Title page

Effectiveness and safety of lung resection surgery among patients with pulmonary multi-drug resistant tuberculosis

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Abstract

Background: The effectiveness of medical treatment for multidrug-resistant tuberculosis (MDR-TB) is still lower than the observed with drug-susceptible TB.

Objectives: To estimate the effect of adjunctive pulmonary resection, either of any extent, total lung resection (pneumonectomy) or partial lung resection (lobectomy, segmentectomy, or wedge resection), on treatment success and death during therapy in patients with MDR-TB. We studied the presence of effect modification by the following variables: number of group A drugs, additional fluoroquinolone resistance, level of experience of the center, timing of surgery relative to the culture conversion date, as well as bilateral and/or cavitary disease.

Methods: We conducted an individual patient data systematic review and meta-analysis of cohorts of patients with pulmonary MDR-TB with a known surgical status. Cohort entry was set at the MDR-TB treatment start date. Follow-up continued until an end-of-treatment outcome (cure, completion, failure, death, recurrence, or loss to follow-up [LTFU]). Patients exposed to surgery (cases) were propensity score-matched with subjects treated only medically (controls) that had survived at least the same amount of time as cases at the moment of surgery. Three sources of controls were used: a) Studies performed at centers where no patients were surgically treated (non-surgical studies); b) Studies performed at centers where >=1 patient underwent surgery (surgical studies), and c) The combination of both. We used mixed-effects generalized linear regression to estimate the odds ratio (OR) for treatment success (cure or completion without recurrence) relative to an unsuccessful response (failure, recurrence, or death) and for death relative to remained alive at the end of treatment. We excluded patients LTFU from these analyses. Modification of effect was assessed through stratified analyses.

Results: We evaluated 6,025 patients from 41 studies; 344 of them underwent surgery (70 pneumonectomy, 259 partial lung resection, and 15 with unknown extent). Lung resection of any extent was not significantly associated with the odds of treatment success (controls from all studies: OR, 0.99; 95% confidence interval [CI], 0.63, 1.56; from surgical studies: OR, 1.09, 95% CI, 0.70 1.71; from non-surgical studies: OR, 0.35; 95% CI, 0.09, 1.40), nor with the odds of death (controls from all studies: OR, 0.83; 95% CI, 0.43, 1.61; from surgical studies: OR, 0.79, 95% CI, 0.42, 1.48; from non-surgical studies: OR, 2.50; 95% CI, 0.23, 27.54).

Partial lung resection was non-significantly associated with higher odds of treatment success and lower odds of death (controls from all the studies: OR, 1.30, 95% CI, 0.74, 2.28; OR, 0.54; 95%

CI, 0.22 1.29, respectively; controls from surgical studies: OR, 1.55, 95% CI, 0.89, 2.69; OR, 0.44; 95% CI, 0.19, 1.01, respectively). Conversely, total lung resection was associated with lower odds of treatment success and higher odds of death (controls from all the studies: OR 0.52; 95% CI, 0.19, 1.41; OR, 1.57, 95% CI, 0.39, 6.31, respectively; controls from non-surgical studies: OR 0.19, 95% CI, 0.04, 0.89; OR 5.33, 95% CI, 0.65, 43.71, respectively).

Among patients with fluoroquinolone-resistant MDR-TB, partial lung resection was associated with a significant decrease in the odds of death (controls from all the studies: OR 0.25; 95% CI, 0.06 to 0.99) and a non-significant increase in the odds of treatment success (controls from all the studies: OR, 1.69; 95% CI, 0.77 to 3.72). We also found a non-significant increase in the odds of treatment success (OR, 1.61; 95% CI, 0.84, 3.08) and a non-significant decrease in the odds of death among patients treated with partial lung resection at more experienced centers (OR, 0.51; 95% CI, 0.2, 1.32).

Conclusion: Partial lung resection might be beneficial in treating patients with MDR-TB, particularly when performed at highly experienced centers or when there is additional resistance to fluoroquinolones.

Résumé

Contexte: L'efficacité du traitement médical de la tuberculose multirésistante (MDR-TB) est toujours inférieure à celle observée lors du traitement de la tuberculose pharmacosensible.

Objectifs: Estimer l'effet de la résection pulmonaire d'appoint, qu'il s'agisse de toute chirurgie de résection, ou par étendue, de la résection pulmonaire totale (pneumonectomie) ou de la résection pulmonaire partielle (lobectomie, segmentectomie ou résection cunéiforme), sur le succès du traitement (guérison ou achèvement) et le décès pendant le traitement chez des patients de tout âge, sexe et contexte atteints de TB mono-résistante à la rifampine ou de TB-MDR (ci-après tous deux appelés TB-MDR).

Méthodes: Nous avons mené une revue systématique des données de patients individuels et une méta-analyse de cohortes de patients atteints de TB-MDR pulmonaire avec un statut chirurgical connu. L'entrée de la cohorte a été fixée à la date de début du traitement de la TB-MR. Le suivi s'est poursuivi jusqu'à un résultat de fin de traitement (guérison, achèvement, échec, décès, récidive ou perte de suivi [LTFU]). Les patients exposés à la chirurgie (cas) ont été appariés par score de propension à des sujets traités uniquement médicalement (contrôles) qui avaient survécu au moins le même temps que les cas au moment de la chirurgie. Trois sources différentes de contrôles ont été utilisées : a) études réalisées dans des centres où aucun patient TB-MDR n'a été traité chirurgicalement (études non chirurgicales) ; b) Des études réalisées dans des centres où >=1 patient a subi une intervention chirurgicale pour une TB-MR (études chirurgicales), et c) La combinaison des deux types d'études. Nous avons utilisé une régression linéaire généralisée à effets mixtes pour estimer l'odds ratio (OR) pour le succès du traitement (guérison ou achèvement sans récidive) par rapport à une réponse infructueuse (échec, récidive ou décès) et l'OR pour le décès par rapport au fait d'être en vie au fin du traitement (succès ou échec du traitement). Nous avons exclu les patients LTFU de ces analyses.

Résultats: Nous avons évalué 6 025 patients de 41 études ; 344 d'entre eux ont été opérés (70 résection pulmonaire totale, 259 résection pulmonaire partielle et 15 résection d'étendue inconnue). Quelle que soit la source des contrôles, la résection pulmonaire de quelque étendue que ce soit n'était pas significativement associée aux chances du succès du traitement (contrôles de toutes les études : RC : 0,99 ; intervalle de confiance à 95 % [IC], 0,63, 1,56 ; à partir des études chirurgicales : RC, 1,09, IC à 95 %, 0,70 1,71 ; à partir d'études non chirurgicales : RC, 0,35 ; IC

à 95 %, 0,09, 1,40) ni avec la probabilité de décès (contrôles de toutes les études : RC : 0,83 ; IC à 95 %, 0,43, 1,61 ; à partir d'études chirurgicales : OR, 0,79, IC à 95 %, 0,42, 1,48 ; à partir d'études non chirurgicales : OR, 2,50 ; IC à 95 %, 0,23, 27,54).

D'un autre côté, la résection pulmonaire partielle n'était pas associée de manière significative à des chances plus élevées du succès du traitement et à des probabilités de décès plus faibles (contrôles de toutes les études : RC, 1,30, IC à 95 % : 0,74, 2,28 ; RC, 0,54 ; IC à 95 % , 0,22 1,29, respectivement ; contrôles issus d'études chirurgicales : OR, 1,55, IC à 95 %, 0,89, 2,69 ; OR, 0,44 ; IC à 95 %, 0,19, 1,01, respectivement). À l'inverse, la résection pulmonaire totale était liée à des probabilités plus faibles du succès du traitement et à des probabilités de décès plus élevées (contrôles de toutes les études : RC 0,52 ; IC à 95 % : 0,19 ; 1,41 ; RC, 1,57, IC à 95 %, 0,39, 6,31, respectivement ; témoins issus d'études non chirurgicales : RC 0,19, IC à 95 %, 0,04, 0,89 ; RC 5,33, IC à 95 %, 0,65, 43,71, respectivement).

Parmi les patients atteints de TB-MR résistante aux fluoroquinolones, la résection pulmonaire partielle a été associée à une diminution significative du risque de décès (contrôles de toutes les études : RC 0,25 ; IC à 95 % : 0,06 à 0,99) et à une augmentation non significative des chances du succès du traitement (contrôles de toutes les études : OR, 1,69 ; IC à 95 %, 0,77 à 3,72). De plus, il y avait des preuves de meilleurs résultats lors de la réalisation d'une résection pulmonaire partielle dans des centres plus expérimentés en presence de maladie cavitaire.

Conclusion: La résection pulmonaire partielle pourrait être bénéfique dans le traitement des patients atteints de TB-RR ou de TB-MDR, en particulier lorsqu'elle est réalisée dans des centres hautement expérimentés ou en présence d'une résistance supplémentaire aux fluoroquinolones ou d'une maladie cavitaire.

Contribution of Authors

I, Edgar Ortiz-Brizuela, participated in the design of this study by formulating the research question and drafting the analysis protocol. Then, I contributed to the acquisition of data by writing to the authors of the original studies to gather additional information relevant to this study. Next, under the guidance of my supervisors, I performed all the analyses and interpreted their results. Finally, all the thesis components were written by me and edited by my thesis supervisor and supervisory committee.

Dr. Dick Menzies conceived and led the Individual Patient Data Meta-analysis of Multi-Drug Resistant Tuberculosis used for the current study. Dr. Menzies supervised all the thesis phases, including study design, analysis, interpretation of the results, and writing.

Dr. Andrea Benedetti provided feedback on the study protocol, co-supervised the analysis, and interpreted the results.

Dr. Jonathon Campbell participated in the original data acquisition, checked analytic code in R, and offered comments in the planning, data analysis, and interpretation of the results.

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List of Abbreviations and Acronyms

ABBREVIATIONS	MEANING
AFB	Acid-fast bacilli
aOR	Adjusted odds ratio
BDQ	Bedaquiline
BMI	Body mass index
CFZ	Clofazimine
DM	Diabetes mellitus
DOT	Directly observed therapy
DR-TB	Drug-resistant tuberculosis
FQ	Fluoroquinolones
HIV	Human Immunodeficiency Virus
IPD MA	Individual patient data meta-analysis
IQR	Interquartile range
LTFU	Loss to follow-up
LZD	Linezolid
MDR-TB	Multidrug-resistant tuberculosis
NA	Not available
OR	Odds ratio
PAS	Para-Amino Salicylic Acid
PHR	Pooled hazard ratio
PRE-XDR-TB	Pre-extensively drug-resistant tuberculosis
RR-TB	Rifampin mono-resistant tuberculosis
SD	Standard deviation
SMD	Standardized mean difference
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

Chapter 1: Introduction

The morbidity, mortality, and economic consequences of drug-resistant TB (DR-TB) are considered catastrophic (Friedman et al., 2020a). It has been estimated that nearly a third of the worldwide deaths related to antimicrobial resistance is caused by TB (Dheda et al., 2019). Moreover, it has been predicted that DR-TB may cause losses of up to $16.7 trillion US dollars globally in the next 30 years (Dheda et al., 2019). According to the World Health Organization (WHO), in 2019, there were 10.0 million (range, 8.9–11.0 million) incident cases of tuberculosis (TB) worldwide (WHO, 2020d). Of them, 465,000 (range, 400,000–535,000) were resistant to rifampin, and 78% of these also presented resistance to isoniazid (i.e., multidrug-resistant TB [MDR-TB]).

In 2018, an individual patient data meta-analysis (IPD MA) showed that the use of linezolid (LZD), later generation fluoroquinolones (FQ), and bedaquiline (BDQ) were associated with expected reductions in mortality of 20%, 6-7%, and 14% respectively (Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment et al., 2018). In the same analysis, the use of specific older therapies such as injectable drugs was associated with worse outcomes (Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment et al., 2018). Based on this evidence, in 2019, the WHO updated its MDR-TB treatment guidelines to remove the injectables as core agents and replace them with BDQ, clofazimine (CFZ), and LZD (WHO, 2020c).

Although the new and repurposed drugs are expected to improve MDR-TB outcomes, these medications are not widely available, and their efficacy is still lower than the observed with drug-susceptible TB (Dheda et al., 2019; Mondoni et al., 2020). Therefore, adjunctive treatments for MDR-TB are continuously evaluated worldwide. In 2016, Fox et al. conducted an IPD MA of studies published before 2008 assessing the effect of adjunctive pulmonary resection surgery when treating MDR-TB (Fox et al., 2016). In this analysis, partial lung resection was associated with higher odds of treatment success (adjusted odds ratio [aOR], 3.0 [95% CI, 1.5 to 5.9]) (Fox et al., 2016).

Given that Fox et al. study was performed before the new and more effective agents were in use, a re-evaluation of the effectiveness of pulmonary resection surgery as adjunctive therapy for MDR-TB is required.

Organization of the Thesis

- First, we summarize the current recommendations for treating MDR-TB, emphasizing the role of adjunctive pulmonary resection surgery and the medical regimens available.
- Second, we list the primary and secondary objectives of this study.
- Third, we outline the statistical and epidemiological research methods used in this thesis.
- Fourth, we describe our results and discuss our findings.
- Fifth, we provide a thesis summary.
- Finally, a list of references is provided.

Chapter 2: Literature Review

Overview of Drug Resistant-TB

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, one of the top causes of death worldwide (WHO, 2020d). When TB is drug-susceptible, the first line of treatment is a combination of isoniazid, rifampin, pyrazinamide, and ethambutol given for six months. This regimen has been associated with treatment success rates near 85% (WHO, 2020d). However, the prognosis worsens considerably when resistance to the core agents is present. For instance, cure rates fall to 57% with isoniazid and rifampin resistant TB (see below) (WHO, 2020d).

Drug resistance in M. tuberculosis (DR-TB) stems from spontaneous chromosomal gene mutations (Almeida Da Silva & Palomino, 2011; Dheda et al., 2017; Pai et al., 2016). Therefore, its diagnosis requires either its detection through genotypic techniques (sequencing or not sequencing) or culture-based phenotypic tests (Cabibbe et al., 2017; WHO, 2020a). When there is resistance to one antituberculosis drug, TB is classified as mono-resistant TB (WHO, 2020d). On the other hand, multidrug-resistant TB (MDR-TB) is diagnosed when M. tuberculosis is resistant to isoniazid and rifampin (WHO, 2020a). If an MDR-TB isolate is also resistant to fluoroquinolones, the patient is categorized as having pre-extensively drug-resistant (pre-XDR-TB) and, if the isolate is also resistant to bedaquiline or linezolid, as extensively drug-resistant TB (XDR-TB) (WHO, 2020a).

DR-TB may be directly acquired from other patients (i.e., transmitted DR-TB) or produced when treating drug-susceptible TB (i.e., acquired DR-TB) (Shah et al., 2017). Several mycobacterial, socio-economical, and individual factors have been related to an increased risk of acquired DR-TB (Dheda et al., 2017). The most consistently reported is a history of incomplete or inappropriate treatment (Pradipta et al., 2018). Hence, conditions related to low treatment adherence, such as no healthcare access or weak social support networks, increase people's vulnerability to DR-TB (Pradipta et al., 2018). Although acquired drug resistance is considered the most frequent etiology of DR-TB, transmitted resistance may also produce a significant number of cases in some settings (Shah et al., 2017).

The Challenge of Rifampin-Resistant-TB and Multi-Drug Resistant TB

Both isoniazid and rifampin are critical for the first-line treatment of drug-susceptible TB (WHO, 2020b), however, rifampin holds the most potent sterilizing activity (Mitnick et al., 2009). Therefore, the effects of isoniazid-monoresistance on prognosis are very different from the observed with rifampin resistance, whether it is mono-resistance (RR-TB) or MDR-TB (WHO, 2020b). According to the WHO, of 131,113 patients from 146 countries who started treatment for MDR-TB in 2017, only 57% completed therapy or were cured, while 7% failed, 15% died, and 21% were lost to follow-up (WHO, 2020d). Outcomes are even worse in the presence of additional drug resistance. For example, among 11,210 patients with pre-XDR-TB, only 47% were cured or completed treatment, while 24% died, 11% failed therapy, and 18% were lost to follow-up (WHO, 2020d). In contrast, in 2018, patients with new and relapse TB cases with possible drug-susceptible TB had treatment success rates of ~85% worldwide (WHO, 2020d), which are similar to the success rates observed with isoniazid-mono resistant TB (Gegia et al., 2017).

Treatment of RR-TB and MDR-TB

Several factors should be considered when planning therapy for patients with RR-TB and MDR-TB (Table 1). First, drug susceptibility tests are critical when designing their treatment regimens; unfortunately, they are often reserved for cases with a high pre-test probability of resistance to other drugs or for surveillance purposes (Dheda et al., 2017). Second, healthcare providers should carefully assess patients' comorbidities, age, and disease severity (Friedman et al., 2020a). Finally, the need for psychological assistance, adherence support strategies, and financial aid must also be evaluated (Dheda et al., 2017; Dheda et al., 2019; Friedman et al., 2020a).

Concerning the drug susceptibility tests, it is also important to consider their reliability, based on the reproducibility of results using well established methodologies (WHO, 2018a, 2018b, 2020b). WHO considers reliable non-sequencing genotypic tests for rifampin, isoniazid, fluoroquinolones, and second-line injectables (Cabibbe et al., 2017; WHO, 2020b). Likewise, WHO deems accurate phenotypic tests for isoniazid, rifampin, fluoroquinolones, bedaquiline, linezolid, clofazimine, delamanid, and pyrazinamide. However, phenotypic tests for cycloserine, terizidone, p-aminosalicylic acid, ethambutol, ethionamide, prothionamide, imipenem, and meropenem are currently not recognized as reliable by the WHO (WHO, 2020b).

Treatment regimens for MDR-TB

Two regimens are currently recommended for treating MDR-TB (WHO, 2020b). The first and preferred is the "shorter all-oral bedaquiline-containing regimen," which has a total length of 9-12 months. Patients receive seven drugs for 4-6 months (i.e., bedaquiline, levofloxacin or moxifloxacin, cefazoline, pyrazinamide, ethambutol, ethionamide, and high doses of isoniazid), followed by 5 months with levofloxacin or moxifloxacin, cefazoline, pyrazinamide, and ethambutol (WHO, 2020b). Nevertheless, patients with one or more of the following conditions are not considered candidates for this treatment:

- **a)** Previous exposure to second-line antituberculosis drugs (>= 1 month),
- **b)** Resistance to fluoroquinolones,
- **c)** Extensive or severe extrapulmonary disease, defined as:
    - i. Adults with bilateral cavitary disease or extensive lung damage on chest radiography,
    - ii. Children with cavities or bilateral disease,
    - iii. Miliary or meningeal TB,
    - iv. Children with extrapulmonary TB (excluding lymphadenopathy),
- **d)** Pregnancy.
- **e)** Children aged < 6 years

For those not considered candidates for the shorter all-oral regimen, an "individualized longer regimen" is recommended (WHO, 2020b). The latter should include 4-5 likely effective drugs, ideally with a backbone of linezolid, fluoroquinolones, and bedaquiline (group A drugs), and complemented with cycloserine or clofazimine (group B drugs) (WHO, 2020b). If needed, group C medications can be used to complete the regimen (i.e., ethambutol, delamanid, pyrazinamide, carbapenems, amikacin, ethionamide, p-aminosalicylic acid) (WHO, 2020b). This treatment has a recommended length of 18-20 months (15–17 months after culture conversion), but its duration can be modified based on treatment response (WHO, 2020b).

Table 1. Tuberculosis prognostic factors.

Mycobacterial factors	Host factors	Program-related factors and other factors
Mycobacterial load	HIV coinfection	Access to effective drugs
Drug-specific resistance profile and, consequently, the number of effective drugs	Diabetes mellitus	Adherence-promoting measures
	Undernutrition (Sinha et al., 2019)	Pill burden (HIV and tuberculosis drugs)
	History of prior tuberculosis	Drug-related adverse events and toxicity
	Radiological disease burden or disease extent (including disseminated tuberculosis)	Social support, including food security, access to shelter
	Substance and alcohol abuse	

Modified from Dheda K et al. (Dheda et al., 2019)

Abbreviations: BMI, body mass index; HIV, Human immunodeficiency virus.

Pulmonary resection surgery for MDR-TB

Adjunctive pulmonary resection surgery may help improve MDR-TB treatment outcomes. This procedure has been considered an option for TB treatment since the 19th century; however, a renewed interest in its use lately emerged due to the increasing rates of DR-TB (Friedman et al., 2020a; Mondoni et al., 2020). The primary purpose of lung resection is to remove as much diseased tissue as possible while preserving functionality (Calligaro et al., 2014; Friedman et al., 2020b).

Up to today, no clinical trials have tested pulmonary resection surgery for MDR-TB. Consequently, current guidelines are based on observational studies and expert opinions. WHO suggests considering adjunctive partial lung resection (i.e., lobectomy or wedge resection) for selected patients with MDR-TB in sites having appropriate surgical facilities and experienced surgeons (conditional recommendation with a very low certainty in evidence) (WHO, 2020b).

Pulmonary resection surgery is usually performed after 3-6 months of medical therapy in patients with localized disease (unilateral or apical bilateral), a proper cardiorespiratory reserve, and a high risk of recurrence based on the drug-resistance profile, a persistent sputum positivity, or clinical progression (Borisov et al., 2019; Calligaro et al., 2014; Dheda et al., 2017; Kempker et al., 2012). This procedure has <5% mortality and complication rates of 12-30% (e.g., prolonged air leak, empyema, bronchopleural fistula, bleeding, respiratory insufficiency, and lengthy hospital admissions) (Borisov et al., 2019; Dheda et al., 2017; Kempker et al., 2012).

Many systematic reviews and aggregate data meta-analyses of observational studies have assessed the effectiveness of pulmonary resection surgery for MDR-TB (Table 2) (Fox et al., 2016; Harris et al., 2016; Johnston et al., 2009; Marrone et al., 2013; Roh et al., 2017; Xu et al., 2011). However, their results may have been biased by the presence of confounding by indication or contraindication, and selection bias (Fox et al., 2016; Harris et al., 2016; Riley et al., 2010; Roh et al., 2017). A methodological approach that can better account for these problems is an induvial patient data systematic review and meta-analysis (IPD MA). This study design allows summarizing information from several studies while adjusting for important confounders and utilizing other methodological tools such as subgroup analysis (Fox et al., 2016; Riley et al., 2010).

In 2016, Fox et al. evaluated the effectiveness of pulmonary resection surgery for MDR-TB through an IPD MA which included studies published before 2008 (Fox et al., 2016). Study

populations from three previous meta-analyses were assessed (Ackcakir, 2010; Johnston et al., 2009; Orenstein et al., 2009). They included original cohorts reporting treatment outcomes of adults with culture confirmed MDR-TB patients, published between 1965 and 2008. Authors excluded case series of surgical patients (Johnston et al., 2009), case series of extensively drug-resistant tuberculosis (Ackcakir, 2010; Orenstein et al., 2009), and case series of extrapulmonary tuberculosis (Ackcakir, 2010). After adjusting for several variables (i.e., sex, age, disease severity, history of TB or MDR-TB, the number of antibiotics used in the intensive phase, and the total length of therapy through propensity score-based matching), segmentectomy or lobectomy was associated with higher odds of treatment success (adjusted odds ratio [aOR], 3.0; 95% CI, 1.5 to 5.9) while pneumonectomy was not beneficial (aOR, 1.1; 95% CI, 0.6-2.3). Moreover, performing surgery after culture conversion was associated with higher odds of treatment success, even after controlling for the length of therapy (aOR, 2.6; 95% CI, 0.9 to 7.1).

In 2019, Borisov et al. described the outcomes of a multinational retrospective cohort of 55 patients with MDR-TB who underwent pulmonary resection surgery adjunctive to bedaquiline-containing regimens (no control group was reported) (Borisov et al., 2019). After a median of 18 months of medical treatment (interquartile range [IQR], 13-28), 38 (65.5%) patients had a successful outcome (36 were cured and 2 completed therapy), while 11 (20%) failed , 1 (1.8%) was lost to follow-up, and 5 (9.1%) were still on treatment (Borisov et al., 2019).

Since the previous studies were performed before the change in the MDR-TB treatment recommendations (Dheda et al., 2019; Fox et al., 2016) or did not include a comparison group (Borisov et al., 2019), a re-evaluation of the effectiveness of pulmonary resection surgery as an adjunctive to medical therapies including new and repurposed drugs is urgently needed.

Table 2. Summary of previous systematic reviews assessing the effect of pulmonary resection surgery for MDR-TB on treatment outcomes.

First author / Meta-analysis type	Number of included studies / Inclusion criteria	Sample size (# of surgeries)	Primary outcome (s)	Measures of effect (95% CI)	Limitations
Roh HF (Roh et al., 2017) / Aggregate	n = 6. Inclusion criteria: Case-control and cohort studies with >=10 patients evaluating pulmonary resection in MDR-TB	n =331 (NA)	Overall survival	Surgery: pHR, 0.68 (0.44–1.07)	Unknown surgery types, confounding, no effect modification assessment.
Fox GJ (Fox et al., 2016) / IPD	n = 26. Inclusion criteria: confirmed MDR-TB and known surgical status	n = 6,431 (478)*	Cure or completion vs. failure, recurrence or death	PLR: aOR, 3.0 (1.5–5.9) TLR: aOR, 1.1 (0.6–2.3)	PLHIV excluded; effect of current treatment guidelines not evaluated.
Harris RC (Harris et al., 2016) / Aggregate	n = 14. Inclusion criteria: confirmed MDR or XDR-TB and assessing the effect of surgery on treatment outcomes (>=10 patients)	n = 2459 (453)	Success (cure or completion)	Surgery: pOR 2.62 (1.94–3.54)	Unknown surgery types, confounding, no effect modification assessment.

First author / Meta-analysis type (continued)	Number of included studies / Inclusion criteria (continued)	Sample size (# of surgeries) (continued)	Primary outcome (s) (continued)	Measures of effect (95% CI) (continued)	Limitations (continued)
Marrone MT (Marrone et al., 2013) / Aggregate	n = 47. Inclusion criteria: Studies reporting surgical outcomes in MDR- and XDR-TB patients (>=10 patients).	n = 6,712 (706)	Success (cure or completion) vs. Failure (Failure, default, or death)	Surgery: pOR 2.24 (1.68–2.97)	Unknown surgery types, confounding.
Xu HB (Xu et al., 2011) / Aggregate	n = 15. Inclusion criteria: confirmed MDR-TB and reported outcomes specified by culture endpoints according to WHO classifications	n = 949 (949)	Success (cure or completion)	Surgery: success rates 84% (78–89%)	No comparison groups.
Johnston JC / Aggregate (Johnston et al., 2009)	n = 36. Inclusion criteria: Culture confirmed MDR-TB with >=10 patients	n = 6,359 (NA)	Success (cure or completion) vs. Failure, recurrence, death, transfer	Surgery: pOR 1.91 (1.44–2.53)	No distinction types of surgery

Abbreviations: aOR, adjusted Odds Ratio; NA, not available; pHR, pooled hazard ratio; pOR, pooled Odds Ratio; PLR, partial-lung resection; TLR, total lung resection; XDR-TB, extensively drug-resistant tuberculosis.

* Total-lung resections: n = 117, Partial-lung resections: n = 229; non-specified, n = 132.

Chapter 3: Objectives

Primary objective: To estimate the effect of adjunctive pulmonary resection surgery, either any resectional surgery, or by extent, total lung resection (i.e., pneumonectomy) or partial lung resection (i.e., lobectomy, segmentectomy, or wedge resection), on treatment success (i.e., cure or completion) and death during therapy (as a safety outcome)[1] in patients with RR-TB or MDR-TB (hereafter both referred to as MDR-TB) of any age, sex, and setting[2].

Secondary objectives: To assess for modification of the effect of pulmonary resection surgery of any extent and of partial lung resection on treatment outcomes (i.e., either success or death) across levels of the following variables[3]:

i. **Number of drugs within group A**: we stratified the analysis in patients receiving 2-3 drugs within WHO group A and those receiving 0-1.
ii. **Additional fluoroquinolone-resistance**: we stratified the analysis in fluoroquinolone-susceptible and fluoroquinolone-resistant MDR-TB.
iii. **Timing of surgery relative to the culture conversion date**: we stratified the analysis in pulmonary resection surgery performed before and after the culture conversion date.
iv. **Volume of surgeries performed at each center**: we stratified the analysis in more and less experienced centers. A center was considered more experienced when they performed more surgeries than the average across the studies that reported at least one surgery for MDR-TB. Otherwise, the center was considered less experienced.
v. **Disease location**: we stratified the analysis in patients with unilateral and bilateral pulmonary disease.
vi. **Presence of lung cavities**: we stratified the analysis in patients with and without cavitary pulmonary disease.

Notes:

1. No other safety outcome was assessed since this information was not available.
2. Complete definitions are provided in Chapter 4 (Definitions of the Exposure, Controls, and Outcomes).
3. Complete definitions are provided in Chapter 4 (Definitions of the Potential Effect Modifiers).

Chapter 4: Methods

Study Design and Source Population

We conducted an individual patient data systematic review and meta-analysis (IPD MA) to estimate the effect of adjunctive pulmonary resection surgery on MDR-TB treatment outcomes. For this analysis, we used an existing database whose original study examined the effect of medical therapy on outcomes (Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment et al., 2018). This IPD included cohorts of patients aged >=12 years with bacteriologically confirmed MDR-TB published between January 1, 2009, and September 15, 2015. Studies only available as grey literature or using regimens with < 12 months of length were excluded[1]. The variables available in this dataset are shown in Table 3. As explained below, information from the previous study (Fox et al., 2016) was excluded from this analysis.

Definition of the Study Cohort

Our study cohort included patients with pulmonary MDR-TB and a known surgical status. Patients lost to follow-up or transferred without a known outcome were excluded from the primary analysis. We also excluded patients if authors from the original studies did not agree to participate or if there was overlap with the study population analyzed previously (Fox et al., 2016) [2]. Cohort entry was set at the MDR-TB treatment start date. Furthermore, to avoid immortal time bias, we eliminated patients that underwent surgery before cohort entry (i.e., defined as <1 month of treatment start). Patients who experienced pulmonary resection surgery after three years of cohort entry were also eliminated since these surgeries were more likely to treat TB complications. Follow-up continued until an end-of-treatment outcome was registered (see below).

Notes:

1. Further details on the sources of information, search strategy, and data collection processes can be found elsewhere (Ahuja et al., 2012; Bastos et al., 2017; Collaborative Group for the Meta-Analysis of Individual Patient Data in et al., 2018).
2. Study populations are described in the Supplementary Tables 1 and 2 (**Appendix**).

Table 3. Variables included in the original dataset from the individual-patient data systematic review of patients with MDR-TB.

Baseline variables
Identification, country, year when treatment started, age at treatment start, sex, weight, height, body mass index, smoking status (ever / never), alcohol abuse, HIV status, antiretroviral treatment status, diabetes mellitus, previous tuberculosis, site (pulmonary or extrapulmonary), cavitary or bilateral pulmonary disease on chest x-rays, sputum smear status (positive or negative).
Pre-treatment drug susceptibility testing variables
Drug susceptibility testing results (resistant or susceptible).*
Treatment variables
Drugs used in the intensive or continuation phase** (>1 month), pulmonary resection surgery, type of pulmonary resection surgery (i.e., total vs. partial vs. not-specified), date of surgery, date of treatment start, date of the end of follow-up, history of hospitalization and length, directly observed therapy, planned and the actual number of months treated, time to culture conversion (months), treatment outcomes (cure, complete, failure, death, lost to follow-up, transfer), and recurrence.

*Drugs assessed: Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, rifabutin, amikacin, capreomycin, kanamycin, ofloxacin, ciprofloxacin, moxifloxacin, levofloxacin, ethionamide, prothionamide, cycloserine, PAS, linezolid, clofazimine, clarithromycin, high-dose isoniazid.

**Drugs included: isoniazid, high-dose isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, rifabutin, amikacin, capreomycin, kanamycin, ofloxacin, ciprofloxacin, moxifloxacin, levofloxacin, gatifloxacin, ethionamide, prothionamide, cycloserine, terizidone, PAS, linezolid, clofazimine, amoxicillin-clavulanic acid, thioacetazone, clarithromycin, imipenem-cilastatin, meropenem, bedaquiline, delamanid.

Definitions of the Exposure, Controls, and Outcomes

Exposure (cases): The exposure of interest was pulmonary resection surgery when used as an adjunctive treatment for MDR-TB. We classified surgeries according to their extent into total lung resection when patients underwent pneumonectomy and partial lung resection when treated with either a lobectomy, segmentectomy, or wedge resection.

Controls: Patients treated only medically were defined as controls. Some of them were treated at centers that do not perform pulmonary resection surgery for MDR-TB at all. However, we did not exclude them since they might have been considered candidates for surgery had this resource been available. To account for their differences, we classified them according to their source populations as follows (separate analyses are presented): a) Studies performed at centers where no MDR-TB patients were surgically treated (non-surgical studies); b) Studies performed at centers where >=1 patient underwent surgery for MDR-TB (surgical studies), and c) The combination of both.

Outcomes: Our primary outcome was the end-of-treatment response according to standardized definitions (Table 4) (Laserson et al., 2005; WHO, 2013). First, we compared the number of patients with treatment success (i.e., cure or completion without recurrence) against those with unsuccessful treatment response (i.e., failure, death, or recurrence). Second, we compared the number of patients who died during therapy with those we knew alive at the end-of-treatment (i.e., cured, completed treatment, or failed). Finally, two additional sensitivity analyses were done where patients lost-to-follow-up or transferred were classified as having a bad outcome (an unsuccessful treatment response for the treatment success outcome and as dead for the death outcome).

Definitions of the Potential Effect Modifiers

a) Number of drugs within group A:

Patients were stratified into those receiving 2-3 vs. 0-1 drugs within group A (WHO, 2020b).

Table 4. Standardized definitions of end-of-treatment outcomes for MDR-TB according to the WHO and Laserson et al. Definitions specifc to this study are also presented.

Outcome	Definitions
Cure	**Laserson**: an MDR-TB patient who has completed treatment according to country protocol and has been consistently culture-negative (with at least five results) for the final 12 months of treatment. **WHO 2013**: treatment completed as recommended by the national policy without failure. Moreover, three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	An MDR-TB patient who has completed treatment according to country protocol but does not meet the definition for cure or treatment failure due to lack of bacteriologic results.
Failure	**Laserson**: treatment is considered as failed if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive, or if a clinical decision has been made to terminate treatment early due to poor response or adverse events. **WHO 2013**: treatment terminated or need for permanent change of at least 2 anti-tuberculosis drugs because of lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions.
Death	An MDR-TB patient that dies for any reason during MDR-TB treatment.
Acquired Drug Resistance	Defined as new resistance on drug-susceptibility testing performed after at least 3 months of MDR therapy compared to baseline or pre-MDR treatment.

Outcome (continued)	Definitions (continued)
Recurrence	An MDR-TB patient who was declared cured or treatment completed at the end of the MDR-TB treatment and was diagnosed with a recurrent episode of MDR-TB after the previous episode (in the primary analyses, failure and recurrence will be considered together). If information is available to distinguish reinfection from recurrence (i.e., using molecular markers), reinfections will be excluded, and only true recurrences will be counted. However, in the great majority of datasets, this information is not available – in these, all recurrences will be counted.
Culture Conversion	Where culture is available, and a patient begins treatment **culture positive;** a patient will be considered to have converted when two consecutive sputum cultures at least 28 days apart are **negative**; the culture conversion date will be the date of sample collection of the earlier of the two negative cultures. If a patient begins treatment as **culture-negative** and has $\leqslant$1 positive sputum culture in the first three months, they will be excluded from any analysis of culture conversion. If a patient's final culture is negative but is not preceded by another negative culture, the culture conversion date is considered missing. In other cases, the patient will be considered not to have converted.
Lost to follow-up	Includes dropout, patient decision to stop therapy, or transferred out without known outcome.

Abbreviations: MDR-TB, multi-drug resistant tuberculosis.

b) Additional fluoroquinolone-resistance:

We stratified the analysis in patients with MDR-TB with and without additional resistance to fluoroquinolones (i.e., fluoroquinolone-resistant and fluoroquinolone-susceptible MDR-TB, respectively). Given that drug-susceptibility testing results for later generation fluoroquinolones were not available for all cases in the study population, we hierarchically defined fluoroquinolone-susceptibility using the information from all fluoroquinolones as follows (percentage of missingness: levofloxacin, 85.9%; moxifloxacin, 82.4%; ciprofloxacin, 67.4%; ofloxacin, 15%).

i. First, we used levofloxacin and moxifloxacin drug-susceptibility data:
   a. If resistance to either moxifloxacin or levofloxacin was detected, we considered the MDR-TB isolate as fluoroquinolone-resistant.
   b. If at least one was susceptible while the other was not resistant (either missing or susceptible), we classified it as fluoroquinolone-susceptible.

ii. Second, if both moxifloxacin and levofloxacin were missing, then we used ciprofloxacin and ofloxacin data:
   a. If resistance to either ciprofloxacin or ofloxacin was detected, we considered an MDR-TB isolate as fluoroquinolone-resistant.
   a. If at least one was susceptible (while the other was either missing or susceptible), we classified it as fluoroquinolone-susceptible.

iii. Finally, if all the results from these drugs were missing, we classified them as not available. Then, we used multiple imputation methods on the resulting variable (see below).

c) Timing of surgery relative to the culture conversion date:

A pulmonary-resection surgery was classified as performed before culture conversion if the date of surgery was previous to the culture conversion date (for definition, refer to Table 4). Otherwise, it was classified as performed after culture conversion.

d) Volume of surgeries performed at each center:

A center was considered more experienced if they performed more surgeries than the mean across all surgical studies. Otherwise, centers were considered as less experienced.

e and d) Bilateral and cavitary pulmonary disease:

TB was classified as bilateral when both lungs were affected on chest-x-rays. Moreover, TB was classified as cavitary when there were one or more lung cavities on a chest-x-ray.

Definition of the Number of Effective Drugs

The number of effective drugs and their class is an important potential confounder of the relationship between pulmonary resection surgery and treatment outcomes. WHO defines a drug as effective if administered to patients with an *M. tuberculosis* isolate susceptible to the drug of interest (WHO, 2020b). However, given that this information is often missing, to classify a drug as effective, first, we imputed drug-susceptibility data in a group-wise manner as follows:

Group A drugs:

Most linezolid and bedaquiline drug-susceptibility information was missing in the study population (90.5 and 100%, respectively). However, these drugs were infrequently used to treat MDR-TB before the study period, and resistance was rarely reported (Khoshnood et al., 2021; Lee et al., 2012; Richter et al., 2007). Therefore, we considered all isolates as linezolid- and bedaquiline-susceptible unless there was evidence of resistance. On the contrary, fluoroquinolones have been widely used to treat MDR-TB, and their resistance rates are relatively high (Dalton et al., 2012). Hence, we used multiple imputation methods to deal with missing fluoroquinolone susceptibility data (5.2% of missingness in the study population)[1].

Group B drugs:

Clofazimine and cycloserine susceptibility results were missing in 98.7% and 53.3% of the study population, respectively. However, these drugs were also infrequently used before the study period (Gopal et al., 2013; Wu et al., 2019). Consequently, we considered all isolates clofazimine- and cycloserine-susceptible unless there was evidence of resistance.

Notes:

1) Further detail is provided in the Data Analysis section in this Chapter.

Group C drugs:

In the study population, ethambutol susceptibility results were missing in 3.6%, delamanid in 100%, pyrazinamide in 31.3%, carbapenems in 100%, amikacin in 37.7%, ethionamide/prothionamide in 20.4%, and p-aminosalicylic acid in 30.9%. Since most of them have been in use for a long time, we only imputed them if < 50% missing. Exceptions to this rule were carbapenems (i.e., imipenem and meropenem) and delamanid. Given that these drugs were rarely used for MDR-TB before the study period and resistance was uncommon, we considered all isolates carbapenems- and delamanid-susceptible (Jaganath et al., 2016; Nguyen et al., 2020).

Number of effective Drugs:

We calculated the number of effective drugs (group-wise) after imputing drug-susceptibility information. We considered a drug as effective when given >=1 month with no evidence of resistance. Additional drug-specific requirements were needed in some cases:

i. **Fluoroquinolones**: only levofloxacin, moxifloxacin, ofloxacin, and gatifloxacin were considered potentially effective (mutually exclusive).
ii. **Cycloserine/terizidone** were considered effective (mutually exclusive) if there was no resistance to any of them.
iii. **Streptomycin** was considered effective according to the WHO criteria (i.e., not given with amikacin and with no evidence of resistance) (WHO, 2020b).
iv. **Para-amino salicylic acid** and **ethionamide/prothionamide** (mutually exclusive) were also considered effective according to the WHO criteria (i.e., if not given with bedaquiline, linezolid, clofazimine, or delamanid) (WHO, 2020b).
v. **Carbapenems** were considered effective if co-administered with clavulanate.

Finally, we did not considered effective drugs not recommended by the WHO to treat MDR-TB (i.e., rifabutin, clarithromycin, kanamycin, capreomycin, high-dose isoniazid, and isoniazid).

Propensity Score Matching

Rationale

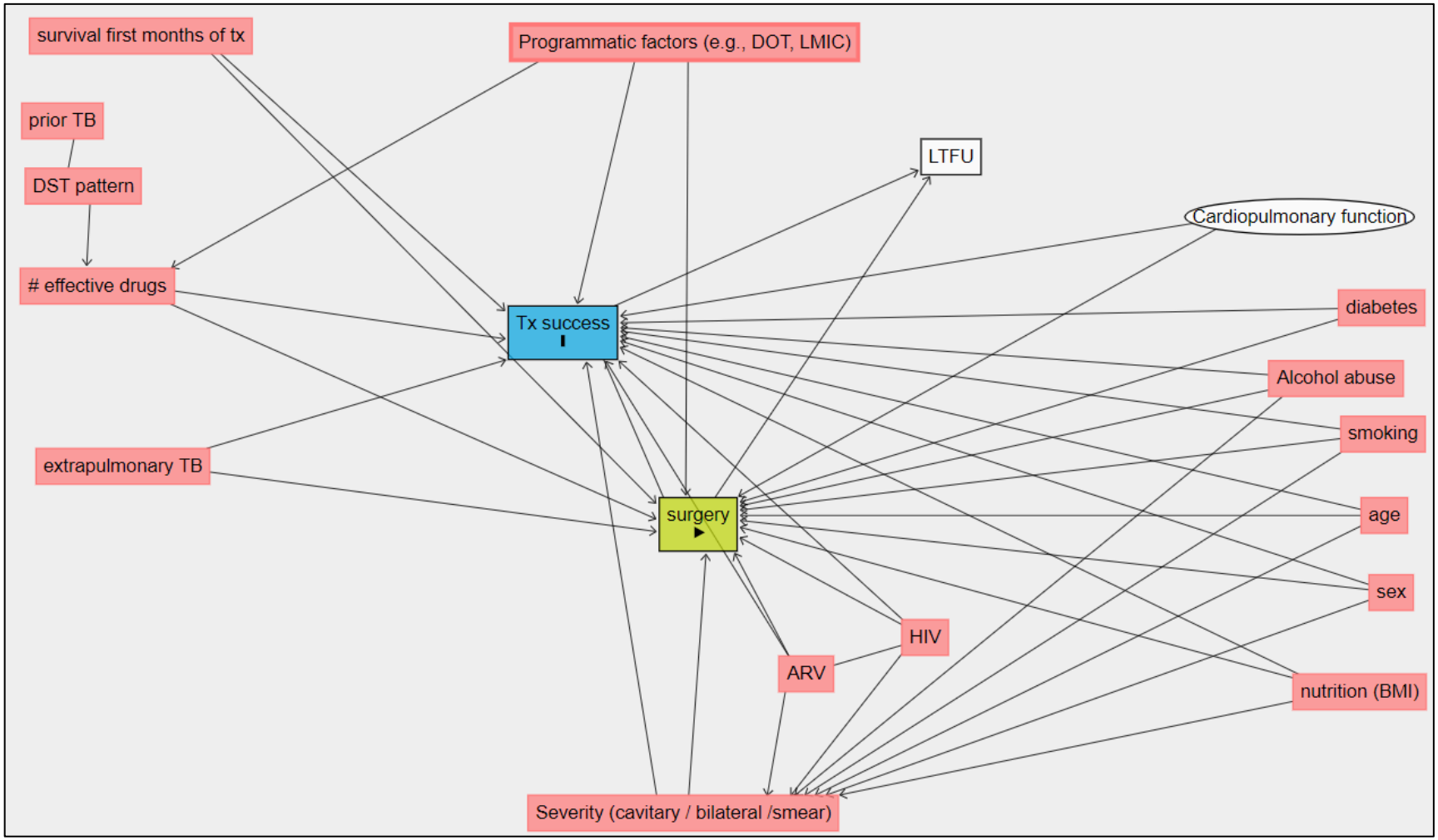
In practice, physicians guide their treatment decisions on several prognostic factors (Jackson et al., 2017). Consequently, these covariates are simultaneously related to the exposure and outcome, producing confounding by indication or contraindication (VanderWeele, 2019; Webster-Clark et al., 2020). For instance, pulmonary resection for MDR-TB may be reserved for patients with non-extensive disease, which, in turn, is also related to a better prognosis, producing confounding bias. Propensity score-based methods have been suggested as a tool to deal with confounding (Webster-Clark et al., 2020). A propensity score summarizes the probability of treatment assignment conditional on all measured factors related to the outcome. Then, propensity scores can be used, for example, to match exposed and unexposed patients (Jackson et al., 2017). The general idea behind these methods is to balance the distribution of prognostic factors between groups, allowing to estimate an unconfounded measure of effect (*Practical Propensity Score Methods Using R*, 2017).

An additional problem of observational studies of effectiveness is that the new users of the treatment of interest are often prevalent users of the strategy used as a comparison (Suissa et al., 2017). In this scenario, selecting controls from patients that never switched to the index strategy can result in immortal time bias (Suissa, 2004; Suissa et al., 2017; Webster-Clark et al., 2020). For instance, candidates for pulmonary resection are usually selected after a short trial of medical treatment; therefore, patients must be alive when surgery is indicated. In this case, selecting controls only from baseline can create immortal time bias. Using a prevalent-new user design can account for this problem (Suissa et al., 2017). With this methodology, time- or prescription-based exposure sets are created, and propensity scores are computed using information measured when a new treatment was indicated (Suissa et al., 2017).

Estimation of the propensity scores

In this study, several covariates measured at cohort entry were possible confounders of the relationship between pulmonary resection surgery and end-of-treatment outcomes (Figure 1).

Figure 1. Directed-acyclic graph of the relationship between pulmonary resection surgery and end-of-treatment outcomes.



Abbreviations: ARV, antiretroviral therapy; DOT, directly observed therapy; DST, drug susceptibility testing; HIV, human immunodeficiency virus; LMIC, lower- and middle-income countries; LTFU, lost-to-follow-up; TB, tuberculosis; Tx, treatment.

However, potential confounders could have changed when surgery was indicated. As mentioned above, this time-varying information is needed to compute time-conditional propensity scores. Since our dataset does not contain data about possible confounders during follow-up, we only used covariates measured at cohort entry to estimate them. Logistic regression models with no interaction terms were employed; variables included are listed in Table 5.

Table 5. Variables used to compute the propensity scores of being assigned to pulmonary resection surgery.

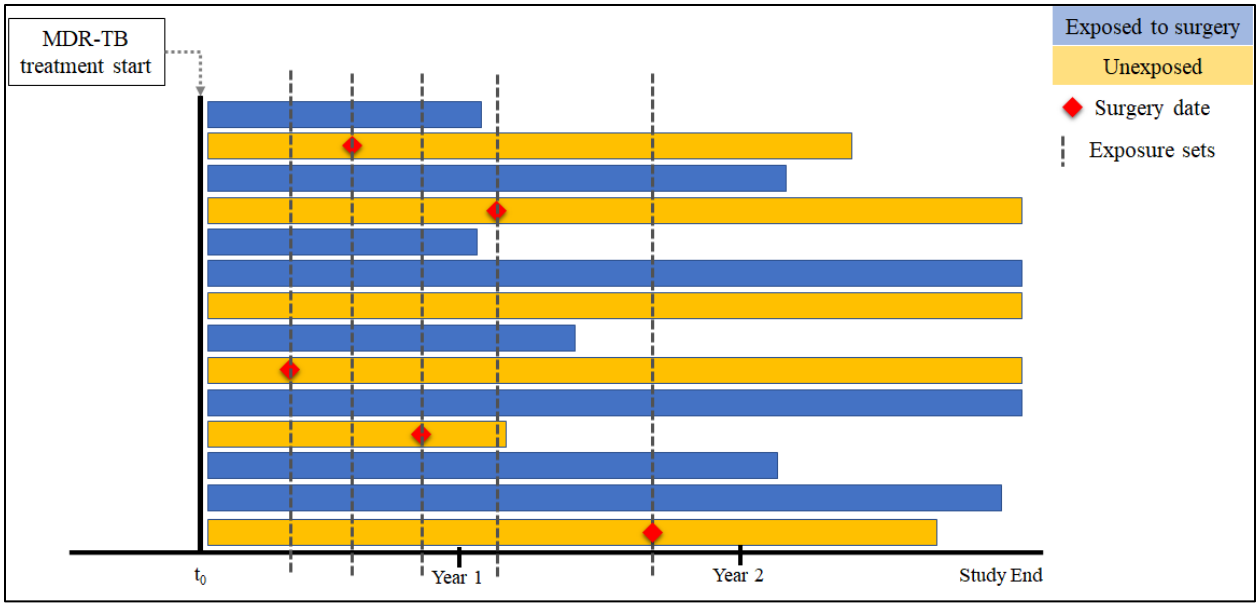
Age at baseline	Directly observed therapy	Past tuberculosis treatment
Alcohol **consumption (defined by study investigators**)	Group A (number of effective drugs)	Sex
Bilateral disease	Group B (number of effective drugs)	Smoking status (ever/never)
Body mass index	Group C (number of effective drugs)	Sputum smear status
Cavitary disease	Human Immunodeficiency Virus infection	Year at baseline
Diabetes mellitus	Country's Income (World Bank)	

Matching procedures

To reduce the risk of immortal time bias, patients exposed to pulmonary resection surgery (cases) were propensity score-matched with controls that survived at least the same amount of time as cases when the surgery was performed. To do this, first, we identified the date of pulmonary resection surgery among cases. If the date of the surgery was missing, an approximation was made based on the local practices. If information about local practices was not available, multiple imputation methods were used (see below). Second, we computed the length of follow-up between cohort entry and surgery. Then, we selected a subset of controls that survived at least the same amount of time as the case to be matched when the surgery was performed (Figure 2). Next, the

case was matched to the control with the nearest propensity score among the selected subset of controls (matching with replacement was used). Finally, these procedures were sequentially repeated for each different day of surgery (measured from cohort entry to the date of surgery) in the dataset (hereafter, referred to as sequential matching).

Figure 2. Sequential matching using propensity scores.



The success of the matching procedures in balancing covariates was assessed with standardized mean differences (SMD). The formers are the differences in covariate means divided by the study population standard deviation (Jackson et al., 2017). An SMD < 0.1 was considered as adequate balance (Jackson et al., 2017). Moreover, density plots were used to evaluate the area of common support of the propensity scores (Webster-Clark et al., 2020). A fair overlap indicates a similar number of subjects across levels of the propensity scores and, therefore, that populations are comparable (Garrido et al., 2014). Finally, if imbalances remained, we iterated over the same processes using different calipers, exact matching variables, and cases-control ratios.

The strategy that provided optimal covariate balance in the overall study population included the following specifications: a nearest-neighbor matching method, a case-control ratio of 1:4 with replacement, and a caliper of 0.2 standard deviations of the logit of the propensity score. However, balance was not achieved across strata of the potential effect modifiers when using the propensity scores computed in the overall study population. Hence, we conducted a subgroup-stratified

approach to compute propensity scores across levels of these variables using the complete study population as the source of controls (Rassen et al., 2012). Finally, if imbalances remained after propensity score matching (SMD > 0.1), we aimed to include unbalanced covariates in the regression model for the primary outcome as a sensitivity analysis. This procedure has been shown to increase model precision (Jackson et al., 2017; Nguyen et al., 2017).

Multiple Imputation Methods

Another problem with our dataset was missing data. To deal with this, we did not use a complete case approach (i.e., excluding subjects with incomplete information) because it considerably decreases sample size and often leads to bias (Kleinke et al., 2020). On the contrary, we used multiple imputation methods since they allow to estimate unbiased effect measures with appropriate standard errors (Kleinke et al., 2020). The overall idea of these methods is to use the available information to generate mathematical models that can predict missing data values (Kleinke et al., 2020). However, to account for the uncertainty of their predictions, several copies of the same dataset are created, only differing on their predictions (Kleinke et al., 2020). Finally, the multiply imputed datasets are analyzed, and their results are pooled (Kleinke et al., 2020).

Multiple imputation methods assume the data is missing either completely at random or that we can predict its values based on the information available (missing at random) (Kleinke et al., 2020). On the contrary, if missingness depends on information not available to the researcher (e.g., if the date of surgery is missing conditional on the results of pulmonary function tests not available in our dataset), the mechanism of missingness is not ignorable. Therefore, assuming the ignorability of the missing data mechanism, we performed multiple imputations methods by chained equations and sequential regressions with the mice package in the R software (Van Buuren, 2011). As a result, we created twenty copies of our dataset (only data with <50% of missingness was imputed).

Data Analysis

Descriptive analysis. Simple pooled descriptive statistics were used to summarize patient features at baseline and during follow-up. Moreover, since we anticipated between-study heterogeneity, univariate aggregate data random-effects meta-analyses were used to summarize the proportion of outcomes across groups (Balduzzi S, 2019). We estimated variance heterogeneity τ^2 using the DerSimonian-Laird methods with the package meta (Balduzzi S, 2019).

Primary analysis. We obtained the odds ratio (OR) for treatment success relative to an unsuccessful response comparing patients treated with a combination of pulmonary resection surgery of any extension with those only medically treated. Additionally, we calculated the OR for death relative to a known alive status at the end of treatment. To estimate the ORs with valid standard errors that account for clustering in our dataset, we performed mixed-effects generalized linear regression using the lme4 package in R (Bates, 2015). Cross-random intercepts were included for original study membership, matched pair membership, and study type (i.e., surgical vs. non-surgical study). We compared exposed patients with patients from the three different sources of controls (i.e., surgical studies, non-surgical studies, and the entire study population).[1]

Secondary analyses: To look for evidence of interaction between pulmonary resection of any extension or partial lung resection and any of the six potential effect modifiers, the same steps performed for the primary analysis were repeated across strata of the potential effect modifiers. We also used mixed-effects generalized linear regression to estimate the OR for treatment outcomes of either lung resection of any extent or partial lung resection. Only patients without missing data for the effect modifier were included in each analysis.[2]

Sensitivity analyses: Additionally, we conducted sensitivity analyses where patients lost to follow-up or transferred to another facility with an unknown outcome were classified as either having an unsuccessful response (for the treatment success outcome) or death (for the outcome of death).[1] For the primary analysis, further sensitivity analyses were performed where unbalanced covariates (i.e., SMD > 0.1) were included in the final model.

Notes:

1) For definitions, please refer to the "Study Design and Source Population" section.

2) For definitions, please refer to the "Definitions of the Potential Effect Modifiers" section.

All P-values were two-tailed; we considered them statistically significant if <0.05. All the analyses were performed using R software version 4.0.2 ("R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.").

Sample Size Calculations

One option to compute the sample size needed in a study based on mixed-effects models is to perform standard sample size calculations and, then, apply a correction factor that accounts for clustering in the data (Twisk, 2019):

a) First, we set the assumptions to calculate the sample size that would be needed under a logistic regression framework (Verma & Verma, 2020): i) probability of treatment success among subjects that underwent lung-resection surgery: 0.697 (based on Fox et al. (Fox et al., 2016)); ii) probability of treatment success among controls: 0.49 (Fox et al., 2016); iii) correlation between lung-resection surgery and the remaining predictors: R^2 of 0.5 (arbitrarily set since no information similar is available for the proposed combination of predictors); and iv) a type I error rate of 0.05, power of 0.8, using a two-tailed test.

b) Second, we calculated the sample size needed for a logistic regression framework using the freeware G-power 3.1.9.7 (Heine Heinrich University, Düsseldorf, Germany). According to these results, a total of 88 subjects (44 per group) are needed.

c) Third, we applied the correction factor for a mixed-effects model using the following formulae (Twisk, 2019):

$$\textbf{Equation 1}: m \times n = N \times [1 + (n-1)\rho]$$

$$\textbf{Equation 2}: N_{\text{effective}} = m \div [1 + (n-1)\rho]$$

Where *N* is the number of subjects from the standard sample size calculations, *m* the number of clusters (i.e., 52, based on the available data); n is the number of observations per cluster (9 is the minimum in our dataset); and ρ for the intra-class correlation coefficient (0.104, based on the primary outcome).

d) Finally, applying the values above to the equation, we obtained a total sample size of 160 subjects (80 per group) (with complete data) in order to have 80% of power to detect a reduction of 20% in the incidence proportion in the primary outcome with an alpha of 0.05.

Ethics Approval

The study was approved by an ethics committee of the Research Institute of the McGill University Health Center (BMB-07021). The Centers for Disease Control (CDC) also approved this protocol. All data sent by authors was non-nominal, and patients were not contacted directly, so ethical issues were minimal. Ethics approval was also obtained at participating sites if considered necessary.

Chapter 5: Results

Description of the Original Dataset

The original dataset contains information from 52 studies performed worldwide (Figure 3 and Supplementary Table 2); 33 were surgical studies. The median number of patients per study was 116 (interquartile-range [IQR], 43 to 199), with a total of 12,938. We excluded 6,909 patients (48 surgically treated), reasons are shown in Figure 4. Thus, the final study population included 6,025 patients from 41 studies (30 surgical and 11 non-surgical studies); 344 of them were exposed to pulmonary resection surgery (70 total lung resections, 259 partial lung resections, and 15 pulmonary resections without a specified extent). Supplementary Table 3 compares the simple pooled characteristics of the study population with those from the excluded subjects.

Figure 3. Number of patients per country included in the original dataset conditional on their surgical status.

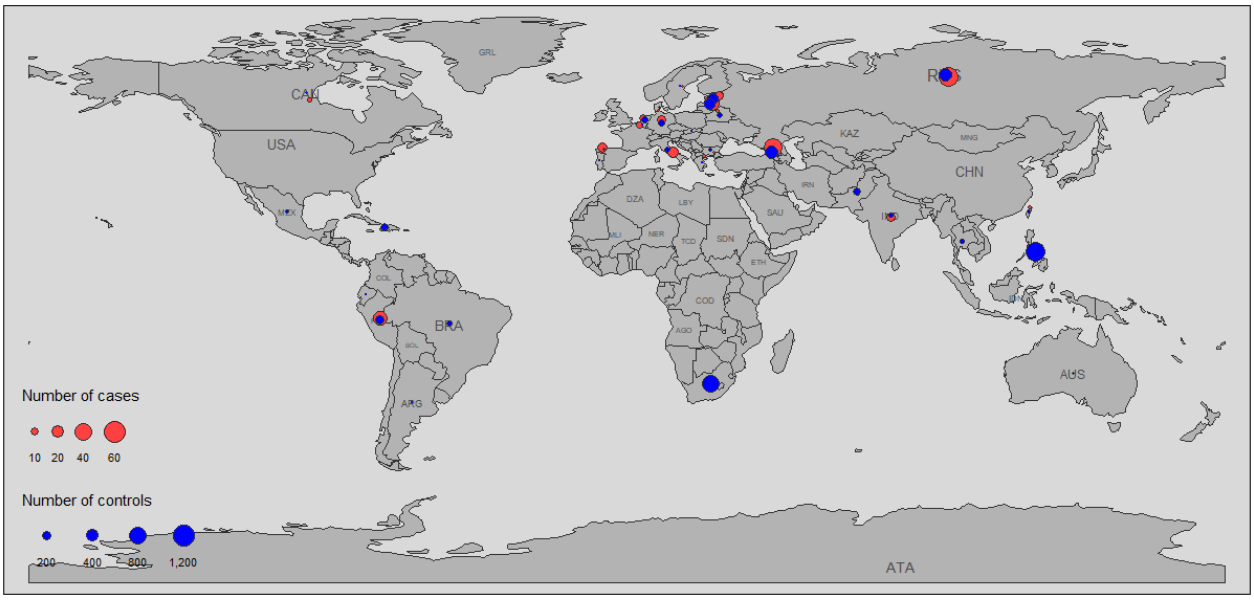
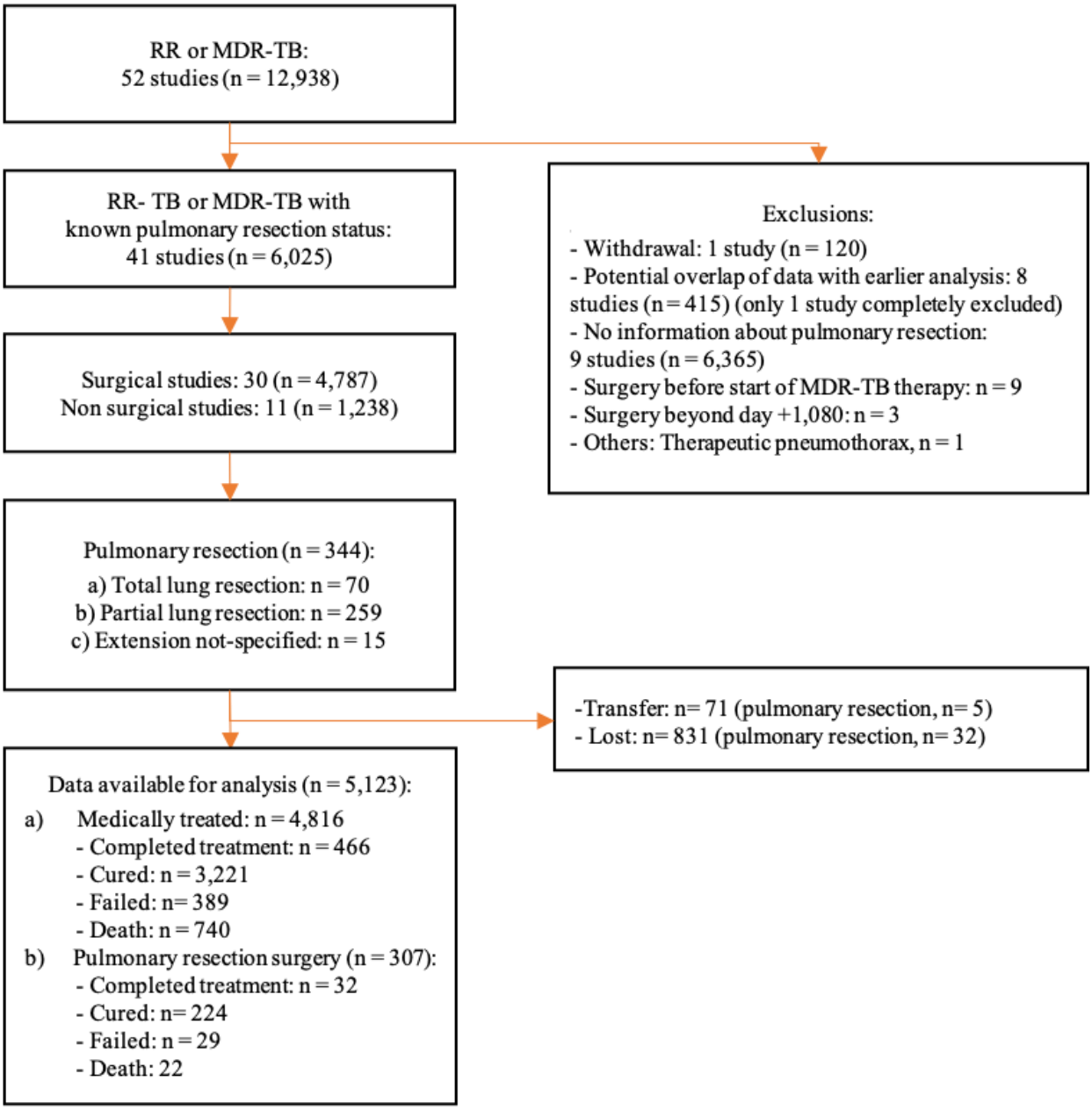


Figure 4. Study population flow chart.



Abbreviations: MDR-TB; multidrug-resistant tuberculosis; RR, rifampin resistant.

Description of the Study Population

Table 6 shows a simple pooled summary of the study population characteristics according to their exposure status. Compared to patients treated only medically, patients with adjunctive pulmonary resection surgery were more frequently from high-income countries and had a higher body mass index. In addition, they were younger and less likely to have comorbidities (i.e., human immunodeficiency virus infection, diabetes mellitus, alcohol consumption). A lower proportion of the surgical patients had bilateral disease or a history of antituberculosis treatment. However, they had a higher frequency of fluoroquinolone resistance and of cavitary disease.

Table 6. Simple pooled summary of the study population baseline characteristics conditional on their exposure status (missing information not imputed).

Covariate	Overall (n = 6,025)	Medically treated (n = 5,681)	Surgically and medically treated (n=344)
STUDY SETTING			
Year of treatment start, mean (SD)	2008.79 (3.20)	2008.79 (3.18)	2008.76 (3.48)
Income, World Bank (%)			
Low	515 (8.5)	514 (9.0)	1 (0.3)
Lower-Middle	1086 (18.0)	1073 (18.9)	13 (3.8)
Upper-Middle	2517 (41.8)	2382 (41.9)	135 (39.2)
High	1907 (31.7)	1712 (30.1)	195 (56.7)
PRE-TREATMENT CHARACTERISTICS			
Age (mean (SD))	38.22 (13.00)	38.43 (13.05)	34.79 (11.53)
Sex (%)			
Female	2192 (36.4)	2047 (36.0)	145 (42.2)
Male	3832 (63.6)	3633 (64.0)	199 (57.8)
Missing	1 (0.0)	1 (0.0)	0 (0.0)
BMI (mean (SD))	20.11 (3.63)	20.07 (3.66)	20.69 (2.99)

Abbreviations: BMI, body mass index; SD, standard deviation.

Covariate (continued)	Overall (n = 6,025) (continued)	Medically treated (n = 5,681) (continued)	Surgically and medically treated (n=344) (continued)
PRE-TREATMENT CHARACTERISTICS (continued)			
Smoking status (%)			
Never	2465 (40.9)	2337 (41.1)	128 (37.2)
Ever	1322 (21.9)	1240 (21.8)	82 (23.8)
Missing	2238 (37.1)	2104 (37.0)	134 (39.0)
Alcohol consumption (%)			
No	2825 (46.9)	2631 (46.3)	194 (56.4)
Yes	1109 (18.4)	1070 (18.8)	39 (11.3)
Missing	2091 (34.7)	1980 (34.9)	111 (32.3)
HIV (%)			
Negative	5313 (88.2)	4979 (87.6)	334 (97.1)
Positive	625 (10.4)	619 (10.9)	6 (1.7)
Missing	87 (1.4)	83 (1.5)	4 (1.2)
Diabetes mellitus (%)			
No	4405 (73.1)	4136 (72.8)	269 (78.2)
Yes	548 (9.1)	526 (9.3)	22 (6.4)
Missing	1072 (17.8)	1019 (17.9)	53 (15.4)
Past antituberculosis treatment (%)			
No	1295 (21.5)	1210 (21.3)	85 (24.7)
Yes	4645 (77.1)	4390 (77.3)	255 (74.1)
Missing	85 (1.4)	81 (1.4)	4 (1.2)
PRE-TREATMENT DISEASE CHARACTERISTICS			
Bilateral disease (%)			
No	1397 (23.2)	1258 (22.1)	139 (40.4)
Yes	3250 (53.9)	3088 (54.4)	162 (47.1)
Missing	1378 (22.9)	1335 (23.5)	43 (12.5)

Covariate (continued)	Overall (n = 6,025) (continued)	Medically treated (n = 5,681) (continued)	Surgically and medically treated (n=344) (continued)
PRE-TREATMENT DISEASE CHARACTERISTICS (continued)			
Acid Fast Bacilli (%)			
Negative	1148 (19.1)	1071 (18.9)	77 (22.4)
Positive	3685 (61.2)	3463 (61.0)	222 (64.5)
Missing	1192 (19.8)	1147 (20.2)	45 (13.1)
Cavitary disease (%)			
No	1872 (31.1)	1780 (31.3)	92 (26.7)
Yes	3187 (52.9)	2939 (51.7)	248 (72.1)
Missing	966 (16.0)	962 (16.9)	4 (1.2)
PRE-TREATMENT DRUG SUSCEPTIBILITY TESTING RESULTS			
Fluoroquinolone-resistance			
Resistant	1429 (23.7)	1270 (22.4)	159 (46.2)
Susceptible	4281 (71.1)	4106 (72.3)	175 (50.9)
Missing	315 (5.2)	305 (5.4)	10 (2.9)
Ethambutol-resistance (%)			
Resistant	4006 (66.5)	3741 (65.9)	265 (77.0)
Susceptible	1803 (29.9)	1730 (30.5)	73 (21.2)
Missing	216 (3.6)	210 (3.7)	6 (1.7)
Pyrazinamide-resistance (%)			
Resistant	2254 (37.4)	2059 (36.2)	195 (56.7)
Susceptible	1887 (31.3)	1828 (32.2)	59 (17.2)
Missing	1884 (31.3)	1794 (31.6)	90 (26.2)
Streptomycin-resistance (%)			
Resistant	4006 (66.5)	3742 (65.9)	264 (76.7)
Susceptible	1475 (24.5)	1415 (24.9)	60 (17.4)
Missing	544 (9.0)	524 (9.2)	20 (5.8)

Covariate (continued)	Overall (n = 6,025) (continued)	Medically treated (n = 5,681) (continued)	Surgically and medically treated (n=344) (continued)
PRE-TREATMENT DRUG SUSCEPTIBILITY TESTING RESULTS* (continued)			
PAS-resistance (%)			
Resistant	728 (12.1)	648 (11.4)	80 (23.3)
Susceptible	3433 (57.0)	3221 (56.7)	212 (61.6)
Missing	1864 (30.9)	1812 (31.9)	52 (15.1)

Abbreviations: PAS, para-aminosalicylic acid.

Note: if there is no missing row, there is no missing information of the corresponding variable.

Table 7 shows a simple pooled summary of treatments and outcomes in the study population conditional on their exposure status.

Patients with adjunctive pulmonary resection surgery had a higher probability of receiving group A drugs (either bedaquiline or linezolid alone or combined with a later generation fluoroquinolone). However, they had a lower probability of being treated with directly observed therapy. Furthermore, patients surgically treated received medical treatment for a longer time.

Concerning the end-of-treatment outcomes, patients treated only medically were more frequently lost to follow-up, while patients treated with adjunctive pulmonary resection surgery more often completed therapy, were cured, or were alive at the end of treatment. Finally, the proportion of recurrence was similar between groups. Nevertheless, recurrence information was missing in 90.2% (5,432) of the study population, mainly because 63% (26/41) of the studies did not record this outcome.

Table 7. Simple pooled summary of the study population treatments and outcomes conditional on their exposure status.

Covariate	Overall (n=6,025)	Medically treated (n=5,681)	Surgically and medically treated (n=344)
TREATMENT			
Directly Observed Therapy (%)			
No	453 (7.5)	381 (6.7)	72 (20.9)
Yes	5150 (85.5)	4902 (86.3)	248 (72.1)
Missing	422 (7.0)	398 (7.0)	24 (7.0)
Group A drugs* (mean (SD))	0.90 (0.62)	0.89 (0.61)	1.07 (0.73)
FQ (%)	3711 (61.6)	3445 (60.6)	266 (77.3)
LZD (%)	916 (15.2)	772 (13.6)	144 (41.9)
BDQ (%)	537 (8.9)	482 (8.5)	55 (16.0)
LZD and BDQ (%)	373 (6.2)	325 (5.7)	48 (14.0)
LZD or BDQ (%)	1080 (17.9)	929 (16.4)	151 (43.9)
LZD or BDQ plus FQ (%)	836 (13.9)	722 (12.7)	114 (33.1)
Group B drugs* (mean (SD))	0.91 (0.46)	0.91 (0.45)	0.97 (0.52)
Group C drugs* (mean (SD))	1.45 (1.11)	1.47 (1.11)	1.09 (0.99)
Treatment length and follow up, days (mean (SD))	588.54 (234.82)	580.29 (224.57)	722.18 (335.91)

Abbreviations: BDQ, bedaquiline; FQ, fluoroquinolones; LZD, linezolid; SD, standard deviation.

* Number of drugs (ever use)

Note: if there is no missing row, there is no missing information of the corresponding variable.

Covariate (continued)	Overall (n=6,025) (continued)	Medically treated (n=5,681) (continued)	Surgically and medically treated (n=344) (continued)
OUTCOMES (SIMPLE POOLING)			
Time to culture conversion, months (mean (SD))	2.63 (3.24)	2.51 (2.75)	4.43 (7.17)
End of treatment outcome (%)			
Completion	498 (8.3)	466 (8.2)	32 (9.3)
Cure	3445 (57.2)	3221 (56.7)	224 (65.1)
Death	762 (12.6)	740 (13.0)	22 (6.4)
Failure	418 (6.9)	389 (6.8)	29 (8.4)
Lost to follow-up	831 (13.8)	799 (14.1)	32 (9.3)
Transfer without a known outcome	71 (1.2)	66 (1.2)	5 (1.5)
Recurrence (%)			
No	577 (9.6)	543 (9.6)	34 (9.9)
Yes	16 (0.3)	14 (0.2)	2 (0.6)
Missing	5432 (90.2)	5124 (90.2)	308 (89.5)

Abbreviations: SD, standard deviation.

Note: if there is no missing row, there is no missing information of the corresponding variable.

Unadjusted Aggregate Data Meta-analysis of Treatment Outcomes

Table 8 shows the results of the unadjusted aggregate data meta-analysis of treatment outcomes conditional to their exposure status, pulmonary resection extent, and study type. In the overall study population, the probability of treatment success and death was 0.71 (95% confidence interval [CI], 0.65 to 0.77) and 0.07 (95% CI, 0.05 to 0.11), respectively. Compared to patients only medically treated, patients receiving adjunctive pulmonary resection surgery had a higher probability of treatment success and a lower probability of death. This effect was mainly driven

by patients treated with partial lung resection. In contrast, subjects exposed to total lung resection had the highest probability of death and the lowest probability of treatment success. Finally, patients treated only medically had the lowest probability of failure or recurrence and the highest probability of being lost to follow-up.

Table 8. Unadjusted aggregate data meta-analysis of treatment outcomes using random-effects models according to their exposure status and to the source of controls (i.e., overall study population, surgical studies, and non-surgical studies).

Group	Events (n/N)	Pooled treatment outcomes, proportions, [95% CI]	I^2 [95% CI]
Treatment success (cure or completion without recurrence)			
Overall population	3927/6025	0.71 [0.65; 0.77]	90.2% [87.6%; 92.2%]
Pulmonary resection (any)	254/344	0.73 [0.63; 0.80]	0.0% [0.0%; 41.3%]
Partial lung resection	199/259	0.77 [0.71; 0.82]	0.0% [0.0%; 43.2%]
Total lung resection	46/70	0.65 [0.42; 0.83]	0.0% [0.0%; 52.3%]
Medically treated (all)	3673/5681	0.71 [0.64; 0.77]	90.7% [88.3%; 92.7%]
From surgical studies	2799/4443	0.69 [0.62; 0.75]	89.8% [86.4%; 92.3%]
From non-surgical studies	874/1238	0.76 [0.60; 0.86]	92.0% [87.7%; 94.8%]
Treatment failure or recurrence			
Overall population	434/6025	0.05 [0.03; 0.07]	79.8% [73.1%; 84.8%]
Pulmonary resection (any)	31/344	0.08 [0.04; 0.14]	0.0% [0.0%; 41.3%]
Partial lung resection	20/259	0.07 [0.03; 0.13]	0.0% [0.0%; 43.2%]
Total lung resection	10/70	0.13 [0.05; 0.28]	0.0% [0.0%; 52.3%]
Medically treated	403/5681	0.04 [0.03; 0.07]	80.6% [74.1%; 85.5%]
From surgical studies	300/4443	0.04 [0.02; 0.07]	78.3% [69.1%; 84.7%]
From non-surgical studies	103/1238	0.05 [0.02; 0.09]	83.1% [71.1%; 90.1%]

Abbreviations: CI, confidence interval.

Group (continued)	Events (n/N) (continued)	Pooled treatment outcomes, proportions, [95% CI] (continued)	I^2 [95% CI] (continued)
Death			
Overall population	762/6025	0.07 [0.05; 0.11]	87.2% [83.5%; 90.0%]
Pulmonary resection (any)	22/344	0.04 [0.01; 0.11]	0.0% [0.0%; 41.3%]
Partial lung resection	10/259	0.03 [0.01; 0.09]	0.0% [0.0%; 43.2%]
Total lung resection	8/70	0.09 [0.02; 0.30]	0.0% [0.0%; 52.3%]
Medically treated	740/5681	0.08 [0.05; 0.11]	87.2% [83.5%; 90.1%]
From surgical studies	594/4443	0.09 [0.06; 0.13]	87.4% [83.0%; 90.7%]
From non-surgical studies	146/1238	0.04 [0.01; 0.14]	87.7% [79.9%; 92.5%]
Lost to follow-up or transfer			
Overall population	902/6025	0.11 [0.08; 0.14]	80.8% [74.5%; 85.5%]
Pulmonary resection (any)	37/344	0.08 [0.04; 0.16]	0.0% [0.0%; 41.3%]
Partial lung resection	30/259	0.09 [0.04; 0.19]	0.0% [0.0%; 43.2%]
Total lung resection	6/70	0.07 [0.01; 0.26]	0.0% [0.0%; 52.3%]
Medically treated	865/5681	0.11 [0.08; 0.14]	80.3% [73.7%; 85.3%]
From surgical studies	750/4443	0.12 [0.09; 0.16]	79.7% [71.3%; 85.7%]
From non-surgical studies	115/1238	0.09 [0.05; 0.15]	75.3% [55.3%; 86.3%]

Abbreviations: CI, confidence interval.

Adjusted Analysis Using Propensity Score Sequential Matching

Table 9 shows the distribution of covariates in the propensity score sequentially matched population when using all studies as the source of controls. None of the covariates used to compute the propensity scores were imbalanced after matching (i.e., standardized mean differences (SMD) > 0.1). However, we could not find controls for four patients treated with adjunctive pulmonary resection surgery. Furthermore, Figure 5 shows a substantial overlap of the propensity scores

distribution between groups of treatment. Finally, Supplementary Tables 4 to 20 compare the baseline characteristics of the propensity score sequentially matched study samples when using either surgical or non-surgical studies as the source of controls (for the primary analysis) and across strata of the potential effect modifiers (Appendix).

Table 9. Covariate balance after propensity score sequential matching patients with adjunctive pulmonary resection surgery with controls from the overall study population.

Covariate	Medically treated (n=1,340)	Surgically and medically treated (n=340)	SMD
STUDY SETTING			
Year of treatment start (mean (SD))	2008.90 (3.36)	2008.86 (3.32)	0.013
Low income	4 (0.3)	1 (0.3)	0.046
Lower-Middle	60 (4.5)	13 (3.8)	
Upper-Middle	549 (41.0)	135 (39.7)	
High income	727 (54.3)	191 (56.2)	
PRE-TREATMENT CHARACTERISTICS			
Age at treatment start (mean (SD))	34.81 (11.90)	34.91 (11.51)	0.009
Male sex (%)	816 (60.9)	198 (58.2)	0.054
Body Mass Index (mean (SD))	20.56 (3.39)	20.47 (3.22)	0.028
Smoking (ever) (%)	742 (55.4)	185 (54.4)	0.019
Alcohol consumption (%)	288 (21.5)	71 (20.9)	0.015
Diabetes Mellitus (%)	90 (6.7)	21 (6.2)	0.022
HIV infection (%)	23 (1.7)	6 (1.8)	0.004
Past tuberculosis treatment (%)	994 (74.2)	256 (75.3)	0.026

Abbreviations: SD, standard deviation; SMD, standardized mean difference.

Note: One imputed dataset selected at random was used to show the covariate balance achieved.

Covariate (continued)	Medically treated (n=1,340) (continued)	Surgically and medically treated (n=340) (continued)	SMD (continued)
PRE-TREATMENT DISEASE CHARACTERISTICS			
Bilateral disease (%)	746 (55.7)	188 (55.3)	0.008
Cavitary disease (%)	994 (74.2)	247 (72.6)	0.035
Sputum sear status (%)	971 (72.5)	246 (72.4)	0.002
TREATMENT (NUMBER OF EFFECTIVE DRUGS PER GROUP)			
Group A (mean (SD))	1.06 (0.66)	1.08 (0.73)	0.032
Group B (mean (SD))	0.96 (0.53)	0.96 (0.51)	<0.001
Group C (mean (SD))	1.30 (1.09)	1.30 (1.10)	0.002
DOT = Yes (%)	969 (72.3)	247 (72.6)	0.007

Abbreviations: SD, standard deviation; SMD, standardized mean difference; DOT, directly observed therapy.

Note: One imputed dataset selected at random was used to show the covariate balance achieved.

Figure 5. Distribution of the propensity scores before (A) and after (B) propensity score sequential matching patients exposed to pulmonary resection surgery with controls from the overall study population.

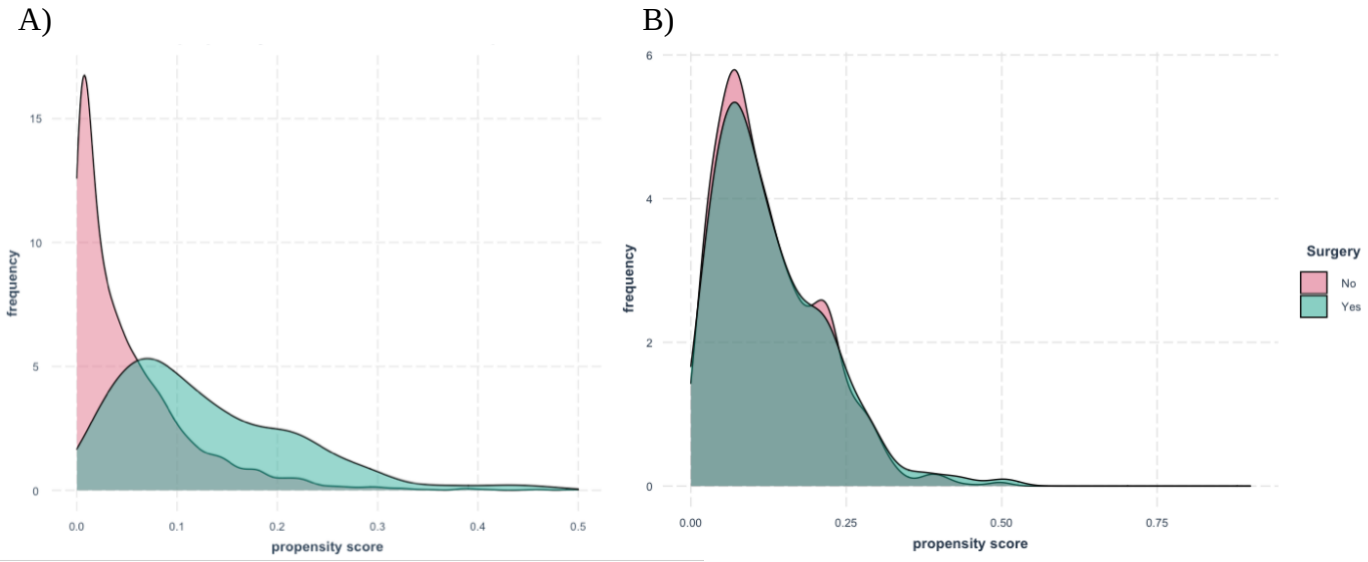


Table 10 shows the results of the adjusted analyses (using the propensity score sequentially matched samples) for the primary outcomes conditional on the extent of pulmonary resection and the source of controls. A lower number of matched pairs was obtained when selecting controls only from non-surgical studies, probably as a consequence of poor matching. In most cases, this resulted in non-precise estimates of the measures of effect.

Irrespective of the source of controls, pulmonary resection surgery of any extent was not significantly associated with the odds of treatment success (controls from all studies: OR, 0.99; 95% confidence interval [CI], 0.63, 1.56; controls from surgical studies: OR, 1.09, 95% CI, 0.70 1.71; controls from non-surgical studies: OR, 0.35; 95% CI, 0.09, 1.40), nor with the odds of death (controls from all studies: OR, 0.83; 95% CI, 0.43, 1.61; controls from surgical studies: OR, 0.79, 95% CI, 0.42, 1.48; controls from non-surgical studies: OR, 2.50; 95% CI, 0.23, 27.54).

When assessing the effects of the extent of pulmonary resection, we found a non-significant increase in the odds of treatment success and a non-significant decrease in the odds of death among patients exposed to partial lung resection (controls from all the studies: OR, 1.30, 95% CI, 0.74, 2.28; OR, 0.54; 95% CI, 0.22 1.29, respectively; controls from surgical studies: OR, 1.55, 95% CI, 0.89, 2.69; OR, 0.44; 95% CI, 0.19, 1.01, respectively). However, when selecting controls from non-surgical studies, very wide confidence intervals were obtained.

On the contrary, total lung resection was related with lower odds treatment success and higher odds of death (controls from all the studies: OR 0.52; 95% CI, 0.19, 1.41; OR, 1.57, 95% CI, 0.39, 6.31, respectively; controls from non-surgical studies: OR 0.19, 95% CI, 0.04, 0.89; OR 5.33, 95% CI, 0.65, 43.71, respectively). This effect was not as evident when selecting controls from surgical studies (treatment success OR, 0.67; 95% CI, 0.26, 1.73; death OR, 1.23; 95% CI, 0.33, 4.54).

Table 10. Results of the mixed-effects models assessing the odds for treatment success and death of pulmonary resection surgery after using propensity score sequential matching (three methods of selecting controls are shown, patients lost to follow-up and transferred were excluded).

Outcome+	Surgically and medically treated, n/N (%)*	Medically treated, n/N (%)	aOR	95% CI (lower)	95% CI (upper)	p-value
PULMONARY RESECTION SURGERY (ANY EXTENT)						
Controls from the overall study population						
Success	252/304 (82.9)	988/1189 (83.1)	0.99	0.63	1.56	0.97
Death	21/304 (6.9)	104/1189 (8.7)	0.83	0.43	1.61	0.58
Controls from surgical studies only						
Success	254/307 (82.7)	992/1204 (82.4)	1.09	0.70	1.71	0.69
Death	22/307 (7.2)	104/1204 (8.6)	0.79	0.42	1.48	0.47
Controls from non-surgical studies only						
Success	184/217 (84.8)	209/224 (93.3)	0.35	0.09	1.40	0.14
Death	14/217 (6.5)	8/224 (3.6)	2.50	0.23	27.54	0.45
PARTIAL LUNG RESECTION (LOBECTOMY, SEGMENTECTOMY, WEDGE RESECTION)						
Controls from the overall study population						
Success	193/221 (87.3)	735/890 (82.6)	1.30	0.74	2.28	0.36
Death	10/221 (4.5)	78/890 (8.8)	0.54	0.22	1.29	0.16
Controls from surgical studies only						
Success	193/221 (87.3)	723/891 (81.1)	1.55	0.89	2.69	0.12
Death	10/221 (4.5)	88/891 (9.9)	0.44	0.19	1.01	0.05
Controls from non-surgical studies only						
Success	43/45 (95.6)	126/136 (92.6)	1.46	0.20	10.95	0.71
Death	1/45 (2.2)	5/136 (3.7)	1.40	0.06	30.76	0.83

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

* Counts were computed from one imputed dataset selected at random.

Outcome+ (continued)	Surgically and medically treated, n/N (%)* (continued)	Medically treated, n/N (%) (continued)	aOR (continued)	95% CI (lower) (cont'd)	95% CI (upper) (cont'd)	p-value (cont'd)
TOTAL LUNG RESECTION (PNEUMONECTOMY)						
Controls from the overall study population						
Success	33/48 (68.8)	133/164 (81.1)	0.52	0.19	1.41	0.19
Death	7/48 (14.6)	19/164 (11.6)	1.57	0.39	6.31	0.52
Controls from surgical studies only						
Success	38/53 (71.7)	166/204 (81.4)	0.67	0.26	1.73	0.40
Death	7/53 (13.2)	25/204 (12.3)	1.23	0.33	4.54	0.76
Controls from non-surgical studies only						
Success	37/50 (74.0)	199/209 (95.2)	0.19	0.04	0.89	0.03
Death	7/50 (14.0)	4/209 (1.9)	5.33	0.65	43.71	0.12

Abbreviations: aOR, adjusted odds ratio; Cont'd, Continued.

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

* Counts were computed from one imputed dataset selected at random.

Stratified Analyses

Table 11 summarizes the results from the stratified analyses comparing any extent of pulmonary resection surgery against controls selected from the overall study population. Among patients with fluoroquinolone-resistant MDR-TB, pulmonary resection surgery was associated with a non-significant decrease in the odds of death (OR 0.47; 95% CI, 0.19, 1.16) and a non-significant increase in the odds of treatment success (OR 1.5; 95% CI, 0.8, 2.83). Moreover, among patients treated with pulmonary resection surgery of any extent at the more experienced centers, we also found a non-significant increase in the odds of treatment success (OR, 1.46; 95% CI, 0.83, 2.58) and a non-significant decrease in the odds of death (OR, 0.59; 95% CI, 0.27, 1.28). On the other hand, performing adjunctive lung resection surgery at less experienced centers was associated with

a non-significant increase in the odds of death death (OR, 1.77; 95% CI, 0.39, 7.91) and a non-significant decrease in the odds of treatment success (OR 0.39; 95% CI, 0.15, 1.02).

Finally, no evidence of effect modification was found across levels of the remaining variables (i.e., the number of drugs within group A [>=2 drugs: treatment success OR 1.45; 95% CI, 0.59, 3.59; death OR 0.75; 95% CI, 0.23, 2.5], the timing of surgery relative to the culture conversion date [surgery after culture conversion: treatment success OR, 1.19; 95% CI, 0.57, 2.5; death OR 0.87, 95% CI, 0.31, 2.46], and the presence or absence of bilateral disease or cavitary pulmonary disease ([cavitary disease: treatment success OR, 0.94; 95% CI, 0.53, 1.65; death OR 1.0, 95% CI, 0.42, 2.39]; [bilateral disease: OR, 1.00; 95% CI, 0.51, 1.93; death OR 0.73, 95% CI, 0.28, 1.88]).

Table 11. Results of the stratified analyses for the primary outcome (excluding patients transferred and lost to follow-up), comparing patients with any extent of pulmonary resection with controls from the overall study population.

Outcome+	Surgically and medically treated n/N (%)	Medically treated, n/N (%)	aOR	95% CI (lower)	95% CI (upper)	p-value
ADDITIONAL FLUOROQUINOLONE-RESISTANCE (USING THE STUDY DEFINITION)						
Fluoroquinolone-susceptible MDR-TB						
Success	115/135 (85.2)	462/533 (86.7)	0.84	0.4	1.78	0.65
Death	8/135 (5.9)	28/533 (5.3)	0.98	0.33	2.92	0.97
Fluoroquinolone-resistant MDR-TB						
Success	108/131 (82.4)	371/492 (75.4)	1.5	0.8	2.83	0.21
Death	8/131 (6.1)	71/492 (14.4)	0.47	0.19	1.16	0.10
VOLUME OF SURGERIES PERFORMED AT EACH CENTER						
More experienced centers						
Success	192/222 (86.5)	693/869 (79.7)	1.46	0.83	2.58	0.19
Death	14/222 (6.3)	86/869 (9.9)	0.59	0.27	1.28	0.18
Less experienced centers						
Success	51/70 (72.9)	244/287 (85.0)	0.39	0.15	1.02	0.05
Death	7/70 (10.0)	24/287 (8.4)	1.77	0.39	7.91	0.46

Outcome+ (continued)	Surgically and medically treated n/N (%) (continued)	Medically treated, n/N (%) (continued)	aOR (Cont'd)	95% CI (lower (Cont'd))	95% CI (upper) (Cont'd)	p-value (Cont'd)
TIMING OF SURGERY RELATIVE TO THE CULTURE CONVERSION DATE						
Surgery before culture conversion						
Success	48/55 (87.3)	156/202 (77.2)	1.55	0.51	4.72	0.44
Death	3/55 (5.5)	18/202 (8.9)	0.85	0.14	5.03	0.86
Surgery after culture conversion						
Success	116/132 (87.9)	446/521 (85.6)	1.19	0.57	2.5	0.64
Death	8/132 (6.1)	36/521 (6.9)	0.87	0.31	2.46	0.8
CONCOMITANT USE OF DRUGS WITHIN THE WHO GROUP A						
>=2 group A drugs						
Success	92/102 (90.2)	313/378 (82.8)	1.45	0.59	3.59	0.42
Death	6/102 (5.9)	35/378 (9.3)	0.75	0.23	2.5	0.64
<2 group A drugs						
Success	143/177 (80.8)	581/716 (81.1)	1.08	0.62	1.87	0.79
Death	12/177 (6.8)	62/716 (8.7)	0.72	0.32	1.59	0.42
CAVITARY DISEASE						
Cavitary disease = Yes						
Success	179/217 (82.5)	720/876 (82.2)	0.94	0.53	1.65	0.82
Death	15/217 (6.9)	76/876 (8.7)	1.00	0.42	2.39	1.00
Cavitary disease = No						
Success	67/76 (88.2)	274/303 (90.4)	0.67	0.20	2.22	0.51
Death	3/76 (3.9)	12/303 (4.0)	1.51	0.22	10.24	0.67

Abbreviations: CI, confidence interval; Cont'd, Continued; aOR, adjusted odds ratio.

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

Outcome+ (continued)	Surgically and medically treated n/N (%) (continued)	Medically treated, n/N (%) (continued)	aOR (Cont'd)	95% CI (lower (Cont'd))	95% CI (upper) (Cont'd)	p-value (Cont'd)
BILATERAL DISEASE						
Bilateral disease = Yes						
Success	108/132 (81.8)	419/538 (77.9)	1.00	0.51	1.93	0.99
Death	9/132 (6.8)	67/538 (12.5)	0.73	0.28	1.88	0.51
Bilateral disease = No						
Success	103/117 (88.0)	400/445 (89.9)	0.93	0.37	2.36	0.88
Death	7/117 (6.0)	18/445 (4.0)	0.99	0.22	4.35	0.99

Abbreviations: CI, confidence interval; Cont'd, Continued; aOR, adjusted odds ratio.

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

Similar results were found in the stratified analyses comparing patients exposed to partial lung resection surgery with controls selected from the overall study population (Table 12). Among patients with fluoroquinolone-resistant MDR-TB, partial lung resection was associated with a significant decrease in the odds of death (OR, 0.25; 95%, CI, 0.06, 0.99) and a non-significant increase in the odds of treatment success (OR, 1.69; 95% CI, 0.77, 3.72). We also found a non-significant increase in the odds of treatment success (OR, 1.61; 95% CI, 0.84, 3.08) and a non-significant decrease in the odds of death among patients treated with partial lung resection at more experienced centers centers (OR, 0.51; 95% CI, 0.2, 1.32). However, non-conclusive results were obtained when assessing patients from less experienced centers due to a low number of events per group. We also found a non-significant increase in the odds of treatment success and a non-significant decrease in the odds of death when performing partial lung resection surgery in patients with cavitary disease. The opposite effect was found with the presence of non-cavitary disease. Although these results suggest the presence of effect modification, confidence intervals are wide and impair our possibility of making meaningful conclusions.

Finally, no evidence of effect modification was found with the remaining variables (i.e., the number of drugs within group A, the timing of surgery relative to the culture conversion date, and the presence or absence of bilateral pulmonary disease).

Table 12. Results of the stratified analyses for the primary outcome (excluding patients transferred and lost to follow-up), comparing patients with partial lung resection with controls from the overall study population.

Outcome+	Surgically and medically treated n/N (%)	Medically treated, n/N (%)	aOR	95% CI (lower)	95% CI (upper)	p-value
ADDITIONAL FLUOROQUINOLONE-RESISTANCE (USING THE STUDY DEFINITION)						
Fluoroquinolone-susceptible MDR-TB						
Success	96/107 (89.7)	379/432 (87.7)	1.1	0.44	2.75	0.84
Death	5/107 (4.7)	20/432 (4.6)	0.91	0.25	3.36	0.89
Fluoroquinolone-resistant MDR-TB						
Success	84/98 (85.7)	278/371 (74.9)	1.69	0.77	3.72	0.19
Death	3/98 (3.1)	48/371 (12.9)	0.25	0.06	0.99	0.05
VOLUME OF SURGERIES PERFORMED AT EACH CENTER						
More experienced centers						
Success	152/172 (88.4)	518/663 (78.1)	1.61	0.84	3.08	0.15
Death	9/172 (5.2)	69/663 (10.4)	0.51	0.2	1.32	0.17
Less experienced centers						
Success	38/45 (84.4)	175/199 (87.9)	0.79	0.22	2.84	0.72
Death	1/45 (2.2)	10/199 (5.0)	0	0	Inf	1
TIMING OF SURGERY RELATIVE TO THE CULTURE CONVERSION DATE						
Surgery before culture conversion						
Success	33/38 (86.8)	114/141 (80.9)	1.42	0.36	5.56	0.61
Death	2/38 (5.3)	9/141 (6.4)	0.89	0.1	7.53	0.91
Surgery after culture conversion						
Success	97/104 (93.3)	365/406 (89.9)	2.08	0.75	5.78	0.16
Death	4/104 (3.8)	16/406 (3.9)	0.65	0.16	2.65	0.54

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

Outcome+ (continued)	Surgically and medically treated n/N (%) (continued)	Medically treated, n/N (%) (continued)	aOR (Cont'd)	95% CI (lower (Cont'd))	95% CI (upper) (Cont'd)	p-value (Cont'd)
CONCOMITANT USE OF DRUGS WITHIN THE WHO GROUP A						
>=2 group A drugs						
Success	65/69 (94.2)	227/259 (87.6)	1.62	0.46	5.64	0.45
Death	2/69 (2.9)	18/259 (6.9)	0.49	0.08	3.07	0.45
<2 group A drugs						
Success	122/143 (85.3)	459/588 (78.1)	1.56	0.81	3	0.18
Death	7/143 (4.9)	62/588 (10.5)	0.45	0.16	1.23	0.12
CAVITARY DISEASE						
Cavitary disease = Yes						
Success	134/150 (89.3)	486/613 (79.3)	1.40	0.67	2.90	0.37
Death	6/150 (4.0)	54/613 (8.8)	0.52	0.16	1.67	0.27
Cavitary disease = No						
Success	54/62 (87.1)	215/244 (88.1)	0.61	0.17	2.15	0.44
Death	3/62 (4.8)	4/244 (1.6)	2.22	0.26	18.91	0.46
BILATERAL DISEASE						
Bilateral disease = Yes						
Success	79/94 (84.0)	289/372 (77.7)	1.16	0.53	2.54	0.71
Death	6/94 (6.4)	46/372 (12.4)	0.68	0.22	2.05	0.49
Bilateral disease = No						
Success	84/92 (91.3)	318/356 (89.3)	1.32	0.42	4.13	0.63
Death	3/92 (3.3)	13/356 (3.7)	0.41	0.04	3.67	0.42

Abbreviations: CI, confidence interval; Cont'd, Continued; aOR, adjusted odds ratio.

+ Success is compared against failure, recurrence, and death; death against failure, cure, and completion

Sensitivity Analyses

Table 13 summarizes the results from the sensitivity analysis when assessing the effect of pulmonary resection surgery but including patients lost to follow-up and transferred with an unknown outcome (all considered as having poor outcomes). As expected, measures of effect deviated towards the null. Finally, sensitivity analysis adjusted for unbalanced covariates after propensity score matching s shown in Supplementary Table 21. No significant changes in the results were found in these analyses.

Table 13. Results of the sensitivity analysis: Including patients who were lost or transferred out (all considered as having poor outcomes).

Outcome	Surgically and medically treated, n/N (%)	Medically treated, n/N (%)	aOR	95% CI (lower)	95% CI (upper)	p-value
CONTROLS FROM OVERALL POPULATION						
Success vs Failure, Recurrence, Death, LTFU and Transfer	252/340 (74.1)	988/1340 (73.7)	1.04	0.73	1.48	0.83
Death, LTFU, Transfer vs Failure, Cure, Completion	57/340 (16.8)	255/1340 (19.0)	0.87	0.57	1.31	0.5
CONTROL FROM SURGICAL STUDIES						
Success vs Failure, Recurrence, Death, LTFU and Transfer	254/344 (73.8)	992/1376 (72.1)	1.12	0.78	1.61	0.54
Death, LTFU, Transfer vs Failure, Cure, Completion	59/344 (17.2)	276/1376 (20.1)	0.84	0.55	1.27	0.4
CONTROLS FROM NON-SURGICAL STUDIES						
Success vs Failure, Recurrence, Death, LTFU and Transfer	184/242 (76.0)	209/242 (86.4)	0.4	0.12	1.35	0.14
Death, LTFU, Transfer vs Failure, Cure, Completion	39/242 (16.1)	26/242 (10.7)	2	0.53	7.53	0.3

Chapter 6: Discussion

In this study, pulmonary resection surgery as an adjunct measure in treating MDR-TB was only associated with better end-of-treatment outcomes when limited in extent (i.e., lobectomy, wedge resection, or segmentectomy). We also found an association of better outcomes with partial lung resection surgery when performed on patients with fluoroquinolone-resistant MDR-TB, cavitary disease, and when done at highly experienced centers. On the contrary, pneumonectomy was associated with worse end-of-treatment outcomes. Nonetheless, most of our confidence intervals were wide and included the null value, preventing us from making definitive conclusions.

Our results were similar in the direction of the measures of effect to those from the previous IPD MA, which used a similar analytic approach (Fox et al., 2016). In that study, partial lung resection was associated with higher odds of treatment success when using as controls patients from surgical studies (adjusted OR [aOR], 3.0; 95% CI, 1.5, 5.9). Moreover, the authors did not find a significant association between partial lung resection and treatment success when selecting controls from non-surgical studies (aOR, 2.0; 95% CI, 0.4, 9.5). However, in contrast to our results, Fox et al. found that performing surgery after the culture conversion date was associated with higher odds of treatment success (aOR, 2.6; 95% CI, 0.9, 7.1).

Several differences between both studies could explain this discrepancy. First, we assessed fewer subjects exposed to surgery (344 vs. 478), reducing our power for assessing effect modification. Second, Fox et al. used traditional hierarchical multivariable logistic regression to assess the effect of timing instead of propensity score-based methods. Additionally, we matched exposed and unexposed patients on the amount of survival at the moment of surgery, which considerably reduced the probability of immortal time bias (this approach was not followed in the previous study). Finally, our dataset included more recent information, and, therefore, patients were probably exposed to better and newer treatments which may make it more challenging to detect modification of effect.

After analyzing more recent data, our study suggests that current recommendations for performing partial lung resection surgery in carefully selected MDR-TB patients remain valid, even under the context of improved TB quality of care (WHO, 2020b). Besides, our study design had better control of immortal time bias, which could explain the findings from previous studies. Finally,

here we also provided evidence in favor of performing partial lung resection surgery among patients with MDR-TB and additional fluoroquinolone resistance. However, although we used a methodological approach that helped us deal with multiple sources of bias, our analysis has significant limitations.

First, confounding by indication or contraindication is a major issue in all observational studies of treatment effectiveness (VanderWeele, 2019; Webster-Clark et al., 2020). Although we used a propensity score-matched analysis to account for or adjust for confounding, these methods rely on the assumption of no unmeasured confounding (Austin, 2011). Unfortunately, this assumption is unrealistic since relevant characteristics used by practitioners to select candidates for surgery were not available to us (e.g., cardiorespiratory reserve, time-varying information of the confounders when surgery was indicated) (Borisov et al., 2019; Calligaro et al., 2014; Dheda et al., 2017; Kempker et al., 2012).

Additional to the propensity score methods, we used different sources of controls as a supplementary strategy to deal with confounding. The rationale for this approach was that some patients from non-surgical studies could have been considered candidates for surgery had this resource been available at their centers. Therefore, considering that surgery is not a treatment option to them, confounding by indication or contraindication is not possible when using this source of controls (Fox et al., 2016). However, as explained above, the propensity-score methods rely on the assumption of no unmeasured confounding (Austin, 2011), which is again unrealistic in this study. In fact, across levels of the propensity scores, controls from surgical studies are likely more comparable than controls from non-surgical studies to patients exposed to surgery since they share several measured and unmeasured characteristics, given that they belong to the same source populations.

Another potential source of bias in this study is exposure misclassification. This could be a problem when trying to assess the effect of the extent of pulmonary resection on end-of-treatment outcomes. Although we classified pulmonary resection into partial or total lung resection, the actual extent of pulmonary resection surgery within the category of partial lung resection could be highly different (e.g., segmentectomy vs. several lobectomies). Moreover, we did not know the actual disease extent and how much of it was removed by the lung resection surgery. Better outcomes may be achieved if a higher proportion of diseased lung is removed while limiting the lung

resected. Therefore, classifying all partial lung resections within the same category could have biased the actual beneficial effect of partial lung resection towards the null (Dosemeci et al., 1990).

Selection bias is also a possibility in this study. In this analysis, patients treated only medically were more frequently lost to follow-up than patients exposed to surgery. Although we accounted for this by matching patients exposed to pulmonary resection surgery and their controls on the amount of survival, providers may have predicted this behaviour and selected more adherent patients to have pulmonary resection surgery.

Finally, as mentioned above, another limitation of our study was the limited sample size available in our stratified analyses. Although we tried to highlight results when there was evidence of qualitative effect modification (i.e., when sub-groups measures of effect estimates are in the opposite direction, with evidence of harm in one subset and benefits in the other) (Hernán MA, 2020) in most cases, we could not rule out important protective or harmful effects across levels of the potential effect modifiers due to the very wide confidence intervals obtained.

Chapter 7: Conclusion and summary

In conclusion, partial lung resection might be beneficial in treating patients with RR-TB or MDR-TB, particularly when performed at highly experienced centers or in patients with additional resistance to fluoroquinolones or with cavitary disease. Although a randomized controlled trial (RCT) would be the best approach to understand the benefits of resectional surgery, the relative rarity of MDR-TB, the small proportion of this judged suitable for lung resection surgery, in addition to the limited availability of surgical resources worldwide, make an RCT unrealistic, at least in the near future. This IPD meta-analysis could help improve the design of future observational studies to answer this research question, including more safety information and time-varying characteristics at the moment when surgery was performed.

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Appendix

Supplementary Table 1. Studies included in the systematic review performed by Fox et al.

FIRST AUTHOR	YEARS	STUDY LOCATION	REFERENCE
BURGOS	1983-2000	USA	Burgos M, Gonzalez LC, Paz EA, Gournis E, Kawamura LM, et al. (2005) Treatment of multidrug-resistant tuberculosis in San Francisco: An outpatient-based approach. Clinical Infectious Diseases 40: 968–75.
CHAN	1984-1998	USA	Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, Iseman MD. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2004 May 15;169(10):1103-9.
CHIANG	1992-1996	Taiwan	Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, Suo J, Lin TP. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. Eur Respir J. 2006 Nov;28(5):980-5.
ESCUDERO	1998-2000	Spain	Escudero E, Peña JM, Alvarez-Sala R, Vázquez JJ, Ortega A. Multidrug-resistant tuberculosis without HIV infection: success with individualised therapy. Int J Tuberc Lung Dis. 2006 Apr;10(4):409-14
GEERLIGS*	1987-1988, 1998-2008	The Netherlands	Geerligs WA, Van Altena R, De Lange WCM, Van Soolingen D, Van Der Werf TS. Multidrug-resistant tuberculosis: long-term treatment

			outcome in the Netherlands. Int J Tuberc Lung Dis. 2000 Aug;4(8):758-64.
DH KIM	2000-2002	South Korea	Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, Kim TH, Kim EK, Lee KM, Lee SS, Park JS, Koh WJ, Lee CH, Kim JY, Shim TS. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med. 2008 Nov 15;178(10):1075-82.
HR KIM **	1980-2007	South Korea	Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW, Han SK, Shim YS, Yim JJ. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis. 2007 Nov 15;45(10):1290-5.
KWON Δ	1995-2005	South Korea	Kwon YS, Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, Choi YS, Kim K, Kim J, Shim YM, Koh WJ. Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis. 2008 Aug 15;47(4):496-502.
MIGLIORI***	2001-2004	Italy	Migliori GB, Lange C, Centis R, Sotgiu G, Mütterlein R, Hoffmann H, Kliiman K, De Iaco G, Lauria FN, Richardson MD, Spanevello A, Cirillo DM; TBNET Study Group. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J. 2008 Jun;31(6):1155-9.
MITNICK	1996-2002	Peru	Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcántara F, Sánchez E, Sarria M, Becerra M, Fawzi MC, Kapiga S, Neuberg D, Maguire JH, Kim

			JY, Farmer P. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med. 2003 Jan 9;348(2):119-28.
MUNSIFF/LI	1992-1997	USA	Munsiff SS, Ahuja SD, Li J, Driver CR. Public-private collaboration for multidrug-resistant tuberculosis control in New York City. Int J Tuberc Lung Dis. 2006 Jun;10(6):639-48.
NARITA	1993-1997	USA	Narita M, Alonso P, Lauzardo M, Hollender ES, Pitchenik AE, Ashkin D. Treatment experience of multidrug-resistant tuberculosis in Florida, 1994-1997. Chest. 2001 Aug;120(2):343-8.
O'RIORDAN	1982-2004	UK	O'Riordan P, Schwab U, Logan S, Cooke G, Wilkinson RJ, Davidson RN, Bassett P, Wall R, Pasvol G, Flanagan KL. Rapid molecular detection of rifampicin resistance facilitates early diagnosis and treatment of multi-drug resistant tuberculosis: case control study. PLoS One. 2008 Sep 9;3(9):e3173.
PALMERO	1996-1999	Argentina	Palmero DJ, Ambroggi M, Brea A, De Lucas M, Fulgenzi A, Martínez D, Mosca C, Musella R, Natiello M, Gonzalez C, Abbate E. Treatment and follow-up of HIV-negative multidrug-resistant tuberculosis patients in an infectious diseases reference hospital, Buenos Aires, Argentina. Int J Tuberc Lung Dis. 2004 Jun;8(6):778-84.
PARK	1998-2002	South Korea	Park SK, Lee WC, Lee DH, Mitnick CD, Han L, Seung KJ. Self-administered, standardized regimens for multidrug-resistant tuberculosis in South Korea. Int J Tuberc Lung Dis. 2004 Mar;8(3):361-8.

SHIN	2000-2004	Russian Federation (Tomsk)	Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, Barnashov A, Karpeichik Y, Andreev YG, Golubchikova VT, Tonkel TP, Yanova GV, Nikiforov M, Yedilbayev A, Mukherjee JS, Furin JJ, Barry DJ, Farmer PE, Rich ML, Keshavjee S. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis. 2006 Apr;10(4):402-8. Erratum in: Int J Tuberc Lung Dis. 2006 Oct;10(10):1183. Mishustin, S [added]; Barnashov, A [added]; Karpeichik, Y [added].
SHIRAISHI	2000-2007	Japan	Shiraishi Y, Nakajima Y, Katsuragi N, Kurai M, Takahashi N. Resectional surgery combined with chemotherapy remains the treatment of choice for multidrug-resistant tuberculosis. J Thorac Cardiovasc Surg. 2004 Oct;128(4):523-8.
UFFREDI	1998-1999	France	Uffredi ML, Truffot-Pernot C, Dautzenberg B, Renard M, Jarlier V, Robert J. An intervention programme for the management of multidrug-resistant tuberculosis in France. Int J Antimicrob Agents. 2007 Apr;29(4):434-9.
COX	2003-2005	Uzbekistan	Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsch-Gerdes S, Karimovich HA, Kebede Y, Mills C. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLoS One. 2007 Nov 7;2(11):e1126.

DERIEMER	1994-2009	Mexico	DeRiemer K, García-García L, Bobadilla-del-Valle M, Palacios-Martínez M, Martínez-Gamboa A, Small PM, Sifuentes-Osornio J, Ponce-de-León A. Does DOTS work in populations with drug-resistant tuberculosis? Lancet. 2005 Apr 2-8;365(9466):1239-45.
HOLTZ	2000-2004	South Africa	Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, Skripconoka V, Wells CD, Leimane V. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med. 2006 May 2;144(9):650-9.
MASJEDI ΔΔ	2002-2006	Iran	Masjedi MR, Tabarsi P, Chitsaz E, Baghaei P, Mirsaeidi M, Amiri MV, Farnia P, Javanmard P, Mansouri D, Velayati AA. Outcome of treatment of MDR-TB patients with standardised regimens, Iran, 2002-2006. Int J Tuberc Lung Dis. 2008 Jul;12(7):750-5.
PEREZ-GUZMAN	1994-1995	Mexico	Pérez-Guzmán C, Vargas MH, Martínez-Rossier LA, Torres-Cruz A, Villarreal-Velarde H. Results of a 12-month regimen for drug-resistant pulmonary tuberculosis. Int J Tuberc Lung Dis. 2002 Dec;6(12):1102-9.
QUY	1998-2000	Vietnam	Quy HT, Cobelens FG, Lan NT, Buu TN, Lambregts CS, Borgdorff MW. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. Int J Tuberc Lung Dis. 2006 Jan;10(1):45-51.

SCHAAF	1998-2002	South Africa	Schaaf HS, Shean K, Donald PR. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. Arch Dis Child. 2003 Dec;88(12):1106-11.
TUPASI °	1999-2003	Philippines	Tupasi TE, Gupta R, Quelapio MI, Orillaza RB, Mira NR, Mangubat NV, Belen V, Arnisto N, Macalintal L, Arabit M, Lagahid JY, Espinal M, Floyd K. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006 Sep;3(9):e352.

Supplementary Table 2. Studies included in the systematic review performed by The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017.

FIRST AUTHOR	YEARS	STUDY LOCATION	REFERENCE
AHMAD N	2012-2013	Peshawar, Pakistan	Ahmad N, Javaid A, Basit A, et al. Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance. Int J Tuberc Lung Dis. 2015. 19(9): p. 1109-14, i-ii.
ANGER HA	2000-2006	New York City, USA	Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM, Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. J Antimicrob Chemother. 2010. 65(4): p. 775-83.
ANDERSON LF	2004-2007	UK	Anderson LF, Tamne S, Watson JP, et al. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. Euro Surveill. 2013. 18(40)
BANG D	1992-2007	Denmark	Bang D, Lillebaek T, Thomsen VO, Andersen AB. Multidrug-resistant tuberculosis: treatment outcome in Denmark, 1992-2007. Scand J Infect Dis. 2010. 42(4): p. 288-93
LEE M	2008-2011	Seoul and Changwon, South Korea	Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012. 367(16): p. 1508-18.

LEE M	2008-2011	Seoul and Changwon, South Korea	Lee M, Cho SN, Barry CE, 3rd, Song T, Kim Y, Jeong I. Linezolid for XDR-TB--Final Study Outcomes. N Engl J Med. 2015. 373(3): p. 290-1.
BARRY PM	2009-2015	California, USA	Barry PM, Flood J, Lowenthal P, Westenhouse J, California Department of Public Health. Unpublished data (California, USA). 2016.
BONNET M	2001-2014	Abkhazia	Bonnet M, Pardini M, Meacci F, et al. Treatment of tuberculosis in a region with high drug resistance: outcomes, drug resistance amplification and re-infection. PLoS One. 2011. 6(8): p. e23081
BRODE S	2010-2014	Toronto, Canada	Brode S, West Park Healthcare Centre. Unpublished data (Toronto, Canada). 2016.
BRUST JC	2000-2003	KwaZulu-Natal, South Africa	Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrugresistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. Int J Tuberc Lung Dis. 2010. 14(4): p. 413-9.
CEGIELSKI JP	2005-2010	Multination (Estonia, Latvia, Philippines, Peru, Russia, South Africa, South Korea, Taiwan, Thailand)	Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. Clin Infect Dis. 2016. 62(4): p. 418-430.

YUEN CM	2005-2010	Multination (Estonia, Latvia, Philippines, Peru, Russia, South Africa, South Korea, Taiwan, Thailand)	Yuen CM, Kurbatova EV, Tupasi T, et al. Association between Regimen Composition and Treatment Response in Patients with Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. PLoS Med. 2015. 12(12): p. e1001932
CHAN ED	1999-2015	Denver, USA	Chan ED, National Jewish Health. Unpublished data (Denver, USA). 2016.
CHAN PC	2000-2008	Taiwan	Chan PC, Huang SH, Yu MC, et al. Effectiveness of a government-organized and hospital-initiated treatment for multidrugresistant tuberculosis patients--a retrospective cohort study. PLoS One. 2013. 8(2): p. e57719
PIETERSEN E	2002-2008	Cape Town, Upington and Johannesburg in South Africa	Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014. 383(9924): p. 1230-9.
SHEAN K	2002-2008	Cape Town, Upington and Johannesburg in South Africa	Shean K, Streicher E, Pieterson E, Symons G, van Zyl Smit R, Theron G, Lehloenya R, Padanilam X, Wilcox P, Victor TC, van Helden P, Grobusch MP, Warren R, Badri M, Dheda K. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively

			drug-resistant tuberculosis in South Africa. PLoS One. 2013 May 7;8(5):e63057.
GEGIA M	2008	Georgia	Gegia M, Kalandadze I, Kempker RR, Magee MJ, Blumberg HM. Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. Int J Infect Dis. 2012. 16(5): p. e391-6.
GUGLIELMETTI L	2010-2013	Paris, France	Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrugresistant tuberculosis. Eur Respir J. 2017. 49(3).
GUGLIELMETTI L	2010-2013	Paris, France	Guglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis. 2015. 60(2): p. 188-94.
HUGHES J	2011-2015	Khayelitsha, South Africa	Hughes J, Isaakidis P, Andries A, et al. Linezolid for multidrug-resistant tuberculosis in HIV-infected and -uninfected patients. Eur Respir J. 2015. 46(1): p. 271-4.
ISAAKIDIS P	2006-2016	Mumbai, India	Isaakidis P, Varghese B, Mansoor H, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One. 2012. 7(7): p. e40781.
JARLSBERG L	2001-2015	San Francisco, USA	Jarlsberg L, Nahid P. Unpublished data (San Francisco, USA). 2016.

KEMPKER RR	2009-2012	Tbilisi, Georgia	Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM. Acquired Drug Resistance in Mycobacterium tuberculosis and Poor Outcomes among Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2015. 21(6): p. 992-1001
CHARLES M	2008-2015	Port-au-Prince, Haiti	Charles M, Vilbrun SC, Koenig SP, et al. Treatment outcomes for patients with multidrug-resistant tuberculosis in postearthquake Port-au-Prince, Haiti. Am J Trop Med Hyg. 2014. 91(4): p. 715-2
JEONG BH	2005-2011	Seoul, South Korea	Jeong BH, Jeon K, Park HY, et al. Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment. J Antimicrob Chemother. 2015. 70(11): p. 3127-33.
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KVASNOVSKY CL	2006-2008	Eastern Cape and KwaZulu-Natal, South Africa	Kvasnovsky CL, Cegielski JP, Erasmus R, Siwisa NO, Thomas K, der Walt ML. Extensively drug-resistant TB in Eastern Cape, South Africa: high mortality in HIV-negative and HIV-positive patients. J Acquir Immune Defic Syndr. 2011. 57(2): p. 146-52.
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CHANG KC	1996-2009	Hong Kong	Chang KC, Leung CC, Yew WW, et al. Pyrazinamide may improve fluoroquinolone-based treatment of multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2012. 56(11): p. 5465-75
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TIBERI S	2003-2015	Multination (Italy, Belgium, Ecuador, Belarus, Greece, Peru, Slovakia, Netherlands, UK)	Tiberi S, Payen MC, Sotgiu G, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016. 47(4): p. 1235-43.
TIBERI S	2003-2015	Multination (Italy, Belgium, Ecuador, Belarus, Greece, Peru, Slovakia, Netherlands, UK)	Tiberi S, Sotgiu G, D'Ambrosio L, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016. 47(6): p. 1758-66.
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O'DONNELL MR	2006-2010	KwaZulu-Natal, South Africa	O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Horsburgh CR, Jr. Treatment outcomes for extensively drugresistant tuberculosis and HIV co-infection. Emerg Infect Dis. 2013. 19(3): p. 416-24.
PALMERO D	2012-2013	Buenos Aires, Argentina	Palmero D, Gonzalez Montaner P, Cufre M, Garcia A, Vescovo M, Poggi S. First series of patients with XDR and pre-XDR TB treated with regimens that included meropenen-clavulanate in Argentina. Arch Bronconeumol. 2015. 51(10): p. e49-52
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RODRIGUEZ M	2006-2010	Dominican Republic	Rodriguez M, Monedero I, Caminero JA, et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013. 17(4): p. 520-5.
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DIACON AH	2008-2009	Multination (Brazil, India, Latvia, Peru, Philippines, Russia, South Africa, Thailand)	Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009. 360(23): p. 2397-405.

PYM AS	2009-2010	Multination (China, South Korea, Philippines, Thailand, Estonia, Latvia, Russia, Turkey, Ukraine)	Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016. 47(2): p. 564-74.
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Supplementary Table 3. Comparison of the included and excluded patients from the source population.

	Overall (Source population)	Study population	Patients excluded
n	12938	6025	6913
Year of treatment start (mean (SD))	2009.58 (4.75)	2008.79 (3.20)	2010.26 (5.68)
Income (%)			
Low	515 (4.0)	515 (8.5)	0 (0.0)
Lower_Middle	1392 (10.8)	1086 (18.0)	306 (4.4)
Upper_Middle	8462 (65.4)	2517 (41.8)	5945 (86.0)
High	2569 (19.9)	1907 (31.7)	662 (9.6)
Age (mean (SD))	37.01 (12.80)	38.22 (13.00)	35.94 (12.53)
Sex (%)			
Female	5062 (39.1)	2192 (36.4)	2870 (41.5)
Male	7874 (60.9)	3832 (63.6)	4042 (58.5)
Missing	2 (0.0)	1 (0.0)	1 (0.0)
BMI (mean (SD))	20.11 (3.79)	20.11 (3.63)	20.10 (4.30)
Smoking ever (%)			
No	2933 (22.7)	2465 (40.9)	468 (6.8)
Yes	1784 (13.8)	1322 (21.9)	462 (6.7)
Missing	8221 (63.5)	2238 (37.1)	5983 (86.5)
Alcohol consumption (%)			
No	3473 (26.8)	2825 (46.9)	648 (9.4)

Yes	1326 (10.2)	1109 (18.4)	217 (3.1)
Missing	8139 (62.9)	2091 (34.7)	6048 (87.5)
HIV (%)			
Negative	8295 (64.1)	5313 (88.2)	2982 (43.1)
Positive	3973 (30.7)	625 (10.4)	3348 (48.4)
Missing	670 (5.2)	87 (1.4)	583 (8.4)
Diabetes Mellitus (%)			
No	5590 (43.2)	4405 (73.1)	1185 (17.1)
Yes	736 (5.7)	548 (9.1)	188 (2.7)
Missing	6612 (51.1)	1072 (17.8)	5540 (80.1)
Past antituberculosis treatment (%)			
No	3762 (29.1)	1295 (21.5)	2467 (35.7)
Yes	8939 (69.1)	4645 (77.1)	4294 (62.1)
Missing	237 (1.8)	85 (1.4)	152 (2.2)
Bilateral disease (%)			
No	1683 (13.0)	1397 (23.2)	286 (4.1)
Yes	3805 (29.4)	3250 (53.9)	555 (8.0)
Missing	7450 (57.6)	1378 (22.9)	6072 (87.8)
Sputum smear status (%)			
Negative	2913 (22.5)	1148 (19.1)	1765 (25.5)
Positive	7327 (56.6)	3685 (61.2)	3642 (52.7)
Missing	2698 (20.9)	1192 (19.8)	1506 (21.8)

Cavitary disease (%)			
No	2497 (19.3)	1872 (31.1)	625 (9.0)
Yes	4025 (31.1)	3187 (52.9)	838 (12.1)
Missing	6416 (49.6)	966 (16.0)	5450 (78.8)
DST-FQ (%)			
Resistant	2923 (22.6)	1429 (23.7)	1494 (21.6)
Susceptible	6615 (51.1)	4281 (71.1)	2334 (33.8)
Missing	3400 (26.3)	315 (5.2)	3085 (44.6)
DST-E (%)			
Resistant	5722 (44.2)	4006 (66.5)	1716 (24.8)
Susceptible	2844 (22.0)	1803 (29.9)	1041 (15.1)
Missing	4372 (33.8)	216 (3.6)	4156 (60.1)
DST-Z (%)			
Resistant	2934 (22.7)	2254 (37.4)	680 (9.8)
Susceptible	2545 (19.7)	1887 (31.3)	658 (9.5)
Missing	7459 (57.7)	1884 (31.3)	5575 (80.6)
DST-S (%)			
Resistant	6158 (47.6)	4006 (66.5)	2152 (31.1)
Susceptible	2573 (19.9)	1475 (24.5)	1098 (15.9)
Missing	4207 (32.5)	544 (9.0)	3663 (53.0)
DST-PAS (%)			
Resistant	889 (6.9)	728 (12.1)	161 (2.3)

Susceptible	4172 (32.2)	3433 (57.0)	739 (10.7)
Missing	7877 (60.9)	1864 (30.9)	6013 (87.0)
Directed observed therapy (%)			
No	1824 (14.1)	453 (7.5)	1371 (19.8)
Yes	10445 (80.7)	5150 (85.5)	5295 (76.6)
Missing	669 (5.2)	422 (7.0)	247 (3.6)
Fluoroquinolone ever = Yes (%)	8500 (65.7)	3711 (61.6)	4789 (69.3)
Linezolid ever = Yes (%)	2028 (15.7)	916 (15.2)	1112 (16.1)
Bedaquiline ever = Yes (%)	2115 (16.3)	537 (8.9)	1578 (22.8)
Time to conversion, months, (mean (SD))	2.61 (3.29)	2.63 (3.24)	2.59 (3.33)
End of treatment outcome (%)			
Complete	1212 (9.4)	498 (8.3)	714 (10.3)
Cure	5934 (45.9)	3445 (57.2)	2489 (36.0)
Death	2030 (15.7)	762 (12.6)	1268 (18.3)
Fail	1000 (7.7)	418 (6.9)	582 (8.4)
Lost	2123 (16.4)	831 (13.8)	1292 (18.7)
Success	526 (4.1)	0 (0.0)	526 (7.6)
Transfer	113 (0.9)	71 (1.2)	42 (0.6)
Recurrence (%)			
No	742 (5.7)	577 (9.6)	165 (2.4)
Yes	18 (0.1)	16 (0.3)	2 (0.0)
Missing	12178 (94.1)	5432 (90.2)	6746 (97.6)

Treatment length, months (mean (SD))	566.51 (241.48)	588.54 (234.82)	548.05 (245.42)

Abbreviations: DST, drug susceptibility testing; E, ethambutol, FQ, fluoroquinolones; PAS, para-amino salicylic acid; S, streptomycin; Z, pyrazinamide.

Supplementary Table 4. Distribution of the pre-treatment covariates after sequential propensity score matching using as controls only patients from non-surgical studies.

	Surgery = No	Surgery = Yes	SMD
n	242	242	
Year (mean (SD))	2009.75 (4.16)	2009.30 (3.12)	0.122
Income (%)			0.41
Low	6 (2.5)	1 (0.4)	
Lower_Middle	7 (2.9)	13 (5.4)	
Upper_Middle	61 (25.2)	99 (40.9)	
High	168 (69.4)	129 (53.3)	
Age (mean (SD))	37.11 (12.80)	35.51 (11.50)	0.131
Sex = M (%)	149 (61.6)	143 (59.1)	0.051
BMI (mean (SD))	19.51 (4.11)	20.27 (3.19)	0.208
Smoking = Yes (%)	132 (54.5)	136 (56.2)	0.033
Alcohol = Yes (%)	20 (8.3)	48 (19.8)	0.338
DM = Yes (%)	25 (10.3)	20 (8.3)	0.071
HIV = Pos (%)	1 (0.4)	5 (2.1)	0.15
Past antituberculosis treatment = Yes (%)	191 (78.9)	192 (79.3)	0.01
Bilateral disease = Yes (%)	165 (68.2)	165 (68.2)	<0.001
Cavitary disease = Yes (%)	190 (78.5)	194 (80.2)	0.041

AFB = Pos (%)	194 (80.2)	181 (74.8)	0.129
groupA (mean (SD))	1.18 (0.63)	1.12 (0.76)	0.089
groupB (mean (SD))	0.94 (0.66)	1.00 (0.51)	0.091
groupC (mean (SD))	1.29 (1.16)	1.26 (1.09)	0.029

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 5. Distribution of the pre-treatment covariates after sequential propensity score matching using as controls only patients from surgical studies.

	Surgery = No	Surgery = Yes	SMD
n	1376	344	
Year (mean (SD))	2008.86 (3.14)	2008.76 (3.48)	0.028
Income (%)			0.04
Low	2 (0.1)	1 (0.3)	
Lower_Middle	59 (4.3)	13 (3.8)	
Upper_Middle	540 (39.2)	135 (39.2)	
High	775 (56.3)	195 (56.7)	
Age (mean (SD))	33.88 (11.79)	34.79 (11.53)	0.078
Sex = M (%)	819 (59.5)	199 (57.8)	0.034
BMI (mean (SD))	20.54 (3.40)	20.49 (3.23)	0.014
Smoking = Yes (%)	746 (54.2)	186 (54.1)	0.003
Alcohol = Yes (%)	278 (20.2)	71 (20.6)	0.011
DM = Yes (%)	90 (6.5)	22 (6.4)	0.006
HIV = Pos (%)	18 (1.3)	6 (1.7)	0.036
Past antituberculosis treatment = Yes (%)	1015 (73.8)	257 (74.7)	0.022
Bilateral disease= Yes (%)	759 (55.2)	189 (54.9)	0.004
Cavitary disease = Yes (%)	988 (71.8)	251 (73.0)	0.026

AFB = Pos (%)	978 (71.1)	249 (72.4)	0.029
groupA (mean (SD))	1.10 (0.67)	1.09 (0.74)	0.014
groupB (mean (SD))	0.98 (0.50)	0.97 (0.52)	0.021
groupC (mean (SD))	1.33 (1.07)	1.29 (1.10)	0.04

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 6. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection according to the timing of surgery relative to the culture conversion date using as controls patients from surgical and non-surgical studies.

	BEFORE CONVERSION			AFTER CONVERSION		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	240	60		576	144	
Year (mean (SD))	2008.74 (3.59)	2008.22 (3.50)	0.147	2008.98 (3.37)	2008.80 (3.12)	0.056
Income (%)			0.092			<0.001
Low	0 (0.0)	0 (0.0)		4 (0.7)	1 (0.7)	
Lower_Middle	2 (0.8)	1 (1.7)		32 (5.6)	8 (5.6)	
Upper_Middle	41 (17.1)	9 (15.0)		212 (36.8)	53 (36.8)	
High	197 (82.1)	50 (83.3)		328 (56.9)	82 (56.9)	
Age (mean (SD))	38.33 (13.11)	37.20 (11.28)	0.092	33.46 (11.58)	33.49 (10.81)	0.003
Sex = M (%)	151 (62.9)	41 (68.3)	0.114	318 (55.2)	76 (52.8)	0.049
BMI (mean (SD))	21.09 (3.37)	21.18 (3.12)	0.028	20.58 (3.48)	20.37 (2.88)	0.065
Smoking = Yes (%)	137 (57.1)	39 (65.0)	0.163	292 (50.7)	71 (49.3)	0.028
Alcohol = Yes (%)	68 (28.3)	16 (26.7)	0.037	123 (21.4)	33 (22.9)	0.038
DM = Yes (%)	32 (13.3)	8 (13.3)	<0.001	14 (2.4)	6 (4.2)	0.097
HIV = Pos (%)	5 (2.1)	1 (1.7)	0.031	8 (1.4)	2 (1.4)	<0.001

Past antituberculosis treatment = Yes (%)	204 (85.0)	49 (81.7)	0.09	373 (64.8)	91 (63.2)	0.033
Bilateral disease = Yes (%)	152 (63.3)	36 (60.0)	0.069	312 (54.2)	78 (54.2)	<0.001
Cavitary disease = Yes (%)	170 (70.8)	41 (68.3)	0.054	354 (61.5)	93 (64.6)	0.065
AFB = Pos (%)	180 (75.0)	43 (71.7)	0.075	417 (72.4)	104 (72.2)	0.004
groupA (mean (SD))	1.07 (0.73)	1.07 (0.73)	<0.001	1.08 (0.65)	1.02 (0.68)	0.091
groupB (mean (SD))	0.82 (0.51)	0.75 (0.54)	0.127	0.95 (0.48)	0.92 (0.41)	0.07
groupC (mean (SD))	0.81 (0.99)	0.88 (0.85)	0.077	1.67 (1.14)	1.67 (1.08)	0.003

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 7. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection according to the additional presence of resistance to fluoroquinolones using as controls patients from surgical and non surgical studies.

	FQS			FQR		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	627	160		560	140	
Year (mean (SD))	2008.19 (3.12)	2008.32 (2.82)	0.042	2009.74 (3.23)	2009.61 (3.15)	0.042
Income (%)			0.003			<0.001
Low	4 (0.6)	1 (0.6)		0 (0.0)	0 (0.0)	
Lower_Middle	12 (1.9)	3 (1.9)		32 (5.7)	8 (5.7)	
Upper_Middle	298 (47.5)	76 (47.5)		172 (30.7)	43 (30.7)	
High	313 (49.9)	80 (50.0)		356 (63.6)	89 (63.6)	
Age (mean (SD))	34.74 (11.64)	34.87 (10.60)	0.012	36.46 (13.05)	34.54 (11.79)	0.154
Sex = M (%)	389 (62.0)	98 (61.3)	0.016	338 (60.4)	76 (54.3)	0.123
BMI (mean (SD))	20.67 (3.48)	20.76 (2.87)	0.026	20.05 (3.23)	20.00 (3.16)	0.015
Smoking = Yes (%)	320 (51.0)	87 (54.4)	0.067	314 (56.1)	78 (55.7)	0.007
Alcohol = Yes (%)	131 (20.9)	32 (20.0)	0.022	128 (22.9)	32 (22.9)	<0.001
DM = Yes (%)	22 (3.5)	7 (4.4)	0.045	44 (7.9)	12 (8.6)	0.026
HIV = Pos (%)	9 (1.4)	3 (1.9)	0.034	8 (1.4)	2 (1.4)	<0.001

Past antituberculosis treatment = Yes (%)	418 (66.7)	108 (67.5)	0.018	483 (86.2)	120 (85.7)	0.015
Bilateral disease = Yes (%)	333 (53.1)	84 (52.5)	0.012	340 (60.7)	87 (62.1)	0.029
Cavitary disease = Yes (%)	446 (71.1)	116 (72.5)	0.03	407 (72.7)	101 (72.1)	0.012
AFB = Pos (%)	448 (71.5)	118 (73.8)	0.052	392 (70.0)	98 (70.0)	<0.001
groupA (mean (SD))	1.23 (0.60)	1.25 (0.58)	0.034	0.76 (0.75)	0.76 (0.75)	<0.001
groupB (mean (SD))	0.93 (0.50)	0.94 (0.46)	0.016	0.99 (0.59)	0.98 (0.58)	0.015
groupC (mean (SD))	1.74 (1.10)	1.71 (1.06)	0.027	1.03 (1.06)	0.99 (1.00)	0.04

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 8. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection according to the ever use of two or more group A drugs using as controls patients from surgical and non-surgical studies.

	>= 2 group A drugs			0-1 group A drugs		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	423	106		832	208	
Year (mean (SD))	2010.95 (3.13)	2010.72 (3.74)	0.066	2007.92 (2.58)	2007.63 (2.47)	0.116
income (%)			0.001			<0.001
Low	0 (0.0)	0 (0.0)		0 (0.0)	4 (0.5)	
Lower_Middle	12 (2.8)	3 (2.8)		23 (4.5)	28 (3.4)	
Upper_Middle	100 (23.6)	25 (23.6)		108 (21.3)	400 (48.1)	
High	311 (73.5)	78 (73.6)		375 (74.1)	400 (48.1)	
Age (mean (SD))	36.71 (12.61)	35.07 (11.16)	0.138	34.68 (12.08)	34.40 (11.69)	0.024
Sex = M (%)	233 (55.1)	58 (54.7)	0.007	479 (57.6)	123 (59.1)	0.032
BMI (mean (SD))	19.92 (3.39)	20.17 (3.06)	0.078	20.80 (3.49)	20.69 (3.03)	0.034
Smoking = Yes (%)	264 (62.4)	63 (59.4)	0.061	413 (49.6)	105 (50.5)	0.017
Alcohol = Yes (%)	80 (18.9)	24 (22.6)	0.092	212 (25.5)	45 (21.6)	0.091
DM = Yes (%)	40 (9.5)	9 (8.5)	0.034	35 (4.2)	12 (5.8)	0.072
HIV = Pos (%)	7 (1.7)	3 (2.8)	0.079	7 (0.8)	2 (1.0)	0.013

Past antituberculosis treatment = Yes (%)	343 (81.1)	84 (79.2)	0.046	613 (73.7)	150 (72.1)	0.035
Bilateral disease = Yes (%)	252 (59.6)	62 (58.5)	0.022	433 (52.0)	111 (53.4)	0.026
Cavitary disease = Yes (%)	329 (77.8)	80 (75.5)	0.055	574 (69.0)	149 (71.6)	0.058
AFB = Pos (%)	352 (83.2)	84 (79.2)	0.102	575 (69.1)	143 (68.8)	0.008
groupA (mean (SD))	1.63 (0.62)	1.68 (0.64)	0.08	0.71 (0.49)	0.70 (0.49)	0.02
groupB (mean (SD))	0.82 (0.49)	0.82 (0.49)	0.006	1.02 (0.51)	1.00 (0.51)	0.028
groupC (mean (SD))	0.80 (0.85)	0.79 (0.85)	0.011	1.54 (1.12)	1.62 (1.13)	0.075

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 9. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection surgery according to the presence of cavitary disease using as controls patients from surgical and non-surgical studies.

	CAVITARY DISEASE			NON CAVITARY DISEASE		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	972	243		336	84	
Year (mean (SD))	2009.13 (3.80)	2008.93 (3.29)	0.055	2008.27 (3.18)	2008.40 (3.46)	0.039
income (%)			0.075			0.062
Low	3 (0.3)	1 (0.4)		0 (0.0)	0 (0.0)	
Lower_Middle	55 (5.7)	12 (4.9)		3 (0.9)	1 (1.2)	
Upper_Middle	371 (38.2)	101 (41.6)		117 (34.8)	27 (32.1)	
High	543 (55.9)	129 (53.1)		216 (64.3)	56 (66.7)	
Age (mean (SD))	35.26 (12.09)	35.20 (10.99)	0.005	34.56 (13.69)	33.17 (11.72)	0.109
Sex = M (%)	602 (61.9)	150 (61.7)	0.004	151 (44.9)	38 (45.2)	0.006
BMI (mean (SD))	20.15 (3.23)	20.33 (3.22)	0.056	21.18 (3.32)	20.82 (2.58)	0.123
Smoking = Yes (%)	554 (57.0)	130 (53.5)	0.07	177 (52.7)	44 (52.4)	0.006
Alcohol = Yes (%)	223 (22.9)	51 (21.0)	0.047	66 (19.6)	17 (20.2)	0.015
DM = Yes (%)	56 (5.8)	16 (6.6)	0.034	24 (7.1)	6 (7.1)	<0.001
HIV = Pos (%)	13 (1.3)	4 (1.6)	0.025	7 (2.1)	2 (2.4)	0.02

Past antituberculosis treatment = Yes (%)	763 (78.5)	193 (79.4)	0.023	213 (63.4)	52 (61.9)	0.031
Bilateral disease = Yes (%)	560 (57.6)	143 (58.8)	0.025	146 (43.5)	38 (45.2)	0.036
Cavitary disease = Yes (%)	972 (100.0)	243 (100.0)	<0.001	0 (0.0)	0 (0.0)	<0.001
AFB = Pos (%)	764 (78.6)	189 (77.8)	0.02	188 (56.0)	49 (58.3)	0.048
groupA (mean (SD))	1.15 (0.69)	1.12 (0.75)	0.041	0.95 (0.66)	0.98 (0.64)	0.046
groupB (mean (SD))	0.97 (0.50)	0.97 (0.52)	0.014	0.94 (0.44)	0.94 (0.50)	0.006
groupC (mean (SD))	1.35 (1.10)	1.35 (1.12)	0.005	1.18 (1.06)	1.15 (1.01)	0.026

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 10. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection according to the presence of bilateral disease using as controls patients from surgical and non-surgical studies.

	BILATERAL DISEASE			NON BILATERAL DISEASE		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	604	151		520	130	
Year (mean (SD))	2008.70 (2.88)	2008.73 (2.76)	0.011	2008.44 (3.40)	2008.42 (3.40)	0.008
income (%)			<0.001			0.037
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	24 (4.0)	6 (4.0)		15 (2.9)	3 (2.3)	
Upper_Middle	224 (37.1)	56 (37.1)		221 (42.5)	56 (43.1)	
High	356 (58.9)	89 (58.9)		284 (54.6)	71 (54.6)	
Age (mean (SD))	35.89 (11.65)	35.44 (10.63)	0.041	34.63 (12.75)	32.99 (10.88)	0.138
Sex = M (%)	412 (68.2)	98 (64.9)	0.07	271 (52.1)	65 (50.0)	0.042
BMI (mean (SD))	20.09 (3.17)	20.01 (2.97)	0.028	20.71 (3.24)	20.81 (3.14)	0.032
Smoking = Yes (%)	337 (55.8)	80 (53.0)	0.057	246 (47.3)	60 (46.2)	0.023
Alcohol = Yes (%)	104 (17.2)	27 (17.9)	0.017	93 (17.9)	21 (16.2)	0.046
DM = Yes (%)	27 (4.5)	11 (7.3)	0.12	19 (3.7)	5 (3.8)	0.01
HIV = Pos (%)	13 (2.2)	4 (2.6)	0.032	0 (0.0)	0 (0.0)	<0.001
Past antituberculosis treatment = Yes (%)	486 (80.5)	120 (79.5)	0.025	387 (74.4)	94 (72.3)	0.048

Bilateral disease = Yes (%)	604 (100.0)	151 (100.0)	<0.001	0 (0.0)	0 (0.0)	<0.001
Cavitary disease = Yes (%)	488 (80.8)	125 (82.8)	0.051	387 (74.4)	91 (70.0)	0.099
AFB = Pos (%)	455 (75.3)	118 (78.1)	0.067	345 (66.3)	81 (62.3)	0.084
groupA (mean (SD))	1.08 (0.60)	1.06 (0.70)	0.028	1.08 (0.62)	1.02 (0.66)	0.09
groupB (mean (SD))	0.94 (0.55)	0.93 (0.52)	0.028	0.95 (0.51)	0.98 (0.49)	0.046
groupC (mean (SD))	1.35 (1.08)	1.36 (1.04)	0.011	1.39 (1.04)	1.38 (1.19)	0.01

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 11. Distribution of baseline covariates after sequential propensity score matching patients with any extent of pulmonary resection according to the level of surgical experience per center using as controls patients from surgical and non-surgical studies.

	MORE EXPERIENCED			LESS EXPERIENCED		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	972	243		336	84	
Year (mean (SD))	2009.19 (2.48)	2009.03 (2.50)	0.063	2008.28 (4.65)	2008.25 (5.03)	0.006
income (%)			<0.001			0.013
Low	0 (0.0)	0 (0.0)		4 (1.2)	1 (1.2)	
Lower_Middle	8 (0.8)	2 (0.8)		36 (10.7)	9 (10.7)	
Upper_Middle	432 (44.4)	108 (44.4)		98 (29.2)	25 (29.8)	
High	532 (54.7)	133 (54.7)		198 (58.9)	49 (58.3)	
Age (mean (SD))	35.29 (12.58)	35.11 (11.15)	0.015	33.52 (12.78)	33.49 (11.98)	0.002
Sex = M (%)	564 (58.0)	147 (60.5)	0.05	189 (56.2)	43 (51.2)	0.102
BMI (mean (SD))	20.82 (3.59)	20.65 (3.03)	0.051	20.28 (3.24)	20.28 (3.45)	0.001
Smoking = Yes (%)	499 (51.3)	125 (51.4)	0.002	218 (64.9)	54 (64.3)	0.012
Alcohol = Yes (%)	236 (24.3)	57 (23.5)	0.019	51 (15.2)	12 (14.3)	0.025
DM = Yes (%)	70 (7.2)	18 (7.4)	0.008	15 (4.5)	3 (3.6)	0.045
HIV = Pos (%)	12 (1.2)	3 (1.2)	<0.001	9 (2.7)	2 (2.4)	0.019

Past antituberculosis treatment = Yes (%)	724 (74.5)	186 (76.5)	0.048	234 (69.6)	58 (69.0)	0.013
Bilateral disease = Yes (%)	556 (57.2)	133 (54.7)	0.05	204 (60.7)	46 (54.8)	0.121
Cavitary disease = Yes (%)	731 (75.2)	186 (76.5)	0.031	207 (61.6)	51 (60.7)	0.018
AFB = Pos (%)	706 (72.6)	172 (70.8)	0.041	253 (75.3)	64 (76.2)	0.021
groupA (mean (SD))	1.04 (0.67)	1.05 (0.70)	0.009	1.07 (0.69)	1.08 (0.81)	0.02
groupB (mean (SD))	0.96 (0.54)	0.95 (0.49)	0.01	0.90 (0.49)	0.88 (0.52)	0.029
groupC (mean (SD))	1.31 (1.14)	1.33 (1.09)	0.012	1.28 (1.00)	1.32 (1.16)	0.036

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 12. Distribution of baseline covariates after sequential propensity score matching according to the extent of pulmonary resection using as controls patients from surgical and non-surgical studies.

	PARTIAL LUNG RESECTION			TOTAL LUNG RESECTION		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	1004	251		196	54	
Year (mean (SD))	2009.13 (3.41)	2008.90 (3.11)	0.073	2008.69 (3.22)	2008.37 (3.05)	0.101
income (%)			<0.001			0.081
Low	0 (0.0)	0 (0.0)		4 (2.0)	1 (1.9)	
Lower_Middle	28 (2.8)	7 (2.8)		12 (6.1)	3 (5.6)	
Upper_Middle	428 (42.6)	107 (42.6)		68 (34.7)	17 (31.5)	
High	548 (54.6)	137 (54.6)		112 (57.1)	33 (61.1)	
Age (mean (SD))	35.22 (12.53)	35.00 (12.00)	0.018	34.86 (11.28)	35.04 (10.18)	0.016
Sex = M (%)	594 (59.2)	146 (58.2)	0.02	121 (61.7)	35 (64.8)	0.064
BMI (mean (SD))	20.89 (3.50)	20.80 (3.05)	0.025	20.23 (3.57)	19.47 (2.53)	0.246
Smoking = Yes (%)	556 (55.4)	140 (55.8)	0.008	95 (48.5)	26 (48.1)	0.006
Alcohol = Yes (%)	222 (22.1)	58 (23.1)	0.024	50 (25.5)	10 (18.5)	0.169
DM = Yes (%)	60 (6.0)	15 (6.0)	<0.001	23 (11.7)	4 (7.4)	0.147
HIV = Pos (%)	10 (1.0)	3 (1.2)	0.019	4 (2.0)	1 (1.9)	0.014
Past antituberculosis treatment = Yes (%)	726 (72.3)	181 (72.1)	0.004	168 (85.7)	48 (88.9)	0.095

Bilateral = Yes (%)	532 (53.0)	132 (52.6)	0.008	135 (68.9)	35 (64.8)	0.086
Cavity = Yes (%)	732 (72.9)	178 (70.9)	0.044	158 (80.6)	44 (81.5)	0.022
AFB = Pos (%)	677 (67.4)	168 (66.9)	0.011	181 (92.3)	49 (90.7)	0.058
groupA (mean (SD))	1.04 (0.67)	1.02 (0.71)	0.042	1.04 (0.60)	1.04 (0.70)	0.006
groupB (mean (SD))	0.98 (0.53)	0.96 (0.52)	0.038	0.89 (0.50)	0.87 (0.44)	0.037
groupC (mean (SD))	1.30 (1.10)	1.29 (1.07)	0.003	1.47 (1.13)	1.70 (1.18)	0.199

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 13. Distribution of baseline covariates after sequential propensity score matching according to the extent of pulmonary resection using as controls patients from non-surgical studies only.

	PARTIAL LUNG RESECTION			TOTAL LUNG RESECTION		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	146	53		220	55	
Year (mean (SD))	2010.53 (3.72)	2010.19 (3.19)	0.098	2010.99 (3.54)	2008.47 (3.29)	0.735
income (%)			0.307			<0.001
Low	0 (0.0)	0 (0.0)			0 (0.0)	
Lower_Middle	15 (10.3)	6 (11.3)			12 (5.5)	
Upper_Middle	60 (41.1)	29 (54.7)			64 (29.1)	
High	71 (48.6)	18 (34.0)			144 (65.5)	
Age (mean (SD))	37.85 (12.91)	35.90 (11.69)	0.158	34.69 (11.27)	34.97 (9.96)	0.026
Sex = M (%)	88 (60.3)	35 (66.0)	0.12	136 (61.8)	35 (63.6)	0.038
BMI (mean (SD))	20.07 (3.95)	20.22 (3.76)	0.037	19.69 (3.30)	19.41 (2.56)	0.093
Smoking = Yes (%)	80 (54.8)	31 (58.5)	0.075	119 (54.1)	28 (50.9)	0.064
Alcohol = Yes (%)	28 (19.2)	12 (22.6)	0.085	25 (11.4)	10 (18.2)	0.193
DM = Yes (%)	27 (18.5)	5 (9.4)	0.264	16 (7.3)	4 (7.3)	<0.001
HIV = Pos (%)	3 (2.1)	1 (1.9)	0.012	4 (1.8)	1 (1.8)	<0.001
Past antituberculosis treatment = Yes (%)	121 (82.9)	43 (81.1)	0.045	200 (90.9)	50 (90.9)	<0.001

Bilateral disease = Yes (%)	109 (74.7)	38 (71.7)	0.067	136 (61.8)	34 (61.8)	<0.001
Cavitary disease = Yes (%)	111 (76.0)	44 (83.0)	0.174	168 (76.4)	45 (81.8)	0.134
AFB = Pos (%)	118 (80.8)	43 (81.1)	0.008	201 (91.4)	50 (90.9)	0.016
groupA (mean (SD))	1.11 (0.54)	1.15 (0.53)	0.077	1.42 (0.69)	1.11 (0.76)	0.43
groupB (mean (SD))	0.84 (0.61)	1.04 (0.59)	0.337	0.81 (0.60)	0.89 (0.42)	0.159
groupC (mean (SD))	1.34 (0.97)	1.13 (0.96)	0.218	0.99 (1.09)	1.62 (1.21)	0.546

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 14. Distribution of baseline covariates after sequential propensity score matching according to the extent of pulmonary resection using as controls patients from surgical studies only.

	PARTIAL LUNG RESECTION			TOTAL LUNG RESECTION		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	1004	251		236	59	
Year (mean (SD))	2009.02 (3.19)	2008.90 (3.11)	0.04	2008.41 (3.07)	2008.56 (3.24)	0.048
Income (%)			<0.001			<0.001
Low	0 (0.0)	0 (0.0)			4 (1.7)	
Lower_Middle	28 (2.8)	7 (2.8)			16 (6.8)	
Upper_Middle	428 (42.6)	107 (42.6)			68 (28.8)	
High	548 (54.6)	137 (54.6)			148 (62.7)	
Age (mean (SD))	35.00 (12.48)	35.00 (12.00)	<0.001	33.88 (10.80)	35.04 (10.25)	0.109
Sex = M (%)	595 (59.3)	146 (58.2)	0.022	148 (62.7)	37 (62.7)	<0.001
BMI (mean (SD))	20.67 (3.73)	20.80 (3.05)	0.04	19.85 (3.15)	19.45 (2.50)	0.143
Smoking = Yes (%)	568 (56.6)	140 (55.8)	0.016	114 (48.3)	29 (49.2)	0.017
Alcohol = Yes (%)	210 (20.9)	58 (23.1)	0.053	39 (16.5)	11 (18.6)	0.056
DM = Yes (%)	64 (6.4)	15 (6.0)	0.017	21 (8.9)	4 (6.8)	0.079
HIV = Pos (%)	12 (1.2)	3 (1.2)	<0.001	11 (4.7)	2 (3.4)	0.065
Past antituberculosis treatment = Yes (%)	699 (69.6)	181 (72.1)	0.055	210 (89.0)	53 (89.8)	0.028

Bilateral disease = Yes (%)	513 (51.1)	132 (52.6)	0.03	153 (64.8)	38 (64.4)	0.009
Cavitary disease = Yes (%)	702 (69.9)	178 (70.9)	0.022	192 (81.4)	49 (83.1)	0.044
AFB = Pos (%)	664 (66.1)	168 (66.9)	0.017	213 (90.3)	54 (91.5)	0.044
groupA (mean (SD))	1.06 (0.65)	1.02 (0.71)	0.063	1.13 (0.63)	1.12 (0.74)	0.012
groupB (mean (SD))	0.98 (0.51)	0.96 (0.52)	0.046	0.90 (0.44)	0.90 (0.44)	<0.001
groupC (mean (SD))	1.29 (1.06)	1.29 (1.07)	0.007	1.52 (1.14)	1.59 (1.19)	0.062

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 15. Distribution of baseline covariates after sequential propensity score matching of patients with partial lung resection according to the timing of surgery relative to the culture conversion date and using as controls patients from surgical and non-surgical studies.

	BEFORE CONVERSION			AFTER CONVERSION		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	160	40		460	115	
Year (mean (SD))	2009.14 (3.08)	2008.67 (3.68)	0.138	2009.01 (3.27)	2008.83 (3.05)	0.058
Income (%)			<0.001			0.067
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	4 (2.5)	1 (2.5)		19 (4.1)	5 (4.3)	
Upper_Middle	24 (15.0)	6 (15.0)		187 (40.7)	43 (37.4)	
High	132 (82.5)	33 (82.5)		254 (55.2)	67 (58.3)	
Age (mean (SD))	35.75 (13.22)	36.92 (11.70)	0.094	33.10 (11.51)	33.07 (10.95)	0.003
Sex = M (%)	101 (63.1)	26 (65.0)	0.039	239 (52.0)	61 (53.0)	0.022
BMI (mean (SD))	21.78 (3.64)	21.84 (3.03)	0.017	20.52 (3.53)	20.59 (2.96)	0.02
Smoking = Yes (%)	110 (68.8)	27 (67.5)	0.027	222 (48.3)	61 (53.0)	0.096
Alcohol = Yes (%)	58 (36.2)	13 (32.5)	0.079	99 (21.5)	28 (24.3)	0.067
DM = Yes (%)	23 (14.4)	5 (12.5)	0.055	27 (5.9)	6 (5.2)	0.029
HIV = Pos (%)	4 (2.5)	1 (2.5)	<0.001	4 (0.9)	2 (1.7)	0.077

Past antituberculosis treatment = Yes (%)	128 (80.0)	32 (80.0)	<0.001	275 (59.8)	66 (57.4)	0.049
Bilateral disease = Yes (%)	88 (55.0)	21 (52.5)	0.05	219 (47.6)	60 (52.2)	0.091
Cavitary disease = Yes (%)	105 (65.6)	25 (62.5)	0.065	265 (57.6)	68 (59.1)	0.031
AFB = Pos (%)	99 (61.9)	24 (60.0)	0.038	295 (64.1)	77 (67.0)	0.059
groupA (mean (SD))	1.09 (0.59)	1.05 (0.75)	0.056	1.03 (0.61)	1.01 (0.67)	0.034
groupB (mean (SD))	0.79 (0.58)	0.78 (0.53)	0.023	0.93 (0.49)	0.92 (0.44)	0.009
groupC (mean (SD))	0.74 (0.85)	0.80 (0.82)	0.067	1.56 (1.15)	1.57 (1.04)	0.014

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 16. Distribution of baseline covariates after sequential propensity score matching patients with partial lung resection according to the additional presence of resistance to fluoroquinolones using as controls patients from surgical and non-surgical studies.

	FQS			FQR		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	516	129		416	104	
Year (mean (SD))	2008.59 (3.30)	2008.52 (2.72)	0.024	2009.40 (3.21)	2009.42 (3.12)	0.008
Income (%)			<0.001			0.074
Low	0 (0.0)	0 (0.0)			0 (0.0)	
Lower_Middle	8 (1.6)	2 (1.6)			5 (4.8)	
Upper_Middle	256 (49.6)	64 (49.6)			34 (32.7)	
High	252 (48.8)	63 (48.8)			65 (62.5)	
Age (mean (SD))	34.94 (12.30)	34.90 (10.82)	0.004	35.94 (12.57)	34.09 (12.24)	0.149
Sex = M (%)	294 (57.0)	77 (59.7)	0.055	238 (57.2)	55 (52.9)	0.087
BMI (mean (SD))	20.82 (3.67)	21.04 (2.96)	0.067	20.55 (3.42)	20.33 (3.15)	0.069
Smoking = Yes (%)	280 (54.3)	71 (55.0)	0.016	234 (56.2)	57 (54.8)	0.029
Alcohol = Yes (%)	115 (22.3)	28 (21.7)	0.014	100 (24.0)	25 (24.0)	<0.001
DM = Yes (%)	23 (4.5)	7 (5.4)	0.045	32 (7.7)	8 (7.7)	<0.001
HIV = Pos (%)	4 (0.8)	2 (1.6)	0.072	4 (1.0)	1 (1.0)	<0.001

Past antituberculosis treatment = Yes (%)	322 (62.4)	82 (63.6)	0.024	355 (85.3)	87 (83.7)	0.047
Bilateral disease = Yes (%)	260 (50.4)	65 (50.4)	<0.001	248 (59.6)	62 (59.6)	<0.001
Cavitary disease = Yes (%)	376 (72.9)	92 (71.3)	0.035	301 (72.4)	72 (69.2)	0.069
AFB = Pos (%)	361 (70.0)	88 (68.2)	0.038	279 (67.1)	67 (64.4)	0.056
groupA (mean (SD))	1.24 (0.66)	1.25 (0.57)	0.006	0.67 (0.70)	0.67 (0.70)	<0.001
groupB (mean (SD))	0.91 (0.51)	0.95 (0.47)	0.063	1.01 (0.59)	0.99 (0.60)	0.04
groupC (mean (SD))	1.69 (1.09)	1.63 (1.02)	0.057	0.96 (0.96)	0.94 (0.97)	0.022

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 17. Distribution of baseline covariates after sequential propensity score matching patients with partial lung resection according to the ever use of two or more group A drugs and using as controls patients from surgical and non-surgical studies.

	>= 2 group A drugs			0-1 group A drugs		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	292	73		672	168	
Year (mean (SD))	2010.98 (3.16)	2011.23 (3.15)	0.079	2007.89 (2.61)	2007.78 (2.43)	0.045
income (%)			0.02			0.071
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	13 (4.5)	3 (4.1)		12 (1.8)	4 (2.4)	
Upper_Middle	77 (26.4)	19 (26.0)		357 (53.1)	84 (50.0)	
High	202 (69.2)	51 (69.9)		303 (45.1)	80 (47.6)	
Age (mean (SD))	35.68 (12.74)	35.30 (11.43)	0.031	34.75 (12.34)	34.35 (11.91)	0.033
Sex = M (%)	171 (58.6)	40 (54.8)	0.076	397 (59.1)	99 (58.9)	0.003
BMI (mean (SD))	19.93 (3.23)	20.45 (2.89)	0.172	20.87 (3.67)	20.96 (3.10)	0.025
Smoking = Yes (%)	175 (59.9)	42 (57.5)	0.049	366 (54.5)	90 (53.6)	0.018
Alcohol = Yes (%)	61 (20.9)	15 (20.5)	0.008	180 (26.8)	41 (24.4)	0.055
DM = Yes (%)	19 (6.5)	6 (8.2)	0.066	31 (4.6)	9 (5.4)	0.034
HIV = Pos (%)	12 (4.1)	2 (2.7)	0.075	2 (0.3)	1 (0.6)	0.045
Past antituberculosis treatment = Yes (%)	160 (54.8)	42 (57.5)	0.055	460 (68.5)	114 (67.9)	0.013

Bilateral disease = Yes (%)	215 (73.6)	52 (71.2)	0.054	332 (49.4)	87 (51.8)	0.048
Cavitary disease = Yes (%)	212 (72.6)	51 (69.9)	0.061	469 (69.8)	117 (69.6)	0.003
AFB = Pos (%)	1.62 (0.68)	1.62 (0.68)	<0.001	448 (66.7)	108 (64.3)	0.05
groupA (mean (SD))	0.87 (0.64)	0.84 (0.47)	0.055	0.70 (0.48)	0.70 (0.48)	<0.001
groupB (mean (SD))	0.80 (0.82)	0.82 (0.86)	0.025	1.08 (0.53)	1.01 (0.54)	0.134
groupC (mean (SD))	160 (54.8)	42 (57.5)	0.055	1.55 (1.18)	1.52 (1.11)	0.026

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 18. Distribution of baseline covariates after sequential propensity score matching patients with partial lung resection according to the level of surgical experience per center and using as controls patients from surgical and non-surgical studies.

	MORE EXPERIENCED			LESS EXPERIENCED		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	756	189		224	56	
Year (mean (SD))	2008.99 (2.46)	2008.88 (2.37)	0.047	2009.06 (4.41)	2009.04 (4.86)	0.006
income (%)			0.047			0.065
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	7 (0.9)	1 (0.5)		20 (8.9)	6 (10.7)	
Upper_Middle	354 (46.8)	89 (47.1)		76 (33.9)	18 (32.1)	
High	395 (52.2)	99 (52.4)		128 (57.1)	32 (57.1)	
Age (mean (SD))	34.87 (12.69)	35.20 (11.50)	0.027	35.44 (13.13)	33.76 (12.66)	0.13
Sex = M (%)	449 (59.4)	116 (61.4)	0.041	104 (46.4)	26 (46.4)	<0.001
BMI (mean (SD))	20.75 (3.59)	20.98 (3.01)	0.069	20.08 (3.33)	20.33 (3.05)	0.078
Smoking = Yes (%)	398 (52.6)	98 (51.9)	0.016	149 (66.5)	38 (67.9)	0.029
Alcohol = Yes (%)	196 (25.9)	48 (25.4)	0.012	32 (14.3)	9 (16.1)	0.05
DM = Yes (%)	47 (6.2)	12 (6.3)	0.005	13 (5.8)	3 (5.4)	0.019
HIV = Pos (%)	5 (0.7)	3 (1.6)	0.088	0 (0.0)	0 (0.0)	<0.001
Past antituberculosis treatment = Yes (%)	555 (73.4)	140 (74.1)	0.015	142 (63.4)	35 (62.5)	0.018

Bilateral disease = Yes (%)	399 (52.8)	99 (52.4)	0.008	118 (52.7)	31 (55.4)	0.054
Cavitary disease = Yes (%)	579 (76.6)	144 (76.2)	0.009	116 (51.8)	29 (51.8)	<0.001
AFB = Pos (%)	496 (65.6)	125 (66.1)	0.011	154 (68.8)	39 (69.6)	0.019
groupA (mean (SD))	1.01 (0.67)	0.98 (0.68)	0.039	1.14 (0.70)	1.09 (0.79)	0.065
groupB (mean (SD))	1.00 (0.56)	0.96 (0.50)	0.077	0.97 (0.49)	0.91 (0.58)	0.108
groupC (mean (SD))	1.34 (1.14)	1.31 (1.07)	0.025	1.22 (0.96)	1.25 (1.10)	0.026

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 19. Distribution of baseline covariates after sequential propensity score matching patients with partial lung resection according to the presence of cavitary disease and using as controls patients from surgical and non-surgical studies.

	CAVITARY DISEASE			NON CAVITARY DISEASE		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	684	171		276	69	
Year (mean (SD))	2008.94 (4.03)	2008.93 (2.96)	0.004	2008.96 (3.09)	2008.83 (3.24)	0.041
income (%)			0.092			<0.001
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	36 (5.3)	6 (3.5)		4 (1.4)	1 (1.4)	
Upper_Middle	299 (43.7)	79 (46.2)		88 (31.9)	22 (31.9)	
High	349 (51.0)	86 (50.3)		184 (66.7)	46 (66.7)	
Age (mean (SD))	36.11 (12.17)	35.19 (11.21)	0.079	32.90 (13.11)	33.53 (11.64)	0.051
Sex = M (%)	426 (62.3)	108 (63.2)	0.018	130 (47.1)	31 (44.9)	0.044
BMI (mean (SD))	20.70 (3.60)	20.75 (3.27)	0.013	21.31 (3.40)	21.05 (2.41)	0.087
Smoking = Yes (%)	374 (54.7)	95 (55.6)	0.018	148 (53.6)	38 (55.1)	0.029
Alcohol = Yes (%)	152 (22.2)	40 (23.4)	0.028	80 (29.0)	16 (23.2)	0.132
DM = Yes (%)	39 (5.7)	10 (5.8)	0.006	22 (8.0)	5 (7.2)	0.027
HIV = Pos (%)	14 (2.0)	3 (1.8)	0.021	0 (0.0)	0 (0.0)	<0.001
Past antituberculosis treatment = Yes (%)	525 (76.8)	129 (75.4)	0.031	178 (64.5)	43 (62.3)	0.045

Bilateral disease = Yes (%)	369 (53.9)	98 (57.3)	0.068	113 (40.9)	29 (42.0)	0.022
Cavitary disease = Yes (%)	684 (100.0)	171 (100.0)	<0.001	0 (0.0)	0 (0.0)	<0.001
AFB = Pos (%)	486 (71.1)	123 (71.9)	0.019	149 (54.0)	36 (52.2)	0.036
groupA (mean (SD))	1.09 (0.71)	1.05 (0.71)	0.06	0.92 (0.62)	0.91 (0.64)	0.017
groupB (mean (SD))	0.99 (0.52)	0.98 (0.54)	0.017	0.93 (0.50)	0.93 (0.46)	<0.001
groupC (mean (SD))	1.29 (1.12)	1.34 (1.09)	0.044	1.26 (1.12)	1.16 (0.95)	0.094

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 20. Distribution of baseline covariates after sequential propensity score matching patients with partial lung resection according to the presence of bilateral disease and using as controls patients from surgical and non-surgical studies.

	BILATERAL DISEASE			NON BILATERAL DISEASE		
	SURGERY		SMD	SURGERY		SMD
	No	Yes		No	Yes	
n	428	107		420	105	
Year (mean (SD))	2008.75 (2.88)	2008.80 (2.64)	0.019	2008.57 (3.31)	2008.34 (3.26)	0.069
income (%)			0.027			0.049
Low	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lower_Middle	14 (3.3)	4 (3.7)		9 (2.1)	3 (2.9)	
Upper_Middle	179 (41.8)	45 (42.1)		178 (42.4)	45 (42.9)	
High	235 (54.9)	58 (54.2)		233 (55.5)	57 (54.3)	
Age (mean (SD))	35.55 (11.48)	35.20 (10.91)	0.031	33.49 (12.43)	33.34 (11.45)	0.013
Sex = M (%)	293 (68.5)	72 (67.3)	0.025	215 (51.2)	51 (48.6)	0.052
BMI (mean (SD))	20.31 (3.41)	20.51 (2.98)	0.063	21.10 (3.52)	21.10 (3.09)	<0.001
Smoking = Yes (%)	229 (53.5)	55 (51.4)	0.042	204 (48.6)	50 (47.6)	0.019
Alcohol = Yes (%)	82 (19.2)	22 (20.6)	0.035	71 (16.9)	18 (17.1)	0.006
DM = Yes (%)	24 (5.6)	7 (6.5)	0.039	22 (5.2)	4 (3.8)	0.069
HIV = Pos (%)	6 (1.4)	3 (2.8)	0.098	0 (0.0)	0 (0.0)	<0.001
Past antituberculosis treatment = Yes (%)	341 (79.7)	83 (77.6)	0.051	293 (69.8)	71 (67.6)	0.046

Bilateral disease = Yes (%)	428 (100.0)	107 (100.0)	<0.001	0 (0.0)	0 (0.0)	<0.001
Cavitary disease = Yes (%)	355 (82.9)	89 (83.2)	0.006	289 (68.8)	70 (66.7)	0.046
AFB = Pos (%)	301 (70.3)	77 (72.0)	0.036	262 (62.4)	61 (58.1)	0.088
groupA (mean (SD))	1.03 (0.59)	0.98 (0.69)	0.069	0.99 (0.64)	0.97 (0.61)	0.023
groupB (mean (SD))	0.94 (0.55)	0.96 (0.51)	0.044	1.00 (0.57)	0.96 (0.52)	0.074
groupC (mean (SD))	1.41 (1.12)	1.37 (1.07)	0.034	1.27 (1.07)	1.27 (1.13)	0.002

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; DM, diabetes mellitus; HIV, Human immunodeficiency virus; M, male sex; SMD, Standardized mean differences.

Supplementary Table 21. Sensitivity analyses adjusted for covariates imbalance after using propensity score matching methods.

Outcome	OR	95% CI (lower)	95% CI (upper)	p-value
Primary analysis (excluding defaulted population) selecting controls from non surgical studies adjusted for residual imbalances				
PARTIAL LUNG RESECTION[+]				
Success vs Failure	1.76	0.17	18.36	0.63
Death vs Others	1.28	0.01	143.74	0.92
TOTAL LUNG RESECTION [++]				
Success vs Failure	0.16	0.03	0.91	0.04
Death vs Others	5.05	0.48	53.21	0.18
Stratified analysis (excluding defaulted population) selecting controls from the overall study population adjusted for residual imbalances				
BEFORE CULTURE CONVERSION[*]				
Success vs Failure, Recurrence, Death	1.60	0.51	5.01	0.42
Death vs Failure, Cure, Completion	0.72	0.11	4.63	0.73
FLUOROQUINOLONE-RESISTANT MDR-TB [**]				
Success vs Failure, Recurrence, Death	1.50	0.79	2.84	0.21
Death vs Failure, Cure, Completion	0.47	0.19	1.17	0.10
>=2 GROUP A DRUGS[***]				
Success vs Failure, Recurrence, Death	1.39	0.55	3.49	0.48
Death vs Failure, Cure, Completion	0.80	0.24	2.68	0.71
<2 GROUP A DRUGS[****]				
Success vs Failure, Recurrence, Death	1.08	0.63	1.87	0.78

Death vs Failure, Cure, Completion	0.71	0.32	1.59	0.41
LESS EXPERIENCED CENTERS ##				
Success vs Failure, Recurrence, Death	0.38	0.14	0.99	0.05
Death vs Failure, Cure, Completion	1.83	0.40	8.34	0.44

+ Adjusted for income, age, sex, diabetes mellitus, cavitary disease, Group B and Group C drugs.

++ Adjusted for year of treatment start, alcohol consumption, cavitary disease, treatment with Group A, B, and C drugs.

* Adjusted for year of treatment start, sex, smoking, group B drugs.

** Adjusted for age and sex.

*** Adjusted for age and sputum smear status.

****Adjusted for year of treatment start.

Adjusted for year, BMI, alcohol, diabetes mellitus, group C drugs.

Adjusted for sex, bilateral disease.