DISCUSSION

Discussion on “estimating vaccine efficacy over time after a randomized study is unblinded” by Anastasios A. Tsiatis and Marie Davidian

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1 | INTRODUCTION

Evaluation of COVID-19 vaccines has proceeded at unprecedented speed and required the quick development of statistical methods to emerging challenges in design and analysis. A major issue emerged shortly after the trials started enrolling. What to do with the placebo group after efficacy was confirmed? Although continued follow-up of the original arms was ideal to assess durability and performance against emerging strains, maintenance of the placebo arm with available efficacious vaccines was both ethically and practically untenable.

A remarkable result was that the placebo controlled vaccine efficacy profile could be recovered long after the placebo group had been vaccinated. This result allows for the assessment of the durability of vaccine effect and can inform when booster vaccinations might become necessary. However, individual initiated unblinding, vaccination, and associated differential behavior can jeopardize the unbiased estimation of vaccine efficacy. In this thoughtful and elegant work Tsiatis and Davidian (TD) develop methods to fix the potential bias, motivated by and applied to the Moderna phase III clinical trial. The results are important and timely as multiple trials do and will grapple with this issue.

In this comment, I provide some detail about how time varying vaccine efficacy is recovered to facilitate understanding and the potential for bias. I discuss possible extensions and provide some details about practical implementation.

2 | THE BACKGROUND

Consider a randomized placebo controlled vaccine trial where at risk volunteers are randomized to vaccine or placebo with equal probability on the same day with a single dose vaccine that immediately provides its full effect. After a period of time, all placebo volunteers receive vaccine and both groups are followed for a second period. The disease cases are tallied for each period; illustrative data are provided in Table 1. By assuming that the vaccine efficacy estimate of 51% over the first period applies to the newly vaccinated in Period 2, we can deduce that, had there been a placebo group in Period 2, it would have had about twice as many cases as the newly vaccinated. This inferred placebo case count can then be used to estimate the placebo controlled vaccine efficacy during the second period. Note that the 51% vaccine efficacy (VE) should apply no matter what the counterfactual placebo attack rate is in Period 2 and thus the method does not require a constant attack rate.

To statistically develop the numbers of Table 1, let $Y_{ZK}$ be the case count for arm $Z = 0, 1$ in Period $K = 1, 2$ where $Z = 1$ denotes the original vaccine arm. In a large trial with a low event rate these counts should be approximately Poisson. This representation can help understand the approach and identify weaknesses. Some key points are given below.

(1) The estimate of vaccine efficacy after placebo vaccination increases in uncertainty. The Period 2 vaccine effi-
Data that illustrate how to recover the Period 2 vaccine efficacy when all placebo volunteers receive vaccine at the end of Period 1. The inferred number of cases for a counterfactual placebo group in Period 2 is given by the Period 1 placebo:vaccine risk ratio times the number of cases for the original placebo/deferred vaccination arm in Period 2.

| Randomization Arm | # cases Period 1 | Period 2 Group | Rebranded Group |
|-------------------|------------------|----------------|-----------------|
| Vaccine           | 49               | 50             | Immediate vaccination |
| Placebo           | 101              | 30             | Deferred vaccination |

\[ \hat{VE}(1) = 1 - \frac{49}{101} \]
\[ \hat{VE}(2) \approx 1 - \frac{50}{61.8} \]
\[ = 0.51 \]
\[ = 0.19 \]

Vaccine efficacy estimate is the product of two ratios.

\[ \hat{VE}(2) = 1 - \frac{Y_{11}Y_{12}}{Y_{01}Y_{02}}, \]

with approximate delta-method variance given by

\[ \text{var}[\log(1 - \hat{VE}(2))] = \frac{1}{Y_{11}} + \frac{1}{Y_{01}} + \frac{1}{Y_{12}} + \frac{1}{Y_{02}}. \]

For \( K \) periods, \( \hat{VE}(K) \) involves the product of \( K \) ratios and the variance of the sum of \( 2K \) terms. Thus if the Period 1 vaccine efficacy is poorly estimated, that is, \( 1/Y_{11} \) and \( 1/Y_{01} \) are large, all subsequent period specific estimates will be poorly estimated as well. This increase in uncertainty is demonstrated by simulation in TD.

With a smooth function for vaccine efficacy as shown in TD

\[ \hat{VE}(\tau) = 1 - \exp(\hat{\theta}_0 + \hat{\theta}_1(\tau - \ell)), \]

where \( \tau > \ell \) is the time since vaccination and \( \ell \) the time to full vaccine effect, a similar phenomenon occurs. If placebo vaccination occurs quickly, the first term of (14) may be based on few events and one is stuck with a poor estimate of \( \hat{\theta}_0 \), even if \( \hat{\theta}_1 \) can be estimated very well.

(2) Based on this representation, one can imagine that with enough data each of the \( K \) periods could shrink to a very small interval, while \( K \) grew larger, yet there would be enough cases to estimate the ratio of case rates accurately. Pushing this further, one should be able to prove that the entire vaccine efficacy curve is nonparametrically recoverable.

(3) With the availability of an efficacious vaccine, there is risk that volunteer initiated unblinding could become commonplace and jeopardize the recovery of vaccine efficacy over time. For example, if at the end of Period 1 the riskiest half of the placebo group all chose to be unblinded, received an outside study vaccine, and were censored, the original placebo/deferred vaccination case count in Table 1 might be 10 instead of 30. The counterfactual placebo case count, would be \( 20.6 = 10 \times 101/49 \) that we then double because half the placebo group is gone. The resultant Period 2 vaccine efficacy estimate is a disturbing \( \hat{VE}(2) = 1 - 50/(20.6 \times 2) = -0.22 \), falsely indicating a late harm of vaccination.

3 | THE FIX

Under the assumption that the newly vaccinated receive the benefit profile from vaccination whether vaccinated in May or March, plus standard assumptions, the vaccine efficacy profile is recoverable. These standard assumptions include avoidance of differential loss to follow-up and/or differential behavior between the two arms, both of which are jeopardized by unblinding. To formulate a remedy TD, start from first principles of infectious disease where disease acquisition is the result of a complex process that involves prevalence of the pathogen, contact between an infectious agent and an uninfected person, and then transmission. The risk of infection at time \( t \) is approximately the product of these three terms \( p(t)c(t)\pi(t) \). This complexity is important because it makes explicit how disease acquisition depends on the per contact transmission rate, \( \pi(t) \), which might change with human behavior or as new variants of the virus emerge and also the contact rate \( c(t) \) that might change with unblinding.

Another aspect, derived from first principles, is the choice of time index. Typically in treatment trials the time index is given by time since randomization, but with the above formulation, it is clear that a more natural metronome for COVID-19 is calendar time as the prevalence \( p(t) \) waxes and wanes over months and seasons. Use of time since vaccination coupled with changing prevalence and a staggered entry trial can distort the risk sets and lead to nonproportional hazards.
The fix for differential unblinding is by weighting based on the likelihood of unblinding. TD demonstrate that by differential weighting we can recover the vaccine efficacy curve for a blinded placebo controlled vaccine efficacy trial. Reassuringly, the simulations of TD indicate that the Moderna trial has little potential for bias; this is partly due to having a relative short window of unblinding when the Pfizer vaccine was available but before Moderna amended their protocol to provide access to the Moderna vaccine. For other studies, this window is larger and there is more unblinding so simulations evaluating longer and more unblinding would be interesting.

TD derive a hazard-based model for the risk of disease. A criticism of hazard models is that they are not causal and thus inference from them can be unsatisfying. TD provide a nice result in the Appendix that deserves a bit more prominence. They show that the population level hazard rate and population level infection rate are similar under the rare disease setting. Specifically that under a rare disease assumption we can bound the ratio by

\[
(1 - \varepsilon) < \frac{\lambda_0(t)}{\int_\Omega \lambda_0(t)(\omega)dP(\omega)} < (1 - \varepsilon)^{-1}.
\]

4 | GENERALIZATIONS

TD are careful to predict unblinding using baseline covariates. As trialists, we are reflexively wary to incorporate post baseline covariates in a model as they are not ensured to have the same distribution by randomization and can introduce bias. Nonetheless, when trying to correct for post baseline problems this may be worth pursuing. Vaccines tend to induce more reactogenicity which might be useful to predict the risk of unblinding, so post vaccination reactogenicity might be a post baseline covariate worth considering. Additionally, in many of the COVID-19 vaccine trials, COVID is diagnosed by PCR using an assay that also identifies other viral infections such as influenza or rhinovirus. Thus a volunteer who has symptoms and gets tested might be positive for a non-SARS-CoV2 virus. The non-SARS-CoV2 infections could be compared between arms and provide hints about whether celebratory or unblinding bias were a problem. Or a history of non-SARS-CoV2 infections could be assessed as a time-varying covariate to predict unblinding.

Another generalization for the approach of TD would be to allow the vaccine efficacy to depend on baseline characteristics. This could be accomplished by stratifying the approach for different baseline groups, or by specifying a smooth interaction between vaccine efficacy and baseline covariates.

The latest scare with COVID-19 is the emergence of variants. As viruses replicate, mutations occur. With enough replications some mutations that provide a fitness advantage will appear that can then dominate. SARS-CoV2 variants are emerging and the efficacy of the current vaccines to emerging variants is complicated to assess once the placebo group is lost. TD make the important point that without additional data, waning vaccine efficacy cannot be disentangled from poorer efficacy against emerging viral variants.

Fortunately, in these trials, the infecting viruses are genotyped that does allow one to address variants. As trialists, we are reflexively wary to incorporate post baseline covariates in a model as they are not ensured to have the same distribution by randomization and can introduce bias. Nonetheless, when trying to correct for post baseline problems this may be worth pursuing. Vaccines tend to induce more reactogenicity which might be useful to predict the risk of unblinding, so post vaccination reactogenicity might be a post baseline covariate worth considering. Additionally, in many of the COVID-19 vaccine trials, COVID is diagnosed by PCR using an assay that also identifies other viral infections such as influenza or rhinovirus. Thus a volunteer who has symptoms and gets tested might be positive for a non-SARS-CoV2 virus. The non-SARS-CoV2 infections could be compared between arms and provide hints about whether celebratory or unblinding bias were a problem. Or a history of non-SARS-CoV2 infections could be assessed as a time-varying covariate to predict unblinding.

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Fortunately, in these trials, the infecting viruses are genotyped that does allow one to address variants. First, we can apply the developed methods for each strain separately using a strain specific approach. For example, for strain \( s = 0 \) original and \( s = 1 \), a variant that emerges later, we can specify

\[
\text{VE}_s(\tau) = 1 - \exp\{\theta_{0s} + \theta_{1s}(\tau - \ell)\}.
\]

for \( s = 0, 1 \) where \( \tau \geq \ell \).

For a variant \( s = 1 \) that emerges after the placebo group has been vaccinated, \( \theta_{01} \) is not estimable. Even so, one can estimate \( \theta_{11} \) to see if the vaccine efficacy for strain \( s = 1 \), whatever it is, is durable. One can also compare \( \theta_{12} \) to \( \theta_{11} \) to see if waning is similar for the two strains.
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