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Analysing vaccine efficacy evaluated in phase 3 clinical trials carried out during outbreaks

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ABSTRACT

In this paper we examine several definitions of vaccine efficacy (VE) that we found in the literature, for diseases that express themselves in outbreaks, that is, when the force of infection grows in time, reaches a maximum and then vanishes. The fact that the disease occurs in outbreaks results in several problems that we analyse. We propose a mathematical model that allows the calculation of VE for several scenarios. Vaccine trials usually needs a large number of volunteers that must be enrolled. Ideally, all volunteers should be enrolled in approximately the same time, but this is generally impossible for logistic reasons and they are enrolled in a fashion that can be replaced by a continuous density function (for example, a Gaussian function). The outbreak can also be replaced by a continuous density function, and the use of these density functions simplifies the calculations. Assuming, for example Gaussian functions, one of the problems one can immediately notice is that the peak of the two curves do not occur at the same time. The model allows us to conclude: First, the calculated vaccine efficacy decreases when the force of infection increases; Second, the calculated vaccine efficacy decreases when the gap between the peak in the force of infection and the peak in the enrollment rate increases; Third, different trial protocols can be simulated with this model; different vaccine efficacy definitions can be calculated and in our simulations, all result are approximately the same. The final, and perhaps most important conclusion of our model, is that vaccine efficacy calculated during outbreaks must be carefully examined and the best way we can suggest to overcome this problem is to stratify the enrolled volunteer's in a cohort-by-cohort basis and do the survival analysis for each cohort, or apply the Cox proportional hazards model for each cohort.

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1. Introduction

Loria et al. (2023), in a recent paper calculated the variation of the estimated vaccine efficacy (VE) resulting from the time interval between the moment the Clinical Trial (CT) begins and the moment when the peak in the outbreak intensity occurs. Using a simple mathematical model, the authors tested the hypothesis that the time difference between the moment the CT begins and the peak in the outbreak intensity determines substantially different values for VE.

In this paper, we examine several definitions of vaccine efficacy that we found in the literature (Halloran et al., 1997; Piatadosi, 1997; Bewick et al., 2004; Halloran et al., 2010, Cox DR and OakesD, 1984). In the paper by Loria et al., 2023, the authors did not use a survival analysis approach, in the sense that data were not organized according to the so-called time-to-event (Kelinbaum and Klein, 1996, Lee & Wnag, 2003, Sullivan, 2023 [https://sphweb.bumc.bu.edu/otlt/mpmodules/bs/bs704_survival/index.html], but rather used the calculation of the attack rate among vaccinated individuals as related to the attack rate among placebo individuals, regardless of the moment individuals are enrolled into the trial (see below).

The proposed a model in this paper allows the calculation of vaccine efficacy according to all definitions present in the literature (Halloran et al., 1997; Piatadosi, 1997; Bewick et al., 2004; Halloran et al., 2010, Cox DR and OakesD, 1984).

The paper is organized as follows. In the third section we examine the different protocols of the clinical trials for vaccine efficacy reported in the literature and critically comment specific aspect of the survival analysis approaches for the calculation of vaccine efficacy. In section four, we describe the mathematical model used in this work. This model allows the simulation of all the clinical trials protocols mentioned above. In the fourth section, we calculate the vaccine efficacy for a hypothetical vaccine in a context in which the force of infection varies with time (outbreak), for four different trial protocols. In section five we show the results of the model simulations. Finally, the last section discusses our results and conclude the paper.

2. Vaccine trial protocols: enrollment of volunteers and vaccine efficacy definitions

2.1. The enrollment process

A vaccine trial begins by drawing two similar groups of volunteers. One of the groups will receive the vaccine and the other the placebo. Typically, we need a protocol of the type called randomized, double-blind, placebo-controlled clinical trial (Halloran et al., 1997; Piatadosi, 1997; Bewick et al., 2004; Halloran et al., 2010, Cox DR and OakesD, 1984). Both groups should represent the population for which the vaccine is aimed. It is common that the two groups of volunteers should have a minimum size to guarantee the power of test. When the disease manifest itself in outbreaks there are some problems in realizing this protocol that will be addressed by this paper, and described below.

Ideally, a vaccine trial should be carried out as follows: All volunteers are enrolled at the same time, that is, in as short period of time as possible (say, one day). Then, the volunteers are followed for a given period. This guarantee that all the volunteers are subjected to the same force of infection, regardless of if it varies with time or not. When the enrollment process is like the one described above, one would interrupt the trial at moment T and count the number of individuals infected in each of the groups since the beginning of the trial. This limited duration of the trial is due to two reasons: First, the total number of infections must reach a threshold that guarantees the power of the test, and so the trial is interrupted. Second, by

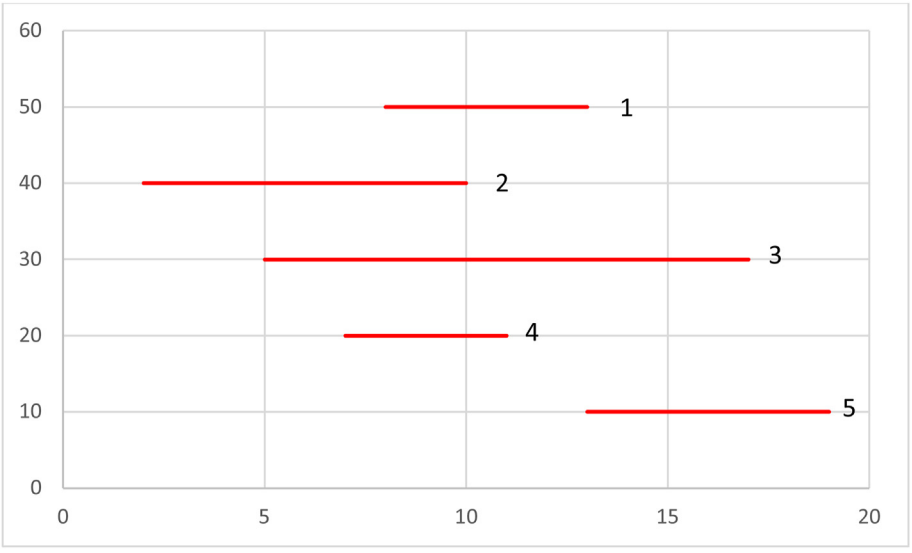

Fig. 1. Entry and withdrawal of five enrolled volunteers in a simulated trial.

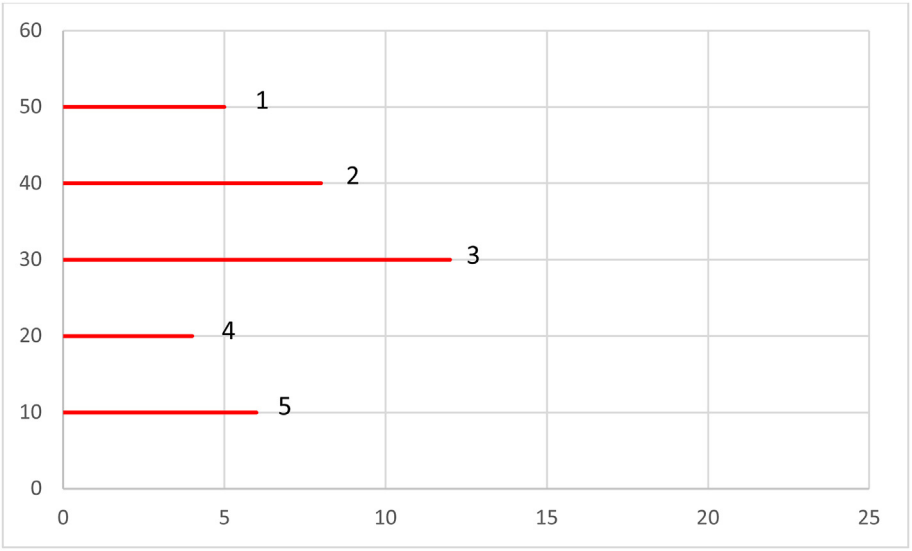

Fig. 2. Redrawn of Fig. 1 so all subjects have a common starting date.

ethical reasons one should not expect more than the necessary time to eventually offering the vaccine to the placebo group. These ethical aspects are particularly critical when the vaccine had already demonstrated some efficacy (Jalilian et al., 2023). With this time protocol, the two groups suffer the same attack rate of the infection (the force of infection, defined latter), vaccine efficacy is easier to estimate.

However, for logistical reasons it is generally impossible to enroll all the volunteers at once, and the latter are enrolled during a time interval, that is they are sampled according to a time dependent distribution. If the number of volunteers is large the time distribution may be very wide. Hence, the enrollment is done in cohorts, and one of the consequences of the time-distribution rate of the enrollment rate is that individuals who enter the trial near the end of the recruiting process suffer less from the infection. This happens when we are dealing with an outbreak in which the force of infection varies with time, like the recent outbreaks of covid-19.

When the force of infection is constant in time, survival analysis organizes the enrollment process (Fig. 1), and subsequent events, according to the time-to-event. Fig. 1 represents what occurs.

In Fig. 2, all the above cohorts are ordered by time-to event.

Fig. 3. Same five enrolled volunteers as in Fig. 1 showing that each one suffers a different force of infection.

If the force of infection is constant, this guarantees that individuals enrolled either in the beginning or the end of the trial are subject to the same risk of infection. When the trial is carried out during an outbreak, however, individuals enrolled in different moments along the trial will be subject to different intensity of the infection. Therefore, organizing data according to time-to-event does not guarantee that enrolled individuals suffer the same risk of infection. In fact, as can be seen in Fig. 3 below, each of the cohorts suffer a different burden of the infection.

The survival analysis (using the Cox proportional hazard model) does not assume that the force of infection is constant in time, but in the literature, it is assumed that this force of infection is the same for all the **times-to-event**, which is false for the situation involving outbreaks. Of course, what the Cox method assumes is that the ratio of the force of infection among treated and among controls is constant in time. In addition, the model assumes proportional hazards, that is, the hazard suffered by vaccinated individuals is proportional to the hazard suffered by individuals who received the placebo, which, although reasonable, is not guaranteed. In our model, described below, the ratio between the hazards suffered by vaccinated is proportional to the hazard suffered by placebo injected individuals, although the hazards themselves are different for different **times-to-event**. Let us elaborate our argument.

Consider two different cohorts of vaccinated and placebo individuals, represented, for instance by cohorts 2 and 5 in Fig. 3.

Let us assume that for cohort 2 the forces of infection for vaccinated and placebo individuals are $\lambda_v(t)$, and $\lambda_{pl}(t)$, respectively. Then, the survivals, or at risk, obey

$$S_v(t) = S_v(0)e^{-\int_{t_0}^{t} \lambda_v(s)ds}$$

and

$$S_{pl}(t) = S_{pl}(0)e^{-\int_{t_0}^{t} \lambda_{pl}(s)ds}$$

Then, the ratio is given by

$$\frac{S_v(t)}{S_{pl}(t)} = e^{-\int_{t_0}^{t} \left(\lambda_v(s) - \lambda_{pl}(s)\right)ds}$$

The same ratio for cohort 5 is:

$$\frac{S'_v(t)}{S'_{pl}(t)} = e^{-\int_{t'_0}^{t'} \left(\lambda'_v(s) - \lambda'_{pl}(s)\right)\right)ds}$$

Note that the ratios are different because the limits of the integrals are different.

These ratios are different, even if we assume that $\lambda_v(t)$ is proportional to $\lambda_{pl}(t)$ at any time, in which case, we have (see the fourth definition of VE below)

$$\lambda_v(t) = \alpha\lambda_{pl}(t)$$

and

$$\frac{S_v(t)}{S_{pl}(t)} = e^{-(1-\alpha)\int_{t_0}^{t} (\lambda_v(s)ds)}$$

which differs from

$$\frac{S'_v(t)}{S'_{pl}(t)} = e^{-(1-\alpha)\int_{t'_0}^{t'}(\lambda_v(s)ds)}$$

because of the limits of the integration, even when $(t - t_0) = (t' - t'_0)$.

It should be clear that when the forces of infections are time-independent, the ratios are equal for equal times-to-event, that is, $(t - t_0) = (t' - t'_0)$.

Therefore, for the case of outbreaks, the hazard ratios may be proportional but are not constant in time.

2.2. The definitions of vaccine efficacy

There are several ways to define vaccine efficacy in the literature (Halloran et al., 1997; 2010, Piantadosi, 1997). Table 1 shows the most common adopted definitions. The first three definitions do not involve classical survival analysis.

In Table 1, λ_v, λ_{pl}, $\overline{h}_v$ and $\overline{h}_{pl}$ are defined below.

1 First definition of Vaccine efficacy

The first definition of vaccine efficacy is to consider the total number of vaccinated and placebo infected individuals that acquired the infection at the end of the trial. We then calculate the relative risk (RR, see below) of acquiring the infection given that an individuals received the vaccine or the placebo such that vaccine efficacy is defined as $1 - RR$ (Orenstein et al., 1985).

$$VE(T) = 1 - RR$$

To understand Relative Risk, consider the following matrix (the contingency table comparing two variables).

	Vaccinated	Placebo
Infected	a	b
Non-infected	c	d

Where a is the number of cases among persons who received the vaccine and c the number of non-cases among vaccinated persons, b is number of cases among people injected with placebos and d the number of non-cases among this group.

In this subsection, RR is defined as RR = ARV/ARU where, ARV and ARU are defined according to the table above as

$$\text{ARV} = (a\,/\,(a+c))$$

and

$$\text{ARU} = (b\,/\,\ (b+d))$$

Note that in this definition the individuals in each category may be enrolled at any time along the trial.

2 The second definition of vaccine efficacy

Table 1
Four different definitions of vaccine efficacy.

Definitions of Vaccine Efficacy		
1. VE (T*) =	$1 - \frac{vaccinated\ infectious/total\ vaccinated}{vaccinated\ infectious/total\ unvaccinated}$	$= 1 - \frac{ARV^{**}(T)}{ARU^{**}(T)}$
2. VE(t) =	$1 - \frac{vaccinated\ event/person-time}{unvaccinated\ event/person-time}$	$= 1 - \frac{\lambda_v(t)}{\lambda_{pl}(t)}$
3. VE (T*) =	$1 - \frac{probability\ of\ vaccinated\ event}{probability\ of\ unvaccinated\ efent}$	$= 1 - \frac{1 - exp[-\int_0^T \lambda_v(t)dt]}{1 - exp[-\int_0^T \lambda_{pl}(t)dt]}$
4. VE (T*) =	$1 - \exp(\beta)$	$= 1 - \frac{h_v(t)}{h_{pl}(t)}$

*End of trial.
**ARV ARU.

The second definition relates vaccine efficacy with the forces of infection (hazard rate, see Halloran et al., 2010, p. 28) of vaccinated and placebo, respectively. In terms of the notation adopted above, it is given by

$$VE(t) = 1 - \frac{\lambda_v(t)}{\lambda_{pl}(t)}$$

where $\lambda_v(t)$ and $\lambda_{pl}(t)$ are the forces of infection among volunteers injected with vaccine and individuals injected with placebo respectively. Note that this definition is time dependent. The force of infection $\lambda_v(t)$ and $\lambda_{pl}(t)$ are also called the hazard in the literature and below in this paper. Note that, if $\lambda_v(t)$ is strictly proportional to $\lambda_{pl}(t)$, then the expression above is time-independent.

3 Third definition of vaccine efficacy

The third definition relates vaccine efficacy with the probabilities of contracting the infection up to time T among vaccinated and placebos, respectively. In terms of the notation adopted above, it is given by

$$VE(T) = 1 - \frac{1 - e^{-\int_0^T \lambda_v(t)dt}}{1 - e^{-\int_0^T \lambda_{pl}(t)dt}}$$

This definition differs from definition (1) in that we are considering the evolution of a cohort enrolled in a small time interval, around time $t = 0$. In addition, to calculate it we need $\lambda_v(t)$ and $\lambda_{pl}(t)$.

4 Fourth definitions of vaccine efficacy

The fourth definition of vaccine efficacy uses the classical survival analysis, including the Proportional Hazard Regression of Cox method (Cox DR and OakesD (1984)). This approach considers the ratio between the hazards to which each group, vaccinated and not vaccinated individuals are subject. In this so-called Kaplan-Meier-Cox type of survival analysis, applied to the present study, we are interested in the time to event, that is, the period between the time that individuals are enrolled into the trial and the moment they get infected.

The proportional hazard model is expressed as (Guo, 2010)

$$h_i(t) = h_0(\mathrm{t})\exp(\beta x_1)$$

where $h_i(t)$ is the dependent variable (operationalized as the hazard rate at time t for subject i), x_1 is the independent variable ($x_1 = 1$ for vaccinates and $x_1 = 0$ for placebos, or covariate, and β *is* the regression coefficient; $h_0(\mathrm{t})$ is a baseline hazard function. The baseline hazard function can be thought of as the hazard function for an individual whose covariates all have values of 0; and $\exp(\beta) =$ *Relative Risk* (see Table 1).

We need a model that is flexible enough to analyses all these different protocols. The model described in this paper is designed to accommodate analyses of any conceivable clinical trial protocol.

3. The model

Since the outbreak and the enrollment protocols in real vaccine trials involves large number of individuals, we propose to replace the incidence of the outbreak and the incidence of the enrollment process by continuous density functions. We begin by defining the functions describing the force of infection of the outbreak and the enrollment function of volunteers.

We illustrate this with the case of covid-19 outbreak in the city of Santos, Southeastern Brazil in 2020. Fig. 4 shows the fitting of a gaussian curve to the actual data of the outbreak mentioned above.

The fitted equation has the form.

$$Incidence(t) = \frac{\alpha_{inc}}{\sqrt{2\pi\sigma_{inc}^2}} e^{-\left[\frac{(t-\mu_{inc})^2}{\sigma_{inc}^2}\right]} \quad (1)$$

where α_{inc} is a scaling parameter, σ_{inc}^2 is the incidence variance and μ_{inc} is the time where the incidence reaches its maximum value. From equation (1) we obtain the force of infection, $\lambda(t)$ by dividing the incidence by the total population at risk.

Note from Fig. 4 that the Gaussian function mimics the actual incidence data with reasonable accuracy. The fitting parameters are.

Parameter	Value
α_{inc}	Variable
σ^2_{inc}	150 *days*
μ_{inc}	800 *days*

In Fig. 5 we show the fitting of a continuous density curve to the enrolment rate, $enr(t)$ for Coronavac phase 3 trial in Brazil in 2020.

The fitting equation has the form:

$$enr(t) = \frac{\alpha_{enr}}{\sqrt{2\pi\sigma^2_{enr}}} e^{-\left[\frac{(t-\mu_{enr})^2}{\sigma^2_{enr}}\right]} \tag{2}$$

where α_{enr} is a scaling parameter, σ^2_{enr} is the enrolment variance and μ_{enr} is the time where the enrolment rate reaches its maximum value.

Note that, again, a Gaussian function mimics the actual data with reasonable accuracy. In the discussion section, we elaborate on this point. The fitting parameters are.

Parameter	Value
α_{enr}	15 000
σ^2_{enr}	150 *days*
μ_{enr}	Variable

The model assumes a phase 3 clinical trial where volunteers receive the first dose of the vaccine or placebo at the entrance in the trial. After a period of τ_1 days, they receive the second dose of the vaccine or placebo. In between the first and the second dose, volunteers may acquire the infection. These infected individuals are disregarded in the analysis.

According to the protocol, the trial begins after a period of τ_2 days after the second dose, when the immune system is assumed to kicks off. Again, in between τ_1 and τ_2 , those individuals may acquire the infection and are disregarded. The trial begins at $n_1\Delta + \tau_1 + \tau_2$ and ends at $n_1\Delta + \tau_1 + \tau_2 + n_2\Delta$ (see Fig. 5 below). Therefore, only those individuals that acquire the infection after $n_1\Delta + \tau_1 + \tau_2$ are considered for the calculation of vaccine efficacy. For simplicity, we consider that there is no censored individuals in that period.

Fig. 6 shows the timeline of events assumed in the model.

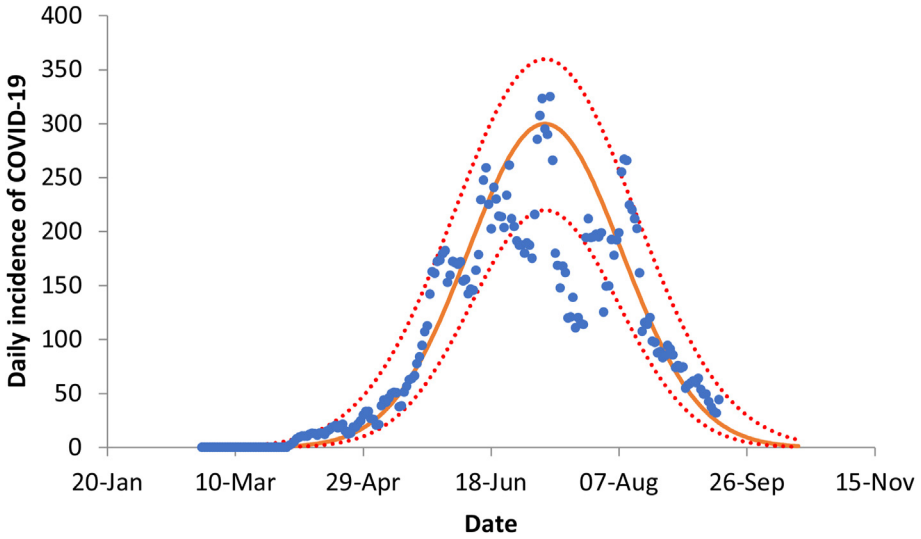

Fig. 4. SARS-CoV 2 outbreak in Santos, Brazil, 2020 with the Gaussian density function fitted (equation (1)). Dots represent real data, continuous line the mean fitted curve and dotted line the 95% confidence interval.

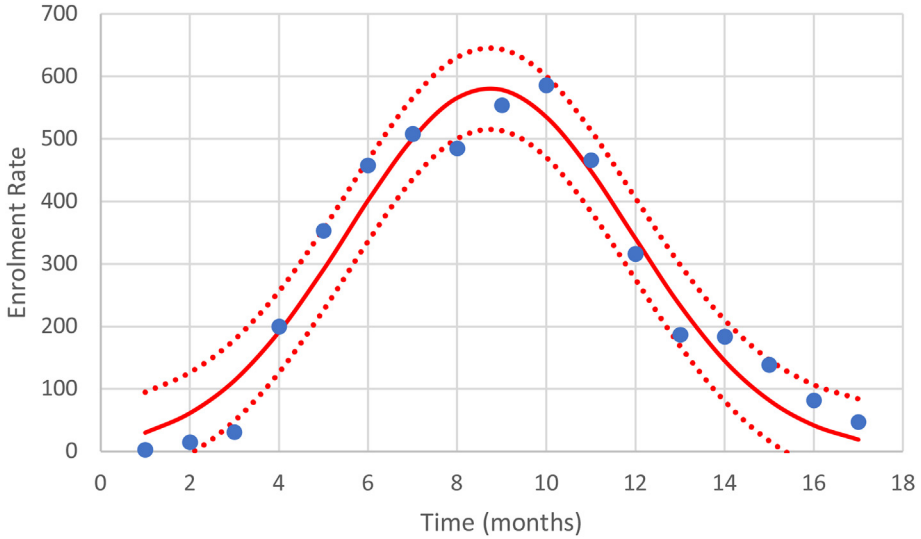

Fig. 5. The SINOVAC-Coronavac vaccine enrolment rate fitted to a Gaussian density function (equation (2)). Dots represent real data, continuous line the mean fitted function and dotted lines the 95% confidence interval.

3.1. Vaccine arm

In the vaccinated arm, individuals are assumed to be enrolled continuously in time but we will consider cohorts in intervals (weeks), defined as individuals enrolled between $n_i\Delta$ and $(n_i+1)\Delta$. Note that individuals in each interval $[n_i\Delta,(n_i+1)\Delta],(n_i=0,1,2,\ldots)$ represent one cohort of enrolled individuals and each one will be followed separately. In this way, we can mimic a classical survival analysis. Therefore, if the enrollment function is denoted $enr(t)$, then individuals enrolled between $n_i\Delta$ and $(n_i+1)\Delta$ are denoted $\Psi_v(n_i,t)$, and is given by

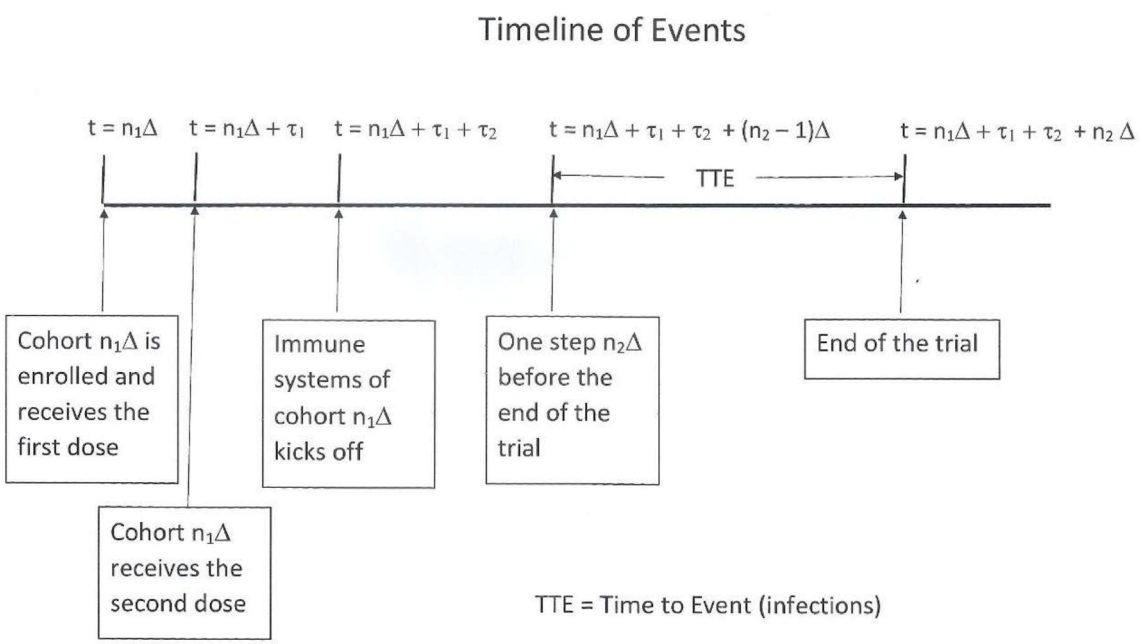

Fig. 6. Timeline representing the model's events (equations 3–12).

$$\Psi_{\nu}(n_i) = \int_0^{\infty} \theta(t - n_i\Delta)\, q\, enr(t)\theta((n_i+1)\Delta - t)dt \tag{3}$$

In equation (3) the function $\theta(t-x)$ and $\theta(x-t)$ are step functions also known as Heaviside functions, introduced to extract cohorts from the enrollment function. In addition, the constant Δ must be such that the number of infections during it negligible but it is otherwise arbitrary. The parameter q is the fraction of the volunteers that received the vaccine. Likewise, 1 - q are those volunteers who received the placebo

As mentioned above, those individuals may escape the disease in one of three phases: in the first phase, individuals denoted $\varphi_1(\tau_1)$, escape the infection between $(n_1+1)\Delta$ and $((n_1+1)\Delta+\tau_1)$ which happens with rate $p_1\lambda(t)$; in the second phase, indivituals, denoted $\varphi_2(\tau_2)$, escape the infection between $((n_1+1)\Delta+\tau_1)$ and $((n_1+1)\Delta+\tau_1+\tau_2)$, which happens with rate $p_2\lambda(t)$; and finally, in the third phase, individuals, denoted χ_{ν}, escape the infection between $((n_1+1)\Delta+\tau_1+\tau_2)$ and $((n_1+1)\Delta+\tau_1+\tau_2+\tau_3)$, which happens with rate $p_3\lambda(t)$. The terms $p_i(i=1,2,3)$ are the probabilities of infection in each phase and the rate $\lambda(t)$ is the time-dependent force of infection. These terms are:

$$\varphi_1(n_1,\tau_1) = \Psi_{\nu}(n_1) exp\left[-\int_0^{\infty} \theta(t-(n_1+1)\Delta)\, p_1\, \lambda(t)\, \theta((n_1+1)\Delta+\tau_1 - t)dt\right] \tag{4}$$

$$\varphi_2(n_1,\tau_1,\tau_2) = \varphi_1(n_1,\tau_1) exp\left[-\int_0^{\infty} \theta\Big(t-(n_1+1)\Delta\tau_1\, p_2\, \lambda(t)\, \theta((n_1+1)\Delta+\tau_1+\tau_2 - t)dt\right] \tag{5}$$

$$\chi_{\nu}(n_1\Delta,n_2\Delta) = \varphi_2(n_1,\tau_1,\tau_2) exp\left[-\int_0^{\infty} \theta(t-(n_1+1)\Delta+\tau_1+\tau_2)\, p_3\, \lambda(t)\, \theta((n_1+1)\Delta+\tau_1+\tau_2+n_2\Delta) - t\Big)dt\right] \tag{6}$$

As we shall argue later, $n_2\Delta$ for this cohort is the *time to event* in the jargon of Kaplan-Meier-Cox survival analysis.

Finally, the individuals who acquired the infection between $(n_1+1)\Delta+\tau_1+\tau_2+(n_2-1)\Delta$ and $(n_1+1)\Delta+\ \tau_1+\ \tau_2+n_2\Delta$, denote $\gamma_{\nu}(n_1,n_2)$ are given by

$$\gamma_{\nu}(n_1,n_2) = \chi_{\nu}(n_1\Delta,(n_2-1)\Delta) - \chi_{\nu}(n_1\Delta,n_2\Delta) \tag{7}$$

that is, those who survived in the uninfected condition (at risk), up to $((n_1+1)\Delta+\tau_1+\tau_2+(n_2-1)\Delta) - ((n_1+1)\Delta+\tau_1+\tau_2+n_2\Delta)$. Therefore, the time to event between the entrance in the trial (after τ_2), which, for this cohort occurred at time $t=(n_1+1)\Delta+\tau_1+\tau_2$, and ended at time $t=((n_1+1)\Delta+\tau_1+\tau_2+n_2\Delta)$ is $n_2\Delta$.

3.2. Placebo arm

In the placebo arm, individuals are also assumed to be enrolled continuously in time but we again will consider cohorts in intervals (weeks), defined as individuals enrolled between $n_i\Delta$ and $(n_i+1)\Delta$. Once again, those individuals in each interval $[n_i\Delta,(n_i+1)\Delta], (n_i=0,1,2,\ldots)$ represent one cohort of enrolled individuals and each one will be followed separately. In this way, we can mimic a classical survival analysis. Therefore, if the enrollment function is denoted $enr(t)$, then individuals enrolled between $n_i\Delta$ and $(n_i+1)\Delta$ are denoted $\Psi_{pl}(n_i,t)$, and is given by

$$\Psi_{pl}(n_i) = \int_0^{\infty} \theta(t-n_i\Delta)\ (1-q)\ enr(t)\theta((n_i+1)\Delta - t)dt \tag{8}$$

The parameter (1-q) is the fraction of the volunteers that received the placebo.

As mentioned above, those individuals may escape the disease in one of three phases: in the first phase, individuals denoted $\varphi_3(\tau_1)$, escape the infection between $(n_1+1)\Delta$ and $((n_1+1)\Delta+\tau_1)$, which happens with rate $p_4\lambda(t)$; in the second phase, indivituals, denoted $\varphi_4(\tau_2)$, escape the infection between $((n_1+1)\Delta+\tau_1)$ and $((n_1+1)\Delta+\tau_1+\tau_2)$, which happens with rate $p_5\lambda(t)$; and finally. In the third phase, individuals, denoted χ_{pl}, escape the infection between $((n_1+1)\Delta+\tau_1+\tau_2)$ and $((n_1+1)\Delta+\tau_1+\tau_2+\tau_3)$, which happens with rate $p_6\lambda(t)$. The terms $p_i(i=4,5,6)$ are the probabilities of infection in each phase and the rate $\lambda(t)$ is the time-dependent force of infection. These terms are:

$$\varphi_3(n_1,\tau_1) = \Psi_{pl}(n_1) exp\left[-\int_0^{\infty} \theta(t-(n_1+1)\Delta)\, p_4\, \lambda(t)\, \theta((n_1+1)\Delta+\tau_1 - t)dt\right] \tag{9}$$

$$\varphi_4(n_1,\tau_1,\tau_2) = \varphi_3(n_1,\tau_1) exp\left[-\int_0^{\infty} \theta\Big(t-(n_1+1)\Delta\tau_1\, p_5\, \lambda(t)\, \theta((n_1+1)\Delta+\tau_1+\tau_2 - t)dt\right] \tag{10}$$

$$\chi_{pl}(n_1\Delta, n_2\Delta) = \varphi_4(n_1, \tau_1, \tau_2) exp\left[- \int_0^{\infty} \theta(t - (n_1+1)\Delta + \tau_1 + \tau_2)\, p_6\, \lambda(t)\, \theta((n_1+1)\Delta + \tau_1 + \tau_2 + n_2\Delta) - t \Big) dt \right] \quad (11)$$

As argue above, $n_2\Delta$ for this cohort is the *time to event* in the jargon of Kaplan-Meier-Cox survival analysis.

Finally, the individuals who acquired the infection between $(n_1+1)\Delta + \tau_1 + \tau_2 + (n_2-1)\Delta$ and $(n_1+1)\Delta + \tau_1 + \tau_2 + n_2\Delta$, denote $\gamma_{pl}(n_1, n_2)$ are given by

$$\gamma_{pl}(n_1, n_2) = \chi_{pl}(n_1\Delta, (n_2-1)\Delta) - \chi_{pl}(n_1\Delta, n_2\Delta) \quad (12)$$

that is, those who survived in the uninfected condition (at risk), up to $((n_1+1)\Delta + \tau_1 + \tau_2 + (n_2-1)\Delta) - ((n_1+1)\Delta + \tau_1 + \tau_2 + n_2\Delta)$. Therefore, the time to event between the entrance in the trial (after τ_2), which, for this cohort occurred at time $t = (n_1+1)\Delta + \tau_1 + \tau_2$, and ended at time $t = ((n_1+1)\Delta + \tau_1 + \tau_2 + n_2\Delta)$ is $n_2\Delta$.

A block diagram of the model is shown in Fig. 7.

4. Calculating vaccine efficacy in terms of the model

In terms of the model the vaccine efficacy given above reads:

For the first definition we have.

In terms of the model's equations, we have (see the contingency table above):

$$a = \sum_{n_1}\sum_{n_2} \gamma_{\nu}(n_1, n_2)$$

$$b = \sum_{n_1}\sum_{n_2} \gamma_{pl}(n_1, n_2)$$

$$a + c = \sum_{n_1} \Psi_{\nu}(n_1)$$

$$b + d = \sum_{n_1} \Psi_{pl}(n_1)$$

This method has been recently used to calculate the efficacy of the Moderna© vaccine against SARS-CoV-2 (Frost, 2023).

For the second definition we relate vaccine efficacy with the forces of infection (hazard rate, see Halloran et al., 2010, p. 28) of vaccinated and placebo, respectively. In terms of the notation adopted above it is given by

$$VE(n_2\Delta) = 1 - \frac{\lambda_{\nu}(n_2\Delta)}{\lambda_{pl}(n_2\Delta)} = 1 - \frac{\gamma_{\nu}(n_1, n_2)/\chi_{\nu}(n_1, n_2)}{\gamma_{pl}(n_1, n_2)/\chi_{pl}(n_1, n_2)}$$

For the third definition we relate vaccine efficacy with the probabilities of acquiring the infection among vaccinated and placebos, respectively. In terms of the notation adopted above it is given by

$$VE(n_2\Delta) = 1 - \frac{1 - exp\left[- \int_0^{n_2\Delta} \lambda_{\nu}(t) dt \right]}{1 - exp\left[- \int_0^{n_2\Delta} \lambda_{pl}(t) dt \right]} = 1 - \frac{\sum_{n_1} \gamma_{\nu}(n_1, n_2) \Big/ \sum_{n_1} \chi_{\nu}(n_1, n_2)}{\sum_{n_1} \gamma_{pl}(n_1, n_2) \Big/ \sum_{n_1} \chi_{pl}(n_1, n_2)}$$

Finally for the fourth definition we use the classical survival analysis, including the Proportional Hazard Regression of Cox method (Cox, 2018). This approach considers the ratio between the hazards to which each group, vaccinated and not vaccinates individuals are subject. In this so-called Kaplan-Meier-Cox type of survival analysis, applied in the present study, we are interested in the time to event, that is, the period between the time that individuals are enrolled into the trial and the moment they get infected. In our model, this is given by the period between $t_i = [(n_1+1)\Delta + \tau_1 + \tau_2]$ and $t_f = [(n_1+1)\Delta + \tau_1 + \tau_2 + n_2\Delta]$.

In this paper we calculated vaccine efficacy as given by one minus de average hazard ratios, that is

$$VE(t) = 1 - \exp(\beta) = 1 - \frac{\overline{h}_{\nu}}{\overline{h}_{pl}}$$

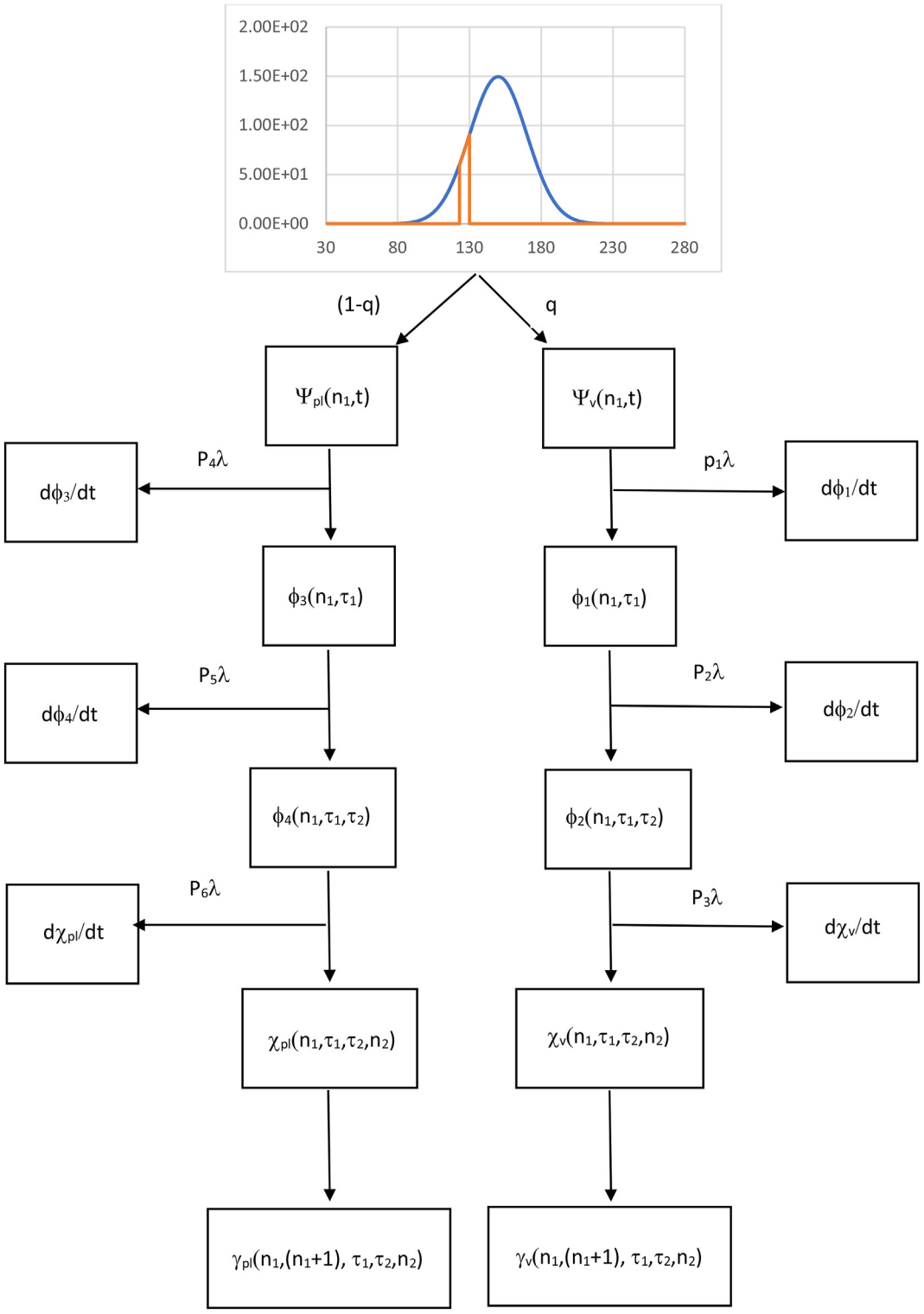

Fig. 7. Block diagram of the model's equations 3–12. In the figure above the diagram represents the enrolment rate curve with one cohort (red bar). Diagram itself represents the evolution of the trial. The horizontal arrows represent individuals who acquired the infection before the beginning of the trial.

where $\overline{h}_v$ and $\overline{h}_{pl}$ are the average hazard rates for vaccinated and placebo individuals, respectively. Each of those average hazard rates are given by (Norman & Strainer, 2008)

$$\overline{h}_v = \frac{\sum_{n_1}\sum_{n_2}\gamma_v(n_1,n_2)}{\sum_{n_2} n_2\Delta}$$

and

$$\overline{h}_{pl} = \frac{\sum_{n_1}\sum_{n_2}\gamma_{pl}(n_1,n_2)}{\sum_{n_2} n_2\Delta}$$

For the calculation of the 95% Confidence Interval (95%CI) of the Vaccine Efficacy we need the following auxiliary parameters (Norman & Strainer, 2008)):

$$V = \sum_i \frac{R_{iv}R_{ipl}D_i(R_i - D_i)}{R_i^2(R_i - 1)}$$

where

$$R_{iv} = (\textit{Vaccinated at risk in the time interval } n_i\Delta) = \chi_v(n_1,n_2)$$

$$R_{ipl} = (\textit{Placebos at risk in the time interval } n_i\Delta) = \chi_{pl}(n_1,n_2)$$

$$D_{iv} = (\textit{Vaccinated infected in the time interval } n_i\Delta) = \gamma_v(n_1,n_2)$$

$$D_{ipl} = (\textit{Placebo infected in the time interval } n_i\Delta) = \gamma_{pl}(n_1,n_2)$$

$$R_i = R_{iv} + R_{ipl}$$

$$D_i = D_{iv} + D_{ipl}$$

Also

$$X = \frac{O_v - E_v}{V} + \frac{O_{pl} - E_{pl}}{V}$$

$$Y = \frac{1.96}{\sqrt{V}}$$

where

$$O_v = \sum_{n_2} R_{iv}$$

$$O_{pl} = \sum_{n_2} R_{ipl}$$

$$E_{iv} = D_i \frac{R_{iv}}{R_{iv} + R_{ipl}}$$

$$E_{ipl} = D_i \frac{R_{ipl}}{R_{iv} + R_{ipl}}$$

Finally

$$95\%CI = e^{(X-Y)} \textit{ to } e^{(X+Y)}$$

5. Results

The results of the calculations of vaccine efficacy using the four different definitions are summarized in Table 2. In the table, the calculations were carried out assuming $\alpha_{inc} = 1$ and $\mu_{inc} = \mu_{enr}$ (the difference $\mu_{inc} - \mu_{enr}$ is called *gap* below)

Table 2
Results of the simulations of vaccine efficacy.

Results of Vaccine Efficacy		
1. VE (T*)	$= 1 - \frac{ARV^{**}(T)}{ARU^{**}(T)}$	52% (48%–56%)
2. VE(t)	$= 1 - \frac{\lambda_v(t)}{\lambda_{pl}(t)}$	53% (49%–58%)
3. VE (T*)	$= 1 - \frac{1 - exp[-\int_0^T \lambda_v(t)dt]}{1 - exp[-\int_0^T \lambda_{pl}(t)dt]}$	53% (49%–58%)
4. VE (T*)	$= 1 - \exp(\hat{\beta})$	53% (49%–58%)

*End of trial.
**ARV ARU.

Table 3
Results of Vaccine Efficacy varying α_{inc}.

Results of Vaccine Efficacy Varying α_{inc}	
1. $\alpha_{inc} = \mathbf{1}$	52% (48%–56%)
2. $\alpha_{inc} = \mathbf{5}$	51% (47%–55%)
3. $\alpha_{inc} = \mathbf{10}$	49% (44%–54%)
4. $\alpha_{inc} = \mathbf{50}$	44% (39%–48%)
5. $\alpha_{inc} = \mathbf{100}$	33% (29%–36%)

*$gap = 0$.

Next, we calculated the vaccine efficacy according to the third definition varying the intensity of the incidence, that is, varying α_{inc}. The results are showed in Table 3 and Fig. 8 below

Note that the higher the incidence, the lower the vaccine efficacy.

In Table 4 and Fig. 10 we show the result of the variation of vaccine efficacy varying μ_{enr}, the moment the enrolment rate reaches its maximum. This is equivalent to creating a time lag between the maximum incidence intensity and the maximum enrollment rate (see Fig. 9), called *gap* below.

Note that the larger the *gap* between the maximum infection intensity and the maximum enrollment rate the lower the calculated vaccine efficacy.

In Fig. 11 we show the result of vaccine efficacy when we divide the entire volunteer population into cohorts of 1 day. We then calculate the efficacy for each cohort, beginning at day 1 of the clinical trial. We set $\mu_{inc} = \mu_{enr}$ ($gap = 0$) in the simulations. The figure also includes the total number of infected individuals in each cohort.

If we take the value of vaccine efficacy at the peak of the number of infected, we have the value of 53%. This is an alternative definition for vaccine efficacy, that is, the efficacy of the vaccine in the cohort that suffer most from the outbreak.

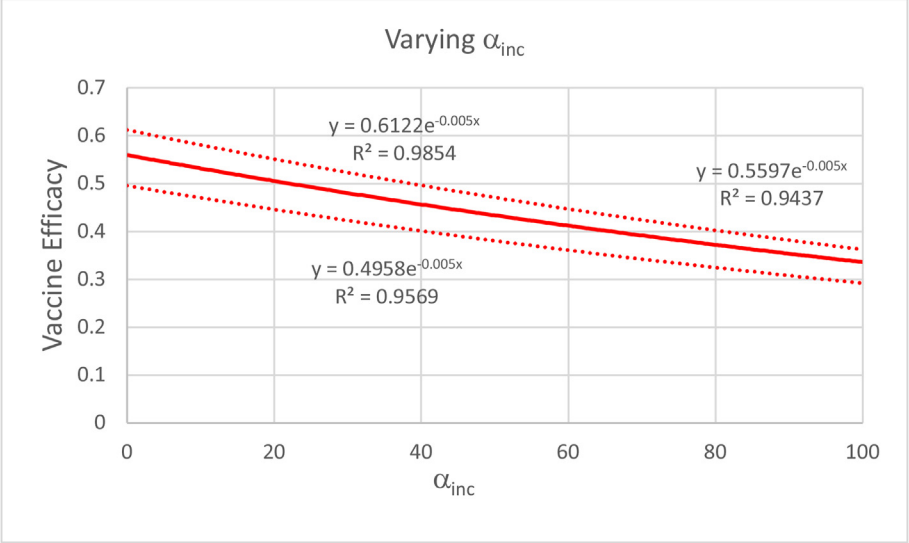

Fig. 8. Results of Vaccine Efficacy varying α_{inc}.

Table 4
Results of the model's simulation varying the *gap*.

Results of Vaccine Efficacy Varying the *gap*[a]	
1. gap = 0	52% (48%–56%)
2. gap = 15	51% (47%–55%)
3. gap = 30	48% (44%–54%)
4. gap = 60	43% (38%–47%)
5. gap = 90	41% (36%–45%)

[a] $\alpha_{inc} = \mathbf{1}$.

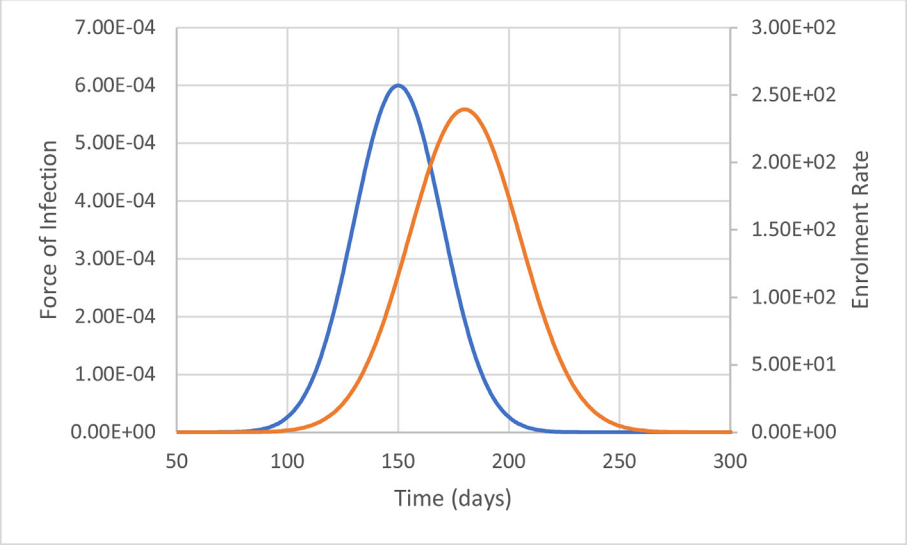

Fig. 9. Force of infection (blue line, from equation (1)) and enrolment rate (orange line, from equation (2)) showing the *gap* between the peaks of the curves.

Finally, Fig. 12 presents the results of vaccine efficacy as a function of the product of the burden of infection, that is, the normalized integral of the force of infection times the number of enrolled volunteers in each 1 day cohort.

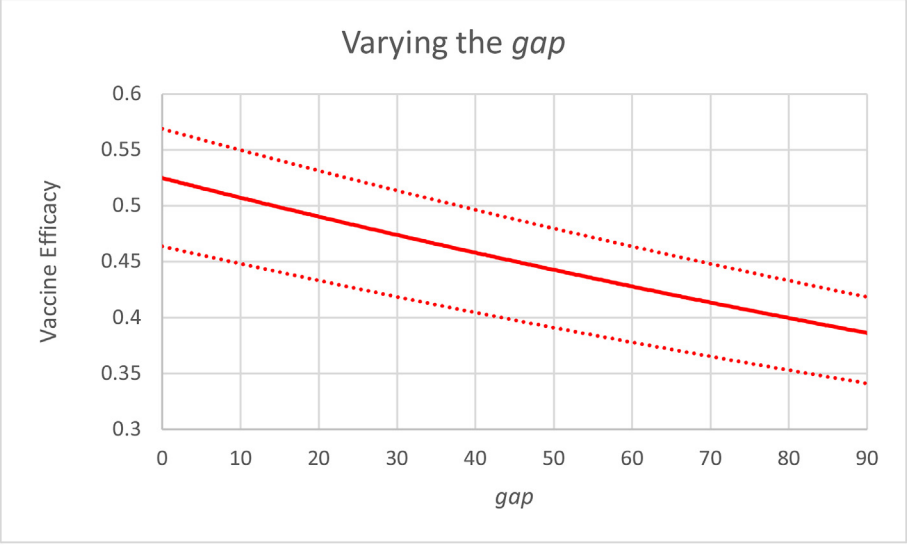

Fig. 10. Results of the model's simulation varying the *gap* that is the time interval between the maximum infection intensity and the maximum enrollment rate.

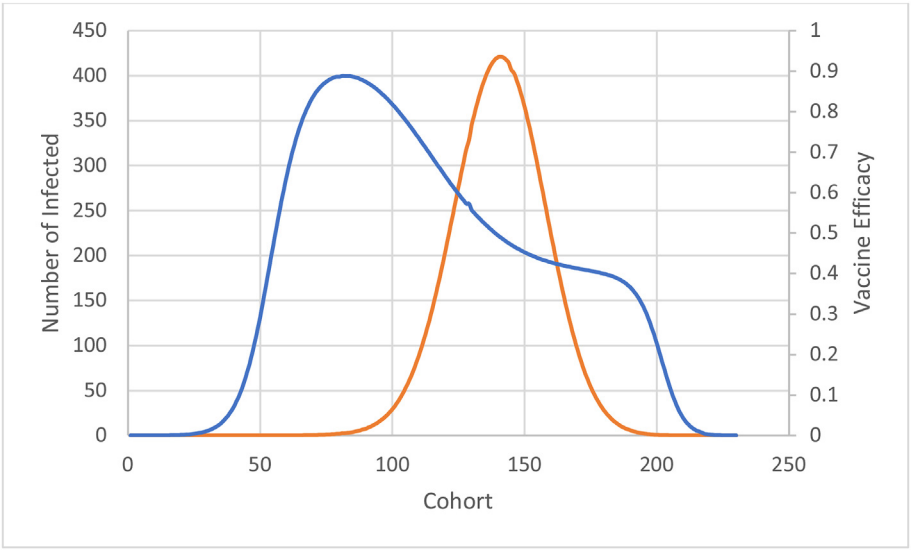

Fig. 11. Result of vaccine efficacy when we divide the entire volunteer population into cohorts of 1 day (blue line). The figure also includes the total number of infected individuals in each cohort (orange line).

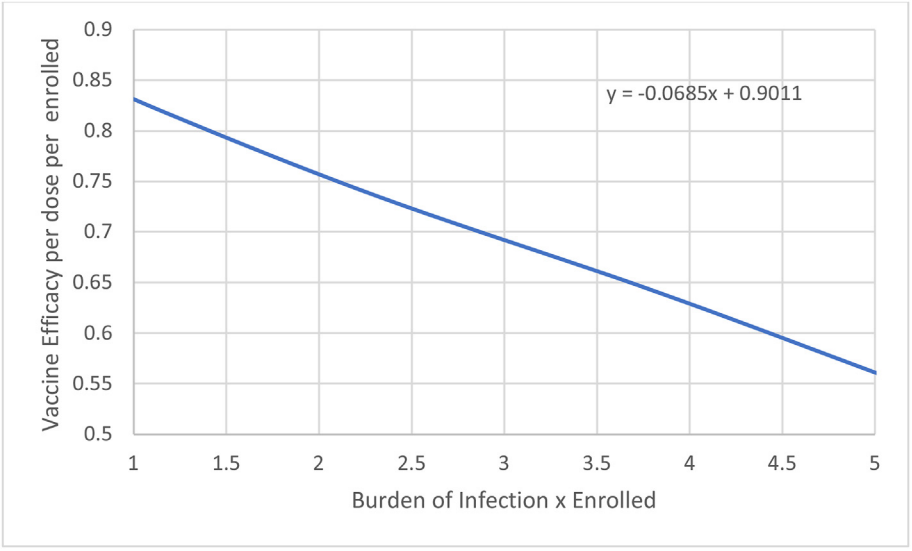

Fig. 12. Results of vaccine efficacy as a function of the product of the burden of infection, that is, the normalized integral of the force of infection times the number of enrolled volunteers (dose of infection) in each 1 day cohort.

Note that the inclination of the curve, that is the first derivative of the function, represents the vaccine efficacy per dose of infection, which resulted in −0.0685. The negative sign means that efficacy drops down in a linear fashion with the dose of infection.

6. Discussion

In this paper we present a mathematical model to calculate vaccine efficacy for diseases which present themselves in outbreaks, that is, when the force of infection is not constant in time. The model was designed to mimic many distinct protocols, each one with a different way of calculating vaccine efficacy (in fact, different definitions of vaccine efficacy). All the protocols considered are of the so-called randomized, double-blind, placebo controlled clinical trials type (Piantadosi, 1997) The different protocols of vaccine trials are presented in Table 1.

The present model differs from the one presented by Loria et al., (2023) in that each enrolled cohort are followed for a certain time during the outbreak. A second difference is that this model, in contrast of Loria's et al., consider two doses of the vaccine. In addition, a time interval is considered, during which the immune system of vaccinated individuals starts to operate. Hence, in this paper, individuals receive two doses of either a vaccine or a placebo and the clinical trial begins after the immune system kicks off. This is the most common protocol used in real vaccine trials. Of course, the model can be immediately simplified for a simpler protocol.

The influence of a time-dependent force of infection on the vaccine efficacy has been explored by Halloran, Longini and Struchiner (2010) (see also, O'Hagan et al, 2014), who correlated the size of the outbreak, measure as the number of cases and vaccine efficacy. In addition, Kaslow's (2021) results suggest that there is a decreasing function of log of vaccine efficacy and the force of infection, that is, the higher the infection intensity the lower the resulted vaccine efficacy. These results are similar to the ones by Loria et al. paper, who proposed a mathematical model designed to study this effect. The results of the present paper are qualitativey similar to the ones by Kaslow (2021), in the sense that the higher the force of infection, the lower the calculated vaccine efficacy.

Another significant result of the present model is that when we vary the magnitude of the “gap", that is, the time interval between the beginning of the enrollment process and the peak in the infection incidence, the resulting vaccine efficacy drops when the gap increases. This result is qualitatively the same found by Loria et al., (2023).

Fig. 8 shows the vaccine efficacy defined as one minus the hazards ratio, that decreases with the cohorts and the increases again (not shown in the figure). It also shows the total number of infections, which increases from the initial cohorts, reaches a maximum and then decreases. The maximum number of total infections gives a vaccine efficacy of 53%, which we propose is the real efficacy (it coincides numerical with all the other definitions of vaccine efficacy).

Noteworthy on our results is that for any of the adopted vaccine efficacy definition are qualitatively and quantitatively the same, that is, irrespective of efficacy definition (see Table 1) our simulations result in the same figure.

Our model demonstrate that vaccine efficacy calculated in the initial phases of an outbreak (when the force of infection is low), results in a high efficacy, when compared to trials carried out when the force of infection is high, that is, in later phases of the outbreak. This may, at least partly, explain why some of the COVID vaccines that were tried during the early stages of the outbreak in 2020, like the Pfiser and Moderna vaccines, where about 95%, whereas the calculated efficacy of the vaccines that were tried later in the epidemic, like the Johnson & Johnson and Astrazeneca vaccines, with calculated efficacy of about 70%. Moreover, as mentioned above, the Sinovac convid-19 vaccine trial was carried out in Brazil among health professionals, who are subject to a relative risk of 3.5 with respect to the population as a whole, and our model shows that the calculated efficacy for this particular population significantly underestimated the efficacy for the population as a whole.

Some important limitations of the model are worth of mention. First, the model is deterministic and disregard any heterogeneity, that is, all individuals enrolled are equally susceptible to the infection. In addition, the model assumes that the volunteers are subject to the same force of infection as the population at whole, although this assumption is relaxed in the simulations. In addition, the value of the critical parameters p_i $(i = 1, \ldots, 6)$ are ad hoc and characterize the vaccine. We fitted continuous functions to both the force of infection and the enrollment rate, although the data used were discrete. We did this to simplify the several calculations involved in the simulation of the vaccine trial protocols. We did not considered individuals who dropped out of the trial in any phase (censored individuals) in the calculations of vaccine efficacy. Also, the vaccine efficacy was calculate for the first epidemic wave of SARS-CoV-2 in Brazil and the results refer to this phase only.

Another important limitation of our model is that we calculated efficacy only with respect to prevention of acquisition of infection and not efficacy with respect to slowing progression, mortality, accelerating recovery and reducing transmission, that is, the various therapeutic efficacies that are not considered in our model.

The model is particularly suitable for helping the calculation of vaccine efficacy in emergency situations, like the trial of the Ebola vaccine carried out during the 2014 outbreak in Africa (Gavi, 2022), and the recent trials of COVID-19 vaccines performed in the middle of the second wave of the outbreak in Brazil (Clinical Trials Arena, 2020, https://www.clinicaltrialsarena.com/news/sinovac-vaccine-brazil-trials/). In the particular case of the Sinovac convid-19 vaccine trial carried out in Brazil among health professionals, who are subject to a relative risk of 3.5 with respect to the population at whole, our model shows that the calculated efficacy was significantly underestimated. This may explain why the same vaccine tried in different countries resulted in higher efficacy numbers. In the Appendix we show how to correct the vaccine efficacy of this trial if the latter were carried in a sample of the general population rather than in health professionals.

As a future extension of the model, would be a modified model that includes more variables, including waning of vaccine-derived antibodies, breakthrough infection and therapeutic benefits of the vaccine, like vaccine slowing progression, mortality, reducing transmission by infected vaccines, among others. These more complete model estimates could be compared with efficacy obtained from using clinical trial data alone. However, this should be the subject of a sequel paper.

In conclusion, the model allows us to conclude: First, the calculated vaccine efficacy decreases when the force of infection increases; Second, the calculated vaccine efficacy decreases when the gap between the peak in the force of infection and the peak in the enrollment rate increases; Third, different trial protocols can be simulated with this model; different vaccine efficacy definitions can be calculated and in our simulations all result in approximately the same value. The final, and perhaps most important conclusion of our model, is that vaccine efficacy calculated during outbreaks must be carefully examined, and the best way we can suggest to overcome this problem is to stratify the enrolled volunteer's cohort-by-cohort and do the survival analysis for each cohort, or apply the Cox proportional hazards model for each cohort.

CRediT authorship contribution statement

Francisco Antonio Bezerra Coutinho: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Marcos Amaku:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Fernanda Castro Boulos:** Writing – review & editing, Supervision, Funding acquisition. **José Alfredo de Sousa Moreira:** Writing – review & editing, Validation, Supervision, Data curation. **João Italo Dias Franca:** Software, Data curation. **Julio Antonio do Amaral:** Data curation. **Eliana Nogueira Castro de Barros:** Validation, Conceptualization. **Claudio José Struchiner:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Esper Jorge Kallas:** Writing – review & editing, Project administration, Funding acquisition. **Eduardo Massad:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare they have no conflict of interest.

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Appendix

In this appendix, we present an approximate correction of vaccine efficacy of SINOVAC-Coronavac vaccine, which phase 3 trial was carried out in 2020 in Brazil in a cohort of health professionals. In this trial, between July 21 and Dec 16, 2020, 12 396 participants were enrolled and received at least one vaccine or placebo dose. There were 9823 participants who received the two doses and were followed for at least 14 days and had, therefore, reached the final efficacy analysis (Palacios et al., 2021). There were 253 confirmed COVID-19 cases in the cohort: 85 cases (11.0/100 person-year) among 4953 participants in the vaccine group, and 168 cases (22·3/100 person-year) among 4870 participants in the placebo group. The primary efficacy against symptomatic COVID-19 was 50·7% (95%CI 36·0–62·0).

This cohort was subject to a risk, calculated below, higher than that of the general population. In table A1 we show the number of cases of covid-19 in health professionals sample as compared to the general population in Brazil at the time of the vaccine trial.

	Covid +	Covid -
Heealth Professionals	161 958	115 062
General Population	1296386	6668319

From the table, the relative risk of acquiring Covid-19 of health professionals, RR^{+} turns out to be 3.5 higher than that of the general population.

The relative risk of escaping the infection, RR^{-} given that one is a health professional in this cohort is 0.5.

The relationship between this latter relative risk with the force of infection is given by the equation:

$$RR^{-} = \frac{exp\left[-\int_0^T \lambda_{HP}(t)dt \right]}{exp\left[-\int_0^T \lambda_{GP}(t)dt \right]} \tag{A1}$$

where $\lambda_{HP}(t)$ and $\lambda_{GP}(t)$ are the forces of infection among health professionals and general population, respectively.

From this equation we obtain

$$\int_0^T \lambda_{HP}(t)dt = -\ln(RR^{-}) + \int_0^T \lambda_{GP}(t)dt \tag{A2}$$

In equation (A2), $\lambda_{GP}(t)$ is the force of infection defined in the model (see its definition below equation (1) of the main text) calculated from the empirical incidence shown In Fig. 1 of the main text. Therefore, from equation (A2) it is possible to calculate the value of α_{inc} for health professionals, given by the ratio

$$\alpha_{inc} = \frac{\int_0^T \lambda_{HP}(t)dt}{\int_0^T \lambda_{GP}(t)dt} \tag{A3}$$

The result is $\alpha_{inc} = 19.78\,(95\%CI : (-2.5) - (64.01))$. Using the fitting equations shown in Fig. 7 of the main text, we calculated what would be the result of Coronavac efficacy if the trial were carried out in a sample of the general population. The result is an efficacy agains symptomatic COVID-19 of 56% (95%CI: 49.3%–64.01%).

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