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ORIGINAL ARTICLE

Impact of prior SARS-COV-2 infection and vaccination on COVID-19 hospital admission and mortality amongst nursing home residents

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Abstract

Background Nursing home residents (NHRs) have experienced disproportionately high risk of severe outcomes due to COVID-19 infection.

Aim We investigated the impact of COVID-19 vaccinations and previous SARS-CoV-2 episodes in preventing hospitalization and mortality in NHRs.

Methods Retrospective study of a cohort of all NHRs in our area who were alive at the start of the vaccination campaign. The first three doses of SARS-CoV-2 vaccine and prior COVID-19 infections were registered. The main outcomes were hospital admission and mortality during each follow up. Random effects time-varying Cox models adjusted for age, sex, and comorbidities were fitted to estimate hazard ratios (HRs) according to vaccination status.

Results COVID-19 hospitalization and death rates for unvaccinated NHRs were respectively 2.39 and 1.42 per 10,000 person-days, falling after administration of the second dose (0.37 and 0.34) and rising with the third dose (1.08 and 0.8). Rates were much lower amongst people who had previously had COVID-19. Adjusted HRs indicated a significant decrease in hospital admission amongst those with a two- and three-dose status; those who had had a previous COVID-19 infection had even lower hospital admission rates. Death rates decreased as NHRs received two and three doses, and the probability of death was much lower among those who had previously had the infection.

Conclusions The effectiveness of current vaccines against severe COVID-19 disease in NHRs remains high and SARS-CoV-2 episodes prior to vaccination entail a major reduction in hospitalization and mortality rates. The protection conferred by vaccines appears to decline in the following months.

Trial registration ClinicalTrials.gov Identifier: NCT04463706.

Keywords SARS-CoV-2 · COVID-19 · COVID-19 vaccines · Hospitalization · Mortality

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Introduction

The outbreak of disease caused by the novel severe respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization on March 11, 2020 [1]. In clinical trials, current SARS-CoV-2 vaccines have performed well in preventing breakthrough infection, hospitalization, and mortality amongst the general population [2–4]. Nursing home residents (NHRs), a frail and vulnerable population, have experienced disproportionately high levels of COVID-19 infection and higher risk for severe COVID-19 outcomes [5]. However, this group was not included in COVID-19 vaccine clinical trials [2, 3] and only limited data are available on the effectiveness of vaccines among NHRs. Throughout the world, there is a scarcity of real-world studies evaluating the efficiency of the vaccine and more such studies are needed.

The coronavirus is constantly mutating, and its variants pose new challenges in terms of transmission, COVID-19 severity, and efficacy of vaccines [6]. Immunity caused by vaccines wanes over time and reinfections have been reported among persons who have completed a primary vaccination series [7–9]. This decrease in vaccine efficacy is greatest amongst persons aged 65 and over [10]. Booster dose campaigns have been introduced to combat a loss in immunity, due to the emergence of new variants such as Delta and Omicron and a possible decline in vaccine-elicited immunity.

In this study, we investigated the effectiveness of licensed mRNA COVID-19 vaccines in preventing COVID-19 adverse outcomes, as measured by hospital admissions and mortality, in NHRs. We estimated the relative effectiveness of a (third) booster dose of vaccine as compared to unvaccinated individuals and those who had received only two doses. We compared the estimated protection among those who had already been infected with SARS-COV-2 before being vaccinated and those who were vaccinated without a prior COVID-19 infection, and evaluated the potential waning of vaccine effectiveness (VE) on adverse outcomes according to the time elapsed since vaccination.

Methods

This is a retrospective study of a cohort of patients living in nursing homes in our area based on data from the electronic database and health records of our public health service.

All patients included in the study were resident in nursing homes in our region. Data identifying people living in nursing homes were obtained from the Basque Health Department. Only patients aged over 60 years were included. We excluded all short-stay NHRs (deceased in a period of less than 30 days, or patients discharged from the residence who had not died within a period of 3 months after discharge), those with erroneous vaccination dates and those who died before the start of the vaccination campaign on December 27, 2020. The study protocol was approved by the Ethics Committee for our area (reference PI2020123). All patient data were kept confidential. All data on patients in the care of our health service are held in a unified electronic database. Analysts retrieved data for all NHRs during the study period including sociodemographic data, baseline comorbidities, prescribed treatments, data related to care provided in hospital, including dates of hospital admission and discharge, and the main outcomes of the study.

We recorded SARS-CoV-2 infections for each patient from the start of the pandemic on March 1, 2020 to January 31, 2022. COVID-19 was laboratory-confirmed by a positive result on the reverse transcriptase-polymerase chain reaction assay for SARS-CoV-2 or a positive antigen test. From March 1, 2020 to July 31, 2020, positive IgM or IgG antibody tests performed due to patients displaying symptoms of the disease or having had contact with a positive case were also included in the sample. Positive readings from the same patient were included if the difference between the date of one positive and the next was ≥ 120 days.

We monitored unvaccinated participants from the beginning of the vaccination campaign until the first vaccine dose plus 14 days, or death, or the end of the study (May 31, 2022). Those with one dose were then switched to "one vaccine dose" status. We monitored participants with one dose from the day they received the first dose plus 14 days until the date of the second dose of vaccine, or death or the end of the study. Those who received a second dose were switched to the "two vaccine dose" status. We monitored participants with two doses from the day they received the second dose until the date of the third dose, or death or the end of the study. Those with a third dose were switched to "three vaccine dose" status. Finally, we monitored participants with three-doses from the day they received the third dose until death or the end of the study. We thus treated exposure as time-varying, and a single participant may be included in all four statuses (unvaccinated, one-dose, two-dose and three-dose).

The outcomes used in the study were as follows: (1) Hospital admission due to COVID-19, defined if admission occurred within 15 days of the patient's testing positive, when the positive test preceded hospitalization, and up to 10 days after admission when the patient tested positive during hospitalization. The follow-up for hospital admission was up to February 15, 2022; and (2) Death was defined as

having occurred during the 3 months following diagnosis or after discharge if admitted to a hospital or during a hospital admission as defined previously or three months from discharge. All patients were monitored to May 31, 2022.

Statistical analysis

Descriptive statistics were generated, including frequency tables for categorical variables and mean and standard deviations (SDs) for continuous variables. Patient characteristics were compared between never-vaccinated and ever-vaccinated NHRs using chi-square or Fisher's exact tests for categorical variables, and Student's *t*-test for continuous variables.

Vaccination was analyzed as a time-varying exposure with four follow-up intervals: (1) No vaccination: from 27 December 2020 until first dose vaccination plus 14 day run-in (where applicable), or outcome, or death or end of the study; (2) One vaccination dose: from date of administration of first dose plus 14 day run-in to date of the second dose, or outcome, or death, or end of the study; (3) Two vaccination doses: from date of administration of the second dose to the third dose, or outcome, or death, or end of the study; and (4) Three vaccination doses: from date of administration of the third dose to the outcome, or death, or the end of the study. For each of these periods, we calculated the rate of outcomes per 10,000 person days. We fitted random effect time-varying Cox models to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for each study outcome according to the vaccination status. All Cox models considered the index date (the month/year in which an individual changed vaccination status) as a random effect and were adjusted for age, sex and baseline comorbidities [11]. We also used the Cox models to estimate HRs for each study outcome according to previous COVID-19 infection in each vaccination status. Kaplan–Meier curves were also plotted stratified by vaccination status and according to previous COVID-19 infection.

All effects were considered significant at $p < 0.05$. All statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Carey, NC), and R© version 4.0.4.

Results

Our study includes 17,475 NHRs. In the online flow-chart (Fig. 1) we show how the samples were obtained. By the end of the study period, 16,856 (96.46%) NHRs had been vaccinated with at least one dose. Online Table 1 compares the main baseline characteristics between never-vaccinated and ever-vaccinated sample groups. Online Table 2 shows data prior to the vaccination period on the incidence of

Table 1 Number and incidence rates for hospital admission for COVID-19 according to vaccination dose status among nursing home residents

Status	Population	Cases	Exposure person-days	Exposure days (mean)	Rate per 10,000 person-days	Adjusted hazard ratio (95% CI)*	*p* value*
Unvaccinated	**17,475**	**177**	**739,555**	**42.32**	**2.39**	**Ref**	**–**
No previous COVID-19	13,014	168	578,945	44.49	2.90	Ref	–
Previous COVID-19	4,461	9	160,610	36	0.56	0.19 (0.10–0.37)	< 0.0001
Vaccinated – one dose, from day 14	**16,719**	**15**	**135,415**	**8.10**	**1.11**	**0.46 (0.19–1.08)**	**0.0750**
No previous COVID-19	11,872	15	94,718	7.98	1.11	–	–
Previous COVID-19	4,847	0	40,697	8.40	0	–	–
Vaccinated – two doses, from 2nd dose date	**16,518**	**139**	**3,727,488**	**225.66**	**0.37**	**0.15 (0.07–0.32)**	**< 0.0001**
No previous COVID-19	11,664	122	2,613,165	224.04	0.47	Ref	–
Previous COVID-19	4,854	17	1,114,323	229.57	0.15	0.34 (0.21–0.57)	< 0.0001
Vaccinated – three doses, from 3rd dose date	**13,108**	**186**	**1,722,273**	**131.39**	**1.08**	**0.13 (0.06–0.30)**	**< 0.0001**
No previous COVID-19	8,721	156	1,144,163	131.20	18.55	Ref	–
Previous COVID-19	4,387	30	578,110	131.78	9.13	0.38 (0.25–0.56)	< 0.0001

Bold is used for remark the 4 groups, as per vaccine doses

The rate is calculated by dividing the number of observed events within a period by the number of days of exposure, multiplied by 10,000

CI Confidence interval

*Adjusted for age, sex and comorbidities

Adjusted hazard ratio (95% CI) of those vaccinated with **two doses vs. one dose** from day 14: **0.33 (0.18–0.61), $p = 0.0004$**

Adjusted hazard ratio (95% CI) of those vaccinated with **three doses vs. two doses**: **0.87 (0.46–1.63), $p = 0.6500$**

hospitalizations and deaths in the same population, with rates of 2.14 and 1.98 per 10,000 person-days, respectively.

Table 1 and Online Figure 2a show hospital admission rates, which decreased from the unvaccinated status (rate of 2.39), to the two-dose status (0.37) and three-dose status (1.08). Adjusted HRs for hospital admission for both two and three-dose statuses were statistically significant ($p < 0.0001$) compared to the unvaccinated status. Within each vaccination status, subjects who had had a previous COVID-19 infection had lower hospital admission rates, with statistically significant adjusted HRs ($p < 0.0001$) (Table 1 and Online Figure 3). Of those who had been infected with COVID-19, hospitalization rates among the unvaccinated and one-dose statuses were high. The rate decreased considerably for two and three- dose statuses, with significant adjusted HRs with respect to the unvaccinated status ($p < 0.0001$) (Table 2, Online Figure 4a). Subjects who had previously had a COVID-19 infection had lower hospitalization rates in the unvaccinated and one-dose status than those with no previous COVID-19 infection (Table 2 and Online Figure 5), but the difference was not significant.

Table 3 and Online Fig. 2b show the results for death rates according to vaccination status and previous COVID-19 infection. We found statistically significant adjusted HRs for death in both two and three-dose statuses as compared to the unvaccinated status (HR = 0.21 with $p < 0.0001$, and HR = 0.12 with $p = 0.0001$, respectively). Moreover, death rates were much lower among those who had previously had the infection in all vaccination statuses (Table 3 and Online Fig. 6), with significant adjusted HRs ($p < 0.0001$). Finally, death rates among those who were infected with COVID-19 (Table 4 and Online Fig. 4b) were high in the unvaccinated and one-dose statuses (rates, 14.62 and 45.96, respectively) and decreased in the two and three dose statuses (rates, 5.38 and 3.81, respectively), with significant adjusted HRs as compared to the unvaccinated status ($p < 0.0001$). We also found significant differences in the adjusted HR between three-dose and two-dose status (HR = 0.53, $p < 0.0001$). Subjects who had previously had a COVID-19 infection had lower death rates in the unvaccinated and one-dose status than those with no previous COVID-19 infection (Table 4 and Online Fig. 7); however we found no significant adjusted HRs.

Discussion

Nursing home residents comprise a significant population that have been underrepresented in clinical trials to date despite being affected to a disproportionately high degree by COVID-19 [5, 11]. NHRs have been shown to have a higher risk of COVID-19 infection, hospitalization, and death than the elder population more generally [12, 13].

Table 2 Number and incidence rates for hospital admission due to COVID-19 among people infected according to vaccination dose status among nursing home residents

Status	COVID + Population	Cases	Exposure person-days	Exposure days (mean)	Rate per 10,000 person-days	Adjusted hazard ratio (95% CI)*	*p* value*
Unvaccinated	**809**	**177**	**61,741**	**76.32**	**28.67**	**Ref**	**–**
No previous COVID-19	758	168	55,713	73.50	30.15	Ref	–
Previous COVID-19	51	9	6,028	118.20	14.93	0.69 (0.35–1.37)	0.2900
Vaccinated – one dose, from day 14	**120**	**15**	**3,823**	**31.86**	**39.24**	**1.23 (0.71–2.12)**	**0.4600**
No previous COVID-19	116	15	3,387	29.20	44.29	–	–
Previous COVID-19	4	0	436	109	0	–	–
Vaccinated – two doses, from 2nd dose date	**805**	**139**	**203,653**	**252.99**	**6.83**	**0.32 (0.23–0.44)**	**< 0.0001**
No previous COVID-19	715	122	178,644	249.85	6.83	Ref	–
Previous COVID-19	90	17	25,009	277.88	6.80	1.07 (0.63–1.81)	0.7900
Vaccinated – three doses, from 3rd dose date	**2,649**	**186**	**357,146**	**134.82**	**5.21**	**0.25 (0.16–0.37)**	**< 0.0001**
No previous COVID-19	2,122	156	285,676	134.63	5.46	Ref	–
Previous COVID-19	527	30	71,470	135.62	4.20	0.74 (0.50–1.09)	0.1300

Bold is used for remark the 4 groups, as per vaccine doses

The rate is calculated by dividing the number of observed events within a period by the number of days of exposure, multiplied by 10,000

CI Confidence interval

*Adjusted for age, sex and comorbidities

Adjusted hazard ratio (95% CI) of those vaccinated with **two doses vs. one dose** from day 14: **0.26 (0.14 – 0.46), $p < 0.0001$**

Adjusted hazard ratio (95% CI) of those vaccinated with **three doses vs. two doses**: **0.78 (0.54 – 1.12), $p = 0.1800$**

Table 3 Number and incidence rates for death due to COVID-19 according to vaccination dose status among nursing home residents

Status	Population	Cases	Exposure person-days	Exposure days (mean)	Rate per 10,000 person-days	Adjusted hazard ratio (95% CI)*	*p* value*
Unvaccinated	**17,475**	**109**	**765,059**	**43.78**	**1.42**	**Ref**	**–**
No previous COVID-19	13,014	104	598,905	46.02	1.74	Ref	–
Previous COVID-19	4,461	5	166,154	37.25	0.30	0.16 (0.06–0.39)	< 0.0001
Vaccinated – one dose, from day 14	**16,719**	**19**	**136,776**	**8.18**	**1.39**	**0.76 (0.42–1.38)**	**0.3700**
No previous COVID-19	11,872	18	95,554	8.05	1.88	–	–
Previous COVID-19	4,847	1	41,222	8.50	0.24	–	–
Vaccinated – two doses, from 2nd dose date	**16,518**	**129**	**3,840,892**	**232.53**	**0.34**	**0.21 (0.13–0.33)**	**< 0.0001**
No previous COVID-19	11,664	117	2,700,330	231.51	0.43	Ref	–
Previous COVID-19	4,854	12	1,140,562	234.97	0.11	0.26 (0.14–0.47)	< 0.0001
Vaccinated – three doses, from 3rd dose date	**13,108**	**235**	**2,939,430**	**224.25**	**0.80**	**0.12 (0.07–0.18)**	**0.0001**
No previous COVID-19	8,721	197	1,946,817	223.23	1.01	Ref	–
Previous COVID-19	4,387	38	992,613	226.26	0.38	0.37 (0.26–0.53)	< 0.0001

Bold is used for remark the 4 groups, as per vaccine doses

The rate is calculated by dividing the number of observed events within a period by the number of days of exposure, multiplied by 10,000

CI Confidence interval

*Adjusted for age, sex and comorbidities

Adjusted hazard ratio (95% CI) of those vaccinated with **two doses vs. one dose** from day 14: **0.28 (0.15–0.50), $p < 0.0001$**

Adjusted hazard ratio (95% CI) of those vaccinated with **three doses vs. two doses**: **0.55 (0.37–0.81), $p = 0.0022$**

Table 4 Number and incidence rates for deaths due to COVID-19 among people infected according vaccination dose status among nursing home residents

Status	COVID + Population	Cases	Exposure person-days	Exposure days (mean)	Rate per 10,000 person-days	Adjusted hazard ratio (95% CI)*	*p* value*
Unvaccinated	**809**	**109**	**74,537**	**92.13**	**14.62**	**Ref**	**–**
No previous COVID-19	758	104	67,252	88.72	15.46	Ref	–
Previous COVID-19	51	5	7,285	142.84	6.86	0.52 (0.21–1.31)	0.1700
Vaccinated – one dose, from day 14	**120**	**19**	**4,134**	**34.45**	**45.96**	**2.35 (1.41–3.91)**	**0.0010**
No previous COVID-19	116	18	3,698	31.88	48.67	–	–
Previous COVID-19	4	1	436	109	22.94	–	–
Vaccinated – two doses, from 2nd dose date	**805**	**129**	**239,725**	**297.80**	**5.38**	**0.46 (0.32–0.64)**	**< 0.0001**
No previous COVID-19	715	117	209,407	292.88	5.59	Ref	–
Previous COVID-19	90	12	30,318	336.87	3.96	0.74 (0.40–1.36)	0.3300
Vaccinated – three doses, from 3rd dose date	**2,649**	**235**	**616,951**	**232.90**	**3.81**	**0.24 (0.17–0.35)**	**< 0.0001**
No previous COVID-19	2,122	197	493,177	232.41	3.99	Ref	–
Previous COVID-19	527	38	123,774	234.87	3.07	0.77 (0.54–1.09)	0.1400

Bold is used for remark the 4 groups, as per vaccine doses

The rate is calculated by dividing the number of observed events within a period by the number of days of exposure, multiplied by 10,000

CI Confidence interval

*Adjusted for age, sex and comorbidities

Adjusted hazard ratio (95% CI) of those vaccinated with **two doses vs. one dose** from day 14: **0.19 (0.11–0.34), $p < 0.0001$**

Adjusted hazard ratio (95% CI) of those vaccinated with **three doses vs. two doses**: **0.53 (0.39–0.71), $p < 0.0001$**

We evaluated COVID-19 VE in preventing severe COVID-19 (measured using hospital admission and mortality). Over this study period, the incidence of hospitalization and mortality among the "unvaccinated", remained at a similarly high level as in the "pre-vaccination" period.

From a clinical perspective, we found greater significance in the VE in reducing the risk of severe COVID-19 outcomes, measured using hospital admission and mortality, among patients with proven COVID-19 infection. We calculated the HRs of hospitalization and mortality for the three-dose vs. two-dose statuses, and for the two-dose vs. one-dose and unvaccinated statuses. We found a significant decrease for all HRs for mortality, and between two-dose status vs one or unvaccinated statuses in hospital admissions as well. These results suggest that individuals who received booster doses have a lower probability of severe disease than those receiving two or one doses. This finding was also consistent with the results from other studies [14–21].

Protection against severe forms of disease remained constant during the period of prevalence of the Omicron variant. This may be because neutralizing antibodies are not the only immune measure of protection, and induced cellular immunity can also protect against these new variants [22, 23]. Previous reports have indicated that T-cell immunity might have a role in preventing severe SARS-CoV-2 infection [24, 25]. T-cell immunity appears to be unaffected by changes in spike protein and remains active in preventing severe disease [26].

For all vaccination statuses, this protection was much more striking among patients who had had a COVID-19 infection prior to vaccination than among those with no previous infection. We found this hybrid immunity even after a single dose. Patients with an infection prior to their vaccination have been shown to generate significantly higher anti-peak IgG titers than those who were also vaccinated but had no prior infection [27]. The risk of serious infection substantially decreased among patients who had recovered from a previous infection and were subsequently vaccinated, and even among individuals who were previously infected but remained unvaccinated. Other authors [28–33] have also reported these results among people with previous primary infection. The immunity response from vaccination is more consistent than that from natural infection, because Ac neutralizers from vaccination bind more broadly to the receptor binding domain (RBD) than do those from SARS-CoV-2 infection [34]. Even after having the infection, the vaccines protect better against SARS-CoV-2, promoting the neutralizing antibody response and the cellular immune response [9, 35].

The present study also showed a decrease in VE over time, principally from the third month after the vaccine was administered, when the loss of effectiveness against infection was more marked and the decrease in protection against hospitalization and mortality less significant. This decrease in VE is probably due to decreased immunity and is associated with Omicron infection. Observational studies have suggested that vaccine protection against SARS-CoV-2 infection wanes over time [7–10]. Receiving three doses vs. two doses counteracts declining immunity in the short term. The third dose induces a much more pronounced IgG response than the second dose [36].

Vaccination is still beneficial for most patients. Given that studies suggest that humoral immunity among NHRs wanes considerably in the months following vaccination, it appears to be necessary to administer an additional dose of COVID-19 to NHRs to optimize immune response. Furthermore, previous SARS-CoV-2 episodes entail a reduction in severe disease for all vaccination statuses, demonstrating clear natural protection. Future studies are needed to assess whether repeated booster doses or new specific bivalent vaccines against Omicron or new variants should be considered to protect this fragile and vulnerable population.

Among its strengths, this is a real-time study among a large NHR cohort of the effectiveness of different vaccine doses and previous SARS-CoV-2 infection, with extensive follow-up and adjustment for multiple variables such as age, sex, and comorbidities, on robust outcomes such as COVID-19 hospital admissions or death.

At the same time, it also has certain limitations. With regard to the identification of previous COVID-19 infections, there is no way of knowing how many asymptomatic vaccinated patients had previously been infected, since PCRs were only performed on symptomatic patients or those suspected of having the disease. Titers of neutralizing antibodies as a response to vaccine were not examined. The genetic characterization of the virus was not available in the study periods, although we know approximately that the predominant variants were Delta (between July and December 2021) and Omicron (December 2021-April 2022).

Conclusions

Based on our results, the effectiveness of current vaccines against severe disease remains high, albeit this protection was lower against Omicron infection and despite a slight decrease three months after full vaccination. Moreover, previous SARS-CoV-2 episodes before vaccination are associated with an important reduction in hospitalization and mortality rates, for all vaccination statuses, indicating a clear hybrid immunity effect. The finding that the protection conferred by mRNA vaccines waned in the months after receipt of a third dose reinforces the importance of further consideration of additional (booster) doses to optimize protective immunity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-023-02446-3.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by PPE, AB-G, NL, IC-S, JP, AV, MJL, MG, and JMQ. The first draft of the manuscript was written by PPE, ABi-G, and JMQ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials The data associated with this study will be made available upon submission of a request to their authors after approval of a proposal and with a signed data access agreement.

Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

Statement of human and animal rights The study protocol was approved by the Ethics Committee of the Basque Country (reference PI2020123).

Informed consent The Basque Country Ethics Committee (PI2020123) approved the waiver of informed consent in this study due to the pandemic exceptional conditions and retrospective design.

Registration ClinicalTrials.gov Identifier: NCT04463706.

References

1. WD-GsORatMBoC–M (2020) https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 20 Apr 2020
2. Polack FP, Thomas SJ, Kitchin N et al (2020) Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 383:2603–15. https://doi.org/10.1056/NEJMoa2034577
3. Baden LR, El Sahly HM, Essink B et al (2021) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 384:403–16. https://doi.org/10.1056/NEJMoa2035389
4. Self Wesley H, Tenforde Mark W et al (2021) Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions – United States, March-August 2021. MMWR Morb Mortal Wkly Rep 70:1337–1343. https://doi.org/10.15585/mmwr.mm7038e1
5. Morciano M, Stokes J, Kontopantelis E et al (2021) Excess mortality for care home residents during the first 23 weeks of the COVID-19 pandemic in England: a national cohort study. BMC Med 19:71. https://doi.org/10.1186/s12916-021-01945-2
6. Sandro MH, Tamires DAS, Renata G et al (2022) SARS-COV-2 variants: differences and potential of immune evasion. Front Cell Infect Microbiol 11:781429. https://doi.org/10.3389/fcimb.2021.781429
7. Feikin DR, Higdon MM, Abu-Raddad LJ et al (2022) Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet 399:924–944. https://doi.org/10.1016/S0140-6736(22)00152-0
8. Andrews N, Tessier E, Stowe J et al (2022) Duration of protection against mild and severe disease by COVID-19 vaccines. N Engl J Med 386:340–350. https://doi.org/10.1056/NEJMoa2115481
9. Zhong D, Xiao S, Debes AK et al (2021) Durability of antibody levels after vaccination with mRNA SARS-CoV-2 vaccine in individuals with or without prior infection. JAMA 326:2524–2526. https://doi.org/10.1001/jama.2021.19996
10. Braeye T, Catteau L, Brondeel R et al (2022) Vaccine effectiveness against onward transmission of SARS-CoV2-infection by variant of concern and time since vaccination, Belgian contact tracing, 2021. Vaccine 40:3027–3037. https://doi.org/10.1016/j.vaccine.2022.04.025
11. Cabezas Carmen, Coma Ermengol, Mora-Fernandez Nuria et al (2021) Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study. BMJ 374:n1868. https://doi.org/10.1136/bmj.n1868
12. Pierobon Silvia, Braggion Marco, Fedeli Ugo et al (2022) Impact of vaccination on the spread of SARS-CoV-2 infection in northeast Italy nursing homes. A propensity score and risk analysis. Age Ageing 51:afab224. https://doi.org/10.1093/ageing/afab224
13. España PP, Bilbao-Gonzalez A, Larrea N et al (2023) Impact of prior SARS-CoV-2 infection and vaccination on COVID-19 infection among nursing home residents. J Am Med Dir Assoc. https://doi.org/10.1016/j.jamda.2023.03.013
14. Muhsen K, Maimon N, Mizrahi A et al (2022) Effects of BNT162b2 Covid-19 vaccine booster in long-term care facilities in Israel. N Engl J Med 386:399–401. https://doi.org/10.1056/NEJMc2117385
15. Ridgway JP, Tideman S, French T et al (2022) Odds of hospitalization for COVID-19 after 3 vs 2 doses of mRNA COVID-19 vaccine by time since booster dose. JAMA 328:1559–1561. https://doi.org/10.1001/jama.2022.17811
16. Ferdinands JM, Rao S, Dixon BE et al (2022) Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19–associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance—VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 71:255–263. https://doi.org/10.15585/mmwr.mm7107e2
17. Accorsi EK, Britton A, Fleming-Dutra KE et al (2022) Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta

variants. JAMA 327:639–651. https://doi.org/10.1001/jama.2022.0470
18. Butt AA, Talisa VB, Shaikh OS et al (2022) Relative vaccine effectiveness of a SARS-CoV-2 mRNA vaccine booster dose against the omicron variant. Clin Infect Dis. https://doi.org/10.1093/cid/ciac328
19. Andrews N, Stowe J, Kirsebom F et al (2022) Effectiveness of COVID-19 booster vaccines against COVID-19-related symptoms, hospitalization and death in England. Nat Med 28:831–837. https://doi.org/10.1038/s41591-022-01699-1
20. Havers FP, Pham H, Taylor CA et al (2022) COVID-19-associated hospitalizations among vaccinated and unvaccinated adults 18 years or older in 13 US States, January 2021 to April 2022. JAMA Intern Med 182:1071–1081. https://doi.org/10.1001/jamainternmed.2022.4299
21. Bar-On YM, Goldberg Y, Mandel M et al (2021) Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 385:1393–1400. https://doi.org/10.1056/NEJMoa2114255
22. Pajon R, Doria-Rose NA, Shen X et al (2022) SARS-CoV-2 omicron variant neutralization after mRNA-1273 booster vaccination. N Engl J Med 386:1088
23. Wu M, Wall EC, Carr EJ et al (2022) Three-dose vaccination elicits neutralising antibodies against omicron. Lancet 399:715
24. Tarke A, Coelho CH, Zhang Z et al (2022) SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from alpha to omicron. Cell 185:847-859.e11. https://doi.org/10.1016/j.cell.2022.01.015
25. Keeton R, Tincho MB, Ngomti A et al (2022) T cell responses to SARS-CoV-2 spike cross-recognize Omicron. Nature 603:488–492. https://doi.org/10.1038/s41586-022-04460-3
26. Hui DS (2022) Hybrid immunity and strategies for COVID-19 vaccination. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(22)00640-5
27. Helle F, Moyet J, Demey B et al (2022) Humoral anti-SARS-CoV-2 immune response after two doses of Comirnaty vaccine in nursing home residents by previous infection status. Vaccine 40:531–535. https://doi.org/10.1016/j.vaccine.2021.11.086
28. DiPiazza AT, Graham BS, Ruckwardt TJ (2021) T cell immunity to SARS-CoV-2 following natural infection and vaccination. Biochem Biophys Res Commun 538:211–217. https://doi.org/10.1016/j.bbrc.2020.10.060
29. Abu-Raddad LJ, Chemaitelly H, Ayoub HH et al (2021) Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. JAMA 326:1930–1939. https://doi.org/10.1001/jama.2021.19623
30. Hammerman A, Sergienko R, Friger M et al (2022) Effectiveness of the BNT162b2 vaccine after recovery from Covid-19. N Engl J Med 386:1221–1229. https://doi.org/10.1056/NEJMoa2119497
31. Hall V, Foulkes S, Insalata F et al (2022) Protection against SARS-CoV-2 after Covid-19 vaccination and previous infection. N Engl J Med 386:1207–1220. https://doi.org/10.1056/NEJMoa2118691
32. Goldberg Y, Mandel M, Bar-On YM et al (2022) Protection and waning of natural and hybrid immunity to SARS-CoV-2. N Engl J Med 386:2201–2212. https://doi.org/10.1056/NEJMoa2118946
33. Nordström P, Ballin M, Nordström A (2022) Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. Lancet Infect Dis 22:781–790. https://doi.org/10.1016/S1473-3099(22)00143-8
34. Greaney Allison J, Loes Andrea N, Gentles Lauren E et al (2021) Antibodies elicited by mRNA-1273 vaccination bind more broadly to the receptor binding domain than do those from SARS-CoV-2 infection. Sci Transl Med 13:eabi9915. https://doi.org/10.1126/scitranslmed.abi9915
35. Clemens SAC, Weckx L, Clemens R et al (2022) Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet 399:521–529. https://doi.org/10.1016/S0140-6736(22)00094-0
36. Jeulin H, Labat C, Duarte K et al (2022) Anti-spike IgG antibody kinetics following the second and third doses of BNT162b2 vaccine in nursing home residents. J Am Geriatr Soc 70:2552–2560. https://doi.org/10.1111/jgs.17837