Quantifying the real-life impacts of vaccination on critical COVID-19

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Abstract

SARS-CoV-2 vaccines have individual prophylaxis effects. However, quantifying the overall vaccine impact on critical COVID-19 forms is difficult because it requires accounting for the reduction in community spread. Using a transmission model validated with hospital data, we investigated counterfactual scenarios with variable vaccine effects. We estimate a transmissibility reduction from vaccine breakthrough infections of 43% ([32 -- 55]% 95%-likelihood interval) and that 39,100 critical care stays ([26,100 -- 57,100] 95% confidence interval) and 47,400 ([36,200-62,800]) hospital deaths were prevented by the French vaccination campaign by August 20 2021, i.e. a 46% and 57% relative prevention of these outcomes. Despite the greater effectiveness of individual prophylaxis, the largest prevention of critical COVID-19 forms originated from the collective component of vaccine protection. These results are consistent with trends we identify in worldwide data and point towards a community benefit of achieving high vaccine coverages.

Keywords

SARS-CoV-2, critical care, hospital mortality, quantitative epidemiology, modelling, public health.

Introduction

The rapid discovery and deployment of the SARS-CoV-2 vaccines, along with their high efficiency in preventing symptomatic COVID-19, which ranges 66.9 and 95% [1]–[5], has put vaccination at the centre of the fight against the ongoing deadly pandemic[6]. To date, we still lack a quantification of how these vaccines prevent the most severe cases of COVID-19, especially in terms of critical care admissions and deaths. This is particularly important because in many countries the occupancy of critical care units (CCU) is the main criteria used to implement or alleviate lockdowns, which have huge medical, economical, and social consequences.

One possibility to assess the impact of vaccination on severe forms of COVID-19 is to harness the worldwide heterogeneity in vaccine coverage and investigate how mortality is impacted by vaccination. However, this approach is limited because mortality may vary for other reasons than vaccination and in order to quantify the effect of vaccination on critical care stays and death, it is necessary to develop a mathematical model capturing transmission dynamics. This is because anti-SARS-CoV-2 vaccines partially prevent infection [7] and secondary transmission [8], thereby reducing viral community spread.

With more than 70% first-dose vaccine coverage by late August, France is one of the top 10 most vaccinated large countries [6]. It is therefore an ideal case study for assessing the hospital deaths and critical care stays the vaccination program had averted so far and is to prevent by the end of the year. Furthermore, its national hospital admission dynamics are well captured by existing models [9].

Using epidemiological modelling we quantify the direct (purely individual and critical-form related prevention) and indirect (purely collective and exposure-related prevention) impacts of vaccination in France.

Methods

We first assessed vaccine-induced reduction in COVID-19 mortality burden by confronting the current worldwide heterogeneity in vaccine coverage to the relative case fatality ratio (rCFR). The rCFR captures the change in fatality among cases over the past 12 months (thus avoiding seasonality bias) and allows comparing countries with different demography, health and surveillance systems. The function linking vaccine coverage to real-life mortality was then inferred by a generalized additive model (Figure 1). For weighting purposes, we focused on large countries with substantial viral circulation, the data of which are compiled in [6].

Using a published modelling framework tailored for the French COVID-19 epidemic [9] (Supplementary Figure 1), we reconstructed the temporal variations in the infectious contact rate. This contact rate aggregates the effect of non pharmaceutical interventions (NPI), variant-related transmissibility increase, as well as behavioural and weather changes, while controlling for post-infection immunity [10] and the age-stratified vaccine rollout (Supplementary Figure 2).

Vaccination was assumed to have three distinct prophylactic components (Figure 2A):

- i) an anti-infection effect, set to 40%[7], [11] and defined as the reduction in the probability of being infected by the SARS-CoV-2 upon exposure, compared to a non-vaccinated non-immunized individual.
- ii) an anti-critical disease effect, defined as the reduction in probability of developing complications which may lead to critical care and/or hospital death if infected by the SARS-CoV-2, compared to a non-vaccinated individual. Its value was set to reach a 88% reduction of the probability of developing a critical COVID-19 upon exposure in vaccinated people [12].
- iii) an anti-secondary transmission effect, defined as the reduction in contagiousness of vaccine breakthrough infections, as supported by recent results [8]. Given the limited data, this parameter was directly inferred by our framework.

Using the inferred baseline infectious contact rate, we simulated the course of the epidemic according to four vaccination scenarios (Figure 2B): the actual vaccines, purely collective vaccines, purely individual vaccines and without vaccination. We then compared the counterfactual dynamics to data and actual vaccine projections to estimate the prevented number of critical care stays and hospital deaths prevented (see the Supplementary Methods for more details).

Results

Figure 1 exhibits a non-linear trend between relative case fatality ratio (rCFR) and vaccine coverage. While rCFR values below 1 may be explained by testing capacities and hospital care improvements, no vaccine-related fatality reduction is evidenced for low coverage (<30%, first dose). In contrast, once half the population is vaccinated, the rCFR steadily decreases by 12.5% every additional 10% coverage. In particular, the CFR of high coverage European countries is now four times lower than the past 12 month average.

The modelling framework estimated transmissibility from vaccine breakthrough infections to be reduced by 43% ([32 -- 55]% 95%-likelihood interval). Figure 2C shows the actual, projected and counterfactual critical care admissions and hospital deaths dynamics simulated according to the scenarios in Figure 2B. Their comparison suggests that up by August 20, 2021 the French vaccination campaign had already prevented 39,100 critical care stays ([26,100 -- 57,100] 95% confidence interval, CI), i.e. a 46% median relative prevention (RP), and 47,400 ([36,200-62,800]) hospital deaths, i.e. a 57% RP (Table 1). By the end of the year, the median estimates are 67,000 (57% RP) and 78,700 (65% RP) respectively.

As highlighted by the relative positions of curves #2 and #3 in Figure 2C and detailed in Supplementary Table 1, the purely collective (i.e. within-host) component of the vaccine accounts for the majority of the prevented critical COVID-19 illnesses.

Discussion

Several clinical studies and few field studies estimated the efficiency of vaccines to prevent SARS-CoV-2 infections, severe COVID-19, or secondary transmission. However, quantifying the vaccination impact on critical COVID-19 forms, while accounting for both collective and individual vaccine benefits, is challenging. Using a mechanistic mathematical model capturing the hospital dynamics of the COVID-19 epidemic in France, we first estimated that breakthrough infection transmissibility is reduced by >40% compared to infections in non-immunized hosts. Furthermore, by performing counterfactual simulations, we estimated that on August 20, 2021 the vaccination campaign had prevented almost 40,000 critical care stays and more than 47,000 deaths, respectively representing reductions by 46% and 57% of these outcomes. This beneficial effect of vaccination is expected to increase by the end of the year.

Despite the lower effectiveness of vaccines in preventing re-infection and secondary transmission compared to critical illness, the collective component of the prophylaxis accounted for the majority of spared critical care admissions and deaths in the model. This finding is consistent with the non-linear decrease in national fatality ratio with vaccine coverage observed worldwide, which is about 5 times greater if half of the population is vaccinated.

Although the model used was shown to accurately capture critical COVID-19 dynamics [13], several limitations must be noted. First, the hospital-related probabilities rely on the SARS-CoV-2 strains circulating in 2020 [14], but studies indicate a potential increased virulence of lineages circulating in 2021 [15]. Furthermore, vaccination is modelled in a simplified way assuming maximum efficiency 14 days after the first dose. Similarly, in all of the scenarios, the extrapolations until the end of the year rely on the assumption that the infectious contact rate estimated in mid August 2020 will not vary, which is unlikely with, for instance, the beginning of the school term.

Performing similar analysis in other countries would help improve public health policies and vaccination campaigns. This is particularly important given the potential non-linear positive effect of vaccination coverage on reducing critical COVID-19 burden.

Figure 1. Relative case fatality ratio as a function of first-dose vaccine coverage.

Each point corresponds to a country (indicated by its 3-letter ISO code) or the aggregated continent or worldwide point (indicated by background color), the coordinates of which is based on the last data available from [6] on August 20, 2021. For weighting purposes, only countries with more than 10 million inhabitants and more than 1,000 COVID-19 deaths over the last 12 months are considered. The case fatality ratio (CFR) is calculated as the weekly-averaged fraction of COVID-19 confirmed deaths among confirmed cases 14 days earlier (as to account for the test-to-death delay). In order to circumvent testing effort, death reporting and age pyramid heterogeneities for comparison purposes, we here show the relative case fatality ratio (rCFR) on the y-axis, defined as the CFR divided by its average value over the last year time period (Aug 21 2020 - Aug 20 2021). The pink curve and grey shaded area corresponds to mean and 95% confidence interval of a generalized additive model (GAM) regression.

Figure 2. Critical care stays and hospital mortality in counterfactual scenarios with variable vaccine effects .

A. Schematic view of vaccine effect modelling. Each shield represents a quantitative reduction in the probability of event occurrence. The three prophylactic components are: prevention against infection (yellow shield), prevention against secondary transmission (red shield) and prevention against critical COVID-19 (blue shield).

B. The counterfactual scenarios include all (1), none (4) or some, either purely collective (2) or purely individual (3), prophylactic components of the vaccine. The anti-infection component has both individual and collective impacts so its reduction has to be transferred to the other components in scenarios 2 and 3 to decipher between direct and indirect vaccine benefits. Note that because scenarios 3 and 4 induce a major increase in critical care stays, NPI (or any equivalent behavioural change) have to be applied to cap CCU overload.

C. Critical care stays and hospital mortality in France in 2021 (including projections). The time window spans over 2021 (the vaccination campaign started on Dec 27, 2020 in France). Dots show the actual cumulative counts, which are initialized on the first day of the French COVID-19-related hospital database SI-VIC [16], on Mar 18 2020. Scenario labels are those of panel B. The projected trends are based on the Aug 14 - Aug 20 2021 reproduction number assuming no other change in the epidemiological dynamics apart from the increase in vaccine and post-infection population immunity. The solid curves represent the median output of the simulated models while the shaded area represents the 95% range spanned by the simulations.

	Up to Aug 20 2021 (data compared to no-vaccine scenario)		Up to Dec 31 2021 (actual vaccine projection compared to no-vaccine scenario)	
Prevented outcomes	<i>n</i> [95% CI]	RP (%) [95% CI]	<i>n</i> [95% CI]	RP (%) [95% CI]
Critical care stays	39,100 [26,100 -- 57,100]	46 [36 -- 55]	67,000 [51,800 -- 86,100]	57 [47 -- 64]
Hospital deaths	47,400 [36,200 -- 62,800]	57 [50 -- 64]	78,700 [65,800 -- 97,300]	65 [58 -- 71]

Table 1. Critical care stays and hospital deaths prevented by the anti-SARS-CoV-2 vaccination in France according to the no-vaccine counterfactual model.

n: median absolute number, CI: compatibility interval, RP: median relative prevention.

Conflict of interest

None.

Funding

None.

Ethics

The Institutional Review Board of the Nîmes university hospital approved this study (see <https://doi.org/10.1016/j.accpm.2020.10.012>).

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References

- [1] F. P. Polack *et al.*, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine', *N. Engl. J. Med.*, vol. 383, no. 27, pp. 2603–2615, Dec. 2020, doi: 10.1056/NEJMoA2034577.
- [2] L. R. Baden *et al.*, 'Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine', *N. Engl. J. Med.*, vol. 0, no. 0, p. null, Dec. 2020, doi: 10.1056/NEJMoA2035389.
- [3] M. Voysey *et al.*, 'Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK', *The Lancet*, vol. 397, no. 10269, pp. 99–111, Jan. 2021, doi: 10.1016/S0140-6736(20)32661-1.
- [4] P. T. Heath *et al.*, 'Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine', *N. Engl. J. Med.*, Jun. 2021, doi: 10.1056/NEJMoA2107659.
- [5] J. Sadoff *et al.*, 'Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19', *N. Engl. J. Med.*, vol. 384, no. 23, pp. 2187–2201, Jun. 2021, doi: 10.1056/NEJMoA2101544.
- [6] M. Roser, H. Ritchie, E. Ortiz-Ospina, and J. Hasell, 'Coronavirus pandemic (COVID-19)', *Our World Data*, 2020, [Online]. Available: <https://ourworldindata.org/coronavirus>
- [7] A. Puranik *et al.*, 'Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence', *Public and Global Health*, preprint, Aug. 2021. doi: 10.1101/2021.08.06.21261707.
- [8] M. C. Shamier *et al.*, 'Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers', Aug. 2021. doi: 10.1101/2021.08.20.21262158.
- [9] M. T. Sofonea *et al.*, 'Memory is key in capturing COVID-19 epidemiological dynamics', *Epidemics*, vol. 35, p. 100459, Jun. 2021, doi: 10.1016/j.epidem.2021.100459.
- [10] V. J. Hall *et al.*, 'SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN)', *The Lancet*, vol. 397, no. 10283, pp. 1459–1469, Apr. 2021, doi: 10.1016/S0140-6736(21)00675-9.
- [11] Health Ministry of Israel, 'Epidemiological report', Jul. 2021. Accessed: Aug. 12, 2021. [Online]. Available: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf
- [12] Public Health England, 'SARS-CoV-2 variants of concern and variants under investigation', 17, Jun. 2021. [Online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1001354/Variants_of_Concern_VOC_Technical_Briefing_17.pdf
- [13] M. T. Sofonea and S. Alizon, 'Anticipating COVID-19 intensive care unit capacity strain: A look back at epidemiological projections in France', *Anaesth. Crit. Care Pain Med.*, (in press), doi: 10.1016/j.accpm.2021.100943.
- [14] M. O'Driscoll, C. Harry, C. A. Donnelly, A. Cori, and I. Dorigatti, 'A comparative analysis of statistical methods to estimate the reproduction number in emerging epidemics with implications for the current COVID-19 pandemic', *Epidemiology*, preprint, May 2020. doi: 10.1101/2020.05.13.20101121.
- [15] K. A. Twohig *et al.*, 'Hospitalisation risk for SARS-CoV-2 Delta (B.1.617.2) compared with Alpha (B.1.1.7) variants of concern: a cohort study', Jul. 2021, doi: 10.17863/CAM.72862.

Supplementary Material

Supplementary Methods

Worldwide overview

The case fatality ratio (CFR), i.e. the frequency of COVID-19 deaths among reported cases, was calculated by dividing the 7-day-averaged daily mortality by the 7-day-averaged daily incidence 14 days earlier. For weighting purposes, we focused on large countries with substantial viral circulation (>10 million inhabitants and >1,000 COVID-19 deaths). For each country, we considered the average CFR calculated on the most recent days of available data in [6]. CFRs are difficult to compare because of strong differences between countries in terms of spatial and temporal testing, death reporting, demography, and epidemic waves. To minimise these effects and reduce the sources of heterogeneity specific to a country, we computed a relative case fatality ratio (rCFR) by scaling each country's CFR with its mean value computed between 21 August 2020 and 20 August, 2021. The 12 months duration was chosen for the normalisation because vaccination was deployed from 0 to almost 80% first-dose vaccine coverage and because a shorter interval could introduce biases related to seasonality. Intuitively, if the rCFR is greater than 1, it means that the countries' CFR decreased in the last 12 months. We then studied the link between the rCFR and the vaccination coverage in the 68 countries analysed using a generalized additive model (GAM) regression to capture non-linear trends.

Epidemiological modelling

The inference proceeded as described in [9], based on the French COVID-19-related hospital database SI-VIC [16] up to Aug 20 2021. The reference model/actual vaccine scenario (#1 in Figure 2B) consisted in a pool of 101 equivalent parameter sets in the sense of hospital mortality likelihood over the whole course of the epidemic. The median relative error on the the cumulative hospital deaths and critical care stays (summed from Mar 19 2020) of the inferred model compared to Santé Publique France data was respectively of -2.7% ([-6.2 -- 1.1]% 95% range) and -0.6% ([-5.8 -- 5.3]%). The epidemic simulated with the reference model after the last datapoint was based on the trend observed on the last documented week (Aug 14 - 20 2021), with no further change in parameters after that time point, thus optimistically assuming a slow decay in epidemic during fall, which is not guaranteed as the schools reopens and the weather cools down.

Based on the aforementioned conservative settings and the underlying inferred baseline contact ratio of the reference model, we investigated three counterfactual scenarios (#2, #3 and #4 in Figure 2B). Because in the counterfactual scenarios #3 (purely individual vaccines) and #4 (no vaccination) the vaccine contribution to the reduction in SARS-CoV-2 community spread is absent, the incidence grows faster than in the reference model once the third metropolitan French lockdown has been lifted. To account for the fact that the epidemic wave would not fully unfolded for various reasons (e.g. local and national implementations non pharmaceutical interventions, spontaneous behavioural change, spatial saturation [18]), we imposed a uniform correction factor on the baseline transmission rate from June 9 2021 (when major national restrictions were lifted) so that the median daily ICU admission would not exceeds 700 patients nationwide, which was the order of magnitude at the peak of the first wave [16]. This translated respectively in a 23% and 30% reduction of the contact rate for the direct-benefit-only model and no-vaccine model respectively. Finally, we estimate the number of ICU admissions and hospital deaths prevented by the vaccine by comparing the simulated outputs of the two counterfactuals models to the actual data and projected reference model respectively for the Aug 20 and Dec 31 2021 time points. Note that the compatibility intervals associated to the latter time point are based on the quantile of pairwise comparisons between runs of each model.

Supplementary Figures & Table

Supplementary Figure 1. Epidemiological model (COVIDSIM) structure with vaccination (for a given age class).

In the model, each age class is split into compartments (here depicted by the figurines) according to their infectious, clinical and immunological statuses. Susceptible individuals (in yellow) can be infected if exposed to the SARS-CoV-2 particles emitted by infected individuals in the community (in pink). A fraction of infected individuals develop a critical COVID-19 form, defined as requiring critical care and/or leading to hospital death. Vaccination is implemented following the VAC-SI time series [17] and assumed to reduce the probability of three events, namely being infected if exposed, transmitting the virus if infected and developing critical complications if infected. Additionally, we assume that all individuals having recovered from a post-vaccine infection are immunized, contrary to unvaccinated individuals a fraction of which can become infected again [10]. Formal and parametrization details are provided in [9], the system of which was updated according to this flow chart.

Supplementary Figure 2. Nationwide vaccine rollout in France (actual and projected). The colored curves represent the relative proportion of first-dose vaccinated people in each age class according to the French VAC-SI database [17], while the black line corresponds to the populationwide vaccine coverage. The vaccine rollout extrapolation is based on the Aug 14 - Aug 20 2021 figures and capped at 99% for each age class. The vertical orange bar represents the day of the last datatpoint.

	purely individual vaccines (scenario 3 compared to scenario 4)				purely collective vaccines (scenario 2 compared to scenario 4)			
	Up to Aug 20 2021		Up to Dec 31 2021		Up to Aug 20 2021		Up to Dec 31 2021	
Prevented outcomes	<i>n</i> [95% CI]	RP (%) [95% CI]	<i>n</i> [95% CI]	RP (%) [95% CI]	<i>n</i> [95% CI]	RP (%) [95% CI]	<i>n</i> [95% CI]	RP (%) [95% CI]
Critical care stays	18,700 [6,900 -- 32,300]	22 [8.7 -- 34]	24,700 [9,900 -- 43,900]	21 [9.1 -- 33]	38,700 [29,300 -- 51,300]	45 [38 -- 53]	55,300 [35,500 -- 76,100]	47 [32 -- 58]
Hospital deaths	34,000 [25,000 -- 45,400]	41 [32 -- 49]	51,600 [38,800 -- 70,200]	43 [35 -- 51]	45,200 [37100 -- 56,000]	54 [48 -- 60]	71,200 [55,600 -- 90,600]	59 [49 -- 66]

Supplementary Table 1. Critical care stays and hospital deaths prevented by the individual and the collective components of anti-SARS-CoV-2 vaccination in France according to counterfactual models.

n: median absolute number, CI: compatibility interval, RP: median relative prevention.

Supplementary bibliography

- [16] Santé Publique France, 'Données hospitalières relatives à l'épidémie de COVID-19 - data.gouv.fr', 2020. <https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19/> (accessed Aug. 13, 2021).
- [17] Santé Publique France, 'Données relatives aux personnes vaccinées contre la Covid-19 (VAC-SI) - data.gouv.fr', 2021. <https://www.data.gouv.fr/fr/datasets/donnees-relatives-aux-personnes-vaccinees-contre-la-covid-19-1/> (accessed Aug. 13, 2021).
- [18] O. Thomine, S. Alizon, M. Barthelemy, C. Boennec, and M. T. Sofonea, 'Emerging dynamics from high-resolution spatial numerical epidemics', Apr. 2021, doi: 10.5281/zenodo.4680003.