Rejoinder: Estimating vaccine efficacy over time after a randomized study is unblinded

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1 | INTRODUCTION

We are honored to have our work critiqued by such distinguished, internationally recognized authorities on vaccine efficacy and vaccine trials. When the first author (AAT) was appointed to the Data and Safety Monitoring Board for the U.S. government-sponsored COVID-19 vaccine trials, we were embarrassingly unacquainted with even the basic concepts in this area, starting with the definition of vaccine efficacy (VE), and it was to the fundamental work of these researchers we turned to get up to speed. Responding to the points they raise has enhanced our understanding of the area and the role of our work within it. We comment on the issues raised in each discussion in turn; because all note challenges posed by viral variants, we address this point separately at the end.

2 | JANES, GAO, AND LUEDTKE

Heterogeneity of vaccine efficacy (HVE) and bias. We thank Drs. Janes, Gao, and Luedtke (JGL henceforth) for raising this issue, as they inspired us to think more deeply about the role of heterogeneity. As JGL note, our assumption (ii), \( E\{\pi_1(t, \tau) \mid \mathbf{X}\} / E\{\pi_0(t) \mid \mathbf{X}\} = q(\tau) \), precludes HVE, as we demonstrate shortly. Our assumption of no HVE embodied in (ii) was based on the emerging evidence in the vaccine trials suggesting little variation in VE across subgroups defined by baseline characteristics \( \mathbf{X} \), which, as cited by JGL, persists to the present, as well as scant information on viral variants available at the time. JGL conjecture that the result in our simulations that the methods with stabilized weights equal to 1 yield unbiased inference similar to that obtained with the inverse probability weighted methods, which adjust for possible confounding, could be a consequence of the no-HVE assumption. Their comments are relevant without reference to VE waning, so, for simplicity, we discuss them in the case \( \pi_1(t, \tau) = \pi_1(t) \), so that VE does not depend on time since vaccination \( \tau \). Here, our assumption (ii) of no HVE becomes \( E\{\pi_1(t) \mid \mathbf{X}\} / E\{\pi_0(t) \mid \mathbf{X}\} = q, a \) constant.

In our framework, \( \mathbf{X} \) comprises individual-specific covariates, such as age, gender, and so on; thus, just as \( c^b(t), c^w(t), c^u(t), c^u_1(t), \pi_1(t), \pi_0(t) \) are inherent, individual-specific characteristics of trial participants (albeit unobservable), so are the components of \( \mathbf{X} \). In contrast, viral variants are external forces to which individuals are exposed. We focus here on HVE due to variation in \( \mathbf{X} \) and discuss heterogeneity in VE across variants in Section 5.

As in most clinical trials, interest focuses on population-averaged inference, so on marginal VE in the overall population, which here, from (2) of our article, is \( VE(t) = 1 - R^b(t) = 1 - E\{p(t,S)c^b(t)\pi_1(t)/E\{p(t,S)c^b(t)\pi_0(t)\}\} \). Analogously, \( VE(t, \mathbf{X}) = 1 - R^b(t, \mathbf{X}) = 1 - E\{p(t,S)c^b(t)\pi_1(t)\mid \mathbf{X}\}/E\{p(t,S)c^b(t)\pi_0(t)\mid \mathbf{X}\} \) is VE in the subpopulation defined by \( \mathbf{X} \), if dependent on \( \mathbf{X} \) implies HVE. Under our assumptions (i) and (ii), \( VE(t, \mathbf{X}) = VE(t) = 1 - q \), so there is no HVE, and VE is constant over time. If (ii) is relaxed to \( E\{\pi_1(t) \mid \mathbf{X}\}/E\{\pi_0(t) \mid \mathbf{X}\} = q(\mathbf{X}) \), then under (i) and this version of (ii), \( VE(t, \mathbf{X}) = 1 - q(\mathbf{X}) \) (HVE), and it is straightforward that the marginal VE is \( VE(t) = 1 - R^b(t) = 1 - E\{w(t, \mathbf{X})q(\mathbf{X})\}/E\{w(t, \mathbf{X})\} = E\{w(t, \mathbf{X})VE(t, \mathbf{X})\}/E\{w(t, \mathbf{X})\} \), where \( w(t, \mathbf{X}) = E\{p(t, S)c^b(t)\mid \mathbf{X}\}E\{\pi_0(t) \mid \mathbf{X}\} \), so can be viewed as a weighted average of \( \mathbf{X} \)-specific VEs.

Thus, HVE introduces the complication that marginal VE is time dependent. Inspection of the weights \( w(t, \mathbf{X}) \) suggests that they may not vary substantially over time; for example, it may be reasonable to assume that \( p(t, S) \)
is independent of all other individual-specific quantities and thus factors out of $R^b(t)$, and that the ratio of $c^b(t)$ for two randomly chosen individuals might stay in roughly constant proportion over time, as some are inherently risk-averse and others not. If $w(t,X)$ do not vary substantially, then neither does marginal VE. Accordingly, we discuss JGL’s conjecture under this scenario, as we believe they implicitly intended, by considering estimation of $VE(t)$, equivalently of $R^b(t)$, at a specific time $t$. Taking infection rates and hazard rates to be equivalent as in Section 4.3 of our article, $R^b(t) = E[w(t,X)q(X)]/E[w(t,X)]$ is approximated by the ratio of the marginal hazard rates for potential infection times under vaccine and placebo and is the estimand of interest.

JGL consider the situation where $X$ contains age, $VE(t,X)$ is lower for older individuals (HVE), and such individuals have a higher probability of being unblinded earlier. They assert that the “standard” analysis based on Cox models, which estimates the marginal hazard ratio by the usual partial likelihood estimator and is roughly equivalent to our approach with stability weights equal to 1, will yield positively biased inference on the marginal VE with HVE but consistent inference under no HVE. To gain insight, we consider the implications of the relationship between HVE and the unblinding process for estimation of marginal VE. It is straightforward to show that, if there were no unblinding at all, or if the unblinding probability does not depend on $X$, then the standard analysis leads to a consistent estimator for $VE(t)$ whether or not there is HVE. If the unblinding probability is $X$-dependent, but there is no HVE, JGL contend that the standard analysis and our method with stabilized weights equal to 1 also lead to consistent inference on marginal VE, which could explain our simulation results. We can show, however, that if the dependence of unblinding probability on $X$ is different for vaccine and placebo, then even with no HVE ($q(X) = q$), bias can arise if $E[\pi_0(t)]$ depends on $X$. This is the configuration in our simulations for unblinding in the interval $[T_p, T_c]$, suggesting the potential for bias; we speculate that the negligible bias seen in our simulations is partially due to the shortness (1 week) of this interval. We can also show that, with both HVE and unblinding probability depending on $X$, bias results and is positive when both $q(X)$ and unblinding probability decrease with $X$, as noted by JGL. Our method with estimated stability weights based on correct models for unblinding depending on $X$ leads to consistent estimation of marginal VE whether or not HVE holds.

The foregoing developments are for a fixed $t$. It is well known that, if the proportional hazards assumption is violated, the standard partial likelihood estimator for the assumed constant hazard ratio estimates a weighted average over time of the time-dependent hazard ratio, $R^b(t)$ in our case. If the $w(t,X)$ do not vary substantially with $t$, as above, neither will $R^b(t)$ and $VE(t)$, and this weighted average may have public health relevance. Here, the results above still apply; under no HVE, marginal VE is constant and consistently estimated, and under HVE and $X$-dependent unblinding, the standard analysis will be biased while our methods consistently estimate this weighted average. If instead the $w(t,X)$ and thus $R^b(t)$ and $VE(t)$ do vary nontrivially with $t$, it may be possible to incorporate estimation of the vaccine and placebo hazard rates via nonparametric smoothing.

### 3. HALLORAN

**Potential contact rates as potential outcomes.** Dr. Halloran raises the subtlety of referring to the individual-specific contact rates as “potential outcomes.” In the causal inference literature, ordinarily, a potential outcome is a characteristic that is potentially observable, as for a clinical outcome if an individual were to receive placebo or active treatment. In contrast, the contact rates are conceptual, unobservable quantities, as are the transmission probabilities. Accordingly, $\{c^b(t), c^u_0(t), c^u_1(t) \mid t > 0, \pi_0(t), \pi_1(t, \tau), \tau \geq 0\}$ are similar to unobservable random effects or frailties that characterize heterogeneity across individuals.

**Model for VE waning.** The model $g(u; \theta_1) = \theta_1 I(u > v)$ we used in the simulations is admittedly simplistic, and we chose it to simplify interpretation of the results. Dr. Halloran rightly notes that the analyst must select the change point $v$ at which efficacy is thought to shift, and clearly inference on waning is predicated on this choice. Such a model is the most likely a considerable simplification of a more complex truth under which waning of VE occurs smoothly over time, but it could be a useful tool for preliminary exploratory analysis: one could estimate $\theta_1$ over a range of $v$ to gain insight, then adopt a linear or cubic spline representation with knot selection informed by these preliminary analyses to obtain a more nuanced approximation to smoothly continuous waning (these choices are built-in options in our R package VEwaning). As Dr. Follmann suggests in his discussion, it may be possible to prove that the VE as a function of $\tau$ is nonparametrically recoverable from the data, although sample size considerations may limit the complexity of how $g(u; \theta_1)$ is represented.

**Symptomatic viral infection.** Dr. Halloran points out that the primary endpoint in the Moderna trial is symptomatic COVID-19 infection, but our presentation is admittedly unclear regarding the meaning of “infection” in our potential outcomes formulation. We tacitly take $\pi_0(t)$ and $\pi_1(t, \tau)$ to be the individual-specific probabilities of transmission per contact leading to symptomatic infection.
and thus lump asymptomatic infection with no infection without comment. We thus do not acknowledge explicitly that symptomatic infection results from transmission that, with some probability, results in symptomatic disease. Dr. Halloran rightly raises the issue of how the formulation should be modified to acknowledge this reality. Let \( \rho_0(t) \) and \( \rho_1(t, \tau) \) be the individual-specific probabilities of transmission per contact and \( s_0(t) \) and \( s_1(t, \tau) \) be individual-specific conditional probabilities of becoming symptomatic given transmission, that is, pathogenicity, under placebo and vaccine. Then \( \pi_0(t) = \rho_0(t) s_0(t) \) and \( \pi_1(t, \tau) = \rho_1(t, \tau) s_1(t, \tau) \). Because pathogenicity is a biological characteristic, (i) can be modified reasonably to \( \{ \pi_1(t, \tau), \rho_0(t), s_1(t, \tau), s_0(t) \} \perp \{ S, c^0(t) \} \) and \( \{ \pi_1(t, \tau), \rho_0(t), s_1(t, \tau), s_0(t) \} \perp \{ S, c^u_{01}(t), c^u_{11}(t) \} \). Assumption (ii) is equivalent to \( E[\pi_1(t, \tau)] = \pi_0(t) \) and \( E[\rho_1(t, \tau)] \perp E[\rho_0(t)] \). To modify (ii) to incorporate pathogenicity, one can assume that (ii)(a) \( s_1(t, \tau) \perp \rho_1(t, \tau) \perp s_0(t) \perp \rho_0(t) \) and (ii)(b) \( E[\rho_1(t, \tau)] \perp E[\rho_0(t)] \). (ii)(b) do not depend on \( t \) or \( X \) so are functions only of \( \tau \). Assumption (ii)(b) can be viewed as Dr. Halloran’s speculated constant of proportionality. If one is willing to assume that there is no effect of vaccine on pathogenicity, then \( s_1(t, \tau) = s_0(t) \) at any \( t \) regardless of \( \tau \), and (ii)(b) is unnecessary.

4    |    FOLLMANN

Dr. Follmann provides an excellent example that clarifies the challenges of estimating VE and waning of VE after unblinding and how differential unblinding can lead to biased inference on waning. This example and Dr. Follmann’s nice summary of the main principles underlying our approach in his Section 3 strongly complement our account of the methodology by making the key issues more accessible. We comment on two main points raised by Dr. Follmann.

Celebratory bias. In our formulation, unblinded placebo participants who receive study vaccine engage in behavior represented by \( c^u_{01}(t) \) prior to reaching full efficacy after an interval of length \( \ell \) and then adopt behavior \( c^u_{11}(t) \), whereas unblinded vaccine participants adopt \( c^u_{01}(t) \) immediately. Dr. Follmann suggests that, while unblinded placebo participants now on study vaccine will behave as \( c^u_{01}(t) \) for the efficacy lag interval, unblinded vaccine participants may experience a celebratory interval of length \( C \) during which they engage in more risky behavior, which we could represent in our framework by \( c^u_{1c}(t) \), say. We agree with Dr. Follmann that it is prudent to remove these individuals from the risk sets during the celebratory interval, just as we remove unblinded placebo participants behaving as \( c^u_{01}(t) \) during the efficacy lag interval. Given that \( C \) would be unknown, a possible sensitivity analysis would involve specifying a range of values for \( C \) and examining the stability of the results.

Time-dependent covariate information. Dr. Follmann raises the possibility of exploiting time-dependent, post-randomization covariate information to account for potential confounding, and he provides interesting examples of such covariates. Our methodology readily incorporates time-dependent covariates. Values of such covariates up to time \( \tau \) could be included in the specifications of models for the unblinding hazard functions \( \lambda_{\Psi}(\tau|X, A, E) \), \( j = 1, 2 \); similarly, such information could be incorporated in the model for \( \text{pr}(\Psi = 1|X, E, \Gamma, R) \).

5    |    VIRAL VARIANTS

All discussants note the potential for variability in VE across emerging new variants of the SARS-CoV-2 virus. Dr. Follmann sketches how, given data on viral genotypes from infected trial participants, variant-specific analyses of VE waning can be carried out. We briefly outline how our framework can be modified to allow for such variant-specific inference, using \( \nu = 1, \ldots, \mathcal{V} \) to index \( \mathcal{V} \) variants of interest.

As noted in Section 2, variants are external forces to which individuals are exposed. Thus, prevalence of infection can differ by variant, represented by defining \( p(t, s, \nu) \) to be the prevalence for variant \( \nu \) at time \( t \) at site \( s \). Likewise, in accordance with emerging evidence (e.g., the delta variant), it is natural to take individual-specific transmission probabilities per contact at time \( t \) to differ by variant, denoted by \( \pi_0(t, \nu) \) and \( \pi_1(t, \nu) \) for variant \( \nu \) under placebo and vaccination with study vaccine for \( t > 0 \) time units. We take the contact rates reflecting individual-specific behavior \( c^0(t), c^u(0\nu)(t), c^u_{01\nu}(t), c^u_{11\nu}(t) \) to remain unchanged. The infection rates in the study population at time \( t \) for variant \( \nu \) if all individuals were to receive placebo or vaccine at time \( t - \tau \) are then \( I^0_0(t, \nu) = E[p(t, s, \nu)c^0(t)\pi_0(t, \nu)] \) and \( I^0_1(t, \nu) = E[p(t, s, \nu)c^0(t)\pi_1(t, \nu)] \), and, analogous to (2) of our article, define VE for variant \( \nu \) at time \( t \) after vaccination at time \( t - \tau \) as \( VE(t, \nu) = 1 - R^0(t, \nu) = 1 - I^0_0(t, \nu)/I^0_1(t, \nu) \). Assumption (i) is generalized to \( \{ \pi_0(t, \nu), \pi_0(t, \nu) \} \perp \{ S, c^0(t) \} \), and \( \{ \pi_1(t, \nu), \pi_0(t, \nu) \} \perp \{ S, c^u(0\nu)(t), c^u_{01\nu}(t), c^u_{11\nu}(t) \} \). Similarly, we modify (ii) to reflect the belief that, while VE can vary by variant, within variants, there is no additional HVE associated with components of \( X \); namely, (ii) becomes \( E[\pi_1(t, \nu)|X]/E[\pi_0(t, \nu)|X] = q(\tau, \nu) \). Under (i) and (ii), \( VE(t, \nu) = VE(\tau, \nu) = 1 - R^0(\tau, \nu) = 1 - q(\tau, \nu) \) is the VE for variant \( \nu = 1, \ldots, \mathcal{V} \). Moreover, with
\( I_1^u(t, \tau, \nu) = E[p(t, S, \nu)c_1^u(t)\pi_1(t, \tau, \nu)], \tau \ge \ell, (4) \) of our article becomes \( I_1^u(t, \tau, \nu) = I_1^b(t, \nu)R^b(\tau, \nu)/R(\ell, \nu), \tau \ge \ell \). Representing the variant-specific infection rate ratio \( R^b(\tau, \nu) = \exp[\zeta_\nu(\tau)\ell + \exp[\theta_0\nu + g_\nu(\tau - \ell; \theta_{1\nu})]](\tau \ge \ell), \) where now \( \zeta_\nu(\cdot) \) and \( g_\nu(\cdot; \cdot) \) are variant-specific, we have for \( \tau \ge \ell \), analogous to \( (8) \), \( I_1^b(t, \tau, \nu) = I_1^b(t, \nu)\exp[\gamma_0\nu + g_\nu(\tau - \ell; \theta_{1\nu})], I_1^0(t, \tau, \nu) = I_1^0(t, \nu)\exp[g_\nu(\tau - \ell; \theta_{1\nu})], \) and thus \( VE(\tau, \nu) = 1 - \exp[\theta_0\nu + g_\nu(\tau - \ell; \theta_{1\nu})], \nu = 1, ..., \Psi, \) as given by Dr. Follmann.

To develop the potential times to infection in Section 4.2 of our article, we take a competing risks perspective. Define \( \{T_0^n(e, r), \Delta_0^n(e, r)\} \) to be the time to infection and variant of infection for an arbitrary participant if s/he were to enter the trial at \( e \), receive placebo and be blinded, and, if not infected by \( r \), cross over to study vaccine at \( r \), where \( \Delta_0^n(e, r) \) takes values \( 1, ..., \Psi, \) and \( \{T_0^n(e), \Delta_0^n(e, r)\} = \{T_0^n(e, \infty), \Delta_0^n(e, \infty)\} \) if never crossed over. Define \( \{T_0^n(e, r), \Delta_0^n(e, r)\} \) analogously for a vaccine participant who, if not infected by \( r \), is unblinded at \( r \), and \( \{T_0^n(e), \Delta_0^n(e)\} = \{T_0^n(e, \infty), \Delta_0^n(e, \infty)\} \). Make the consistency assumption \( \{T_0^n(e, r), \Delta_0^n(e, r)\} = \{T_0^n(e), \Delta_0^n(e)\} \) if \( T_0^n(e) < r, a = 0, 1 \). Then for \( a = 0, 1 \), analogous to \( (9) \) of our article, assume the cause-specific (variant-specific) hazard function

\[
\lambda_a(t, e, r, \nu) = \lim_{dt \to 0} (dt)^{-1} \Pr[t \leq T_a^n(e, r) + e < t + dt, \Delta_a^n(e, r) = \nu | T_a^n(e, r) + e \geq t],
\]

\( \nu = 1, ..., \Psi. \)

It is then possible to argue as in Web Appendix C that variant-specific infection rates and hazard rates are approximately equivalent and to express \( \lambda_a(t, e, r, \nu), t > e, \) analogous to \( (10) \) and \( (11) \) of our article for \( \nu = 1, ..., \Psi; \) and defining the counting process for infection by variant \( \nu \) as \( N_\nu^n(t, e, r, \nu) = \{I^n_0(t, e, r) + e \leq t, \Delta^n(t, e, r) = \nu\} \) and \( N_\nu^n(t, e, \nu) = N_\nu^n(t, e, \nu, \nu), \) develop estimating functions in terms of \( \Psi_\nu^n = \{T_\nu^n(e, r), \Delta_\nu^n(e, r); e > 0, r > e\}, a = 0, 1. \)

With the observed data as in \( (1) \) of our article, redefine \( \Delta \) so \( \Delta = 0 \) if \( U > L \) and \( \Delta = 1, ..., \Psi \) according to the infection variant otherwise, and define \( dN(t, \nu) = I(U = t, \Delta = \nu), \nu = 1, ..., \Psi. \) Then, under obvious modifications of the consistency assumptions \( (16) \) and \( (17) \)–\( (20) \), results analogous to \( (21) \)–\( (24) \) hold, and observed data-estimating functions analogous to those in Section 4.4 can be formulated. Defining \( d\tilde{N}_\nu^n(t, \nu), \tilde{Y}_\nu^n(t, \nu), d\tilde{Y}_\nu^n(t, \nu), Z^n_\nu(t, \nu), \) and \( Z^n_\nu(t, \nu), \nu = 1, ..., \Psi, \) as \( d\tilde{N}_\nu^n(t), \tilde{Y}_\nu^n(t), d\tilde{Y}_\nu^n(t), \tilde{Y}_\nu^n(t), Z^n_\nu(t), \) and \( Z^n_\nu(t) \) in Section 4.4 with \( d\tilde{N}_\nu^n(t) \) replaced by \( dN(t, \nu), g(u, \theta_1) \) by \( g_\nu(u, \theta_{1\nu}), \) and \( (\theta_0, \theta_1) \) by \( (\theta_{0\nu}, \theta_{1\nu}), \) one is led to an estimating equation of the form \( (30), \) solution of which in \( (\theta_{0\nu}, \theta_{1\nu}), \nu = 1, ..., \Psi, \) reduces to solving separate equations in \( (\theta_{0\nu}, \theta_{1\nu}) \) for each \( \nu. \)

Elaborating on Dr. Follmann’s final key point, information on a given variant will be available only during time intervals when it was/is in circulation. If these intervals traverse blinded and unblinded periods of the trial, estimation of both \( \theta_{0\nu} \) and \( \theta_{1\nu} \) is possible, whereas, as Dr. Follmann notes, if the intervals are primarily within the unblinded phase, only \( \theta_{1\nu} \) will be estimable, but will still provide evidence of possibly waning for variant \( \nu. \)

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