Supplementary Materials for: The impact of COVID-19 vaccines on the Case Fatality Rate: The importance of monitoring breakthrough infections

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Case fatality rate (CFR) with vaccines

Let $\mathcal{D}^U_{t,a}$ be the total number of COVID-associated deaths until time t in the age group a who are unvaccinated (U) and let $\mathcal{D}^V_{t,a}$ be the total number of COVID-associated deaths until time t in the age group a after being vaccinated (V). Let denote by $\mathcal{I}^U_{t,a}$ the total number of COVID-associated people ever infected until time t in the age group a who are unvaccinated and by $\mathcal{I}^V_{t,a}$ the total number of COVID-associated people ever infected until time t in the age group a after being vaccinated. Let $d^U_{t,a}$ be the COVID-associated detection rate until time t of the age group a among the ever infected who are unvaccinated and let $d^V_{t,a}$ be the COVID-associated detection rate until time t of age group a of those who are ever infected after being vaccinated. Using the previously defined variables, we can write the COVID-associated case fatality rate (CFR) at time t for the age group a as

$$\text{CFR}_{t,a} = \frac{\mathcal{D}^U_{t,a} + \mathcal{D}^V_{t,a}}{d^U_{t,a}\mathcal{I}^U_{t,a} + d^V_{t,a}\mathcal{I}^V_{t,a}}. \tag{1}$$

Let $m_a > 0$ be the COVID-associated fatality rate for the age group a and let $\beta_a \in (0, 1)$ be the effectiveness of COVID vaccines preventing deaths among the infected.[1] Thus, the fatality rate of the unvaccinated is m_a, while the fatality rate of the vaccinated becomes $m_a(1 - \beta_a)$, which is by definition smaller than m_a. Since the total number of deaths is given by the total number of infected times

[1]The total effectiveness of vaccines is one minus the total failure of vaccines. The total failure of vaccines is given by the product of two terms: ones minus the effectiveness of vaccines preventing infections, $1 - \lambda_a$, and ones minus the effectiveness of vaccines preventing deaths among the infected, $1 - \beta_a$.

the associated fatality rate, we can rewrite (1) as

$$\mathrm{CFR}_{t,a} = \frac{m_a \mathcal{I}^U_{t,a} + m_a(1-\beta_a)\mathcal{I}^V_{t,a}}{d^U_{t,a}\mathcal{I}^U_{t,a} + d^V_{t,a}\mathcal{I}^V_{t,a}}. \tag{2}$$

Taking m_a as common factor and multiplying and dividing by $d^U_{t,a}$ in (2) give

$$\mathrm{CFR}_{t,a} = \frac{m_a}{d^U_{t,a}} \frac{d^U_{t,a}\mathcal{I}^U_{t,a} + (1-\beta_a)d^U_{t,a}\mathcal{I}^V_{t,a}}{d^U_{t,a}\mathcal{I}^U_{t,a} + d^V_{t,a}\mathcal{I}^V_{t,a}}. \tag{3}$$

Next, let us denote by $\gamma_{t,a} = d^V_{t,a}\mathcal{I}^V_{t,a}/(d^U_{t,a}\mathcal{I}^U_{t,a} + d^V_{t,a}\mathcal{I}^V_{t,a})$ the ratio between the total number of COVID vaccine breakthroughs and the total number of COVID-associated ever infected and detected cases. Equivalently, $\gamma_{t,a}$ is the proportion of people ever infected and detected after being vaccinated among all the ever detected people until time t for the age group a. Note that the value of $\gamma_{t,a} \in [0,1)$ will increase the higher is the number of breakthroughs. Using $\gamma_{t,a}$ in (3), the case fatality rate can be written as

$$\mathrm{CFR}_{t,a} = \frac{m_a}{d^U_{t,a}} \left((1-\gamma_{t,a}) + (1-\beta_a)\frac{d^U_{t,a}}{d^V_{t,a}}\gamma_{t,a} \right). \tag{4}$$

Let us denote by $Z_{t,a} = d^V_{t,a}/d^U_{t,a} \leq 1$ the ratio of the detection rates between the vaccinated and the unvaccinated against COVID or, equivalently, the proportion detected among the ever infected after being vaccinated and the proportion detected among the ever infected and unvaccinated, which is realistically assumed to be lower or equal than one. $Z_{t,a} = 1$ implies that the government makes the same effort in detecting infected people among the vaccinated than among the unvaccinated. Substituting $Z_{t,a}$ in (4) gives

$$\mathrm{CFR}_{t,a} = \frac{m_a}{d^U_{t,a}} \left((1-\gamma_{t,a}) + \frac{1-\beta_a}{Z_{t,a}}\gamma_{t,a} \right). \tag{5}$$

Eq. (5) shows that the observed $\mathrm{CFR}_{t,a}$ is the weighted sum of the CFR of the unvaccinated, $\mathrm{CFR}^U_{t,a} = m_a/d^U_{t,a}$, and the CFR of the vaccinated, $\mathrm{CFR}^V_{t,a} = (m_a/d^U_{t,a})((1-\beta_a)/Z_{t,a}) = m_a(1-\beta_a)/d^V_{t,a}$,

$$\mathrm{CFR}_{t,a} = \mathrm{CFR}^U_{t,a}(1-\gamma_{t,a}) + \underbrace{\mathrm{CFR}^U_{t,a}\frac{1-\beta_a}{Z_{t,a}}}_{\mathrm{CFR}^V_{t,a}}\gamma_{t,a}. \tag{6}$$

Thus, Eq. (6) explicitly shows that the observed CFR is driven by the ratio between one minus the effectiveness of the vaccines preventing deaths, $1-\beta_a$, and the ratio of the detection rates between the vaccinated and the unvaccinated, $Z_{t,a}$. Moreover, it is worth noticing that Eq. (6) can be used before the onset of the vaccination campaign (i.e., $\gamma_{t,a} = 0$) as well as once that the vaccination campaign has started (i.e., $\gamma_{t,a} > 0$).

The influence of the detection strategy of breakthroughs on the CFR and the derivation of $\gamma_{t,a}$

It should be expected that the introduction of vaccines would lead the CFR to decline, since vaccinated individuals can still get infected but develop less severe symptoms than unvaccinated individuals (Dagan et al., 2021; Haas et al., 2021; Hall et al., 2021). If the same testing strategy is maintained before and after vaccines and vaccinated people can still get infected, albeit with a lower probability, a declining CFR would unambiguously imply that vaccines are preventing deaths. However, as $\gamma_{t,a}$ increases, Eq. (4) shows that the CFR can either increase or decrease depending on the value of the ratio $(1-\beta_a)/Z_{t,a}$. According to Eq. (4), for $(1-\beta_a)/Z_{t,a}$ greater (resp. lower) than one, the observed CFR will increase (resp. decrease) when $\gamma_{t,a}$ increases. When $(1-\beta_a) = Z_{t,a}$ the CFR will remain unchanged, regardless the fact that the infection fatality rate of the vaccinated is lower than the infection fatality rate of the unvaccinated. To see the impact of the ratio $(1-\beta_a)/Z_{t,a}$ on the CFR, Fig. 3 in the manuscript shows three panels (A, B, and C). Each panel depicts three hypothetical evolutions of the CFR that results from combining a hypothetical effectiveness of the vaccines preventing deaths (conditional on being infected), β_a, and three alternative values of $Z_{t,a}$.

To calculate the numerator of $\gamma_{t,a}$, or the total number of breakthroughs, we slightly modify the standard SIR epidemiological formula in order to account for the vaccinated people. In a standard SIR model the total number of people ever infected until time t, $\mathcal{I}_t$, can be calculated as $\sum_{\tau=0}^{t} R_\tau^{\text{eff}} i_\tau S_\tau$, where R^{eff} is the effective reproduction number, i is the daily incidence rate, and S is the size of the susceptible population. Note that $R_\tau^{\text{eff}} i_\tau$ is equal to $\beta I_\tau / N_\tau$ or the force of infection. Following a similar reasoning, we introduce three modifications. First, we substitute S for the total population vaccinated, which we denote by N^V. Second, taking into account that actual data on the incidence rate only accounts for individuals who are infected and detected, we substitute i for i^d, to make explicit that the incidence rate is calculated with detected people, and multiply i^d by Z in order to specify that the detected corresponds to vaccinated people. This is because most infected people are expected to not be vaccinated. Third, since vaccines can reduce the probability of getting infected, we multiply the effective reproduction number, R^{eff}, by ones minus the effectiveness of vaccines preventing infections, $1-\lambda_a$. Thus, we simulate the proportion of people ever infected and detected after being vaccinated as

$$\frac{d_{t,a}^V \mathcal{I}_{t,a}^V}{d_{t,a}^U \mathcal{I}_{t,a}^U + d_{t,a}^V \mathcal{I}_{t,a}^V} = \frac{\sum_{\tau=0}^{t} ((1-\lambda_a) R_\tau^{\text{eff}})(Z_{\tau,a} i_\tau^d) N_{\tau,a}^V}{\text{Ever infected and detected}_{t,a}}, \tag{7}$$

where the value of λ_a only influences on the amplitude of the difference between

the simulated CFR and the actual CFR values, and not on the direction of the change in the estimated CFR. Effective reproduction numbers are taken from Richter, Schmid, and Stadlober (2020), time series data on incidence rates, population vaccinated, deaths and population ever infected and detected are taken from BMSGPK, Österreichisches COVID-19 Open Data Informationsportal (2021).