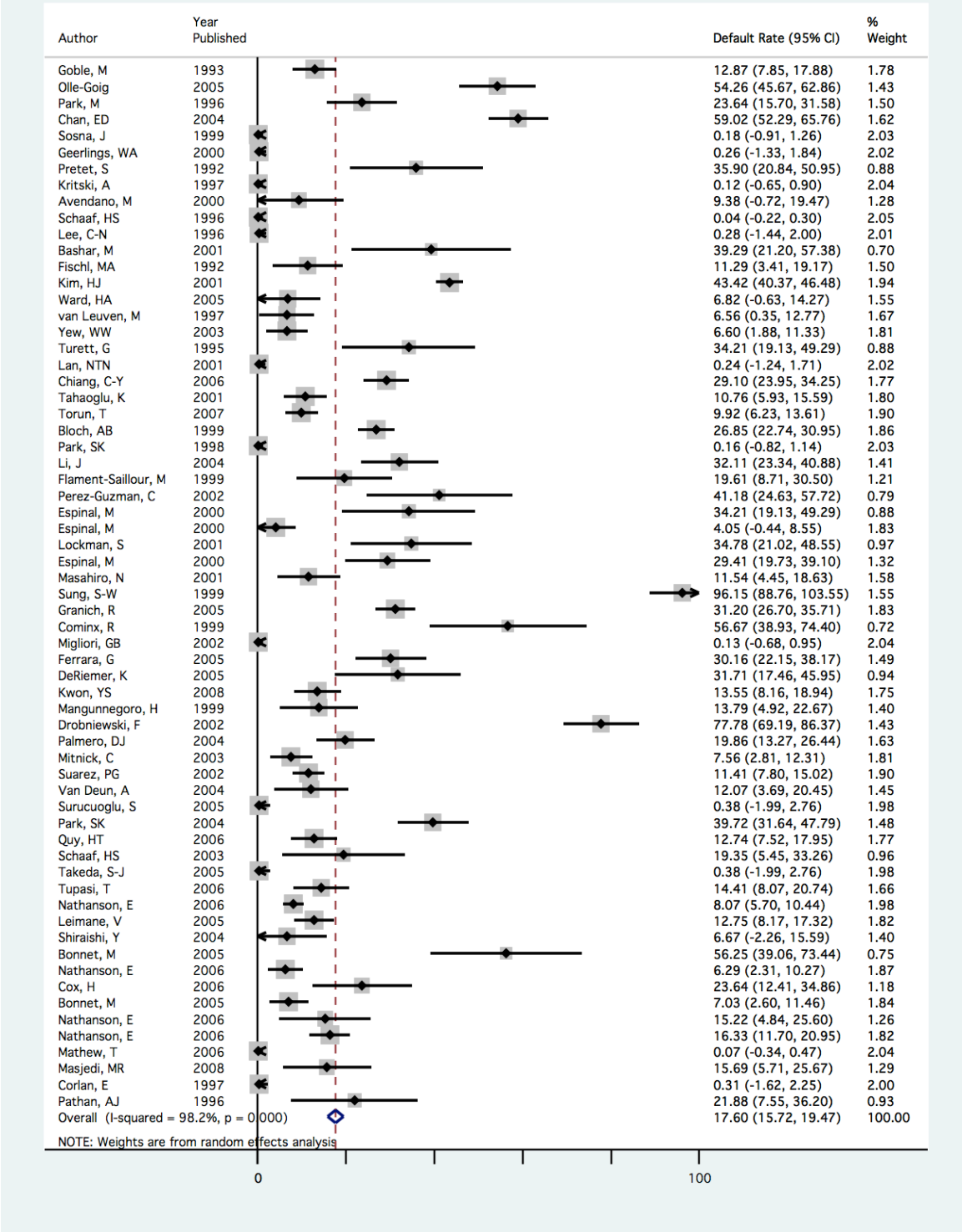
[2] Studies are ordered by the start year of the patient enrolment period and by its duration

Figure 4 Forest Plot for pooled death[3]



[3] Studies are ordered by the start year of the patient enrolment period and by its duration

Figure 5 Forest Plot for pooled default[4]



[4] Studies are ordered by the start year of the patient enrolment period and by its duration

Table 1 Individual study data for all 64 cohorts, arranged chronologically from start year of patient enrolment period

Table 1A Study design & methodology

Absent values indicate that the variable was not reported for that cohort.

Author	Year of publication	Study design	First and last years of patient enrolment period	Duration of patient enrolment period (months)	Method of drug sensitivity testing (most complete information after contacting principle investigators)	Quality control of drug sensitivity testing by WHO standards
Goble, M [54]	1993	Retrospective cohort	1973, 1983	132	Proportion method	
Olle-Goig [55]	2005	Retrospective cohort	1983, 1993	132	Proportion method (Canetti)	Yes
Park, M [56]	1996	Retrospective cohort	1983, 1993	132		
Chan, ED [57]	2004	Retrospective cohort	1984, 1998	170		
* Sosna, J [58]	1999	Retrospective cohort	1985, 1994	120	Resistance ratio method	Yes
* Geerligs, WA [59]	2000	Retrospective cohort	1985, 1998	165	Modified absolute concentration method	
Kritski, A [60]	1997	Prospective cohort	1986, 1989	48	Proportion method (Canetti)	
* Avendano, M [61]	2000	Retrospective cohort	1986, 1999	162		Yes
Pretet, S [62]	1992	Prospective cohort	1986, 1988	31	Proportion method, Canetti	
Bashar, M [63]	2001	Case-control study	1987, 1997	132		
* Lee, C-N [64]	1996	Prospective cohort	1987, 1989	35	Modified proportion method	
* Schaaf, HS [65]	1996	Retrospective cohort	1987, 1988	24	Indirect proportion method	
Fischl, MA [66]	1992	Retrospective cohort	1988, 1990	36	Agar-modified proportional method	Yes
* Kim, HJ [67]	2001	Retrospective cohort	1988, 1996	108	Proportions method	

* Ward, HA [68]	2005	Retrospective cohort	1989, 2000	138	Direct proportion method	Yes
Yew, WW [69]	2003	Retrospective cohort	1990, 2000	131	Resistance ratio method or proportions method	
* van Leuven, M [70]	1997	Surgical series	1990, 1994	59		
* Turett, G [71]	1995	Retrospective cohort	1991, 1993	36	Proportion method	
Lan, NTN [72]	2001	Retrospective cohort	1991, 1994	42	Proportion method	
* Torun, T [73]	2007	Retrospective cohort	1992, 2003	142	Proportion method	No
* Tahaoglu, K [74]	2001	Retrospective cohort	1992, 1999	92	Proportion method	No
* Chiang, C-Y [75]	2006	Retrospective cohort	1992, 1996	60	Absolute concentration method	Yes
* Li, J [76]	2004	Retrospective cohort	1993, 1997	61	Kent method	Yes
* Park, SK [77]	1998	Retrospective cohort	1993, 1995	37	Absolute concentration method (Canetti)	
Bloch, AB [78]	1999	Retrospective	1993, 1994	12		
Granich, R [79]	2005	Retrospective cohort	1994, 2003	120		
* Lockman, S [80]	2001	Retrospective matched cohort study	1994, 1996	36	Proportion method	Yes
Espinal, M [48]	2000	Retrospective cohort	1994, 1996	36	Absolute concentration/resistance ratio method/proportion method (BACTEC)	Yes
Espinal, M [48]	2000	Retrospective cohort	1994, 1996	36	Absolute concentration/resistance ratio method/proportion method (BACTEC)	Yes
Sung, S-W [81]	1999	Surgical series	1994, 1997	51		
* Perez-Guzman, C [82]	2002	Prospective cohort	1994, 1995	21	Proportion method	Yes
Flament-Saillour, M [83]	1999	Case-control study	1994, 1995	12		
*Masahiro, N [84]	2001	Retrospective cohort	1994, 1997	43		Yes

Espinal, M [48]	2000	Retrospective cohort	1994, 1996	36	Absolute concentration/resistance ratio method/proportion method (BACTEC)	Yes
* Ferrara, G [85]	2005	Retrospective cohort	1995, 1999	60	Proportion, concentration, MGIT	Yes
* Coninx, R [86]	1999	Retrospective cohort	1995, 1996	28	Proportion method (Canetti)	Yes
Mangunnegoro, H [87]	1999	Retrospective	1995, unknown	unknown		
* Migliori, GB [88]	2002	Retrospective	1995, 1999	54		Yes
* Kwon, YS [89]	2008	Retrospective cohort	1995, 2004	120	Absolute concentration method	Yes
* DeRiemer, K [90]	2005	Prospective cohort	1995, 1999	60		Yes
* Drobniewski, F [91]	2002	Retrospective cohort	1996, 1997	18	Resistance ratio or Proportion method	Yes
* Mitnick, C [92]	2003	Retrospective cohort	1996, 2000	56	Proportion method	Yes
* Palmero, DJ [93]	2004	Retrospective cohort	1996, 1999	48	Proportion method	Yes
* Van Deun, A [94]	2004	Retrospective cohort	1997, 1999	24	Proportion method	Yes
Suarez, PG [95]	2002	Retrospective cohort	1997, 1998	18	Proportion method	Yes
* Surucuoglu, S [96]	2005	Retrospective cohort	1997, 2003	84	Indirect proportion method (Canetti)	Yes
* Schaaf, HS [97]	2003	Prospective cohort	1998, 2001	48	Indirect proportion method	Yes
* Park, SK [98]	2004	Retrospective cohort	1998, 2000	30	Absolute concentration method	
Takeda, S-J [99]	2005	Surgical series	1998, 2003	72		
Quy, HT [100]	2006	Prospective cohort	1998, 2000	36	Proportion method	
* Tupasi, T [101]	2006	Cohort	1999, 2001	36	Indirect proportion method (Kent)	Yes
* Nathanson, E [102]	2006	Prospective cohort	1999, 2003	59		Yes
# Leimane, V	2005	Retrospective cohort	2000, 2001	12	Absolute concentration	Yes

[103]					method	
* Nathanson, E [102]	2006	Prospective cohort	2000, 2002	40		Yes
* Bonnet, M [104]	2005	Retrospective cohort	2000, 2002	36	Proportion method	Yes
* Shiraishi, Y [105]	2004	Surgical series	2000, 2002	36		Yes
* Nathanson, E [102]	2006	Prospective cohort	2001, 2002	29		Yes
* Nathanson, E [102]	2006	Prospective cohort	2001, 2003	36		Yes
* Bonnet, M [104]	2005	Retrospective cohort	2001, 2002	12	Proportion method	Yes
# Cox, H [106]	2006	Retrospective cohort	2001, 2001	7	Proportion method	Yes
Mathew, T [107]	2006	Retrospective cohort	2002, 2003	24		
Masjedi, MR [108]	2008	Retrospective	2002, 2006	60		Yes
Pathan, AJ [109]	1996	Retrospective cohort	unknown	unknown	Concentration method	
Corlan, E [110]	1997	Interventional study	unknown	unknown		

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1B Population characteristics

Absent values indicate that the variable was not reported for that cohort.

Author	Country	Total number of patients in the cohort	Percent of the cohort that is female	Average, or median, age of the cohort	Percent of the cohort with HIV	Percent of the cohort with a history of previous tuberculosis treatment
Goble, M [54]	USA	171	28	46		100
Olle-Goig [55]	Bolivia	129	49	34		72
Park, M [56]	USA	110	8	40	69	
Chan, ED [57]	USA	205	42	40		100
* Sosna, J [58]	Israel	57	31	50	2	31
* Geerligs, WA [59]	Netherlands	39	30	33	0	34
Kritski, A [60]	Brazil	80	30	42	0	100
* Avendano, M [61]	Canada	32	48	41	0	55
Pretet, S [62]	France	39	28	38	0	100
Bashar, M [63]	USA	28	15	46	48	
* Lee, C-N [64]	Taiwan	36	33	42	10	100
* Schaaf, HS [65]	South Africa	240	43	37	0	
Fischl, MA [66]	USA	62	23	34	100	
* Kim, HJ [67]	South Korea	1011	33	39		100
* Ward, HA [68]	Vietnam	44	41	49		77
Yew, WW [69]	Hong Kong	106	24	46	0	100
* van Leuven, M [70]	South Africa	61	47	34	0	75
* Turett, G [71]	USA	38	29	41	89	59
Lan, NTN [72]	Vietnam	42	38	37		100
* Torun, T [73]	Turkey	252	19	38	0	76
* Tahaoglu, K [74]	Turkey	158	13	37	0	78
* Chiang, C-Y [75]	Taiwan	299	28	47	0	89
* Li, J [76]	USA	109	44	37	24	33
* Park, SK [77]	South Korea	63	25	42		100
Bloch, AB [78]	USA	447	37	42		5
Granich, R [79]	USA	407	41	43	4	31

* Lockman, S [80]	Estonia	46	44	44	0	0
Espinal, M [48]	Peru	74	36	37	6	68
Espinal, M [48]	Dominican Republic	38	36	37	6	50
Sung, S-W [81]	South Korea	26	33	40		
* Perez-Guzman, C [82]	Mexico	34	46	45	0	100
Flament-Saillour, M [83]	France	51	26	45	16	78
*Masahiro, N [84]	USA	78	32	40	49	62
Espinal, M [48]	South Korea	85	36	37	6	58
* Ferrara, G [85]	Italy	126	35	44	12	59
* Coninx, R [86]	Azerbaijan	30	0	30	0	73
Mangunnegoro, H [87]	Indonesia	58	48	38	0	100
* Migliori, GB [88]	Russia	76				
* Kwon, YS [89]	South Korea	155	47	40	0	88
* DeRiemer, K [90]	Mexico	41	41	43	20	85
* Drobniewski, F [91]	UK	90	28	37	29	49
* Mitnick, C [92]	Peru	119	51	27	2	100
* Palmero, DJ [93]	Argentina	141	53	36	0	65
* Van Deun, A [94]	Bangladesh	58	16	35	0	100
Suarez, PG [95]	Peru	298	63	27		100
* Surucuoglu, S [96]	Turkey	26	4	45	0	50
* Schaaf, HS [97]	South Africa	31	49	6	21	15
* Park, SK [98]	South Korea	141	18	42	0	100
Takeda, S-J [99]	Japan	26	34	48		85
Quy, HT [100]	Vietnam	157	24	39	2	65
* Tupasi, T [101]	Philippines	118	27	38	0	96
* Nathanson, E [102]	Peru	508			1	100
# Leimane, V [103]	Latvia	204	20		1	73
* Nathanson, E [102]	Russia	143			0	100
* Bonnet, M [104]	Georgia	32	27	42		81

* Shiraishi, Y [105]	Japan	30	30	48	0	30
* Nathanson, E [102]	Estonia	46			0	52
* Nathanson, E [102]	Latvia	245			4	63
* Bonnet, M [104]	Russia	128	0	32		53
# Cox, H [106]	Uzbekistan	55	36	35		75
Mathew, T [107]	Russia	152	31	42	0	14
Masjedi, MR [108]	Iran	51	31	44	0	100
Pathan, AJ [109]	Pakistan	32	9	33		100
Corlan, E [110]	Romania	32	23	42		100

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1C Health system factors

Absent values indicate that the variable was not reported for that cohort.

Author	Government expenditure on health care, per capita in US dollars[5]	National Income Level	National proportion of primary MDR-TB among all TB cases	National proportion of acquired MDR-TB among all TB cases
Goble, M [54]	1997	High Income	1	5
Olle-Goig [55]	37	Lower Middle Income	1	5
Park, M [56]	1997	High Income	1	5
Chan, ED [57]	1997	High Income	1	5
* Sosna, J [58]	1103	High Income	6	18
* Geerligs, WA [59]	1214	High Income	1	3
Kritski, A [60]	107	Lower Middle Income	1	5
* Avendano, M [61]	1461	High Income	1	10
Pretet, S [62]	1684	High Income	2	
Bashar, M [63]	1997	High Income	1	5
* Lee, C-N [64]		High Income	2	2
* Schaaf, HS [65]	100	Upper Middle Income	2	7
Fischl, MA [66]	1997	High Income	1	5
* Kim, HJ [67]	9	High Income	3	14
* Ward, HA [68]	6	Low Income	3	19
Yew, WW [69]		High Income	1	16
* van Leuven, M [70]	100	Upper Middle Income	2	7
* Turett, G [71]	1997	High Income	1	5
Lan, NTN [72]	6	Low Income	3	19
* Torun, T [73]	122	Upper Middle Income	3	10
* Tahaoglu, K [74]	122	Upper Middle Income	3	10
* Chiang, C-Y [75]		High Income	2	2
* Li, J [76]	1997	High Income	1	5
* Park, SK [77]	9	High Income	3	14
Bloch, AB [78]	1997	High Income	1	5
Granich, R [79]	1997	High Income	1	5

[5] Information on the per capita government health expenditure was not available for the cohorts from Taiwan and Hong Kong (principle investigators Lee, Yew, Chiang), because they are no recognized countries by the WHO

* Lockman, S [80]	170	Upper Middle Income	13	52
Espinal, M [48]	52	Lower Middle Income	5	12
Espinal, M [48]	49	Lower Middle Income	7	20
Sung, S-W [81]	9	High Income	3	14
* Perez-Guzman, C [82]	152	Upper Middle Income	2	22
Flament-Saillour, M [83]	1684	High Income	2	
*Masahiro, N [84]	1997	High Income	1	5
Espinal, M [48]	9	High Income	3	14
* Ferrara, G [85]	1122	High Income	2	24
* Coninx, R [86]	6	Lower Middle Income	22	56
Mangunnegoro, H [87]	5	Lower Middle Income	2	14
* Migliori, GB [88]	57	Upper Middle Income	13	51
* Kwon, YS [89]	9	High Income	3	14
* DeRiemer, K [90]	152	Upper Middle Income	2	22
* Drobniewski, F [91]	1441	High Income	1	
* Mitnick, C [92]	52	Lower Middle Income	5	12
* Palmero, DJ [93]	382	Upper Middle Income	2	15
* Van Deun, A [94]	3	Low Income	2	14
Suarez, PG [95]	52	Lower Middle Income	5	12
* Surucuoglu, S [96]	122	Upper Middle Income	3	10
* Schaaf, HS [97]	100	Upper Middle Income	2	7
* Park, SK [98]	9	High Income	3	14
Takeda, S-J [99]	2298	High Income	1	10
Quy, HT [100]	6	Low Income	3	19
* Tupasi, T [101]	16	Lower Middle Income	4	21
* Nathanson, E [102]	52	Lower Middle Income	5	12
# Leimane, V [103]	108	Upper Middle Income	11	36
* Nathanson, E [102]	57	Upper Middle Income	13	51
* Bonnet, M [104]	8	Lower Middle Income	7	27
* Shiraishi, Y [105]	2298	High Income	1	10
* Nathanson, E [102]	170	Upper Middle Income	13	52
* Nathanson, E [102]	268	Upper Middle Income	11	36
* Bonnet, M [104]	57	Upper Middle Income	13	51
# Cox, H [106]	14	Low Income	15	60
Mathew, T [107]	171	Upper Middle Income	13	51

Masjedi, MR [108]	119	Lower Middle Income	5	48
Pathan, AJ [109]	2	Low Income	2	28
Corlan, E [110]	60	Upper Middle Income	3	11

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1D Disease characteristics

Absent values indicate that the variable was not reported for that cohort.

Author	Percent of the cohort with exclusively pulmonary tuberculosis	Percent of the cohort with positive smear	Average, or median, number of drugs resistant to, in addition to isoniazid and rifampin	Percent of the cohort resistant to fluoroquinolones	Percent of the cohort resistant to PZA
Goble, M [54]	100	87	4.0		49
Olle-Goig [55]	100		0.8		
Park, M [56]	69	55			
Chan, ED [57]	100		6.0	20	59
* Sosna, J [58]	100				
* Geerligs, WA [59]	86	50	3.0	2	25
Kritski, A [60]	100		0.8		
* Avendano, M [61]	80		2.1	8	24
Pretet, S [62]	100	85	2.6	5	21
Bashar, M [63]			1.3	4	
* Lee, C-N [64]	100		1.0		
* Schaaf, HS [65]	100		1.3		
Fischl, MA [66]	63	58	1.2		
* Kim, HJ [67]	100		1.7	0	
* Ward, HA [68]	100		2.5		50
Yew, WW [69]		81	1.3	25	
* van Leuven, M [70]	100				
* Turett, G [71]	50	68	0.9	0	29
Lan, NTN [72]	100	100	1.2		
* Torun, T [73]	100		2.1		

* Tahaoglu, K [74]			2.4		
* Chiang, C-Y [75]	100	88	1.0		
* Li, J [76]	83		1.8		
* Park, SK [77]	100		2.5	22	12
Bloch, AB [78]	78	37			
Granich, R [79]	90	62		12	24
* Lockman, S [80]	100	70			
Espinal, M [48]	100				
Espinal, M [48]	100				
Sung, S-W [81]	100	59	2.4		
* Perez-Guzman, C [82]	100		1.0		52
Flament-Saillour, M [83]	78	84		16	
*Masahiro, N [84]	81		2.8		
Espinal, M [48]					
* Ferrara, G [85]	95	87	1.7	15	54
* Coninx, R [86]	100		1.8		
Mangunnegoro, H [87]	100		0.6		0
* Migliori, GB [88]					
* Kwon, YS [89]	100	85	3.0	42	59
* DeRiemer, K [90]	100				
* Drobniewski, F [91]	81	83			32
* Mitnick, C [92]	95		4.0		
* Palmero, DJ [93]			2.1		
* Van Deun, A [94]	100		1.2		
Suarez, PG [95]	100	100			
* Surucuoglu, S [96]	100	92	1.2		
* Schaaf, HS [97]	95	50	1.0	7	100
* Park, SK [98]	100		2.0	26	27
Takeda, S-J [99]	100	100	1.4		
Quy, HT [100]	100		1.2		
* Tupasi, T [101]	91				
* Nathanson, E [102]	100				
# Leimane, V [103]	96	31	2.0	3	46
* Nathanson, E [102]	100				
* Bonnet, M [104]	100		1.7		

* Shiraishi, Y [105]	100	33	4.0		
* Nathanson, E [102]	100				
* Nathanson, E [102]	100				
* Bonnet, M [104]	100	100	1.7		
# Cox, H [106]	100				
Mathew, T [107]	100				
Masjedi, MR [108]			2.3	0	19
Pathan, AJ [109]	100		2.0		
Corlan, E [110]	100	96			

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1E Treatment characteristics

Absent values indicate that the variable was not reported for that cohort.

Author	Average, or median, duration of treatment (months)	Average, or median, duration of follow-up (months)	Type of drug regimen	Directly Observed Therapy (DOT)	Type of institution providing treatment	Percent of cohort with adjunctive surgical therapy
Goble, M [54]	8	51	Individualized	Yes	Specialized TB hospital	5
Olle-Goig [55]	23		Individualized	No	Regional TB treatment program	
Park, M [56]	18		Individualized		Specialized TB hospital	
Chan, ED [57]			Individualized	Some but not all doses were observed	Specialized TB hospital	63
* Sosna, J [58]	24		Individualized	Some but not all doses were observed	Specialized TB hospital	5
* Geerligs, WA [59]	22	33	Individualized		Specialized TB hospital	14
Kritski, A [60]		21	Individualized		Specialized TB hospital	
* Avendano, M [61]	30	33	Individualized	Some but not all doses were observed	Specialized TB hospital	15
Pretet, S [62]			Individualized	Some but not all doses were observed	Specialized TB hospital	
Bashar, M [63]				Some but not all doses were observed	Specialized TB hospital	21
* Lee, C-N [64]	11	30	Individualized	Yes	Specialized TB hospital	
* Schaaf, HS [65]	6		Individualized		Regional TB treatment program	
Fischl, MA [66]			Individualized		Specialized TB hospital	0
* Kim, HJ [67]	23	25	Individualized	No	Specialized TB hospital	0

* Ward, HA [68]	23		Individualized	Yes	Specialized regional MDR-TB program	
Yew, WW [69]	14	32	Individualized	Some but not all doses were observed	Specialized TB hospital	
* van Leuven, M [70]	9	24	Individualized	Some but not all doses were observed	Specialized TB hospital	100
* Turett, G [71]	21		Individualized	Some but not all doses were observed	Specialized TB hospital	
Lan, NTN [72]	8	0	Standardized	Yes	Regional TB treatment program	
* Torun, T [73]	22	58	Individualized	Some but not all doses were observed	Specialized TB hospital	26
* Tahaoglu, K [74]		27	Individualized	Some but not all doses were observed	Specialized TB hospital	23
* Chiang, C-Y [75]	18	72	Individualized	No	Specialized TB hospital	4
* Li, J [76]	23		Individualized	Yes	Specialized TB hospital	6
* Park, SK [77]		17	Individualized		Specialized TB hospital	0
Bloch, AB [78]	24		Individualized	Some but not all doses were observed	Other	
Granich, R [79]	19			Some but not all doses were observed	Other	
* Lockman, S [80]	10	22	Individualized	No	Specialized TB hospital	4
Espinal, M [48]	7	0	Standardized	Yes	Regional TB treatment program	
Espinal, M [48]	7	0	Standardized	No	Regional TB treatment program	
Sung, S-W [81]	32		Individualized		Specialized TB hospital	100
* Perez-Guzman, C [82]	12	6	Individualized	No	Specialized TB hospital	

Flament-Saillour, M [83]	8		Individualized	Some but not all doses were observed	Other	
*Masahiro, N [84]			Individualized	Some but not all doses were observed	Other	6
Espinal, M [48]	7	0	Standardized	Some but not all doses were observed	Regional TB treatment program	
* Ferrara, G [85]	12	0	Individualized	Some but not all doses were observed	Other	
* Coninx, R [86]	7		Standardized	Yes	Regional TB treatment program	
Mangunnegoro, H [87]	9	14	Standardized		Specialized TB hospital	
* Migliori, GB [88]	7	11	Standardized	Yes	Regional TB treatment program	
* Kwon, YS [89]	24		Individualized	Some but not all doses were observed	Specialized TB hospital	23
* DeRiemer, K [90]			Both standardized and individualized regimens were used in the cohort	Yes	Regional TB treatment program	
* Drobniewski, F [91]	21	84	Individualized	No	Other	
* Mitnick, C [92]	23	46	Individualized	Yes	Specialized regional MDR-TB program	
* Palmero, DJ [93]	18	19	Individualized	Some but not all doses were observed	Specialized TB hospital	6
* Van Deun, A [94]	21	24	Standardized	Some but not all doses were observed	Specialized regional MDR-TB program	
Suarez, PG [95]	18	0	Standardized	Yes	Specialized regional MDR-TB program	
* Surucuoglu, S [96]	12		Standardized	No	Specialized TB hospital	
* Schaaf, HS [97]		15	Individualized	Yes	Other	
* Park, SK [98]		2	Standardized	Some but not all doses were observed	Specialized TB hospital	4

Takeda, S-J [99]	22	62	Individualized		Specialized TB hospital	100
Quy, HT [100]	7		Standardized	Some but not all doses were observed	Regional TB treatment program	
* Tupasi, T [101]	21		Individualized	Some but not all doses were observed	Specialized regional MDR-TB program	
* Nathanson, E [102]	21	12	Individualized	Yes	Specialized regional MDR-TB program	15
# Leimane, V [103]	18		Individualized	Yes	Specialized regional MDR-TB program	9
* Nathanson, E [102]	21	12	Individualized	Yes	Specialized regional MDR-TB program	12
* Bonnet, M [104]	7		Standardized	Yes	Regional TB treatment program	
* Shiraishi, Y [105]	21	24	Individualized	Yes	Specialized TB hospital	100
* Nathanson, E [102]	21	36	Individualized	Yes	Specialized regional MDR-TB program	2
* Nathanson, E [102]	24	24	Individualized	Yes	Specialized regional MDR-TB program	7
* Bonnet, M [104]	8		Standardized	Yes	Regional TB treatment program	
# Cox, H [106]	7		Standardized	Yes	Regional TB treatment program	
Mathew, T [107]	8				Specialized regional MDR-TB program	
Masjedi, MR [108]	24		Individualized	Yes	Specialized regional MDR-TB program	0
Pathan, AJ [109]	12	12	Standardized	Some but not all doses were observed	Specialized TB hospital	
Corlan, E [110]	6	18	Standardized	No	Specialized TB hospital	

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1F Characteristics of the drug pharmacotherapy

Absent values indicate that the variable was not reported for that cohort.

Author	Average, or median, number of total drugs given in the regimen during both the intensive and continuation phase	Average, or median, number of sensitive drugs given in the regimen during both the intensive and continuation phase	Use of second-line drugs in therapy	Percent of cohort taking fluoroquinolones	Percent of cohort taking an injectable drug	Percent of cohort taking PZA
Goble, M [54]		2.4	Yes		117	59
Olle-Goig [55]	4		No			
Park, M [56]	2	2				
Chan, ED [57]			Yes	80	96	
* Sosna, J [58]		2.4				
* Geerligs, WA [59]	6		Yes	86	91	86
Kritski, A [60]			Yes			
* Avendano, M [61]	5	3	Yes	65	83	55
Pretet, S [62]	4	4	Yes	82	56	49
Bashar, M [63]						
* Lee, C-N [64]			Yes		22	72
* Schaaf, HS [65]	3.5		No	0		100
Fischl, MA [66]	5.4	2.1	Yes	70	63	83
* Kim, HJ [67]	5.3	4.2	Yes			
* Ward, HA [68]	8	4	Yes			
Yew, WW [69]	4.7	3.5	Yes	100	76	60
* van Leuven, M [70]						
* Turett, G [71]		2				
Lan, NTN [72]	5		No	0	100	100
* Torun, T [73]	5.4	4.5	Yes	85	98	28
* Tahaoglu, K [74]	5.5	4.4	Yes	80	91	32
* Chiang, C-Y [75]		3.7	Yes	42		
* Li, J [76]			Yes	50	15	

* Park, SK [77]	5		Yes			
Bloch, AB [78]	2					
Granich, R [79]						
* Lockman, S [80]		3	Yes			
Espinal, M [48]	4.5		No	0		100
Espinal, M [48]	4.5		No	0		100
Sung, S-W [81]		5.6	Yes			
* Perez-Guzman, C [82]	5		Yes	48	84	55
Flament-Saillour, M [83]						
*Masahiro, N [84]	4.3				50	
Espinal, M [48]	4.5		No	0		100
* Ferrara, G [85]		3.5	Yes	80		30
* Coninx, R [86]	4.7		No	0	0	0
Mangunnegoro, H [87]	3.9	2.9	Yes	100	93	100
* Migliori, GB [88]			No			
* Kwon, YS [89]	6	4	Yes	95	73	
* DeRiemer, K [90]			No			
* Drobniewski, F [91]		3	Yes			
* Mitnick, C [92]	6	5	Yes	100	100	35
* Palmero, DJ [93]	4.2		Yes	82	52	26
* Van Deun, A [94]	8		Yes	100	100	100
Suarez, PG [95]	5		Yes	100	100	100
* Surucuoglu, S [96]						
* Schaaf, HS [97]			Yes	89	56	89
* Park, SK [98]	5	4	Yes	100	100	50
Takeda, S-J [99]			Yes			
Quy, HT [100]	5		No	0	100	100
* Tupasi, T [101]	2.4		Yes	100	115	73
* Nathanson, E [102]			Yes	59	93	29
# Leimane, V [103]	6	6	Yes	98	111	36

* Nathanson, E [102]	5.3		Yes	99	99	59
* Bonnet, M [104]	4		No	0	81	100
* Shiraishi, Y [105]	4		Yes	80		
* Nathanson, E [102]	5.4		Yes	100	100	2
* Nathanson, E [102]	5.5		Yes	99	53	40
* Bonnet, M [104]	4.7		No	0	0	100
# Cox, H [106]	4.7		No	0	75	100
Mathew, T [107]			Yes			
Masjedi, MR [108]	5	4	Yes	100	100	81
Pathan, AJ [109]	3		Yes	0	100	0
Corlan, E [110]	4		No		100	100

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 1G Treatment outcomes

Absent values indicate that the variable was not reported for that cohort

Author	Percent of the cohort that was cured	Percent of the cohort with successful outcome (cure or treatment complete)	Percent of the cohort that failed	Percent of the cohort that defaulted	Percent of the cohort that died	Percent of the cohort that relapsed	Percent of the cohort with cumulative success	Percent of the cohort with cumulative failure
Goble, M [54]			17	13	22		44	19
Olle-Goig [55]	32	32		54	14		32	
Park, M [56]		26		24	50		26	
Chan, ED [57]				59	25			16
* Sosna, J [58]	63	63	23	0	14		63	23
* Geerligs, WA [59]	95	95	0	0	5	3	92	3
Kritski, A [60]				0			23	
* Avendano, M [61]	75	75		9	16	17	63	13
Pretet, S [62]	36	36	23	36	5	0	36	23
Bashar, M [63]		50		39	11		50	
* Lee, C-N [64]	47	47	42	0	11	12	42	47
* Schaaf, HS [65]	27	27		0			27	
Fischl, MA [66]	3	3		11	85		3	
* Kim, HJ [67]	48	48	8	43	0	2	47	9
* Ward, HA [68]		86	2	7	5		86	2
Yew, WW [69]	78	78	15	7		3	76	17
* van Leuven, M [70]		84	5	7	7		84	5
* Turett, G [71]			8	34	58			
Lan, NTN [72]	33	33	64	0	2		33	64
* Torun, T [73]	77	77	6	10	7	2	75	8
* Tahaoglu, K [74]	49	77	8	11	4	2	76	9
* Chiang, C-Y	51	51	10	29	9	7	48	14

[75]								
* Li, J [76]	58	58		32	10		58	
* Park, SK [77]			17	0	0	0	83	17
Bloch, AB [78]		36		27	37		36	
Granich, R [79]	57	57		31	12		57	
* Lockman, S [80]	37	37	13	35	22	46	0	54
Espinal, M [48]		43	38	4	15		43	8
Espinal, M [48]		42	18	34	5		42	8
Sung, S-W [81]			8	96				8
* Perez-Guzman, C [82]	50	50	9	41	0	6	47	12
Flament-Saillour, M [83]			47	20				47
*Masahiro, N [84]		59		12	29		59	
Espinal, M [48]		38	31	29	2		38	13
* Ferrara, G [85]	23	39	22	30	9		39	22
* Coninx, R [86]		27		57	17		27	
Mangunnegoro, H [87]	62	62	24	14		11	55	31
* Migliori, GB [88]		28		0		28	21	7
* Kwon, YS [89]	55	66	14	14	6		66	14
* DeRiemer, K [90]		20	37	32	12		20	37
* Drobniewski, F [91]				78	22			
* Mitnick, C [92]	72	72	1	8	19	1	71	2
* Palmero, DJ [93]	52	52	9	20	19	12	47	14
* Van Deun, A [94]	69	69	5	12	14	13	60	14
Suarez, PG [95]		46	32	11	11		46	32
* Surucuoglu, S [96]	54	54	46	0			54	46
* Schaaf, HS [97]	68	68		19	13	5	65	3
* Park, SK [98]	45	45	13	40	3	0	45	13
Takeda, S-J [99]			8	0	4	9		15

Quy, HT [100]	50	50	29	13	8		50	29
* Tupasi, T [101]	59	60	10	14	15		60	10
* Nathanson, E [102]	69	69	3	8	19	1	68	4
# Leimane, V [103]	62	66	14	13	7		66	14
* Nathanson, E [102]	83	83	6	6	5	2	82	7
* Bonnet, M [104]	0	3	31	56	9		3	31
* Shiraishi, Y [105]		90		7	3	10	90	10
* Nathanson, E [102]	61	65	9	15	11	10	59	15
* Nathanson, E [102]	67	69	11	16	4	3	67	13
* Bonnet, M [104]	0	41	45	7	7		41	45
# Cox, H [106]	22	29	18	24	29	63	11	36
Mathew, T [107]				0	18			
Masjedi, MR [108]	20	57	12	16	16		57	12
Pathan, AJ [109]	56	56	16	22	6	6	53	19
Corlan, E [110]				0	16			

* Authors who provided additional information not published in the article.
# Authors who were not contacted because their articles were not missing any of the key variables defined in section 3.8.

Table 2 Descriptive statistics of the 64 cohorts included in the analysis of the systematic review

Table 2a Descriptive statistics of the population characteristics

Variable	Proportion of cohorts reporting this variable	Normal distribution	Mean	Standard deviation	Median	Inter-quartile range	Total range
Number of MDR-TB patients	64/64	No	124	152	74	39 - 143	26 -1011
Midyear of patient enrolment period (year)	62/64	Yes	1996	5	1996	1992-2000	1978 – 204
% of the cohort that is female	60/64	Yes	31%	13%	31%	25 – 41%	0% – 63%
Average, or median, age of the cohort (year)	59/64	Yes	39 years	7 years	40 years	37 – 43 years	6 – 50 years
% of the cohort with HIV co-infection	48/64	No	11%	18%	0.2%	0.0 – 9.0%	0.0% - 100%
% of the cohort with history of previous TB treatment	58/64	No	73%	30%	77%	55% – 100%	0 %- 100%

% who failed previous TB treatment	11/64	No	47%	39%	44%	0 – 98	0 – 100%
% who relapsed after successful previous TB treatment	11/64	No	61%	39%	28 %	0- 78	0 – 100%
% who returned after default from previous TB treatment	9/64	No	0.7%	1%	0 %	0.0% – 0.0%	0.0 – 4.0%

Table 2b Descriptive statistics of health system factors

Variable	Proportion of cohorts reporting this variable	Normal distribution	Mean	Standard deviation	Median	Inter-quartile range	Total range
Per capita total health expenditure, exchange rate (US dollars)	62/64	No	$ 1173	$ 1658	$ 237	$ 95 - $ 1925	$ 11 - $ 4570
Per capita government health expenditure, (US dollars)	62/64	No	$ 603	$ 831	$ 108	$ 14 - $ 1441	$ 2 – $ 2298
National proportion of primary MDR-TB among all TB cases	64/64	No	4.2 %	4.2 %	2.6 %	1.2 – 5.3 %	0.7 – 22.3 %
National proportion of acquired MDR-TB among all TB cases	61/64	No	18.6 %	16.1 %	14 %	5.4 – 22.4 %	2.0 – 60.0 %

Variable		**Count**	**Percentage**
National income level	High Income	28	44%
	Upper Middle Income	18	28%
	Lower Middle Income	12	19%
	Low Income	7	11%

Table 2c Descriptive statistics of disease characteristics

Variable	Proportion of cohorts reporting this variable	Normal distribution	Mean	Standard deviation	Median	Inter-quartile range	Total range
% cohort with only pulmonary TB	59/64	No	95	10	100	95 - 100	50 - 100
% cohort with pulmonary & extra-pulmonary TB	58/64	No	4	9	0	0 -3	0 - 46
% cohort with extra-pulmonary TB	58/64	No	2	5	0	0 - 0	0 - 25
% of the cohort with positive sputum smear	25/64	Yes	74%	22%	83%	58 – 88	31% – 100%
% of the cohort with cavitary disease	25/64	Yes	52	24	71	43 – 81	18 – 96
% of the cohort with bilateral pulmonary disease	11/64	No	64	23	71	46 – 84	14 – 90

Average, or median, number of drugs resistant to, in addition to isoniazid and rifampin	43/64	No	2	1	2	1 – 2	0.6 - 6
% resistant to fluoroquinolone	18/64		13	12	10	3 – 22	0 – 42
% resistant to PZA	18/64	No	38	23	31	24 – 52	0 - 100

Table 2d Descriptive statistics of treatment characteristics

Variable	Proportion of cohorts reporting this variable	Normal distribution	Mean	Standard deviation	Median	Inter-quartile range	Total range
Average length of treatment (months)	54/64	No	16	7	18	8 – 22	6 – 32
Average length of follow-up for studies reporting relapse (months)	30/64	No	29	20	24	15 - 33	2 - 84
Average, or median, number of drugs given in the regimen	42/64	No	5	1.2	5	4– 5	2 – 8
Average, or median, number of sensitive drugs given in the regimen	23/64	No	4	1	4	3 – 4	2 – 6
% of the cohort receiving a fluoroquinolone	39/64	No	61%	42%	80%	0– 100%	0 – 100
% of the cohort receiving PZA	37/64	No	66	34	72	36 – 100	0 - 100

% of the cohort receiving an injectable drug	36/64	No	79	31	93	68 – 100	0 - 100
% of the cohort with surgical resection	29/64	No	23%	34%	7%	4 – 23%	0 – 100

Variable		Count	Percentage
Directly Observed Treatment (DOT)	Yes	22	34%
	No	9	14%
	Partial	23	36%
	Not reported	10	16%
Type of Drug Regimen	Individualized	43	67%
	Standardized	17	27%
	Both individualized and standardized reported in the cohort	1	1.5%
	Not reported	3	5%
Institution	Specialized TB hospital (total)	32	50%
	Specialized TB hospital (2^{nd} line drugs used)	25	(25/32= 78%)
	Specialized TB hospital (only 1^{st} line drugs used)	1	(1/32= 3%)
	Specialized TB hospital (type of drug use not specified)	6	(6/32= 19%)
	Regular TB program (only first line drugs used)	13	20%
	Specialized MDR-TB program (second-line drugs used)	12	19%
	Other	7	11%
Second-line drugs in regimen	Included in regimen	40	63%
	Not included in regimen	14	22%
	Not reported	10	15%

Table 3 Pooled treatment outcomes of the 64 cohorts, using random effects

Treatment Outcome	Cohorts reporting the outcome	Normal distribution	Mean	95% Confidence Interval	Median	Inter-quartile range	Total range	I^2
Cure[6]	39/64	Yes	50 %	40 – 61 %	51 %	37 – 62 %	0 – 84 %	99.5 %
Treatment Complete[7]	29/64	No	27 %	18 – 37 %	23 %	2 – 43 %	0 – 90 %	99.0 %
Success (Cure + Treatment Complete)	53/64	Yes	53 %	46 – 59 %	51 %	37 – 66 %	3 – 90 %	97.1 %
Cumulative success[8] (Success – Relapse)	56/64	Yes	50 %	42 – 59 %	48 %	36 – 60 %	0 – 90 %	98.9 %
Serious Adverse Events[9]	27/64	No	30 %	22 – 37 %	23 %	10 – 39 %	0 – 95 %	99.4 %
Default[10]	64/64	No	18 %	16 – 19 %	15 %	10 – 25 %	0 – 49 %	98.2 %
Death[11]	56/64	No	13 %	11 – 16 %	11 %	5 – 19 %	0 – 98 %	96.2 %
Failure[12]	45/64	No	16 %	14 – 19 %	12 %	8 – 22 %	0 – 64 %	93.3 %
Relapse[13]	27/64	No	5 %	3 – 6 %	5 %	2 – 11 %	0 – 63 %	89.8 %
Cumulative failure[14] (Failure and/or Relapse)	49/64	No	17 %	14 – 20 %	14 %	8 – 29 %	2 – 64 %	91.2 %

[6] Cure: culture converted by the end of the treatment period.
[7] Treatment Complete: completed the prescribed treatment with no bacteriological evidence of either cure or failure
[8] Cumulative success: total number of treatment complete and/or cure, minus those who relapsed.
[9] Serious Adverse Events were reported as number of persons with events, as opposed to number of events.
[10] Default: treatment was interrupted for two consecutive months or more, or transferred out and treatment outcome unknown. In addition, patients who were unaccounted for in the study were considered to have defaulted.
[11] Death: death due to any cause during the course of TB treatment.
[12] Failure: persistence of culture-positive status after five or more months of treatment.
[13] Relapse: recurrence of bacteriological confirmed TB after treatment success (cure or treatment complete)
[14] Cumulative failure: total number of failure and/or relapse

Table 4 Subgroup analysis for the treatment outcome cumulative success,[15] stratified by one variable

Table 4a Subgroup analysis of population characteristics for the treatment outcome cumulative success

Statistically significant differences between strata are bolded

Variable	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
% Female[16]					
0-28.0%	17	963/ 1705	50	35 -65	98.3
28.1-36.0%	16	1053/ 2269	48	39-58	95.0
36.0-100.0%	18	1150/ 2434	49	34-65	99.2
Not reported	5	670/1018	60	43-76	96.6

Average or median age (years)[17]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 - 37.0	19	776/ 1771	46	34-58	97.3
37.1 - 42.0	15	1268/ 2379	51	39-63	97.3
> 42.0	16	987/ 2054	51	33-68	99.2
Not reported	6	805/1222	61	48-74	95.8

% HIV co-infection[18]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 – 6.0%	34	2500/4277	56	43-69	99.2
6.1% - 100.0%	9	246/621	40	23-57	96.4
Not reported	13	1090/2528	41	30-52	97.0

% Prior treatment[19]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 – 33.0	6	477/ 1018	52	22 - 81	99.5
33.1 – 66.9	13	663/ 1250	54	45 - 64	91.2
67.0 – 100.0	32	2571/ 4642	52	45 - 60	96.8
Not reported	5	125/ 516	24	11 - 37	94.0

[15] Cumulative success: total number of treatment complete and/or cure, minus those who relapsed.
[16] This variable has a normal distribution, and ranges from 0-63%. The strata cutoffs were at the terciles.
[17] This variable has a normal distribution, and ranges from 6- 50. The strata cutoffs were at the terciles, which created three groups that can be considered young, middle-aged, and old.
[18] This variable does not have a normal distribution; there is a large cluster below 6%, and an even distribution above 6%. Therefore, 6% was chosen as the cutoff point.
[19] This variable does not have a normal distribution, and ranges from 0-100%. The cutoffs were chosen to create strata with low, moderate, and high prevalence of prior treatment, for these categories are relevant in the clinical setting.

Mid-year of patient enrolment period[20]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
< 1992	15	908/ 2137	44	31 - 57	97.6
1993 – 1995	13	802/ 1581	53	32 - 74	99.3
1996 – 2000	17	1308/ 2380	51	44 - 59	93.0
2001 – 2008	9	769/ 1238	53	33 - 73	98.6
Not reported	2	49/ 90	54	44 - 65	0

[20] This variable has a normal distribution. Strata were defined by quartiles.

Table 4b Subgroup analysis of health system setting for cumulative success

Statistically significant differences between strata are bolded

Variable	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
Per capita total health expenditure (US $)[21]					
0 – 228	27	1690/ 3007	49	34 - 63	99.2
229 – 677	11	1036/ 2102	52	40 - 64	96.4
678 - 5000	15	871/ 1876	51	37 - 64	97.7
Not reported (Hong Kong & Taiwan)	3	239/ 441	56	34 - 77	94.4

National income level (US $)[22]	**Cohorts**	**Success/ N treated**	**Pooled cumulative success**		**I^2**
			Estimate	**95% CI**	
Low Income	6	189/ 388	49	26 - 72	96.4
Lower Middle Income	12	816/ 1535	44	30 - 58	97.3
Upper Middle Income	16	1059/ 1872	52	31 - 72	99.4
High Income	22	1772/ 3631	53	43 - 62	97.3

National proportion of primary MDR-TB among all TB cases[23]	**Cohorts**	**Success/ N treated**	**Pooled cumulative success**		**I^2**
			Estimate	**95% CI**	
0.0 – 2.6 % (low)	27	1376/ 3024	49	40 - 58	96.9
> 2.7 % (high)	29	2460/ 4402	51	38 - 64	99.3

National proportion of acquired MDR-TB among all TB cases[24]	**Cohorts**	**Success/ N treated**	**Pooled cumulative success**		**I^2**
			Estimate	**95% CI**	
0 - 14.0% (low)	32	2777/ 5395	54	46 - 61	97.4

[21] This variable does not have a normal distribution. The strata were defined by clusters of the data points.
[22] The income categories were defined by the World Bank. High income was defined as Gross National Income per capita (GNIPC) greater than $11,456 US dollars. Upper middle income was defined as GNIPC between $3,706- $11,455. Lower middle income was defined as GNIPC between $936- $3,705. Low income was defined as GNIPC less than $935.
[23] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (2.6 %).
[24] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (14.0 %).

>14.1 % (high)	23	1045/ 1992	46	30 - 61	99.1
Not reported	1	14/ 39	36	21 - 51	--

Table 4c Subgroup analysis of disease characteristics for cumulative success

Statistically significant differences between strata are bolded

Variable	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
% positive smear[25]					
0.0 – 50.0%	5	381/ 751	70	45 - 94	97.9
50.1 – 74.9	4	262/ 625	22	0 - 48	99.4
75.0 – 100.0	10	680/ 1390	49	40 - 57	89.2
Not reported	37	2513/ 4660	51	44 - 58	96.6

Average or median number of drugs resistant to in addition to isoniazid & rifampin[26]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0 – 1.9	21	1240/ 2822	**42**	**32 - 51**	96.6
2.0 – 2.9	12	790/ 1235	**63**	**54 - 71**	90.5
> 3.0	5	325/ 514	**73**	**55 - 90**	95.5
Not reported	18	1481/ 2855	46	29 - 62	99.4

[25] This variable does not have a normal distribution. Values range from 31 – 100%. Strata were defined to create clinically relevant categories of low, moderate and high prevalence of smear positivity.

[26] This variable does not have a normal distribution. Values range from 0.6 – 6.0. Strata were defined by integers.

Table 4d Subgroup analysis of treatment characteristics for cumulative success

Statistically significant differences between strata are bolded

Variable	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
Directly Observed Therapy					
Yes	22	1414/2513	50	39-61	97.3
Partial (some doses)	20	1480/2678	57	50-64	93.1
None	7	709/1583	44	38-50	64.5
Not reported	7	233/652	44	19-69	98.8

Regimen Type	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
Individualized	37	3030/5620	**57**	**50-65**	97.5
Standardized	16	553/1330	**38**	**29-48**	93.2
Mixed/Not reported	3	253/476	42	17-68	93.6

Total number of drugs used in regimen[27]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
1-3	4	280/ 707	43	29 - 58	91.4
3.1 - 4	5	165/ 489	41	16 - 66	98.1
4.1 - 5	18	762/ 1592	47	39 - 55	91.9
>5	13	1529/ 2536	65	51 - 80	98.6
Not reported	16	1100/ 2102	46	28 - 64	99.3

Total number of sensitive drugs used in regimen[28]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
1 - 2	1	29/ 110	**26**	**18 - 35**	N/A
2.1 – 3	6	165/ 426	37	18 - 56	98.5
3.1 - 4	7	505/ 922	**59**	**50 - 72**	93.7
> 4.1	6	1023/ 1783	**63**	**50 - 76**	96.4
Not reported	36	2114/ 4185	49	41 - 57	96.7

[27] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

[28] The values are for the average or median number of sensitive drugs used in the regimen in both the intensive and continuation phase. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

Total number of sensitive or other drugs used in regimen[29]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
1 - 2	2	192/ 557	**32**	**22 - 42**	77.6
2.1 – 3	8	253/ 576	42	23 - 61	98.7
3.1 - 4	11	638/ 1385	51	36 - 67	97.8
> 4.1	24	1956/ 3537	**55**	**47 - 62**	95.5
Not reported	11	797/ 1403	49	37 - 61	95.4

Duration of Treatment (months)[30]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
6-12	20	589/1547	**37**	**25-49**	98.1
13-20	7	821/1565	52	42-62	94.1
21-33	19	2069/3593	**65**	**60-73**	95.9
Not reported	10	357/ 721	46	24-67	98.2

Institution	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
Specialized Hospital (80% of the hospitals administered second-line drugs)	27	1775/ 3376	**53**	**40 - 67**	99.2
National/Regional MDR-TB treatment program (second-line drugs administered)	11	1183/ 1834	**66**	**59 - 73**	89.7
National/Regional TB program (only first-line drugs administered)	13	369/ 1127	**30**	**21 - 38**	91.4
Other (non-programmatic MDR-TB treatment)	5	509/ 1089	**50**	**39 - 62**	91.9

% receiving fluoroquinolones[31]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 – 48.0%	13	480/ 1246	**35**	**25 - 45**	93.6%
48.1 – 96.9%	11	973/ 1542	60	41 - 78	98.8
97.0% - 100%	12	974/ 1587	**62**	**55 - 70**	90.0
Not reported	20	1409/ 3051	47	33 - 62	99.1

[29] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. If the mean number of sensitive drugs used was not available, the cohort was still included in the stratum if the mean number of drugs used was reported. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.
[30] The average or median length of treatment was used for this variable. The cutoffs for the strata were chosen to address the current debate in the optimal length of MDR-TB treatment.
[31] This variable does not have a normal distribution. Strata were defined by terciles, which also corresponded to the observed clusters in the distribution.

% receiving PZA[32]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 - 33.0	8	824/ 1293	56	46 - 67	93.5
33.1 – 66.9	10	769/ 1234	60	51 - 70	91.9
67.0 – 100.0	17	652/ 1571	41	29 - 54	97.4
Not reported	21	1591/ 3328	51	36 - 65	99.2

% receiving an injectable drug[33]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 - 33.0	4	138/ 303	43	30 - 55	78.0
33.1 – 66.9	5	291/ 565	42	12 - 73	98.8
67.0 – 100.0	24	1834/ 3009	57	47 - 66	97.0
Not reported	23	1573/ 3549	46	34 - 59	99.1

Receiving second-line drugs	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
Yes	35	2883/ 5085	**57**	**45 - 69**	99.3
No	13	369/ 1127	**30**	**21 - 38**	91.4
Not reported	8	584/ 1214	53	41 - 66	94.7

% receiving adjunctive surgery[34]	Cohorts	Success/ N treated	Pooled cumulative success		I^2
			Estimate	95% CI	
0.0 – 8.0 %	14	1244/ 2520	**48**	**31 - 65**	99.3
8.1 – 100%	11	1159/ 1610	**75**	**69 - 81**	84.3
Not reported	31	1433/ 3296	42	35 - 49	95.0

[32] This variable does not have a normal distribution. There is a cluster in the 90-100% range. Strata were created for low, moderate, and high prevalence of PZA usage.
[33] This variable does not have a normal distribution. Strata were created for low, moderate, and high prevalence of injectable drug usage.
[34] This variable does not have a normal distribution. There are two clusters <8% and >80%. They are captured by strata defined by the median of prevalence of surgical adjunctive therapy (8%).

Table 5 Subgroup analysis of the treatment outcome death,[35] stratified by one variable

Table 5a Subgroup analysis of population characteristics for the treatment outcome death

Statistically significant differences between strata are bolded

Variable	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
% Female[36]					
0-28.0%	17	237/ 1695	16	10 - 22	97.0
28.1-36.0%	18	208/ 2405	13	8 - 17	93.5
36.0-100.0%	17	416/ 2341	13	8 - 18	94.8
Not reported	4	120/ 942	10	1 - 18	94.9

Average or median age (years)[37]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 - 37.0	19	250/ 1621	16	9 - 22	95.0
37.1 - 42.0	17	266/ 2668	14	10 - 17	95.7
> 42.0	15	331/ 1948	12	6 - 17	95.0
Not reported	5	134/ 1146	9	3 - 15	93.3

% HIV[38]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 – 6.0%	30	426/ 3919	**9**	**7 - 12**	86.1
6.1% - 100.0%	11	211/ 749	**28**	**13 - 43**	96.8
Not reported	15	344/ 2715	12	8 - 16	96.9

% Prior treatment[39]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 – 33.0	7	263/ 1170	17	7 - 27	94.2
33.1 – 66.9	14	161/ 1352	13	8 - 17	87.7
67.0 – 100.0	32	446/ 4661	9	7 - 12	93.5
Not reported	3	111/200	49	8 - 90	98.1

[35] Death due to any cause during the course of TB treatment
[36] This variable has a normal distribution, and ranges from 0-63%. The strata cutoffs were at the terciles.
[37] This variable has a normal distribution, and ranges from 6- 50. The strata cutoffs were at the terciles, which created three groups that can be considered young, middle aged, and old.
[38] This variable does not have a normal distribution; there is a large cluster below 6%, and an even distribution above 6%. Therefore, 6% was chosen as the cutoff point.
[39] This variable does not have a normal distribution, and ranges from 0-100%. The cutoffs were chosen to create strata with low, moderate, and high prevalence of prior treatment, for these categories are relevant in the clinical setting.

Mid year of patient enrolment period[40]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
< 1992	15	268/ 2060	21	12 - 31	97.9
1993 – 1995	12	260/ 1475	11	6 - 16	96.6
1996 – 2000	16	261/ 2368	11	9 - 14	75.8
2001 – 2008	11	185/ 1416	11	6 - 15	88.4
Not reported	2	7/ 64	10	1 - 19	32.3

[40] This variable has a normal distribution. Strata were defined by quartiles.

Table 5b Subgroup analysis of health system factors for the treatment outcome death

Statistically significant differences between strata are bolded

Variable	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
Per capita total health expenditure (US $)[41]					
0 – 228	25	338/ 2879	**10**	**8 - 13**	79.5
229 – 677	10	66/1934	**4**	**2 - 5**	86.1
678 - 5000	19	545/ 2235	**23**	**15 - 30**	96.2
Not reported (Hong Kong & Taiwan)	2	32/335	10	6 - 13	0.0

National income level (US $)[42]	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	
Low Income	6	42/ 388	9	4 - 15	75.1
Lower Middle Income	10	219/ 1397	14	11 - 17	59.0
Upper Middle Income	15	151/ 1714	9	6 - 11	82.9
High Income	25	569/ 3884	17	13 - 21	97.7

National proportion of primary MDR-TB among all TB cases[43]	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	
0.0 – 2.6 % (low)	27	610/ 2899	**18**	**13 - 24**	96.4
> 2.7 % (high)	29	371/ 4484	**9**	**7 - 11**	92.6

National proportion of acquired MDR-TB among all TB cases[44]	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	

[41] This variable does not have a normal distribution. The strata were defined by clusters of the data points.
[42] The income categories were defined by the World Bank. High income was defined as Gross National Income per capita (GNIPC) greater than $11,456 US dollars. Upper middle income was defined as GNIPC between $3,706- $11,455. Lower middle income was defined as GNIPC between $936- $3,705. Low income was defined as GNIPC less than $935.
[43] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (2.6 %).
[44] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (14.0 %).

0 - 14.0% (low)	32	757/ 5292	16	12 - 19	97.5
>14.1 % (high)	22	202/1962	10	7 - 12	82.1
Not reported	2	22/ 129	13	0 - 30	89.2

Table 5c Subgroup analysis of disease characteristics for the treatment outcome death

Statistically significant differences between strata are bolded

Variable	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
% positive smear[45]					
0.0 – 50.0%	5	185/ 751	13	0 - 28	97.0
50.1 – 74.9	5	189/ 663	**45**	**14 - 77**	98.6
75.0 – 100.0	11	156/ 1406	**10**	**6 - 13**	75.4
Not reported	35	451/ 4563	10	8 - 12	93.0

Average or median number of drugs resistant to in addition to isoniazid & rifampin[46]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0 – 1.9	18	197/ 2376	14	9 - 19	96.8
2.0 – 2.9	12	112/ 1235	8	5 - 12	89.3
> 3.0	6	124/ 719	13	6 - 21	90.1
Not reported	20	548/ 3053	16	11 - 21	94.1

[45] This variable does not have a normal distribution. Values range from 31 – 100%. Strata were defined to create clinically relevant categories of low, moderate and high prevalence of smear positivity.

[46] This variable does not have a normal distribution. Values range from 0.6 – 6.0. Strata were defined by integers.

Table 5d Subgroup analysis of treatment characteristics for the treatment outcome death

Statistically significant differences between strata are bolded

Variable	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
Directly Observed Therapy					
Yes	21	306/ 2437	11	8 - 14	83.0
Partial (some doses)	21	451/ 2815	14	9 - 18	93.2
None	8	86/ 1679	9	5 - 13	92.4
Not reported	6	138/ 452	27	5 - 49	99.0

Regimen Type	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	
Individualized	38	784/ 5553	**15**	**12 - 18**	97.1
Standardized	14	113/ 1202	**9**	**6 - 11**	72.6
Mixed/Not reported	4	84/ 628	13	10 - 16	0.0

Total number of drugs used in regimen[47]	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	
1-3	4	239/ 707	27	10 - 44	96.1
3.1 - 4	4	27/ 223	10	4 - 16	54.4
4.1 - 5	17	160/ 1486	9	6 - 12	89.7
>5	13	161/ 2536	12	7 - 18	97.4
Not reported	18	394/ 2431	15	12 - 19	81.9

Total number of sensitive drugs used in regimen[48]	**Cohorts**	**Death/ N treated**	**Pooled death**		I^2
			Estimate	**95% CI**	
1 - 2	2	77/ 148	**52**	**44 - 60**	0.0
2.1 – 3	6	133/ 458	30	8 - 52	97.3
3.1 - 4	6	63/ 816	**7**	**4 - 10**	64.5
> 4.1	6	67/ 1783	**7**	**2 - 11**	92.4
Not reported	36	641/ 4178	11	9 - 14	94.0

[47] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. If the mean number of drugs used was not available, the cohort was still included in the stratum if the mean number of sensitive drugs used was reported. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

[48] The values are for the average or median number of sensitive drugs used in the regimen in both the intensive and continuation phase. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

Total number of sensitive or other drugs used in regimen[49]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
1 - 2	3	241/ 595	**47**	**34 - 59**	82.6
2.1 – 3	8	153/ 608	25	9 - 42	96.8
3.1 - 4	10	90/ 1279	**8**	**5 - 11**	61.4
> 4.1	24	239/ 3537	**7**	**5 - 9**	90.7
Not reported	10	258/ 1604	13	9 - 17	75.6

Duration of Treatment (months)[50]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
6-12	18	162/ 1331	10	7 - 14	85.4
13-20	6	205/ 1459	17	10 - 23	93.7
21-33	22	462/ 3747	13	9 - 17	96.4
Not reported	10	152/ 846	18	9 - 28	98.0

Institution	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
Specialized Hospital (80% of the hospitals administered second-line drugs)	27	373/ 3407	14	11 - 17	96.6
National/Regional MDR-TB treatment program (second-line drugs administered)	12	252/ 1986	12	8 - 15	87.4
National/Regional TB program (only first-line drugs administered)	11	85/ 811	9	6 - 13	73.3
Other (non-programmatic MDR-TB treatment)	6	271/ 1179	20	10 - 31	95.0

% receiving fluoroquinolones[51]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 – 48.0%	12	92/ 1006	8	4 - 11	82.2
48.1 – 96.9%	12	286/ 1747	17	9 - 25	97.0
97.0% - 100%	10	128/ 1423	9	6 - 12	80.0
Not reported	22	475/ 3207	16	13 - 20	96.9

[49] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. If the mean number of sensitive drugs used was not available, the cohort was still included in the stratum if the mean number of drugs used was reported. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.
[50] The average or median length of treatment was used for this variable. The cutoffs for the strata were chosen to address the current debate in the optimal length of MDR-TB treatment.
[51] This variable does not have a normal distribution. Strata were defined by terciles, which also corresponded to the observed clusters in the distribution.

% receiving PZA[52]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 - 33.0	8	174/ 1293	11	6 - 16	86.9
33.1 – 66.9	9	101/ 1128	8	4 - 11	88.9
67.0 – 100.0	16	187/ 1305	15	8 - 23	95.6
Not reported	23	519/ 3657	15	12 - 19	96.9

% receiving an injectable[53]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 - 33.0	4	29/ 303	9	6 - 12	0.0
33.1 – 66.9	5	114/ 565	28	4 - 53	98.8
67.0 – 100.0	24	388/ 3082	11	8 - 14	89.6
Not reported	23	450/ 3433	13	10 - 17	96.5

Receiving second-line drugs	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
Yes	36	563/ 5314	12	9 - 14	96.1
No	12	90/ 843	10	6 - 13	72.0
Not reported	8	328/ 1226	27	15 - 38	95.8

% receiving adjunctive surgery[54]	Cohorts	Death/ N treated	Pooled death		I^2
			Estimate	95% CI	
0.0 – 8.0 %	14	226/ 2520	16	12 - 20	97.6
8.1 – 100%	13	222/ 1841	9	5 - 13	86.4
Not reported	29	533/ 3022	14	10 - 18	93.5

[52] This variable does not have a normal distribution. There is a cluster in the 90-100% range. Strata were created for low, moderate, and high prevalence of PZA usage.
[53] This variable does not have a normal distribution. Strata were created for low, moderate, and high prevalence of injectable drug usage.
[54] This variable does not have a normal distribution. There are two clusters <8% and >80%. They are captured by strata defined by the median of prevalence of surgical adjunctive therapy (8%).

Table 6 Subgroup analysis for the treatment outcome default,[55] stratified by one variable

Table 6a Subgroup analysis of population characteristics for the treatment outcome default

Statistically significant differences between strata are bolded

Variable	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
% Female[56]					
0-28.0%	20	350/ 1878	19	14 - 25	96.6
28.1-36.0%	20	711/2511	19	15 - 23	98.9
36.0-100.0%	19	632/ 2639	21	15 - 27	98.3
Not reported	5	97/ 1018	9	2 - 15	95.7

Average or median age (years)[57]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 - 37.0	20	357/ 1861	19	15 - 24	97.5
37.1 - 42.0	20	776/ 2832	20	16 - 25	99.0
> 42.0	18	534/ 2131	20	13 - 26	97.3
Not reported	6	123/ 1222	9	3 - 15	95.6

% HIV co-infection[58]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 – 6.0%	35	671/ 4429	**11**	**10 - 13**	96.1
6.1% - 100.0%	12	238/ 800	**27**	**14 - 41**	97.5
Not reported	17	881/ 2817	24	17 - 30	99.2

% prior treatment[59]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 – 33.0	7	271/ 1170	16	9 - 22	98.4
33.1 – 66.9	15	310/ 1378	21	14 - 29	97.2
67.0 – 100.0	36	1140/ 4956	17	14 - 21	97.9
Not reported	6	69/ 542	26	18 - 33	99.3

[55] Default: treatment was interrupted for two consecutive months or more, or transferred out and treatment outcome unknown. In addition, patients who were unaccounted for in the study were considered to have defaulted.
[56] This variable has a normal distribution, and ranges from 0-63%. The strata cutoffs were at the terciles.
[57] This variable has a normal distribution, and ranges from 6- 50. The strata cutoffs were at the terciles, which created three groups that can be considered young, middle aged, and old.
[58] This variable does not have a normal distribution; there is a large cluster below 6%, and an even distribution above 6%. Therefore, 6% was chosen as the cutoff point.
[59] This variable does not have a normal distribution, and ranges from 0-100%. The cutoffs were chosen to create strata with low, moderate, and high prevalence of prior treatment, for these categories are relevant in the clinical setting.

Mid year of patient enrolment period[60]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
< 1992	17	730/ 2380	17	13 - 20	98.8
1993 – 1995	14	359/ 1632	20	12 - 27	96.8
1996 – 2000	19	539/ 2496	26	17 - 34	98.7
2001 – 2008	11	147/ 1416	11	6 - 15	94.4
Not reported	3	15/ 122	11	0 - 24	87.9

[60] This variable has a normal distribution. Strata were defined by quartiles.

Table 6b Subgroup analysis health system factors for the treatment outcome default

Statistically significant differences between strata are bolded

Variable	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
Per capita total health expenditure (US $)[61]					
0 – 228	28	422/ 3039	14	11 - 17	94.6
229 – 677	13	618/ 2280	20	16 - 24	99.3
678 - 5000	20	656/ 2286	24	17 - 30	98.2
Not reported (Hong Kong & Taiwan)	3	94/ 441	12	0 - 28	98.2

National income level (US $)[62]	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	
Low Income	6	50/ 388	12	4 - 20	90.1
Lower Middle Income	12	238/ 1535	**20**	**13 - 27**	96.8
Upper Middle Income	18	214/ 2056	**6**	**5 - 8**	93.5
High Income	28	1288/ 4067	**25**	**19 - 31**	98.9

National proportion of primary MDR-TB among all TB cases[63]	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	
0.0 – 2.6 % (low)	32	879/ 3434	21	18 - 24	98.0
> 2.7 % (high)	32	911/ 4612	16	13 - 19	98.4

National proportion of acquired MDR-TB among all TB cases[64]	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	

[61] This variable does not have a normal distribution. The strata were defined by clusters of the data points.
[62] The income categories were defined by the World Bank. High income was defined as Gross National Income per capita (GNIPC) greater than $11,456 US dollars. Upper middle income was defined as GNIPC between $3,706- $11,455. Lower middle income was defined as GNIPC between $936- $3,705. Low income was defined as GNIPC less than $935.
[63] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (2.6 %).
[64] This variable does not have a normal distribution. It was split into low and high prevalence categories at the median point (14.0 %).

0 - 14.0% (low)	37	1373/ 5722	18	15 - 21	98.7
>14.1 % (high)	24	323/ 2144	13	11 - 15	94.7
Not reported	3	94/ 180	45	6 - 84	97.3

Table 6c Subgroup analysis of disease characteristics for the treatment outcome default

Statistically significant differences between strata are bolded

Variable	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
% positive smear[65]					
0.0 – 50.0%	5	154/ 751	13	0 - 26	97.5
50.1 – 74.9	6	214/ 689	39	13 - 64	98.4
75.0 – 100.0	14	312/ 1589	16	10 - 22	97.6
Not reported	39	1110/ 5017	15	13 - 17	97.9

Average or median number of drugs resistant to in addition to isoniazid & rifampin[66]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0 – 1.9	23	806/ 2886	18	14 - 22	98.4
2.0 – 2.9	13	221/ 1261	22	11 - 34	98.5
> 3.0	6	175/ 719	17	2 - 31	98.3
Not reported	22	588/ 3180	17	13 - 20	97.8

[65] This variable does not have a normal distribution. Values range from 31 – 100%. Strata were defined to create clinically relevant categories of low, moderate and high prevalence of smear positivity.

[66] This variable does not have a normal distribution. Values range from 0.6 – 6.0. Strata were defined by integers.

Table 6d Subgroup analysis of treatment characteristics for the treatment outcome **default**

Statistically significant differences between strata are bolded

Variable	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
Directly Observed Therapy					
Yes	22	315/ 2513	**12**	**9 - 15**	93.9
Partial (some doses)	23	700/ 2972	21	15 - 27	97.2
None	9	709/ 1705	**35**	**19 - 51**	99.2
Not reported	10	66/ 856	9	6 - 12	98.7

Regimen Type	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	
Individualized	43	1409/ 6056	19	16 - 22	98.6
Standardized	17	230/ 1362	14	11 - 18	95.0
Mixed/Not reported	4	151/ 628	25	2 - 47	98.6

Total number of drugs used in regimen[67]	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	
1-3	4	170/ 707	22	15 - 29	71.3
3.1 - 4	6	98/ 521	18	10 - 27	97.6
4.1 - 5	18	273/ 1592	17	13 - 21	94.6
>5	13	610/ 2536	13	5 - 21	98.1
Not reported	23	639/ 2690	22	18 - 26	98.8

Total number of sensitive drugs used in regimen[68]	**Cohorts**	**Default/ N treated**	**Pooled default**		I^2
			Estimate	**95% CI**	
1 - 2	2	39/ 148	27	17 - 36	32.4
2.1 – 3	7	126/ 516	23	6 - 40	98.3
3.1 - 4	7	220/ 922	20	11 - 30	93.2
> 4.1	7	555/ 1809	31	12 - 50	99.1
Not reported	41	851/ 4651	12	10 - 14	97.0

[67] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

[68] The values are for the average or median number of sensitive drugs used in the regimen in both the intensive and continuation phase. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.

Total number of sensitive or other drugs used in regimen[69]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
1-2	3	159/ 595	27	23 - 30	0.0
2.1 – 3	9	150/ 666	22	8 – 35	97.9
3.1 - 4	12	310/ 1385	20	13 - 27	97.8
>4	25	803/ 3563	20	14 - 25	98.5
Not reported	15	368/ 1837	12	9 - 15	97.8

Duration of Treatment (months)[70]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
6-12	23	237/ 1782	**7**	**5 - 8**	93.7
13-20	7	335/ 1565	**19**	**12 - 27**	93.6
21-33	23	964/ 3773	**22**	**15 - 29**	98.8
Not reported	11	254/ 926	22	15 - 28	97.9

Institution	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
Specialized Hospital (80% of the hospitals administered second-line drugs)	32	1008/ 3703	19	15 - 23	98.5
National/Regional MDR-TB treatment program (second-line drugs administered)	12	201/ 1986	10	6 - 15	94.7
National/Regional TB program (only first-line drugs administered)	13	201/ 1127	15	12 - 18	96.6
Other (non-programmatic MDR-TB treatment)	7	380/ 1230	31	18 - 44	96.1

% receiving fluoroquinolones[71]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 – 48.0%	13	226/ 1246	20	14 - 25	96.5
48.1 – 96.9%	12	317/ 1747	17	10 - 25	97.0
97.0% - 100%	12	228/ 1587	14	10 - 18	83.5
Not reported	27	1019/ 3466	20	17 - 24	98.9

[69] The values are for the average or median number of drugs used in the regimen in both the intensive and continuation phase. If the mean number of sensitive drugs used was not available, the cohort was still included in the stratum if the mean number of drugs used was reported. The cutoffs for the strata were chosen to address the current debate in the number of drugs recommended for use in MDR-TB therapy.
[70] The average or median length of treatment was used for this variable. The cutoffs for the strata were chosen to address the current debate in the optimal length of MDR-TB treatment.
[71] This variable does not have a normal distribution. Strata were defined by terciles, which also corresponded to the observed clusters in the distribution.

% receiving PZA[72]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 - 33.0	8	180/ 1293	**19**	**12 - 25**	88.9
33.1 – 66.9	10	200/ 1234	17	11 - 23	89.6
67.0 – 100.0	18	182/ 1603	**9**	**6 - 11**	92.8
Not reported	28	1228/ 3916	24	20 - 27	99.0

% receiving an injectable drug[73]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 - 33.0	4	61/ 303	21	7 - 36	96.7
33.1 – 66.9	5	98/ 565	17	12 - 22	63.4
67.0 – 100.0	26	510/ 3246	15	11 - 19	95.7
Not reported	29	1121/ 3932	20	18 - 23	98.9

Receiving second-line drugs	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
Yes	40	1269/ 5584	19	16 - 22	98.5
No	14	201/ 1159	13	10 - 16	96.4
Not reported	10	320/ 1303	18	10 - 27	97.6

% receiving adjunctive surgery[74]	Cohorts	Default/ N treated	Pooled default		I^2
			Estimate	95% CI	
0.0 – 8.0 %	14	754/ 2520	20	12 - 27	98.8
8.1 – 100%	14	305/ 1867	19	11 - 28	98.6
Not reported	36	731/ 3659	15	13 - 16	97.3

[72] This variable does not have a normal distribution. There is a cluster in the 90-100% range. Strata were created for low, moderate, and high prevalence of PZA usage.
[73] This variable does not have a normal distribution. Strata were created for low, moderate, and high prevalence of injectable drug usage.
[74] This variable does not have a normal distribution. There are two clusters <8% and >80%. They are captured by strata defined by the median of prevalence of surgical adjunctive therapy (8%).

Table 7 Adjusted rates of cumulative success, death, and default using four models defined a priori.

Analysis was by multivariate linear meta-regression using random effects. The estimates are the coefficients of the variable in the model; they represent the percent change in the treatment outcome given a one unit increase of that variable while keeping all other factors in the model constant.

Treatment characteristics

	Cumulative Success (95% CI)	**Death during treatment (95% CI)**	**Default (95% CI)**
Number of studies included in the model	34	32	35
R^2 [75]	61.10%	68.70%	-0.79%
Number of drugs given in regimen [76]			
Per added drug	3.5% (-1.4% to 8.4%)	-0.9% (-3.3% to 1.4%)	-2.4% (-7.6% to 2.9%)
Duration of treatment[77]			
Per additional month	0.4% (-0.7% to 1.5%)	0.3% (-0.3% to 0.8%)	0.64% (-0.56% to 1.85%)
Use of second line drugs[78] **(none used was the reference)**			
Any used	**26.9% (10.3% to 43.5%)**	-4.0% (-12.6% to 4.6%)	-9.7% (-42.2% to 22.7%)
Not reported	4.0 % (-25.9% to 33.8%)	**26.6% (11.8% to 41.3%)**	-12.6% (-30.4% to 5.2%)

[75] R^2 value is the proportion of the between-study variance that is explained by the covariates; values closer to 0% indicate that the covariates do not explain much of the variability in the treatment outcome.
[76] Average, or median, number of drugs given in regimen
[77] Average, or median, duration of treatment regimen
[78] Use of any second-line drugs by either all or part of the cohort. This variable had three categorical possibilities: yes, no, or not reported.

Type of drugs used in regimen

	Cumulative Success (95% CI)	**Death during treatment (95% CI)**	**Default (95% CI)**
Number of studies included in the model	29	27	29
R^2	35.98%	-8.04%	1.60%
Use of fluoroquinolone			
Per 1% increase in use	**0.3% (0.1% to 0.5 %)**	0.04% (-0.14% to 0.22%)	-0.07 (-0.21% to 0.06%)
Use of injectable drug			
Per 1% increase in use	0.1 % (-0.1% to 0.4 %)	-0.11% (-0.35% to 0.14%)	-0.10% (-0.21% to 0.06%)
Use of Pyrazinamide			
Per 1% increase in use	-0.2% (-0.4% to 0.1 %)	0.07% (-0.13% to 0.27 %)	-0.09% (-0.25% to 0.06%)

Health system factors

	Cumulative Success (95% CI)	**Death during treatment (95% CI)**	**Default (95% CI)**
Number of studies included in the model	52	52	58
R^2	34.21%	30.09%	-1.88%
Total expenditure on health care			
per $100 US per capita increase	-0.4 % (-0.8 % to 0.05 %)	**0.6 % (0.3% to 0.9%)**	0.17% (-0.22% to 0.55%)
National proportion of acquired MDR-TB among all TB cases			
per 1% increase	**-0.4 % (-0.8% to -0.02 %)**	0.08% (-0.2% to 0.4 %)	0.14 % (-0.24% to 0.53%)
Type of institution providing treatment **(**Regular TB program where only first line drugs were administered was used as the reference)			
Specialized TB referral hospital	**23.4% (8.3% to 38.6%)**	-5.1 % (-15.9% to 5.8%)	-2.7 % (-17.7% to 12.3 %)
Specialized regional MDR-TB program (second-line drugs administered)	**36.5 % (21.0% to 52.0%)**	0.5% (-10.2% to 11.2%)	-12.6% (-28.0% to 2.8 %)
Other	**24.9 % (0.9% to 48.9 %)**	-8.0% (-24.2% to 8.1%)	-1.1% (-24.7% to 22.6%)

Final model of treatment characteristics and health system factors[79]

	Cumulative Success (95% CI)	Death during treatment (95% CI)	Default (95% CI)
Number of studies included in the model	22	21	22
R^2	50.13%	-60.25%	-9.57%
Total expenditure on health care			
per $100 US per capita increase	0.8% (-1.2% to 2.7%)	-0.2% (-1.2% to 0.8%)	-0.1% (-1.7% to 1.6%)
National prevalence of acquired MDR-TB among all TB cases			
per 1% increase	-0.1% (-0.6% to 0.4%0	0.04% (-0.24% to 0.31%)	0.05% (-0.41% to 0.50%)
Use of fluoroquinolone			
Per 1% increase in use	0.2% (-0.1% to 0.5%)	-0.03% (-0.25% to 0.19%)	-0.002% (-0.274% to 0.270%)
Use of injectable drug			
Per 1% increase in use	0.08% (-0.23% to 0.39%)	-0.03% (-0.18% to 0.13%)	-0.07% (-0.34% to 0.20%)
Use of Pyrazinamide			
Per 1% increase in use	-0.11% (-0.35% to 0.13%)	0.03% (-0.10% to 0.15%)	-0.13% (-0.34% to 0.08%)
Number of drugs given in regimen			
Per added drug	2.9% (-4.4% to 10.1%)	-0.9% (-4.8% to 2.9%)	-1.4% (-7.6% to 4.8%)
Duration of treatment			
Per additional month	0.3% (-2.1% to 2.8%)	0.5% (-1.1% to 2.1%)	-0.7% (-2.8% to 1.4%)

[79] Neither population nor disease factors were included because the important covariates, such as smear positive status, were poorly reported across the studies, and the other factors were not suspected to be strong predictors of treatment outcome. The final model includes important predictors from other models: total health care expenditure, prevalence of acquired MDR-TB, use of fluoroquinolones, use of injectable drugs, use of Pyrazinamide, total number of drugs given in the regimen, and duration of treatment. The variables institution, second-line drug use, and type of regimen were dropped from the model due to collinearity.

Appendix 1- Countries with multiple publications that met the inclusion criteria.

To account for duplicated reports of the same cohort, the study with the longest patient enrolment period and post-treatment follow-up period was selected as the most representative; this study appears bolded in the "Overalapping cohorts" column. All of the cohorts that ultimately appear in the systematic review are bolded.

Country	Overlapping cohorts	Articles with unique cohorts	Total number of cohorts for each country
Estonia		• **(Nathanson, 2006)[102]** • **(Lockman, 2001)[80]**	2
France		• **(Flament-Saillour, 1999)[83]** • **(Pretet, 1992)[62]**	2
Hong Kong	• **(Yew, 2003)**[46] & (Espinal, 2000)[48] & (Yew, 2000)[47]		1
Italy	• **(Ferrara, 2005)[85]** & (Centis, 2000)[111] & (Espinal, 2000)[48]		1
Japan		• **(Takeda, 2005)[99]** • **(Shiraishi, 2004)[105]**	2
Latvia	• **(Leimane, 2005)[103]** & (Holtz, 2006)[112] • **(Nathanson, 2006)[102]** & (Riekstina, 2007)[113]		2
Mexico	• **(DeRiemar, 2005)**[90] & (Garcia-Garcia, 2002)[114] & (Garcia-Garcia, 2000)[115]	• **(Perez-Guzman, 2002)[82]**	2
Peru	• **(Nathanson, 2006)[102]** & (Somocurcio, 2007)[116] (subset-surg.) & (Drobac, 2006)[117] (subset-kids) & (Kawai, 2006)[118] (some overlap) • **(Mitnick, 2003)[92]** & (Shin, 2006)[119]	• **(Suarez, 2002)[95]** • **(Espinal, 2000)[48]**	4
Philippines	• **(Tupasi, 2006)[101] &** (Nathanson, 2006)[102]		1
Russia	• **(Migliori, 2002)[36]** & (Espinal, 2000)[48]	• **(Mathew, 2006)[107]** • **(Nathanson, 2006)[102]** • **(Bonnet, 2005)[104]**	3
South Africa		• **(Schaaf, 2003)[70, 97]** • **(van Leuven, 1997)[70]**	3

		• **(Schaaf, 1996)[65]**	
South Korea		• **(Kwon, 2008)[89]** • **(Park, 2004)[98]** • **(Kim, 2001)[67]** • **(Espinal, 2000)[48]** • **(Sung, 1999)[81]** • **(Park, 1998)[77]**	6
Taiwan	• **(Chiang, 2006)[75]** & (Chiang, 2001)[120]	• **(Lee, 1996)[64]**	2
Turkey	• **(Kir, 2006)**[121] & (Torun, 2007)[73] & (Torun, 2005)[53]	• **(Surucuoglu, 2005)[96]** • **(Tahaoglu, 2001)[74]**	3
USA	• **(Chan, 2004)[57]** & (Iseman, 1990)[122] • **(Granich, 2005)[79]** & (Burgos, 2005)[123]	• **(Bloch, 1999)[78]** • **(Goble, 1993)[54]**	4
Florida, USA		• **(Narita, 2001)[84]** • **(Fischl, 1992)[66]**	2
NYC, USA	• **(Li, 2004)[76]** & (Munsiff, 2006)[124]	• **(Park, 1996){Park, 1996 #2405}** • **(Turett, 1995)[71]** • **(Bashar, 2001)[125]**	4
Vietnam		• **(Quy, 2006)[100]** • **(Ward, 2005)[68]** • **(Lan, 2001)[72]**	3

Appendix 2 Data abstraction form

Study ID

Reviewer: Date of Review:

→ Citation Information

Type of study	Corresponding Author:
Primary Author:	Corresponding Author's Email:
Journal:	
Year of Pub.:	Title
Volume:	
Issue:	
Pages:	

→Methods

Lab-confirmed MDR-TB: Yes No Not reported

Method of DST:

Method of culture:

Method of smear:

→ Definition of Outcomes

Cure:

Treatment completed:

Failure:

Relapse (length of follow-up period):

→ Population Characteristics

Country:

Patient recruitment during time period:

→ Population & Disease Characteristics

		Number of Patients (include the **denominator**)
Total enrolled at the beginning	Pulmonary	
	Pulm + Extra-Pulm.	
	Extra-Pulm. only	
Patient-level Characteristics	(of MDR specific cohort only? YES/ NO)	
General	Men:Women distribution	
	Average age	
	% foreign born (HIC)	
Co-morbidity	HIV	
	Diabetes	
Disease	Primary:Acquired	
--prior treatment history	Relapse	
	Return after default	
	Failure	
	% with prior treatment history	
--Severity	Smear status	
	Cavitary disease	
	Bilateral disease	
Resistance pattern	Average number of drugs resistant to (excluding INH & RIF)	
	% resistant to a quinolone?	
	% resistant to PZA	

→ **Treatment Characteristics**

Variable	(circle the correct category)			
Directly observed treatment:	• yes	• no	• partial	• NR
Institution:	• Specialized Hospital (used first and/or second line drugs)	• Specialized national/regional MDR-TB treatment program (used second-line drugs)	• National/Regional TB program (used first-line drugs only)	• Other
Drug Regimen:	• Individualized	• Standardized	• Mixed Individualized & Standardized	• NR
Different treatment subgroups?	• No	• Yes (then include additional columns below)		

Average length of treatment		
Average length of follow-up		
Average number of drugs given in treatment regimen		
Average number of drugs given in treatment regimen to which they are sensitive		
% (num/den) patients receiving a fluoroquinolone?		
% (num/den) patients receiving PZA?		
% (num/den) patients receiving an injectable drug?		
% (num/den) of patients with surgical resection		
Acquired resistance during course of treatment? # of drugs, $1^{st}/2^{nd}$ line?		

→ **Treatment outcomes (circle reported outcomes)**

	Number (%)
Intermediate outcome: sputum culture/smear conversion reported at 2/4/6 mos?	
Cure	
Treatment Complete	
Death (all cause)	
Treatment failure	
Treatment default (include transfer patients if outcome is unknown, and unaccounted patients)	
Adverse reactions causing interruption of treatment, hospitalization, or change in therapy **(termination of therapy?)**	
Miscellaneous (eg. Ongoing treatment)	
Relapse [--DNA fingerprinting? Y/N]	
Censored (lost to follow-up)	

Additional outcomes used in the study:

Confounding variables adjusted for:

QUALITY ASSESSMENT CRITERIA

- Selection Bias

A) Sampling strategy? Is the cohort representative of the target patient population?

Census Convenience Random Not Reported

B) % of patients **during treatment phase** not evaluated because
   i) Default/transfer
   ii) not accounted for
   iii) still on treatment

C) Relapse reported?

Yes No

D) % of cure or treatment complete patients that are followed-up (follow-up: time patient is monitored after treatment completion). Average length of follow-up.

- Information Bias

A) Do DST and culture laboratory methods conform to international standards? (i.e. recognized and referenced method)

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