

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

Shalome Hanisha Tatapudi¹

¹ University of South Florida

Potential competing interests: No potential competing interests to declare.

The authors highlight a very important factor that results in incorrect estimation of vaccine efficiency identified in clinical trials and applied to the general population. They also mention the complex and multi-faceted nature of the factors and problems they are studying. However, I found the analysis and results to be over-simplified and not granular enough to capture the solution to the problem. Although the outcomes of vaccine effectiveness depend on the time of the trial and the proportion of infected people, the simplifying assumptions made to estimate these factors may not be enough to enable a policymaker in informed decision-making. The long introduction and explanation of terms don't help clarify the methods and results section. I would suggest the authors re-evaluate what they want to convey, who it might be useful for, and how, and perform a more comprehensive analysis.

General

1. The paper has grammatical errors that need revision.
2. The paper is not always well structured, and things explained are most times out of order, written redundantly, or read like they were written in a hurry, which creates a lot of confusion for the reader. I would suggest they write each sentence very deliberately, understanding what was written before, what is written after, and what it conveys to the paper.
3. Errors throughout the paper that, if corrected, could greatly improve the quality of writing. Some examples are:
 - a. *"The efficacy is not known a priori,..."*
4. Sentence formation at times is redundant or not well structured. Some examples are:
 - a. *"The basic reproduction number allows to estimate the herd immunity threshold (HIT), i.e. the fraction $p^* = 1 - 1/R_0$ of immune individuals beyond which no epidemic overburst can happen [9]."* This could be rewritten as follows, *"The basic reproduction number allows estimating the herd immunity threshold (HIT), i.e. the fraction of immune individuals beyond which no epidemic overburst can happen, defined as $p^* = 1 - 1/R_0$ [9]."* I think both of these sentences convey different information, please be sure to use the one that makes the most sense to you and conveys what the authors are thinking.
 - b. *"The vaccine rush caused by the COVID19 pandemic has led to perform clinical trials with procedures that reflect the exceptional circumstances [1] and to the establishment of unprecedented public-private partnership [2]."* This could be rewritten as follows, *"The vaccine rush caused by the COVID19 pandemic has led to performing clinical*

trials with procedures that reflect the exceptional circumstances [1], and to establishing unprecedented public-private partnership [2].” The verbs “performing” and “establishing” must be in the same tense to structure this statement the way you had intended it to read.

- c. *“As noted by Hallorane et al [10], to avoid that equivalent populations with the same transmission conditions could yield different efficacy estimates, the amount of exposure to infection should be taken into account either by study design or by mathematical modeling.”* This can be rewritten as follows *“As noted by Halloran et al [10], to avoid the problem of yielding different efficacy estimates despite using equivalent populations under the same transmission conditions, researchers should consider accounting for the amount of exposure to infection, either by study, design, or mathematical modeling.”*

Abstract

1. “we show that when” is repeated
2. “...even in absence of confounding factors,” it would help to mention some of the factors

Introduction

1. Line 10: the starting apostrophe for instructing is incorrect
2. The introduction is well-written, and the objective is clearly stated in the first paragraph.
3. “especially troublesome low- and middle-income countries”, please clarify why you use the word “troublesome”. Is it because the effectiveness studies are difficult to implement or other specific reasons?
4. The paper by Halloran et al. is not cited correctly.
5. This sentence needs to be rewritten. *“However, what happens if clinical trials are performed on large cohorts and during an epidemic, so that it is possible that “optimal conditions” cannot be strictly enforced?”*
6. This is a very long sentence and the message the authors are trying to convey is not clear. Please break it down into several, more meaningful statements. *“To isolate the effect of pursuing clinical trials during an ongoing epidemic, we will consider the theoretical case where no confounding factors [6,7] intervene in the effectiveness – measured as the experimental ratio of infected individuals in a vaccinated and a placebo cohort – showing in long trials performed during an ongoing epidemic the effectiveness underestimates the vaccine efficacy; such underestimation grows both with the fraction of infectious individuals present in the population during the experiment and with the severity R_0 of the infection.”*
7. Although I like the explanation of the terms, such as vaccine efficacy, vaccine effectiveness, relative risk, reproductive number, and HIT, the paper lacks a background into existing work and why the research done here is important. What value would this research convey and who can use this, and how can they use this? Please state these carefully.

Results

1. Figure 1:
 - a. Please clarify if Figure 1 is based on Equation 1 or 4.

b. Please add a legend for the black line and red dots within the image.

Methods

1. The methods are not clearly explained. First explain the SIR model used by the study, the various components, and how they are solved.
2. Why doesn't the study consider the unvaccinated population when measuring vaccine effectiveness in the whole population?