# Estimation of Causal Effects under Treatment Misclassification: A Semi-Parametric Bias Correction Framework with Application to Vaccine Effectiveness Study

**Qiong Wu, PhD[1,2,3], Huiyuan Wang, PhD[2,3], and Yong Chen, PhD[2,3]**

1. **Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA, USA**
2. **Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA**
3. **The Center for Health Analytics and Synthesis of Evidence (CHASE), University of Pennsylvania, Philadelphia, PA, USA**

## Background

The effectiveness of COVID-19 vaccines in preventing symptomatic and severe COVID-19 has been assessed through randomized controlled trials (RCTs[1,2]) and subsequent observational vaccine-effectiveness studies[3–5]. However, our understanding of how a COVID-19 vaccine administered prior to infection impacts long COVID outcomes is still unclear. Research conducted to date has been mainly centered on adults and has produced inconsistent findings. Some studies suggest a significant protective effect[6–8], e.g., a reduced risk of the diagnosis of post-acute sequalae of COVID-19 (PASC) or experiencing certain PASC symptoms. Meanwhile, other studies indicate mixed effects revealing considerable variations across different age groups, various dominant virus strains, and distinct PASC symptoms[9,10], or even suggesting counter-protective effects[11,12]. One of the primary challenges in extracting reliable evidence from real-world data (e.g., electronic health records) in the United States is the under-reporting of vaccine status in EHR data due to the lack of immunization registry linkage. In the U.S., immunization records are often disconnected due to logistic, technical, and political barriers. Such incomplete vaccine information can lead to biased estimates in the comparative effectiveness research of COVID-19 vaccines[5].

Motivated by this important challenge, we developed a novel semi-parametric bias correction framework for estimating average treatment effects in the presence of treatment misclassification. We introduce the identifying formula and the efficient influence function where such partial validation of vaccination status is available. This is a reasonable assumption given a substantial number of patients in the PEDSnet network[13] were able to conduct linkage with their local immunization registry data. Subsequently, we constructed an efficient estimator to correct the potential bias of the incomplete vaccine data while achieves full statistical efficiency. Our method allows the misclassification rate of vaccine status captured by the EHR system to be dependent on the characteristics of the patients (i.e., differential misclassification) in a flexible form.

We demonstrated the validity of our method using simulated synthesis data, mimicking the characteristics of the patients in the PEDSnet dataset, and studied the effectiveness of BNT162b2 on long COVID risks during the Omicron period.

## Methods

We consider a general setting where vaccine data from linked immunization registration database at a subset

of the database to create an internal validation dataset with reliable vaccination records. The intervention of interest was vaccination by BNT162b2, in comparison with no receipt of any type of COVID-19 vaccine. The two outcomes of long COVID were the diagnosis of PASC based on ICD10 codes U09.9 and the diagnosis of long COVID based on a computable phenotype algorithm 28 to 179 days following a documented SARS-CoV-2 infection. Three negative control outcomes were pre-selected for the purpose of evaluating the performance: injury by hand, injury by leg, and myopia. We can adjust for a large number of measured confounders including demographic variables, clinical factors, and healthcare utilization factors.

Let $V^*$ be the error-prone or misclassified treatment (i.e., vaccination status) defined based on the EHR only, and $V$ the true treatment integrating the vaccine data from immunization information systems. The average treatment effect $\tau_0 = E(Y_1) - E(Y_0)$ can be identified through

$$E\left\{\frac{E(Y|\boldsymbol{X}, V^*=1) - E(Y|\boldsymbol{X}, V^*=0)}{P(V=1|\boldsymbol{X}, V^*=1) - P(V=1|\boldsymbol{X}, V^*=0)}\right\}.$$

To achieve full statistical efficiency using the entire study cohort, we estimate the average treatment effect by using a sample splitting algorithm based on the efficient influence function:

$$\psi_{EIF}(\tau, \eta; O) = \frac{\tau^*(\boldsymbol{X})}{\delta(\boldsymbol{X})} + \frac{1}{\delta(\boldsymbol{X})}\left[\frac{V^*}{p(\boldsymbol{X})}\{Y - \mu_1(\boldsymbol{X})\} - \frac{1-V^*}{1-p(\boldsymbol{X})}\{Y - \mu_0(\boldsymbol{X})\}\right]$$
$$- \frac{\tau^*(\boldsymbol{X})}{\delta(\boldsymbol{X})}\frac{1}{\delta(\boldsymbol{X})}\left[\frac{R}{\pi_1(\boldsymbol{X})}\frac{V^*}{p(\boldsymbol{X})}\{V - \alpha_1(\boldsymbol{X})\} - \frac{R}{\pi_0(\boldsymbol{X})}\frac{1-V^*}{1-p(\boldsymbol{X})}\{V - \alpha_0(\boldsymbol{X})\}\right] - \tau_0$$

where $\eta = \{p(\boldsymbol{X}),\ \mu_v(\boldsymbol{X}, V^*), \alpha_v(\boldsymbol{X}), \pi_v(\boldsymbol{X}): v = 0,1\}$ represents nuisance parameters related to the data-generating distribution.

**Simulation Results**

**Figure 1** presents the biases of the average treatment effect (ATE) estimated from four methods in different simulation scenarios, including:

1. *Gold Standard*: The method where the true treatment status is available for all participants, which is not practical in our application setting.
2. *Ignoring Misclassification Issue*: The conventional doubly robust estimator using the misclassified treatment.
3. *Plugin Estimator*: The method where we first estimate the misclassification model using the internal validation data and reweight the sample to correct the bias.
4. *Efficient Estimator*: The proposed method corrects the bias with full statistical efficiency.

The results demonstrate a large bias when ignoring the misclassification issue in the EHR immunization data for comparative effectiveness studies. Both the Plugin estimator and the proposed Efficient estimator exhibit small bias, with the proposed method having smaller standard errors, confirming its statistical efficiency.

**Figure 2** summarizes the average treatment effect (risk differences) quantifying the vaccine's effectiveness on two long COVID outcomes. The results demonstrate a significant reduction in long COVID risks with the BNT162b2 vaccine. The method ignoring the misclassification issue could underestimate the vaccine's effectiveness compared to the proposed method that corrects the bias using the internal validation data. **Figure 3**, showing the vaccine's estimated effect on negative control outcomes, demonstrates no statistically significant results. The Plugin estimator shows unstable results (wide confidence intervals) in the analysis of both long COVID and negative control outcomes in **Figures 2** and **3**.

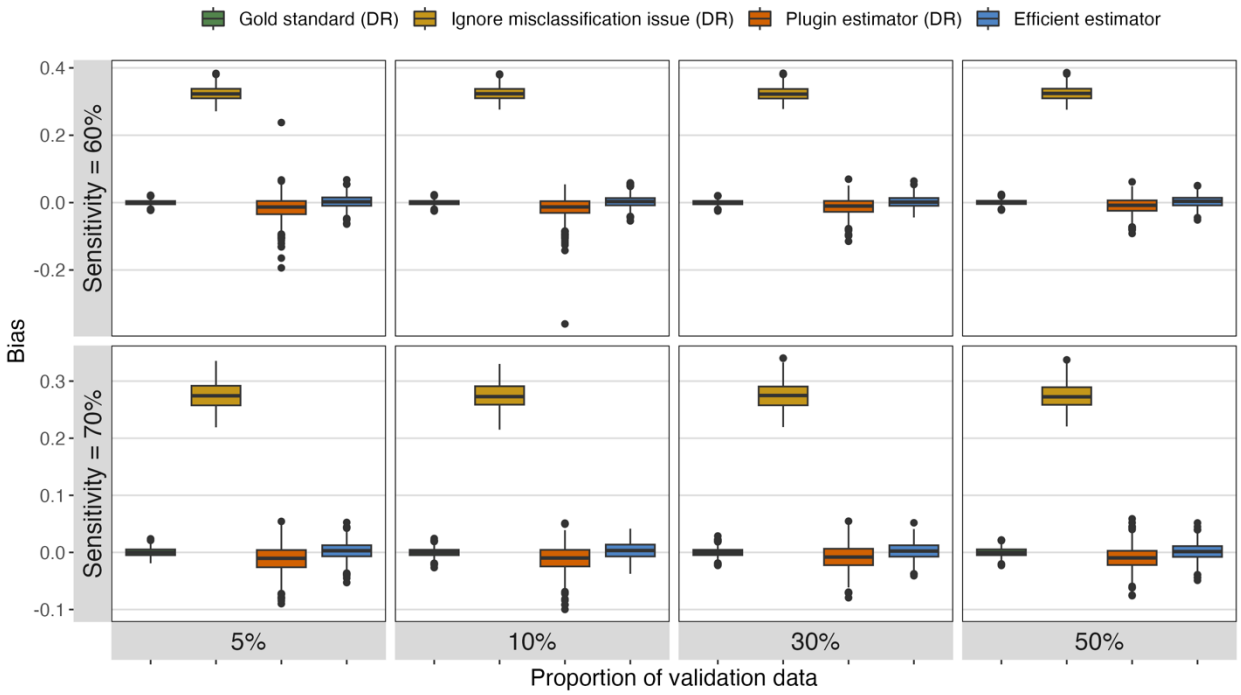


**Figure 1: Bias of estimated average treatment effect from four methods under different simulation settings.**

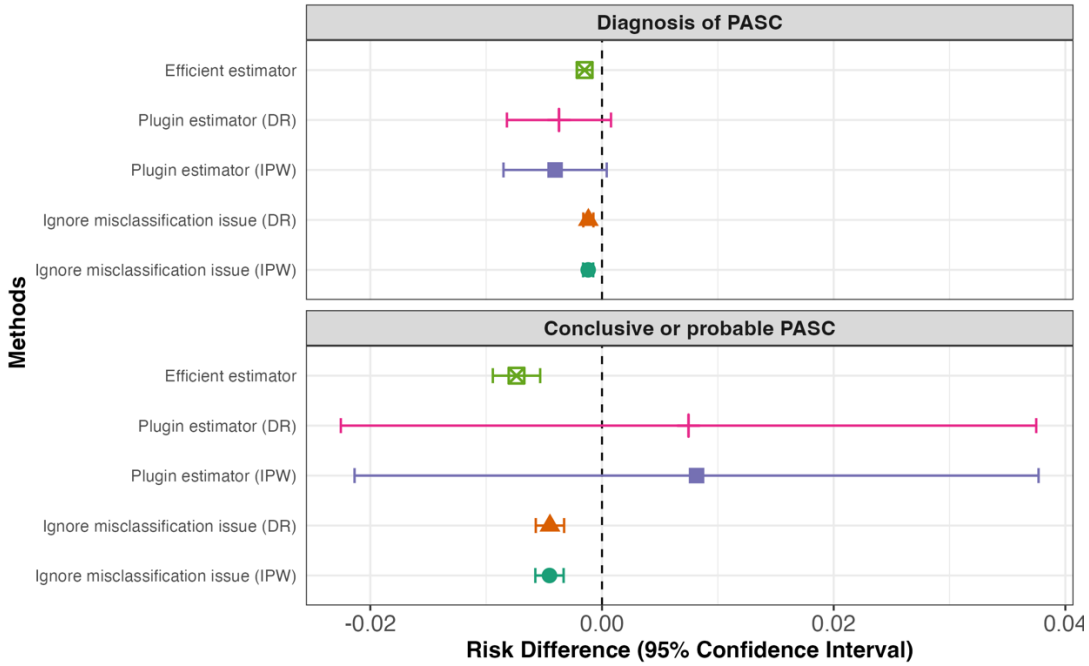


**Figure 2: Estimated effectiveness of the BNT162b2 vaccine in preventing two long COVID outcomes in adolescents.**

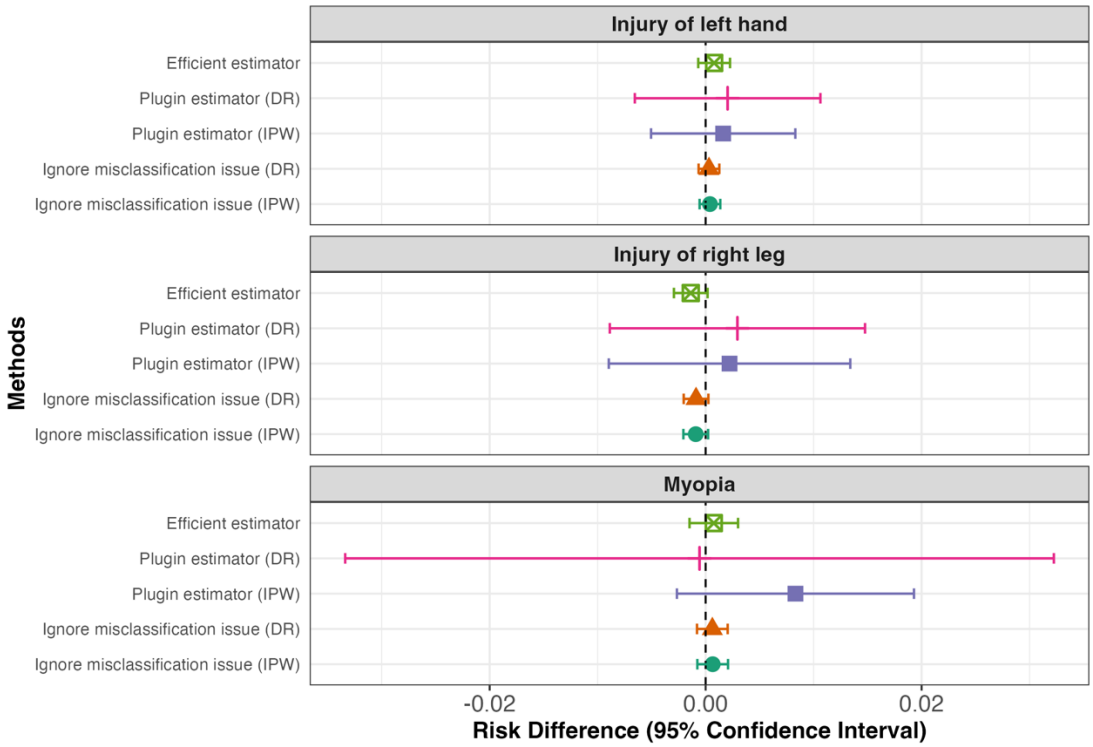


**Figure 3: Estimated effect of the BNT162b2 vaccine on three negative control outcomes in adolescents.**

## Conclusion

The proposed novel framework produces robust estimation of the vaccine effectiveness, while addressing the under-reporting of vaccine status in EHR data due to the lack of immunization registry linkage. An open-source R package is currently under development and will be presented at the OHDSI Annual Symposium.

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