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Emily Alexy Date

Concordance between programmatically- and laboratory-determined treatment outcomes for multidrug-resistant tuberculosis patients in Peru

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Global Epidemiology

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2006

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Abstract

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By Emily Alexy

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Results: Using laboratory outcomes as the gold standard, clinicians had 98.9% sensitivity but only 45.7% specificity in assigning successful (cured or completed) treatment outcomes (versus failed). Laboratory results showed that 123 of 1152 (10.7%) patients declared cured and 27 of 287 (9.4%) categorized as completed by a clinician were bacteriologic failures. Overall, 10.4% of patients with programmatically-determined successful treatment outcomes still had positive bacteriologic results for MDR TB. Only treatment strategy type (individualized or standardized) was a significant predictor of concordance between laboratory- and programmatically-determined outcomes.

Conclusion: Clinicians in Peru correctly identify most successful treatment outcomes, yet miss many treatment failures. Until rapid diagnostics are readily available, treatment decisions will continue to rely on clinical judgment. Due to the implications of premature discontinuation of treatment, accurate final treatment outcomes are critical. Studies are needed to identify means to improve the diagnostic accuracy of programmatically-determined MDR TB treatment outcomes.

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BACKGROUND/LITERATURE REVIEW

Overview of Tuberculosis

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* (1). It is an airborne disease, spread from person to person through the coughing, sneezing, speaking or singing of a person with active pulmonary TB disease. Others who inhale the airborne droplet nuclei may become infected with TB, which can lead to TB disease. TB disease occurs when the TB bacteria become active and the immune system is unable to prevent their replication. Most people who get TB disease will do so within five years after TB infection, but it can also happen at any point later in life, sometimes many years after infection. Of those who become infected with TB, about 10% of individuals have immune systems which will completely eradicate the pathogen (2). In the remaining 90% of people multiplication of the bacteria will be prevented but it will not be eliminated. These individuals will remain infected yet not get sick with TB disease, which is referred to as latent TB infection (LTBI). People with LTBI do not have any symptoms and cannot spread TB to others (3). Some people will never progress beyond LTBI. For a person with LTBI, TB disease can occur when the immune system becomes weak for another reason, allowing the TB bacteria to multiply (4, 5). Some of the risk factors for developing TB disease include malnutrition, alcoholism, immunosuppression (due to either disease or medication), and the postpartum period (3). It is estimated that currently about one third of the worldwide population is infected with *Mycobacterium tuberculosis*, and 5-10% of these infected individuals will likely develop active TB disease at some point in their lives (2).

Despite being a preventable and curable disease, TB kills nearly two million people every year, mostly in developing countries (2, 4). While incidence of TB disease is relatively low in most countries, the high case fatality rate for this infectious disease makes it a major concern worldwide. If smear-positive TB patients are left untreated, roughly two thirds of them will die within 8 years (1). Even in populations of patients on TB treatment, the case-fatality rate can exceed 10% if there are high HIV rates, high levels of drug resistance, or poor treatment adherence rates.

Tuberculosis Treatment

There are many antibiotics available that can be used in combination to cure a person of TB. One of the difficulties of treating TB is the lengthy treatment period required. A standard TB treatment regimen is six months for drug susceptible cases, and can be much longer for cases that are resistant to any first line drugs (6). While taking TB medications, adherence is extremely important in order to prevent the development of drug resistance and the spread of TB to others in the community. TB medications quickly destroy most of the mycobacteria in the body, at which point the patient will feel as if he or she has recovered. However, effectively clearing all TB from the body requires continued treatment for many months. Once a patient feels better, sustained adherence and follow up can be a challenge, particularly if the patient moves during the treatment period.

In order to address these and other challenges, Directly Observed Therapy – Short Course (DOTS) has been adopted as the World Health Organization (WHO) recommended TB therapy (1). The full DOTS strategy consists of five elements: political commitment; diagnosis primarily by sputum-smear microscopy among patients attending

health facilities; short-course chemotherapy with effective case management (including direct observation of treatment); a regular drug supply; and systematic monitoring to evaluate the outcomes of every patient started on treatment. Direct observation of treatment is the aspect of DOTS that helps ensure adherence among patients on TB regimens. The implementation of DOTS in countries around the world has contributed to reductions in mortality, resulting in millions of lives saved (4). However, challenges still remain, particularly in resource-poor settings, where access to health care services that can diagnose and treat TB is often limited.

Multidrug-Resistant Tuberculosis

Multidrug-resistant (MDR) TB is TB with resistance to the two most effective anti-tuberculosis drugs, isoniazid and rifampicin (7). An effective cure can be achieved for these patients through the use of second-line medications, but additional challenges are faced due to the higher costs, more severe side effects, and longer treatment periods of these drugs. Treatment for MDR TB consists of a combination of at least four drugs with known effectiveness, based on either individual drug susceptibility testing or population level drug resistance surveillance. An MDR TB treatment regimen comprises an injectable agent (kanamycin, amikacin or capreomycin), a flouoroquinolone (levofloxacin, moxifloxacin or ofloxacin), any first line agents that have efficacy (pyrazinamide or ethambutol), and one or more second-line oral agents (p-aminosalicylic acid, cycloserine, terizadone, ethionamide or protionamide) for a duration of 18-24 months (8). Once TB is identified and a patient referred for treatment, drug-susceptible TB regimens can be managed well at the local level under the DOTS model. However MDR TB treatment management is more difficult, requiring laboratory tests that often

must be performed by a central site (9). Nonetheless, studies have shown that MDR TB patients can be successfully treated at the community level in developing countries, despite the increased difficulty in ensuring adherence in non-hospital settings (2).

The mortality rate for patients with MDR TB is also much worse than for drug-susceptible TB, with 5-20% of HIV-uninfected patients and as many as 66% of HIV-infected patients dying while on treatment (10). Despite the additional difficulties and higher costs associated with treating MDR TB patients, appropriate treatment has been found to be not only possible but also cost-effective as an intervention to control TB spread in resource-poor settings.

Standardized treatment and individualized treatment are two different strategies that can be used to treat patients with MDR TB. Standardized treatment uses drug resistance surveillance at the population level to determine a patient's treatment regimen, with all MDR TB patients in a given category or segment of the population receiving the same regimen. This is done in the absence of individual drug susceptibility testing (DST). The other option is individualized treatment, which uses the patient's DST results to design a regimen for that patient based on previous history of antituberculosis medicine taken and DST resistance patterns for that individual. For either strategy, regimens should include at least four drugs with known effectiveness, and they should last for at least 18 months after culture conversion (8).

A positive culture of *M. tuberculosis* from sputum or tissue is the gold standard method for diagnosing TB (2). Culture conversion is when a culture-positive TB patient switches to being culture-negative, as evidenced by two negative cultures done at least one month apart. During MDR TB treatment, it is recommended that sputum smears and

cultures are done monthly until culture conversion; after culture conversion sputum smears should still be monthly and cultures at least quarterly (8). Patients who successfully complete their treatment regimens are assigned an outcome based on international consensus definitions. These outcomes are based on records of laboratory tests and adherence to a treatment regimen, and are defined in Laserson, et al. (11).

TB and MDR TB in Peru

In Peru there were an estimated 33,000 incident cases of TB in 2009; a 2006 survey identified 5.3% of new and 23.6% of retreatment cases as MDR TB (12, 13). As a middle income country that has successfully implemented DOTS as part of its National TB Program, Peru has been making improvements in the treatment of TB and MDR TB patients throughout the country (14). Between 1990 and 2000 Peru successfully reduced overall TB incidence through the use of WHO-supported strategies and increased use of sputum smear microscopy and standardized first-line treatment. However, during the same time period rates of MDR TB actually increased, and many obstacles still remain to the effective detection and treatment of TB throughout the country (9).

A 2009 survey of health care providers working in TB clinics in one district of Lima assessed their knowledge and attitudes about TB (15). It found that less than one third of these individuals identified testing sputum samples as the correct method for determining treatment outcomes. Additionally, over half of those surveyed did not recognize that inadequate or incomplete treatment could result in resistant TB or its spread. This study might indicate a need to further educate TB healthcare providers on disease transmission and treatment. Another study found that health care providers frequently fail to adhere to guidelines from the Peruvian National Tuberculosis Control

Program (NTP) for some procedures (9). This may suggest a need to re-examine these policies to ensure that they represent best practices, as well as a need to educate health care providers on national policies.

Laboratory Services in Peru

In Peru, delays in DST processing have been tracked to determine what accounts for the lengthy turnaround time between a provider submitting a specimen to the national laboratory for testing, and receiving the results of those tests. It was found that while processing time at the national laboratory accounted for over half of the turnaround time, specimen transport, specimen processing, dissemination of results to the health center and scheduling of clinical evaluation after the results were received all added substantial time to the overall turnaround time (9). In order to effectively improve accessibility of laboratory results in this setting, all of these sources of delays will need to be addressed.

Between 1996 and 2005 the Laboratory Improvement Project was implemented in Peru, which was responsible for scaling up laboratory services in the country in order to increase support for MDR TB treatment (9). Despite this scaling up of laboratory services, health professionals in Peru continued to cite a lack of coordination between laboratories and clinicians in the country (16). Until these issues are addressed, reliable and prompt receipt of laboratory results for TB patients in Peru will continue to be a challenge.

Consequences of Inappropriate or Incomplete MDR TB Treatment

Completing a full course of treatment and achieving a confirmed cure is critical for every case of MDR TB. If treatment regimens are inadequate or incomplete the consequences can include an increased risk for morbidity and mortality for the patient,

additional spread of drug resistant TB within the community, and acquisition of additional drug resistance. The second-line drugs necessary for the treatment of MDR TB can often be associated with adverse events. Sometimes the discontinuation of medication, either temporary or permanent, is required; as a result, rates of negative outcomes (treatment failure, mortality) are higher for MDR TB than for drug-susceptible TB (17).

Drug resistance in TB develops as a result of inadequate or inappropriate treatment of active TB disease (7). The mechanism for drug resistance in *Mycobacterium tuberculosis* is genetic mutation, which occurs when the bacterium remains in contact with a given drug for a sufficient amount of time at concentrations below the minimum inhibitory concentration. Alternatively, the strain can undergo a specific natural mutation that confers resistance, and the resistant strain can then be selected by inappropriate treatment regimens that do not combat the mutated strain (18). Additional drug resistance in MDR TB patients is concerning due to the increased difficulty in treating such cases. Many known risk factors for drug-resistant TB are factors related to treatment adherence; these risk factors include inadequate drug intake by patients, irregular treatment, previous TB treatment, and migration or frequent movement by the patient (19).

One study of a cohort of MDR TB patients who were treated with first-line drugs found that within four years 61% of them had been re-diagnosed with TB, and nearly half of these relapsed cases later died of TB (20). Rates of negative outcomes (TB recurrence, death) were high even for MDR TB patients judged to have been cured following first line drug treatment. For this reason it is vital to ensure that patients are given appropriate

drug regimens and that they are completely cured before being released from further treatment by their health care provider.

It is also very important that drug susceptibility testing is done, so that cases of MDR TB can receive the most effective second line drugs. Every patient with recurrent MDR TB has the potential to spread drug-resistant strains to others in the community, negatively impacting TB control efforts in the region and country. Even a smear microscopy-confirmed cure determination has been demonstrated to be a poor predictor of a long-term successful outcome for those patients treated with standard first-line therapy (20). A systematic review of the literature concluded that treating MDR TB patients for longer than 18 months and with direct observation of therapy for the entire treatment period significantly increases the proportion of patients with successful treatment outcomes (21). One study of MDR TB patients in Brazil found that of patients with a 'failure' treatment outcome, most died within 8 years (18). Issues with compliance with MDR TB treatment regimens were responsible for these deaths.

Difficulty in Changing a Physician's Diagnosing Behavior

When laboratory techniques have been improved in developing countries for other diseases, clinicians may be reluctant to adopt or trust the new technology. For example, the rapid diagnostic tests (RDTs) that are now available for diagnosis of malaria have been validated and shown to be accurate, and yet health care providers regularly rely on their own clinical judgment to make treatment decisions, even when it contradicts RDT results (22). One study found that even though health care providers were of the opinion that RDTs improved malaria diagnosis, more than half of the patients prescribed antimalarials had negative RDT results (23). Another study found that the majority of

providers expressed doubts regarding the accuracy of RDTs (24). These results suggest that even if more accessible laboratory methods are developed for TB, challenges will still be faced in changing physician diagnosing or outcome determining behavior.

Accuracy of Clinical Judgment

Several studies have been conducted examining the diagnostic accuracy of clinicians. In some circumstances experienced health care providers have been shown to have good predictive accuracy, for example when looking at physicians' prognoses of intensive care unit patients (25). Judgments made by physicians were found to be superior to two different objective models, a result that was attributed to a wider array of knowledge and available patient information than was considered in the objective models.

However, in other situations health care providers are sometimes less reliable than laboratory testing for diagnosing certain infections. This is particularly a problem in areas where laboratory tests are difficult to come by and/or unreliable. It may foster a culture of providers who rely on their own judgment, even when contradictory laboratory results are available. As a result, some patients are misdiagnosed and do not receive appropriate treatment. One example of this is the misdiagnosis of STDs; investigators looked at the use of laboratory test results in diagnosing various STDS in one region of China (26). They found that physicians would sometimes make diagnoses despite a lack of positive laboratory tests, while at other times a positive result for one infection would be returned, and yet the patient would be diagnosed with a different STD. The difficulty lies in the risk of losing a patient to follow-up before accurate laboratory results are obtained when there is a shortage of adequate laboratory facilities. If a physician waits for results to

come back to make a diagnosis, there is a risk that the patient will remain untreated. Therefore, many choose to use their best judgment in order to make a diagnosis based solely on clinical presentation, despite the low accuracy of their determinations.

The severity of the disease in question and risks associated with inappropriate treatment also factor into whether proxies for laboratory tests are acceptable substitutions. A study looking at the accuracy of diagnosing anemia based on pallor in children in Bangladesh and Uganda found that treating all children with at least one of a number of signs of anemia resulted in good sensitivity but poor specificity in recognizing cases of moderate or severe anemia (27). In this situation these results are acceptable, because recognizing all cases is a priority, and treatment with iron in the doses prescribed does not have negative consequences for those without anemia.

Accuracy of physician judgments of treatment adherence for patients with TB has also been examined. A study of adherence to standard TB treatment regimens found nonadherence to be extremely common and health care professionals to have a poor record of assessing nonadherence in patients (28). Patients' self-reported frequency of missing doses was more reliable than the opinions of doctors or nurses, using urine isoniazid levels as a reference. Health care providers consistently underestimated nonadherence. This brings into question the professional judgment that clinicians frequently rely upon.

MANUSCRIPT

TITLE

Concordance between programmatically- and laboratory-determined treatment outcomes for multidrug-resistant tuberculosis (MDR TB) patients in Peru

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ABSTRACT

Background: Confirmation of cure for an MDR TB patient is based on laboratory tests for *Mycobacterium tuberculosis* growth on culture media. Testing takes 4-6 weeks and laboratory capacity is often limited in resource-poor settings; these factors contribute to a convention of programmatically-determined treatment outcomes. Outcome decisions dictate patient management and inaccuracies place patients at an increased risk of morbidity and mortality, and may contribute to community transmission of MDR TB.

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Methods: Data were abstracted from medical records of all MDR TB patients in Peru who initiated treatment between August 1996 and March 2002. Patients with both programmatic and laboratory outcomes were included in the present analysis (n=1658). Laboratory outcomes were based on international standards requiring at least five consecutive negative cultures in the last 12 months of treatment to confirm cure.

Results: Using laboratory outcomes as the gold standard, clinicians had 98.9% sensitivity but only 45.7% specificity in assigning successful (cured or completed) treatment outcomes (versus failed). Laboratory results showed that 123 of 1152 (10.7%) patients declared cured and 27 of 287 (9.4%) categorized as completed by a clinician were bacteriologic failures. Overall, 10.4% of patients with programmatically-determined successful treatment outcomes still had positive bacteriologic results for MDR TB. Only treatment strategy type (individualized or standardized) was a significant predictor of concordance between laboratory- and programmatically-determined outcomes.

Conclusion: Clinicians in Peru correctly identify most successful treatment outcomes, yet miss many treatment failures. Until rapid diagnostics are readily available, treatment decisions will continue to rely on clinical judgment. Due to the implications of premature discontinuation of treatment, accurate final treatment outcomes are critical. Studies are needed to identify means to improve the diagnostic accuracy of programmatically-determined MDR TB treatment outcomes.

INTRODUCTION

Worldwide there are an estimated 14 million cases of tuberculosis (TB), with multidrug-resistant (MDR) TB making up a growing percentage those. MDR TB is defined as a strain of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, two of the most effective first-line drugs (29, 30). Treatment of MDR TB cases is longer and more complex than treatment for drug-susceptible TB. MDR TB treatment regimens require a minimum of four second-line medications, and these drugs are more expensive, can have severe side effects, and must be taken regularly for at least 18-24 months (7, 17). It can be difficult to ensure that patients are adherent during this lengthy treatment period, particularly for patients who experience adverse events related to their medication. Curing MDR TB is possible, but, due to these challenges, negative outcomes among patients with MDR TB are far more common than for those with drug-susceptible TB (2, 31).

Patients with confirmed MDR TB should be placed on an appropriate treatment regimen and continually treated until international standards for a ‘cured’ or ‘completed’ outcome are met. If treatment for MDR TB ends prematurely, before a patient is effectively cured, it can result in worse outcomes for that individual, including relapse and death, as well as the possible development of further drug resistance (7). Additional resistance in an MDR TB patient means that finding an effective treatment regimen will become increasingly difficult, and without appropriate treatment the risk of death is even higher. Also, these patients may contribute to the ongoing spread of MDR TB strains to the community, compromising TB control efforts and endangering other lives.

Therefore, proper and complete treatment for individuals with MDR TB is extremely important. The gold standard method of determining whether a patient is cured of TB is based on bacteriologic laboratory testing for the growth of *Mycobacterium tuberculosis* on culture media. Consistently negative cultures over the final 12 months of treatment, including at least five cultures, are required for a 'cured' outcome determination, indicating that additional drug treatment regimens are not necessary (11). However, in resource-poor areas these laboratory results are often difficult to obtain, due to weak laboratory systems and services. Challenges regularly faced include shortages in equipment and human resources, inadequate infrastructure, and a lack of strong transportation and management systems (32). In addition, the culture process requires at least 4-6 weeks to complete, and may take longer in an under-resourced laboratory. These factors contribute to lab results being not only difficult to obtain but also at times unreliable. Health care providers therefore frequently rely primarily on their own clinical observations and judgment to make treatment outcome determinations. These programmatically-based outcomes have become convention in many areas, even when laboratory testing services are available (33).

Given this culture of basing treatment decisions on provider-determined outcomes, in addition to the difficulties of obtaining laboratory results in resource-poor settings, it is important to establish the accuracy of programmatically-determined treatment outcomes. If a provider's knowledge of the patient's experience and clinical presentation leads to an accurate judgment, even in the absence of laboratory confirmation, then the clinician's determination can serve as an acceptable proxy for bacteriologic evidence in settings where laboratory results are difficult to obtain.

However, if the clinicians' decisions are not matching the gold standard determinations then inevitably some patients may be inappropriately released from care or given excess treatment regimens. In this situation, measures need to be taken to increase programmatically-determined outcome accuracy and ensure that all MDR TB patients receive sufficient treatment to achieve efficacious cure and prevent further spread of disease.

METHODS

Study Population

All adult TB patients in Peru who initiated treatment for MDR TB between August 1996 and March 2002 were eligible to be included in the study. All individuals at least 18 years old with a treatment start date during the study period were examined for programmatic- and laboratory-based outcomes (n=2961). Patients missing a programmatically-determined treatment outcome (n=269) or who did not have bacteriologically-determined laboratory outcome (n=1224) were excluded from analysis. The final analysis population comprised 1,658 individuals.

Study Design

A retrospective cohort study was conducted to compare MDR TB outcomes among patients who received standardized versus individualized treatment regimens. Eligible patients were identified from an electronic database maintained by the Technical Unit of the National TB Control Program in Peru, where all patients treated for MDR TB are automatically registered. Individuals were identified based on the date of treatment initiation and all eligible patients' medical records were reviewed. Information related to

demographics, exposures, and other covariates was abstracted onto a standard patient data form (see Appendix B) by study investigators and trained local team members. The study was reviewed and approved by the ethics board of all participating institutions, and Emory University IRB reviewed this secondary analysis and determined it to not be human subjects research (see Appendix A). Informed consent was not sought but patient privacy was protected by using form numbers instead of personal identifiers and by removing the links to patient names once the project ended.

The subset of patients whose outcome was evaluated using both programmatically-based and laboratory-based methods was examined to determine concordance between programmatic and laboratory outcomes, and to establish if any sociodemographic, behavioral, or clinical characteristics were predictors of this concordance.

MDR TB Treatment Outcome Definitions

Programmatically-determined outcomes

Programmatically-determined outcomes were final MDR TB treatment outcomes assigned by the provider and recorded in the patient medical record. These outcomes were based on clinical judgment, taking into account medical history, treatment compliance, available laboratory results and clinical presentation. Programmatically-determined treatment outcome categories included cured, completed, defaulted, failed, died, discontinued due to adverse events, treatment suspended, transferred, in treatment, and not available. Definitions of programmatically-determined outcome categories were not standardized.

Laboratory-determined outcomes

International consensus definitions were used for laboratory-determined treatment outcomes, as defined in Laserson, et al (11). Possible outcome categories included cured, completed, defaulted, failed, died, and no outcome (transferred, suspended, or with insufficient culture data). However, only three of these categories were determined using bacteriological data (cured, completed, failed), with the remaining categories based on programmatic data. Given the goal of the current research to compare programmatically-based outcomes to bacteriologic laboratory outcomes, these programmatic categories were excluded from analysis. Cure is defined as completion of treatment per country standards, in addition to a minimum of 5 cultures in the last 12 months of treatment testing consistently negative for the presence of *Mycobacterium tuberculosis*. Patients with a single positive culture within this time frame can still be considered cured with supporting clinical and radiologic evidence, as long as the positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart. MDR TB Patients are considered to have failed treatment if, based on a minimum of 5 cultures performed in the last 12 months of treatment, they have more than one positive culture result. Further, patients with one of the final three specimens taken during treatment testing culture positive, or for whom a clinical decision has been made to terminate treatment due to persistent culture positivity or adverse drug reactions are also considered treatment failures. The treatment outcome completed is assigned to patients who have adequately completed treatment per the country protocol, but have insufficient bacteriologic evidence to conclusively establish cure or failure.

Patient Sociodemographic and Clinical Characteristics

All medical and social history variables were categorized as "Known history of ___" and "No known history of ____", with any missing information for a given variable being included in the latter category. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared, using the patient's height and weight at treatment start date. BMI and age were examined as both continuous and categorical variables: BMI categories included underweight, normal, overweight, and obese, while age was split into groups by decade. Results were the same whether continuous or categorical classifications were used for these variables, so age was included in all models as continuous. Urban was defined as residing in Lima or Callao province, as this is the metropolitan Lima area. A count variable of social risk factors was generated which tallied the number of the following characteristics that the individual had a known history of: homelessness, smoking, alcoholism, drug addiction, commercial sex work, criminal activity, imprisonment, unemployment, institutionalization, and military service.

Statistical Analyses

To begin, a kappa statistic was calculated to assess agreement between laboratory and programmatic outcomes. Since the laboratory outcome variable had only 3 categories (cured, completed, failed) the programmatic outcome variable was also limited to these 3 categories. A value and 95% confidence interval was obtained for a simple kappa.

Next, the three outcome categories (cured, completed, failed) were dichotomized into 'cured or completed' and 'failed' categories. These binary categories were chosen based on convention and programmatic relevance, given that these categories determine patient management: anyone with a 'cured' or 'completed' designation would be

considered a successful outcome, not given further treatment regimens, and released from TB care. Conversely, anyone classified with a 'failed' outcome would be judged to still have active MDR TB disease and would be referred for additional treatment regimens. Measures of concordance (sensitivity, specificity, positive predictive value, and negative predictive value) were calculated from the 2x2 frequency table obtained from a crosstab of binary laboratory outcomes and binary programmatic outcomes. Laboratory outcome was considered the gold standard, and the accuracy of programmatic outcomes was compared to this gold standard.

Finally, logistic modeling was used to examine possible predictors of concordance between the two outcome measures. All available demographic, treatment, medical, and social history variables were examined for univariate association with an outcome agreement variable, defined as 1 if laboratory and programmatic outcomes matched, and 0 if they were different. Chi squared tests were used for categorical variables and t-tests were used for continuous variables.

All variables included in logistic models were checked for confounding by examining the change in odds ratios as a given variable was removed from the model. Two-way interaction was not assessed due to the lack of previous literature on predictors of concordance of laboratory and programmatically-determined MDR TB outcomes. Without any reason to suspect that the results were affected by interaction, and without a primary exposure to examine interaction with, it was impractical to look at all two-way combinations of the 39 potential predictors of concordance.

Using these univariate associations, three logistic regression models were constructed: one containing the full analysis population, one containing only those who

received individualized treatment regimens, and one containing those who received only standardized treatment regimens. All models used the outcome match variable as the dependent variable. For the potential predictors with more than two levels (treatment start year and treatment end year) dummy variables were created to represent the different levels of the categorical variable. Any covariate with a univariate association p-value ≤ 0.2 was considered for inclusion in a multivariate logistic regression model. All models also included age and sex as potential confounders. Final models predicting concordance for each of the three populations were constructed using manual backwards elimination, retaining only variables with $p<0.05$. All analyses were done using SAS, version 9.2.

RESULTS

Population characteristics of the original study cohort, excluded groups, and patients included in the present analysis are summarized in Table 1. The final study population was 60% male and 49% were in the 20-29 age group. Residence in the Lima/Callao metropolitan area was reported for 81% of the study population, and 58% were known to be a household contact of another TB case.

Concordance between Programmatically- and Laboratory-Determined Treatment Outcomes

Concordance of programmatic and laboratory outcomes was initially examined by cross tabulation of all categories (Table 2). Of the 1152 patients declared to be cured by a clinician, 123 (10.7%) were bacteriologically deemed to be treatment failures. Similarly, 27 (9.4%) of the 287 individuals clinically categorized as completed were bacteriologic failures. Together, these misclassified categories total 150 of the 1658 patients (9.0% of

all MDR TB patients in this analysis) who were programmatically considered treatment successes, yet had laboratory evidence of persistent infection with MDR TB.

At the same time, 9 (6.4%) patients deemed failed by their healthcare providers were cured and an additional 5 (3.6%) completed treatment based on their lab results. Of the 71 individuals still in treatment, 31 (43.7%) had sufficient laboratory results to be considered cured and 20 (28.2%) had lab results establishing treatment completion.

Comparing only the three categories shared by both outcome types (cured, completed, and failed), the overall kappa statistic for percent agreement was 0.30 (95% confidence interval: 0.25-0.34).

With both outcome variables dichotomized into successful (cured or completed) and unsuccessful (failed) categories, the accuracy of programmatically-determined outcomes was evaluated using the outcome based on bacteriologic laboratory results as the gold standard. The sensitivity of the clinicians' determinations was 98.9%, but the specificity was only 45.7% (Table 3). The positive and negative predictive values (PPV and NPV) were 89.6% and 90.1%, respectively.

Modeling for Predictors of Concordance

Overall, 1063 of 1658 (64.1%) MDR TB patients had concordant programmatic and laboratory outcomes, and 595 (35.9%) were discordant. In order to model predictors of this concordance using logistic regression, sociodemographic covariates were first screened for univariate association with the outcome. Table 4 shows the p-values for univariate association between the outcome match variable and each available covariate. p-values ≤ 0.2 and the associated variables are in bold; all of these were included as potential predictors in the models.

Model 1 included the full analysis population and, based on table 4, incorporated the following variables as possible predictors: HIV positive status, known contact of a TB case, known history as a health care worker, treatment strategy type – individualized or standardized, having any advanced (post-secondary or technical) education, year MDR TB treatment was started, and year MDR TB treatment was ended. Collinearity diagnostics were run first using a SAS macro for nonlinear regression. The dummy variables for year MDR TB treatment was started were highly collinear with each other, the intercept, and year MDR TB treatment was ended dummy variables, so year treatment started was removed from the model and collinearity diagnostics were rerun. The intercept was then slightly collinear with the year treatment ended dummy variables (CI=26), but since the CI<30, year treatment ended dummy variables were left in the model. Backwards elimination was run (manually), which resulted in advanced education, HIV status, contact of TB case, year treatment ended, and history as a health care worker being removed from the model (in that order) because all were insignificant at the $\alpha=0.05$ level. The final model contained treatment strategy as the only significant predictor of the outcome match variable ($p<0.0001$), as well as age and sex as possible confounders. The coefficient of the treatment strategy variable was 0.6912.

The second model was for those who received individualized treatment regimens and included HIV status, parent of any children at treatment start, history as a health care worker, and advanced education as potential predictors of concordance, as well as age and sex as possible confounders. Collinearity diagnostics were run and no collinearity was found. Using manual backward elimination, history as a health care worker was taken out of the model, followed by advanced education, parent of any children at

treatment start, and HIV status, because all were insignificant at the $\alpha=0.05$ level. This left Model 2 with only possible confounders and no predictors of concordance.

Model 3 was for those who were treated with standardized regimens, and it included contact of TB case, history as a health care worker, and year MDR TB treatment started as potential predictors. Collinearity diagnostics were run first, and year MDR TB treatment started was removed from the model due to collinearity among the dummy variables and with the intercept. Then backward elimination was run and history as a health care worker and contact of TB case were removed from the model for being insignificant, leaving Model 3 with only the confounders age and sex in the model.

DISCUSSION

In this cohort of 1658 MDR TB patients in Peru, clinicians classified 1152 as cured, 287 as completed, and 141 as failed, while 71 were still in treatment, 4 were discontinued and 3 had transferred. In the same population, consensus definitions based on laboratory results determined that 1093 patients were cured, 263 were completed, and 302 were treatment failures.

While the majority of MDR TB patients are being correctly classified by their health care provider's treatment outcome determination, the proportion being misclassified is concerning. Overall, 10.4% of patients (150 of 1439) declared to be cured or completed by their health care providers were in fact treatment failures, based on bacteriologic results. Once the provider decides on a cured or completed outcome, these individuals are released from care as "TB free" and are not given further treatment regimens. However, given that these patients are, in fact, still infected with MDR TB,

their release potentially means a huge risk of relapse, further drug resistance development, and even death for the individual. The community is also threatened, as these individuals with highly resistant strains of TB are removed from care and are then potentially spreading drug resistant TB strains to their friends and family. This lack of specificity in providers' outcome determinations represents a gaping hole in TB treatment systems in Peru and other countries with high MDR TB burdens and limited laboratory resources.

Misclassification in the opposite direction is also a reason for concern. This cohort contained 65 patients (4.0% of the study population) who were effectively cured of MDR TB, with bacteriologic results indicating a cured or completed outcome, yet were either still receiving treatment or else had been deemed treatment failures, and so would be referred for additional drug treatment regimens. This unnecessary treatment could have negative consequences for the patients, including increased costs associated with treatment and potentially toxic side effects resulting from the second line medications given to those infected with MDR TB.

The kappa statistic of 0.30 indicates fair agreement between programmatic and laboratory outcomes. There is some concordance between the two outcome determination methods; however, given the vital importance of accurate treatment outcomes for MDR TB and the implications of misclassification, this 'fair' level of agreement is not adequate.

The sensitivity and specificity illustrate where providers are most often inaccurate. A sensitivity of 98.9% is very good and shows that most laboratory-based successful outcomes are being correctly identified as successful outcomes using

programmatic methods. However, the low specificity of 45.7% indicates that less than half of the bacteriologically unsuccessful MDR TB treatment outcomes are being recognized as such by clinicians. This points to a need to educate health care providers about the importance of continuing treatment for an MDR TB patient until a successful outcome can be confirmed. Further, given research showing that, in one survey of health care providers in Peru, not even half of the respondents were aware that inadequate or incomplete treatment could lead to drug resistant TB and its spread, there is a clear need to ensure that all clinicians are aware of the causes of drug-resistant TB and the consequences of premature discontinuation of therapy. While individuals surveyed were mostly those who perform the day-to-day tasks of distributing medicine and following up with patients, and not necessarily those making outcome determinations for patients with MDR TB, these gaps in TB knowledge among health care workers could be negatively affecting tuberculosis management in this part of Peru (15).

Only one of the three logistic regression models identified any significant predictors of concordance. In Model 1, which included the full final analysis population, a variable indicating whether the patient received an individualized or standardized treatment regimen was able to predict the concordance of programmatically- and laboratory-based MDR treatment regimens. An odds ratio of 2.00 (95% CI: 1.48-2.70) was found, controlling for age and sex. Therefore, MDR TB patients who received individualized treatment regimens had twice the odds of having concordant programmatic and laboratory outcomes than those who received standardized treatment regimens. Patients receiving individualized treatment regimens had different physicians from those who received standardized treatment regimens, and may have been different in other

ways as well. The similarities and differences of patients who received individualized rather than standardized treatment regiments should be investigated to further understand this characteristic as a predictor of concordance.

Models 2 and 3, which stratified the analysis population according to strategy type, both found that none of the available covariates were significant at the $\alpha=0.05$ level as predictors of outcome concordance. This indicates that, given the available data, none of the characteristics examined were able to predict whether an individual received concordant or discordant laboratory and programmatic outcome determinations. It suggests a need to examine other factors that may extend beyond the individual patient level that was investigated here.

Study Limitations

This study had several limitations due to the constraints of available data. One shortcoming was the lack of information on physician characteristics. A physician's training, experience, background, or location (e.g. in a relatively high or low TB prevalence area) could conceivably affect his or her ability to correctly judge MDR TB treatment outcomes. Some individual providers or facilities may have better track records than others at correctly determining outcomes, and future research could look at provider characteristics that may predict outcome concordance.

All data for this analysis were abstracted from medical charts and program data, which were not intended for systematically collecting information. Therefore missing data was common, which could have biased the results. Many of the social and medical history variables were missing for a majority of patients. Further, there was no mechanism for verifying the accuracy of abstracted information or to fill in the gaps. In

the future, if it were possible to interview individual TB patients and compare this data with chart-abstracted data, perhaps more complete and reliable background information could be obtained. The missing data might be one reason that none of the social history factors were found to be significant predictors of concordance, and this should be investigated.

Additionally, nearly half of this cohort of MDR TB patients in Peru was missing either a programmatic- or laboratory-based outcome. The final analysis population was statistically different from the full patient population on a number of characteristics. Therefore, the necessary exclusion of this subset of patients may have distorted the final results, if those without both outcome determinations were either more or less likely to be properly categorized by physicians. Again, a cohort with more complete treatment and outcome information could provide confirmation of the results in this analysis. Finally, district of residence was used to determine residence in the metropolitan Lima area, but this is not an exact urban/rural breakdown of the country. More detailed information on the living conditions of patients would have been a better indicator, and in the future it could be investigated whether neighborhood or living condition is correlated with outcome concordance.

Further research addressing these limitations would add to and complement the results presented here. Also, data on additional covariates, such as socioeconomic status and additional co-morbidities, would be important to collect as well in future research.

Conclusions

There are many reasons why programmatic outcomes do not always agree with laboratory results. In some cases, the bacteriologic results are probably not

communicated back to the physician, even if tests are performed and recorded at the national level. In other cases, the results might be returned to the clinician, but could be delayed so that the patient's outcome has already been established without the guidance of the laboratory results. Finally, some clinicians will rely on their own clinical judgment over the determination of a laboratory, perhaps because they have received previous unreliable lab results that lead to distrust of lab methods, or because they trust their own observation or opinion above that of a test result. Whatever the reason for the discordant outcomes, steps need to be taken to increase concordance between health care providers and the internationally-recognized bacteriologic outcome definitions. Until a rapid diagnostic test for TB treatment status becomes readily available, outcome determinations made by clinicians will continue to be the norm. Given the shortcomings in these determinations identified above, it is necessary to create, evaluate and implement a mechanism or algorithm to improve the accuracy of health care providers' outcome determination. Additional research needs to be done on what patient or physician characteristics influence accurate clinical determinations. Studies looking at what characteristics clinicians rely upon to make these decisions would be important as well in determining how to best influence and improve their categorizations. It is also imperative that increased laboratory capacity and quality assurance are emphasized, as well as increased training for providers on the importance of bacteriologic results. If clinicians have a greater awareness of why laboratory results are so vital to making outcome determinations, then as laboratory services become more readily available these clinicians will hopefully rely on them to a greater extent in order to improve their

accuracy. Ensuring that outcome determinations are accurate is an essential step towards controlling and reducing the spread of MDR TB.

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TABLES

Table 1. Sociodemographic & clinical characteristics of MDR TB patients in Peru, 1996-2002

Table 1: Sociodemographic & clinical characteristics of MDR TB patients in Peru, 1996-2002

	All study participants n=2961 n (%)	No lab outcome n=1224 n (%)	No clinic outcome n=269 n (%)	Final analysis population n=1658 n (%)	p-values*
Age [missing=3**]					
18-19	228 (7.7)	98 (8.0)	24 (9.0)	124 (7.5)	*p=0.002*
20-29	1362 (46.1)	508 (41.6)	110 (41.0)	815 (49.2)	
30-39	673 (22.8)	292 (23.9)	64 (23.9)	362 (21.9)	
40-49	314 (10.6)	145 (11.9)	35 (13.1)	160 (9.7)	
50-59	211 (7.1)	93 (7.6)	15 (5.6)	116 (7.0)	
60+	168 (5.7)	86 (7.1)	20 (7.5)	78 (4.7)	
Sex [missing=1]					
Male	1778 (60.1)	743 (60.7)	155 (57.6)	994 (60.0)	*p=0.921*
Female	1182 (39.9)	481 (39.3)	114 (42.4)	663 (40.0)	
BMI [missing=908]					
Underweight	296 (22.5)	164 (30.7)	31 (29.0)	126 (16.8)	*p<0.001*
Normal	806 (61.4)	308 (57.7)	62 (57.9)	479 (63.9)	
Overweight	174 (13.3)	54 (10.1)	12 (11.2)	117 (15.6)	
Obese	37 (2.8)	8 (1.5)	2 (1.9)	28 (3.7)	
Marital Status [missing=96]					
Single	1317 (48.0)	494 (44.5)	100 (42.4)	788 (50.5)	*p=0.021*
Married or living together	1214 (44.2)	526 (47.3)	118 (50.0)	657 (42.1)	
Divorced or separated	112 (4.1)	44 (4.0)	10 (4.2)	65 (4.2)	
Widowed	101 (3.7)	47 (4.2)	8 (3.4)	52 (3.3)	
Level of education [missing=123]					
None	66 (2.4)	28 (2.6)	7 (3.0)	36 (2.4)	*p<0.001*
Primary	411 (15.2)	202 (18.5)	42 (17.7)	198 (12.9)	
Secondary	1679 (62.1)	702 (64.2)	137 (57.8)	934 (60.9)	
Post-secondary	450 (16.7)	126 (11.5)	43 (18.1)	308 (20.1)	
Technical	97 (3.6)	36 (3.3)	8 (3.4)	59 (3.8)	
Occupation [missing=1]					
Professional/Skilled/Office worker	421 (14.2)	168 (13.7)	32 (11.9)	240 (14.5)	*p=0.014*
Laborer/Farmer/Artisan	459 (15.5)	191 (15.6)	47 (17.5)	261 (15.8)	
Household worker	1230 (41.6)	529 (43.2)	111 (41.3)	664 (40.1)	
Health care worker	32 (1.1)	10 (0.8)	3 (1.1)	21 (1.3)	
Student	253 (8.6)	80 (6.5)	19 (7.1)	168 (10.1)	
Military/police/other	189 (6.4)	85 (6.9)	20 (7.4)	100 (6.0)	
Unemployed/In prison/Retired	376 (12.7)	161 (13.2)	37 (13.8)	203 (12.3)	
Urban or rural residence					
Lives in Lima/Callao metropolitan area	2305 (77.9)	902 (73.7)	175 (65.1)	1341 (80.9)	*p<0.001*

Known history of homelessness					
Yes	104 (3.5)	53 (4.3)	9 (3.4)	48 (2.9)	*p=0.040*
Known history of smoking					
Yes	251 (8.5)	119 (9.7)	26 (9.7)	122 (7.4)	*p=0.014*
Known history of alcoholism					
Yes	503 (17.0)	241 (19.7)	44 (16.4)	250 (15.1)	*p=0.002*
Known history of drug addiction					
Yes	184 (6.2)	114 (9.3)	22 (8.2)	65 (3.9)	*p<0.001*
Known history of crime, prison or institutionalization					
Yes	81 (2.7)	52 (4.3)	6 (2.2)	28 (1.7)	*p=0.011*
Count of social risk factors***					
0	1737 (58.7)	664 (54.3)	169 (62.8)	1027 (61.9)	*p<0.001*
1	775 (26.2)	337 (27.5)	63 (23.4)	416 (25.1)	
2+	449 (15.2)	223 (18.2)	37 (13.8)	215 (13.0)	
Known experience as a health care worker					
Yes	46 (1.6)	19 (1.6)	6 (2.2)	25 (1.5)	*p=0.821*
Known household contact of TB case					
Yes	1702 (57.5)	691 (56.5)	143 (53.2)	962 (58.0)	*p=0.502*
Known BCG Immunization					
Yes	2448 (82.7)	979 (80.0)	213 (79.2)	1401 (84.5)	*p=0.003*
Known diabetes at treatment start					
Yes	153 (5.2)	66 (5.4)	15 (5.6)	82 (5.0)	*p=0.539*
Known HIV positive at treatment start					
Yes	67 (2.3)	49 (4.0)	5 (1.9)	17 (1.0)	*p<0.001*
Treatment strategy					
Individualized	399 (13.5)	113 (9.2)	34 (12.6)	271 (16.3)	*p<0.001*
Standardized	2562 (86.5)	1111 (90.8)	235 (87.4)	1387 (83.7)	

* p-values based on chi-square (for categorical variables) or t-test (continuous variables) comparisons of the final analysis population to those excluded from analysis

** Number of missing values listed are for the final analysis population

*** Social risk factors included a known history of homelessness, smoking, alcoholism, drug addition, commercial sex work, criminal activity, imprisonment, institutionalization, unemployment, or military service

Table 2. Concordance of programmatically-based and laboratory-determined treatment outcomes (all categories) for MDR TB patients in Peru, 1996-2002

Table 2: Concordance of programmatically-based and laboratory-determined treatment outcomes (all categories) for MDR TB patients in Peru, 1996-2002					
		Lab Outcome			
		Cured	Completed	Failed	Total
Treatment Outcome	Cured	864 (75.0)*	165 (14.3)	123 (10.7)	1152
	Completed	188 (65.5)	72 (25.1)	27 (9.4)	287
	Failed	9 (6.4)	5 (3.6)	127 (90.1)	141
	Discontinued	0 (0.0)	0 (0.0)	4 (100.0)	4
	In treatment	31 (43.7)	20 (28.2)	20 (28.2)	71
	Transfer	1 (33.3)	1 (33.3)	1 (33.3)	3
	Total	1093	263	302	1658

* Number of patients (row percentage)

Table 3. Concordance of programmatically-based and laboratory-determined treatment outcomes in binary categories for MDR TB patients in Peru, 1996-2002

Table 3: Concordance of programmatically-based and laboratory-determined treatment outcomes in binary categories for MDR TB patients in Peru, 1996-2002

		Laboratory Outcome		
		Cured/Completed	Failed	Total
Programmatic Outcome	Cured/Completed	1289*	150	1439
	Failed	14	127	141
	Total	1303	277	1580

Sensitivity	98.9%
Specificity	45.8%
PPV	89.6%
NPV	90.1%

* Number of patients

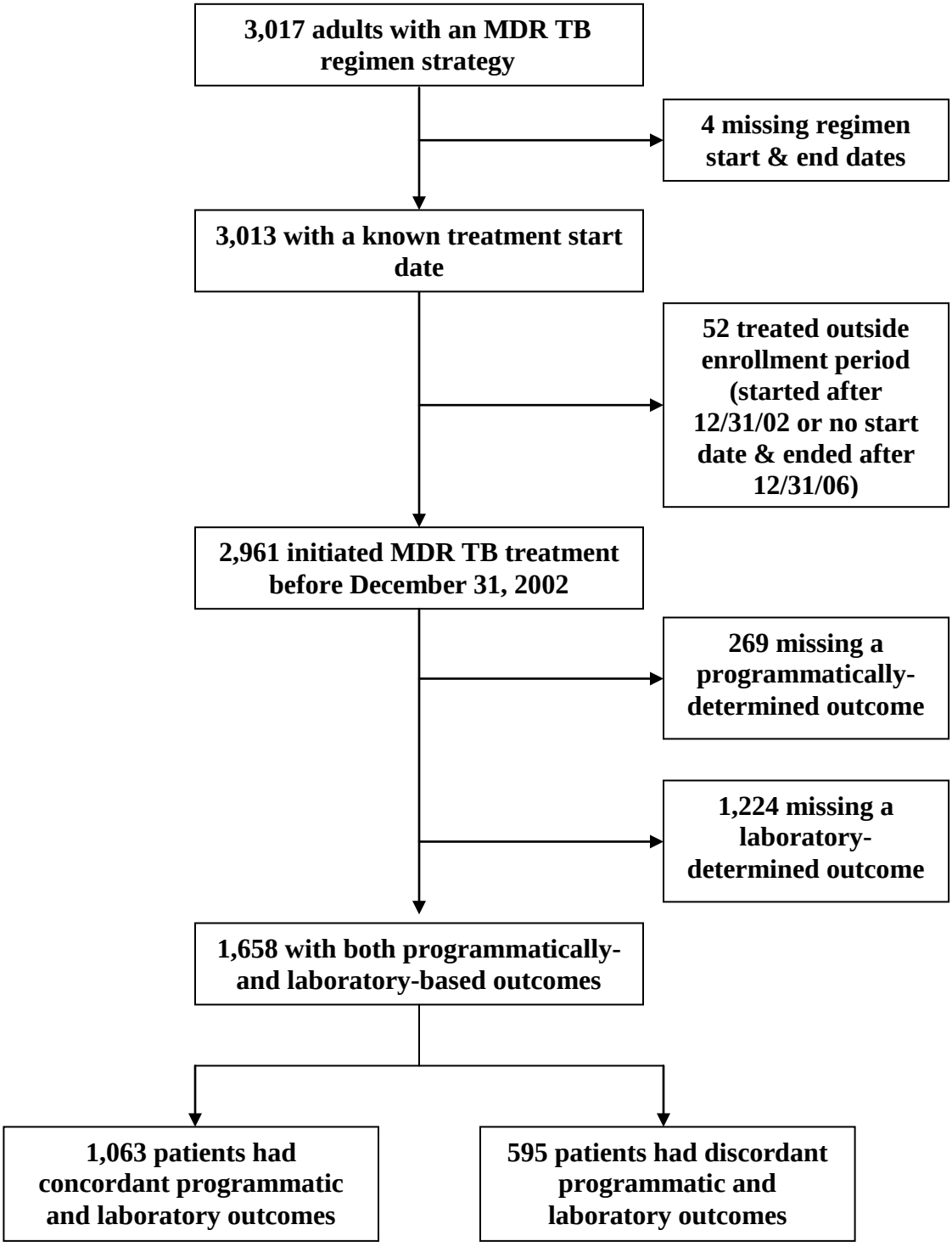
Table 4. P-values for chisquare univariate associations with outcome match variable

Variable	Full analysis pop (Model 1)	Individualized strategy (Model 2)	Standardized strategy (Model 3)
BCG vaccination (y/n)	0.4997	0.6779	0.3088
Diabetes (y/n)	0.7103	0.3613*	0.8617
HIV positive (y/n)	**0.1406**	**0.1399***	0.3647
Parent of any children (y/n)	0.7633	**0.1471**	0.5849
Contact of TB case (y/n)	**0.1699**	0.9101	**0.2017**
Contact of TB death (y/n)	0.2819	0.8894	0.4190
Contact of MDR TB case (y/n)	0.9828	0.8064	0.5434
History of homelessness (y/n)	0.4968	0.5948*	0.6412
History of smoking (y/n)	0.6636	1.0000*	0.7067
History of alcoholism (y/n)	0.9183	0.9280	0.7522
History of drug addiction (y/n)	0.8589	0.7047*	0.9873
History of commercial sex work (y/n)	0.5396*	-	0.5271*
History of criminal activity (y/n)	0.7895	0.3378*	1.0000*
History of imprisonment	0.9115	0.3378*	0.6636
History of unemployment (y/n)	0.5499	0.7452	0.6457
History of institutionalization (y/n)	1.0000*	-	1.0000*
History of military service (y/n)	0.7387	1.0000*	0.5671*
Experience as health care worker (y/n)	**0.0367**	**0.2045***	**0.2079**
History of crime or instit. (y/n)	0.6770	0.6700*	0.6381
Count of social risk factors	*	*	*
Count of social risk factors (0/1+)	0.4968	0.5543	0.4987
Count of social risk factors (0/1/2+)	0.6890	0.5260	0.5159
BMI categorized (4 levels)	0.5704	*	0.3877
Age categorized (6 levels, by decade)	0.2952	*	0.2665
Treatment strategy (ind./stand.)	**<0.0001**	-	-
Sex (male/female)	0.4854	0.8422	0.5480
Marital status	0.7794	*	0.3587
Education level	0.3436	*	0.6984
Any advanced education (y/n)	**0.1172**	**0.1806**	0.3157
Occupation	*	*	*
Occupation category	0.6051	*	0.4039
Currently employed (y/n)	0.6650	0.2436	0.3746
Lives in metropolitan Lima (y/n)	0.4166	0.2457*	0.9090
Year treatment started	**0.0008**	*	**<0.0001**
Year treatment ended	**<0.0001**	*	*
Length of treatment (years)	0.6824	*	0.6052
Length of treatment (months)**	0.7602	0.3806	0.7515
Age (continuous)**	0.9824	0.7744	0.7327
BMI (continuous)**	0.5797	0.8945	0.4568

* chi-square invalid b/c expected cell counts <5. Fisher's Exact measure reported where available
** t-test used for continuous variables

FIGURES

Figure 1. Flow chart for inclusion in analysis of outcome concordance for MDR TB patients in Peru, 1996-2002



APPENDICES

Appendix A: IRB letter of non-HSR status

March 9, 2011

Emily Alexy
Department of Epidemiology
Rollins School of Public Health
Emory University
Atlanta GA 30322

RE: Determination: No IRB Review Required
Title: ***Concordance between programmatically and laboratory-determined treatment outcomes for Multidrug-Resistant Tuberculosis (MDR TB) patients in Peru.***
PI: Emily Alexy

Dear Ms. Alexy:

Thank you for submitting your protocol to our office about the above-referenced project. Based on our review of the information you provided, we have determined that it does not require IRB review because it does not meet the definition of research involving "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, Emory's involvement is limited to work with de-identified data. Emory will neither seek nor be given access to any key that could relink the data to individual human subjects.

This determination could be affected by substantive changes in the study design or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Sarah K. Clark, CIP
Senior Research Protocol Analyst

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An equal opportunity, affirmative action university

Appendix B: Patient Data Form

PATIENT DATA FORM

I. COVER SHEET

Patient name_____

Patient registry number_____

Form Number_____

Date of Abstraction: _____ Initials of Abstractor: _____
(dd-mmm-yy)

II. Personal Information:

Date of birth: (**mmm-yy**) _____ OR
Age: ___ years (at treatment initiation)
Gender: [ ] male [ ] female
Marital status: [ ] single [ ] married/living together [ ] divorced/separated [ ] widow [ ] 999
Area:
District:
Health Center:
Neighborhood:

III. Clinical History:

BCG vaccination reported? [ ] yes [ ] no [ ] 999
BCG scar [ ] yes [ ] no [ ] 999
Diabetes: [ ] yes [ ] no Diagnosis date:
HIV [ ] positive [ ] negative [ ] 999

Liver abnormality_____
Renal abnormality_____
Number of pregnancies_____ Number of live births_____
History of ever being hospitalized? [ ] yes [ ] no

If yes,

Dates-Month/Year	*Hospital Name*	*Reason*

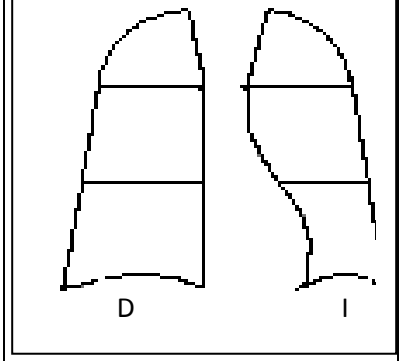
History of prior TB surgery? [ ] yes [ ] no

If yes,

Dates-Month/Year	*Description*

Initial chest radiograph:

Date: _____
dd/mm/yyyy



1) Cavity
2) Fibrosis
3) Infiltrate
4) Pneumothorax
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

IV. Adverse Events

Has the patient ever experienced adverse events due to TB treatment? [ ] yes [ ] no

If yes, how many times?_____

Did these adverse effect episodes result in hospitalization? [ ] yes [ ] no

If yes,

Date-Month/Year	*Hospital Name*

Did these adverse effect episodes result in treatment interruptions of <=1 week? [ ] yes [ ] no If yes, how many times?_____

Did these adverse effect episodes result in treatment interruptions of >1 week? [ ] yes [ ] no If yes, how many times?_____

Has the patient ever had contact with another TB case? [ ] yes [ ] no

If yes, did these individual(s) die on treatment? [ ] yes [ ] no

did these individual(s) have confirmed MDR TB [ ] yes [ ] no

Number of household members at time of treatment initiation _____

V. Social/Occupational Factors

History of homelessness prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99

If yes, homelessness in year prior to MDR TB diagnosis [ ] yes [ ] no [ ] 99

History of smoking prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99
If yes, smoking in year prior to MDR TB diagnosis [ ] yes [ ] no [ ] 99
Packs/day_____ years_____ [ ] 99

History of alcohol use/abuse to MDR TB diagnosis? [ ] yes [ ] no [ ] 99
If yes, alcohol use/abuse in year prior to MDR TB diagnosis [ ] yes [ ] no [ ] 99
Drinks/day _____ [ ] 99

History of drug use/abuse in year prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99
If yes, drug use/abuse in year prior to MDR TB diagnosis [ ] yes [ ] no [ ] 99

History of being in jail in year prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99
If yes, jail in year prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99

History of being in a shelter/ institution prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99
If yes, shelter/ institution in year prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99

History of military service prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99

History of health care work prior to MDR TB diagnosis? [ ] yes [ ] no [ ] 99

VI. Previous treatment regimens

Treatment start date (dd-mm-yyyy)	Treatment End date (dd-mm-yyyy)	Duration	Category								Site	Outcome
		m	I	II	III	IIR	Retr	STR	Other	H		*C F A T R
		d										
		m	I	II	III	IIR	Retr	STR	Other	H		C F A T R
		d										
		m	I	II	III	IIR	Retr	STR	Other	H		C F A T R
		d										

		m	I	II	III	Retr	STR	Other	H			C F A T R
		d										
		m	I	II	III	Retr	STR	Other	H			C F A T R
		d										
		m	I	II	III	Retr	STR	Other	H			C F A T R
		d										
		m	I	II	III	Retr	STR	Other	H			C F A T R

*C=cure; F=failure: A=abandon/default; T=transfer; R=Discontinued for adverse events

VII. Current or most recent regimen

	Treatment Initiation Date (dd-mm-yyyy)	Treatment End Date (dd-mm-yyyy)	Category		Health Care Establishment
			STR	ITR	

If ITR, please specify drugs and dose.

Drug name	**Daily Dose (mg, ml)**	**Number of doses**
INH		
RIF		
PZA		
EMB		
CS		
CPX		
Ethio		
PAS		
CM		
AMX-CLV		
KM		

AUG		
OFX		
CFZ		
SFX		
RFB		
CLR		
LFX		
THZ		

VIII. Bacteriology (current or most recent regimen):

Date specimen collected (DD/MMM/YYYY)	*Smear result (pos/neg/999)*	*Smear strength (1-9 AFB),* 1+, 2+ 3+,*999)*	*Culture result (pos/neg/999) (quantify, if <=20)*

IX. Treatment regularity (current or most recent regimen)

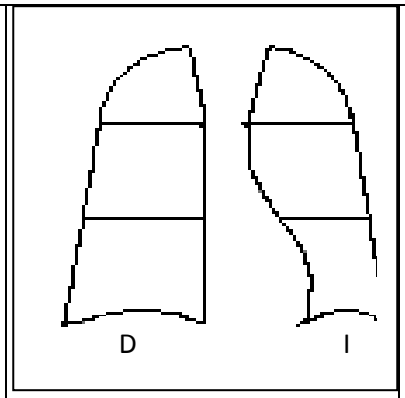
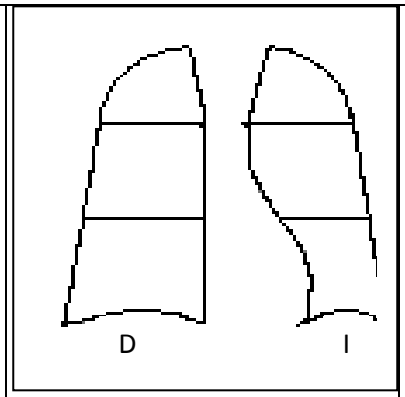
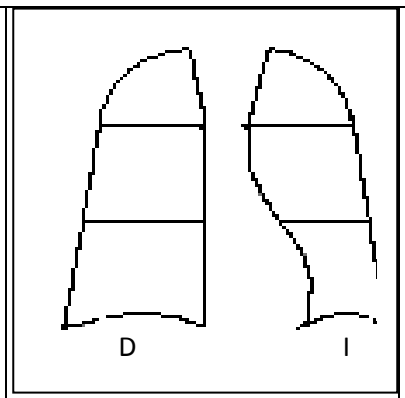
Intensive phase

Number of missed doses (from treatment card)/ # received doses_____

Continuation phase

Number of missed doses (from treatment card)/ # received doses_____

X. Chest x-ray results for current or most recent regimen

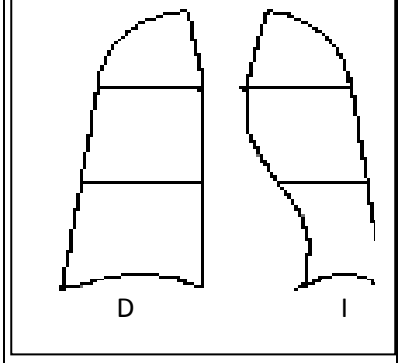
Initial chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes
Chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes
Chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



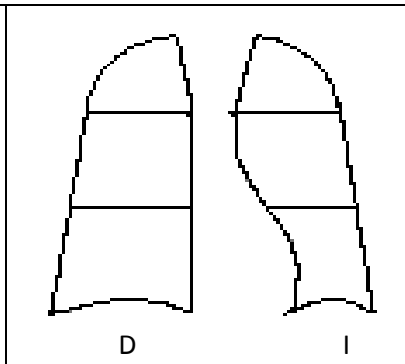
1) Cavity
2) Fibrosis
3) Infiltrate
4) Pneumothorax
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



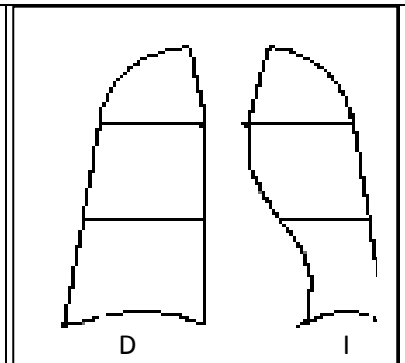
1) Cavity
2) Fibrosis
3) Infiltrate
4) Pneumothorax
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



1) Cavity
2) Fibrosis
3) Infiltrate
4) Pneumothorax
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

XI. Final treatment outcome in patient's chart (using program definition for either ITR or STR)

Outcome: [ ] cure [ ] completed treatment [ ] failure [ ] death [ ] default [ ] transfer [ ] unknown

XII. Follow up

Was the patient ever seen after final outcome was given? [ ] yes [ ] no [ ] 999
Were there bacteriology results after final outcome? [ ] yes [ ] no [999]

If yes, enter below:

Date specimen collected (DD/MMM/YYYY)	*Smear result (pos/neg/999)*	*Smear strength (1-9 AFB), 1+, 2+ 3+,999)*	*Culture result (pos/neg/999) (quantify, if <=20)*

Was a subsequent TB diagnosis made? [ ] yes [ ] no [999]
If yes, date _____

Patient's current status: [ ] cured [ ] died [ ] in treatment [ ] 999

If most recent regimen is <u>ITR</u>, did the patient receive an <u>STR</u> or another regimen for MDR-TB prior to this regimen?
[ ] yes [ ] no

If yes,
Please complete the following sections for the previous MDR regimen:

Extension for Previous MDR regimen

VIIB. Previous MDR regimen

	Treatment Initiation Date (dd-mm-yyyy)	Treatment End Date (dd-mm-yyyy)	Category		Health Care Establishment
			STR	ITR	

If there was any variation to STR regimen, or it was an ITR, please specify drugs and dose below.

Drug name	**Daily Dose (mg, ml)**	**Number of doses**
INH		
RIF		
PZA		
EMB		
CS		
CPX		
Ethio		
PAS		
CM		
AMX-CLV		
KM		
AUG		
OFX		
CFZ		
SFX		
RFB		
CLR		
LFX		
THZ		

VIIIB. Bacteriology:

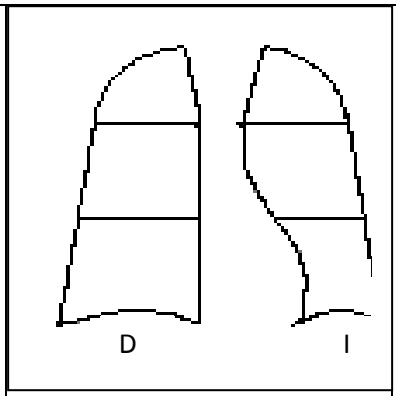
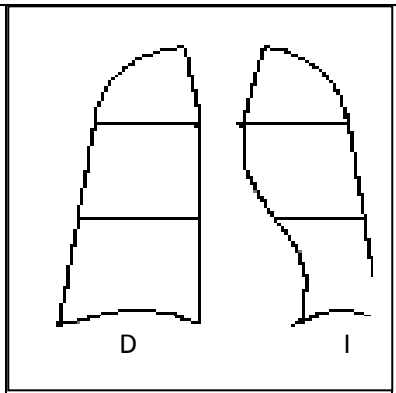
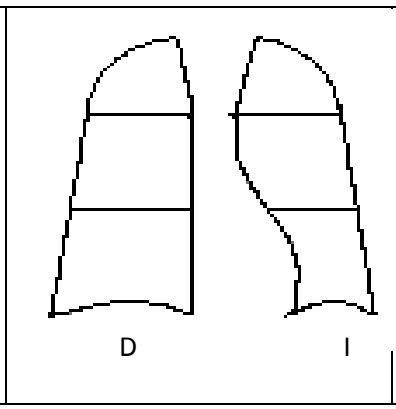
Date specimen collected (DD/MMM/YYYY)	*Smear result (pos/neg/999)*	*Smear strength (1-9 AFB),* 1+, 2+ 3+,*999)*	*Culture result (pos/neg/999) (quantify, if <=20)*

IXB. Treatment regularity

Intensive phase
Number of missed doses (from treatment card)/ # received doses_____

Continuation phase
Number of missed doses (from treatment card)/ # received doses_____

XB. Radiography on STR, previous MDR regimen

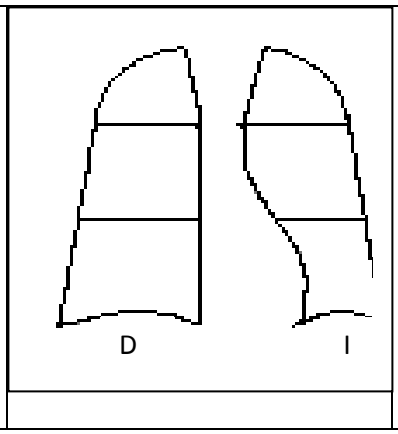
Initial Chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes
Chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes
Chest radiograph: Date: _____ dd/mm/yyyy		1) Cavity 2) Fibrosis 3) Infiltrate 4) Pneumothorax 5) Pleural Effusion 6) Nodule 7) Disseminated/Miliary 8) Bullae 9)Intrathoracic lymphadenopathy 1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



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2) Fibrosis
3) Infiltrate
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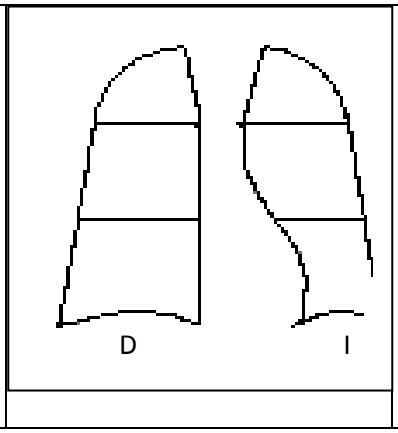
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



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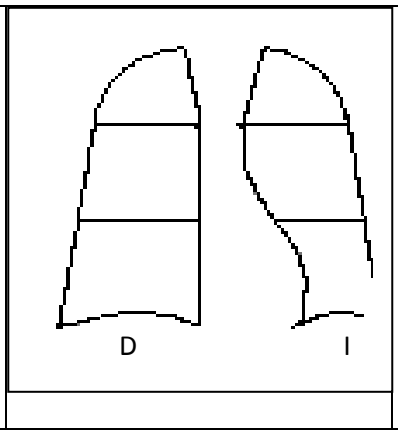
5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

Chest radiograph:

Date:

_____

dd/mm/yyyy



1) Cavity
2) Fibrosis
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5) Pleural Effusion
6) Nodule
7) Disseminated/Miliary
8) Bullae
9)Intrathoracic lymphadenopathy
1Ø) Surgical changes

XIB. Final treatment outcome in patient's chart

Outcome: [ ] cure [ ] completed treatment [ ] failure [ ] death [ ] default [ ] transfer [ ] unknown

Appendix C: SAS code and output

```
* Dichotomize the outcome variables;
data work.temp5;
        set work.temp3;

        if outcome_std=1 or outcome_std=2 then bin4lab=1;
        if outcome_std=4 then bin4lab=2;

        if txoutcome=1 or txoutcome=2 then bin4tx=1;
        if txoutcome=4 then bin4tx=2;
run;

* Create formats for the binary outcomes;
proc format;
        value bin4frmt
                1='Cured or Completed'
                2='Failed';
run;

*** Dichotomized outcome table;
proc freq data=work.temp5;
        tables bin4lab*bin4tx;
        format bin4lab bin4frmt. bin4tx bin4frmt.;
run;
* Sens=98.94  Spec=45.68  PPV=89.61  NPV=90.07 ;
```

The FREQ Procedure

Table of bin4lab by bin4tx

bin4lab	bin4tx: Cured or Completed	bin4tx: Failed	Total
Cured or Completed	1289 81.58 98.93 89.58	14 0.89 1.07 9.93	1303 82.47
Failed	150 9.49 54.15 10.42	127 8.04 45.85 90.07	277 17.53
Total	1439 91.08	141 8.92	1580 100.00

Frequency
Percent
Row Pct
Col Pct

Frequency Missing = 78

```
*** Calculate a kappa statistic for agreement between outcome variables ***;
** Use just the observations that were in 'Cure', 'Complete', or 'Fail' for both outcomes;
data temp6;
        set temp3;

        * lab outcomes are already limited to these 3 categories in the final analysis dataset temp3;
        where txoutcome in (1,2,4);
run;

proc freq data=temp6;
        tables outcome_std*txoutcome/agree;
        test kappa wtkap;
```

```
        format outcome_std laboc. txoutcome txoc.;
run;
```

Table of OUTCOME_STD by txoutcome

OUTCOME_STD(final_outcome)	txoutcome			
	Cured	**Complete**	**Failure**	**Total**
Cured	864	188	9	1061
	54.68	11.90	0.57	67.15
	81.43	17.72	0.85	
	75.00	65.51	6.38	
Completed	165	72	5	242
	10.44	4.56	0.32	15.32
	68.18	29.75	2.07	
	14.32	25.09	3.55	
Failed (includes AEs)	123	27	127	277
	7.78	1.71	8.04	17.53
	44.40	9.75	45.85	
	10.68	9.41	90.07	
Total	1152	287	141	1580
	72.91	18.16	8.92	100.00

Frequency
Percent
Row Pct
Col Pct

Statistics for Table of OUTCOME_STD by txoutcome

Test of Symmetry	
Statistic (S)	115.0781
DF	3
Pr > S	<.0001

Simple Kappa Coefficient	
Kappa	0.2992
ASE	0.0230
95% Lower Conf Limit	0.2541
95% Upper Conf Limit	0.3443

Test of H0: Kappa = 0	
ASE under H0	0.0185
Z	16.1635
One-sided Pr > Z	<.0001
Two-sided Pr > |Z|	<.0001

Weighted Kappa Coefficient	
Weighted Kappa	0.4205
ASE	0.0250
95% Lower Conf Limit	0.3715
95% Upper Conf Limit	0.4696

Test of H0: Weighted Kappa = 0	
ASE under H0	0.0197
Z	21.3147
One-sided Pr > Z	<.0001

Two-sided Pr > |Z|	<.0001

Sample Size = 1580

```
***********************************
***** Create a logistic model *****
***********************************;

** Check for univariate associations with the outcome match variable for categorical variables
        within the entire analysis population;
proc freq data=temp2;
        tables bcg*ocmatch/chisq;
        where included=1;
run;
```

This was repeated for the following variables (replacing bcg):
diabetes, hiv, parent, tbcontact, tbmortality, mdrcontact, homeless, smoke, alcohol, drugadic, commsex, crime, prison, unemp, instit, military, hcw, criminst, countsrf, ctsrf2, ctsrf3, bmicat, agecat, strat, sex, marstat, education, adveduc, occupat, jobcat, curremp, urban, starttxyear, endtxyear, txyrs

```
** Check for univariate associations with the outcome match variable for categorical variables
        within those who received an individualized treatment strategy;
proc freq data=temp2;
        tables bcg*ocmatch/chisq;
        where included=1 and strat=1;
run;
```

This was repeated for the following variables (replacing bcg):
diabetes, hiv, parent, tbcontact, tbmortality, mdrcontact, homeless, smoke, alcohol, drugadic, commsex, crime, prison, unemp, instit, military, hcw, criminst, countsrf, ctsrf2, ctsrf3, bmicat, agecat, strat, sex, marstat, education, adveduc, occupat, jobcat, curremp, urban, starttxyear, endtxyear, txyrs

```
** Check for univariate associations with the outcome match variable for categorical variables
        within those who received a standardized treatment strategy;
proc freq data=temp2;
        tables bcg*ocmatch/chisq;
        where included=1 and strat=0;
run;
```

This was repeated for the following variables (replacing bcg):
diabetes, hiv, parent, tbcontact, tbmortality, mdrcontact, homeless, smoke, alcohol, drugadic, commsex, crime, prison, unemp, instit, military, hcw, criminst, countsrf, ctsrf2, ctsrf3, bmicat, agecat, strat, sex, marstat, education, adveduc, occupat, jobcat, curremp, urban, starttxyear, endtxyear, txyrs

```
** Check for univariate associations with the outcome match variable for continuous variables
        within the entire analysis population;
proc ttest data=temp2;
        class ocmatch;
        where included=1;
        var txmonths;
run;
```

This was repeated for the variables edad and bmi (replacing txmonths)

```
** Check for univariate associations with the outcome match variable for continuous variables
        within those who received an individualized treatment regimen;
proc ttest data=temp2;
        class ocmatch;
        where included=1 and strat=1;
        var txmonths;
run;
```

This was repeated for the variables edad and bmi (replacing txmonths)

```
** Check for univariate associations with the outcome match variable for continuous variables
        within those who received a standardized treatment regimen;
proc ttest data=temp2;
        class ocmatch;
        where included=1 and strat=0;
        var txmonths;
run;
```

This was repeated for the variables edad and bmi (replacing txmonths)

```
** Create dummy variables for potential predictors with more than 2 categories;
data temp4;
        set work.temp3;

        syear1=(starttxyear=1997);
        syear2=(starttxyear=1998);
        syear3=(starttxyear=1999);
        syear4=(starttxyear=2000);
        syear5=(starttxyear=2001);
        syear6=(starttxyear=2002);

        eyear1=(endtxyear=1999);
        eyear2=(endtxyear=2000);
        eyear3=(endtxyear=2001);
        eyear4=(endtxyear=2002);
        eyear5=(endtxyear=2003);
        eyear6=(endtxyear=2004);
        eyear7=(endtxyear=2005);
run;


****** MODEL 1 - FULL ANALYSIS POPULATION ******
**********************************************;
%include 'S:\course\Epi740\MACRO\collinearity_macro 09.sas';

** Run collinearity diagnostics;
** Logistic model with all potential predictors and confounders included;
proc logistic data=temp4 covout outest=mod1;
        model ocmatch(descending)=hiv tbcontact hcw strat adveduc syear1 syear2 syear3 syear4 syear5
        syear6 eyear1 eyear2 eyear3 eyear4 eyear5 eyear6 eyear7 edad sex;
run;
%collin(covdsn=mod1, procdr=, parminfo=);
run;
```

```
** starttxyear dummy variables are highly collinear with each other and with the intercept, so
   they are removed from the model and collinearity diagnostics rerun;
proc logistic data=temp4 covout outest=mod1;
          model ocmatch(descending)=hiv tbcontact hcw strat adveduc eyear1 eyear2
          eyear3 eyear4 eyear5 eyear6 eyear7 edad sex;
run;
%collin(covdsn=mod1, procdr=, parminfo=);
run;

** The highest CI is now 26 - this is acceptable - no further collinearity exists;
** Use backward elimination;
```

The LOGISTIC Procedure

Model Information	
Data Set	WORK.TEMP4
Response Variable	ocmatch
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	1658
Number of Observations Used	1655

Response Profile		
Ordered Value	**ocmatch**	**Total Frequency**
1	1	1061
2	0	594

Probability modeled is ocmatch=1.

Note: 3 observations were deleted due to missing values for the response or explanatory variables.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	2162.734	2104.508
SC	2168.146	2185.682
-2 Log L	2160.734	2074.508

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	86.2261	14	<.0001
Score	83.5163	14	<.0001
Wald	78.6974	14	<.0001

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.1139	0.4826	0.0558	0.8133
hiv	1	-0.7109	0.5086	1.9536	0.1622
tbcontact	1	0.1695	0.1085	2.4423	0.1181
hcw	1	0.9500	0.5657	2.8207	0.0931
strat	1	0.8500	0.1626	27.3240	<.0001
adveduc	1	0.1072	0.1322	0.6576	0.4174
eyear1	1	0.0956	0.5050	0.0359	0.8498
eyear2	1	0.4495	0.4835	0.8642	0.3526
eyear3	1	0.5094	0.4818	1.1179	0.2904
eyear4	1	0.6875	0.4777	2.0715	0.1501
eyear5	1	0.7241	0.4672	2.4024	0.1212
eyear6	1	-0.1942	0.4634	0.1756	0.6752
eyear7	1	-1.1690	1.2441	0.8828	0.3474
EDAD	1	0.00268	0.00426	0.3978	0.5282
sex	1	0.0124	0.1083	0.0131	0.9089

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
hiv	0.491	0.181	1.331
tbcontact	1.185	0.958	1.465
hcw	2.586	0.853	7.836
strat	2.340	1.701	3.218
adveduc	1.113	0.859	1.443
eyear1	1.100	0.409	2.960
eyear2	1.567	0.608	4.044
eyear3	1.664	0.647	4.279
eyear4	1.989	0.780	5.072
eyear5	2.063	0.826	5.154
eyear6	0.823	0.332	2.042
eyear7	0.311	0.027	3.559
EDAD	1.003	0.994	1.011
sex	1.012	0.819	1.252

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	62.2	**Somers' D**	0.254
Percent Discordant	36.8	**Gamma**	0.256
Percent Tied	0.9	**Tau-a**	0.117
Pairs	630234	**c**	0.627

Iterations of the model produced using backward elimination:

* adveduc is the least significant predictor (p=.4174), so it is removed;

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.0718	0.4799	0.0224	0.8811
hiv	1	-0.7195	0.5081	2.0053	0.1568
tbcontact	1	0.1651	0.1083	2.3246	0.1273
hcw	1	1.0224	0.5590	3.3455	0.0674
strat	1	0.8515	0.1625	27.4476	<.0001
eyear1	1	0.0871	0.5049	0.0297	0.8631
eyear2	1	0.4458	0.4835	0.8499	0.3566
eyear3	1	0.5075	0.4818	1.1093	0.2922
eyear4	1	0.6876	0.4777	2.0719	0.1500
eyear5	1	0.7235	0.4672	2.3978	0.1215
eyear6	1	-0.1991	0.4635	0.1846	0.6674
eyear7	1	-1.1690	1.2435	0.8838	0.3472
EDAD	1	0.00221	0.00422	0.2751	0.5999
sex	1	0.0127	0.1083	0.0138	0.9064

* hiv is the least significant predictor (p=.1568), so it is removed;

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.0700	0.4798	0.0213	0.8841
tbcontact	1	0.1584	0.1081	2.1463	0.1429
hcw	1	1.0317	0.5589	3.4078	0.0649
strat	1	0.8517	0.1624	27.5044	<.0001
eyear1	1	0.0807	0.5049	0.0255	0.8731
eyear2	1	0.4472	0.4835	0.8556	0.3550
eyear3	1	0.5089	0.4818	1.1157	0.2909
eyear4	1	0.6865	0.4776	2.0654	0.1507
eyear5	1	0.7111	0.4670	2.3180	0.1279
eyear6	1	-0.2084	0.4634	0.2022	0.6530
eyear7	1	-1.1678	1.2434	0.8821	0.3476
EDAD	1	0.00228	0.00422	0.2923	0.5888
sex	1	0.00808	0.1082	0.0056	0.9405

* tbcontact is the least significant predictor (p=.1429), so it is removed;

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	-0.00260	0.4778	0.0000	0.9957
hcw	1	1.0079	0.5581	3.2618	0.0709
strat	1	0.8595	0.1622	28.0931	<.0001
eyear1	1	0.1053	0.5049	0.0435	0.8348
eyear2	1	0.4817	0.4832	0.9940	0.3188

eyear3	1	0.5378	0.4816	1.2471	0.2641
eyear4	1	0.7318	0.4769	2.3548	0.1249
eyear5	1	0.7514	0.4665	2.5943	0.1072
eyear6	1	-0.1571	0.4623	0.1155	0.7340
eyear7	1	-1.1397	1.2427	0.8411	0.3591
EDAD	1	0.00155	0.00418	0.1376	0.7106
sex	1	0.0211	0.1078	0.0385	0.8444

* endtxyear is the least significant predictor (most significant dummy variable: p=.1072), so it is removed;

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	0.4120	0.1480	7.7453	0.0054
hcw	1	0.9972	0.5519	3.2649	0.0708
strat	1	0.6799	0.1538	19.5352	<.0001
EDAD	1	0.00111	0.00409	0.0741	0.7854
sex	1	0.0513	0.1058	0.2352	0.6277

* hcw is the least significant predictor (p=.0708), so it is removed;

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	1	0.4235	0.1480	8.1932	0.0042
strat	1	0.6912	0.1536	20.2590	<.0001
EDAD	1	0.000937	0.00409	0.0525	0.8188
sex	1	0.0624	0.1055	0.3497	0.5543

*strat remains significant at the p=0.05 level, so remains in the model;
* The coefficient of strat is 0.6912;

** Assess confounding by comparing the strat coefficient in models without age or sex;

```
proc logistic data=temp4;
        model ocmatch(descending)=strat sex;
run;
```

* The coefficient of strat is 0.6933;

```
proc logistic data=temp4;
        model ocmatch(descending)=strat edad;
run;
```

* The coefficient of strat is 0.6923;

```
proc logistic data=temp4;
        model ocmatch(descending)=strat;
run;
```

* The coefficient of strat is 0.6963;

* None of the estimates for strat differ by more than 10%, therefore age and sex do not confound the relationship between strat and ocmatch;