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A Bayesian Approach to Estimating Causal Vaccine Effects on Binary Post-infection Outcomes

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Abstract

To estimate causal effects of vaccine on post-infection outcomes, Hudgens and Halloran (2006) defined a post-infection causal vaccine efficacy estimand VE_I based on the principal stratification framework. They also derived closed forms for the maximum likelihood estimators (MLEs) of the causal estimand under some assumptions. Extending their research, we propose a Bayesian approach to estimating the causal vaccine effects on binary post-infection outcomes. The identifiability of the causal vaccine effect VE_I is discussed under different assumptions on selection bias. The performance of the proposed Bayesian method is compared with the maximum likelihood method through simulation studies and two case studies — a clinical trial of a rotavirus vaccine candidate and a field study of pertussis vaccination. For both case studies, the Bayesian approach provided similar inference as the frequentist analysis. However, simulation studies with small sample sizes suggest that the Bayesian approach provides smaller bias and shorter confidence interval length.

Keywords

Bayesian methods; causal inferences; principal stratification; vaccine effects

1. Introduction

Estimating vaccine efficacy is crucial in evaluating the benefits of vaccines for public health. Evaluating the efficacy of prophylactic vaccines, i.e., whether the vaccine can prevent or ameliorate disease, is very important to reduce the burden of infectious disease [1]. In particular, a common objective of interest in vaccine studies is to evaluate and to compare post-infection outcomes, such as morbidity, mortality and secondary transmission

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to others, in vaccinated individuals with those in unvaccinated individuals. However, treatment comparisons conditional on intermediate post-randomization outcomes using standard analytic methods would not necessarily allow a causal interpretation [2, 3]. Because the set of vaccinated individuals who become infected is not necessarily comparable to the set of unvaccinated individuals who become infected, comparisons of vaccine effects on outcomes conditional on infection could be biased [3, 4].

To address this problem, methods have been developed to assess causal treatment effects on post-infection outcomes. Kalbfleisch and Prentice [5] first discussed in the context of outcomes censored by death, about the importance of causal estimations in the subgroup of individuals whose outcomes hold meaning. Later, many pointed out that comparing outcomes only in the subpopulation in which individuals would become infected regardless of treatment assignment is a causal comparison [6-8]. Then in 2002, Frangakis and Rubin [9, 10] proposed a general framework of principal stratification, which stratifies on the joint potential post-treatment variables, to estimate causal effects based on the potential outcomes framework [11, 12].

Principal strata are determined by the joint potential post-randomization outcomes under each treatment being compared. For example, *principal effects* are defined as the causal effects of treatment on a main outcome of interest (e.g., disease severity) within these principal strata [9]. Because these latent principal strata are not affected by treatment assignment, principal effects are causal effects that do not suffer from the complications of standard post-treatment adjusted estimands. More recently, this principal stratification framework has been adapted within the infectious disease context. For example, a few important methodological contributions have been developed to analyze principal effects in HIV prevention studies [13, 14]. However, generally we cannot directly observe the principal stratum to which a subject belongs because we usually cannot directly observe the potential post-randomization outcomes on different treatment assignments for the same subject [9].

Using the principal stratification framework, Hudgens and Halloran [15] defined a post-infection causal vaccine efficacy estimand in the principal stratum of individuals who would be infected regardless of randomization to vaccine or placebo. They also investigated its estimation and identifiability under the standard assumptions: the stable unit treatment value assumption (SUTVA), independent treatment assignment, and monotonicity. Closed form maximum likelihood estimators (MLEs) were derived under some constraints. The methods were used to evaluate post-infection vaccine effects in a clinical trial of a rotavirus vaccine candidate and in a field study of a pertussis vaccination. Frequentist inference has also been commonly used in causal inference and other models in previous work [16, 17]. However, frequentist MLE inference can be biased, particularly when the sample size is small. Furthermore, maximum likelihood methods generally do not perform well when parameter estimates are on the boundary of the parameter space [18]. To deal with these issues, we propose a novel Bayesian approach via Markov chain Monte Carlo (MCMC) method to estimate the post-infection causal vaccine efficacy estimand. We compare the performance of the Bayesian method with a frequentist approach via maximum likelihood method with application to the two case studies mentioned above.

The Bayesian approach has been increasingly used in recent years on clinical trials [19-24]. Under Frangakis and Rubin's principal stratification and the Bayesian framework, Graham [20] defined a generalized population attributable fraction and applied it to an analysis of the low birth-weight cohort study. Odoni and McNamee [22] presented an optimal model selection predicting arm-specific compliance and produced causal risk ratio estimates for each principal stratum. Gao *et al* [23] discussed joint modeling of compliance and outcome for longitudinal studies when noncompliance was present. In general, a Bayesian approach provides a natural way to combine prior information with current data to make posterior inference that is exact conditional on the data without relying on asymptotic approximation [24]. It also provides better small-sample inferences and direct construction of equal-tail credible intervals on general functions of the estimated parameters [24, 25].

The remaining part of the paper is organized as follows. In Section 2, we review the assumptions, estimation and identifiability of the post-infection vaccine effect estimand from Hudgens and Halloran [15]. We also present their two motivating case studies, a field study of pertussis vaccination and a clinical trial of a rotavirus vaccine. In Section 3, we present a Bayesian approach to estimating the causal vaccine effects on binary post-infection outcomes through MCMC methods. In Section 4, we compare the results for the two motivating examples presented in Section 2. The performance of the proposed Bayesian approach is investigated through a series of simulations in Section 5. Finally we conclude with a brief discussion in Section 6. SAS code included in the Appendix describes the procedures to implement both the maximum likelihood method and the Bayesian approach.

2. Preliminaries

2.1 Assumptions and notation

Suppose that a group of n non-infected individuals receive treatment (vaccine) or control (placebo). Data on the intermediate outcome (infection status), as well as the outcome of interest (post-infection status), are collected. Assume the following:

A1. Stable Unit Treatment Value Assumption (SUTVA) [26-27]—Treatment assignment of one individual does not affect another individual's outcomes (no interference), and there are not multiple versions of treatment.

Under SUTVA, let $S_i(Z_i)$ denote the infection status (potential intermediate outcome) and $Y_i(Z_i)$ denote the post-infection status (outcome of interest) of the i^{th} individual given treatment assignment Z_i , where $Z_i = p$ for placebo (control) and $Z_i = v$ for receiving vaccine (treatment). Let $S_i(Z_i) = 1$ if the i^{th} individual is infected when received treatment Z_i and $S_i(Z_i) = 0$ if uninfected. If $S_i(Z_i) = 1$ then let $Y_i(Z_i) = 1$ if the i^{th} individual develops a severe post-infection outcome; and $Y_i(Z_i) = 0$ if no severe post-infection outcome observed. If $S_i(Z_i) = 0$ then we adopt the convention that $Y_i(Z_i)$ is undefined and denoted by * [15, 28, 29].

Principal strata S^{P_0} are defined by classifying individuals according to the pair of potential infection outcomes, $(S_i(v), S_i(p))$. Basic principal stratification based on the potential infection outcomes with potential post-infection outcomes are listed in Table I.

A2. Independent treatment assignment—The treatment assignment is independent of the potential outcomes, i.e., Z is independent of $\{Y(v), Y(p), S(v), S(p)\}$.

A3. Monotonicity— $S_i(v) \geq S_i(p)$ for all $i \in \{1, \dots, n\}$.

Under assumption A3, an individual who would become infected under vaccine would also become infected under placebo, so the “Harmed” principal stratum $S^{P_0} = (1, 0)$ is empty.

We suppose that all observed $Z_i, S_i, Y_i(Z)$ are independent and identically distributed. Let $n_{sy}(z)$ be the number of each combination of infection outcome and post-infection outcome observed in the study population, where $s = 0, 1$ is the observed infection outcome; $y = 0, 1, *$ is the observed post-infection outcome; and $z = v, p$. That is,

$n_{0*}(p) = \sum_i I(Z_i = p, S_i(p) = 0, Y_i(p) = *)$, $n_{10}(p) = \sum_i I(Z_i = p, S_i(p) = 1, Y_i(p) = 0)$,
 $n_{11}(p) = \sum_i I(Z_i = p, S_i(p) = 1, Y_i(p) = 1)$, $n_{0*}(v) = \sum_i I(Z_i = v, S_i(v) = 0, Y_i(v) = *)$,
 $n_{10}(v) = \sum_i I(Z_i = v, S_i(v) = 1, Y_i(v) = 0)$, and $n_{11}(v) = \sum_i I(Z_i = v, S_i(v) = 1, Y_i(v) = 1)$
 where the summations are over $i = 1, \dots, n$. Let $n(p) = n_{0*}(p) + n_{10}(p) + n_{11}(p)$, and
 $n(v) = n_{0*}(v) + n_{10}(v) + n_{11}(v)$ denote the total number of individuals who receive placebo and vaccine, respectively.

2.2 Parameterization and estimation

Let the parameters $\theta = (\theta_{00}, \theta_{01}, \theta_{11})$ be the probabilities associated with the principal strata, where $Pr\{S^{P_0} = (j, k); \theta\} = \theta$ for $j, k = 0, 1; j \leq k$. Let parameters $\phi = (\phi_{00}, \phi_{01}, \phi_{10}, \phi_{11})$ be the probabilities associated with the joint potential post-infection outcomes in the doomed principal stratum $S^{P_0} = (1, 1)$, where
 $Pr\{(Y(v), Y(p)) = (k, m) | S^{P_0} = (1, 1); \phi\} = \phi_{km}$ for $k, m = 0, 1$. Let the parameters $\gamma = (\gamma_0, \gamma_1)$ be the probabilities associated with the two possible potential post-infection outcomes under placebo in the protected principal stratum $S^{P_0} = (1, 0)$, where
 $Pr\{Y(p) = i | S^{P_0} = (0, 1); \gamma\} = \gamma_i$ for $i = 0, 1$. Hudgens and Halloran [15] defined a post-infection causal vaccine efficacy estimand VE_I within the doomed principal stratum $S^{P_0} = (1, 1)$ as

$$VE_I = 1 - \frac{E\{Y(v) | S^{P_0} = (1, 1)\}}{E\{Y(p) | S^{P_0} = (1, 1)\}} = 1 - \frac{\phi_{1\cdot}}{\phi_{\cdot 1}} \quad (1)$$

where $\phi_{1\cdot} = \phi_{10} + \phi_{11} = Pr\{Y(v) = 1 | S^{P_0}\} = (1, 1)$ and
 $\phi_{\cdot 1} = \phi_{01} + \phi_{11} = Pr\{Y(p) = 1 | S^{P_0}\} = (1, 1)$.

2.3 Identifiability

Hudgens and Halloran [15] showed that VE_I is not identifiable under the standard assumptions A1-A3 (SUTVA, independence, and monotonicity). In particular, regarding the right hand side of equation (1), the numerator $\phi_{1\cdot}$ is identified by the observable random

variables but the denominator $\phi_{.1}$ is not identifiable. The MLE of $\phi_{.1}$ is

$\hat{\phi}_{.1} = n_{11}(v) / (n_{10}(v) + n_{11}(v))$ which is the observed secondary attack rate in the vaccine arm. By considering different additional assumptions about the selective effect of the vaccine on susceptibility to infection, VE_I becomes identifiable. The following are two situations we used in doing sensitivity analyses and simulation studies in Section 3 and 4.

2.3.1 No selection bias—The simplest assumption is that there is no selection bias; that is, the probability of the post-infection outcome conditional on infection under placebo is independent of infection status under vaccine, i.e.,

$Pr\{Y(p)=i|S^{P_0}=(1,1);\phi\} = Pr\{Y(p)=i|S^{P_0}=(0,1);\gamma\}$ for $i=0,1$. It is equivalent to say that the odds ratio of having the severe post-infection endpoint under placebo in the doomed versus protected principal strata is 1. Denote this odds ratio as $\exp(\beta)$, we have

$$e^\beta = \frac{Pr\{Y(p)=1|S^{P_0}=(1,1)\} / Pr\{Y(p)=0|S^{P_0}=(1,1)\}}{Pr\{Y(p)=1|S^{P_0}=(0,1)\} / Pr\{Y(p)=0|S^{P_0}=(0,1)\}} = 1.$$

The no selection bias assumption implies $\phi_{.1} = \gamma_1$, thus the MLE of $\phi_{.1}$ is identifiable as $\hat{\phi}_{.1} = n_{11}(p) / (n_{10}(p) + n_{11}(p))$. See equation (20) in Hudgens and Halloran [15]. Through the definition of VE_I given in equation (1), it follows immediately that VE_I becomes

$$\widehat{VE_I} = 1 - \frac{n_{11}(v) / (n_{10}(v) + n_{11}(v))}{n_{11}(p) / (n_{10}(p) + n_{11}(p))}.$$

2.3.2 Specified selection bias and/or fixed γ —When selection bias exists, e^β is not equal to 1. From the definitions of θ , ϕ and γ , one can identify that

$$Pr\{Y(p)=1|S(p)=1;\theta,\phi,\gamma\} = \frac{\gamma_1 + \theta_{01}}{\theta_{01} + \theta_{11}} + \frac{\phi_{.1} \cdot \theta_{11}}{\theta_{01} + \theta_{11}}. \text{ Also, in terms of the definitions of } \phi_{.1},$$

γ_1 and e^β , one can easily derive that $\phi_{.1} = \frac{\gamma_1 \cdot e^\beta}{(1 - \gamma_1 + \gamma_1) \cdot e^\beta}$. Therefore, γ_1 and $\pi_{.1}$ can be solved for a specified e^β , and in turn, VE_I becomes identifiable. A sensitivity analysis can then be performed over different value of e^β . The selection models we use in the Section 3

are given by $e^\beta = \frac{1}{3}$, 1 and 3. In Section 5, we do simulation studies on given values of e^β and γ_1 .

2.4 Two case studies

2.4.1 Rhesus rotavirus vaccine study—As the first motivating example, a randomized, double-blinded, placebo-controlled trial of a *Rhesus* rotavirus candidate vaccine [30] was conducted in children age 2-5 months from 1985 to 1987 in Finland. Children were randomized to vaccine or placebo, with 100 in each arm, i.e. $n(v) = n(p) = 100$. The vaccine efficacy was evaluated by comparing severity (mild vs. severe or moderately severe) between those vaccinated and unvaccinated children with confirmed rotavirus diarrhea. The observed data are shown in Table II.

2.4.2 Pertussis vaccine study—The second motivating example is an observational field study of pertussis vaccination [31], which was conducted in Niakhar, Senegal from

January 1 to December 31, 1993, among children age 6 months through 8 years. The purpose of this study was to assess the beneficial effects of pertussis vaccination on preventing severe disease in breakthrough cases. The pertussis vaccine analysis included exactly one calendar year of follow-up, thus the person-years at risk can be used for $n(v)$ and $n(p)$, which were 3,845 and 1,020, respectively. Because there was no evidence of systematic differences between the vaccinated and unvaccinated groups, the independent treatment assignment assumption was reasonable. (See Section 3.4.2 in Hudgens and Halloran [15] for detailed discussion.) The observed data are shown in Table II.

3. Statistical Methods

3.1 The likelihood and posterior distribution

Since $n(p) = n_{0*}(p) + n_{11}(p)$ and each of the three combinations is assumed to be observed at least once, the $(n_{0*}(p), n_{11}(p))$ follows a multinomial distribution with $n = n(p)$ and parameter vector $\pi(p) = (\pi_{0*}(p), \pi_{10}(p), \pi_{11}(p))$, where $\sum \pi_{sy}(p) = 1$ and $0 < \pi_{sy}(Z) < 1$ for $(s, y) = (0, *)$, $(1, 0), (1, 1)$. Similarly, $(n_{0*}(v), n_{10}(v), n_{11}(v))$ follows a multinomial distribution with parameter $\pi(v) = (\pi_{0*}(v), \pi_{10}(v), \pi_{11}(v))$. As all observed (S_i, Y_i) in placebo and vaccine groups are independent and identically distributed, these two multinomial distributions are independent conditional on the parameters $\pi(p)$ and $\pi(v)$.

Using the same notations as in Hudgens and Halloran [15], the log-likelihood is proportional to $\pi_{0*}(p)^{n_{0*}(p)} \pi_{10}(p)^{n_{10}(p)} \pi_{11}(p)^{n_{11}(p)} \pi_{0*}(v)^{n_{0*}(v)} \pi_{10}(v)^{n_{10}(v)} \pi_{11}(v)^{n_{11}(v)}$ where $\pi_{0*}(p) = \theta_{00}$, $\pi_{10}(p) = \theta_{01} + \theta_{11} - \xi$, and $\pi_{11}(p) = \xi = \theta_{01}\gamma_1 + \theta_{11}\phi_{1\cdot}$, and $\pi_{0*}(v) = \theta_{00} + \theta_{01}$.

To simplify prior specifications, let $\theta_{00} = \frac{\exp(\alpha_1)}{1 + \exp(\alpha_1) + \exp(\alpha_2)}$,

$$\theta_{01} = \frac{\exp(\alpha_2)}{1 + \exp(\alpha_1) + \exp(\alpha_2)}, \theta_{11} = 1 - \theta_{00} - \theta_{01}, \gamma_1 = \frac{\exp(\alpha_\gamma)}{1 + \exp(\alpha_\gamma)}, \phi_{1\cdot} = \frac{\exp(\alpha_\phi)}{1 + \exp(\alpha_\phi)},$$

$\phi_{1\cdot} = \frac{\gamma_1 \cdot \exp(\beta)}{1 - \gamma_1 + \gamma_1 \cdot \exp(\beta)}$ and $\xi = \theta_{01}\gamma_1 + \theta_{11}\phi_{1\cdot}$. $f(\alpha_1, \alpha_2, \alpha_\gamma, \alpha_\phi, \beta)$ be prior joint distribution of $\alpha_1, \alpha_2, \alpha_\gamma, \alpha_\phi$ and β , is proportional to

$$\pi_{0*}(p)^{n_{0*}(p)} \pi_{10}(p)^{n_{10}(p)} \pi_{11}(p)^{n_{11}(p)} \pi_{0*}(v)^{n_{0*}(v)} \pi_{10}(v)^{n_{10}(v)} \pi_{11}(v)^{n_{11}(v)} f(\alpha_1, \alpha_2, \alpha_\gamma, \alpha_\phi, \beta)$$

Under most circumstances, inferences obtained by Bayesian and frequentist methods agree when weak prior distributions are specified. However, when suitable prior distributions can be constructed to incorporate known subject-matter information on model parameters, the Bayesian framework is particularly appealing [24, 32-33].

3.2 Posterior computation by using the Markov chain Monte Carlo method

Posterior computation was conducted using PROC MCMC procedure in SAS version 9.4 (SAS Institute Inc. Cary NC). The SAS code is included in the Appendix. The burn-in consisted of 100,000 iterations, and 100,000 subsequent iterations were used for posterior summaries. Convergence of the MCMC chain was assessed using visual analysis via the SAS 9.4 PROC MCMC convergence diagnostic panel, including trace plots, sample autocorrelations, and kernel density plots, as well as the Gelman and Rubin convergence

statistics [34, 35]. The equal-tail 95% posterior credible intervals for VE_I were directly available from the posterior samples.

3.3 Selection of prior distributions and sensitivity analyses

For the prior distributions of $\alpha_1, \alpha_2, \alpha_\gamma$ and α_ϕ , weak prior [36] $N(0, 2.5^2)$ was specified such that the 95% prior probability intervals for any of $\pi_{0*}(p), \pi_{10}(p), \pi_{11}(p)$ covered a sufficiently wide range of (0.001, 0.984), (0.002, 0.948) and (0.001, 0.943), respectively. Sensitivity analyses were performed for both Bayesian and frequentist methods over a range of different values of β , such that e^β , the odds ratio of having a severe post-infection endpoint under placebo in the doomed versus protected principal strata ranges from 1/3 to 3. When using the point-mass priors on β , the result from the Bayesian approach is comparable to that from the maximum likelihood method, but the former does not rely on large sample approximations. In addition, to incorporate the uncertainty related to the selection bias parameter e^β , we allow the prior of β to follow a normal distribution with unit variance in the Bayesian analysis.

3.4 Maximum likelihood method for comparison

By using a maximum likelihood based method, Hudgens and Halloran [15] derived closed forms for the MLE of the causal vaccine effect under some assumptions. To compare the performance of the Bayesian approach with that of the maximum likelihood method, the maximum likelihood estimation (MLE), 95% Wald type confidence intervals and profile likelihood confidence intervals [37] were also implemented with the SAS 9.4 PROC NLMIXED and PROC NLP procedures. The closed form MLE is derived under the assumption of $n_{sy}(Z) > 0$ (see the Appendix in Hudgens and Halloran [15].) Thus, when using the maximum likelihood method, we check the condition of $n_{sy}(Z) > 0$ for $(s, y) = (0, *), (1, 0), (1, 1)$ and $z = v, p$ first. The corresponding SAS code is included in the Appendix. The Wald type confidence intervals were obtained based on the normal approximation of $\log(1 - VE_I$

4. Results

The two case studies described in Section 2.4 were reanalyzed using Bayesian methods proposed in Section 3. Table III presents the VE_I results under three values of e_β , for the pertussis vaccination and rotavirus vaccine case studies, respectively. Table III includes the maximum likelihood estimate, 95% Wald-type confidence interval, 95% profile likelihood confidence interval, posterior medians and 95% equal tailed credible intervals for VE_I . The last two columns report VE_I posterior results assuming that the prior distribution of VE_I follows a normal distribution with variance 1. For the results of Bayesian analysis, columns at the left are posterior estimates when we specify point-mass priors on β , and the far right columns indicate results of fully Bayesian analysis (when we allow the prior of β to follow a normal distribution with unit variance).

We noticed that the last column of equal-tailed CI is wider than other CIs, probably due to the uncertainty introduced by the prior on β , which should be taken into consideration in the

data analysis. Other than that, no noticeable difference is observed in the VE_I estimates or the average CI length between the maximum likelihood method and the Bayesian approach.

Figure 1 shows the MLE and Bayesian posterior median of VE_I , with 95% Wald-type confidence interval, profile likelihood confidence interval, and Bayesian credible interval of VE_I , over a range of e^β , where e^β is the odds ratio.

The results clearly demonstrate that the Bayesian posterior median is very close to the MLE of VE_I . The 95% Wald-type confidence interval, profile likelihood confidence interval, and Bayesian credible interval are also similar, especially for the pertussis data, which has a relatively large sample size. However, for the rotavirus data, the posterior median is slightly lower than the maximum likelihood estimate. Moreover, the Bayesian credible interval tends to be narrower than the corresponding profile likelihood confidence interval. In addition, there is a notable difference between the Wald-type confidence interval and the other CIs for the rotavirus data. This is probably due to the poor performance of the asymptotic approximation for Wald type confidence intervals in studies with small to moderate sample sizes.

5. Simulation Study

5.1 Simulated data and analysis methods

We considered two sample sizes: 1) $n(p) = 1,000$, $n(v) = 4,000$; and 2) $n(p) = n(v) = 100$, which correspond to the pertussis vaccine study and rotavirus vaccine study, respectively. For each sample sizes, nine sets of simulations with different selection biases and vaccine effects were performed to evaluate the performance of the frequentist approach via the maximum likelihood methods and the Bayesian approach via MCMC methods. In particular, true values of VE_I were set as 0.2, 0.5, and 0.8, respectively, while the odds ratio e^β values were set as 1/3, 1, and 3, thus nine combinations of true values were generated. True values of parameter π for the multinomial distributions were given as $\pi(p) = (\pi_{0*}(p), \pi_{10}(p), \pi_{11}(p)) = (0.8, 0.1, 0.1)$, which were close to the probabilities in the two case studies. By the relationship among parameters given in Section 3.1, $\pi(v) = (\pi_{0*}(v), \pi_{10}(v), \pi_{11}(v))$ were calculated under different values of VE_I and e^β . Note that (i) γ_1 was set as 0.4 when $e^\beta = 3$, and 0.6 when $e^\beta = 1/3$, to make sure all parameters are reasonable; (ii) when $e^\beta = 1$, $\theta_{01} = \theta_{11}$ was assumed, and γ_1 was calculated as a fixed value $\pi_{11}(p)/(1 - \pi_{0*}(p)) = 0.5$. For each set of simulations, 1,000 replications were used.

5.2 Simulation results

Table IV summarizes the estimated bias, coverage of the 95% confidence/credible intervals, and average confidence/credible interval lengths of VE_I from the frequentist approach and the Bayesian approach based on 1000 replications. As discussed in Section 3.4, if the condition $n_{sy}(Z) > 0$ for $(s, y) = (0, *), (1, 0), (1, 1)$ is not met, some of the parameter estimates from MLE will be on the boundary of parameter spaces leading to some non-convergence computing issues through the frequentist approach. We only reported the number of simulations out of 1000 replicates that satisfy the condition for the maximum likelihood method. For the Bayesian approach, results are based on all 1000 replications, as Bayesian inference via MCMC algorithms permits full posterior inference (e.g., accurate credible

intervals) even in the absence of approximate normality [38], and does not have issues with parameter estimates on the boundary. To make the simulation results through the Bayesian approach directly comparable with those of the maximum likelihood method, we also reported the Bayesian simulation results for the subset in which the MLE is computable.

Similar findings on VE_I were obtained by the proposed Bayesian method and the frequentist approach for large sample size. For small sample sizes, the Bayesian approach provided shorter CI length, and generally smaller bias. The Wald-type confidence interval gave the largest average CI length for small sample sizes, because of its poor performance of asymptotic approximation on small sample sizes. However, it may not be generalizable for the comparison based on the subset in which the MLE is directly computable, as it is a special subgroup from the 1000 replicates. For the Bayesian approach, we also reported biases based on all 1000 replicates. Meanwhile, the coverage probabilities are similar from those different methods.

6. Discussion

In this article, we proposed a Bayesian approach for estimating causal vaccine effects on binary post-infection outcomes, extending the MLE method by Hudgens and Halloran [15], with two application case studies. We further compared the performance of these two approaches through simulations. The use of the Bayesian approach provided similar inference with the frequentist analysis for both case studies. The Bayesian approach can give us smaller bias and shorter confidence interval length based on simulations for small datasets.

Recently, some concerns have been raised on the commonly used prior distributions for parameters [36, 39-41]. When prior information is not available, non-informative priors are often used to carry out Bayesian inference. However, in some situations, non-informative prior distributions may lead to high auto-correlation, where weakly informative priors based on the natural constraints of parameters are desired [36]. In our study, we specified weak prior distributions $N(0, 2.5^2)$ for $\alpha_1, \alpha_2, \alpha_\gamma$ and α_ϕ , so that the 95% prior probability intervals for any of $\pi_{0*}(p), \pi_{10}(p), \pi_{11}(p)$ would cover a sufficiently wide range of (0,1). For the selection bias parameter β , we first specified a point-mass prior on β (to make $e^\beta = 1/3, 1$ and 3 , respectively), such that the Bayesian approach is comparable to the frequentist sensitivity analysis. Then we allowed β to follow a normal distribution with a unit variance to incorporate the uncertainty related to e^β . Additionally, as pointed out by the reviewers, eliciting informative prior distributions on β would be worthwhile to further extend the research, especially for small datasets. Prior information is usually obtained from external data sources [42]. Several researchers have proposed methods to effectively incorporate expert opinions [43, 44, 46, 47] or published data via meta-analysis [45] as informative priors to improve posterior inference. For example, Liu et al proposed a Bayesian adjustment for misclassification of a binary exposure variable with informative prior from experts [46]. Scharfstein *et al* [47] discussed methods on eliciting informative priors for selection parameters from subject matter experts. Furthermore, as discussed in Section 2.3, VE_I is not identifiable only under the standard assumptions A1-A3 (SUTVA, independence, and monotonicity). As Bayesian hierarchical models may include many latent and

unobservable variables, non-identifiability is an inevitable concern when using such models. Although non-identifiability might cause issues, Gustafson [44] showed that assigning a crude subjective prior to non-identifiable parameters (e.g. the β in our model) can perform better than fixing such parameters at best guess values.

Posterior computation can be accomplished using SAS PROC MCMC, as shown in the Appendix. The proposed Bayesian approach provides a useful alternative in estimating the post-infection causal vaccine effect. Although the Bayesian method has some advantages in this setting, as the frequentist method uses a different framework, and it is more familiar to most researchers, these two methods can be considered complementary. In most cases, inferences made by frequentist method and Bayesian approach agree when sample sizes are large and when weak prior distributions are specified [24, 25]. However, the Bayesian framework is particularly attractive when suitable prior distributions can be constructed to incorporate known constraints and subject-matter knowledge on model parameters [18], when the maximum likelihood estimates lie on the boundary of the parameters, or when the sample sizes are very small [48].

In addition to the possible extension on eliciting informative prior distributions on β , there are other areas of future research. For example, in this re-analysis of existed data, we only considered binary outcome. However, as discussed by Hudgens and Halloran [15] and pointed out by a referee, direct extensions to handle ordinal potential post-infection outcomes await for future research. Furthermore, additional research is needed on the consequences of relaxing key assumptions. The assumptions of A1-A3 can be violated [4, 15], especially in observational studies on infectious diseases, which in turn will increase the complexity of defining, identifying and estimating causal effects. Some extensions have been developed and more are undergoing on estimating causal inference in the presence of interference [16, 49-51], noncompliance [52, 49], as well as incorporating baseline covariates [28, 53].

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Appendix

SAS code for the frequentist and Bayesian approaches

```

/* Data */
data jsa2006;
input study $12. n0sp n0sv n10p n10v n11p n11v y;
datalines;
pertussis      814 3297      77      372 129 176      0
rotavirus      84 90      3      5      13      5      0
;
run;

/* MLE with Wald type confidence intervals, beta=log(3) */
proc nlmixed data=jsa2006 fd gtol=1e-10;
parms alpha1=0 alpha2=0 alpha_r=-1 alpha_phi=0;
beta = log(3); * or 0 or log(1/3), define constant beta;
gamma1 = 1/(1+exp(-alpha_r));
theta00 = exp(alpha1)/(1+exp(alpha1)+exp(alpha2));
theta01 = exp(alpha2)/(1+exp(alpha1)+exp(alpha2));
theta11 = 1/(1+exp(alpha1)+exp(alpha2));
phiid = 1/(1+exp(-alpha_phi));
phiid1 = gamma1*exp(beta)/(1-gamma1+gamma1*exp(beta));
xi = theta01 * gamma1 + theta11*phiid1;
logl = n0sp*log(theta00)+n10p*log(theta01+theta11 - xi)+
      n11p*log(xi)+n0sv*log(theta00+theta01) +
      n10v*log(theta11*(1-phiid)) + n11v*log(theta11*phiid);
model y~general(logl);
estimate "log(1-VEi)" log(phiid)-log(phiid1);
by study;
run;

/* MLE with profile likelihood confidence intervals, beta=log(3) */
proc nlp data=jsa2006 fd gtol=1e-10 tech=QUANEW outest=out1;
parms alpha1=0, alpha2=0, alpha_r=1, l_Vei=-0.69;
VEi=1-exp(l_Vei);
profile l_Vei/alpha =0.05 forchi=chi;
beta = log(3); * or 0 or log(1/3), define constant beta;
gamma1 = 1/(1+exp(-alpha_r));
theta00 = exp(alpha1)/(1+exp(alpha1)+exp(alpha2));
theta01 = exp(alpha2)/(1+exp(alpha1)+exp(alpha2));
theta11 = 1/(1+exp(alpha1)+exp(alpha2));
phiid1 = gamma1*exp(beta)/(1-gamma1+gamma1*exp(beta));
phiid = phiid1*(1-VEi);
xi = theta01 * gamma1 + theta11*phiid1;
logl = n0sp*log(theta00)+n10p*log(theta01+theta11 - xi)+
      n11p*log(xi)+n0sv*log(theta00+theta01) +
      n10v*log(theta11*(1-phiid)) + n11v*log(theta11*phiid);

max logl;
by study;
run;

/* Bayesian analysis with credible intervals, beta=normal(log(3), var=1) */
proc mcmc data=jsa2006 nmc=100000 nbis=100000 propcov=QUANEW PROPDIST=T seed=17 thin=10
STATS(ALPHA=0.05)=(INT SUM) MISSING=AC monitor=(VEi);
parms alpha1 0 alpha2 0 alpha_r -1 alpha_phi 0 beta 0;
prior alpha1 ~ normal(0, sd=2.5);
prior alpha2 ~ normal(0, sd=2.5);
prior alpha_r ~ normal(0, sd=2.5);
prior alpha_phi ~ normal(0, sd=2.5);
prior beta ~ normal(log(3), var=1);
gamma1 = 1/(1+exp(-alpha_r));
theta00 = exp(alpha1)/(1+exp(alpha1)+exp(alpha2));
theta01 = exp(alpha2)/(1+exp(alpha1)+exp(alpha2));
theta11 = 1/(1+exp(alpha1)+exp(alpha2));
phiid = 1/(1+exp(-alpha_phi));
phiid1 = gamma1*exp(beta)/(1-gamma1+gamma1*exp(beta));

xi = theta01 * gamma1 + theta11*phiid1;
VEi = 1-phiid/phiid1;
logl = n0sp*log(theta00)+n10p*log(theta01+theta11 - xi)+
      n11p*log(xi)+n0sv*log(theta00+theta01) +
      n10v*log(theta11*(1-phiid)) + n11v*log(theta11*phiid);
model y ~general(logl);
by study;
run;

```

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Figure 1.

Comparison of VE_I estimate* with 95% CI† using frequentist and Bayesian approach, as a function of the odds ratio e^β . a. Rotavirus vaccine study case; b. pertussis vaccine study case.

* MLE (bold dashed line), Bayesian posterior median (bold solid line).

† Wald-type confidence interval (fine dotted line), profile likelihood based confidence interval (fine dashed line), equal-tail credible interval (fine solid line).

The vertical dotted line corresponds to the assumption of no selection bias.

Table I

Basic principal stratification S^{P0} based on the potential infection outcomes $(S_i(v), S_i(p))$ with potential post-infection strata based on $(Y_i(v), Y_i(p))$

Principal stratum S^{P0}	Potential infection outcomes $(S_i(v), S_i(p))$	Potential post-infection outcomes $(Y_i(v), Y_i(p))$
Immune	(0, 0)	(*, *)
Harmed	(1, 0)	(0, *), (1, *)
Protected	(0, 1)	(*, 0), (*, 1)
Doomed	(1, 1)	(0, 0), (1, 0), (0, 1), (1, 1)

Table II

Observed data for the two case studies described in Section 2.4

Study	$n_{0*}(p)$	$n_{10}(p)$	$n_{11}(p)$	$n_{0*}(v)$	$n_{10}(v)$	$n_{11}(v)$
<i>Rhesus</i> rotavirus vaccine ($n(p)=100$, ($n(v)=100$))	84	3	13	90	5	5
Pertussis vaccine ($n(p)=1020$, ($n(v)=3845$))	814	77	129	3297	372	176

Table IIISummary of (estimates^{*} and 95% CI[†]) based on maximum likelihood and Bayesian approaches

Study	e^{β}	Maximum likelihood method			Bayesian approach			
		VE_I	Wald CI	Profile	VE_I	Equal-tail CI	$VE_I^{\ddagger}$	Equal-tail CI [‡]
Rhesus rotavirus vaccine	1/3	0.340	(-0.334, 0.674)	(-0.293, 0.724)	0.327	(-0.238, 0.702)	0.336	(-0.324, 0.709)
	1	0.385	(-0.194, 0.683)	(-0.081, 0.738)	0.376	(-0.091, 0.733)	0.375	(-0.118, 0.727)
	3	0.430	(-0.085, 0.701)	(0.026, 0.755)	0.407	(0.025, 0.750)	0.411	(-0.009, 0.745)
Pertussis vaccine	1/3	0.424	(0.307, 0.521)	(0.303, 0.519)	0.426	(0.303, 0.520)	0.439	(0.267, 0.563)
	1	0.487	(0.397, 0.563)	(0.397, 0.563)	0.486	(0.395, 0.563)	0.493	(0.337, 0.602)
	3	0.543	(0.467, 0.609)	(0.466, 0.609)	0.541	(0.462, 0.607)	0.542	(0.408, 0.634)

* MLE of VE_I for maximum likelihood method, posterior median of VE_I for Bayesian approach.

[†] CI: Wald-type confidence interval based on normality assumption for the maximum likelihood method with standard errors derived from the observed information; profile likelihood confidence interval based on the value which maximizes the likelihood given the value of β ; equal-tail credible interval for the Bayesian approach.

[‡] The estimates when the prior of β follows a normal distribution with same mean and a unit variance.

Table IV

Estimated bias^{*}, empirical coverage probability of a 95% confidence/credible interval, and CI[†] length on VE_i based on 1000 replications

Maximum Likelihood Method							Bayesian Approach						
VE_i	ϵ^{δ}	$n^{\frac{\delta}{2}}$	Bias	Wald CI		Profile CI		Equal-tail CI ($n=n^{\frac{\delta}{2}}$)		Equal-tail CI ($n=1000$)			
				Coverage probability	CI length	Coverage probability	CI length	Bias	CI length	Coverage probability	CI length		
For small sample size ($n(p) = 100, n(v) = 100$)													
0.2	1/3	872	-0.223	0.950	3.710	0.956	3.167	-0.173	0.959	2.812	-0.100	0.933	2.706
	1	975	-0.074	0.958	1.873	0.942	1.783	-0.075	0.942	1.715	-0.066	0.927	1.702
	3	950	-0.025	0.975	1.522	0.976	1.454	-0.046	0.977	1.423	-0.049	0.959	1.417
0.5	1/3	718	-0.297	0.933	3.508	0.964	2.793	-0.271	0.964	2.488	-0.112	0.959	2.200
	1	921	-0.093	0.942	1.718	0.955	1.477	-0.104	0.957	1.424	-0.066	0.935	1.369
	3	915	-0.077	0.943	1.497	0.969	1.279	-0.101	0.966	1.256	-0.072	0.942	1.218
0.8	1/3	427	-0.391	0.869	3.381	0.941	2.432	-0.391	0.916	1.188	-0.152	0.962	1.680
	1	629	-0.147	0.917	1.565	0.957	1.578	-0.169	0.943	1.128	-0.064	0.964	0.940
	3	628	-0.143	0.912	1.419	0.960	1.030	-0.170	0.949	1.023	-0.067	0.966	0.865
For large sample size ($n(p) = 1,000, n(v) = 4,000$)													
0.2	1/3	1000	-0.004	0.948	0.452	0.948	0.453	-0.002	0.948	0.452			
	1	1000	0.001	0.952	0.297	0.950	0.299	0.0005	0.949	0.298			
	3	1000	-0.003	0.950	0.238	0.945	0.241	-0.004	0.946	0.241			
0.5	1/3	1000	-0.002	0.951	0.333	0.951	0.332	-0.002	0.948	0.331			
	1	1000	0.001	0.952	0.222	0.952	0.222	0.001	0.952	0.222			
	3	1000	-0.001	0.949	0.192	0.941	0.193	-0.003	0.942	0.193			
0.8	1/3	1000	-0.001	0.951	0.196	0.947	0.192	-0.002	0.948	0.191			
	1	1000	0.001	0.955	0.132	0.951	0.131	0.001	0.948	0.131			
	3	1000	-0.001	0.941	0.125	0.938	0.123	-0.001	0.938	0.123			

* Bias: MLE of VE_i minus true value of VE_i for maximum likelihood method; posterior median of VE_i minus true value of VE_i for Bayesian approach.

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CI: Wald-type confidence interval based on normality assumption of $\log(1 - VEI)$ for the maximum likelihood method derived from the observed information; profile likelihood confidence interval based on the VEI value which maximizes the likelihood given the value of β equal-tail credible interval for the Bayesian approach.

n: the number of replications that satisfy the condition $n_{SY}(z) > 0$ for $(s, y) = (0, *)$, $(1, 0)$, $(1, 1)$.