Title: Meta-analysis of Individual patient Data (IPD) of Patients with INH (mono or poly-drug) Resistant Tuberculosis.

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Evidence base for treatment of INH resistant TB (non-MDR):

One of the major challenges impeding global tuberculosis (TB) control is emergence of drug resistant TB (DR-TB). The World Health Organization (WHO) has estimated that 17% of isolates from patients newly diagnosed with active TB have some form of drug resistance. Approximately 2/3 of these drug resistant TB cases, or approximately 10% of all new cases, have INH resistant TB (other than MDR-TB). The impact on treatment outcomes is not as serious as MDR but nevertheless is important. Combined failure and relapse rates in randomized trials are 12-13% ie: one out of 8 persons with INH resistance either fails or relapses when given therapy with first line drugs (data from previous meta-analyses). Rates of failure and relapse are much higher in published studies of cohorts treated under programme conditions, and are considerably higher than the rates in drug sensitive cases.

To date there have been few published phase 3 randomized trials in INH-R TB; all those that were conducted ended more than 20 years ago. In the past two decades there has been little interest in this problem, despite widespread recognition that the therapy recommended for patients at risk for this resistance is inadequate. In most low and middle income countries access to drug susceptibility testing (DST) is very limited. Hence, newly diagnosed patients do not have DST, and are treated with a standardized regimen. However this standard therapy is well recognized to have excellent results, and is based on results of over 50 randomized trials that involved more than 25,000 patients. Some patients will relapse or fail this initial therapy, often with acquired drug resistance. In most countries even these patients are treated with a standardized regimen (The WHO Category 2, or retreatment regimen), without use of DST. This regimen is also comprised of first line drugs, even though the prevalence of resistance to first line TB drugs is high. Interestingly, although the WHO recommended Retreatment regimen has been used for over 20 years, and given to millions of patients, there have been no randomized trials to evaluate efficacy and effectiveness of this particular regimen. Cohort studies have reported very high rates of failure and relapse in patients with INH mono-resistance, and in those with failure or relapse, many had further acquisition of drug resistance (ie progression from INH mono-resistance to multi-drug resistance).

In the absence of a strong evidence base, recommendations for INH-R TB therapy have been largely guided by expert opinion. This opinion is based upon experience, and varies considerably in different centers due to differences in the patient populations, and resources available. Hence, there is no consensus on therapy of INH-R TB; use of certain drugs, such as the fluoroquinolones, is extremely controversial.

Meta- Analysis of Individual Patient Data in MDR TB:

In 2009 WHO issued a call for evidence to inform planned new recommendations for treatment of MDR-TB. They initially called for systematic reviews and meta-analyses of published literature. However in 2009, 3 such systematic reviews had been completed. In these reviews pooled treatment success was 60 – 65%. Identification of optimal treatment regimens was extremely difficult as pooling of results across studies was limited by the complexity of the patients due to differences in extent of disease, previous treatment, additional drug resistance, and because the treatment given varied widely between centers. In addition treatment was individualized in the majority of centers further limiting the ability to pool data in order to conduct a traditional aggregate level meta- analysis (group level).

In view of these problems the McGill group proposed an individual patient data meta-analysis- a proposal that was accepted by WHO. In 2010 a data base was assembled of individual patient records from almost 10,000 patients with MDR-TB from 32 centers. These centers were located in 20 countries representing both high, and low to middle income settings. Data for each patient included age and gender, history of prior therapy, clinical characteristics including AFB smear and chest x-ray findings, HIV co-infection, drug sensitivity test results pre treatment, TB therapy given and treatment outcomes. Information was limited at some centers but nevertheless the final data base included a large amount of standardized information.

Analysis of this data set produced the majority of evidence which the expert committee, constituted by WHO, used to make new recommendations for MDR TB treatment which were published in 2011. The analysis included the effect of individual drugs, the optimal number of drugs and duration of the initial and continuation phases of treatment. These results were summarized in a manuscript which was published in PLoS Medicine.

Within the data base there were 405 patients with extensive drug resistant (XDR) TB, defined as MDR plus resistance to fluoroquinolones, and at least one second line injectable. A number of correlates of treatment success in these patients were also found. These findings were summarized in a second publication (ERJ). When a report in Clinical Infectious Diseases of the outcomes of six patients with "totally drug resistant" strains of TB attracted global media attention, we identified between 40 and 60 patients within the database that met a definition of "TDR". The clinical characteristics and outcomes of these patients were presented to a special meeting convened by WHO regarding TDR in March 2012. A paper summarizing these findings has also been published (ERJ).

The association of DST results for second line drugs and treatment outcomes with use of those second line drugs was requested by WHO and presented at a meeting of a committee convened to review and recommend methods for second line DST held in Geneva in March 2012. This paper has been published in CID. Approximately 500 patients underwent thoracic resectional surgery as part of their treatment of MDR-TB. Outcomes were better with lobectomy although this may represent confounding. A revised manuscript is now ready for submission.

To date we have used random effects logistic regression (PROC Glimmix in SAS) for all individual level meta-analyses. However other methods are available which may be equally or more appropriate, depending on the question of interest. This large and rich data-base offers an important opportunity for innovative analytic approaches. A paper describing various (8) analytic approaches has been prepared but is still undergoing comments and revisions. Finally, with the new analytic techniques assessed above, we will assess the role of Group 5 drugs.

In summary, this rich data base has allowed seven distinct set of analyses to address different important questions regarding interpretation of DST, role of surgery, prognosis and correlates of treatment success of MDR-TB. Five papers have been published and the results have influenced several sets of WHO recommendations.

Proposed INH Resistant TB IPD meta-analysis:

Objectives:
We propose to create a data base of individual patient data to examine five questions:

1. What is the optimal duration of a daily regimen of rifampin, ethambutol and pyrazinamide (REZ) – 6 months or 8-9 months?
2. What is the benefit of adding a fluoroquinolone (FQ) to 6 months or more of REZ;
3. (A related sub-question) What is the benefit of adding a FQ to a regimen with 6 months or more of RE but only 1-3 months Z;
4. What is the benefit of adding streptomycin (SM) to a core regimen of 6 or more months of RE but only 1-3 months Z (essentially the regimen formerly recommended by WHO for retreatment).
5. What is the benefit of including isoniazid for each of the regimens considered in Q1-4?

Methods:
"IPDinMDR group: All collaborators in the IPDinMDR Group will be contacted to ask if they have cohorts of patients with INH resistance – treated since 1990.

"New INHR Group" A systematic review will be performed – using PubMed only, to identify publications, since 1990, of reports of treatment outcomes in patients with INH-R-TB. Cohorts or RCT will be included. No language restrictions. Additional specific criteria for this meta-analysis are: the study authors can be contacted and are willing to share their data; the cohort included at least 20 subjects treated for INH-R-TB; and, at least treatment success, as defined by Laserson et al (or WHO 2013), was reported. Authors of all potentially relevant studies will be contacted to see if they agree to share data.

Authors that agree to share data will be asked to sign a collaborative letter of agreement regarding data sharing. The McGill investigators will also sign these formal data sharing agreements with all collaborating investigators regarding sharing of results, publications, and "ownership" of the data. This project has been approved by the Research Ethics Board of the Montreal Chest Institute, McGill University Health Centre, and if deemed necessary by local ethics boards of originally approved studies.

Each 'new' author will provide centre level information such as diagnostic laboratory methods, treatment regimen doses and supervision, and outcome definitions. (Authors who participated in the MDR collaboration have already provided this information). Regimens will be considered individualized if regimens were tailored to individual patients' characteristics such as prior therapy, or drug susceptibility testing (DST) results. Treatment outcome definitions, provided by each author, will be compared to the consensus definitions published by Laserson et al [9] (or by WHO in 2013) and rated as the same, closely similar, or not similar.

All authors will provide de-identified patient level information including age, sex, HIV infection, site of disease, results of chest x-ray, acid fast bacilli (AFB) smear, culture, and DST for first and second line drugs, drugs used and duration for initial and continuous phases of treatment, surgical resection, and outcomes, including adverse events that required a change in therapy. Relapse will be any recurrence of disease within two years after successful treatment completion, and combined with failure for all analyses.

Authors may be contacted to request additional data, and clarify variable definitions and coding. Variables from each original dataset will be extracted, their meaning and coding verified, then mapped to a common set of variables for all patients. Hence datasets from each centre will have the same variables for all patients, but each dataset will be kept distinct. As a final verification, the clinical characteristics of each study population will be compared with the original published papers.

Quality assessment:
Quality of the included studies will be judged based on 8 criteria:
Two will be judged critical criteria:
1) What is the sampling method in the study: census (all patients), random sampling, or convenience sampling? (Must be census or random)
2) Was the end of treatment outcome "cure" confirmed with culture, or were at least 80% of patients with cure/complete outcome followed for at least 1 year for recurrence? (Must be yes to either).
Six will be judged important criteria:
3) Was the participation rate in the study >80%
4) Was the lost to follow-up rate - defined as : LFU + transferred out (if in DOT or surveillance program, not counted if in tertiary hospital) + unknown outcome. LFU rate must be <=10%.
5) Was age reported in at least 90% of the participants?
6) Was HIV status reported in at least 80% of the participants? (If HIV prevalence is known to be less than 10% in TB cases, or less than 1% in the general population in the country (i.e., low HIV prevalence), this item will be considered acceptable even if HIV status for individuals is not reported)
7) Were chest X-ray findings (cavitary vs non-cavitary) reported in at least 80% of the participants?
8) Was AFB smear reported in at least 80% of the participants?

Studies will be judged to be of high quality if they meet both critical criteria and at least four of the six important criteria. Studies of moderate quality will meet one of the two critical parameters and at least four of the important criteria, or two critical parameters and at least three of the important criteria. Remaining studies will be considered of low quality.

Data analysis:
We will consider three types of drug-exposure in our meta-analysis: (i) specific drugs administered (particularly the new FQN and any injectable as specified in the Objectives), (ii) duration of treatment regimen.

We will estimate adjusted odds and adjusted risk differences of three outcomes: (i) treatment success (defined as treatment cure or completion) compared to treatment failure or relapse (recurrence); [ii] Death during TB treatment – compared to success, fail or relapse (ie known to have survived a full course of treatment and excluding only those who default or transfer out from this analysis); and [iii] Acquired RIF resistance (ie acquired MDR) among those with treatment failure or relapse (this analysis will exclude those who die, or default during therapy, or who fail or relapse without acquired MDR).

We will use random effects (random intercept and random slope) multi-variable logistic regression on propensity score matched pairs. Cases with regimens of interest will be propensity matched to controls who received the comparator regimens for each question, on the basis of age, gender, HIV co-infection, AFB smear, past history of TB treatment and resistance to other first line drugs, if the drug was used, in order to estimate the adjusted odds and 95% confidence intervals. Analyses will be performed in all patients and in subgroups - stratified by cavitation on chest radiography, in patients with this information, and also stratified by country income level (high vs low-middle). We will also conduct all analyses in all patients, and in the sub-group who did not receive any INH (considered a marker of patients in whom INH resistance was known or strongly suspected from the outset of treatment.) For the fluoroquinolone questions, we will restrict to patients who received levofloxacin or moxifloxacin only.

Heterogeneity will be assessed visually using Forest plots of study specific estimates, and estimated quantitatively via the I^2 and its associated 95% confidence interval. The I squared will be estimated based on the Tau squared estimated for the propensity score matched adjusted odds ratios (work in development, Benedetti).

All analysis will be performed using SAS, version 9.4 (SAS Institute, Carey, N.C.).

Ethical considerations:

This study can be classified as minimal risk to study participants. No data gathering is planned – only analysis of already gathered data. Patients will not be contacted. The individual patient data will be transferred to McGill in non-nominal fashion. Local investigators will know the identity of individual patients – in case any data needs to be verified, but this will not be known by anyone at McGill, nor those doing the data analysis. All data will be kept under lock and key, and on secure computers/servers at the Montreal Chest Institute, of the MUHC under the supervision of Dr Menzies.