Effectiveness of a Second Dose of an mRNA Vaccine Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Omicron Infection in Individuals Previously Infected by Other Variants

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Background. Single-dose vaccination was widely recommended in the pre-Omicron era for persons with previous SARS-CoV-2 infection. The effectiveness of a second vaccine dose in this group in the Omicron era is unknown.

Methods. We linked nationwide population registries in Spain to identify community-dwelling individuals aged 18–64, with a positive SARS-CoV-2 test before single-dose mRNA vaccination (mRNA-1273 or BNT162b2). Every day between 3 January and 6 February 2022 we matched 1:1 individuals receiving a second mRNA vaccine dose and controls on sex, age, province, first dose type and time, month of primary infection, and number of previous tests. We then estimated Kaplan–Meier risks of confirmed SARS-CoV-2 reinfection. We performed a similar analysis in a Delta-dominant period, between 19 July and 30 November 2021.

Results. In the Omicron period, estimated effectiveness (95% CI) of a second dose was 62.2% (58.2–66.4%) 7–34 days after administration, similar across groups defined by age, sex, type of first vaccine, and time since the first dose. Estimated effectiveness was 65.4% (61.1–69.9%) for mRNA-1273 and 52.0% (41.8–63.1%) for BNT162b2. Estimated effectiveness was 78.5% (67.4–89.9%), 66.1% (54.9–77.5%), and 60.2% (55.5–64.8%) when primary infection had occurred in the Delta, Alpha, and pre-Alpha periods, respectively. In the Delta period, the estimated effectiveness of a second dose was 8.8% (−55.3% to 81.1%).

Conclusions. Our results suggest that, over 1 month after administration, a second dose of mRNA vaccine increases protection against SARS-CoV-2 reinfection with the Omicron variant among individuals with single-dose vaccination and previously infected with another variant.

Keywords. COVID-19; SARS-CoV-2; Omicron; vaccines; effectiveness.

Adequate protection against infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant requires at least 2 doses of mRNA vaccines in persons not previously infected. However, it is unknown whether a second dose is necessary in individuals with prior infection. In fact, 13 countries in Europe, Spain among them, considered single-dose vaccination as complete vaccination for individuals with a previously confirmed SARS-CoV-2 infection [1–3].

The decision to withhold the second dose was supported by findings of high vaccine effectiveness and long-term preservation of the protection afforded by 1 vaccine dose in previously infected individuals [4–14]. However, these findings predated the emergence of the Omicron variant, which has an increased capacity to elude immunity [15–18]. Even if a second vaccine dose were unnecessary to protect previously infected individuals against reinfection with the Delta variant, a second dose may be necessary to provide adequate protection against reinfection with the Omicron variant. Several countries, including Spain, recommended a second dose to individuals with prior infection in the Omicron era as part of the population-wide booster campaign [2].

Here we estimate the effectiveness of a second dose of mRNA vaccine against confirmed SARS-CoV-2 reinfection, during a period of Omicron predominance, in individuals under 65 years of age with previous infection and who had received a single

dose after the primary infection. We estimated the effectiveness among residents of Spain overall and by age, sex, calendar period of the primary infection, interval between the first and the second vaccine dose, type of vaccine used as first dose, and type of vaccine used as second dose.

METHODS

Study Population

We used a unique personal identifier to link individual-level data from the Vaccination Registry (REGVACU) and the Laboratory Results Registry (SERLAB), both updated daily and with nationwide coverage. SERLAB includes all SARS-CoV-2 polymerase chain reaction (PCR) and rapid antigen tests performed by healthcare providers and, since 21 December 2021, it also includes results from self-administered rapid antigen tests from certain regions. We subtracted 2 days from PCR test results to approximate the date of sample collection. To increase the probability that individuals were present in Spain during the study period, we restricted the study to individuals successfully matched in the National Health System registry, which virtually includes the full population accessing the healthcare system in Spain. We excluded individuals who were only temporarily entitled to access the health system.

Specification of the Target Trial

Our observational study emulated a target trial to estimate the effect of the administration of a second dose of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines for the prevention of reinfection with SARS-CoV-2 in a period of Omicron SARS-CoV-2 dominance among individuals who had a previous infection followed by just 1 dose of the vaccine. Recruitment was from 3 January 2022, when Omicron was more than 90% [19] of SARS-CoV-2–detected variants in Spain, to 6 February 2022.

Eligibility criteria were age between 18 and 64 years at first vaccine dose, laboratory-confirmed SARS-CoV-2 infection before first vaccine dose and before Omicron became more than 50% of circulating variants (27 December 2021), entitlement to access healthcare in Spain, vaccination with a first vaccine dose of mRNA-1273 or BNT162b2 at least 19 days ago and during the period recommended for their age group (to exclude essential workers, particularly in the education sector, immunosuppressed individuals, and others with different probability of infection than the general population), not a member of groups with specific vaccine recommendations (eg, nursing home residents, institutionalized individuals, healthcare workers), and no documented SARS-CoV-2 reinfection after first vaccine dose.

In the target trial, eligible persons would be randomly assigned to either administration of a second dose of an mRNA vaccine (mRNA-1273 or BNT162b2) or to no additional vaccine dose within strata defined by age, sex, province, time since first vaccination, time since previous infection, type of vaccine used as primary vaccination, and number of previous SARS-CoV-2 diagnostic tests. The outcome of interest was laboratory-confirmed SARS-CoV-2 infection.

Emulation of the Target Trial

We extracted the data on 14 February 2022. Each day between 3 January and 6 February 2022 we identified persons who met the eligibility criteria and classified them as either having or not having received a second dose on that day. Each person who received a second dose was matched to a randomly selected control (with replacement) on sex, age (5-year groups), province, type of vaccine used in the first dose, week of the first dose, month of the previous SARS-CoV-2 positive test, and total number of SARS-CoV-2 tests (both positive and negative) since the beginning of the pandemic (1, 2, ≥3). Eligible individuals could be selected as controls up to the day before the second dose. For each matched pair, follow-up started on the day of administration of the second dose and finished at the earliest of laboratory-confirmed SARS-CoV-2 infection, death or discontinuation of registration in the National Health System database, or 6 February 2022. We censored both members of a matched pair if/when the control received a second vaccine dose.

Statistical Analysis

We constructed cumulative incidence (risk) curves of laboratory-confirmed SARS-CoV-2 infection using the Kaplan–Meier estimator [20]. We compared the risks 7 or more days after the second vaccine dose via differences and ratios, and estimated effectiveness as 1 – risk ratio in all matched pairs in which both individuals were still at risk by day 7. We conducted analyses in the entire eligible population and in subgroups defined by age group, sex, type of vaccine used in the first dose, type of vaccine used in the second dose and time interval between the first and the second vaccine dose, and by calendar period when the primary infection occurred: pre-Alpha period (up to 7 February 2021), Alpha period (from 8 February to 4 July 2021), and Delta period (from 5 July to 26 December 2021).

For comparison purposes, we emulated a similar target trial, except that we included individuals who received the second vaccine dose between 19 July and 30 November 2021 (the period where Delta was ≥ 90% of all circulating variants) and their controls.

We carried out sensitivity analyses (1) restricted to persons with no test in the 7 days before time zero (to exclude contacts of cases or other persons exposed to SARS-CoV-2 who had tested early in their infection); in other sensitivity analyses, we (2) restricted to persons without any reported positive test in the previous 90 days, (3) used dates of laboratory tests as recorded
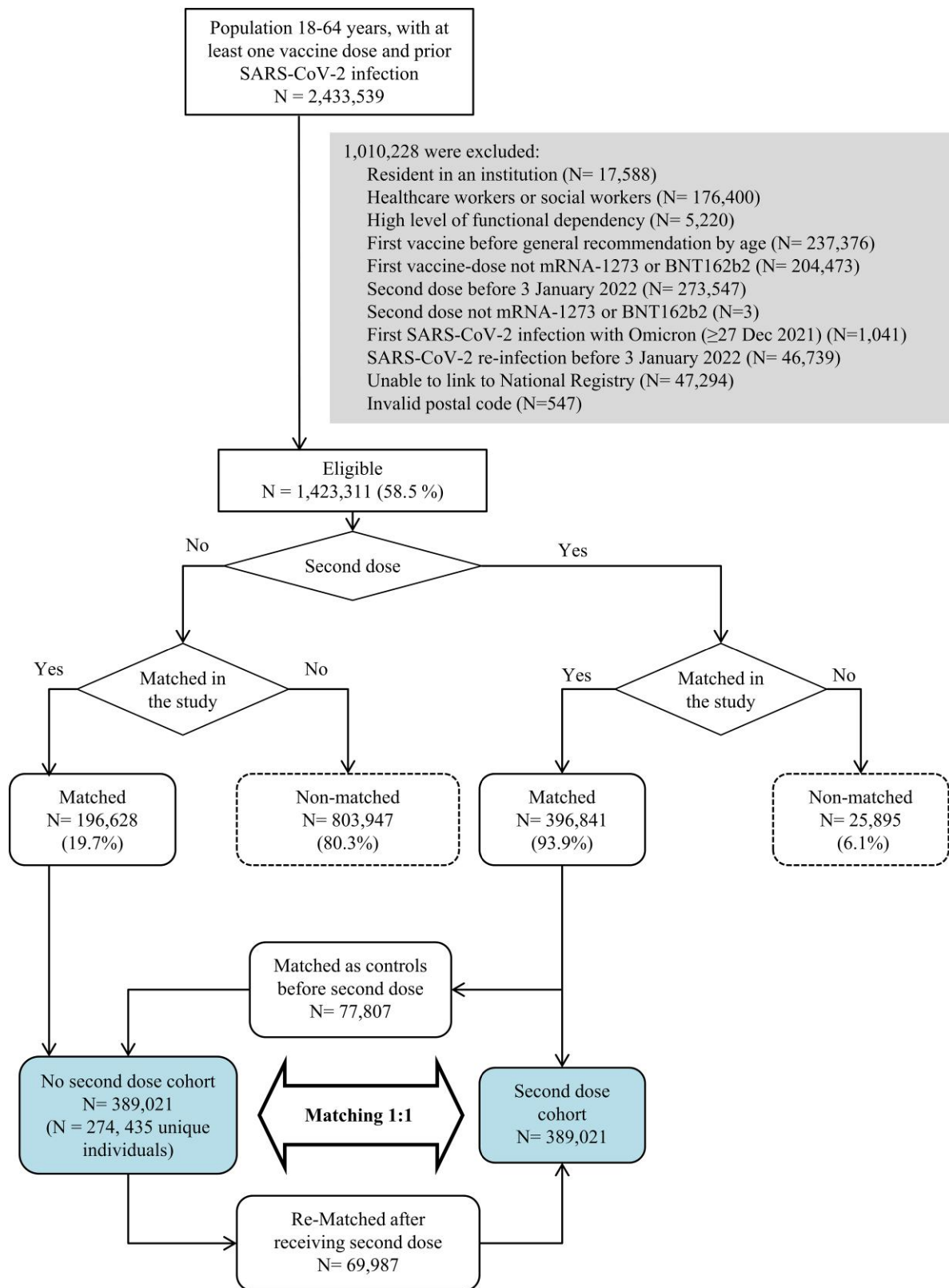
Figure 1. Sample selection flowchart. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Baseline Characteristics of the Matched Study Population, Spain: 3 January–6 February 2022

	Second Dose (n = 389 021)	No Second Dose (n = 389 021)
Age (years)		
18–24	39 634 (10.2%)	40 289 (10.4%)
25–29	28 184 (7.2%)	28 204 (7.2%)
30–34	37 831 (9.7%)	37 156 (9.6%)
35–39	39 138 (10.1%)	40 047 (10.3%)
40–44	61 104 (15.7%)	61 286 (15.8%)
45–49	58 242 (15.0%)	58 391 (15.0%)
50–54	67 199 (17.3%)	66 497 (17.1%)
55–59	47 454 (12.2%)	46 588 (12.0%)
60–64	10 235 (2.6%)	10 563 (2.7%)
Sex		
Female	193 464 (49.7%)	193 464 (49.7%)
Male	195 557 (50.3%)	195 557 (50.3%)
Number of previous SARS-CoV-2 tests		
1	129 127 (33.2%)	129 127 (33.2%)
2	106 158 (27.3%)	106 158 (27.3%)
≥3	153 736 (39.5%)	153 736 (39.5%)
Type of vaccine used as first dose		
mRNA-1273	74 281 (19.1%)	74 281 (19.1%)
BNT162b2	314 740 (80.9%)	314 740 (80.9%)
Type of vaccine used as second dose		
mRNA-1273	268 869 (69.1%)	…
BNT162b2	120 152 (30.9%)	…
Time interval since vaccination with first dose		
≤90 days	5179 (1.3%)	5179 (1.3%)
91–150 days	26 136 (6.7%)	26 136 (6.7%)
151–180 days	109 646 (28.2%)	109 646 (28.2%)
>180 days	248 060 (63.8%)	248 060 (63.8%)
Period of primary infection		
Pre-Alpha	296 929 (76.3%)	297 372 (76.4%)
Alpha	73 239 (18.8%)	72 923 (18.7%)
Delta	18 853 (4.8%)	18 726 (4.8%)

Data are presented as n (%). Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(rather than subtracting 2 days for PCR tests), and (4) censored matched pairs 7 days after the control received a booster (rather than on the date of the booster).

We computed 95% confidence intervals (CIs) using nonparametric bootstrapping with 500 samples. Analyses were performed with R software version 4.1.2 (R Foundation for Statistical Computing).

This study was approved by the Research Ethics Committee at the Instituto de Salud Carlos III (approval no. CEI PI 98_2020 and CEI PI 08_2022).

RESULTS

Omicron Period

Of 2.4 million eligible individuals, 0.4 million received a second vaccine dose during the Omicron period, 69.2% with mRNA-1273 and 30.8% with BNT162b2 (Figure 1). We could match 389 021 individuals who received a second dose to the same number of controls who had not received the second dose up to that day (Table 1). Compared with the originally eligible population, the matched sample was slightly older, had used more frequently the BNT162b2 vaccine, both as the first and second dose, and corresponded more frequently to individuals first infected in the pre-Alpha period (Supplementary Table 1). The median age was 44 years.

Maximum follow-up was 34 days, and the median (interquartile range [IQR]) follow-up was 10 (5–17) days; 32% of pairs were censored because the control individual received a second dose. During 9.1 million person-days, 3212 laboratory-confirmed SARS-CoV-2 infections occurred in the group who received the second dose and 6147 in the control group. The 34-day risk was 15.6 per 1000 in the second-dose group and 33.6 per 1000 in the control group (Figure 2). The number of tests per 1000 person-days 7 or more days after the booster (and before a coronavirus disease 2019 [COVID-19] diagnosis) was 2.0 in the group who received the second dose and 2.3 in the control group, of which less than 0.01% were recorded as self-tests in both groups. The respective positivity rates were 9.7% and 21.4% (Supplementary Figure 1).

The overall estimated effectiveness (95% CI) of the second dose was 62.2% (57.9–66.0%) at days 7–34 and 60.4% (53.8–66.7%) at days 14–34. Estimated effectiveness increased progressively to stabilize around day 7 (Supplementary Figure 2). The estimated number of cases averted at days 7–34 was 14.9 per 1000 individuals (13.4–16.4) (Figure 2, Table 2).

The estimated effectiveness (95% CI) was similar in subgroups defined by age, sex, type of vaccine used as first dose, or time elapsed since the first dose (Supplementary Figures 3–6, Table 2), but decreased with time since period of primary infection: 78.5% (64.4–87.0%) for individuals infected during the Delta period, 66.1% (52.7–75.8%) for the Alpha period, and 60.2% (55.2–65.1%) for the pre-Alpha period (Figure 3, Table 2). The estimated effectiveness of the second dose was higher for the mRNA-1273 vaccine (65.4%; 60.8–69.8%) than for the BNT162b2 vaccine (52.0%; 39.9–61.3%) (Supplementary Figure 7, Table 2). The effectiveness of a second dose of mRNA-1273 was 61.1% (47.9–71.4%) when the first dose had been mRNA-1273 and 66.3% (61.3–70.8%) when the first dose had been BNT162b2. The effectiveness of a second dose of BNT162b2 was 51.8% (39.8–61.2%) when the first dose had been BNT162b2, and 63.0% (29.4–83.8%) when the first dose had been mRNA-1273.

In sensitivity analyses, the estimated effectiveness of an mRNA booster at days 7–34 in the Omicron era ranged between 59.8% and 64.1% (Supplementary Table 2).

Delta Period

We could match 56 819 individuals who received a second dose to the same number of controls who had not received the
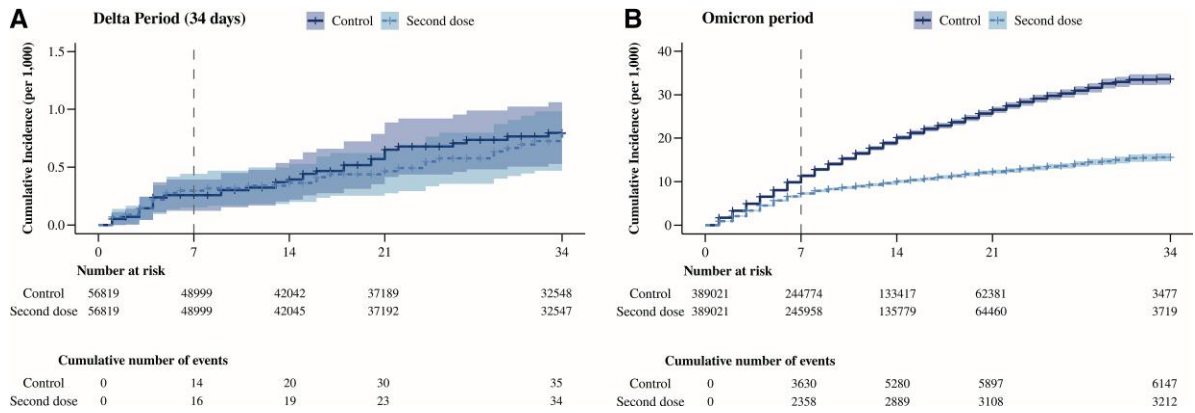
Figure 2. Estimates of COVID-19 risk by administration of a second vaccine dose, in individuals with infection prior to first vaccination, by period of administration of the second vaccine dose, Spain. (*A*) Delta period: 19 July–30 November 2021; (*B*) Omicron period: 3 January–6 February 2022. Abbreviation: COVID-19, coronavirus disease 2019.

second dose up to that day (Supplementary Figure 8, Supplementary Table 3). The median age was 37 years and maximum follow-up was 133 days; the median (IQR) follow-up was 47 (13–98) days. During 6.4 million person-days, 65 laboratory-confirmed SARS-CoV-2 infections occurred in the group who received the second dose and 65 in the control group. In the first 34 days after study entry, during 2.8 million

person-days, 34 and 35 laboratory-confirmed SARS-CoV-2 infections occurred, respectively.

The number of tests per 1000 person-days 7 or more days after the booster (and before a COVID-19 diagnosis) was 1.4 in the group who received the second dose and 0.9 in the control group. The positivity rates were 1.1% and 1.8%, respectively. In the first 34 days of follow up, the number of tests were,

Table 2. Estimated Effectiveness of a Second COVID-19 Vaccine Dose Against Laboratory-Confirmed SARS-CoV-2 Infection, Among Individuals Who Had Received a Single Vaccine Dose and Had a Laboratory-Confirmed Infection Before the First Vaccination, Spain: 3 January 3–6 February 2022

	Second Dose		No Second Dose			
	Events	Risk per 1000	Events	Risk per 1000	1 − Risk Ratio (95% CI)	Risk Difference per 1000 (95% CI)
Overall	999	9.1	2,858	24.0	62.2% (57.9–66.0%)	14.9 (13.4–16.4)
Age (years)						
18–24	72	7.6	190	22.8	66.9% (52.9–76.2%)	15.3 (10.2–19.7)
25–49	645	11.1	1775	27.3	59.5% (53.5–64.9%)	16.2 (14.0–18.8)
50–64	282	7.0	893	19.7	64.7% (57.1–71.3%)	12.8 (10.8–15.0)
Sex						
Female	548	10.0	1594	26.7	62.6% (56.6–68.1%)	16.7 (14.6–19.0)
Male	451	8.2	1264	21.4	61.7% (55.4–67.8%)	13.2 (11.2–15.4)
Type of vaccine used as first dose						
mRNA-1273	158	7.6	399	19.6	61.0% (48.2–71.4%)	11.9 (8.9–15.3)
BNT162b2	841	9.4	2459	25.0	62.4% (57.8–66.5%)	15.6 (13.8–17.2)
Type of vaccine used as second dose						
mRNA-1273	704	8.7	2179	25.1	65.4% (60.8–69.8%)	16.4 (14.7–18.1)
BNT162b2	295	10.2	679	21.3	52.0% (39.9–61.3%)	11.1 (8.2–14.0)
Time interval since vaccination with first dose						
≤90 days	22	6.2	48	17.6	65.0% (41.9–81.0%)	11.4 (5.3–18.0)
91–150 days	64	8.4	184	24.0	65.1% (51.4–76.9%)	15.6 (10.9–21.0)
151–180 days	225	8.8	651	21.9	59.9% (48.4–68.8%)	13.1 (9.8–16.2)
>180 days	688	9.4	1975	24.6	61.6% (56.7–66.4%)	15.2 (13.4–17.2)
Period of primary infection						
Pre-Alpha	854	9.7	2,354	24.5	60.2% (55.2–65.1%)	14.7 (13.0–16.5)
Alpha	119	6.8	407	20.1	66.1% (52.7–75.8%)	13.3 (9.7–16.9)
Delta	26	5.8	97	27.1	78.5% (64.4–87.0%)	21.2 (14.0–28.4)

Analyses based on 242 892 matched pairs who remained under follow-up by day 7 after the booster dose. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
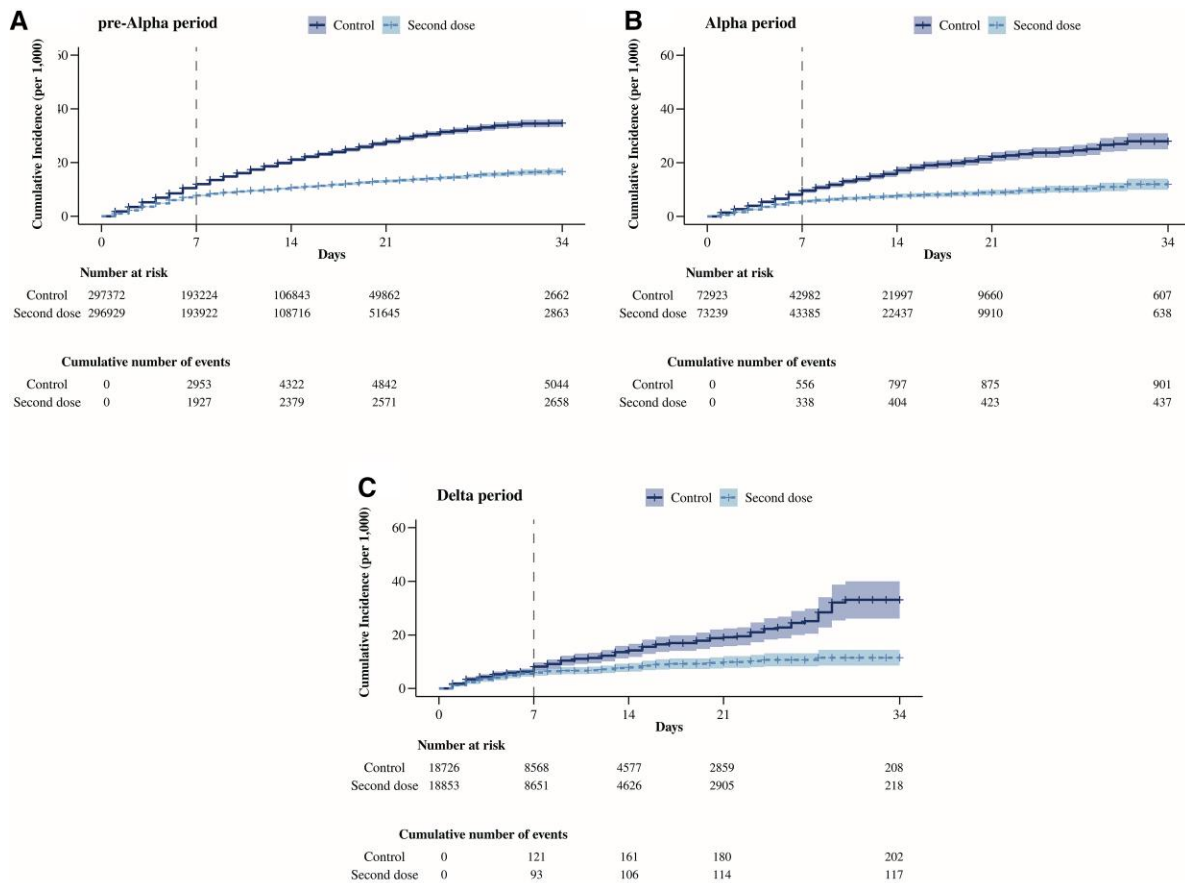
Figure 3. Estimates of COVID-19 risk in individuals with SARS-CoV-2 infection before the first dose, by period of previous infection, Spain: 3 January to 6 February 2022. (*A*) Pre-Alpha period: up to 7 February 2021; (*B*) Alpha period: 8 February to 4 July 2021; (*C*) Delta period: 5 July–26 December 2021. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

respectively, 2.0 and 3.1 per 1000 person-days, and positivity rates were 1.1% and 1.8%.

The 34-day risk was 0.80 per 1000 in both groups; the 133-day risk was 2.75 per 1000 in the group who received the second dose and 2.36 per 1000 in the control group (Figure 3). The estimated effectiveness (95% CI) was 8.8% (−79.8% to 54.2%) at days 7–34, −5% (−122.5% to 49.6%) at days 14–34, −16.9% (−93.1% to 33.8%) at days 7–133, and −21.3% (−109.9% to 28.2%) at days 14–133 (Supplementary Figure 9).

In sensitivity analyses, the estimated effectiveness of an mRNA booster at days 7–133 in the Delta period ranged between −35.1% and 28.6% (Supplementary Table 4) and at days 7–34 ranged between −50.3% and 12.1% (Supplementary Table 5).

DISCUSSION

In a nationwide follow-up study among individuals who had prior SARS-CoV-2 infection and had received a single-dose vaccine, we estimated that a second dose of an mRNA vaccine had an effectiveness of 62% during the Omicron period and of 8.8% during the Delta period, although this latter estimate was imprecise. These findings support current vaccination policies that recommend a second dose in the Omicron period, even if a second dose was not estimated to provide any benefit during the Delta period.

Our estimates are compatible with, but more precise than, those from a recent study in the Omicron era in people with previous infection [10], which also estimated a lower incidence of infection (hazard ratio: .77; 95% CI: .53–1.12) and symptomatic COVID-19 (hazard ratio: .36; 95% CI: .23–.57) among those who did versus those who did not receive a second dose. We did not find a benefit of administering a second vaccine dose to people with previous infection during the Delta period, which is consistent with previous findings of no benefit of a second dose in periods with circulation of Alpha or Delta [1, 7, 9, 10, 21]. The shorter time elapsed between the first and the second dose in the study sample for the Delta period is unlikely to explain this lower estimated effectiveness, since vaccine effectiveness did not vary by time since vaccination in the Omicron period.

In this analysis we estimated a higher effectiveness (95% CI) of a second dose among individuals with a prior SARS-CoV-2

infection (62.2%; 58.2–66.4%) than the effectiveness of a third dose in individuals without previously documented infection (51%; 50–52%) in the same population [22]. Also, the absolute risk of infection between days 7–34 of follow-up was lower in people with previous infection and a single vaccine dose (24.0 per 1000) than in people without previously documented infection with 2 vaccine doses (36.2 per 1000). The effectiveness was higher for an additional dose of the mRNA-1273 vaccine than of the BNT162b2 vaccine, which is consistent with previous findings in studies of individuals without documented infection [22, 23]. Effectiveness was estimated to be greater for heterologous regimens, especially when the first dose was BNT162b2, than for homologous regimens.

Like previous studies [1, 24], our findings indicate that the protection afforded by 1 vaccine dose in people with previous infection does not wane after a few months. For example, we found a risk of infection of 24.0 per 1000 in people who had received their vaccine dose 91–150 days ago and of 24.6 per 1000 in those who had received it more than 180 days ago. Also, the estimated effectiveness of the second vaccine dose did not vary depending on the elapsed interval since the first dose, as was also seen in a recent study in the United Kingdom [24].

Our study has some limitations. First, the higher number of tests in the first days of follow-up in the control group suggests that some symptomatic individuals who were already infected could not be excluded from that group. However, this bias is transient and of limited magnitude, and thus unlikely to influence our estimates of effectiveness. Second, self-tests are not consistently captured in the registry. Although the similar number of recorded tests during follow-up in the 2 groups makes it unlikely that this misclassification is differential, the absolute risks may be underestimated. Third, we could only estimate the effectiveness through 34 days of follow-up. The duration of protection against Omicron conferred by an additional vaccine in those people with previous infection will need to be monitored over time. Finally, severity of disease and/or symptoms were not assessed.

In conclusion, our study suggests that a second dose increases protection against infection with the SARS-CoV-2 Omicron variant up to 34 days after administration among individuals previously infected with another variant and who had received 1 vaccine dose.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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