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

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Measuring the efficacy of a vaccine during an epidemic

The paper “Measuring the efficacy of a vaccine during an epidemic” by Scala & Cavallo uses a simple SIR model to argue that vaccine effectiveness can be underestimated when measured near the epidemic peak. The authors raise an important point, namely that the outcome of a vaccine trial may be affected by the epidemiology at the site where a clinical trial is conducted, specifically the proportion of infected individuals.

General points:

The paper could benefit from firming up the terminology. First, the authors use non-standard definitions of vaccine efficacy and vaccine effectiveness which may be confusing to readers used to the standard definitions as applied in clinical trial protocols and by WHO, GAVI or the US CDC among others. See e.g.:

https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection

https://www.gavi.org/vaccineswork/what-difference-between-efficacy-and-effectiveness

https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm

The manuscript defines the “true” efficacy of a vaccine as the relative reduction in the transmission rate β. This is a valid operationalisation of vaccine efficacy. In practice vaccine efficacy is defined as the relative risk reduction in a defined outcome measure observed in a controlled randomised clinical trial. In the context of COVID-19 vaccine phase III trials the primary endpoint was frequently the relative reduction in symptomatic laboratory confirmed cases.

This corresponds to Equation 1 on page 3 in the Results section of the paper. However, it seems that the authors use Equation 1 to define vaccine effectiveness η. As the authors rightly observe, vaccine effectiveness refers to the risk reduction in a defined outcome under real-world conditions, for example, in an observational cohort study comparing disease incidence in vaccinated vs unvaccinated individuals. Therefore, vaccine effectiveness is not normally used as an estimator of vaccine efficacy, as they are measured in different contexts.

Estimating the transmission rate β and the relative reduction in the transmission rate achieved by a vaccine is still useful, especially to calibrate models that can be used as part of clinical trial simulations to optimise clinical trial design or for vaccine impact assessments.

Moreover, vaccine “efficacy” and “effectiveness” are not always used consistently as defined at the beginning the manuscript. In lines 84-86, Equation 1 is said to be a term for the “efficacy” but the symbol used η has previously been defined as “effectiveness” and the preceding text also suggests that Equation 1 is an expression of what the authors defined as vaccine effectiveness. In lines 249-250 “efficiency” is used although “efficacy” is probably meant as the text refers to ϵ which was previously defined as vaccine efficacy. In line 269 on page 10 “efficiency” is used although probably “effectiveness” is meant as the methods described refer to the y-axis in Figure 1 which represents the vaccine effectiveness η.

The Discussion and Conclusion are written as if we were still in the early phase of the pandemic. However, most COVID-19 vaccine trials and a number of effectiveness studies have been concluded. Perhaps it would be worth discussing how the theoretical results derived in this study relate to specific empirical results or to studies that have tackled vaccine efficacy and vaccine effectiveness definitions from the statistical point of view, e.g. https://doi.org/10.1016/S2666-5247(21)00069-0

Although the analysis presented in this manuscript was conducted with COVID-19 in mind, many more infectious diseases for which vaccines are currently under development are outbreak- or epidemic-prone. It may be helpful to extrapolate the conclusions from this study to other diseases for which clinical trials are still ongoing or planned, e.g. Ebola, dengue, RSV.

Specific points:

In the second sentence in the Abstract, “We show that” is repeated.

In line 57 the name of the first author of reference 10 is spelt “Hallorane” but in the reference itself it is “Halloran”.

In line 195 the term “biological efficacy of the vaccine” is used and contrasted with the efficacy of the vaccine measured in clinical trials. It would be helpful to clearly articulate what is meant by “biological efficacy”.

The stochastic model to simulate statistical fluctuations in measured vaccine effectiveness uses a Poisson process. However, SARS-CoV-2 transmission has been observed to be highly overdispersed (including so-called “super-spreading” events, see Endo *et al.* 2020 doi: 10.12688/wellcomeopenres.15842.3). Is it possible that the Poisson process underestimates the stochasticity affecting measures of vaccine effectiveness?

In various places in the text, it happens that the adjective “infectious” is used in isolation and should be replaced by the noun “infections” or in conjunction with a noun, e.g. “infectious individuals”.

Line 158-164: It is not clear how digital contact tracing data will support the evaluation of vaccine side effects.

The statements in lines 164-170 are repetitive.

Lines 173-175: This is why in blinded randomised clinical trials participants are not told if they have been vaccinated with the candidate vaccine or placebo. The argument is more applicable to observational cohort studies in which individuals

know which vaccine they received.

Depending on the target audience of the paper, it may be helpful to explain the theory behind the expansion of Equation 4 into Equations 5 and 6. This could be done in the form of a short appendix.

In reference 27 the name of the first author is missing the umlaut ü.