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Generalization of the causal effect of a given regimen in a network meta-analysis using AIPTW and TMLE

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Generalization of the Causal Effect of a given regimen in a Network Meta-Analysis using AIPTW and TMLE

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Résumé

Cette mémoire vise à développer une méthode de pondération par l'inverse de le probabilité de traitement (Augmented Inverse Probability of Treatment Weighting; AIPTW) et estimation par maximum de vraisemblance ciblée (Targeted Maximum Likelihood Estimation; TMLE) dans le contexte d'une méta-analyse en réseau avec données individuelles (Individual Patient Data Network Meta-Analysis; IPD-NMA) avec données observationnelles. Nous proposons également des méthodes pour estimer le score de propension généralisé (Generalized Propensity Score; GPS) pour finalement estimer l'effet causal d'une combinaison donnée de traitements (un régime) interprété à partir de d'une population globale. Cette recherche a été motivée par une mise à jour récente des données de patients atteints de la tuberculose multirésistante (Multidrug-Resistant Tuberculosis ; MDR-TB), une maladie infectieuse respiratoire causée par le bacillus mycobactérie avec un taux de mortalité élevé. Une compléxité notable de notre scénario est que toutes les régimes de traitements n'ont pas été observés dans toutes les études.

L'inférence causale est définie comme l'étude de l'effet des traitements sur un résultat. Bien que les études cliniques randomisées sont l'étalon-or pour l'investigation des causes et effets, en raison de certaines limitations, leur utilisation n'est pas toujours faisable. Ainsi, l'analyse de données observationnelles est proposée. Donc, il est important de développer des méthodes qui nous permettent d'utiliser les informations provenant des données observationnelles. L'utilisation des informations provenant de plusieurs études individuelles nous permet d'évaluer les associations entre les traitements et les résultats qui sont spécifiques aux sous-populations. Aussi, une méta-analyse en réseau nous permet comparer plusieurs régimes au lieu de seulement deux.

Nous estimons le taux de succès d'un régime donné à partir d'un ensemble d'études dans lesquelles le régime était disponible, puis le généralisons à l'ensemble de la population source. La théorie et les résultats d'une étude de simulation démontre que les méthodes développées sont doublement robustes. Cependant, TMLE démontre plus de robustesse, en particulier lorsqu'une méthode nouvellement proposée pour estimer le GPS est utilisée. Le résultat de

l'application donne des estimations d'un taux de succès de traitement généralisé entre 50 à 61 % pour le régime $\{Pyrazinamide, Kanamycin, Ofloxacin, Ethionamide, Cyloserine\}$ tandis que le taux observé de l'ensemble des données était de 59 %.

Mots-clés: Causal Inference, AIPTW, TMLE, IPD-NMA, MDR-TB.

Abstract

This thesis aims for developing Augmented Inverse Probability of Treatment Weighting (AIPTW) and Targeted Maximum Likelihood Estimation (TMLE) in the setting of Individual Patient Data Network Meta-Analysis (IPD-NMA) of observational data and propose a method to estimate the Generalized Propensity Score (GPS) to eventually estimate the causal effect of a given combination of treatments (a regimen) and generalize it to a global population. This research was motivated by a recent update on IPD_NMA of Multidrug-Resistant Tuberculosis (MDR-TB) - a respiratory infectious disease caused by bacillus mycobacterium with a high rate of mortality - where not all the regimens observed in all the studies.

Although Randomized Controlled Trials (RCTs) are known to be the gold standard in investigating cause-and-effect including in causal inference (defined as the study of the effect of treatments on an outcome), but because of some known limitations using them is not always feasible. Thus, observational data are being proposed. Therefore, developing methods that enable us to use the information from observational data is important. In addition, using the information coming from individual studies allows us to evaluate associations between treatments and outcome which are specific to subpopulations. Also, a network meta-analysis allows us to study the effect of multiple treatments instead of two.

We estimate the rate of treatment success for a given regimen from a set of studies where the regimen was available, and then generalize it to the whole network. The simulation result shows that the developed methods are doubly robust, however TMLE shows more robustness specially when the new proposed approach to estimate the GPS is being used. The application result shows a range of 50-61% for the generalized success rate of regimen $\{Pyrazinamide, Kanamycin, Ofloxacin, Ethionamide, Cyloserine\}$ while the observed rate was 59% from multiple regimens.

Keywords: Causal Inference, AIPTW, TMLE, IPD-NMA, MDR-TB.

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List of Abbreviations

NMA: Network Meta-Analysis

RCT: Randomized Controlled Trials

PS: Propensity Score

GPS: Generalized Propensity Score

OM: Outcome Model

AIPTW: Augmented Inverse Probability of Treatment Weighting

TMLE: Targeted Maximum Likelihood Estimation

LASSO: Least Absolute Shrinkage and Selection Operator

ALASSO: Adaptive Least Absolute Shrinkage and Selection Operator

OALASSO: Outcome Adaptive Least Absolute Shrinkage and Selection Operator

BMI: Body Mass Index

DM: Diabetes

AFB: Acid-Fast Bacillus

CXR: Chest X-Ray

SE: Standard Error

In dedication to

My family. A special feeling of gratitude to my loving parents, Hossein Aghamolaei and Shahin Iranmanesh whose love for me know no bounds, who teach me the value of hard work and the beauties of being a good human. I love you so much "madar, baba". My one and only brother Ramin who always encourages me to follow my dreams, whose words of encouragement and push for tenacity ring in my ears every day. Who always has my back no matter what. I love you so much "Doctor joon".

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Chapter 1 – [Introduction]

Our study concerns treatment for tuberculosis (TB), an infectious disease caused by the bacillus mycobacterium with a high rate of mortality. The latest report from the World Health Organization (WHO) shows an estimated 10 million TB positive cases along with 1.408 million deaths in 2019 (World Health Organization). Multi Drug-Resistant Tuberculosis (MDR-TB) (Yu et al., 2020) is defined as TB infection that is resistant to both isoniazid and rifampin, the two most commonly used antimicrobial TB drugs (World Health Organization, 2021a). Patients with MDR-TB are placed on regimens (treatment combinations) of second-and third-line antibiotics that they need to take concurrently. Treatment often begins before drug sensitivity can be assessed. Notably, the long duration of MDR-TB treatment (18-24 months as proposed by the WHO) makes it difficult to conduct trials to assess the effect of drug combinations (Loeffler et al., 2004). Although these drugs are proven to be efficacious, in practice patients are often unable to complete the course of treatment (Hirsch-Moverman et al., 2008; Njie et al., 2018) and may experience serious side-effects such as toxic hepatitis(Menzies et al., 2008). New drugs have been added to the list of available treatments (Dheda et al., 2019), but the issue remains regarding whether regimens that include these new drugs are more effective than existing regimens. The identification of effective regimens with shorter treatment periods has become an important question for researchers and is one of the WHO's research priorities (World Health Organization, 2019). More evidence of real-world relative treatment effectiveness is currently needed. Furthermore, given the extensive treatment time and also the potential toxicity of these drugs precludes Randomized Controlled Trials (RCTs) in most contexts. Therefore, observational studies and the development of relevant analytical methods in this setting are very important for furthering research in this area.

To have more assurance about the answer to a particular research question, researchers sometimes perform repeated experiments or studies addressing the same scientific question. Meta-analysis is a statistical quantitative technique that allows us to pool together the individual results of many experiments or studies to obtain a precise unified answer (Egger & Smith, 1997;

Naylor, 1997; The Lancet, 1997). In settings where there exist more than two active treatments or interventions that we are interested in comparing, a network meta-analysis (NMA) is a solution that allows us to make comparisons between multiple treatments. This is sometimes done through standard meta-analysis by performing pairwise comparisons among different treatments (Li et al., 2011; Lumley, 2002; Pogue & Yusuf, 1998). Because RCTs may limit time to follow-up, incur high costs, require a priori treatment equipoise, have limiting ethical considerations, etc., in some settings, we may rely on observational studies rather than RCTs to obtain evidence of relative effectiveness.

In an NMA, the data type could be either aggregated data (AD) or Individual Patient Data (IPD). AD is the summary results of the studies included in the NMA. IPD is the raw data collected on each patient across multiple studies (Hasselblad & McCrory, 1995). Advantages of the AD include easy availability. Disadvantages include reliance on the quality of each individual study and the information reported in them. Also, AD does not allow us to perform subgroup analysis if corresponding subgroup analyses weren't reported by each study. IPD on the other hand has various advantages. It allows for subgroup analysis to investigate differences in treatment effects as well as the detailed data checking and standardizing of the outcome across the individual studies, allows for the analyst to ensure the appropriateness of the analysis, and allows for updated follow-up information (Hasselblad & McCrory, 1995) (Debray et al., 2018). Since meta-analysis with IPD requires collaboration between the investigators who conducted each study, this approach allows for better identification of relevant studies and allows for collaboration on further studies. IPD is often considered to be the gold standard of meta-analytical structures (Stewart & Clarke, 1995) (Stewart & Tierney, 2002). Importantly, when conducting NMA or meta-analysis, we may face heterogeneity in the data and effectiveness across studies. The source of this variability can come from individual-level covariates, like the distribution of participants' ages within each study, or study-level covariates, like information about the study's geographical area. One of the considerable disadvantages of AD is that it doesn't allow for investigating between-studies heterogeneity.

Causal inference is defined as the study of the effect of treatments or interventions on an outcome to establish cause-and-effect. The counterfactual outcome is a key concept in causal

inference: it is an unobserved outcome that the outcome value under the hypothetical imposition of a given treatment. It allows us to define the causal effect as the response to such questions as "What would have happened had everyone received the treatment?" (Rubin, 1974). Causal inference methods apply to both experimental and observational studies (Rubin, 1974). However, sometimes the treatment is not available for all the patients due to various reasons (in experimental studies) or it is not observed (in observational studies), thus implementing the methods that allow us to investigate the effect of the treatment for the global population is important.

When the target population is broader than but includes the population where the available data arose, the estimation of the causal parameter in the target population is called generalizability (Holland, 1986; Little & Rubin, 2000; Rubin, 1974). Generalizability from a causal perspective has been discussed in multiple studies mostly where RCTs were the source of the data. However, RCTs are more subject to violation of external validity than observational studies since they may not be a good representative of the target population, something that is crucial in this setting (Black, 1996; Chatton et al., 2020; Hannan, 2008; Kramer & Shapiro, 1984; Rothwell, 2005; Steckler & McLeroy, 2008). In observational studies, causal estimation often relies on modelling the relationships between the treatment and the covariates. The propensity score (PS) or the Generalized Propensity Score (GPS) is defined as the probability of taking one or a combination of treatments, respectively, conditional on a set of covariates. We define the outcome model (OM) as the model used to specify the expectation of the outcome conditional on treatment and covariates. The choice of which covariates to include in these models has major impacts -- any mistake in modelling the relevant associations or omission of an important confounder can cause a bias in the estimation of the causal effect (De Luna et al., 2011; Gail et al., 1984; George, 2000; Enrique F. Schisterman et al., 2009). The Least Absolute Shrinkage and Selection Operator (LASSO) is a technique for selecting relevant covariates for prediction. However, it does not necessarily select the true model covariates, even in large sample sizes. As a solution, Zou developed the adaptive LASSO for the consistent (oracle) variable selection under certain conditions (Zou, 2006). But some covariates in the true PS model can cause estimation bias and loss of efficiency when used in estimation; it is preferable to limit this model to condition only on confounders (Velentgas

et al., 2013). Shortreed and Ertefaie developed the outcome adaptive LASSO for the estimation of the propensity score model. This method carries out the variable selection by prioritizing covariates that are related to both the outcome and exposure and thus account for the confounding bias while improving statistical efficiency (Shortreed & Ertefaie, 2017).

In the setting of MDR-TB, researchers are interested in the effectiveness of a combination of treatments and not necessarily of a single treatment. In this thesis, we develop TMLE and AIPTW estimators for observational IPD-NMA to estimate the causal effect of a regimen of interest for MDR-TB. But because some frequently used regimens are not observed across all the studies, this research was motivated to specifically focus on generalizing the causal effect of a given regimen to the target population, defined as the union of the population of all the individual studies of MDR-TB (Schnitzer, Steele, et al., 2016).

Previous work on developing estimators and generalizability has made considerable improvements in the setting with IPD; however, they were mostly either based on the inverse probability of treatment weights (IPTW) or propensity score matching. These methods depend on the correct specification of the PS model or post-stratification and therefore have limitations in dealing with large numbers and continuous types of covariates (Cole & Stuart, 2010; Miettinen, 1972; Rudolph & M.J. van der Laan, 2017; Stuart et al., 2001). These gaps have been addressed by Rudolph and van der Laan who introduced three methods applicable for both observational studies and RCTs where they used the Targeted Maximum Likelihood Estimation (TMLE), a doubly robust approach that can incorporate machine learning techniques to avoid bias due to modelling errors (Rudolph & M.J. van der Laan, 2017). Dahabreh and colleagues (Dahabreh et al., 2019) proposed three estimators including one to address the unbounded estimates for the OM based on the Augmented Inverse Probability of Treatment Weighting (AIPTW) for RCTs to estimate and generalize the causal parameter of interest. They also proposed methods for generalization from an RCT when the treatment effect modifiers have an effect on participation in the RCTs (Dahabreh & Hernán, 2019), and also discussed analytical methods for generalizing the causal effect from an RCT to a target population (Dahabreh et al., 2020). Hu and Qin (Hu & Qin, 2018) improved the existing methods including the IPTW and AIPTW in generalizing the causal parameter in observational studies under retrospective convenience sampling. Balzer and colleagues (Balzer et

al., 2016) developed the generalization in observational studies by using TMLE to estimate the sample average treatment effect.

Several published studies developed causal inference estimators applied to investigating treatment effectiveness for MDR-TB. Siddique and colleagues (Siddique et al., 2019) estimated the mean of the counterfactual outcome of different regimens for MDR-TB with both parametric and non-parametric techniques to estimate the propensity score model. However, as their proposed method depended on the categorization of regimens, this approach might have resulted in information loss. This may be particularly detrimental when we have common treatments but rare regimens. This study also did not address the IPD-NMA structure. Liu and colleagues (Liu et al., 2021) developed a TMLE estimator to model effect modification based on individual and study level covariates in an observational IPD-NMA of MDR-TB. Wang and colleagues (Wang et al., 2020) developed a TMLE estimator to generalize the estimate of the causal parameter in the observational IPD-NMA of MDR-TB but they focused on contrasting individual treatments rather than regimens. Therefore, these studies either incorporated the meta-analytical structure but focused on the individual treatments rather than a combination of them (Wang et al., 2020) (Liu et al., 2021) or investigated the effectiveness of treatment combinations without the meta-analytical structure (Siddique et al., 2019). But there is a challenge that may arise when contrasting multiple treatments with data from multiple studies: we may not be able to observe certain treatments of interest in all of the studies. This means that we have no direct information regarding the effectiveness of certain treatments in populations where the treatment was not observed (Wang et al., 2020). Thus, developing estimators for generalizing the causal effect of regimens of interest in an observational IPD-NMA using causal methods is a gap in the current literature.

This thesis is aimed at developing TMLE and AIPTW estimators for contrasts between drug regimens in the setting of observational IPD-NMA with an application on MDR-TB. Through a simulation study, it evaluates the performance of the TMLE and AIPTW estimators using the two different methods to estimate the GPS. The first method is called the Binary Approach where we estimate the GPS through a logistic regression by considering the regimen of interest as a binary variable. The second method is called the Sequential Approach where the regimen of interest is

represented by a vector of binary indicators, representing treatments. To address variable selection due to data sparsity in the covariates, this thesis considers the adaptive LASSO and the outcome adaptive LASSO for the estimation of GPS in TMLE and AIPTW. The application of the proposed methods is then shown on a real dataset of MDR-TB to estimate the generalized effect contrasting the two most frequent regimens. For this research project, we have been granted access to observational IPD of MDR-TB patients participating in 52 studies (Bisson et al., 2020).

In Chapter 2 the literature review is conducted. In Chapter 3 the objectives of the study are given. In Chapter 4 the methods on how to construct the AIPTW and the TMLE in an observational IPD-NMA are given along with a cluster sandwich estimator for the estimation of the variance. In Chapter 4 the simulation studies evaluating the proposed estimators are shown and the application of the proposed methods on MDR-TB data are reported. In Chapter 5 we discuss strengths, limitations, and the directions for further studies.

Chapter 2 – [Literature Review]

This chapter includes 4 sections that are going through the literature related to the definitions, methods and concepts that this thesis focuses on. Section 2-1 focuses on causal inference including the definitions, assumptions and some methods we implemented in this research along with their properties. The next section introduces the individual patient data network meta-analysis and reviews the literature that shows its importance. In section 2-3 generalizability is discussed and in the last section, a definition of multidrug-resistant tuberculosis along with the to-date developments on treatments is given.

2-1. Causal Inference

This section includes the literature review on causal inference starting with a brief introduction to the fundamentals of causal inference related to this thesis. I thus define the counterfactual outcome and explain the assumptions of causal inference and how they relate to parameter identifiability. Then I describe the GPS, AIPTW and TMLE and the two data-adaptive methods adaptive LASSO and outcome adaptive LASSO.

2-1-1. Counterfactual Model and Causal Inference

Causal inference is defined as the study of the effect of treatments or interventions on an outcome to establish cause-and-effect. Objectives in this field include the development of theory and tools to investigate relationships between the potential cause (treatment or exposure) and effect (outcome of interest) and distinguish between correlation and causation (Pearl, 2010a). In 1974 Rubin (Rubin, 1974) introduced a straightforward framework to describe cause-and-effect relationships using counterfactual outcomes. Under Rubin's counterfactual model, we consider the simple setting of a vector of observations for an arbitrary patient as $O = \{W, A, Y\}$ where A is a binary treatment with two values such that $A = 1$ if the patient receives the treatment and $A = 0$ otherwise, W is a vector of covariates and Y is a binary or continuous outcome. In Rubin's framework, the outcome Y could get a value under the two potential scenarios of receiving A. The two potential values of Y under $A = 1$ and $A = 0$ are denoted as $Y^{(1)}$ and $Y^{(0)}$ respectively.

These are also called the counterfactual outcomes because they represent hypothetical values for the outcome corresponding to a situation, possibly counter to the fact, where the patient received $A = 1$ *or* $A = 0$, respectively. The difference between these two counterfactual outcomes for an individual patient is the individual causal effect for that patient (Greenland & Brumback, 2002). But because a patient can only receive one or the other treatment, we can observe only one of these values which is the fundamental problem of causal inference. A common effect measure is the average causal effect which is the contrast between the means of the counterfactual outcomes $E\left(Y^{(1)}\right) - E\left(Y^{(0)}\right)$. In general, causal effects can be the contrasts of any functions of counterfactual outcomes like means, medians, cumulative distribution functions, etc (Hernán, 2004).

Randomized controlled trials are experiments that help us to confront the fundamental problem of causal inference and estimate a causal parameter of interest such as the average causal effect. We consider a data sample of *n* patients drawn independently from a source population and with identical data distribution, where each patient is then randomized to treatment $A = 1$ or 0. Since the randomization has the effect of balancing both measured and unmeasured covariates across the randomized groups, $\{ Y^{(1)}, Y^{(0)}\} \perp A$. In the counterfactual framework it is typically assumed from SUTVA which will be explained later in sub-section 2-1-2, that the observed outcome is equal to the counterfactual outcome under the observed treatment, meaning that if $A = a$, then $Y = Y^{(a)}$. In this case the contrast between the mean estimators $\frac{1}{n_1}\sum_{A=1} y_i - \frac{1}{n_0}\sum_{A=0} y_i$ is the unbiased and consistent estimate for the average causal effect. Thus, if we have two groups with sample sizes n_1 and n_0 who had been randomized to treatments $A = 1$ and $A = 0$, respectively, then the mean of the outcomes of either group is:

$$E\left(\frac{1}{n_a}\sum_{A=a} y_i\right) \xrightarrow{\substack{independent\ identically \\ distributed\ sample\ of\ patients}} E(Y|A = a) \xrightarrow{Causal\ assumptions} E\left(Y^{(a)}\middle|A = a\right)$$

$$\xrightarrow{Randomly\ assigned\ treatment} E\left(Y^{(a)}\right) \qquad (2.1)$$

But running RCTs is not always feasible, especially when the allocation of the treatment in a randomized way is unethical or impractical, when the disease is rare or when there are time constraints (Shadish et al., 2008). Observational studies can be a solution in situations where RCTs are infeasible. However, for casual decisions to be made in a non-randomized study, one needs to consider the situation as if it is a pseudo-randomized study (Hernán & Robins, 2010). The next section describes "causal assumptions" sufficient for the estimation of the average causal effect.

2-1-2. Causal Assumptions

Causal assumptions are needed so that we can estimate the causal parameter.

Ignorability:

An accurate estimation of the cause-and-effect relationship between the exposure and outcome is the goal of the causal inference. To reach that, finding the measured covariates and conditioning on them help us to get away from unmeasured confounders that affect the relationship between the exposure and the outcome because these measured covariates account for bias and therefore confront the hidden bias due to unmeasured confounders. An important assumption that helps us to get to that point is called the ignorability assumption. Ignorability implies that conditional on the measured covariates, the treatment assignment is independent of the counterfactual outcome. This means that we can assume for those who are in the same category or level of W, the treatment is effectively randomly assigned. This assumption is also known as conditional exchangeability (Hernán, 2012). Ignorability can be expressed as:

$$E\left(Y^{(a)}\middle|A=1,W\right)=E\left(Y^{(a)}\middle|A=0,W\right)=E\left(Y^{(a)}\middle|W\right) \quad (2.2)$$

SUTVA and Consistency:

The Stable Unit Treatment Value Assumption (SUTVA) (Rubin, 1980) implies that the treatment assignment for one patient and the counterfactual outcome don't affect other patients. Further, the exposure of one patient does not depend on other patients' outcomes. From SUTVA we have the consistency assumption (Pearl, 2010b) implying that if the actual treatment being received is $A=a$ then the counterfactual outcome under a is equal to the observed outcome:

$$E(Y|A=a,W) = E\left(Y^{(a)}\middle|A=a,W\right) \quad (2.3)$$

This allows us to use the counterfactual framework to represent average outcomes had everyone received or not received the treatment/exposure through functions of the observed data (Rubin, 1980; Schwartz et al., 2012).

Positivity:

Positivity implies that given a set of covariates W, the assignment of the treatment is nondeterministic. This means essentially that everyone has a chance to receive either treatment.

$$P(A=a|W) > 0 \quad (2.4)$$

2-1-3. Identifiability of the Average Causal Effect

If we can determine a parameter of interest from an infinite sample that parameter is said to be identifiable. From consistency and conditional exchangeability, we can identify the causal effect.

From the independent identically distributed observed data that we have, we get: $E(Y|A=a,W)$.

Then from consistency, we get: $E(Y|A=a,W) = E\left(Y^{(a)}\middle|A=a,W\right)$.

And eventually from ignorability we have: $E\left(Y^{(a)}\middle|A=a,W\right) = E\left(E\left(Y^{(a)}\middle|W\right)\right) = E\left(Y^{(a)}\right)$.

In non-randomized studies such as observational studies, SUTVA and consistency are likely to still be held in many settings. But because of the imbalanced number of patients in each level of the categorical covariates, the ignorability and positivity assumptions may not be held. This can even happen during follow-up in RCTs if, for instance, the treating physician decides that continuing treatment is not possible for some patients due to their clinical or individual conditions. In observational studies to mimic the randomization process in RCTs- which randomly distributes the known or unknown confounders among the two treatment groups- and to account for the effect of confounders, one way is to use the propensity scores. There are methods to control for confounders that utilize the propensity score which will be discussed in the next sections.

2-1-4. Propensity Score and the Generalized Propensity Score

Rosenbaum and Rubin (Rosenbaum & Rubin, 1983) defined the propensity score (PS) as the conditional probability of receiving a treatment given a set of pretreatment covariates. Given a set of covariates W and a binary treatment A, the propensity score is given as follows:

$$g(a, W) = P(A = a|W) \qquad \text{where} \quad a \in \{0,1\} \tag{2.5}$$

Although in RCTs because of the randomization, the effect of confounders is accounted and the distribution of covariates between the two treatment groups is balanced (Suresh, 2011), estimating the PS would increase the estimation precision (Senn, 1989; Williamson et al., 2014). However, this function is unknown in observational studies because it is not controlled by the study design, but it can be estimated.

The generalized propensity score (GPS) is defined in a situation where we have a continuous treatment or multiple treatments instead of just one binary treatment (Imbens, 2000).

The PS or GPS is used to control the confounding bias in the analysis of observational data. To model the PS, if for instance, the treatment is binary, one can use logistic regression. A PS value for each patient can be obtained by taking the predicted values. The estimation of average causal effects can use the PS or GPS in a weighting, matching or stratification procedure to solve the confounding issue.

But the validity of each method that is based on the PS depends on the correct specification of the PS/GPS model. This sensitivity can be moderated by using methods that have a doubly robust property.

2-1-5. The Doubly Robust Property

When estimating the average causal effect, it is important to control for all confounders to avoid bias (Rubin, 1974; Splawa-Neyman et al., 1990). In general, one can adjust for confounding in two ways; by modelling the expectation of the outcome conditional on a set of covariates (and treatments) or by modelling the probability of the treatment(s) given a set of covariates (the propensity score). Doubly robust estimators use both of these two models

to achieve a consistent estimator. Doubly robustness was first introduced by Robins and others (Bang & Robins, 2005; Robins et al., 2007; Robins, 2000; Robins et al., 1995). Doubly robust estimators in causal inference avoid bias due to model misspecification because the estimator remains consistent under misspecification of either the outcome or the PS model. It is worth noting that consistency doesn't hold if both models are misspecified.

One way to show the doubly robust property of an estimator is through a function called efficient influence function which will be explained in the next section.

2-1-6. Efficient Influence Function

The effect of a change in one observation on an estimator can be explained by the influence function, thus, it is a very useful tool to study estimator robustness. Introduced by Hampel in 1974 (Hampel, 1974) the influence function depends on the distribution function F of a random vector of observations and the parameter of interest. Let F_n be an estimator for the empirical distribution function F while F_0 is the true distribution function. Suppose that we are interested in estimating a parameter equal to $\psi = \tau(F_0)$ where $\tau(\cdot)$ is a differentiable function. Then we call $\tau(F_n)$ the "plug-in" estimator of ψ. Given a vector of observations O_i, and a term $o_F\left(\frac{1}{\sqrt{n}}\right)$ which gets close to 0 when the sample size is large, the plug-in estimator is asymptotically linear if the following conditions hold:

$$1: \qquad [\tau(F_n) - \tau(F_0)] = \frac{1}{n}\sum_{i=1}^{n} IF(F_0;\psi)(O_i) + o_F\left(\frac{1}{\sqrt{n}}\right) \tag{2.6}$$

$$2: \qquad E[\, IF(F_0;\psi)(O_i)] = 0 \tag{2.7}$$

The influence function is the $IF(F_0;\psi)$ term in Equation (2.6). An estimating equation for ψ involves solving $\frac{1}{n}\sum_{i=1}^{n} IF(F_n;\psi)(O_i) = 0$ for ψ. In fact, any estimator $\hat{\psi} = \tau(F_n)$ that can solve this estimating equation, is characterized by the influence function $IF(F_0;\psi)$ in large samples (Tsiatis, 2006). This estimator is then said to be an asymptotically linear (Klaassen, 1987; Schick, 1987) and has a unique influence function (Tsiatis, 2006). Now, every asymptotically linear estimator for instance $\tau(F_n)$, has a unique IF that we denote by IF^*,

that holds the non-negative definite $E(IF - IF^T) - E\left(IF^* - IF^{*T}\right)$ for every other influence function of $\tau(F_n)$. IF^* is then called the efficient influence function (EIF) (Tsiatis, 2006).

Assume now that we have a vector of observations O_i and a parameter of interest ψ - for instance, the average causal effect - with an estimator ψ_n with EIF_ψ satisfying Equation (2.6). Under ignorable treatment assignment, an efficient estimator is doubly robust. In this case, the EIF_ψ depends on two components - called the nuisance functions - for instance, the PS and the $Q(a, W)$- and when the consistent estimation of either of the two functions solves the given estimating equation for ψ. This property gives the analysts two chances to estimate the causal effect because just one of the two models, PS or the $Q(a, W)$, needs to be correctly specified for consistent estimation. Correct specification means the model reflects the true relationship between the covariates and the treatment (for the PS model) or the outcome (for the $Q(a, W)$).

Two specific doubly robust estimators will be discussed in the next section.

2-1-7. Doubly Robust Estimators

Let $\hat{Q}(a, W) = \hat{E}(Y|W, A = a)$ be the estimator for $Q(a, W)$ and $\hat{g}(a, W)$ the estimator for the PS model under the binary treatment A. Given the causal assumptions, to estimate for instance the average causal effect we could have the following estimators.

Outcome-based estimator:

Based on the assumptions and definitions that this thesis has discussed so far, the outcome-based estimator can be used to estimate the average causal effect (Cochran, 1968; PEARL, 1995, 2000; Robins, 1986) as follows:

$$\frac{1}{n}\sum_{i=1}^{n}\{\hat{E}(Y_i|W = w_i, A = 1) - \hat{E}(Y_i|W = w_i, A = 0)\} \quad (2.8)$$

The conditional expectation $E(Y|W, A = a) = Q(a, W)$ can be estimated by any parametric method such as generalized linear models. But the performance of this estimator depends on the correct specification of the model for $Q(a, W)$, and this is less likely when the dimension of covariates increases or with a rare outcome. Therefore, such methods may end up biased

depending on the implementation (King & Zeng, 2006). Due to this situation, researchers sometimes prefer estimators that use the PS model instead of $Q(a, W)$.

PS-based estimator:

Propensity score-based estimators rely on the correct specification of a model for the probability of treatment $g(a, W)$ instead of $Q(a, W)$. Propensity scores have been used for matching and in weighted estimators, among which the inverse probability of treatment weighting (IPTW) is most popular. IPTW was proposed for causal inference by Lunceford and Davidian (Lunceford & Davidian, 2004) in 2004, though it is closely related to the Horvitz-Thompson estimator (Horvitz & Thompson, 1952) in survey sampling and missing data analysis. IPTW uses the inverse of the estimated propensity scores (Rosenbaum & Rubin, 1983) as weights to form the following estimator for the average causal effect:

$$\hat{\psi}_{IPTW} = \frac{1}{n}\sum_{i=1}^{n}\{\frac{a_i y_i}{\hat{g}(w_i)} - \frac{(1-a_i)y_i}{1-\hat{g}(w_i)}\} \tag{2.9}$$

This estimator is consistent when the PS model is correctly specified (Tsiatis, 2006). But this estimator has a weakness when some units have very small (close to zero) or very large (close to one) propensity scores. In this situation, some weights will be very large and thus the contribution of each participant to estimate the parameter of interest will vary a lot, leading to highly variable estimation. However, there have been developments to this estimator to confront this issue which will be explained in the next section (Imbens, 2004) (Lunceford & Davidian, 2004).

AIPTW as a doubly robust estimator:

Augmented inverse probability of treatment weighting (AIPTW) has been introduced as a doubly robust estimator applicable in causal inference setting (Robins et al., 1994; Scharfstein et al., 1999a, 1999b) . Like IPTW, AIPTW uses inverse PS weights, but it also uses the information from $Q(a, W)$. One specification of AIPTW for the average causal effect is:

$$\hat{\psi}_{AIPTW} = \frac{1}{n}\sum_{i=1}^{n}\{\frac{a_i y_i}{\hat{g}(w_i)} - \frac{(1-a_i)y_i}{1-\hat{g}(w_i)}\}$$
$$-\frac{\big(a_i - \hat{g}(w_i)\big)}{\big(1-\hat{g}(w_i)\big)\,\hat{g}(w_i)}\{\big(1-\hat{g}(w_i)\big)\,\hat{E}(Y|W=w_i, A=1)$$
$$+\hat{g}(w_i)\,\hat{E}(Y|W=w_i,\ A=0)\} \qquad (2.10)$$

AIPTW is a consistent and asymptotically unbiased estimator (Robins et al., 1995) if either of the PS model or the OM are correctly specified.

Doubly robust estimators including AIPTW have been the subject of a lot of development and hotly discussed in the causal inference literature (Bang & Robins, 2005; Cao et al., 2009; Kang & Schafer, 2007; Robins et al., 2007; Rotnitzky et al., 2012; Tan, 2006, 2010). One of the drawbacks of this estimator is that when the PS is very close to zero or one the variance can become large due to the variation in the inverse PS weights. This can be caused by the estimation of the PS model and data sparsity. Kang and Schafer (Kang & Schafer, 2007) showed that PSs close to zero can be due to misspecification of the model rather than rare treatments or sparse data. Robins et al. (Robins et al., 2007) noted that different constructions of AIPTW will have different sensitivities to large weights and proposed normalizing weights to confront this issue. However, when there is data sparsity, typical implementations of AIPTW are still subject to increased variance (M.J. van der Laan & Rose, 2011; Neugebauer & van der Laan, 2005; Porter et al., 2011). TMLE estimator, which will be defined in the next section, is a response to some of the limitations of the AIPTW.

TMLE as a doubly robust estimator:

Targeted maximum likelihood estimation (TMLE) was introduced by Van der Laan and Rubin (M.J. van der Laan & Rubin, 2006) as a doubly robust estimator based on the same semiparametric theory as AIPTW (Robins, 2000; Scharfstein et al., 1999a). TMLE is a plug-in estimator which requires an initial estimate for the PS and the $Q(a, W)$; it then has a targeting step where it optimizes the bias-variance trade-off of the parameter of interest (e.g., the average causal effect).

One algorithm to implement a TMLE estimator for the estimation of the average causal effect is as follows (Rosenblum & M.J. van der Laan, 2010):

Step I; deriving initial estimates for $\mathrm{Q}(\mathrm{a},\mathrm{W})$:

In this step, we predict $Q(a,W)$ which is the conditional expectation of the outcome given a set of covariates W and the treatment A denoted by $\hat{Q}(a,w)$. This is the initial estimation for the OM. If for instance, the outcome is binary, then this prediction can be done using logistic regression as follows:

$$\hat{Q}(a,W) = logit\,\{P(Y|W=w,A=a)\} = \beta_0 + \beta_1 a + \beta_2 w \qquad (2.11)$$

Step II; deriving the propensity scores:

After estimating the OM, we estimate the PS model. The predictions in this step can also be done by the use of logistic regression:

$$\hat{g}(a,W) = logit\{P(A=a|W=w)\} = \alpha_0 + \sum_{j=1}^{p} \alpha_j w_{ij} \qquad (2.12)$$

Step III; building the clever covariate:

In this step, we update the predictions for the OM that we got from step one using the estimated PS. We call the updates of the OM as $\hat{Q}^*(a,w)$. The updating includes two steps; we first use the estimated PS in a clever covariate called $H^*(a,W) = \frac{I(A=a)}{\hat{g}(a,W)}$

Step IV; fluctuating the initial estimates of $\mathrm{Q}(\mathrm{a},\mathrm{W})$:

In this step a fluctuation parameter called ε will be estimated by fitting a logistic regression without an intercept on Y and $H^*(a,W)$ with the logit of $\hat{Q}(a,W)$ as an offset. The outcome function is then updated using:

$$logit\,\hat{Q}^*(a,W) = logit\,\hat{Q}(a,W) + H^*(a,W)\hat{\varepsilon} \qquad (2.13)$$

The aim of this step is to reduce the bias in the initial estimates of $Q(a, W)$. The bounded-outcomes whether binary or continuous are then fluctuated on the scale of the logit function to make sure that the model space is also respecting the bounds (Gruber & M.J. van der Laan, 2009).

Step V; constructing the TMLE estimator:

The predictions from step 4 are then being averaged to estimate the causal parameter for instance the average causal effect:

$$\psi^{a}_{TMLE} = \frac{1}{n}\sum_{i=1}^{n} \hat{Q}^{*}(a, w_i) \qquad (2.14)$$

Doubly robust estimators including AIPTW and TMLE are asymptotically unbiased if either the PS or $Q(a, W)$ is consistently estimated and they are locally efficient estimators if both models are correctly specified. However, unlike AIPTW, TMLE is more robust against the outliers and will not produce estimates that lie outside the range of the parameter of interest as it is a plug-in estimator. (M.J. van der Laan & Rose, 2011; M.J. van der Laan & Rubin, 2006; Neugebauer & van der Laan, 2005; Porter et al., 2011) Given the properties of doubly robust estimators, accounting for confounders is still essential in observational studies. To reduce the chance of misspecification in these models, implementing the machine learning techniques is suggested (M.J. van der Laan et al., 2007; M.J. van der Laan & Rose, 2011).

2-1-8. Propensity-Score Based Estimators and Data Adaptive Methods

When we have observational studies, PS models allow us to replicate the features of RCTs by equalizing the covariate distribution between the two treatment groups. Thus, the correct specification of this model is important. One of the commonly used methods to estimate the propensity scores is the regression (D'Agostino Jr, 1998; Weitzen et al., 2004), however, the parametric nature of this method makes it vulnerable to misspecification so recent studies proposed other methods including machine learning algorithms (Lee et al., 2010; M.J. van der Laan et al., 2007; Setoguchi et al., 2008; Westreich et al., 2010; Zivich & Breskin, 2021).

Machine learning techniques have been widely used in literature. Breiman (Breiman, 2001) suggested neural networks as a machine learning algorithm when one is facing high dimensional data. Other methods such as decision trees, boosting algorithms and support vector machines

were also part of the suggested methods (Duda et al., 2000). Machine learning methods were also proposed for estimating the PS model to improve the predictions, McCaffrey et al. (McCaffrey et al., 2004) suggested the implication of the generalized boosted models for prediction of the PS model. Neural networks and classification trees were suggested by Setoguchi (Setoguchi et al., 2008) as an approach to estimate the PS model. In addition to these methods, a combination of some machine learning methods - called ensemble learning - was introduced by some researchers among which, Van der Laan and colleagues (M.J. van der Laan et al., 2007) introduced the super learner method where later on was proposed by Pirracchio and colleagues (Pirracchio et al., 2015) as a method to fit propensity scores. However, in estimators that are based on the inverse of the propensity score - for instance the IPTW - any violation of the positivity assumption on its own may cause high weights while using machine learning techniques can increase the risk of bias due to these high weights (Schnitzer, Lok, et al., 2016). This shows the importance of doubly robust estimators as they remove the dependency on just the PS model by also depending on $Q(a, W)$.

To improve the estimation of the PS model, incorporating adaptive regression methods to fit the regression was suggested in the literature (Karim et al., 2017; Lee et al., 2010; M.J. van der Laan & Rubin, 2006; Wyss et al., 2018). Adaptive least absolute shrinkage and selection operation (adaptive LASSO) and the outcome adaptive LASSO, which was specifically developed for predictions of the PS model, are the machine learning algorithms that have shown improvements in estimating the PS model (Bahamyirou & Schnitzer, 2021; Ye et al., 2021).

Selecting a proper set of confounders especially in high dimensional data is a challenge in estimating the average causal effect. Inability to fit the propensity score model, violation of the positivity assumption caused by predictors that do not reduce the confounding bias or including those variables that are contributing to the PS model but not $Q(a, W)$ can affect the variance of the estimator compared to when these variables are not part of the modelling (Ju et al., 2019; Rotnitzky et al., 2010; Enrique F Schisterman et al., 2009). Thus, incorporating the right methods in these situations is important.

LASSO regression:

Consider a vector of observations for an arbitrary patient as $O = \{W, A, Y\}$ where A is a binary treatment with two values such that $A = 1$ if the patient receives the treatment and $A = 0$ otherwise, W is a vector of covariates, Y is a binary outcome for n patients and p treatments, and $g(a, W) = P(A = a|W)$ be the PS model fitted by logistic regression as follow:

$$logit\{P(A = a|W = w)\} = \alpha_0 + \sum_{j=1}^{p} \alpha_j w_{ij} \quad (2.15)$$

In 1996 Tibshirani (Tibshirani, 1996) introduced the LASSO regression which is a regularization technique that does the variable selection. LASSO does the variable selection by shrinking some of the coefficients to zero to get a simple model. If we let $\alpha = (\alpha_1, \ldots., \alpha_p)$ be a vector of coefficients and denote a non-negative regularization parameter λ, then the logistic regression LASSO-estimated propensity score coefficients are as follow where a_i is the realization of the binary treatment A for the i^{th} patient:

$$\hat{\alpha}_{LASSO} = argmin_{\alpha} \sum_{i=1}^{n} -[a_i w_i \alpha + (1 - a_i) log(1 - \exp(w_i \alpha))] + \lambda \sum_{j=1}^{p} |\alpha_j| \quad (2.16)$$

In general, as λ increases, the coefficients shrink towards zero and if λ is sufficiently large then the corresponding coefficients would be exactly zero. Selecting an optimal degree of shrinking establishes an optimal bias-variance trade-off (Zou, 2006). However, LASSO is not an oracle procedure (i.e. does not identify the true model covariates in large sample sizes) nor does it produce consistent estimates of the coefficients (Fan & Li, 2001; Meinshausen & Bühlmann, 2006). Adaptive lasso was proposed as a solution to these problems.

Adaptive lasso:

One variant of the LASSO regression that was developed by Zou (Zou, 2006) in 2006 and is called the adaptive LASSO (ALASSO). It has improved statistical properties compared to the standard LASSO. It possesses the oracle property and produces consistent estimations of the coefficient values. Adaptive LASSO uses weights to penalize the coefficients in the third term of 2.16. Let $\hat{\alpha}^*$ be the consistent estimator for α and let $\gamma > 0$, then we define a vector of weights as $\widehat{K} = \frac{1}{|\hat{\alpha}|^{\gamma}}$

where $\hat{\alpha}$ is a vector of estimated coefficients in Equation (2.15), excluding the intercept term. The equation for the logistic ALASSO would be:

$$\hat{\alpha}^*_{ALASSO} = argmin_\alpha \sum_{i=1}^{n} -[a_i w_i \alpha + (1-a_i) log(1-\exp(w_i\alpha))] + \lambda_n \sum_{j=1}^{p} \widehat{K}_j |\alpha_j| \quad (2.17)$$

Adaptive lasso has the oracle property under certain conditions. Thus, the adaptive lasso performs as well as the actual model. Meaning that when we use the adaptive lasso to estimate the PS model, it selects covariates that are in the true treatment model. In terms of the estimation of the causal parameter, the literature shows that including those covariates that are only related to the treatment and not the outcome may inflate the variance while those that are related to the outcome but unrelated to the treatment(s) may increase the precision (Brookhart et al., 2006; De Luna et al., 2011; Patrick et al., 2011; Shortreed & Ertefaie, 2017). Outcome adaptive lasso is being proposed as an approach that enable us select those covariates.

Outcome adaptive lasso:

Outcome adaptive lasso (OALASSO) was developed by Shortreed and Ertefaie (Shortreed & Ertefaie, 2017) in 2017. It incorporates the outcome regression model coefficient estimates (β) in the penalized term to improve the estimations of the coefficients in the PS model. This allows for the algorithm to select those variables that are related to just the outcome by putting less weight on their penalty. The penalty weights in OALASSO are defined as $\widehat{T} = \frac{1}{|\hat{\beta}|^\gamma}$ where $\hat{\beta}$ are the estimated coefficients from the outcome regression model, excluding the intercept term, and $\gamma > 1$. The equation for the logistic OALASSO is:

$$\hat{\alpha}^*_{OALASSO} = argmin_\alpha \sum_{i=1}^{n} -[a_i w_i \alpha + (1-a_i) log(1-\exp(w_i\alpha))] + \lambda_n \sum_{j=1}^{p} \widehat{T}_j |\alpha_j| \quad (2.18)$$

2-1-9. Variance

In this section, we describe the cluster sandwich estimator for AIPTW and TMLE that derives from the efficient influence function.

When the sample size goes to infinity, by referring to the central limit theorem (Rosenblatt, 1956) and Slutsky theorem (Delbaen, 1998) we have (Schnitzer et al., 2014):

$$\frac{1}{n}\sum_{i=1}^{n} IF(F_0;\psi)(O_i) \rightarrow N\{0, E(IF(F_0;\psi)(O_i)\ IF(F_0;\psi)(O_i)^T)\} \quad (2.19)$$

$$\frac{1}{n}[\tau(F_n) - \tau(F_0)] \rightarrow N\{0, E(IF(F_0;\psi)(O_i)\ IF(F_0;\psi)(O_i)^T)\} \quad (2.20)$$

Therefore, to estimate the standard error and the variance of an estimator we can estimate and use the influence function through $\widehat{Var}(\hat{\psi}) = \frac{1}{n^2}\sum_{i=1}^{n}[IF(O_i)^2]$.

Variance for AIPTW:

as shown by Lunceford and Davidian (Lunceford & Davidian, 2004), the variance for the AIPTW estimator is as follows:

$$\widehat{Var}(\hat{\psi}_{AIPTW}) = \frac{1}{n^2}\sum_{i=1}^{n} IF_{AIPTW}(o_i)^2 \quad (2.21)$$

Where the influence function is estimated using:

$$IF_{AIPTW}(O) = H^*(a,W)\left(\mathrm{Y} - \hat{Q}(a,W)\right) + \hat{Q}(a,W) - \hat{\psi}_{AIPTW} \quad (2.22)$$

Variance for TMLE:

Assuming the data structure and the notation from sections 2-1-1 and 2-1-7 for the TMLE algorithm, the sandwich estimator of the variance for the TMLE estimator would be (Gruber & M.J. van der Laan, 2009):

$$\widehat{Var}(\hat{\psi}_{TMLE}) = \frac{1}{n^2}\sum_{i=1}^{n} IF_{TMLE}(o_i)^2 \quad (2.23)$$

where the influence function is estimated using:

$$IF_{TMLE}(O) = H^*(a,W)\left(Y - \hat{Q}^*(a,W)\right) + \hat{Q}^*(a,W) - \hat{\psi}_{TMLE} \quad (2.24)$$

The sandwich estimator of the variance for AIPTW and TMLE:

Assume we have n participants with K_j clusters where $j = 1, \dots, J$ represents the number of clusters, and consider i and m be two participants in cluster K_j. Then the general equation for the sandwich estimator for parameter $\psi^{(r)}$ would be (Cameron et al., 2008):

$$Var\left(\psi^{(r)}\right) = \frac{1}{n^2}\sum_{j=1}^{J}[\{\sum_{\substack{i,m\epsilon K_j \\ i\neq m}} E(IF(F_0;\psi)(O_i).IF(F_0;\psi)(O_i)^T)\}$$
$$+ \{\sum_{i=m} {}_{i,m\epsilon K_j} E(IF(F_0;\psi)(O_i).IF(F_0;\psi)(O_i)^T)\}] \quad (2.25)$$

Where IF is the influence function of AIPTW or TMLE in Equations (2.22) and (2.24).

2-2. Individual Patient Data Network Meta-Analysis

Meta-analysis is an approach to summarize information for instance in the health and medical fields to evaluate the effectiveness of the interventions/treatment(s) on the outcome (Blettner et al., 1999). Quantitative methods are used to analyze the information coming from multiple studies. Aggregated data meta-analysis is one of the most commonly used quantitative methods. This method combines the published results of multiple studies to, for example, investigate the relationship between treatment(s) and outcome(s). This approach has several advantages including low cost and easily accessed published data. However, publication bias and different sources of heterogeneities including the differences between studies caused by study designs or population characteristics, different analytical methods, different categories of variables etc. are drawbacks of this approach (Deeks, 2021; Higgins et al., 2003; Sterne et al., 2011).

Another quantitative approach is known as the individual patient data meta-analysis. This approach uses the individual information of patients in published and unpublished studies to evaluate relationships between outcome(s) and treatment(s). Unlike aggregate data, accessing such data may be costly and time-consuming because it involves multiple data-sharing requests and agreements. Despite these challenges, the most significant benefit of this approach is that researchers have access to the original data and thus can control and decrease some of the

heterogeneities between studies resulting from different analytical methods used or different patient inclusion-exclusion criteria. In addition, one can investigate research questions different from those of the original studies (Cooper & Patall, 2009; Riley et al., 2010; Stewart & Tierney, 2002).

When one is interested in studying the effect of a combination of treatments and not necessarily just one, the network meta-analysis is being used (Caldwell et al., 2005). In particular, individual patient data network meta-analysis (IPD-NMA) has more precision and validity compared to analysis of aggregated data. It is also possible to incorporate causal inference by defining a causal parameter of interest and deriving sufficient assumptions for estimation (Kanters et al., 2021; Wang et al., 2020).

2-3. Generalizability

Generalization has long been of central interest for researchers. Because the available information is based on a sample of a population inference involves generating conclusions in a broader population. Causal relationships depend on context, so a result in one population does not necessarily directly translate to another. Thus having proper tools to make decisions for populations in diverging settings is important (Cook et al., 2002). When the sample with the available data is a representative sample of a subset of the population where one wishes to generalize the findings, the estimation of the target parameter in that population is called generalizability. Transferring the measured association of the desired research question from one population to another is called transportation. Thus generalization is a type of transportation (Pearl & Bareinboim, 2011). A formal observational transportability implies that given two populations Ω_1 and Ω_2 with two associated probability distributions $\mathrm{P}_1$and P_2, a relationship $R(P_1) = \sum_w P_1(y|w,A)P_1(w)$ is observationally transportable from Ω_1 to Ω_2 if $R(P_2) = \sum_w P_2(y|w,A)P_2(w)$ is identifiable from Ω_1 and Ω_2, P_1 and $P_2(V_2)$ where the latter is the marginal distribution of P_2 on a subset of variables called V_2 (Pearl & Bareinboim, 2011).

Cronbach and colleagues (Cronbach et al., 1963) introduced generalizability theory in 1963. Brennan (Brennan, 1992) in 1983 stated the importance of generalizability in the evaluation of educational tools. Later on, many developments were made in the field of generalizability. For

instance, Cole and Stuart (Cole & Stuart, 2010) illustrated a model-based approach to generalize the results from an HIV treatment trial to a specific target population by developing a cox proportional hazard and PS-based estimator. To combat the lack of external validity in RCTs, Tipton (Tipton, 2013) focused on propensity score subclassification to improve the generalization process in these trials. Hartman and colleagues (Hartman et al., 2015) stated that although RCTs provide unbiased estimates of the average treatment effect they may be biased when one generalizes this effect to a target population thus, they derived the necessary assumptions to generalize the average treatment effect estimated under this circumstance. Muircheartaigh and Hedges (O'Muircheartaigh & Hedges, 2014) used stratification based on propensity score matching to construct an estimator for generalizing the average treatment effect to a target population. Zhang and colleagues (Zhang et al., 2016) introduced two estimators: one based on the conditional effect and the outcome regression model and the other one a doubly robust estimator based on the PS, the conditional and the outcome regression models to calibrate the treatment effect from a clinical trial to a target population. Colnet and colleagues (Colnet et al., 2020) discussed estimation methods that improve the generalizability in RCTs and observational studies and then discussed methods that combine RCTs and observational studies to improve the estimation of the average treatment effect and compared the main methods through a simulation study and real-world data.

There are previous methods for generalizability that are extendable to observational data. Rudolph and Van der Laan (Rudolph & M.J. van der Laan, 2017) developed a transportability TMLE to estimate causal parameters in encouragement designs. Dahabreh and colleagues (Dahabreh et al., 2019) developed three AIPTW estimators, incorporating normalized weights to generalize the treatment effect in RCTs. However, limited studies have been focused in the setting where the source of data is from an IPD-NMA of observational studies. Among which, Wang and colleagues (Wang et al., 2020) recently developed a TMLE estimator in an IPD-NMA in the setting of multiple binary treatments. Thus, our research focuses on developing AIPTW and TMLE estimators to generalize the causal effect of a combination of treatments (called a regimen) on the global population.

2-4. Multidrug Resistant Tuberculosis

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis (M. tuberculosis) strains and is transmittable through the air. Infected patients are given first-line anti TB drugs. Other comorbidities can also increase the risk of infection for this disease; the World Health Organization (WHO) (World Health Organization, 2021b) reports that "those with compromised immune systems such as people living with HIV, malnutrition, or diabetes or people who use tobacco have a higher risk of falling ill" (World Health Organization, 2021b). Infected patients can infect 5–15 other people through close contact in a year. The WHO reports that, "Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die." (World Health Organization, 2021b). TB is one of the top-ten causes of death worldwide with a total of 1.4 million death in 2019. However, there has been a 7% decline in the total number of TB deaths since 2018 and 15% since 2015 (Fukunaga et al., 2021). According to the WHO (World Health Organization, 2021b), about one-quarter of the world population is infected by TB although they cannot transmit it and are not ill (yet). The challenge with controlling TB is the high rate of multidrug-resistant TB (MDR-TB) infection around the globe.

MDR-TB is defined as TB infection that is resistant to the two key first-line TB drugs: rifampicin (RMP/RIF) and isoniazid (INH) (Espinal et al., 2001; Migliori et al., 2020; Pablos-Méndez et al., 1998). In 2019, there was an estimated 500,000 cases of MDR-TB, among which, only 186,772 were diagnosed (Tiberi et al., 2021). In 2018, 59% of MDR-TB patients were successfully treated while in 2019 this rate was 57% (World Health Organization, 2020b) (World Health Organization, 2021b). To encourage patients to complete the course of treatment, the WHO suggested a shorter more effective regimen that takes 9 to 11 months, almost 10 months less than the alternative regimen (Mirzayev et al., 2021). However, the optimal duration required for these treatments is not known yet thus a minimum of 18-24 months is recommended by the WHO (World Health Organization, 2019). Although curable, MDR-TB is treated with medications that are highly toxic and expensive. Patients also require about 2 years of chemotherapy (Conradie et al., 2020).

There are different groups of treatments available for MDR-TB patients:

Group I: First-line drugs including ethambutol and pyrazinamide.

Group II: Second-line drugs including amikacin, kanamycin, capreomycin.

Group III: Fluoroquinolones including ofloxacin, levofloxacin, moxifloxacin.

Group IV: Second-line drugs including ethionamide or prothionamide, cycloserin or terizidone, para-aminosalicylic acid (PAS).

Group V: Including high-dose isoniazid, linezolid, amoxicillin, clarithromycin, thioacetazone, imipenem.

The adverse clinical effects of these treatments are considerable; amikacin, kanamycin and capreomycin have ototoxicity and nephrotoxicity; ethionamide and prothionamide have hepatotoxicity. On top of that there are other clinical side effects of these drugs including psychosis, seizure, paresthesia and depression for cycloserine and terizidone; gastrointestinal disturbance and hypothyroidism for PAS; gastrointestinal disturbance, insomnia, arthralgia for fluoroquinolones; gastrointestinal, hepatotoxicity and hypothyroidism for ethionamide and prothionamide; myelosuppression or thrombocytopenia, lactic acidosis, peripheral neuropathy, pancreatitis and optic neuritis for linezolid (Arnold et al., 2017; Nagasawa & Mikami, 1964; Prasad et al., 2021). The recommended regimen for drug-resistant infections (World Health Organization, 2019) involves a combination of at least four drugs including all of the first-line drugs and at least two of the second-line drugs. To date, the recommended regimen for MDR-TB includes second-line drugs and fluoroquinolone from the third group (Falzon et al., 2017).

Treatment recommendations have evolved over time. In 2000 the WHO suggested the use of second-line drugs when there are resource limitations (World Health Organization, 2000). In 2006 for the first time WHO introduced the five-group categorization of MDR-TB drugs and suggested 18 months of treatments (Raviglione & Uplekar, 2006). In 2011 WHO suggested a 20-month regimen with a combination of at least four drugs that they introduced to be the most effective including all fluoroquinolones, prothionamide or ethionamide, pyrazinamide and either PAS or cycloserine; they also mentioned that ethambutol or any of the drugs from group V can be used however they shouldn't be replaced with any of the four recommended drugs (Falzon et al.,

2017). Eventually in 2019 they recommended using the shorter 9-12 months regimens if the situation allows but if not, they recommended the longer 18-20 months regimen with a new classification of three groups (Ackerman et al., 2021; World Health Organization, 2019). The first group included levofloxacin or moxifloxacin, bedaquiline and linezolid, the second group includes clofazamine and terizidone or cycloserine that can be added to other regimens, and group three includes every other drug that can replace any of the four drugs in the recommended regimen if necessary (Ackerman et al., 2021; World Health Organization, 2019).

The number of studies that investigated the treatment effectiveness for MDR-TB to date includes RCTs (Borisov et al., 2017; Chand et al., 2014; Conradie et al., 2018; Dawson et al., 2015; Nunn et al., 2019; Somoskovi et al., 2015) and observational studies (Hire et al., 2014; Makhado et al., 2018; Ngabonziza et al., 2017; Nunn et al., 2019; Piubello et al., 2014; Sun et al., 2018; Van Deun et al., 2010). Previous systematic reviews (Johnston et al., 2009; Orenstein et al., 2009) and individual patient data network meta-analysis (Ahuja et al., 2012; Menzies et al.; Siddique et al., 2019; Wang et al., 2020) (Liu et al., 2021) have made major contributions to the investigation of treatment effectiveness for MDR-TB. In 2012 the Collaborative Group for Meta-Analysis of Individual Patient Data (Ahuja et al., 2012), led by Dr. Dick Menzies, ran the first largest IPD-NMA for MDR-TB combining data obtained from studies identified in three recent systematic reviews (Akçakir, 2010; Johnston et al., 2009; Orenstein et al., 2009). The studies collected in the systematic review provided data on treatment outcomes in confirmed MDR-TB, involving 9153 patients from 32 cites.

Single studies may be underpowered to establish treatment effectiveness or to identify optimal combinations. Combining multiple studies can provide us with more robust and precise results thus using IPD-NMA to investigate the treatments for MDR-TB would be an asset.

Chapter 3 – [Objectives]

In this chapter, the objectives are given in three separate sections. The first section gives the general objective of this research. In the second section, we explain the theoretical and methodological objectives and the third section talks about the real-world application that motivated the two developed estimators. The last section sums up the objectives by asking four questions that this thesis tries to answer.

3-1. General Objectives

The general objective of this thesis is to estimate the causal effect of a regimen of interest in a network meta-analysis and generalize it to a target population by incorporating two doubly robust estimators each implemented in four different ways.

3-2. Theoretical and Methodological Objectives

1. Explain the causal assumptions and the causal parameter in the setting with IPD from multiple observational studies where the goal is to generalize the effect of a given set of treatments to a global population. Explain the theoretical foundations of the AIPTW and TMLE including the components and the properties of each estimator.

2. Propose and define methods to estimate the GPS for treatment regimens for usage in AIPTW and TMLE.

3. Run a simulation study with 50 clusters (representing studies with IPD) to compare the performance of each estimator. This is done in the setting where the exposure of interest is the effect of a given combination of treatments (regimen) and not all clusters have patients taking this regimen. The goal is to generalize the rate of treatment success to the global population including those clusters without patients taking this regimen.

Study the doubly robust property of AIPTW and TMLE through 8 different estimation scenarios through a simulation study.

3-3. Application Objectives

1. Apply the two developed estimators on the real-world observational IPD of patients with MDR-TB to estimate the treatment success from studies where the regimen was available and then generalize it.

2. Give a coherent summary of the findings which may provide information for researchers in the field of MDR-TB.

3-4. Research Questions

1. How can we construct AIPTW and TMLE to generalize the treatment success in an IPD-NMA of observational data? And what causal parameter is being estimated?

2. What assumptions are needed to use these estimators in this setting?

3. What are the properties of each estimator in general? Do these properties hold when the goal is to use these estimators in an IPD-NMA of observational data to generalize the treatment success?

4. Which one of the two estimators works better in generalizability, concerning the different proposed methods to estimate the GPS, in the setting of an IPD-NMA of observational data?

5. What are the challenges in the application of the AIPTW and TMLE in generalizing the causal parameter in an IPD-NMA of observational data?

Chapter 4 – [Methods]

In the first section of this chapter, we describe the MDR-TB data used in this thesis. We then introduce the parameter of interest representing the causal effect of the regimen of interest and give the identifiability assumptions. We then explain the two proposed estimators AIPTW and TMLE and the related variance estimator along with the methods to estimate the GPS. We then give an overview of the analytical procedures. Finally, we describe the simulation study to evaluate the proposed methods.

4-1. MDR-TB Data

We analyzed the data collected by the group for the Meta-Analysis of Individual Patient Data in MDR-TB founded by Dr. Dick Menzies. In 2012, this group collected IPD (Menzies et al.) from the studies identified in three systematic reviews done by Basu et.al, (Orenstein et al., 2009) Johnston et.al (Johnston et al., 2009) and Akcakir (Akçakir, 2010), each with a different objective related to MDR-TB. The objective of the IPD NMA was to study the effect of type, number and the duration of MDR-TB treatments on the outcome (treatment success). Some specific criteria for inclusion in this NMA included: whether the author of the target study was still reachable, whether the treatment success was reported in the study and whether at least 25 patients were included in the cohort (Johnston et al., 2009; Orenstein et al., 2009).

The data were updated in 2018 and 2019 and the included patients began treatment between 1993 and 2016. In the recent update, we have access to 12,938 patients diagnosed with MDR-TB and extensively drug-resistant (XDR) TB who participated in 52 studies in 37 countries with an overall of 29 treatments. However, not all of the treatments were observed in all the 52 studies.

The variables used in this thesis include the following: clinical information including the age, sex, HIV infection, previous treatment with first-line or second-line tuberculosis drugs, BMI, bilateral disease and diabetes mellitus; diagnostic information including sputum acid-fast bacilli microscopy results, cavitation on chest radiography; treatment information including the drugs used for the duration of treatment; and patients' outcomes defined as cure or death. Two study level covariates were considered: Country income levels (categorized as low, middle/upper-

middle, and high) and the year of treatment initiation. After subsetting to include patients over the age of 18 years 12,557 patients were included in the analysis.

4-2. Data Structure

In this part we give the structure for: Outcome, treatment, regimen and regimen availability, baseline covariates and eventually the observed data structure.

Outcome

The 52 studies are indexed by $j = 1, \dots, 52$. In each study, the patients are indexed by $i = 1, \dots, N_j$ where N_j is the included sample size of study *j*. Each patient has a binary outcome denoted by Y, an indicator of treatment success (meaning the treatment was completed and cured the disease) versus treatment failure (meaning the patient still had a culture-positive MDR-TB infection, was lost to follow-up, or died). The realization of the outcome for each patient i in study *j* is denoted y_{ij}.

Treatment

The t^{th} medication is denoted by t where $t = 1, \dots, 29$ in our case. The 29 medications that we have are isoniazid (H), high dose of isoniazid (HighH), rifampicin (R), ethambutol (E), pyrazinamide (Z), streptomycin (S), rifabutin (Rfb), amikacin (Am), capreomycin (Cm), kanamycin (Km), ofloxacin (Ofx), ciprofloxacin (Cfx), moxifloxacin (Mfx), levofloxacin (Lfx), gatifloxacin (Gfx), ethionamide (Eto), prothionamide (Pto), cycloserine (Cs), terizidone (Trd), para-aminosalicylic acid (PAS), linezolid (Lzd), clofazimine (Cfz), amoxicillin-clavulanic acid (AmxClv), thioacetazone (Thz), clarithromycin (Clr), imipenem-cilastatin (Ipm), meropenem (Mpm), bedaquiline (Bdq), delamanid (Dlm). For an arbitrary patient, the binary variable $A^{(t)}$ represents the exposure to medication *t*.

Regimen and regimen availability

The vector $A = \left(A^{(1)}, \dots, A^{(29)}\right)$ represent the regimen received by a patient. A regimen is defined as a combination of treatments so that the realization of A, which will be denoted $a_{ij} = (a_{ij}^{(1)}, \dots, a_{ij}^{(29)})$, is a vector of 0s and 1s. To indicate if a patient received some fixed regimen r,

the binary variable $R^{(r)}$ is defined which takes 1 if the given regimen r was received and 0 otherwise.

The binary variable $D^{(r)}$ is defined as the regimen availability in a given study. Not all of the studies had a patient observation under a given regimen; thus $D^{(r)}$ takes 1 if at least one patient in the given study had received the fixed regimen *r* and takes 0 otherwise. Hypothetically, the realization $d_{ij}^{(r)} = d_j^{(r)} = 1$ implies that the given regimen r was available to all subjects i in study j because at least one patient in this study received this regimen.

Baseline covariates

The baseline covariates include two sets of variables, the individual-level and the study-level covariates.

Nine individual-level covariates denoted by W: age, sex categorized as male/female, HIV infection categorized as positive/negative, any received previous treatment with first-line or second-line tuberculosis drugs categorized as yes/no (pastTx), BMI, bilateral disease on chest radiography categorized as yes/no (bilateral), diabetes mellitus categorized as yes/no (DM), sputum acid-fast bacilli microscopy results categorized as positive/negative (AFB), and cavitation on chest radiography categorized as yes/no (CXR) .

Two study-level covariates are denoted by S: start year of MDR-TB treatment and the countries' income levels were categorized into three levels; low and lower-middle, upper-middle, and high-income countries (The World Bank, 2020).

Structure for the observed data

Thus, for a given regimen of interest *r*, the observed data structure can be written as $O = \left(W, S, \{A^{(t)}, t = 1, \dots, 29\}, D^{(r)}, Y\right)$.

The data realizations can be defined as follows:

$$o_{ij} = \left(w_{ij}, s_{ij}, \left\{ a_{ij}{}^{(t)}, t = 1, \dots, 29 \right\}, d_j{}^{(r)}, y_{ij} \right); \quad i = \left\{1, \dots, N_j\right\} \quad , j = 1, \dots, 52.$$

Some of the studies had missing covariate and outcome values which were filled in by using multiple imputations, resulting in 30 competed datasets. Multiple imputation is a missing-data method introduced by Rubin (Rubin, 1987) in 1987 that creates multiple complete datasets based on a simulation-based method to fill in the missing values. We used the MICE package in R version 4.1.2 to impute the complete datasets. The multivariate imputation by chained equations (MICE) is a well-known multiple imputations method. The imputation by chained made conditional on the outcome information and used predictive mean matching and the logistic regression for the continuous and categorical variables with missingness (Moons et al., 2006; Morris et al., 2014).

4-3. Parameter of Interest and Assumptions

In this research, we aim to estimate the causal parameter of interest from the observed data where the given regimen r is available and then generalize to the global population which refers to the union of super-populations specific to each of the studies in the dataset (Schnitzer, Steele, et al., 2016). The parameter of interest in this research is given as $\psi^{(r)} = E(Y^{(r)})$ and defined as the finite population mean of the counterfactual outcome under a given regimen r.

4-3-1. Causal Assumptions

The following assumptions allow for the identifiability of this parameter using the observed IPD structure *O*.

1. Given a set of covariates $W$and S, the expectation of the counterfactual outcome among patients receiving the given regimen r where it is available $\left(D^{(r)} = 1\right)$ is equal to the observed outcome. (The consistency of the counterfactual outcome):

$$E(Y \mid D^{(r)} = 1, R^{(r)} = 1, W, S)$$
$$= E(Y^{(r)} \mid D^{(r)} = 1, R^{(r)} = 1, W, S) \qquad (4.1)$$

2. Given a set of covariates $W\text{and}\, S$ and regimen r availability ($D^{(r)} = 1$), the expectation of the counterfactual outcome is independent of the reception of the regimen. (The exchangeability over $R^{(r)}$):

$$E(Y^{(r)} \mid D^{(r)} = 1, R^{(r)} = 1, W, S)$$
$$= E(Y^{(r)} \mid D^{(r)} = 1, W, S) \quad (4.2)$$

3. Given a set of covariates W and S, the expectation of the counterfactual outcome is independent of the regimen availability. (The generalizability of the mean of counterfactual outcome or the exchangeability over $D^{(r)}$)

$$E(Y^{(r)} \mid D^{(r)} = 1, R^{(r)} = 1, W, S)$$
$$= E(Y^{(r)} \mid W, S) \quad (4.3)$$

4. Given a set of study-level covariates S, regimen availability for each study is nondeterministic over the support of *S*. (The positivity of regimen observability)

$$P(D^{(r)} = 1|S) > 0 \quad (4.4)$$

5. Given a set of covariates and the availability of the regimen, the receipt of the regimen (*r*) is nondeterministic over the support of the joint covariate distribution. (The positivity of receiving the regimen)

$$P(R^{(r)} = 1|D^{(r)} = 1, W, S) > 0 \quad (4.5)$$

Now given the above assumptions we can re-write the causal parameter of interest as follows:

By 1: The generalizability of the mean of the counterfactual outcome

$$E\left(Y^{(r)}\right) = E\{E\left(Y^{(r)}\middle|W, S\right)\}$$
$$= E\{E\left(Y^{(r)}\middle|D^{(r)} = 1, W, S\right)\} \quad (4.6)$$

By 2: The exchangeability over $\mathrm{R}^{(\mathrm{r})}$

$$E\{E\left(Y^{(r)}\middle|D^{(r)}=1,W,S\right)\}$$
$$=E\left\{E\left(Y^{(r)}\middle|R^{(r)}=1,D^{(r)}=1,W,S\right)\right\} \quad (4.7)$$

By 3: Consistency of the counterfactual outcome

$$E\left\{E\left(Y^{(r)}\middle|R^{(r)}=1,D^{(r)}=1,W,S\right)\right\}$$
$$=E\left\{E\left(Y\middle|R^{(r)}=1,D^{(r)}=1,W,S\right)\right\} \quad (4.8)$$

4-3-2. Estimators

This section describes the developed AIPTW and TMLE estimators and their doubly-robust property, the methods to estimate the GPS component and the sandwich estimator to estimate the variance.

AIPTW for generalizing the causal parameter in an IPD-NMA

Given the data structure above, let $\hat{Q}(W,S)$ be the estimate of the conditional outcome expectation $E\left(Y\middle|R^{(r)}=1,D^{(r)}=1,W,S\right)$, let $\hat{g}_1(W,S)$ be the estimate of $P(R^{(r)}=1|W,S)$ (i.e. the GPS), let $\hat{g}_2(S)$ be the estimate of $P(D^{(r)}|S)$ (the regimen availability), and let $\widehat{H}^*=\frac{I\left(D^{(r)}=1\right)I\left(R^{(r)}=1\right)}{\hat{g}_1(W,S)\hat{g}_2(S)}$ represent the weights. Then the AIPTW estimator (closely related to (Dahabreh et al., 2019; Liu et al., 2021; Wang et al., 2020)) for the causal parameter of interest is

$$\hat{\psi}^{(r)}_{AIPTW}=\ \sum_{j=1}^{M}[\frac{1}{N_j}\sum_{i=1}^{N_j}\frac{I(d_j=1)\,I(r_{ij}=r)}{\widehat{g_1}(w_{ij},s_{ij})\widehat{g_2}(s_{ij})}\left\{y_{ij}-\hat{Q}\left(w_{ij},s_{ij}\right)\right\}+\hat{Q}\left(w_{ij},s_{ij}\right)] \quad (4.9)$$

Doubly robust property of AIPTW

To show the double robustness property, we first start by considering the following different scenarios when the sample size is large:

Scenario I: $Q(W,S)$ is correctly specified but $g_1(W,S)$ and $g_2(S)$ are incorrectly specified

$$\hat{Q}(W,S) \rightarrow E\left(Y \left| R^{(r)}=1, D^{(r)}=1, W,S\right.\right) \tag{4.10}$$

$$\hat{g}_1(W,S) \rightarrow \tilde{g}_1(W,S) \tag{4.11}$$

$$\hat{g}_2(S) \rightarrow \tilde{g}_2(S) \tag{4.12}$$

Where $\tilde{g}_1(W,S)$ and $\tilde{g}_2(S)$ are not equal to $P(R^{(r)}=1|W,S)$ and $P(D^{(r)}=1|S)$, the correct distributions, respectively.

As the number of samples increases, we would have:

$$\hat{\psi}^{(r)}_{AIPTW} \rightarrow E\left(\frac{I\left(R^{(r)}=1\right) I\left(D^{(r)}=1\right)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\{Y-Q(W,S)\}+Q(W,S)\right)$$

$$= E\left(\frac{I\left(R^{(r)}=1\right) I\left(D^{(r)}=1\right)Y}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right) - E\left(\frac{I\left(R^{(r)}=1\right) I\left(D^{(r)}=1\right)Q(W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right) + E\left(Q(W,S)\right) \tag{4.13}$$

Now, since $Q(W,S)$ is correctly specified, the above is equal to:

$$E\left(\frac{I\left(R^{(r)}=1\right) I\left(D^{(r)}=1\right)Y}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right) - E\left(\frac{I\left(R^{(r)}=1\right) I\left(D^{(r)}=1\right)Q(W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right)$$

$$+E[E\left(Y \left| R^{(r)}=1, D^{(r)}=1, W,S\right.\right)] \tag{4.14}$$

$$= E\left[E\left(\frac{I\left(R^{(r)}=1\right)I\left(D^{(r)}=1\right)Y}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\middle|W,S\right)\right]$$
$$- E\left[E\left(\frac{I\left(R^{(r)}=1\right)I\left(D^{(r)}=1\right)Q(W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\middle|W,S\right)\right]$$
$$+E\left[E\left(Y\middle|R^{(r)}=1,D^{(r)}=1,\ W,S\right)\right] \quad (4.15)$$

$$= E\left[\frac{E(Y|R^{(r)}=1,D^{(r)}=1,\ W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}P\left(D^{(r)}=1\middle|S\right)P\left(R^{(r)}=1\mid W,S\right)\right]$$
$$- E\left[E\left(I\left(R^{(r)}=1\right)I\left(D^{(r)}=1\right)|W,S\right)\frac{Q(W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right]$$
$$+E[E(\left(Y\middle|R^{(r)}=1,D^{(r)}=1,\ W,S\right)] \quad (4.16)$$

Now re-writing the second term of the right-hand side of 4.16, this is equal to

$$E\left[\frac{E(Y|R^{(r)}=1,D^{(r)}=1,\ W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}P\left(D^{(r)}=1\middle|S\right)P\left(R^{(r)}=1\mid W,S\right)\right]$$
$$- E\left[P\left(D^{(r)}=1\middle|S\right)P\left(R^{(r)}=1\mid W,S\right)\frac{Q(W,S)}{\tilde{g}_1(W,S)\tilde{g}_2(S)}\right]$$
$$\underbrace{E\left[E\left(Y\middle|R^{(r)}=1,D^{(r)}=1,\ W,S\right)\right]}_{\psi^{(r)}} \quad (4.17)$$

$$= \psi^{(r)} \quad (4.18)$$

Scenario II: $g_1(W,S)$ and $g_2(S)$ *are correctly specified but* $Q(W,S)$ is incorrectly specified

$$\hat{Q}(W,S) \rightarrow \tilde{Q}(W,S) \tag{4.19}$$

$$\hat{g}_1(W,S) \rightarrow P(R^{(r)}=1|W,S) \tag{4.20}$$

$$\hat{g}_2(S) \rightarrow P(D^{(r)}=1|S) \tag{4.21}$$

In this scenario by knowing the correct specification of the models for $g_1(W,S)$ and $g_2(S)$ we would have:

$$\hat{\psi}^{(r)}_{AIPTW} \rightarrow E\left(\frac{I(R^{(r)}=1)\,I(D^{(r)}=1)}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}\{Y-\tilde{Q}(W,S)\}+\tilde{Q}(W,S)\right)$$

$$= E\left(\frac{I(R^{(r)}=1)\,I(D^{(r)}=1)Y}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}\right) - E\left(\frac{I(R^{(r)}=1)\,I(D^{(r)}=1)\tilde{Q}(W,S)}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}\right)$$

$$+E\left(\tilde{Q}(W,S)\right) \tag{4.22}$$

Now we continue by re-writing each term of the right-hand side of the above equation which gives us:

$$E\left[E\left(\frac{I(R^{(r)}=1)\,I(D^{(r)}=1)Y}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}\,|W,S\right)\right]$$

$$-E\left[E\big(I(R^{(r)}=1)\,I(D^{(r)}=1)\,|W,S\big)\frac{\tilde{Q}(W,S)}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}\right]$$

$$+E(\tilde{Q}(W,S)) \tag{4.23}$$

$$= E\left[\frac{E(Y|R^{(r)}=1,\,D^{(r)}=1,W,S)}{P(R^{(r)}=1|W,S)P(D^{(r)}=1|S)}P(D^{(r)}=1|S)P(R^{(r)}=1|W,S)\right]$$

$$-E\left[P\left(R^{(r)}=1\middle|W,S\right)P\left(D^{(r)}=1\middle|S\right)\frac{\tilde{Q}(W,S)}{P\left(R^{(r)}=1\middle|W,S\right)P\left(D^{(r)}=1\middle|S\right)}\right]$$

$$+E(\tilde{Q}(W,S)) \tag{4.24}$$

$$=\psi^{(r)}-E\left(\tilde{Q}(W,S)\right)+E(\tilde{Q}(W,S)) \tag{4.25}$$

$$=\psi^{(r)} \tag{4.26}$$

So, in large samples, the AIPTW estimator is equal to the true parameter of interest if either the treatment and availability models or $Q(a,W)$ is correctly specified, which shows the doubly-robust property.

The AIPTW estimator inherits its property of double robustness as it incorporates the efficient influence functions for the marginal expected counterfactual outcome under i.i.d data. We also note that because our data are not i.i.d., it is not necessarily efficient in our case. AIPTW solves the influence function estimating equation:

$$\sum_{i,j}\left[\widehat{H}_{ij}*\left(\mathrm{y}_{ij}-\hat{Q}\left(w_{ij},s_{ij}\right)\right)\right]+\hat{Q}\left(w_{ij},s_{ij}\right)-\hat{\psi}_{AIPTW}^{(r)}=0 \tag{4.27}$$

TMLE for generalizing the causal parameter in an IPD-NMA

With the same structure of data explained above, the TMLE (Wang et al., 2020) estimator for the causal parameter of interest in this setting would be:

$$\hat{\psi}_{TMLE}^{(r)}=\sum_{j=1}^{M}\left[\frac{1}{N_j}\sum_{i=1}^{N_j}\widehat{Q}^{*}\left(w_{ij},s_{ij}\right)\right] \tag{4.28}$$

In this project, the following steps were followed to estimate the parameter ψ with TMLE.

Step I; deriving the initial estimates for $Q(a,W)$*:*

For the first step, we fit a logistic regression to the binary outcome using data from the studies where the regimen is available. We then predict to get the initial estimates for $E\left(Y\middle|R^{(r)}=1,D^{(r)}=1,\ W,S\right)$ for all patients in all studies:

$$\hat{Q}(W,S) = logit\left\{\hat{P}\left(Y=1\middle|R^{(r)}=1, D^{(r)}=1,\ W,S\right)\right\} = \hat{\beta}_0 + \hat{\beta}_1 W + \hat{\beta}_2 S \qquad (4.29)$$

Step II; deriving the generalized propensity scores g_1*:*

At the second step, we used one of several methods (to be discussed later) to obtain estimates for the generalized propensity score P ($R^{(r)} = 1 \mid D^{(r)} = 1,\ W,S$).

Step III; deriving estimates for g_2*:*

At this step, a logistic regression was fitted to estimate $P(D^{(r)} = 1|S)$:

$$\hat{g}_2 = logit\left\{\hat{P}(D^{(r)} = 1|S)\right\} = \gamma_0 + \gamma_1 S \qquad (4.30)$$

Step VI; updating the predictions of $Q(a,W)$ from step I:

In this step, we are updating the initial estimates from step I in order to improve them. As discussed by Robins et al. (Robins et al., 2007) when there is a chance of large weights due to small estimated probabilities of treatment, TMLE could be impacted. In this project we plugged in the estimates $\hat{g}_1$ and $\hat{g}_2$ to the weights $H^* = \frac{I(D^{(r)}=1)\, I(R^{(r)}=1)}{P\left(R^{(r)}=1\middle|W,S\right)P\left(D^{(r)}=1\middle|S\right)}$ which were then used in a weighted logistic regression for the updating step. This is in contrast to the clever covariate method explained in the literature review. The TMLE package in R (Gruber & M.J. van der Laan, 2012) also uses the weighting method rather than the clever covariate method.

After using the estimates from step II and step III to form weights, a covariate-free logistic regression of *Y* will be fitted with an offset l$ogit(\hat{Q})$ from step I and the weights $\widehat{H}^*$ in order to estimate a fluctuation parameter $\hat{\varepsilon}$, corresponding to the estimate of the intercept. Subsequently, this fluctuation parameter will be used to update the initial estimates for $Q(a,W)$ which is denoted by $\hat{Q}^*$:

$$logit\left\{\hat{Q}^*(W,S)\right\} = logit\left\{\hat{Q}(W,S)\right\} + \widehat{H}^*\,\hat{\varepsilon} \qquad (4.31)$$

Step V; estimating the causal parameter

After obtaining updated estimates for the outcome function, the final TMLE estimate of the causal parameter is:

$$\hat{\psi}_{TMLE}^{(r)} = \sum_{j=1}^{M} \left[\frac{1}{N_j} \sum_{i=1}^{N_j} \hat{Q}^*(w_{ij}, s_{ij}) \right] \quad (4.32)$$

Doubly-robust property of TMLE

The influence function of TMLE corresponds to the one for AIPTW.

$$\mathrm{IF}_{\mathrm{TMLE}}(O) = \left[\left(\mathrm{Y} - Q(W,S) \right) * H^* \right] + Q(W,S) - \psi \quad (4.33)$$

In fact, TMLE is constructed in order to solve the same influence function estimation equation as in Equation (4.27). Thus, proof of double-robustness for the TMLE is identical to that of AIPTW.

4-3-3. Proposed Methods to Estimate $g_1(W,S)$

Both AIPTW and TMLE can incorporate different methods to estimate the nuisance functions, including the GPS (g_1). In this research, we used four methods to estimate g_1. All methods use the data from those studies where the regimen of interest was observed ($D = 1$) to fit one or more regressions. Then in the prediction step, in order to generalize the findings, the estimates will be predicted for the whole sample including those individuals from studies where the regimen was not observed.

Methods to estimate g_1:

In this section, we talk about four methods that we used to estimate the GPS.

1. **Binary method**

This method treats the variable $R^{(r)}$ as a binary variable with two values: 1 when the regimen *r* was received by the given patient and 0 otherwise. Correspondingly, logistic regression will be fitted to estimate the GPS:

$$\hat{g}_1 = logit\left\{ \hat{P}\left(R^{(r)} = 1 \middle| W, S, D^{(r)} = 1 \right) \right\} = \hat{\alpha}_0 + \hat{\alpha}_1 W + \hat{\alpha}_2 S \quad (4.34)$$

The approach of treating regimen as a binary variable has been taken in a paper by Siddique et al. (Siddique et al., 2019) where different machine learning methods were applied to estimate the GPS.

2. Sequential method

This method treats the random variable representing regimen as a multivariate binary variable. Given some treatment order, this method sequentially fits a logistic regression to each of the binary treatments' indicators, given a set of covariates *W* and *S* and the previous treatments. We make predictions from each of these model fits while setting the treatment indicators to the values corresponding to the regimen of interest. Then we multiply these sequential predictions for each subject to obtain the estimate for g_1.

Given $r = \left(a^{(1)}, a^{(2)}, \dots, a^{(29)}\right)$ a fixed regimen, we have the following equation:

$$P(R^{(r)} = 1|W, S, D^{(r)} = 1) = P\left(a^{(1)}, a^{(2)}, \dots, a^{(29)} \middle| W, S, D^{(r)} = 1\right)$$
$$= P\left(a^{(1)} \middle| a^{(2)}, \dots, a^{(29)}, W, S, D^{(r)} = 1\right)$$
$$* P\left(a^{(2)} \middle| a^{(3)}, \dots, a^{(29)}, W, S, D^{(r)} = 1\right) * \dots * P(a^{(29)}|W, S, D^{(r)} = 1) \quad (4.35)$$

Where:

$\hat{P}_1 =$

$$\hat{P}\left(a^{(1)} \middle| a^{(2)}, \dots, a^{(29)}, W, S, D^{(r)} = 1\right) = \alpha_{0,1} + \alpha_{1,1}W + \alpha_{2,1}S + \alpha_{3,1}a^{(2)} + \dots + \alpha_{29,1}a^{(29)}$$

$\hat{P}_2 =$

$$\hat{P}\left(a^{(2)} \middle| a^{(3)}, \dots, a^{(29)}, W, S, D^{(r)} = 1\right) = \alpha_{02} + \alpha_{12}W + \alpha_{22}S + \alpha_{3,2}a^{(3)} + \dots + \alpha_{29,2}a^{(29)}$$

$\hat{P}_3 =$

$$\hat{P}\left(a^{(3)}\middle|a^{(4)},\dots,a^{(29)},W,S,D^{(r)}=1\right)=\ \alpha_{0,3}+\alpha_{1,3}W\ +\alpha_{2,3}S+\alpha_{3,3}a^{(4)}+\cdots+\alpha_{29,3}a^{(29)}$$

.

.

$$\hat{P}_{29}=\hat{P}\left(a^{(29)}\middle|\ W,S,D^{(r)}=1\right)=\ \alpha_{0,29}+\alpha_{1,29}W\ +\alpha_{2,29}S$$

Then:

$$\hat{g}_1=\ \hat{P}_1*\ \ \hat{P}_2*\ \hat{P}_3*\dots*\ \hat{P}_{29} \qquad (4.36)$$

Then, in each of the binary and sequential methods, three approaches will be used for fitting the GPS; logistic regression, adaptive LASSO and outcome adaptive LASSO. The logistic regression is explained in Equations (4.34) and (4.36).

Adaptive LASSO

This method follows the same structure that was explained for the sequential logistic regression to estimate g_1, except that instead of fitting the logistic regression to predict $\hat{P}_t$, the adaptive LASSO is being used. To do so, first, we run the lasso regression for the treatment model with cross-validation to obtain the coefficients. The coefficients at the error-minimizing lambda are extracted. Then we run the adaptive LASSO (ALASSO) with penalty weights corresponding to $\widehat{K}=\frac{1}{|\hat{\alpha}|^{\gamma}}$ where $\hat{\alpha}$ are the extracted coefficients by using cross-validation. We make predictions with the selected model. Package glmnet in R is used for ALASSO.

Outcome Adaptive LASSO

Here we follow the same structure as for sequential logistic regression, but apply the outcome adaptive LASSO (OALASSO) to predict each $\hat{p}_t$ instead of the adaptive LASSO. In outcome adaptive LASSO, the penalty weights are created by using the coefficients from outcome instead of the PS

model once for AIPTW and once for TMLE (Shortreed & Ertefaie, 2017). Then the penalty weights are defined as $\hat{T} = \frac{1}{|\hat{\beta}|^{\gamma}}$ where $\hat{\beta}$ are the estimated coefficients selected by using cross-validation. We then make predictions with the selected model. Package glmnet in R version 4.1.2 is used to perform OALASSO.

The equations for ALASSO and OALASSO are provided in 2.17 and 2.18. In our setting, the list of covariates when using them in Binary method would be $X = \{W, S\}$ while in Sequential method the individual treatments $A^{(1)}, A^{(2)}, \ldots, A^{(29)}$ are also added to this set depending on the $\hat{P}$ that is being estimated as explained in Equation (4.35).

4-3-4. Variance

As explained in chapter two, the variance estimation for the AIPTW and TMLE estimators is based on the efficient influence function. Clustering was also considered when estimating the variance because we assumed that each study is independent of the other but there are dependencies inside each study. Ignoring the clustering may bias the estimation of the variance (Schnitzer et al., 2014; Wang et al., 2020).

Recall that we used multiple imputations for missing data. Thus, we also must consider two components for estimating the variance; the within-imputation and the between-imputation components. In this section, we first give the complete-data cluster sandwich estimator for each of the estimators and then we explain how the within and between imputation components are computed and combined.

Assume we have a total of n participants within J clusters where $j = 1, \ldots, J$ indexes the cluster, and consider i and m to be two participants in cluster j. Then the general equation for the sandwich estimator of $\psi^{(r)}$ is (Schnitzer et al., 2014)

$$Var\left(\psi^{(r)}\right) = \frac{1}{n^2}\sum_{j=1}^{J}[\{\sum_{\substack{i,m\epsilon K_j \\ i\neq m}} E(IF(F_0;\psi)(O_i)IF(F_0;\psi)(O_m)^T)\}$$
$$+ \{\sum_{i\epsilon K_j} E(IF(F_0;\psi)(O_i)IF(F_0;\psi)(O_i)^T)\}] \qquad (4.37)$$

Where IF is the influence function of the estimator. Thus, by replacing IF with the relevant function for the AIPTW and TMLE estimators we would have the sandwich estimator of the variance for either of them.

Within-imputation and the between-imputation components:

Each imputed dataset $l = 1, \dots, m$ has an estimated clustered variance for AIPTW and TMLE, denoted $\hat{V}_{within(l)}$. Let $\hat{V}_{between}$ denote the between-imputation estimated variance and V_{within} denote the within-imputation variance under m imputed datasets. The "within" variance component is estimated as follows:

$$\bar{V}_{within} = \frac{1}{m}\sum_{l=1}^{m} \hat{V}_{within(l)}. \quad (4.38)$$

The between-imputation variance is estimated by estimating the variance of the estimated variances across the imputed datasets:

$$V_{between} = \frac{1}{m-1}\sum_{l=1}^{m}\left(\hat{V}_{within(l)} - \bar{V}_{within}\right)^2 \quad (4.39)$$

And from this, the variance of each estimator is approximated as:

$$V_{Total} = \bar{V}_B + \frac{m+1}{m}V_W. \quad (4.40)$$

4-4. Overview of the Estimation Procedure

We use AIPTW and TMLE in both a simulation study and the application of the MDR-TB data. The followings steps are being followed in this project to estimate the counterfactual causal parameter $E(Y^{(r)}) = \psi^{(r)}$ and apply the IPD-NMA AIPTW and IPD-NMA TMLE to generalize the effect of this parameter to a global population:

1. Estimate $Q(W, S)$ by fitting the logistic regression of the binary outcome. $Q(a, W)$ is fitted on the subset of patients that received the regimen of interest ($R^{(r)} = 1$), which could include patients from multiple studies. Prediction is done on the whole sample of patients, including those studies where the regimen was not observed.

$$\hat{Q}(w,s) = logit\left\{\hat{P}\left(Y\middle|R^{(r)}=1, D^{(r)}=1,\ W,S\right)\right\} = \hat{\beta}_0 + \hat{\beta}_1 W + \hat{\beta}_2 S \quad (4.41)$$

2. Estimate the GPS by using one of the 4 different methods; binary method, sequential logistic regression, adaptive lasso and outcome adaptive lasso. The models are fit using the IPD from those studies where the regimen of interest was observed for at least one patient ($D^{(r)}=1$). Predictions are then made for the whole sample of patients including those in studies where the regimen of interest was not observed.
3. Estimate $g_2(S)$ by fitting a logistic regression on $D^{(r)}$ and S the study level covariates:

$$\hat{g}_2(S) = logit\left\{P\left(D^{(r)}=1\middle|S\right)\right\} = \gamma_0 + \gamma_1 S \quad (4.42)$$

4. Compute weights as $\widehat{H}^{*}=\frac{I\left(D^{(r)}=1\right) I\left(R^{(r)}=1\right)}{\hat{g}_1(W,S)\hat{g}_2(S)}$
5. For AIPTW replacing the estimates into the equation

$$\hat{\psi}^{(r)}_{AIPTW} = \sum_{j=1}^{M}\left[\frac{1}{N_j}\sum_{i=1}^{N_j} \widehat{H}_{ij}{}^{*}\left\{y_{ij} - \hat{Q}\left(w_{ij}, s_{ij}\right)\right\} + \hat{Q}\left(w_{ij}, s_{ij}\right)\right] \quad (4.43)$$

6. For TMLE, follow the steps explained in section 4-3-2 for the TMLE algorithm and get the estimated causal parameter through the following equation.

$$\hat{\psi}^{(r)}_{TMLE} = \sum_{j=1}^{M}\ \left[\ \frac{1}{N_j}\sum_{i=1}^{N_j} \hat{Q}^{*}\left(w_{ij}, s_{ij}\right)\right] \quad (4.44)$$

Quantity	Model	Estimation Subset	Prediction Subset
$Q(w,s)$ $= P\left(Y\middle\vert R^{(r)}=1, D^{(r)}=1,\ W, S\right)$	Logistic regression	$\{R^{(r)}=1, D^{(r)}=1\}$	All of the subjects
$g_1 = P\left(R^{(r)}=1\middle\vert W, S, D^{(r)}=1\right)$	1) Logistic regression 2) Sequential logistic regression 3) ALASSO[1] 4) OALASSO[2]	$\{D^{(r)}=1\}$	All of the subjects
$g_2(S) = P\left(D^{(r)}=1\middle\vert S\right)$	Logistic regression	52 studies as units of observation	All of the subjects

Table 4-1. Model Specifications to Estimate the Parameter

This section includes the simulation study design for the evaluation of the two proposed estimators AIPTW and TMLE. The objective is to evaluate their finite-sample performance, validate their double robustness property, and compare the coverage of the confidence intervals computed with the clustered sandwich variance estimator. The following is a description of the simulation process.

4-5-1. Design of Data Generating Function

The strategy to design and generate the data was based on the real-world MDR-TB data, excluding the missing data aspect. 1000 random seeds were drawn and stored to generate 1000 datasets each with 50 clusters representing 50 studies, each with a sample size of $Nj = 250$. Thus, the total sample size of each dataset was 25000. We generated one continuous study-level covariate S for each cluster *j*. For study-level covariates, all subjects in the same cluster are assigned the

[1] ALASSO: Adaptive LASSO
[2] OALASSO: Outcome Adaptive LASSO

same value, denoted $s_{ij} = s_j$. We then generated two individual-level covariates W_1 and W_2, one continuous and one binary that was generated conditional on the drawn value s_{ij}. We also created one continuous unmeasured study-level covariate U where all the subjects in the same study had the same value so that $u_{ij} = u_j$. This last covariate, assumed to be unobserved, was used to create study-specific "random effects" in the outcome. Three indicator variables denoted $A^{(k)}, k = 1,2,3$, representing observed treatments, were generated as dependent on individual and study-level covariates. These treatment variables were generated in order and also depended on the previous treatment. For instance, $A^{(2)}$ depended on $A^{(1)}$ in addition to study and individual-level covariates as explained in Equation (4.35).

Since the focus of this research was on studying the effect of a given regimen, we opted to define the regimen of interest as the regimen that was observed with the highest probability. Thus, the most frequent combination of the three generated treatments $A = (A^{(1)}, A^{(2)}, A^{(3)})$ corresponded to the chosen regimen denoted $r = \left(a^{(1)}, a^{(2)}, a^{(3)}\right)$. The random variable $R^{(r)}$ indicated whether this fixed regimen had been received or not. Corresponding to the real MDR-TB data, in the simulation study we ensured the most frequent regimen was not observed in all clusters (studies). Therefore, we incorporated $D^{(r)}$ - the regimen availability in each study - generated as a binary variable from a Bernoulli distribution depending on the study-level covariate. In order to ensure that no subjects in studies where $D^{(r)} = 0$ had the regimen of interest, we forced the last treatment to be discordant with the regimen of interest for these subjects.

Then the binary outcome Y was generated from a Bernoulli distribution depending on the individual-level covariates, study-level covariates, treatments, and also the unmeasured cluster-level covariate. Therefore, the data structure for the simulation study is as follows:

$$O = \left(S, W_1, W_2, U, A, R^{(r)}, D^{(r)}, Y\right). \quad (4.45)$$

Table 4-2 shows the data generation design of the simulation study.

Variable		Generation Design
S		$Normal: mean = 0.3, SD = 0.3, n = 50$
W	W_1	$Normal: mean = 0.1S, SD = 0.1, n = 12500$
	W_2	$Binomial: p = expit(-0.5 - 0.8S), n = 12500$
U		$Normal: mean = 0.2S + 0.1, SD = 0.5, n = 50$
D		$Binomial: p = \exp(-1 - 2S), n = 50$
A	$A^{(1)}$	$Binomial: p = \exp(-0.5 - 0.8S + 0.4W_1 + 0.1W_2), n = 12500$
	$A^{(2)}$	$Binomial: p = \exp\left(-1 + 2.05S + 1.7W_1 - 0.02W_2 + 0.02A^{(1)}\right), n = 12500$
	$A^{(3)}$	$Binomial: p = \exp\left(-1.5 + 0.7S + 1.2W_1 + 0.2W_2 - 0.01A^{(1)} + 0.2A^{(2)}\right), n = 12500$
$R^{(r)}$		Indicator variable defined based on the receipt of r
Y		$Binomial: p = \exp\left(-2 + 8.8S + 0.3W_1 + 0.4W_2 - 0.1U + 1.2A^{(1)} + 1.21A^{(2)} + 0.1A^{(3)} + 2.01A^{(1)}A^{(3)}\right), n = 12500$

Table 4-2. Data Generation Design

The regimen with the highest probability was found to be $r = (1,0,0)$ based on the treatment generation (when setting $D^{(r)} = 1$). The parameter of interest in the simulation study is defined as $\psi^{(r)} = E(Y^{(r)})$.

To find the true value for the parameter, the data were generated as explained above but for generating the Y we forced $A^{(1)} = 1$, $A^{(2)} = 0$, $A^{(3)} = 0$ and then took the mean of the generated outcomes. The true value for the outcome was investigated by increasing the number and the size of clusters in 5 steps; 20 clusters each with the size of 200, 30 clusters each with the size of 300, 50 clusters each with the size of 250, 50 clusters each with the size of 500, 60 clusters each with the size of 600. Then the mean of the outcome was calculated in 1000 samples for each step, and for 50 clusters each with the size of 250, there was no significant variation showing that the sample size is large enough so we can estimate the mean of the outcome close to the true value. Thus, the true value was set to be 0.73.

To evaluate the estimators, we applied them to each of the generated datasets and then compared the respective mean estimates to the true value of the parameter. This gives an estimate of the estimation bias. We also compared AIPTW and TMLE using the two GPS methods binary g_1 and sequential logistic g_1. The standard error (SE) for each estimator was estimated using the sandwich estimator from Equation (4.37).

To evaluate the double robustness property, we intentionally misspecified the models in 8 scenarios by using the intercept-only logistic regression without any covariates (the null model):

Scenario I: all of the models were correctly specified *($g_1 g_2 Q_c$)*

As explained in sections 4-3-2 and 4-3-3, two methods including the binary and also the sequential logistic regressions were fit to estimate the GPS (g_1), and the logistic regression to fit the probability of regimen availability (g_2) and $Q(a, W)$. It has to be noted that the adaptive LASSO and the outcome adaptive LASSO were only used to estimate the GPS in the MDR-TB data because of the data complexity and the need to incorporate other methods.

Thus:

$$g_1 = logit\{P(R^{(r)} = 1 | W, S, D^{(r)} = 1)\} = \alpha_0 + \alpha_1 W_1 + \alpha_2 W_2 + \alpha_3 S \quad (4.46)$$

$$g_2 = logit\{P(D^{(r)} = 1 | S)\} = \gamma_0 + \gamma_1 S \quad (4.47)$$

$$Q(W, S) = logit\{P(Y | W, S, R^{(r)} = 1, D^{(r)} = 1)\}$$

$$= \beta_0 + \beta_1 W_1 + \beta_2 W_2 + \beta_3 A^{(1)} + \beta_4 A^{(2)} + \beta_5 A^{(3)} + \beta_6 A^{(1)} A^{(3)} + \beta_7 U + \beta_8 S \quad (4.48)$$

Scenario II: $\mathbf{g_1}$ was misspecified ($g_1 m\_g_2 Qc$)

An intercept-only logistic regression without covariates (the null model) was fitted to estimate the g_1:

$$\tilde{g}_1 = logit\{P(R^{(r)} = 1 | W, S, D^{(r)} = 1)\} = \alpha_0 \quad (4.49)$$

But the regimen availability g_2 and Q were correctly specified by fitting Equations (4.47) and (4.48), respectively.

Scenario III: $\mathbf{g_2}$ was misspecified ($g_2 m\_g_1 Qc$)

An intercept logistic regression without covariates was fitted to estimate the regimen availability g_2:

$$\tilde{g}_2 = logit\{P(D^{(r)} = 1 | S)\} = \gamma_0 \quad (4.50)$$

But the generalized propensity score g_1 and $Q(a, W)$ were correctly specified by fitting Equations (4.46) and (4.48), respectively.

Scenario IIV: $\mathbf{g_1}$ and $\mathbf{g_2}$ were misspecified ($g_1 g_2 m\_Qc$)

Equations (4.49) and (4.50) were used to estimate the GPS and the probability of regimen availability while Q was correctly specified by using Equation (4.48).

Scenario V: Q was misspecified ($Qm\_g_1 g_2 c$)

Equations (4.46) and (4.47) were used to estimate the GPS and the probability of regimen availability correctly while Q was incorrectly specified by fitting a logistic regression without covariates:

$$\tilde{Q}(W, S) = logit\{P(Y | W, S, R^{(r)} = 1, D^{(r)} = 1)\} = \beta_0 \quad (4.51)$$

Scenario VI: $\mathbf{g_1}$ and Q were misspecified ($g_1 Qm\_g_2 c$)

Equations (4.49) and (4.51) were used to incorrectly estimate the GPS and Q while Equation (4.47) was used to correctly specify the regimen availability g_2.

Scenario VII: $\mathbf{g_2}$ and Q were misspecified $(g_2Qm\_g_1c)$

Equations (4.50) and (4.51) were used to incorrectly estimate the regimen availability and the OM while (4.46) was used to correctly specify the GPS.

Scenario VIII: all the models were misspecified $(g_1g_2Q\_m)$

Equations (4.49), (4.50) and (4.51) were used to incorrectly estimate the GPS, the regimen availability and the OM.

Then for each scenario, the AIPTW and TMLE estimators explained in section 4-3-2 were used to estimate the parameter of interest and the results of each estimator under each scenario were compared. In addition, the standard error (SE) of each was estimated using the sandwich estimator explained in section 4-3-4. Finally, the coverage rates of the confidence interval for each estimator under each scenario were given. Coverage rates indicate how often the confidence interval contains the true value of the parameter.

The sample size was increased in 4 steps by increasing the number of clusters and also the sample size within each. We generated 20 clusters each with a sample size of 200; 30 clusters each with sample size 300; 50 clusters each with sample size 500; and 60 clusters each with sample size 600. The coverage rate was compared to show the effect of sample size on inference.

Chapter 5 – [Results]

This chapter provides the results of the simulation study in the first section to show the consistency of the two developed estimators. In the second section, we present the results of the application of the two proposed estimators on the real-world MDR-TB data to estimate the expected counterfactual outcome under two common regimens in the global population of MDR-TB patients.

5-1. Simulation Results

A simulation study was conducted to demonstrate the consistency and evaluate the doubly-robust property of the two developed estimators AIPTW and TMLE. 50 clusters each with the size of 250 were considered to imitate the application data. The statistical goal was to estimate the effect of the given regimen $r = (1,0,0)$ using the outcomes in those clusters where the regimen r was available ($D^{(r)} = 1$), generalized to the whole population including where $D^{(r)} = 0$. The simulation study aimed to evaluate the doubly-robust property of two estimators AIPTW and TMLE by estimating the causal effect of r under eight different scenarios. We also evaluate the performance of the two methods for the estimation of the GPS. These are referred to as the binary and sequential logistic regression approaches. Thus, for each estimator, we present the results under each scenario for both GPS-estimation approaches. The true value of the parameter of interest was found to be 0.73.

The results of the AIPTW and TMLE under each of the eight scenarios and two methods to estimate the GPS are in Tables 3 and 4.

The abbreviations used to denote each scenario are given below where m indicates that the model was misspecified and c indicates that it was correctly specified while g is defined as $g = \{g_1, g_2\}$:

1. $gQ\ c$*:* When $\hat{Q}(W,S)$, $\hat{g}_1$ and $\hat{g}_2$ are all correctly specified
2. $g_1 m$: When only $\hat{g}_1$ is misspecified
3. $g_2 m$: When only $\hat{g}_2$ is misspecified

4. gm: When $\hat{g}_1$ and $\hat{g}_2$ are both misspecified
5. Qm : When only $\hat{Q}(W,S)$ is misspecified
6. g_1Qm : When $\hat{g}_1$ and $\hat{Q}(W,S)$ are misspecified
7. g_2Qm *:* When $\hat{g}_2$ and $\hat{Q}(W,S)$ are misspecified
8. $gQ\ m$: When $\hat{Q}(W,S)$, $\hat{g}_1$ and $\hat{g}_2$ are all misspecified

Results for AIPTW:

Table 5-1 and 5-2 show the results for the binary and the sequential logistic methods to estimate the GPS in AIPTW. The Monte-Carlo standard error and the mean estimated standard error (SE) estimated by the sandwich estimator were also provided. The true value of the outcome was 0.73.

Scenario	Model specification	Bias	Average estimate	Sandwich estimator of SE	Monte-Carlo SE
1	$gQ\ c$	0.01	0.72	0.024	0.025
2	g_1m	0.01	0.72	0.024	0.025
3	g_2m	0.01	0.72	0.024	0.025
4	gm	0.01	0.72	0.024	0.025
5	Qm	0.03	0.70	0.044	0.045
6	g_1Qm	0.15	0.58	0.075	0.046
7	g_2Qm	0.14	0.59	0.056	0.056
8	$gQ\ m$	0.25	0.48	0.056	0.060

Table 5-1. Estimation from AIPTW under 8 Scenarios using Binary Method to Estimate GPS

From the table, using the AIPTW to generalize the parameter, the estimates remain almost unbiased if either the Q or both of Q and g are correctly specified.

The estimates are biased under the following situations:

1. g_2 is correctly specified but g_1 and Q are misspecified. (Scenario 6)
2. g_1 is correctly specified but g_2 and Q are misspecified. (Scenario 7)
3. g_1, g_2 and Q are misspecified. (Scenario 8)

As shown by this table and as mentioned above, the estimates remain consistent under the misspecifications although the estimated variance is larger when the OM is misspecified compared to the situation where it is correctly specified.

Scenario	Model specification	Bias	Average estimate	Sandwich estimator of SE	Monte_Carlo SE
1	$gQ\ c$	0.01	0.72	0.024	0.025
2	$g_1 m$	0.01	0.72	0.024	0.025
3	$g_2 m$	0.01	0.72	0.024	0.025
4	gm	0.01	0.72	0.024	0.025
5	Qm	0.02	0.71	0.043	0.044
6	$g_1 Qm$	0.12	0.61	0.064	0.041
7	$g_2 Qm$	0.14	0.59	0.058	0.056
8	$gQ\ m$	0.25	0.48	0.074	0.060

Table 5-2. Estimation from AIPTW under 8 Scenarios using Sequential Method to Estimate GPS

From this table, the estimates remain unbiased if either the Q or both of Q and g are correctly specified.

The estimates are biased under the following situations:

1. g_2 is correctly specified but g_1 and Q are misspecified. (Scenario 6)
2. g_1 is correctly specified but g_2 and Q are misspecified. (Scenario 7)
3. g_1, g_2 and Q are misspecified. (Scenario 8)

As shown by this table and as mentioned above, the estimates remain consistent under misspecification although the estimated variance is larger when the OM is misspecified compared to the situation where it is correctly specified. However, the sequential method resulted in a slightly better estimate when Q is misspecified (0.70 for binary method versus 0.71 for the sequential method). Thus, from these two tables, when using AIPTW, under the misspecification of Q, the sequential method for the GPS is slightly more robust.

Results for TMLE:

Tables 5-3 and 5-4 show the results of TMLE estimation of the mean of counterfactual outcome under r using Binary and Sequential methods to estimate GPS.

Scenario	Model specification	Bias	Average estimate	Sandwich estimator of SE	Monte-Carlo SE
1	$gQ\ c$	0	0.73	0.024	0.025
2	$g_1 m$	0	0.73	0.024	0.025
3	$g_2 m$	0	0.73	0.024	0.025
4	gm	0	0.73	0.024	0.025
5	Qm	0.02	0.71	0.043	0.045
6	$g_1 Qm$	0.12	0.61	0.047	0.040
7	$g_2 Qm$	0.14	0.59	0.053	0.056
8	$gQ\ m$	0.24	0.49	0.056	0.060

Table 5-3. Estimation from TMLE under 8 Scenarios using Binary Method to Estimate GPS

As for the TMLE, this estimator gives less biased estimates compared to AIPTW. When there is misspecification of Q, the TMLE under binary approach works almost the same as the AIPTW under the sequential approach using the logistic regression. (Average estimate of 0.71 for TMLE under binary approach versus 0.71 for AIPTW under sequential approach.)

Scenario	Model specification	Bias	Average estimate	Sandwich estimator of SE	Monte-Carlo SE
1	$gQ\ c$	0	0.73	0.024	0.025
2	$g_1 m$	0	0.73	0.024	0.025
3	$g_2 m$	0	0.73	0.024	0.025
4	gm	0	0.73	0.024	0.025
5	Qm	0.01	0.72	0.044	0.045
6	$g_1 Qm$	0.12	0.61	0.048	0.040
7	$g_2 Qm$	0.14	0.59	0.054	0.056
8	$gQ\ m$	0.25	0.48	0.074	0.060

Table 5-4. Estimation from TMLE under 8 Scenarios using Sequential Method to Estimate GPS

This table shows that overall, TMLE had better performance than AIPTW in particular under misspecification of the OM when we apply the sequential logistic regression to estimate the GPS.

Table 6 shows that TMLE has the most unbiased estimates when Q is misspecified especially when the sequential logistic regression is being used. Thus, from the simulations results, TMLE is more robust against any misspecification of the GPS or Q than AIPTW.

Table 5-5 presents the coverage rate of the confidence intervals that were calculated from the estimated variance from the sandwich estimator with respect to different sample sizes.

Size of cluster	No. of subjects per cluster	Coverage rate (%)	
		AIPTW	TMLE
30	300	90	90
50	250	98	98
50	500	99	99
60	600	99	99

Table 5-5. Coverage Rate in Different Sample Sizes

The table shows that the coverage rate increases when the sample size and size of the clusters increases. More specifically, we can see that a sufficient number of clusters is needed for coverage above 95%.

Figures 5-1 and 5-2 illustrate the estimates from the AIPTW and TMLE when either of the binary or sequential method with the implementation of the logistic regression to estimate GPS were used. The vertical line shows the true value of 0.73 for the outcome.

Figure 5-1. Boxplots of the Estimated Values from AIPTW and TMLE from Simulation Study under 8 Scnarios_Binary Method

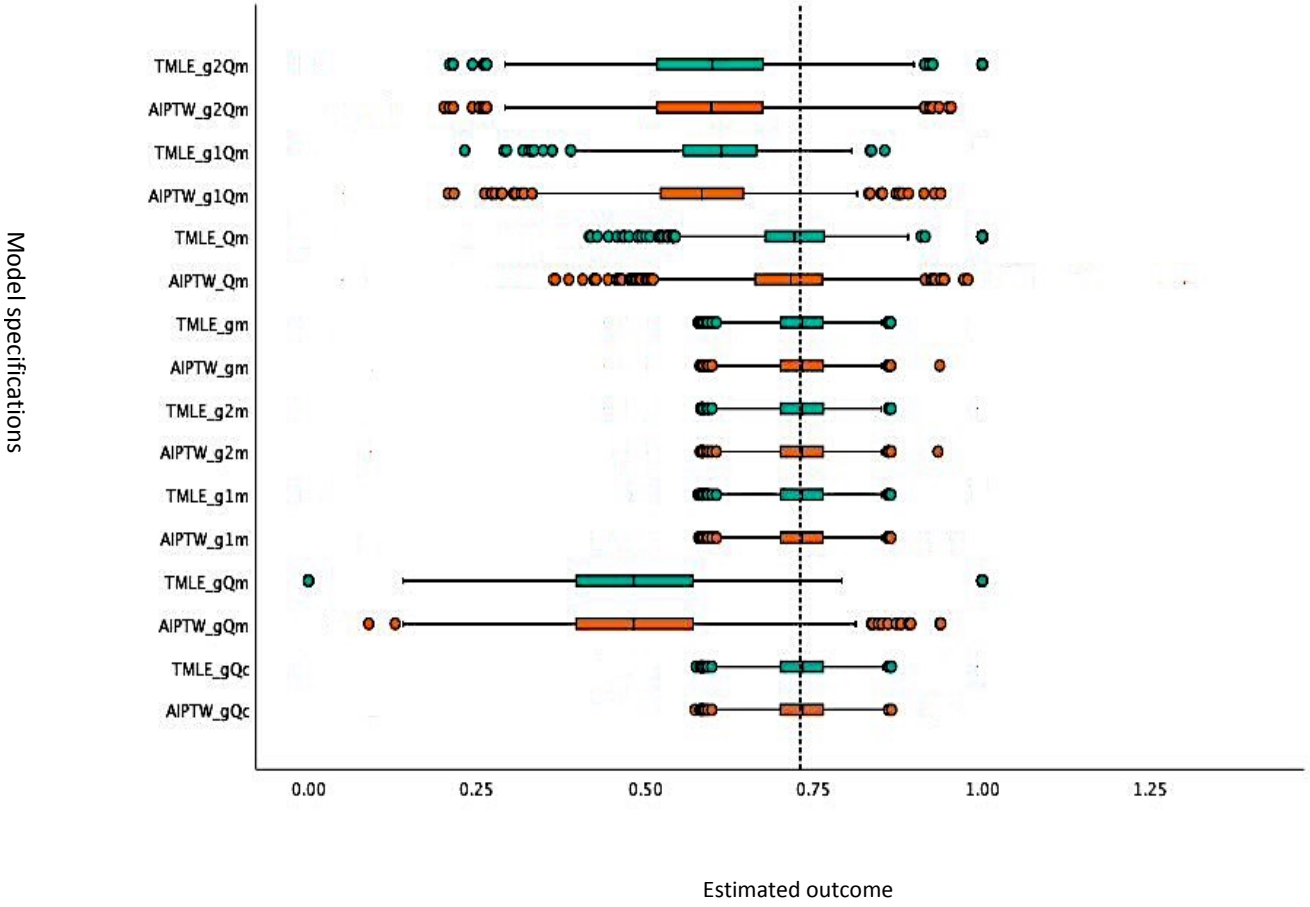
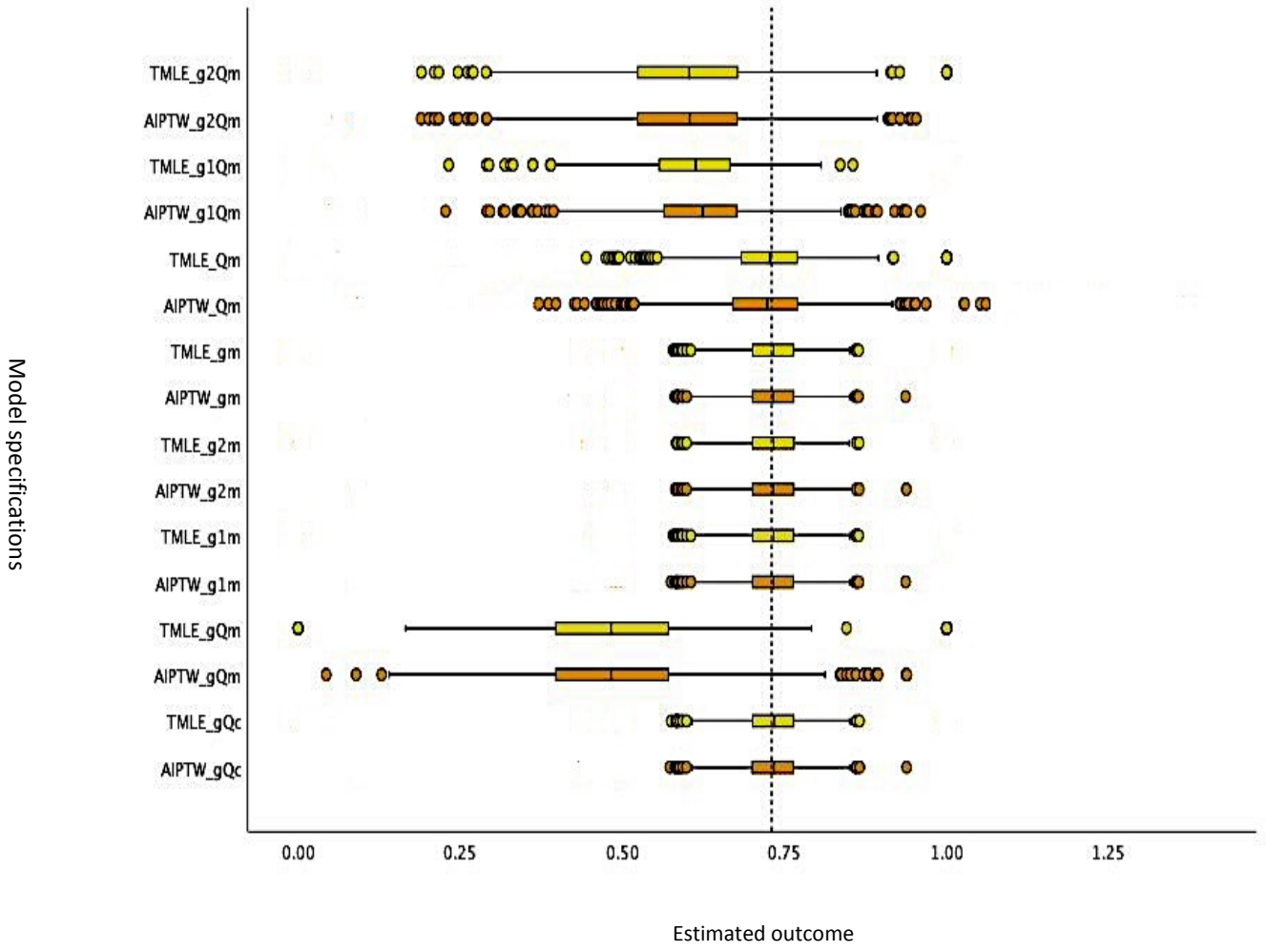


Figure 5-2. Boxplots of the Estimated Values from AIPTW and TMLE from Simulation Study under 8 Scnarios_Sequential Method



5-2. Results of MDR-TB

The MDR-TB data set in this research consists of 52 studies, 37 countries and 12,557 patients. 64.7% of patients were from low and low-middle-income countries, 11.8% were from upper-middle-income countries, and 23.5% were from high-income countries. The median of patients in each study was 110 with the inter quartile range (IQR) of 155. The year of treatment initiation ranged from 1993 to 2016 with the median of 2009. The mean age among the 12,557 patients was 37.7 with the median of 36 ranging from 18 to 94 years. By study, the range of the mean age varied from 30.6 to 47.8 years. The mean BMI was 19.7 with a median of 19.5 (IQR $= 4.6$) among 12,557 patients. The majority of patients (62%) were male with the median proportion of 62.65% across studies (IQR $= 0.18$). Most patients were HIV-negative (64%) with the median proportion

of 95% (IQR $= 0.18$) across studies. Among 12,557 patients, 43.7% were not diabetic with the median proportion of 89.40% (IQR $= 0.12$) across 52 studies. Among the patients, 41% had previously received TB drugs with the median proportion of 66.70% (IQR $= 0.47$). Overall, 31.4% of patients had cavitation and 30% were reported to have bilateral disease shown on chest radiography. Across 52 studies, the median proportion for the positive cavitation was 60.70% (IQR $= 0.28$) and 65.15% (IQR $= 0.26$) for the positive bilateral disease. The acid-fast bacillus smear test was positive for 57% of patients with the median proportion of 75.85% (IQR $= 0.29$) across studies. The rate of treatment success - defined as the outcome - was 59% while 0.9% of the overall sample had no reported outcome. Table 5-6 shows the descriptive statistics of the covariates and outcome including the median proportion (MP) of categorical variables across studies.

Covariates		No. of Patients (%)/ Median (IQR[3])	Missing (%)	MP[4] (IQR) across studies
Year of Tr. Initiation (IQR)		2009 (9)	-	-
Income group (%) (IQR)	Low/low-middle	8124 (64.7)		0 (0.99)
	Upper-middle	1483 (11.8)	-	0
	High	2950 (23.5)		20.4 (0.99)
BMI		19.7 (4.6)	-	-
Age		36 (17.1)	-	-
Sex (Male) (%) (IQR)		7702 (61.3)	-	62.65 (0.18)
HIV (Negative) (%) (IQR)		8037 (64)	637 (5.1)	95.75 (0.18)
DM[5] (Negative) (%) (IQR)		5483 (43.7)	6340 (50)	89.40 (0.12)
Past_Tx[6] (Yes) (%) (IQR)		5145 (41)	5276 (42)	66.70 (0.47)
Cavitation (Yes) (%) (IQR)		3947 (31.4)	6173 (49.2)	60.70 (0.28)
Bilateral disease (Yes) (%) (IQR)		3768 (30)	7148 (56.9)	65.15 (0.26)
AFB[7] (Positive) (%) (IQR)		7159 (57)	2614 (20.8)	75.85 (0.29)
Outcome (Success) (%) (IQR)		7405 (59)	113 (0.9)	71.80 (0.22)

Table 5-6: Descriptive Statistics for individual and study level covariates of patients with MDR-TB

Number of patients who used each of the 29 treatments is provided in Table 5-7.

[3] IQR: Interquartile range
[4] MOP: Median proportion
[5] DM: Diabetes

[6] Past_Tx: Received previous TB treatments of first- or second-line drugs
[7] AFB: Acid-fast bacillus

Treatment	No. of patients (%)	MP (IQR) across studies
Pyrazinamide (Z)	10144 (84)	68.35 (0.45)
Kanamycin (Km)	6299 (52.2)	13.95 (0.50)
Ethionamide (Eto)	6170 (51.1)	24.23 (0.52)
Cycloserine (Cs)	5589 (46.3)	62.40 (0.53)
Ethambutol (E)	5266 (43.6)	44.35 (0.47)
Para-aminoacidic acid (PAS)	5236 (43.4)	55.80 (0.40)
Moxifloxacin (Mfx)	5125 (42.5)	43.60 (0.45)
Terizidone (Trd)	4470 (37)	0 (0.29)
Prothionamid (Pto)	3829 (31.7)	17.05 (0.66)
Ofloxacin (Ofx)	3374 (28)	0 (0.09)
Levofloxacin (Lfx)	3254 (27)	34.05 (0.49)
Capreomycin (Cm)	2905 (24.1)	25.95 (0.49)
Bedaquiline (Bdq)	2021 (16.7)	0 (0.10)
Linezolid (Lzd)	1891 (15.7)	20.25 (0.59)
Amikacin (Am)	1636 (13.6)	12.50 (0.37)
Amoxicillin-clavulanic acid (AmxClv)	1524 (12.6)	12.10 (0.46)
Clofazamine (Cfz)	1466 (12.1)	3 (0.23)
High dose isoniazid (HighH)	1182 (9.8)	0 (0.04)
Isoniazid (H)	1124 (9.3)	2.5 (0.12)
Clarithromycin (Clr)	986 (8.2)	3.70 (0.14)
Streptomycin (S)	967 (8)	0 (0.09)
Rifampicin (R)	906 (7.5)	0 (0.05)
Ciprofloxacin (Cfx)	448 (3.7)	0
Rifabutin (Rfb)	186 (1.5)	0 (0.04)
Imipenem-cilastatin (Ipm)	152 (1.3)	0 (0.006)
Thioacetazone (Thz)	89 (0.7)	0
Metopenem (Mpm)	79 (0.7)	0

Delamanid (Dlm)	65 (0.5)	0
Gatifloxacin (Gfx)	19 (0.2)	0

Table 5-7. Number and proportion of patients using each of the 29 treatments

As described in chapter 4, this study aimed to estimate the mean counterfactual outcome under a given regimen in the global population. The regimen of interest here was defined to be the most frequent regimen that had been used by these patients. Thus, we consider the regimen *r* corresponding to treatments $\{Z, Km, Ofx, Eto, Cs\}$ which was observed in 3 studies and was taken by 689 (5.7%) patients. Among 12,557, 40.63% of those patients who were taking regimen r, were successfully treated.

Table 5-8 presents the top ten regimens concerning the number of studies that the regimen was available and the patients that were taking the regimen. The regimens are sorted based on the number of patients who took them.

Regimen	No. of patients (no. of studies)
$\{Z, Km, Ofx, Eto, Cs\}$	689 (4)
$\{Z, Km, Mfx, Eto, Trd\}$	646 (1)
$\{E, Z, Km, Mfx, Eto, Trd\}$	623 (1)
$\{E, Z, Km, Ofx, Eto\}$	536 (3)
$\{Z, Km, Pto, Cs, PAS, Lfx\}$	402 (10)
$\{Z, Cm, Pto, Cs, PAS, Lfx\}$	271 (6)
$\{Z, Km, Ofx, Pto, Cs\}$	101 (3)
$\{E, Z, Cm, Eto, PAS\}$	94 (2)
$\{E, Z, Cm, Eto, Cs, PAS\}$	84 (2)
$\{Z, Am, Eto, Cs, PAS, Lfx\}$	79 (1)

Table 5-8. Distribution of the top 10 regimens with respect to the number of studies and number of patients taking each regimen

The following tables show the estimated rate of treatment success using AIPTW and TMLE, respectively. ALASSO and OALASSO were also implemented to estimate the GPS. Data sparsity was a challenge when estimating the treatment success in the binary and sequential method

using logistic regression to estimate the GPS. Thus, the process of variable selection was done by hand in order to have an efficient number of patients in each of the two levels of regimen (in binary method) and individual treatments (in sequential method). This challenge motivated us to also implement the ALASSO and OALASSO where the process of variable selection has been done automatically.

Method used to estimate the GPS		Estimate	Standard Error	Confidence Interval
Binary method	Logistic Regression	0.612	0.170	(0.277, 0.946)
	ALASSO	0.569	0.105	(0.363, 0.775)
	OALASSO	0.530	0.127	(0.325, 0.751)
Sequential method	Logistic Regression	0.586	0.096	(0.397, 0.775)
	ALASSO	0.579	0.183	(0.218, 0.939)
	OALASSO	0.541	0.145	(0.256, 0.827)

Table 5-9. Estimated generalized treatment success from AIPTW after taking regimen {Z,Km,Ofx,Eto,Cs}

Method used to estimate the GPS		Estimate	Standard Error	Confidence Interval
Binary method	Logistic Regression	0.603	0.175	(0.258, 0.947)
	ALASSO	0.553	0.114	(0.329, 0.777)
	OALASSO	0.510	0.106	(0.379, 0.740)
Sequential method	Logistic Regression	0.589	0.094	(0.404, 0.774)
	ALASSO	0.544	0.179	(0.193, 0.895)
	OALASSO	0.503	0.136	(0.236, 0.771)

Table5-10. Estimated generalized treatment success from TMLE after taking regimen {Z,Km,Ofx,Eto,Cs}

From tables 5-9 and 5-10, the estimated rate of treatment success for r using the binary method with logistic regression to estimate the GPS was 0.612 and 0.603, using ALASSO was 0.569 and 0.5 and using OALASSO was 0.510 and 0.503 for AIPTW and TMLE respectively. The ALASSO in

binary approach gave the estimates of 0.569 and 0. 553 for AIPTW and TMLE respectively. In binary method with OALASSO the estimate from AIPTW was 0.530 while this estimate for TMLE was 0.510. The sequential method using logistic regressions to sequentially fit the GPS gave the estimates of 0.586 and 0.589 for AIPTW and TMLE respectively. Using the ALASSO to sequentially fit the GPS resulted in estimates of 0.579 and 0.544 for the causal effect of this regimen for AIPTW and TMLE respectively. The estimates after using the OALASSO to sequentially fit the GPS were 0.541 and 0.503 for AIPTW and TMLE, respectively. Among the proposed methods to estimate GPS, the standard errors for TMLE were slightly smaller than those for AIPTW. Also, the crude rate of treatment success by taking regimen r was 40.63% and the observed rate from multiple regimens was 59%, while if everyone had received this regimen, the minimum rate of treatment success would have been 50% (from TMLE by using OALASSO to sequentially estimate the GPS) and maximum rate would have been 61% (from AIPTW from the binary method by using the logistic regression to estimate the GPS).

From the simulation results and by comparing the standard errors from tables 5-9 and 5-10, the TMLE estimates for the average estimate of outcome when the GPS was estimated through the sequential method by ALASSO and OALASSO appear to be the best results. This is because the estimates of these two implementations of TMLE have slightly lower standard errors (0.179 for ALASSO and 0.136 for OALASSO) compared to the same scenarios for AIPTW (0.183 for ALASSO and 0.145 for OALASSO). However, the overlap of the confidence intervals does not suggest a significant statistical difference between the different implementations.

Chapter 6 – [Discussion]

In this thesis, we described the basic concepts of causal inference including counterfactual outcomes, causal assumptions, propensity scores and methods for the estimation of the propensity score; inverse probability of treatment weighting, augmented inverse probability of treatment weighting, and targeted maximum likelihood estimation was explained. Moreover, the ALASSO and the OALASSO have been described as data-adaptive methods that can be applied to estimate the propensity score. The latter was designed specifically to increase the efficiency of inverse probability of treatment weighting. We also explained the nature of influence functions and the efficient influence function and gave the influence function-based variance estimator. Under clustering, we gave a variation of the typical sandwich estimator. Finally, we gave a short epidemiological overview of MDR-TB and a summary of statistical methods used for network meta-analysis and generalizability in order to support key parts of this thesis. In the method chapter, we described an estimator to estimate the generalized causal parameter in the setting of IPD-NMA along with the assumptions needed for identifiability. The simulation study was designed to demonstrate the consistency of the proposed estimators and to show their doubly robust property. To do so, eight scenarios were defined. The details about the MDR-TB data were also given in methods and the plan to show the application of the developed estimators was explained including an example of the TMLE algorithm to estimate the average causal effect. Eventually, the evaluation of the proposed methods along with the results of the application was given in chapter 5.

6-1. Discussion of Results

The simulation results demonstrated that both AIPTW and TMLE performed the same with unbiased estimates just to a slight difference. The doubly robust property of both methods was investigated through eight scenarios. The results proved the doubly robust property of both AIPTW and TMLE estimators. As expected, estimation was biased when either the GPS (g_1) or g_2 along with Q were not correctly specified or when all the three models (g_1, $g_2$and Q) were misspecified. The simulation results demonstrated that TMLE is more slightly more robust than

AIPTW especially when the sequential approach is being used to fit the GPS. Finally, the coverage rate of the confidence intervals was shown to surpass the optimal value of 95% when the number and the size of the clusters were increased. By increasing the sample size to 60 clusters each with the size of 600, the coverage rate increased to 99%. This also implied that the usage of the influence function to estimate the variance is conservative when we use a sufficient number of clusters. Past work suggested the appropriateness of these confidence intervals under similar settings. (Wang et al., 2020)

The results for MDR-TB demonstrated that the most frequent regimen was $\{Z, Km, Ofx, Eto, Cs\}$ which refers to pyrazinamide, kanamycin, ofloxacin, ethionamide and cycloserine. 5.4% of the patients were under this regimen while the of treatment success among these patients was 40.63%. The results from the AIPTW and TMLE showed that taking this combination of drugs leads to a generalized rate of treatment success of approximately 50% to 61%. This shows that the expected success rate of this regimen is closed to the observed average success rate of 59%.

In terms of the proposed methods, TMLE had slightly smaller standard errors among all proposed methods for estimating GPS compare to AIPTW. The maximum estimates for the estimated rate of treatment success for $\{Z, Km, Ofx, Eto, Cs\}$ was 0.61 for AIPTW in binary approach with logistic regression which showed a 20% increase in the rate of treatment success. This estimate for TMLE was 0.60 in binary approach with logistic regression which also showed a 20% increase in the rate of treatment success. However, the regimen we studied was not in accordance with the latest WHO recommendation for MDR-TB patients. (World Health Organization, 2019) One of the reasons could be the start year of treatment initiation which was from 2000 to 2015 in the studies where this regimen was available, therefore, the guidelines were different. Based on the latest update on the guideline, the recommended regimen for MDR-TB patients includes all the first-line treatments (bedaquiline (Bdq), linezolid (Lzd), and levofloxacin (Lfx) or moxifloxacin (Mfx)) and at least one of the second-line treatments (clofazimine (Cfz), cycloserine (Cs) or terizidone (Trz)). (World Health Organization, 2019) Thus our proposed regimen has only cycloserine in common with the currently proposed regimen. In a study evaluating older regimens for MDR-TB, the collaborative group for MDR-TB network meta-analysis showed that ofloxacin, ethionamide or prothionamide and group four drugs including the amikacin, capreomycin and

kanamycin individually associated with better MDR-TB outcomes.(Menzies et al.) Wang et al. (Wang et al., 2020) developed the TMLE estimator for generalizing the causal effect of single treatments and showed the application of their method on an older version of the MDR-TB IPD. They showed that, when evaluated individually, ciprofloxacin, amikacin, capreomycin, ethionamide and streptomycin were associated with better outcomes for MDR-TB. Liu et al. (Liu et al., 2021) applied their methods to the same data as Wang et al and focused on treatment effect modification. They also allowed for differential availability of treatments among studies and random effects by study. They showed that ethambutol and kanamycin would increase the effect of streptomycin while cycloserine, prothionamide and kanamycin could potentially lower this effect. (Liu et al., 2021) Bisson et al. (Bisson et al., 2020) used the same update of MDR-TB IPD as us but their focus was on mortality of those patients who were HIV positive. They concluded that those HIV-positive patients who use at least one of the first-line drugs and followed a specific usage of moxifloxacin, levofloxacin, bed aquiline or linezolid, had significantly lower odds of death in comparison with those who didn't take these treatments.(Bisson et al., 2020) However, the focus of this thesis was to estimate the treatment success rather than studying single treatments separately. The previous work on this setting was either focused on the effect of individual treatments (Wang et al., 2020) or on the development of estimators, including AIPTW and TMLE, for the generalization of the causal effect of the regimen while ignoring the meta-analytical structure of the data (Siddique et al., 2019). Thus, the objectives of this research were novel.

6-2. Contribution to the Field

Being able to evaluate the total effect of a combination of treatments is very important to evaluate medication effectiveness. Our methods will give the researchers the opportunity to study different combinations of treatments even when the data arise from multiple studies. Moreover, unlike the traditional meta-analytical structures, we directly targeted the parameter defined as the mean outcome under a regimen applied to the full population rather than the common measures of effects like odds ratios representing the relative effect of individual medications. Statistical methods for IPD-NMA allow researchers to study other research questions than what the data were collected for. Estimators that specifically aim for

generalizability allow us to use the available information, especially in low-resource settings and generalize the findings to the target population. This avoids selection bias, allowing for the estimation of more interpretable effect parameters.

Evaluating the combined effect of multiple medications is difficult and few methods have been proposed in the statistics literature. The sequential method for the estimation of the GPS that we proposed allows us to evaluate the association of each covariate with the usage of individual treatments, while the binary method doesn't allow for this. Also, in the case of rare regimens, the sequential method may allow for estimation since we have the option to evaluate the combined effect of the treatments by using individual treatments. While the binary method doesn't give us this option as we are obliged to categorize the regimen.

6-3. Limitations and Future Work

One of the limitations of this study is that the regimen availability is based on study units that were in fact treated by the regimen, thus, we may not get robust estimates when the number of studies or the number of patients treated with the regimen of interest is very small. Another limitation is that since we have observational data, we need to assume that there are no unmeasured covariates while this may not be true realistically. The antibiotic resistance, for instance, was an unmeasured confounder in the MDR-TB dataset measured only in a subset of data. Additionally, when one is evaluating combinations of treatments, data sparsity is one of the most challenging limitations.

This thesis estimated the mean of the outcome under one regimen and the rate of treatment success was generalized. In future work, we will compare the expected treatment success of different regimens to identify the most effective combinations of treatments. We also note that while our simulation study contrasted AIPTW and TMLE with a different implementation of the propensity score, future work could evaluate the performance of AIPTW and TMLE under ALASSO and OALASSO in this or similar NMA contexts.

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