Identifying vaccine-mechanism bias in mathematical models of vaccine impact: the case of tuberculosis

Mario Tovar[1,2], Yamir Moreno[1,2,3] & Joaquín Sanz[1,2]

1. Institute for Biocomputation and Physics of Complex Systems (BIFI), University of Zaragoza, Zaragoza 50009, Spain.
2. Department of Theoretical Physics, University of Zaragoza, Zaragoza 50009, Spain.
3. Centai Institute S.p.A, Corso Inghilterra 3, 10138 Torino, Italy

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Background: Despite the decay in Tuberculosis (TB) incidence and mortality achieved worldwide since 1990 [3], its yearly rate of reduction is arguably too slow to meet the goal settled by the World Health Organization (WHO) in the End-TB strategy, which consists of completing a reduction of TB incidence and mortality rates by 90% and 95%, between 2015 and 2035 [8]. Instead, during 2020, and for the first time in decades, the world suffered an increase in global TB burden levels with respect to previous years, while, during that same year, the WHO estimated that TB was the cause of death of more than 1.5 million people worldwide, combining HIV negative and positive cases [5].

The cause of this increase was the irruption of the COVID-19 pandemics, which threatens, in countries like India or Indonesia, to raise the TB death toll back to even higher levels in the next few years [1, 7]. This issue, alongside with the ever-increasing rates of emergence of drug resistance [4], evidence the need of new epidemiological interventions and tools against TB. Among those tools and interventions, the development of a new and better vaccine than the current bacillus Calmette-Guerin (BCG) seems necessary, as in the former, the efficacy against the more transmissible respiratory forms of the disease in young adults is disputed [2].

For such a task, specially on TB, where several candidates are under development, a robust impact forecast which is based on epidemiological model arises as a powerfully tool to help evaluating those vaccines before introducing them in the general population. Nonetheless, in the development of vaccines against TB, a number of factors represent burdensome difficulties for the design and interpretation of randomized control trials (RCTs) of vaccine efficacy. Among them, the complexity of the transmission chain of TB allows the co-existence of several routes to disease that can be observed within the populations from where vaccine efficacy trial participants are sampled. Ultimately, this makes it difficult to derive mechanistic descriptions of the vaccines in terms of the mathematical model if only trial-derived readouts of vaccine efficacy are used. This happens since, intuitively, the same efficacy readouts may lean on the ability of a vaccine to arrest only some, but not all, the possible routes to disease. This increases uncertainty in evaluations of vaccine impact based on transmission models, since different vaccine descriptions of the same efficacy readout typically lead to different impact forecasts.

Methods: Aiming to address some of the difficulties in translating real RCTs results to spreading models, in this work, we develop a Bayesian framework to evaluate the relative compatibility of different vaccine descriptions with the observations emanating from a randomized clinical trial of vaccine efficacy. This offers an unbiased framework to estimate vaccine impact even when the specific mechanisms of action of the given vaccine are not explicitly known, providing a more agnostic impact evaluation of those vaccines.

The method we propose combines *in-silico* trials of the real RCT with a Bayesian framework that allows to capture the realtive compatibility of the vaccine descriptions with the real outcome of the trial. For this, we first proposed 7 different vaccine descriptions that capture the three routes to disease that might be observed in TB and in a IGRA-positive trial, which are related to natural TB history, and then simulated each one of them in the context of the RCT. Then, we compute the relative compatibility of each vaccine descriptions with the real results along with

the most probable intrinsic-efficacy value (ε) which can be used directly in the spreading models to model such a vaccine. Using our methodology, we analyzed the results reported for the vaccine M72/AS01$_E$ clinical trial as a case study [6].

Results: We applied our bayesian framework to the case study in order to weight the relative compatibility of each one of the possible mechanistic effects of the vaccine that might be observed in an IGRA-positive trial. Figure 1 shows the core results of this procedure in which, first, we produced *in-silico* simulations for a myriad of possible intrinsic-vaccine efficacy (those are the spreading model-related efficacies of the vaccine) in the RCT, which are reported in the clouds. Then, we applied the Bayes rule to those clouds for deriving the posterior probabilities of both the intrinsic efficacy values, that are introduced later in spreading models, and the relative compatibility of the whole mechanistic decription with the real efficacy of $\text{VE}_{dis} = 49.7\%$ observed in the trial.

Those posterior probabilities, that are shown in Figure 1 B and C, enables the possibility to forecast the impact of the vaccine using an spreading model, as we get the most compatible value of ε, that captures the intrinsic efficacy of the vaccine in the model, along with the overall compatibility of this description with the real outcome of the trial. Moreover, we derived an agnostic estimate of the impact of the vaccine using the posterior probabilities reported in Figure 1 B to produce a weighted forecast that is agnostic to the mechanistic description of the vaccine.

Conclusions: This work enlightens the problem of translating the outcome of TB vaccine's RCTs to the spreading models while aiming to produce robust forecast impact evaluations. We shown here that, even in cases with high uncertainty, such as the case study, a clean-well designed procedure allows to disentangle the effect of the vaccine at the mechanistic level. This, ultimately, leads to the possibility of producing agnostic impact evaluation of new vaccines, which reduces the gap betweeen reality and models. Moreover, the type of RCTs considered here, conducted on IGRA-positive individuals, emerged as a promising design architecture after the encouraging results reported for the vaccine M72/AS01$_E$ clinical trial, as they might also be analyzed with this -or a similar- method to improve our knowledge of the effect of a new vaccine, both at the biological level, at the model level, and at the population level.

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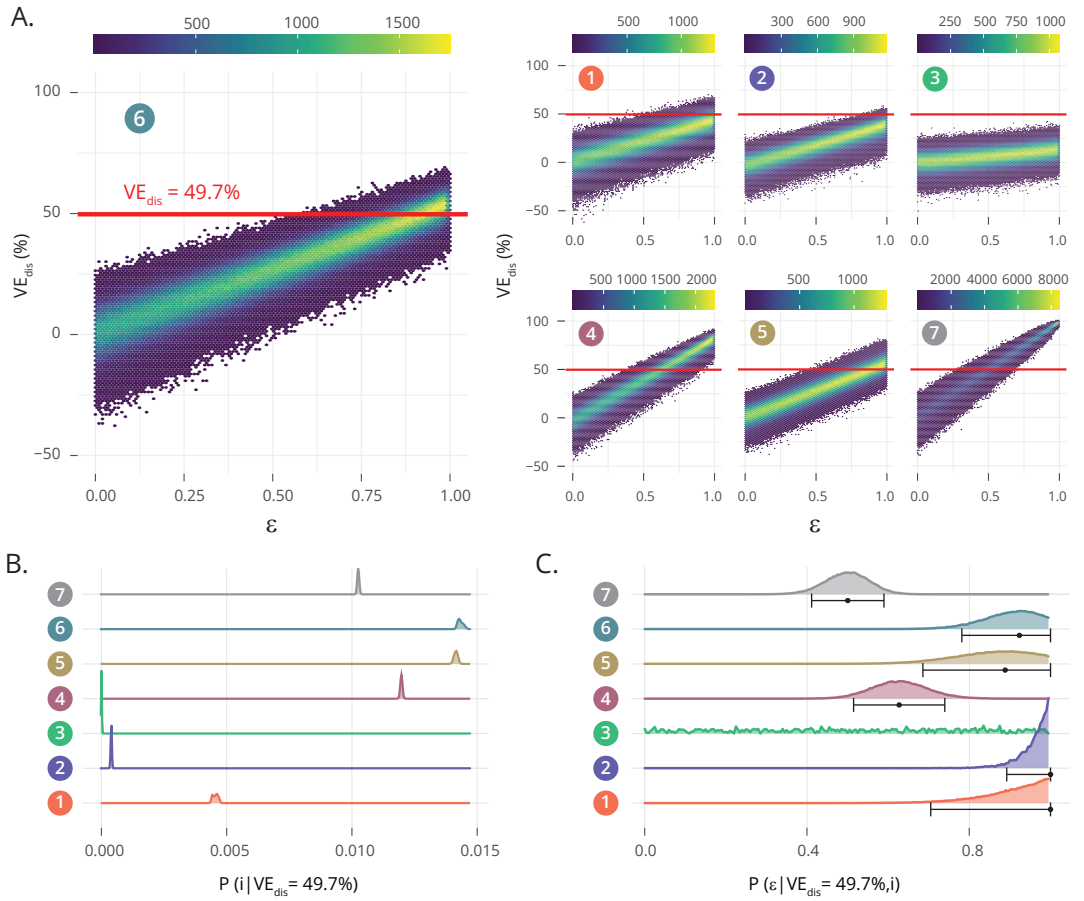

Figure 1: Bayesian analysis of possible modeling architectures underlying a trial-derived observation of vaccine efficacy. **A:** Absolute frequency density clouds of efficacy values VE_{dis} obtained in sets of $N = 2 \cdot 10^6$ clinical trial simulations per model, uniformly distributed across the intrinsic vaccine efficacy parameter ε(10000 points for each ε value, yielding $N = 2 \cdot 10^6$ points inside the cloud). Red horizontal lines mark the PoD efficacy observed in the M72/AS01$_E$ trial $\mathrm{VE}_{dis} = 49.7\%$. **B:** Marginal posteriors $P(i|\mathrm{VE}_{dis} = 49.7\%)$, capturing the relative compatibility of each model with respect to the efficacy observed in the M72AS01E trial. **C:** Distribution $P(\varepsilon|\mathrm{VE}_{dis} = 49.7\%, i)$ of the intrinsic vaccine efficacy parameter ε in each model type, given the observed efficacy $\mathrm{VE}_{dis} = 49.7\%$, along with mean and 95% confidence intervals associated to them. For M3, the CI was omitted, for it spans the entire range $\varepsilon \in [0, 1]$, as the model fails systematically to produce simulation instances compatible with the observed $\mathrm{VE}_{dis} = 49.7\%$.