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Yuan Zhao Date

Targeted Maximum Likelihood Estimation to Evaluate Effect of Novel Regimens on Multidrug Resistant Tuberculosis

By

Yuan Zhao

Master of Public Health

Department of Biostatistics and Bioinformatics

_____

David Benkeser, Ph.D.

Committee Chair

_____

Robert Lyles, Ph.D.

Committee Member

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By

Yuan Zhao

Bachelor of Science

Peking University

2012

Master of Health Science

Johns Hopkins University

2014

Thesis Committee Chair: David Benkeser, Ph.D.

An abstract of

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Abstract

Targeted Maximum Likelihood Estimation to Evaluate Effect of Novel Regimens on Multidrug Resistant Tuberculosis

By Yuan Zhao

Introduction Multidrug resistant tuberculosis (MDR-TB) is a growing threat to public health and the cure rate of MDR-TB in the real world is still low. We applied super learning and targeted maximum likelihood estimation (TMLE) techniques to estimate the effect of novel regimens of bedaquiline and delamanid on MDR-TB patients using data from a small observational study.

Methods The study included a total of 100 MDR-TB patients from Georgia and the two primary outcomes were sputum culture conversion (SCC) within 2 and 6 months. We assessed the applicability of TMLE with super learner for estimating effects in this setting via simulation. The best-performing estimators from the simulation study were then applied to compare the rates of 2- and 6-month SCC for bedaquiline- and delamanid-based regimens.

Results All estimators had relatively good performance in the simulation study with low mean squared error (<0.015) and near nominal 95% confidence interval coverage (90%-95%). Our analysis showed that the bedaquiline-based regimen had a higher culture conversion rate than the delaminid-based regimen with an estimated difference in probability of SCC of 0.199 (95%CI -0.007, 0.405; p-value 0.059) at 2 months and 0.187 (95%CI 0.050, 0.324; p-value 0.007) at 6 months.

Discussion Our results indicate that bedaquiline-based regimens are associated with better sputum culture conversion rate within 2 months and 6 months than delamanid-based regimens, supporting the inclusion of bedaquiline in routine MDR tuberculosis regimens. We also demonstrated that TMLE with the super learner method is advantageous in causal estimation in settings of observational studies with small sample sizes. Future studies can focus on generalizing the conclusion using additional simulation data sets and fine tuning the hyperparameters of machine learning algorithms inside super learner by adding another layer of cross-validation to ensure that super learner always selects optimal algorithm combinations.

Key words: Multidrug-resistant TB, causal inference, super learner, targeted maximum likelihood estimation (TMLE)

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Introduction

Tuberculosis (TB) is a highly contagious infectious disease caused by the bacillus *Mycobacterium tuberculosis*. TB generally affects the lungs (pulmonary TB), but can also affect other parts of the body (extrapulmonary TB). The disease can spread when the bacteria are released into the air via coughs and sneezes. Although TB is highly infectious, 90% of the 1.3 billion people infected with *M. tuberculosis* will not develop TB disease during their life time (1). However, the probability of developing TB is much higher among people who are infected with HIV and diabetes (2).

As of 2017, TB is the leading cause of death from a single infectious agent worldwide, causing an estimated 1.6 million deaths (3). An estimated 10 million developed TB in 2017 globally, among which 10% were children and 9% were people living with HIV. The highest disease burden was in the South-east Asia and Western Pacific regions, which accounted for 62% of new cases, followed by the African region, which accounted for 25% of new cases. While morbidity and mortality due to TB remain high, they are both declining at an annual rate of approximately 2%. This decline is due in large part to more effective diagnosis and treatment of TB. The WHO currently recommends the Xpert® MTB/RIF assay for diagnosis of pulmonary TB and a 6-month regimen of four drugs for treating drug susceptible TB: isoniazid, rifampicin, ethambutol and pyrazinamide. The latest studies showed standard regimens have achieved a global treatment success rate of 82% in 2016 (4).

Despite this progress, multidrug-resistant (MDR) TB is a growing threat to public health. MDR TB is defined by resistance of *M. tuberculosis* to at least two of the most powerful TB drugs: rifampicin and isoniazid. MDR TB is often caused by inappropriate clinical use of TB treatment (5). In 2017, 160, 684 cases of MDR TB were detected worldwide, an increase of more than 20% per year since 2009 (3). Without access to comprehensive drug susceptibility testing of TB, most MDR patients receive standardized treatment regimens, so the rate of treatment success remains low for MDR TB at just 55% globally (6). These ineffective treatment strategies increase the risk of MDR TB transmission in the community and risk the development of extensively drug-resistant (XDR) tuberculosis, defined as MDR-

TB with additional resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin or kanamycin).

The primary strategy to combat MDR-TB is to increase case-finding and to deliver effective chemotherapy. However, only 25% of the estimated 558,000 people who developed MDR-TB in 2017 were enrolled in a second-line treatment, and effective treatment requires more drugs that are both more expensive (⩾US$ 1000 per person) and more toxic (3).

Currently, there are 20 TB drugs in clinical trials, including combination regimens with 11 new compounds (7). Results from a phase II clinical trial provide evidence that the newly developed anti-tuberculosis compounds bedaquiline and delamanid have significantly higher cure rates for MDR-TB and theses two drugs have received accelerated or conditional regulatory approval (8). However, results from other phase III trials of delamanid were inconclusive as the treatment and control arms were not significantly different in cure rate (9).

While these recent trials mark definite progress in the fight against MDR-TB, much work remains to optimize treatment regimens, understand adverse events associated with the use of these new drugs, and to determine the efficacy of these drugs outside the context of a controlled trial. Therefore, it will be important to continue to monitor use of these new drugs in clinical settings. Observational studies of patients with MDR-TB who are receiving these drugs provide a unique opportunity to study these questions.

However, observational studies present challenges to estimating treatment effects. In particular, lack of randomized treatment assignment makes causal inference drawn from observational studies much less convincing than inference drawn from clinical trials. To compensate for the lack of randomized assignment and ensure exchangeability of treated and untreated individuals in observational settings, we need to adjust for all confounders of treatment receipt and study outcome in the statistical analysis. However, there is often uncertainty as to which, if any, of the potentially high-dimensional set of measured covariates are confounders. This poses unique challenges when sample size is small, as there is

a delicate tradeoff between controlling for bias due to confounding and controlling for variability induced by adjustment for a large number of confounders (10). Furthermore, in settings with little knowledge of how treatment is being prescribed and/or how covariates and treatment affect outcomes, it is difficult to correctly specify a parametric regression model, such as a linear or logistic regression model. When misspecified, these methods lead to effect estimates with residual confounding.

Nevertheless, many epidemiologic studies of treatment effects often rely on parametric models to infer causal effects, for example by using G-computation or inverse probability-of-treatment weighting (IPTW) methods. G-computation typically uses a parametric regression model to describe the mean outcome as a function of the exposure and covariates, the so-called outcome regression. Correct specification of this model is essential to obtain consistent estimates of the true causal effect. Alternatively, IPTW typically relies on a parametric regression model to describe the probability of receiving treatment as a function of covariates, the so-called propensity score (11). Weighting subjects by the inverse propensity score mimics a synthetic sample in which treatment assignment is independent of baseline covariates. As such, the IPTW approach heavily relies on correct specification of propensity scores to obtain consistent estimates of the true causal effect. Also, extremely low or high propensity scores can lead to extremely large weights, resulting in unstable causal estimates with high variance or values outside the constraints of the statistical model (for example, risk difference estimates of less than -1 or greater than 1) (12). Other methods of using propensity score, such as stratification, matching and covariate adjustment using propensity score as a covariate, also have limitations and are not necessarily superior to conventional causal inference methods (13).

An alternative to G-computation and IPTW are so-called doubly robust approaches, including targeted maximum likelihood estimation (TMLE)(14). These methods yield consistent estimates if either the outcome regression or the propensity score is consistently estimated. Moreover, TMLE is asymptotically efficient when both quantities are consistently estimated and can be more robust to outliers and sparsity than competing methods (15). Therefore, TMLE may be particularly advantageous in observational studies with small samples (16).

Despite putative benefits of doubly robust approaches, in observational studies the fact remains that it is difficult to correctly specify even one of the outcome regression or propensity score using parametric models. Therefore, we are interested in considering more flexible regression techniques. One appealing paradigm for flexible regression is super learner (17), which uses cross-validation methods to identify the optimal (with respect to, e.g., mean squared error) combination of predictions from a list of algorithms. Therefore, we can choose from a diverse combination of candidate algorithms to suit the practical questions. For example, a collection of algorithms including linear or logistic regression estimators, or algorithms coupled with screening procedures to reduce the number of covariates and so on. It is demonstrated that in large samples the super learner performs essentially as well as the best choice among the library of candidate algorithms (18). Therefore, super learner may generate the closest approximation to the real data generating mechanism (19).

This method has been widely applied in studies with large sample size and proved to have more accurate prediction than classical approaches (20). However, it remains unclear how to select the optimal library of candidate algorithms and cross-validation parameters when sample size is relatively small ($n<100$). As super learner can be sensitive to overparameterized regression models, which may cause highly variable effect estimates. In this study, we evaluate and compare the performance of super learner in combination with TMLE under different cross-validation and regression model selection strategies in simulated small size datasets. The optimal strategy is applied to TB study data to compare the average treatment effect of bedaquiline- and delaminid-based regimens.

Methods

1. Study Design

Our data were generated by a study of novel TB drug regimens conducted at the National Center for Tuberculosis and Lung Diseases (NCTLD) in Tbilisi, Georgia. Study enrollment took place from December 2015 through May 2017. All patients older than 16 years with sputum culture-confirmed MDR-TB and who started either bedaquiline, linezolid, clofazimine, or delaminid or some combination of these in the prior two weeks were eligible for study enrollment. During the early study period a preference was given to enroll patients from Tbilisi and later on in an effort to meet enrollment goals we included patients from outside Tbilisi. Written informed consent was required for participation and ethics approval was obtained from the IRBs of Emory University and the NCTLD.

All patients were recommended to be hospitalized for the initiation of drug-resistant TB treatment for close monitoring of clinical status and drug tolerability. Patients in general remained hospitalized until they had conversion of the sputum smear microscopy and clinical improvement. The standard of care for treatment duration during the study period for MDR and XDR TB was 20 to 24 months. Treatment regimens were individualized based on drug-susceptibility testing results (DST). Doctors were recommended to prescribe bedaquiline to patients with pre-XDR and XDR TB and an albumin < 3 grams/dL, and to prescribe delaminid to patients with HIV, Hepatitis C and diabetes due to less potential for hepatoxicity and drug-drug interactions. However, beyond these recommendations, no oversight was provided into how drug regimens were assigned.

Case report forms were created to collect baseline information on patient demographics, medical history, TB clinical and laboratory disease characteristics and comorbidities and to prospectively collect data on sputum culture and general laboratory results, drug adherence, adverse events and final clinical treatment outcomes. Data was collected by study team members. All data was entered into an online HIPPA compliant REDCap database. Our primary outcome was defined as sputum culture conversion from initiation of TB treatment within two and six months.

2. Causal Estimation Methods

We are interested in estimating the probability of culture conversion within two and six months if, possibly counter-to-fact, all patients had been assigned a bedaquiline-based or a delamanid-based treatment regimen. In this section, we introduce notation and review some methods for estimating counterfactual parameters and causal effects.

2.1 Notation

For patient i, we denote the observed data by O_i, which includes A_i, a binary variable where $A_i = 1$ denotes prescription of a bedaquiline-based regimen and $A_i = 0$ denotes taking a delamanid-based regimen. We use Y_i to denote the binary outcome of sputum culture conversion within a given time frame (e.g. 2 or 6 months). We use W_i to denote a vector of baseline covariates recorded prior to treatment assignment, which includes age, height, weight, body mass index (BMI), gender, history of imprisonment, tobacco use, alcohol use, diabetes mellitus, hepatitis C, prior TB diagnosis, case definition (new, treated with first-line drugs, treated with second-line drugs), TB location (pulmonary, pulmonary and extrapulmonary), acid-fast bacilli (AFB) smear and chest radiology results (multilobar, bilateral, cavitary, bilateral cavitary). We assume that the observed data consist of n independent and identically distributed copies of random variable $O = (W, A, Y)$. The goal of analysis is to estimate $E(Y^a)$ for $a = 0,1$, where Y_i^1 and Y_i^0 represent the potential outcome of patient i had they received the treatment corresponding to the $\mathrm{A} = 1$ or $\mathrm{A} = 0$. We can then compare the difference in treatment effect by comparing $E(Y^a) = \Pr(Y^a = 1)$ across levels of A. The regimen with higher probability of sputum culture conversion within 2 or 6 months can be interpreted as having greater effectiveness than the other regimen. Under key causal assumptions (21), $E(Y^a)$ can be estimated from the observed data through estimation of the quantity $E[E(Y|A = a, W)]$, where the outer expectation is taken with respect to the distribution of W.

2.2 G-computation

A common approach to estimate $E(Y^a)$ is based on the plug-in principle and is commonly referred to as G-computation (22). In this approach, we fit a so-called outcome regression by regressing the binary outcome on treatment and covariates. We use $\mathrm{Q(a, w)}$ to denote the conditional mean of Y given $\mathrm{A = a}$ and $\mathrm{W = w}$. We denote by $Q_n(a, w)$ the estimate of this conditional mean based on the observed data. To compute the G-computation estimator, we predict outcomes for each observation on a new data set where treatment $\mathrm{A = a}$ for each observation and for $\mathrm{a = 0,1}$ (irrespective of their observed treatment). These predictions are averaged to obtain an estimate of $E(Y^a)$. For example, if we model the outcome regression using logistic regression: $logit(Q_n(A_i, W_i)) = \hat{\beta}_0 + \hat{\beta}_1 A_i + \hat{\beta}_2 W_i$. To compute the G-computation estimator, we would compute $Q_i^1 = Q_n(1, W_i) = logit^{-1}(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 W_i)$ and $Q_i^0 = Q_n(0, W_i) = logit^{-1}(\hat{\beta}_0 + \hat{\beta}_2 W_i)$. The G-computation estimate of $E(Y^a)$ is $\hat{E}(Y^a) = \frac{1}{n}\Sigma_{i=1}^n Q_i^a$, while the estimate of the average treatment effect is $\widehat{ATE} = \hat{E}(Y^1) - \hat{E}(Y^0)$.

2.3 Inverse Probability of Treatment Weighting (IPTW)

Another popular method for estimating counterfactual parameters is IPTW (23). These estimators are based on the observation that $\mathrm{E[E(Y|A = a, W)]}$ can be equivalently written as $E[\frac{I(A=a)}{Pr(A=a|W)}Y]$, where the outer expectation is taken with respect to the joint distribution of $\mathrm{(W, A, Y)}$. In this view, the plug-in principle suggests that to estimate $E(Y^a)$, we could find an estimate $g_n(\mathrm{a \mid W}_i)$ of $g(\mathrm{a \mid W}_i) = \mathrm{Pr(A = a \mid W = W}_i)$ for $\mathrm{i = 1, .., n}$, the so-called propensity score, and use it to take an inverse-weighted average of outcomes. For example, if we model the propensity score using logistic regression, we can compute $\hat{g}_i = g_n(1 \mid \mathrm{W}_i) = logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 W_i)$. The IPTW estimate of $E(Y^1)$ is $\hat{E}(Y^1) = \frac{1}{n}\Sigma_{i=1}^n \frac{I(A_i=1)}{\hat{g}_i}Y_i$, the IPTW estimate of $E(Y^0)$ is $\hat{E}(Y^0) = \frac{1}{n}\Sigma_{i=1}^n \frac{I(A_i=0)}{1-\hat{g}_i}Y_i$, and the estimate of the average treatment effect is the difference between the two (24).

2.4 Limitations of parametric regression models

For both G-computation and IPTW to consistently estimate treatment effect, respectively, the outcome regression or propensity score must be consistently estimated. Consistently estimating these quantities using parametric regression models can be challenging in observational contexts. In our setting, because the drugs under study are new and MDR-TB is poorly understood, it is difficult to know a priori which, if any, of the measured variables may be acting as effect modifiers. It may also be challenging to specify a priori which, if any, of the measured variables may have non-linear relationships with probability of SCC or probability of receiving each drug regimen. Thus, we are motivated to consider more flexible regression techniques, such as nonparametric, semiparametric regression, and machine learning. A particularly appealing choice is the super learner (17). Super learner is an ensemble-based approach for combining estimates from a pre-specified library of candidate estimators. Thus, the prediction for a super learner regression model is a weighted combination of the predictions from the various candidate regressions, where the weights are typically constrained to sum to 1. The weights are selected to maximize the cross-validated fit of the super learner (25). Cross-validation divides the dataset into k mutually exclusive sets of equal size, and each set and its complement act as validation and training samples. The training sample is used to fit the candidate regressions and the validation sample is used to assess the performance of the estimators using relevant criteria, such as mean squared error (26). In large samples, the super learner has been shown to have cross-validated performance that is essentially equivalent to the performance of the unknown best possible weighted combination of the candidate regressions. In this sense super learner provides an optimal way to choose between regression estimators in the face of model uncertainty.

Unfortunately, we are not able to easily combine flexible regression techniques with the G-computation and IPTW frameworks. In general, such estimators have irregular behavior and fail even to satisfy the conditions necessary to employ the nonparametric bootstrap. This makes constructing valid confidence intervals for such estimators quite challenging. In order to utilize flexible techniques as part of effect estimation, while maintaining the ability to perform statistical inference we must consider alternative frameworks.

2.5 Targeted Maximum Likelihood Estimation (TMLE)

An alternative estimator that overcomes the limitations of both G-computation and IPTW is TMLE. TMLE is a doubly robust substitution estimator with a "targeting" step to yield unbiased estimation of causal effect. The estimation procedure is outlined in Figure 1 alongside G-computation and IPTW. A key difference between TMLE relative to G-computation and IPTW is that the latter require an estimate of either the propensity score or outcome regression, while TMLE requires both. As above, we use Q_n and g_n to denote estimates of outcome regression and propensity score, respectively. Given these estimates, the TMLE procedure requires computing a term similar to inverse probability weights: $H_a(A_i, W_i)$ for each individual, defined as $H_a(A_i, W_i) = \frac{I(A_i=a)}{g_n(a \mid W_i)}$ for $a = 0,1$. We then update the initial estimates of $E(Y|A, W)$ by fitting an additional logistic regression model (27):

$$logit\big(Q(A,W)\big) = logit\big(Q_n(A,W)\big) + \delta_1 H_1(A,W) + \delta_0 H_0(A,W)$$

This is a logistic regression of the outcome onto the predictors $H_1(A, W)$ and $H_0(A, W)$ with no intercept term and with offset equal to $logit\big(Q_n(A, W)\big)$.As with the G-computation estimator, we then predict outcomes for each observation on a new data set where treatment for each observation are set to $A = 0$ and $A = 1$, respectively. That is letting $\hat{\delta}_a$ denote the estimated coefficient from this logistic regression model for $a = 0,1$, we compute $\hat{Q}_a^* = logit^{-1}[logit\big(Q_n(a, W_i)\big) + \delta_1 H_1(1, W_i) + \delta_0 H_0(0, W_i)$ and the estimated average treatment effect is $\text{ATE}^* = \frac{1}{n}\Sigma_{i=1}^{n}[\widehat{Q}_1^*(W_i) - \widehat{Q}_0^*(W_i)]$.

There are several benefits of TMLE relative to G-computation and IPTW estimators. Foremost, is that it is possible to utilize flexible regression techniques to estimate the outcome regression and propensity score, while maintaining regular behavior of the estimator in large samples under suitable regularity conditions. This enables confidence intervals and hypothesis tests to be constructed even when very flexible techniques like super learner are utilized. A second major benefit of TMLE is that the estimate of the ATE is consistent so long as either the outcome regression or the propensity score is estimated consistently, a property referred to as double robustness (15).

G-Computation	TMLE	IPTW
Step 1: Predicting outcome $E\ (Y\|A,W)$ using $Q\ (A,W)$ for both treatment	**Step 1:** Predicting $E\ (Y\|A,W)$ using $Q\ (A,W)$ for both treatment	
	Step 2: Using $Pr(A\|W)$ to update initial outcome estimator, and get "targeted" predicted outcomes	**Step 1:** Estimate propensity score $Pr(A\ \|W)$ using $g_i(A,W)$ and create inverse probability weight
Step 2: Calculate ATE as mean difference of predicted outcome	**Step 3:** Calculate ATE as Mean Difference in Targeted Predicted Outcome	**Step 2:** Calculate ATE as mean difference of weighted outcome

Figure 1: Comparison in the estimation steps across 3 different estimators for the average treatment effect (ATE)

Simulation Study

While we have theory that guarantees performance of super learner and TMLE in large samples, it is still an open question as to whether this approach can be applied in small samples, like our study of drug effects on MDR-TB. In particular, there are two important questions to consider with respect to how super learner should be constructed in these contexts. First is the question of whether there is a benefit to include only simple regressions (e.g. logistic regression) in the super learner library or whether more aggressive regressions (e.g. machine learning) should also be included. We were concerned that including machine learning algorithms as candidate regressions in the super learner may run the risk of overfitting in small samples. While super learner's use of cross-validation should, in theory, prevent this overfitting from propagating to the super learner itself, we wished to study whether this was true via simulation. The

second key question that we considered was how to select the number of folds for cross-validation. Selection of the folds involves a tradeoff: large number of folds mean more data for fitting the regression – putatively resulting in more stable regression estimators – but less data for evaluating the goodness-of-fit of the regression – putatively resulting in worse super learner weights. In large samples, this is a minor issue and typically 10 folds is used. However, in small samples, we hypothesized that this choice may have an effect on the performance of the estimators of treatment effects.

To address these questions, we applied estimators based on super learner and TMLE to simulated datasets with a known data generating distribution. We generated 1,000 simulated data sets by sampling with replacement from the observed outcomes while holding the observed covariates and treatment assignments fixed. In this way, we preserve the distribution of baseline covariates and their relationship to the probability of receiving the two regimens. However, because outcomes are randomly sampled, there is, by design, no difference in SCC rates between the two arms: the true probability of sputum culture conversion in 2 and 6 months for both bedaquiline-based and delamanid-based regimen is the sample mean of SCC in 2 and 6 months, respectively, 0.621 and 0.895.

We considered six different TMLEs, each based on a different super learner. The super leaners utilized different numbers of cross-validation folds (2, 10, and 20) and different candidate libraries (simple and complicated). To keep the comparison simple, we utilized the same candidate libraries for both outcome regression and propensity score. The simple library included candidate regressions of only logistic regression models with 3 covariates and no interaction specified between covariates. The 3 covariates in the regressions were selected by super learner using the fixed screening algorithms for both outcome regression and propensity score. We specified screening algorithms as forward and step selections based on AIC or by Wald test, in which the ones with highest significant effect were retained in the model. Since we were running the TMLEs on 1000 datasets, it was possible that different predictors were selected by super learner for each dataset. The complicated library included all the algorithms in the simple library and commonly used machine learning algorithms of random forest (28), Bayesian additive regression trees (29), Lasso and ridge regression (30), gradient boosted decision trees (31) and

multivariate adaptive regression splines (32). We implemented the analysis using R packages drtmle (33) and SuperLearner (17).

Table 1, 2 and Figure 2, 3 give the mean squared error (MSE) and proportion of samples for which the known parameter was contained in the 95% confidence interval (CI) for the six TMLE estimators by sampling both 2-month and 6-month SCC. TMLE-I is the super learner with simple library and TMLE-II is complicated library. Both TMLE-I and TMLE-II showed similar low MSE and over 90% coverage probability for the 95% CI. Results of both 2-month and 6-month simulation showed over coverage of 95% CI for bedaquiline-based regimen, nominal coverage for delaminid-based regimen and slightly under coverage for difference between the two regimens. The mean squared error was also lowest for bedaquiline and highest for treatment difference. Higher numbers of cross-validation folds added to the computational burden significantly but did not add much benefit to the simple library and only improved the performance of the complicated library slightly. Therefore, to efficiently evaluate our study data, we chose 10-fold cross-validation for TMLE-I and 20-fold for TMLE-II.

Analysis of MDR-TB data

64 patients received the bedaquiline-based regimen and 30 received the delaminid-based regimen (Table 3). Most of the baseline covariates had similar distributions between the two groups, except that a higher proportion of patients who were assigned the delaminid-based regimen had previous TB treatment and first-line TB drugs.

We applied the super learner with both libraries with the best performing cross-validation fold from simulation studies, which is 10-fold for the simple library and 20-fold for the complicated library. Table 4 shows the estimated proportion of SCC within 2 and 6 months for both the bedaquiline-based regimen and the delamanid-based regimen and the difference between the two regimens with 95% confidence intervals. Both simple and complicated super-learner-based TMLE yielded similar results: for the simple library the estimated probability of SCC within 2 months treated with bedaquiline-based regimen was 0.704 (95% CI 0.593, 0.816), and for the delamanid-based regimen it was 0.503 (95% CI 0.328, 0.677). And the estimated difference between the two regimens was 0.202 (95% CI -0.004, 0.408)

with p-value of 0.055. For the complicated library, the estimated probability of SCC in 2 months treated with bedaquiline-based regimen was 0.703 (95% CI 0.592, 0.815) and for the delamanid-based regimen it was 0.505 (95% CI 0.331, 0.679). And the estimated difference between the two regimens was 0.199 (95% CI -0.007, 0.405), with p-value of 0.059. For 6 months SCC probabilities: simple library yielded 0.957 (95% CI 0.904, 1.011) for the bedaquiline-based regimen and 0.769 (95% CI 0.640, 0.898) for the delamanid-based regimen, while the difference between the two was 0.188 (95% CI 0.051, 0.325), with p-value of 0.007. The complicated library yielded 0.954 (95% CI 0.899, 1.008) for the bedaquiline-based regimen and 0.767 (95% CI 0.636, 0.897) for the delamanid-based regimen, while the difference between the two was 0.187 (95% CI 0.050, 0.324), with p-value of 0.007.

Discussion

Both 2-month and 6-month sputum culture conversion results indicated patients treated with the bedaquiline-based regimen had more favorable outcomes than those treated with the delamanid-based regimen after adjusting for measured variables. Our results are consistent with other observational studies assessing the effect of bedaquiline and delamanid in clinical settings (34, 35). These results can inform the selection of drugs and provide evidence to support the inclusion of bedaquiline in MDR tuberculosis regimens.

Our simulation results suggest that, at least in a null scenario, super learner and TMLE may be an advantageous approach even in small samples. In future work, we will compare the impact of decision points for super learner on effect estimates in more complex scenarios to generalize this conclusion. There are also possibilities to use an additional layer of cross-validation for fine tuning hyperparameters of machine learning algorithms to ensure super leaner will always select optimal algorithms combinations in finite samples. The current method to apply TMLE requires a complete dataset for measured covariates, which slightly shrank our sample size due to missingness of the covariates (5%). We also noticed that some upper bounds of the 95% confidence intervals for the proportion generated by TMLE exceeded 1, indicating possibilities to use other modified estimators to address this issue (33).

Table 1: Simulation Results for 2 months SCC

SIM=1000	Time	Diff 95% CI Coverage	MSE	Bed 95% CI Coverage	MSE	Del 95% CI Coverage	MSE
Simple							
CV=2	1267.18	0.921	0.013	0.999	0.002	0.950	0.006
CV=10	4244.34	0.928	0.014	0.995	0.002	0.971	0.005
CV=20	7877.35	0.900	0.015	1	0.002	0.966	0.005
Complicated							
CV=2	4447.14	0.898	0.014	0.998	0.002	0.950	0.005
CV=10	11368.16	0.913	0.013	0.994	0.002	0.944	0.005
CV=20	21236.30	0.890	0.015	0.993	0.002	0.957	0.005

Table 2: Simulation Results for 6 months SCC

SIM=1000	Time	Diff 95% CI Coverage	MSE	Bed 95% CI Coverage	MSE	Del 95% CI Coverage	MSE
Simple							
CV=2	1038.10	0.902	0.0049	0.977	0.00066	0.915	0.002
CV=10	3435.88	0.908	0.0049	0.979	0.00070	0.921	0.002
CV=20	5848.06	0.896	0.0052	0.979	0.00071	0.902	0.002
Complicated							
CV=2	10467.48	0.904	0.0048	0.983	0.00065	0.919	0.002
CV=10	41156.22	0.882	0.0049	0.981	0.00067	0.912	0.002
CV=20	77021.84	0.880	0.0048	0.980	0.00068	0.904	0.002

Table 3: Baseline Characteristics for Patients Receiving Bedaquiline-based Regimen and Delaminid-based Regimen

	Bedaquiline (N=64)	**Delaminid (N=30)**
Achieved SCC (n, %)	62 (96.9%)	24 (80.0%)
Days to SCC (mean, sd)	60.43 (56.13)	46.00 (32.52)
SCC in 2 Month (n, %)	44 (68.9%)	15 (50.0%)
SCC in 6 Month (n, %)	61 (95.3%)	23 (76.7%)
Age	39.28 (13.13)	38.22 (11.92)
Male	57 (89.1%)	20 (66.7%)
Weight (kg)	65.00 (13.14)	66.10 (12.25)
BMI	21.66 (3.61)	21.96 (4.11)
Imprisonment	17 (26.6%)	7 (23.3%)
HIV status	2 (3.12%)	0
Diabetes Mellitus	8 (12.5%)	3 (10.0%)
Tobacco Use		
None	29 (45.3%)	17 (56.7%)
<1 pack	19 (29.7%)	5 (16.7%)
>= 1 pack	16 (25.0%)	8 (26.7%)
Alcohol Use		
None	45 (70.3%)	19 (63.3%)
Moderate	11 (17.2%)	8 (26.7%)
Heavy	8 (12.5%)	3 (10.0%)
Hepatitis C	13 (20.3%)	7 (23.3%)
Types of TB		
Pulmonary	62 (96.9%)	29 (96.7%)
Extrapulmonary	2 (3.12%)	1 (3.33%)
History of previous TB treatment	34 (53.1%)	23 (76.7%)
Case Definition		
New	31 (48.4%)	9 (30.0%)
Treated with first-line drugs	8 (12.5%)	6 (20.0%)
Treated with second-line drugs	24 (37.5%)	11 (36.7%)
Acid-fast Bacilli (AFB) smear		
0	16 (25.0%)	7 (23.3%)
+1	22 (34.4%)	15 (50.0%)
+2	12 (18.8%)	5 (16.7%)
+3	10 (15.6%)	2 (6.7%)
+4	4 (6.3%)	2 (6.7%)
Chest Radiology		
Multilobar	52 (81.3%)	20 (66.7%)
Bilateral	37 (57.8%)	18 (60.0%)
Cavitary	37 (57.8%)	21 (70.0%)
Billateral Cavitary	13 (20.3%)	5 (16.7%)

Table 4: TMLE Proportion of SCC in 2 and 6 months by two regimens and the difference between Bedaquiline and Delamanid-based regimens

		Bedaquiline (95%CI)	Delamanid (95%CI)	Difference (95%CI)	P-value for Difference
SCC in 2 Month	**Unadjusted**	0.689 (0.564, 0.791)	0.500 (0.332, 0.668)	0.189 (-0.025, 0.402)	0.083
	TMLE I[1]	0.704 (0.593,0.816)	0.503 (0.328,0.677)	0.202 (-0.004,0.408)	0.055
	TMLE II[2]	0.703 (0.592,0.815)	0.505 (0.331,0.679)	0.199 (-0.007,0.405)	0.059
SCC in 6 Month	**Unadjusted**	0.967 (0.882, 0.998)	0.767 (0.588, 0.885)	0.200 (0.043, 0.358)	0.013*
	TMLE I	0.957 (0.904,1.011)	0.769 (0.640, 0.898)	0.188 (0.051,0.325)	0.007**
	TMLE II	0.954 (0.899, 1.008)	0.767 (0.636, 0.897)	0.187 (0.050, 0.324)	0.007**

1. TMLE I is super learner with simple algorithm library
2. TMLE II is super learner with complicated algorithm library

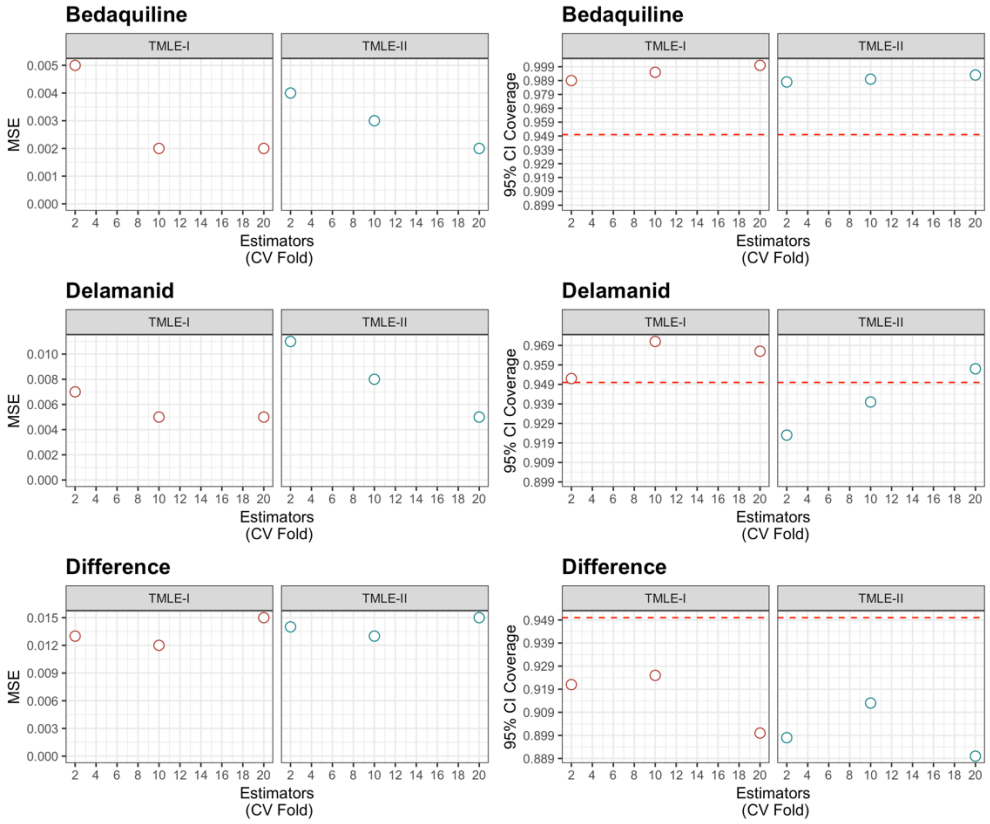

Figure 2: Simulation results of six different TMLEs using 2-month SCC

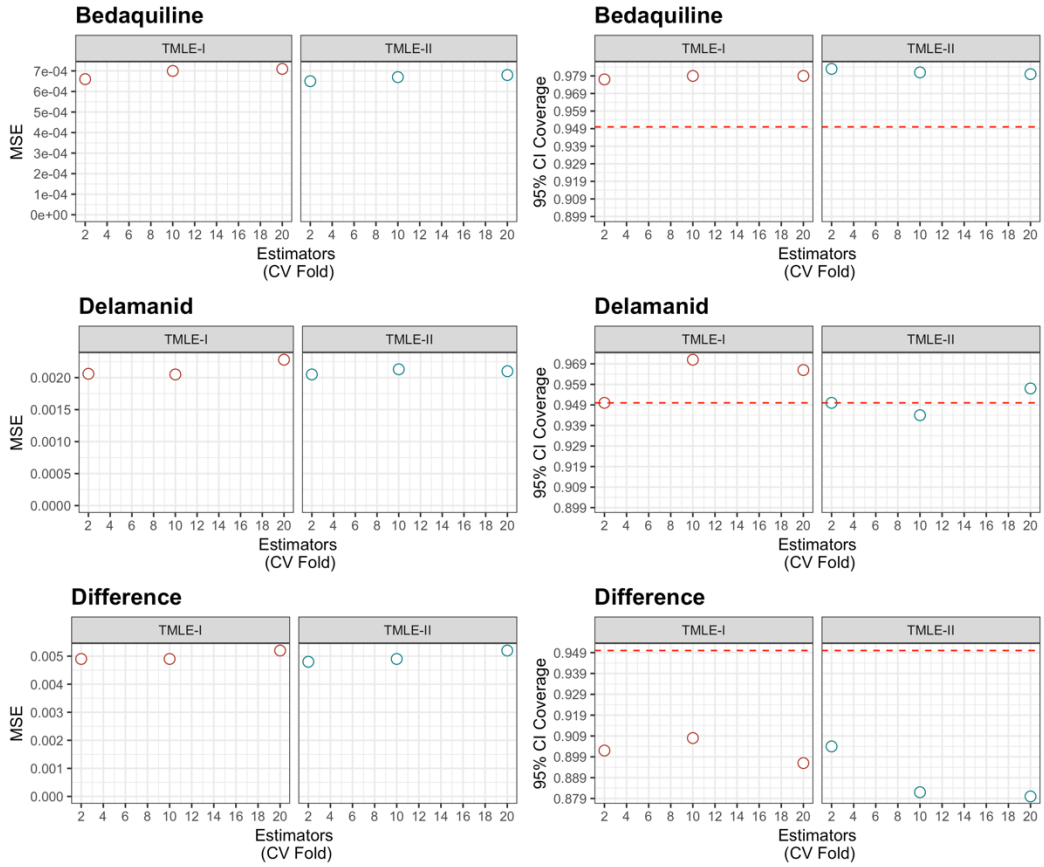

Figure 3: Simulation results of six different TMLE using 6-month SCC

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