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Evaluating the effectiveness of vaccination campaigns: Insights from unvaccinated mortality data

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ABSTRACT

This paper examines a recently developed statistical approach for evaluating the effectiveness of vaccination campaigns in terms of deaths averted. The statistical approach makes predictions by comparing death rates in the vaccinated and unvaccinated populations. The statistical approach is preferred for its simplicity and straightforwardness, especially when compared to the difficulties involved when fitting the many parameters of a dynamic SIRD-type model, which may even be an impossible task.

We compared the estimated number of deaths averted by the statistical approach to the "ground truth" number of deaths averted in a relatively simple scheme (e.g., constant vaccination, constant R_0, pure SIR dynamics, no age stratification) through mathematical analysis, and quantified the difference and degree of underestimation. The results indicate that the statistical approach consistently produces conservative estimates and will always underestimate the number of deaths averted by the direct effect of vaccination, and thus obviously the combined total effect (direct and indirect effect).

For high R_0 values (e.g. $R_0 \geq 8$), the underestimation is relatively small as long as the vaccination level (v) remains below the herd immunity vaccination threshold. However, for low R_0 values (e.g. $R_0 \leq 1.5$), the statistical approach significantly underestimates the number of deaths averted by vaccination, with the underestimation greater than 20%. Applying an approximate correction to the statistical approach, however, can improve the accuracy of estimates for low R_0 and low v.

In conclusion, the statistical approach can provide reasonable estimates in scenarios involving high R_0 values and low v, such as during the Omicron variant epidemic in Australia. For low R_0 values and low v, applying an approximate correction to the statistical approach can lead to more accurate estimates, although there are caveats even for this. These results suggest that the statistical method needs to be used with caution.

1. Introduction

The vaccination campaigns that were put in place during the COVID-19 pandemic across the globe saved millions of lives (He et al., 2022; Jia et al., 2023; Watson et al., 2022). Recent modelling studies have attempted to estimate the number of lives

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saved or deaths averted (DA) for any given country or state considering their specific contexts. The following paper is an attempt to examine a widely used statistical approach (Haas et al., 2022; Jia et al., 2023; Kayano et al., 2022; Lin et al., 2024a) for evaluating the effectiveness of vaccination campaigns.

Finding the number of deaths averted (DA) by vaccination in a population is a two-step process. It requires (i) determining Z, the actual number of lives lost observed after the vaccination campaigns has been implemented (e.g., as determined from mortality records) and (ii) estimating Z^*, the number of lives lost in the absence of the vaccination campaigns, which can be determined through modelling. The number of deaths averted (DA) by the vaccination campaigns is simply the difference, $DA = Z^* - Z$. The usual approach to estimate DA is to fit the country's mortality timeseries over the epidemic period, (for which Z is already known), with a dynamic epidemiological Susceptible-Infectious-Recovered-Deceased (SIRD) type model (Feng et al., 2022; Ghosh & Ghosh, 2023; Lin et al., 2022; Moore et al., 2021; Somekh et al., 2022). Ideally, the model should include the vaccination over the epidemic as based on known data. Once the model parameters have been fitted, it is a simple matter to switch off vaccination and rerun the model to obtain Z^*, and thus, DA. However, building such a model can be challenging as it "has to take into account various complex interactions between multiple factors affecting the dynamics of the epidemic, like the initial disease prevalence, the compliance with nonpharmaceutical interventions (NPIs), the rate of growth or decay of infection at various times, the speed of the vaccine rollout, and its targeting and uptake" (Somekh et al., 2022).

For these reasons, a number of recent studies have attempted to avoid the epidemic SIRD-type model and make use of a simple statistical approach that focuses on separately analyzing observed mortality timeseries data for vaccinated and unvaccinated populations (Haas et al., 2022; Jia et al., 2023; Kayano et al., 2022; Lin et al., 2024a). This approach estimates the number of lives lost in the absence of vaccination, under the assumption that individuals in the unvaccinated population would experience the same mortality rate as observed in the actual vaccination scenario. Based on this, it calculates the number of deaths averted due to vaccination. However, this approach is unable to incorporate the impact of indirect vaccination effects. These emerge because vaccinated individuals block transmission chains in the larger population thereby additionally limiting disease transmission (Arinaminpathy et al., 2017; Eichner et al., 2017; Haber, 1999). These indirect effects, if large or widespread enough, can give rise to herd immunity (Fine et al., 2011). To correctly evaluate the effectiveness of vaccination campaigns, one must consider both direct and indirect effects, the latter being absent by using this statistical approach.

The statistical approach is preferred for its simplicity and straightforwardness compared to fitting a dynamic epidemiological SIRD-type model to data, especially when estimating the many parameters of such a model is difficult or impossible. However, the statistical approach would underestimate the effectiveness of vaccination campaigns. Haas et al. (2022) comment that their "analysis does not include potential indirect effects that could have reduced disease burden among the unvaccinated population … If indirect effects stemming from the vaccination program were substantial, our results likely underestimate the effect of the nationwide vaccination program." Although this underestimation is recognized, its extent remains unclear and has not been thoroughly quantified. Quantifying the degree of underestimation could be crucial for researchers using this approach, as it would provide insight into how much the effectiveness is being underestimated and enable them to provide a more accurate estimate of the effectiveness of vaccination campaigns.

To achieve this, we first applied the final size formula (Ma & Earn, 2006) to calculate the number of deaths in an SIRD epidemic model both with and without vaccination, by applying the same parameter values, thereby determining DA, the number of deaths averted. The latter served as the "ground truth" (Murayama et al., 2023) of vaccination impact. Next, we applied the statistical approach to estimate the number of deaths without vaccination. This is implemented using the mortality rate of the unvaccinated as found in the observed data. From this, the number of deaths averted could be estimated. Finally, we calculated the underestimation as a fraction by comparing the "ground truth" number of deaths averted to that estimated by the statistical approach.

2. SIRD epidemics with vaccination

The SIRD epidemic model can be represented by the following differential equations (Bailey, 1975):

$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta SI}{N},\\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I - \mu I,\\ \frac{dR}{dt} &= \gamma I,\\ \frac{dD}{dt} &= \mu I.\end{aligned} \tag{1}$$

In these equations, S, I, R and D represent the number of Susceptible, Infectious, Recovered and Deceased individuals, respectively. The total population size N is assumed to be constant over time, i.e., $N = S + I + R + D$. Note that this requires

that, during the epidemic, the number of births and natural (non-disease-related) deaths are balanced, and the number of disease-related deaths remains insignificant relative to the total population. This assumption holds if the infection fatality ratio is low. The parameters β, γ and μ are the rates of infection, recovery, and mortality, respectively. The basic reproduction number is defined as $R_0 = \frac{\beta}{\gamma+\mu}$ and in simple terms might be considered the number of secondary infections a typical infected individual can generate when the whole population is susceptible. The infection fatality ratio is defined as $\theta = \frac{\mu}{\gamma+\mu}$. This ratio quantifies the probability that an infected individual will die from the disease, given that they either recover or die from the infection. The initial conditions are such that almost all individuals in the population are susceptible, and the number of initially infected individuals is negligible. We can therefore approximate the initial conditions as follows: $S(0) = N, I(0) = R(0) = D(0) = 0$.

A simple model of "perfect" vaccination (i.e., with 100% efficacy) can be explored by changing the initial conditions. Suppose that νN (where $0 < \nu < 1$) of the initially susceptible population are vaccinated at $t = 0$, making them fully protected from infection. For simplicity, these vaccinated individuals can then be considered as recovered individuals and belong to the recovered class R. Thus, the initial conditions are: $S(0) = (1-\nu)N, R(0) = \nu N, I(0) = D(0) = 0$. Assume that as time goes to infinity ($t \to \infty$), the epidemic ends and no infectives remain, i.e., $I(\infty) = 0$. By integrating Eq. (1) over t, we obtain the following Eqs. (2) and (3):

$$S(\infty) = S(0)\, e^{-R_0\left[\frac{S(0)-S(\infty)}{N}\right]}, \tag{2}$$

$$R(\infty) - R(0) = \frac{\gamma}{\mu}\,(D(\infty) - D(0))\,. \tag{3}$$

Details can be found in prior research (Hethcote, 2000). Since $I(\infty) = 0$, it follows that $S(\infty) = N - R(\infty) - D(\infty)$. Consequently, we can determine the Final Size of deaths, denoted as $Z = Z(\nu)$, by solving for $Z(\nu) = D(\infty) - D(0)$.This gives the implicit relation:

$$Z(\nu) = (1-\nu)N\theta\left(1 - e^{-R_0\frac{Z(\nu)}{N\theta}}\right). \tag{4}$$

Ma and Earn (Ma & Earn, 2006) give a comprehensive discussion of the Final Size formula. In the absence of vaccination ($\nu = 0$), we denote the final size of deaths as $Z^* = Z(0)$ and is given by the solution of:

$$Z^* = N\theta\left(1 - e^{-R_0\frac{Z^*}{N\theta}}\right). \tag{5}$$

Deaths averted $DA(\nu)$ Our main interest centers on estimating the number of deaths averted $DA(\nu)$ by virtue of modelling a vaccination campaign in which ν of the population has been vaccinated, or has had "coverage" ν. The number of deaths averted $DA(\nu)$ is just the difference in the number of deaths that would have occurred in the absence of a vaccine (Z^*) and the deaths for the same population if there were a vaccine ($Z(\nu)$) of coverage ν. That is:

$$DA(\nu) = Z^* - Z(\nu)\,. \tag{6}$$

By working with the SIRD model, when the same parameter values are applied but vaccination is switched off (i.e., $\nu = 0$), the estimated Final Size of deaths without vaccination (Z^*, as shown in Eq. (5)) can be seen as the "ground truth" of estimated Final Size of deaths. Thus, $DA(\nu)$, as shown in Eq. (6) can be seen as the "ground truth" of estimated number of deaths averted by vaccination. See also Table 1 for a summary of the main symbols used in this work.

Fig. 1 shows that the number of deaths averted, $DA(\nu)$ (blue lines) increases with ν and reaches its maximum, Z^*, at the herd immunity vaccination threshold $\nu = \nu_h = 1 - \frac{1}{R_0}$, which is the vaccination level needed to achieve herd immunity (Fine et al., 2011). The plots are derived from the SIRD model above with results for a high R_0 value of 8 in Fig. 1a and a low R_0 value of 1.5 in Fig. 1b, as a function of ν.

Table 1
The key variables.

Symbol	Meaning
$Z(\nu)$	The Final Size of deaths of an epidemic given the vaccination campaign (with coverage ν)
Z^*	The "ground truth" Final Size of deaths of an epidemic if there were no vaccination campaign
$Z_s(\nu)$	The estimated Final Size of deaths of an epidemic if there were no vaccination campaign, based on the statistical approach
$Z'_s(\nu)$	The estimated Final Size of deaths of an epidemic if there were no vaccination campaign, based on the "corrected" statistical approach
$DA(\nu)$	$Z^* - Z(\nu)$, the "ground truth" number of deaths averted by the vaccination campaign
$DA_s(\nu)$	$Z_s(\nu) - Z(\nu)$, the estimated number of deaths averted by the vaccination campaign, based on the statistical approach
$DA'_s(\nu)$	$Z'_s(\nu) - Z(\nu)$, the estimated number of deaths averted by the vaccination campaign, based on the "corrected" statistical approach

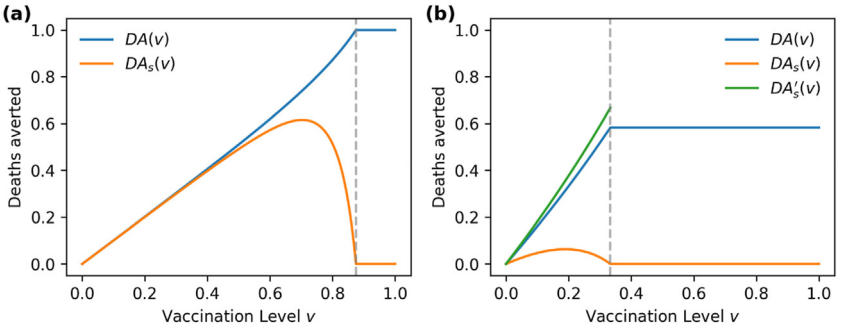

Fig. 1. The relationship between the number of deaths averted by vaccination $DA(v)$ (blue) for **(a)** $\boldsymbol{R_0}$ **=8** and **(b) For** $\boldsymbol{R_0}$ **=1.5**. The estimated number of deaths averted based on the statistical approach, $DA_s(v)$ (orange); and the estimated deaths averted before vaccination level reaches the herd immunity vaccination threshold, based on the statistical approach but with an approximate correction, $DA'_s(v)$ (green), as a function of the vaccination level v. This figure plots $DA(v)$, $DA_s(v)$, and $DA'_s(v)$, scaled by the total population N and the infection fatality ratio θ. More precisely, the figure presents the values of $\frac{DA(v)}{N\theta}$, $\frac{DA_s(v)}{N\theta}$ and $\frac{DA'_s(v)}{N\theta}$, which are derived from solving Eqs. (6), (12), and (17), respectively. The dashed line shows the herd immunity vaccination threshold v_h (e.g., for $R_0 = 8$, $v_h = 1 - \frac{1}{R_0} = 0.875$).

The total vaccination effect in terms of the number of deaths averted $DA(v)$ includes both the direct vaccination effect $\Delta_D(v)$ and the indirect vaccination effect $\Delta_I(v)$. The direct vaccination effect is the number of deaths averted among those protected by the vaccine. For a perfect vaccine,

$$\Delta_D(v) = v\,Z^* \,. \tag{7}$$

A formal derivation is given in Lin et al. (2024a), but see also Scutt et al. (Scutt et al., 2022) who studied a simpler discrete time model. The result can also be understood intuitively (see Supplementary Information (SI) Note 1).

The indirect vaccination effect, is the number of deaths averted among the unvaccinated individuals due to population-level immunity (i.e., herd immunity effects), and is easily seen to be:

$$\Delta_I(v) = DA(v) - \Delta_D(v) = Z^* - Z(v) - v\,Z^* \,. \tag{8}$$

As plotted in Fig. S1 in SI Note 2, the number of deaths averted by the direct vaccination effect $\Delta_D(v)$ increases with v, reaching its maximum Z^* when $v = 1$. The number of deaths averted by the indirect vaccination effect $\Delta_I(v)$ increases with v and reaches its maximum $(1 - v_h)Z^*$ when $v = v_h$, and then decreases to 0 when $v = 1$.

2.1. The statistical approach

The statistical approach used in (Haas et al., 2022; Jia et al., 2023; Kayano et al., 2022; Lin et al., 2024a) provides an estimate of the number of deaths in a population if there were no vaccination campaign (the "coverage" v), notated here as $Z_s(v)$. This is determined by assuming that individuals in the unvaccinated population will experience the same death rate as that observed for the unvaccinated individuals in a population that is partially vaccinated.

Recall that, in the actual scenario, we assumed that vN of the initially susceptible population N is vaccinated at $t = 0$ and immediately fully protected (perfect vaccination). Thus, deaths $Z(v)$ only occur in the unvaccinated subpopulation $(1 - v)N$. This leads to an observed overall death rate $\frac{Z(v)}{(1-v)N}$ in the unvaccinated subpopulation. For the scenario of no vaccine, the unvaccinated subpopulation would now be N, and thus, the overall death rate of this unvaccinated population would be taken to be the same as when there was vaccination, namely $\frac{Z(v)}{(1-v)N}$. An estimate of the Final Size of deaths in the absence of vaccination, derived from the statistical approach, i.e., $Z_s(v)$, depends on the actual scenario's vaccination campaign "coverage" v:

$$Z_s(v) = \frac{Z(v)}{(1-v)N}\,N = \frac{Z(v)}{1-v}\,. \tag{11}$$

More generally, the daily or weekly observed death rate in the unvaccinated subpopulation would be used for the calculation rather than the overall. For the example here, the vaccination level is fixed over time, and we can use the overall death rate without lose generality.

The number of deaths averted estimated by the statistical approach is thus:

$$DA_s(v) = Z_s(v) - Z(v) = \frac{v}{1-v} Z(v) \,. \tag{12}$$

Combining Eqs. (6) and (8) and (11–12), the difference between the number of deaths averted $DA(v)$, and the estimated number of deaths averted based on the statistical approach $DA_s(v)$ can be given by:

$$DA(v) - DA_s(v) = Z^* - Z_s(v) = \frac{Z^* - Z(v) - v\,Z^*}{1-v} = \frac{\Delta_I(v)}{1-v} \,. \tag{13}$$

Combining this with Eqs. (4) and (5), we have

$$DA(v) - DA_s(v) = N\theta\left(e^{-R_0\frac{Z(v)}{N\theta}} - e^{-R_0\frac{Z^*}{N\theta}}\right).$$

Given that $0<v<1$, thus $Z^*>Z(v)$, it follows that $DA(v) - DA_s(v) > 0$, meaning the statistical approach always underestimates the number of deaths averted by the vaccination campaigns. Since $Z(v)$ decreases as v increases and reaches zero at the herd immunity vaccination threshold $v_h = 1 - \frac{1}{R_0}$, the underestimation $DA(v) - DA_s(v)$ increases with v and reaches its maximum at Z^* when herd immunity is achieved. Fig. 1 shows how $DA_s(v)$ (orange lines) changes with v, and by comparing it to $DA(v)$ (blue lines), the underestimation is evident. In Fig. 1a, for a high R_0 value of 8, the underestimation is minor as long as the vaccination level is not close to the herd immunity vaccination threshold v_h. However, for a low R_0 value of 1.5 in Fig. 1b, the underestimation is obvious.

Haas et al. (2022) correctly pointed out that this statistical approach cannot capture indirect effects and thus underestimates the effect of vaccination. Thus, whether this approach can at least capture the direct effect will be of great importance. The difference of the number of deaths averted by the direct vaccination effect $\Delta_D(v)$, and the estimated number of deaths averted based on the statistical approach $DA_s(v)$ is:

$$\Delta_D(v) - DA_s(v) = \frac{v}{1-v}(Z^* - Z(v) - vZ^*) = \frac{v}{1-v}\Delta_I(v) \,. \tag{14}$$

Combined this with Eqs. (4) and (5), we have

$$\Delta_D(v) - DA_s(v) = vN\theta\left(e^{-R_0\frac{Z(v)}{N\theta}} - e^{-R_0\frac{Z^*}{N\theta}}\right).$$

Since $Z^*>Z(v)$, it follows that: $\Delta_D(v) - DA_s(v) > 0$. This means that the statistical approach underestimates the number of deaths averted by the direct vaccination effect. Also, this can be seen by comparing $\Delta_D(v)$ with $DA_s(v)$ in Fig. S2 in SI Note 3.

2.2. A correction for the statistical approach

As mentioned earlier, for a low value of R_0, the statistical approach significantly underestimates the number of deaths averted by vaccination. To improve its accuracy, we propose an approximate correction that accounts for the indirect vaccination effect, $\Delta_I(v)$, which is ignored by the statistical approach.

As shown in Fig. 1b, for a low value of R_0, before the vaccination level v reaches the herd immunity vaccination level $v_h = 1 - \frac{1}{R_0}$, it can be seen that the number of deaths averted $DA(v)$ (blue line) varies almost linearly with v. Since $DA(0) = 0$, and $DA(v_h) = Z^*$, it can therefore be expressed as: $DA(v) \approx \frac{Z^*}{v_h} v = \frac{Z^*}{1-\frac{1}{R_0}} v$ for $v \le v_h$. Given that $DA(v) = Z^* - Z(v)$, we have: $Z^* - Z(v) \approx \frac{Z^*}{1-\frac{1}{R_0}} v$, which simplifies to:

$$Z(v) \approx Z^*\left(1 - \frac{v}{1-\frac{1}{R_0}}\right) \,. \tag{15}$$

Combining this with Eq. (11), we have:

$$Z^* \approx \frac{Z_s(v)}{1 - \frac{v}{(R_0-1)(1-v)}} \,.$$

Thus, for $v \le v_h$, an approximate corrected estimate of the Final Size of deaths in the absence of vaccination is:

$$Z'_s(v) = \frac{Z_s(v)}{\delta(v)}, \tag{16}$$

where $\delta(v) = 1 - \frac{v}{(R_0-1)(1-v)}$. Here, $Z'_s(v)$ is our notation for the "corrected" value of the Final Size by the statistical approach. The "corrected" estimate of the number of deaths averted based on the statistical approach is:

$$DA'_s(v) = Z'_s(v) - Z(v)\ . \tag{17}$$

Fig. 1b shows the "corrected" estimated number of deaths averted, $DA'_s(v)$ (green line), as a function of v for a low R_0 value of 1.5, where $v < v_h = 1 - \frac{1}{R_0}$. Fig. 1b makes clear that $DA'_s(v)$ (green) is much closer to $DA(v)$ (blue) than $DA_s(v)$ (orange). This indicates that the "correction" scheme significantly improves the accuracy of the statistical approach for low R_0 values.

It is also possible to use the "correction" to help derive an estimate for the ratio of indirect to direct vaccination effects. Combining Eq. (15) with Eqs. (7) and (8), gives:

$$\frac{\Delta_I(v)}{\Delta_D(v)} = \frac{Z^* - Z(v) - vZ^*}{vZ^*} \approx \frac{Z^* - Z^*\left(1 - \frac{v}{1-\frac{1}{R_0}}\right) - vZ^*}{vZ^*} = \frac{1}{R_0 - 1}\ .$$

The ratio of indirect to direct vaccination effects is also found in (Lin et al., 2024b) and (Eichner et al., 2017).

2.3. Determining underestimation in the statistical approach

To quantify the extent to which the statistical approach underestimates the number of deaths averted, we calculated the bias as a proportion of the true amount, i.e.

$$\rho(v) = \frac{DA(v) - DA_s(v)}{DA(v)}. \tag{18}$$

As a reference we suppose that when the bias $\rho(v)$ >20% or $\rho(v)$ <-20% (Centers for Disease Control and Prevention, 2023), the statistical approach is problematic in estimating the number of deaths averted by the vaccination campaigns; otherwise, it can provide a reasonable estimation. Note that if the bias is negative, this means that the approach provides an overestimate. To the best of our knowledge, there is no work that quantifies the extent to which the under- or over-estimation becomes significantly impactful on the inferences. However, (Centers for Disease Control and Prevention, 2023) discusses that an interval estimate with a width of 20% would give a greater certainty about the true effect of a vaccine.

Similarly, to quantify the extent to which the statistical approach with an approximate correction misestimates the number of deaths averted, the bias as a proportion of the true amount is calculated as:

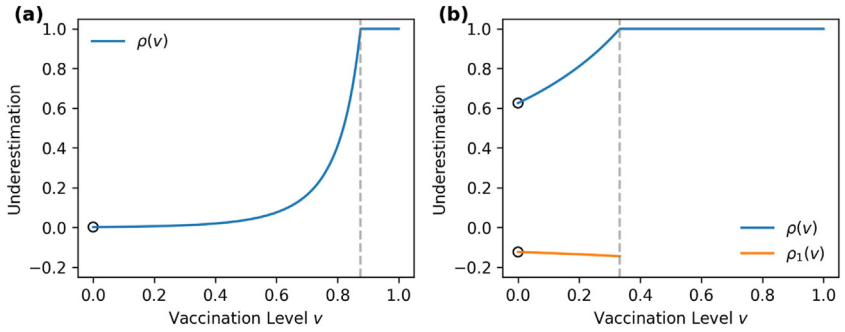

Fig. 2. (a) R_0 =8; (b) R_0 =1.5. The underestimation that arises with the statistical approach, $\rho(v)$ (blue). The underestimation arising from the "corrected" statistical approach is $\rho_1(v)$ (orange). These are plotted as a function of the vaccination level v, as calculated by solving Eqs. 18 and 19. The dashed line shows the herd immunity vaccination threshold v_h (e.g., for $R_0 = 8$, $v_h = 1 - \frac{1}{R_0} = 0.875$). The black circles indicate that the underestimation does not exist when $v = 0$. And when $v = 0^+$, as proved in SI Note 4, the underestimation is calculated as $\rho(0^+) = R_0\left(1 - \frac{Z^*}{N\theta}\right)$, and $\rho_1(0^+) = R_0 + 1 - \frac{R_0^2}{(R_0-1)}\frac{Z^*}{N\theta}$, where $\frac{Z^*}{N\theta}$ can be obtained by solving Eq. (5).

$$\rho_1(v) = \frac{DA(v) - DA'_s(v)}{DA(v)}. \tag{19}$$

Fig. 2a shows the bias $\rho(v)$ (blue line) as it varies with v for a high R_0 value of 8. It indicates that $\rho(v)$ remains low as long as the vaccination level v is not close to the herd immunity vaccination threshold v_h. This implies that the statistical approach provides a reasonably accurate estimate when R_0 is high and v is low.

Fig. 2b shows the bias $\rho(v)$ (blue line) as it varies with v for a low R_0 value of 1.5. Here, $\rho(v)$ is high, exceeding 60%. This implies that the statistical approach leads to a significantly underestimation for low R_0 values. However, an approximate correction to the statistical approach can improve its accuracy. Fig. 2b shows the bias $\rho_1(v)$ (orange line) arisen from the "corrected" statistical approach before the vaccination level reaches the herd immunity vaccination threshold. Although $\rho_1(v)$ becomes negative, meaning the correction causes a slight overestimation, the overestimation remains small since $\rho_1(v) < -20\%$.

2.4. A simulation method

SI Note 5 examines the Final Size of deaths with vaccination $Z(v)$ and without vaccination Z^* using a simulation method based on the SIRD model, rather than directly applying the Final Size formula (Ma & Earn, 2006) presented in Eqs. (4) and (5). We then calculate the number of deaths averted $DA(v)$ and the estimated number of deaths averted $DA_s(v)$. As expected, the simulation results of $DA(v)$ and $DA_s(v)$ shown in Fig. S3 are consistent with those obtained analytically by directly solving Eqs. (6) and (12) and shown in Fig. 1.

2.5. Sensitivity analysis and initial conditions

(1). SI Note 6 examines the performance of the statistical approach across various R_0 values (including $R_0 = 1.5, 2, 3, 4, 5$ and 8), with results shown in Figs. S4–5. The findings indicate that the plain vanilla statistical approach provides a reasonable estimate only when R_0 is high (e.g., $R_0 = 8$) and v is low. In all other cases, this approach tends to yield poor estimates, with underestimations exceeding 20%, particularly when R_0 is low or moderate (e.g., $R_0 = 1.5, 2, 3$). The reason why the statistical approach only works well for high R_0 and low v is that in this case the indirect effects are insignificant. This can be seen in Fig. S1. Thus, even if the statistical approach ignored the indirect effects, it would still give a reasonable estimate. This will be discussed in more detail below. In contrast, the "corrected" statistical approach can provide a reasonable estimate only when R_0 is low (e.g., $R_0 = 1.5$) and v is low. This is because the assumption of a linear relationship between the number of deaths averted $DA(v)$ and v only holds for a low value of R_0 (see Fig. S4).

(2). In many real-world situations, vaccines for newly invading diseases may not be immediately available at $t = 0$; instead, they may only become available after a significant proportion of the population is infected. It is useful to examine what might happen if vaccination v initiates at time $t = k > 0$ after the epidemic initiates at time $t = 0$. When running a simulation, at time $t = k$ we set $p = I(k)/N$ and $q = R(k)/N$. Clearly what follows is equivalent to initiating vaccination at $t = 0$ with $I(0) = pN$ and $R(0) = qN$. This allows us to examine the performance of the statistical approach in cases where vaccination begins at $t = k$, as detailed in SI Note 7. In the SI we consider a special case, where vaccination begins at $t = k$, when 20% of the population has already been infected (i.e., $p + q = 20\%$). The results are shown in Figs. S6–S7. Consistent with previous findings, we observe that the statistical approach provides a reasonable estimate only when R_0 is high (e.g., $R_0 = 8$) and v is low. While the "corrected" statistical approach fails to yield accurate estimates even when R_0 is low (e.g. $R_0 = 1.5$) and v is also low. This is because the assumption of a linear relationship between the number of deaths averted $DA(v)$ and v dose not hold well when the initially infected individuals are non-negligible (see Fig. S6). Thus, the effectiveness of the "corrected" statistical approach is dependent on initial conditions and thus has limitations when applied to broader scenarios.

3. Discussion

Our concern stems from our observation that the statistical approach (Haas et al., 2022; Jia et al., 2023; Kayano et al., 2022; Lin et al., 2024a) may significantly underestimate the effectiveness of vaccination campaigns. Sometimes, this approach is used to evaluate the impact of initiating vaccination campaigns earlier (Jia et al., 2023; Lin et al., 2024a). We have observed such a disparity in the following studies. Somekh et al. (2022) used an SIRD-type model to estimate that approximately 650,000 cases of SARS-CoV-2 were averted by vaccination efforts in the entire population of Israel during the first two months of the vaccination campaign (January and February 2021). However, another study conducted in Israel using a statistical approach (Haas et al., 2022) estimated that the Israeli vaccination campaign (from January 3, 2021, to April 10, 2021) averted approximately 159,000 SARS-CoV-2 infections, which is only a quarter of the number estimated in (Somekh et al., 2022). This implies that the statistical approach may significantly underestimate the effectiveness of vaccination campaigns by up to 75%, far exceeding the 20% threshold discussed above (Centers for Disease Control and Prevention, 2023). Additionally, Kayano et al. (2022) found that during Japan's vaccination campaign from March 2021 to November 2021, the number of

infections and deaths averted attributable to the vaccination campaign, as predicted by an SIRD-type model, were 100 times and 30 times higher, respectively, than those predicted by a statistical approach.

Studies using a statistical approach (Haas et al., 2022; Jia et al., 2023; Kayano et al., 2022; Lin et al., 2024a) often suggest that their evaluation of the effectiveness of vaccination campaigns may be conservative because their method typically captures only the direct effect of vaccination, neglecting the indirect effect in calculations.However, as shown in Eq. (14), by comparing $\Delta_D(\nu)$ and $DA_s(\nu)$, it appears that the statistical approach even underestimates the number of deaths averted by the direct vaccination effect. This is because with vaccination, unvaccinated individuals receive some degree of protection against infection or death due to the indirect effect of vaccination in the real population. Thus in the absence of vaccination, the mortality rate in the unvaccinated population would be higher than that observed in the actual vaccination scenario.

Interestingly, as shown in Fig. 2a, when the basic reproduction number (R_0) is high and the vaccination level (ν) is low, the underestimation rate remains low. According to Eq. (13), the underestimation of deaths averted is $\frac{\Delta_I(\nu)}{1-\nu}$, which is $\frac{1}{1-\nu}$ times the number of deaths averted by the indirect vaccination effect. Thus, when ν is low, the underestimation of the number of deaths averted is almost equal to or several times greater than the number of deaths averted by the indirect vaccination effect. Moreover, the influence of the indirect effect is less pronounced for highly transmissible diseases (R_0 >2, such as COVID-19), as observed in previous studies (Eichner et al., 2017; Lin et al., 2024b; Scutt et al., 2022). Thus, the statistical approach works best for cases concerning highly transmissible diseases and low vaccination levels.

For example, in an Australia's study (Lin et al., 2024a), the epidemic was mainly driven by the Omicron variant, which has an estimated R_0 as large as 10 (Burki, 2022). Although the Australian population was highly vaccinated, its net vaccination level can be considered low, as the efficacy of three doses of BNT162b2 was only about 50% effective against infection with Omicron (Altarawneh et al., 2022). However, in other studies (Haas et al., 2022; Kayano et al., 2022) where the epidemic was mainly caused by the wild-type strain or the Alpha (B.1.1.7) variant with a relatively low R_0 compared with the Omicron variant (He et al., 2023a), the effectiveness of vaccination may be significantly underestimated by using the statistical approach. In addition, recent work of Jia et al. (Jia et al., 2024) has shown that this approach provides a lower bound in a SIRD model only when parameters are constant over time, but the statistical approach fails to give the lower bound under common violations to the standard assumptions. This implies that, in real data analyses, it is inadvisable to use the statistical approach to estimate a lower bound on overall effectiveness of vaccination campaigns, and it needs to be used with caution as found here.

There are several critical simplifying assumptions in this study. We consider epidemics with a fixed basic reproduction number (R_0) and initial constant vaccination level (ν), and assume a 100% efficacy of vaccines. In a broader context, these parameters could vary as the epidemic progresses. Therefore, in certain extreme cases, our main conclusions regarding the underestimation of the effectiveness of vaccination by using the statistical approach may not be applicable, especially considering the difficulties in accounting for the rate of immunity loss from infection or vaccination (Feng et al., 2022; He et al., 2022, 2023b).

4. Conclusion

In this study, we examine a widely used statistical approach for evaluating the effectiveness of vaccination campaigns in terms of the number of deaths averted. Under the simplest possible scheme (e.g., constant vaccination, constant R_0, pure SIR dynamics, no age stratification), the statistical approach generally provides poor estimates for low R_0 values (e.g. $R_0 = 1.5$), with underestimations exceeding 20%. Given its poor performance in these simple scenarios, it is unlikely to provide better estimates in more complicated schemes. Our results suggest that this method should be used with caution. The only case where the statistical approach performs well is at high R_0 values (e.g. $R_0 = 8$) and low vaccination levels, such as during the Omicron variant epidemic in Australia.

CRediT authorship contribution statement

Lixin Lin: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Haydar Demirhan:** Writing – review & editing, Methodology, Investigation. **Lewi Stone:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Data accessibility

All data and models are provided in the manuscript and supplementary information.

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Declaration of competing interest

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Appendix A. Supplementary data

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