Review of: "Measuring the efficacy of a vaccine during an epidemic"

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This article addresses an important topic: what measures of vaccine efficacy and effectiveness are truly estimated in clinical trials that are conducted during epidemics? As the authors note, this is a particularly urgent question in light of the COVID-19 pandemic and the vaccine trials conducted therein.

The authors correctly and persuasively argue that a vaccine efficacy estimate, even from a randomized trial, can be biased in an epidemic context if it is based on a cumulative incidence measure. In particular, this bias depends on the duration of the trial and when in the epidemic curve it is conducted, as noted by the authors. While they show that this true mathematically and through simulations, they do not explain *why* it is true, which is what reveals the importance of the question and how to solve it. Implicit in their analysis is a leaky vaccine, which reduces the per-contact transmission probability by a fixed proportion. Since vaccinated individuals may have multiple contacts with infectious individuals over the course of a trial, their actual reduction in risk of any infections is smaller than this proportion, leading to a biased estimate. The number of such contacts depends on trial duration and the fraction infectious throughout the trial, leading to the results observed by the authors. This is an important consideration for interpreting vaccine trials.

This effect, however, is well-known in the field, and has been described numerous times. In particular, Ch. 7 of Halloran et al. (2010), which the authors cite, goes into this phenomenon in some detail. In particular, they note that this is a phenomenon of leaky vaccines, as opposed to all-or-nothing vaccines. The authors need to address this difference in the article, and would do well to cite established literature on the topic. Two recent examples of this phenomenon discussed in regard to COVID vaccine studies include Kahn et al. (2021; DOI:10.1093/aje/kwaa188) and Kahn et al. (2022; DOI:10.1093/aje/kwac015). Even subtler forms of this bias can occur in heterogeneous populations, as discussed in Fay et al. (2022; DOI:10.7326/M21-3609).

More problematic is that this bias is specific to the estimator described in this article, which is not commonly used to evaluate vaccine efficacy. For example, the COVID-19 vaccine primary analyses used either proportional hazards models (Baden et al. 2021, DOI:10.1056/NEJMoa2035389) or adjusted for person-time at risk (Polack et al. 2020, DOI:10.1056/NEJMoa2035389; Sadoff et al. 2021, DOI:10.1056/NEJMoa2101544; Voysey et al. 2021, DOI:10.1016/S0140-6736(20)32661-1). As discussed by Halloran et al. (2010), these do not suffer from the same bias as the estimator comparing cumulative incidences.

This article interestingly raises the possibility of correcting for this bias using coarse measures of infectious fraction

throughout the trial. That could be a useful result if it is described in more detail and comparisons are given to other, more commonly used methods. In particular, that might be more useful outside of the randomized trial setting, where follow-up time or time-at-risk may not be available. Discussion of the performance of such an estimator should be specific about the assumptions of the vaccine mode of action.