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

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Potential competing interests: Sanofi employee

We would like to thank you for the opportunity to review this manuscript. The paper by A. Scala and P. Cavallo presents a mathematical model to describe time dependence of efficacy grows of COVI19 vaccination.

The presentation of the manuscript generally is simple, easy to follow, and informative. However, in its whole, this article seems more an opinion view than a research article (like most of the cited references) as it is poorly argued and discussed regarding literature on the prevention management by vaccination during emergencies. Authors would be welcome to review their models with more realistic parameters, such as the impact of variants on infectious rates, impact of RT-PCR false positive on accuracy of number of infected individuals, impact of potential immune escape on efficacy of coronavirus-based vaccines, etc… For such a subject the manuscript does not seem acceptable without major revision with critical points.

Abstract:

“We show that we show…” must be rephrased.

page 1 line 4-7:

a) When the term efficacy it used, it is necessary to precise efficacy to prevent transmission/infection, to prevent hospitalization for acute respiratory syndrome? Is efficacy considered by the different manufacturers the same (which criteria) and could the author really compare?

b) It is now well established that the efficacies firstly announced by manufactured are much lower in real-life**It is a major point of revision** to take into account the actual efficiencies (eCDC, Feikin et al) as well as the fact that the vaccine does not impact on SARS-CoV-2 infection (Mehrotra et al). The vaccines efficiencies were therefore initially over-estimated and the epsilon transmission factor needs to be reconsidered or corrected. These two points need to be discussed in the light of the bibliography and the reasoning that follows should be reviewed over the whole manuscript, as it affects the modelling, its parameters and its interpretation.

page 1 line 7-12:

Here authors prevent mentioning a key point about the epidemic dynamics specific to each strain, which are very variable as we have seen with the SARS-CoV-2 variants. To be integrated in the Introduction section.

page 1-2 line 20-26:

a. “a vaccinated person has a probability δ times lower of getting infected” statement is wrong replace by “1/ δ times lower” or by “δ times that of an unvaccinated person” in addition ϵ is an average over the whole vaccinated population not an individual probability.
b. Authors applied general rules for transmission rate without considering coronavirus specificities, especially their high ability to create mutants. This point needs to be integrated to adjust transmission rate calculation, considering that successive mutants were more and more easily transmitted in populations. Furthermore, knowing now that COVID19 vaccination didn’t really prevent transmission, the d parameter must be reviewed as it is based on a too simpler hypothesis for coronaviruses.
c. Another major point avoided from authors is immune escape that could be induced by vaccination with non-circulating S protein (variants). Authors must include this point in their models, integrate references (for example: Hu, J., Peng, P., Cao, X. et al. Increased immune escape of the new SARS-CoV-2 variant of concern Omicron. Cell Mol Immunol 19, 293–295 (2022). https://doi.org/10.1038/s41423-021-00836-z) and at least consider it in Introduction and Discussion sections.
d. Knowing that successive variant mutations led to lower virulence of viruses and various transmission rates (decreasing with time), a dedicated parameter must be considered in models to reach more realistic descriptions of vaccine efficacy.

page 2 line 34: “In large cohort (i.e. phase III) studies”: please specify because it’s not the case for the 2 mRNA vaccine clinical RCT trials. What is the meaning of “fraction of infectious individual” (precise the virus each time the infection notion is used in the manuscript: “fraction of Covid-19 infectious individuals”): symptomatic (moderate, severe?) PCR positive?

page 2 line 42-44: The reasoning is too simplifying as we heard a lot for vulgarization purpose. Need to refine this because the R0 is extremely variable. List and discuss the impacting factors.

page 2 line 37-52:

a. Give some more references for this part.
b. “… the lower the efficacy, the higher the fraction of individuals to vaccinate.” Needs to be moderated considering that increasing the fraction of individuals to vaccinate don’t improve efficacy of vaccines since R0 is high.

page 2 line 45 “The efficacy is not known a priori, but must be estimated through an experimental procedure”: precise who use this experimental procedure and if it’s the same procedure for pharmaceutical industry, health authorities etc.

page 2 line 55 “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?”. **It is a major point of revision** to consider the reflection of several years (*e.g.* R. Rappuoli) on the acceleration of the vaccine development, clinical included, to be more effective in the implementation of a prevention at the time of emergences which considered then known vaccine platforms unlike the mRNA Covid-19 vaccine.

page 2 line 57-60 must be moderated as the cited reference [10] was about HIV vaccines, maybe not transposable to Covid vaccines.

page 2 line 61-67:

a. “showing in long trials performed during an ongoing epidemic the effectiveness underestimates the vaccine efficacy” Why in the case of the Covid-19 vaccines the vaccine efficacy has been so much over-estimated (and reevaluated overtime): please develop a new discussion part with appropriate literature.
b. “… measured as the experimental ratio of infected individuals”. To clarify how infected individuals were defined. If authors thought about PCR tests, they must consider false positive results obtained with a such methodology and their impacts on models. Dedicated paragraphs and references must be added (for example https://doi.org/10.1016/S2213-2600(20)30453-7).

page 5 Fig. 2: Curves for lower ϵ (down to 0.6) must be added and commented.

page 5 line 141 “to set new standards for valid clinical trials in humans”; no need to change standards that have taken decades years to be refined and by time-tested! Since, no scientific consensus is reach, developing in a rush cannot become a standard at all. Please reformulate.

As already mentioned above, no words about the fact that the transmission was not reduce in the case of the COVID-19 vaccines: how the model proposed by authors could deal with this specific case, prevent it or fix it?

Page 6 line 149 Which “indirect effects” means? adverse effects? Please specify (and give examples) because it’s not defined anywhere and correct the wording in the whole manuscript. Explain how they will be taken into account?

Page 6 line 158 « digital contact tracing » could be an expensive option while some applications are already used to collect data on a regular basis. Please extend the purpose with references.

Page 6 line 165 “we have shown that starting to collect more reliable coarser data, like the fraction of infectious individuals in a population, would greatly help interpreting the results of medical trials”. This is where the discussion should start indeed: consolidated data on infection that are long to obtain (how to consolidate them faster? -with references) and the nature/quality of the data that is needed to properly interpret the current epidemic.

Page 6 line 169 “could help to correct phase III” why only phase III?

Page 6 line 175 “vaccinated people may alter their habits if they believe the vaccine is protective” Of course, the vaccine definition means infection protection. How would contact pattern could be integrated in the modelling as it should be included in the R0? Please, detail and discuss.

Page 6 line 183 “partial immunity acquired”: there is an acquired immunity or not. Delete “partial”.

Page 6 line 189 “such an issue has not been fully addressed before” another time, there is literature on using prevention during epidemics

Page 6 line 185 "our study concentrates on the systematic decrease on the estimated vaccine effectiveness in large cohort studies due to the presence of a high number of infectious individuals in the population." This sentence opens the door to multiple interpretations leading to very low confidence in developed models. Authors would be welcome to review their models with more exhaustive parameters, as listed above (i.e. impact of variants on infectious rates, impact of RT-PCR false positive on accuracy of number of infected individuals, impact of potential immune escape on efficacy of coronavirus-based vaccines, etc…).

Page 7 line 193 “most models of epidemics do not differentiate between infection and disease”. This notion come too late, *a minima* it must be discussed otherwise presented in the introduction. Make a parallel with diagnosis nature. Furthermore, considering that Covid-19 mainly impacted fragile (comorbidity) and old populations, notion of over-mortality covering at least last decade must be introduced and discussed to better develop models able to differentiate between infection and disease.

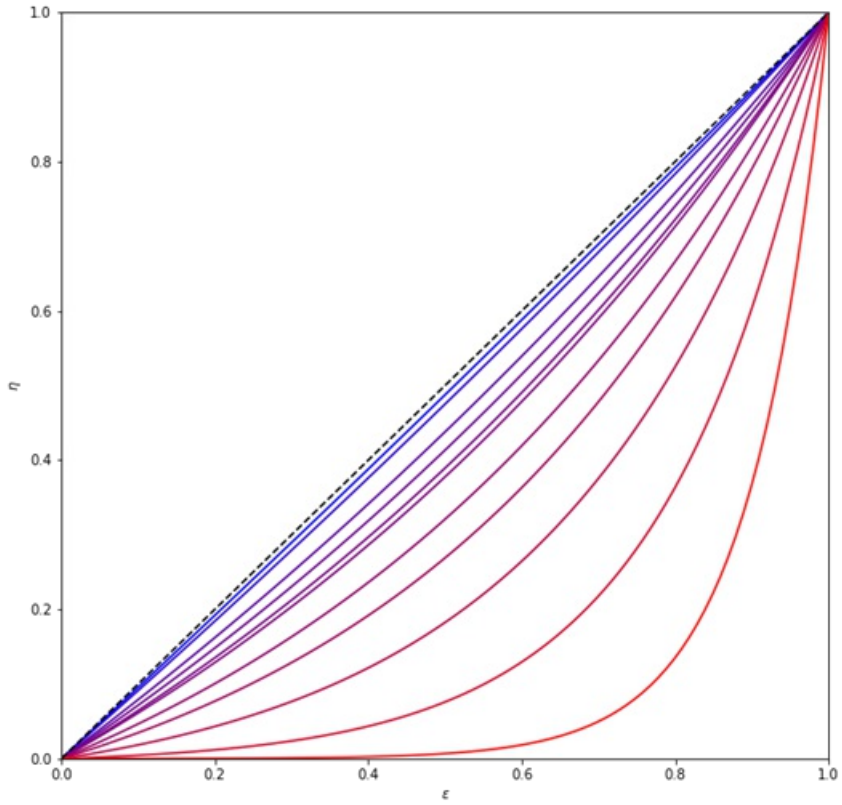
Page 7 line 199-215 These developments should take place in the discussion. Add the fact that the antibody could rapidly vanished as observed, that the pathogen could escape with another dynamics.

Page 7 line 213 “Thus, for two trials - one before the epidemic peak, the other after - with identical time-spans and attack rates, we expect a lower estimate of the vaccine efficacy (*i.e.* a larger systematic error) for the trial in the decreasing phase.” This sentence corresponds to the starting work hypothesis. Please reword the conclusion.

Page 7-8, Line 239-250:

a. η is referred to as tree different parameters, namely “efficacy” (i.e. Eq. 1), “measured effectiveness and “observed effectiveness”. Authors should clarify this point to prevent misunderstanding, considering that ϵ is also referred to as “efficacy”.
b. Regarding mathematical methodology, an average probability was used. However, a probability distribution would be more realistic. What append if the efficacity ϵ is expressed as a probability distribution over the patients (including vaccine failure and variation in the efficacity) instead of an average probability? This question must be addressed and, if possible, answer to improve confidence in developed models.
c. From Equation 4 it is possible to plot the relation between η and ϵ for various values of βc.

Figure below displays relation between measured effectiveness and efficacy from equation 4. High values of βc in red and low values in blue. This plot should be included in addition/replacement of equations 5 and 6.



In the Method section, as previously highlighted, modeling must integrate the epidemic dynamics specific to each strain, which are very variable as we have seen with the SARS-CoV-2 variants, and obviously this must be based on real data in order to better adjust the modeling.

Please address all correspondence concerning this manuscript to me. I would be happy to contribute.