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Effectiveness of mRNA vaccine boosters against infection with the SARS-CoV-2 omicron (B.1.1.529) variant in Spain: a nationwide cohort study

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Summary

Background The omicron (B.1.1.529) variant of SARS-CoV-2 has increased capacity to elude immunity and cause breakthrough infections. The aim of this study was to estimate the effectiveness of mRNA-based vaccine boosters (third dose) against infection with the omicron variant by age, sex, time since complete vaccination, type of primary vaccine, and type of booster.

Methods In this nationwide cohort study, we linked data from three nationwide population registries in Spain (Vaccination Registry, Laboratory Results Registry, and National Health System registry) to select community-dwelling individuals aged 40 years or older, who completed their primary vaccine schedule at least 3 months before the start of follow-up, and had not tested positive for SARS-CoV-2 since the start of the pandemic. On each day between Jan 3, and Feb 6, 2022, we matched individuals who received a booster mRNA vaccine and controls of the same sex, age group, postal code, type of vaccine, time since primary vaccination, and number of previous tests. We estimated risk of laboratory-confirmed SARS-CoV-2 infection using the Kaplan-Meier method and compared groups using risk ratios (RR) and risk differences. Vaccine effectiveness was calculated as one minus RR.

Findings Between Jan 3, and Feb 6, 2022, 3 111 159 matched pairs were included in our study. Overall, the estimated effectiveness from day 7 to 34 after a booster was 51·3% (95% CI 50·2–52·4). Estimated effectiveness was 52·5% (51·3–53·7) for an mRNA-1273 booster and 46·2% (43·5–48·7) for a BNT162b2 booster. Effectiveness was 58·6% (55·5–61·6) if primary vaccination had been with ChAdOx1 nCoV-19 (Oxford–AstraZeneca), 55·3% (52·3–58·2) with mRNA-1273 (Moderna), 49·7% (48·3–51·1) with BNT162b2 (Pfizer–BioNTech), and 48·0% (42·5–53·7) with Ad26.COV2.S (Janssen). Estimated effectiveness was 43·6% (40·0–47·1) when the booster was administered between 151 days and 180 days after complete vaccination and 52·2% (51·0–53·3) if administered more than 180 days after primary scheduled completion.

Interpretation Booster mRNA vaccine-doses were moderately effective in preventing infection with the omicron variant of SARS-CoV-2 for over a month after administration, which indicates their suitability as a strategy to limit the health effects of COVID-19 in periods of omicron variant domination. Estimated effectiveness was higher for mRNA-1273 compared with BNT162b2 and increased with time between completed primary vaccination and booster.

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Introduction

Two doses of mRNA vaccines greatly reduce the risk of both SARS-CoV-2 infections and severe COVID-19, but protection starts to wane a few months after their administration.[1–3] For the delta (B.1.617.2) variant of SARS-CoV-2, the administration of a booster at least 5 months after the second dose of an mRNA vaccine restores or increases the protection against infection and disease in all age groups,[4–7] and thus boosters 3–6 months after the second dose have been recommended by many countries.[8,9]

Between September, 2021, and January, 2022, the use of an mRNA booster in Spain was approved for increasingly younger age groups to encompass all individuals aged 40 years or older.[10] The recommended interval between completing the primary vaccination schedule and receiving a booster was 6 months (changed to 5 months on Jan 13, 2022) for those vaccinated with mRNA vaccines and 3 months for those who received other vaccines.[11,12] As of Jan 3, 2022, 90% of the population older than 12 years were fully vaccinated and 52% of people over 40 years old had received a booster.[13]

In December, 2021, the omicron variant (B.1.1.529) of SARS-CoV-2 rapidly became dominant worldwide.[14] The emergence of the omicron variant resulted in the highest ever COVID-19 incidence rates globally, even in countries with high vaccination coverage like Spain. The omicron variant carries about 34 mutations in the spike protein and has increased capacity to elude immunity and cause reinfections and breakthrough infections.[15,16]

Research in context

Evidence before this study

We searched PubMed for research papers from the inception of the database to March 18, 2022, using the terms ("COVID-19" OR "SARS-CoV-2") AND ("vaccine" OR "vaccination") AND ("effectiveness" OR "effect"), not restricted by language. Results were complemented by a Google search and snowball literature review using the same search terms and dates. We identified four studies with a test-negative design, and one follow-up study, that reported the effectiveness of booster vaccine doses in preventing infections with SARS-CoV-2 or severe cases of COVID-19 caused by the omicron variant. No follow-up study was found addressing vaccine effectiveness in subgroups defined by age, sex, time since completion of primary vaccination schedule, type of vaccine used for primary schedule. Additionally, the effectiveness of the two most widely used mRNA vaccine boosters, BNT162b2 and mRNA-1273, have not been quantified during a period of omicron predominance.

Added value of this study

In this nationwide representative study, we estimate that mRNA booster vaccine-doses were moderately effective (51%) in preventing infection with the omicron variant of SARS-CoV-2 up to 34 days after administration. We add to existing evidence by estimating a higher effectiveness for mRNA-1273 boosters compared with BNT162b2 boosters that increased with time since completion of the primary vaccination and was lower in people primed with Ad26.COV2.S (one dose) or BNT162b2 than in those primed with mRNA-1273 or ChAdOx1 nCoV-19 (two doses) vaccines. We also provide an estimation of the effect of booster doses, with about 1000 cases averted by booster doses per 100 000 persons in 14 days in the period between Jan 3, and Feb 6, 2022.

Implications of all the available evidence

These findings suggest that boosters continue to be an effective strategy to limit the health effects of COVID-19 in the current omicron variant-dominated epidemic. However, a future analysis of severe infections by subgroups is also needed to assess the full effect of booster doses on COVID-19 morbidity and mortality during the omicron era. Additionally, the duration of protection will also need to be monitored over time.

Although COVID-19 vaccine boosters can induce neutralising immunity against the omicron variant,[17–19] and some studies have already shown effectiveness of boosters in preventing COVID-19 infections[20–23] and severe cases,[24–26] population-based follow-up studies are needed to assess the effect of the booster vaccine on COVID-19 risk in subgroups defined by age, sex, time since last dose of the vaccination schedule, and type of vaccine during the time of the COVID-19 pandemic in which the omicron variant was responsible for most infections. Also, the comparative effectiveness of boosters in preventing infection with the two most widely used mRNA vaccines, BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), has not been evaluated.

Using nationwide population registries, we aimed to estimate the effect of an mRNA vaccine booster on the risk of laboratory-confirmed SARS-CoV-2 infection in the community-dwelling Spanish population aged 40 years and older since the emergence of the omicron variant.

Methods

Study design and population

In this nationwide cohort study, we linked individual-level data from three nationwide population registries (Vaccination Registry [REGVACU], Laboratory Results Registry [SERLAB], and National Health System [NHS] registry) using a unique semi-anonymous personal identifier. REGVACU is updated daily and includes all COVID-19 vaccine doses administered in Spain. SERLAB, also updated daily, includes the date and result of all SARS-CoV-2 tests, both PCR and rapid antigenic tests, done by health-care providers. Since Dec 21, 2021, it also includes a sample of results from self-administered rapid antigenic tests. We subtracted 2 days from PCR test results to approximate the date of sample collection. The NHS registry includes demographic data on all people with access to the health-care system in Spain. Because health-care coverage is universal, this database includes virtually the entire population. We used the national health-card number (semi-anonymised with a hash code) to link the three databases. To increase the probability that individuals were present in Spain throughout the study period, we excluded people who were only temporarily entitled to access the health system (eg, irregular migrants).

Our observational study emulated a target trial of an mRNA-based (BNT162b2 or mRNA-1273) booster dose for the prevention of documented infection with SARS-CoV-2 in a period of omicron SARS-CoV-2 dominance.

Individuals who were residents in Spain, 40 years old or older between Jan 3, and Feb 6, 2022, had completed their primary vaccination scheduled (two doses of a mRNA vaccine or ChAdOx1 nCoV-19 [Oxford–AstraZeneca], or one dose of Ad26.COV2.S [Janssen]) at least 3 months before the start of follow-up, with no additional vaccine doses within these 3 months, had no previous laboratory-confirmed SARS-CoV-2 positive test, and who were not part of a special population (eg, nursing home residents, institutionalised individuals, and health-care workers) with different probability of

infection compared with the general population were eligible for inclusion. Only individuals who received their first dose after the recommended vaccination date for their age group were included (appendix p 2); this was done to exclude essential workers—particularly those in the education sector, immunosuppressed individuals, and others with different probability of infection than the general population.

This study was approved by the research ethics committee at the Instituto de Salud Carlos III (CEI PI 98_2020 and CEI PI 08_2022). Informed consent was not required because this study is based on national population registries.

Procedures

In a target trial, eligible people would be randomly assigned to receive either an mRNA booster vaccine or to no booster within strata defined by age, sex, postal code, time since completion of the primary vaccination schedule, type of vaccine used in the primary vaccination, and total number of previous SARS-CoV-2 diagnostic tests. The outcome of interest was laboratory-confirmed SARS-CoV-2 infection. The study period started on Jan 1, 2022, when more than 90% of SARS-CoV-2 detected variants in Spain were identified as omicron,[14] and ended on Feb 6, 2022, when more than 99% of detected variants were omicron.

We extracted the data, from all databases on Feb 11, 2022. For each day between Jan 3, and Feb 6, 2022, we identified people who met the eligibility criteria and classified them as either having received an mRNA vaccine booster (booster group) on that day or not having received it (no booster group). Each person in the booster group was matched to a randomly selected control (with replacement) in the no booster group. The matching factors were identified as those potentially associated with the probability of receiving a booster dose as well as with the risk of a documented SARS-CoV-2 infection: sex, age (5-year groups), postal code, type of vaccine used for primary vaccination (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, or Ad26.COV2.S), week when the vaccination schedule was completed, and number of

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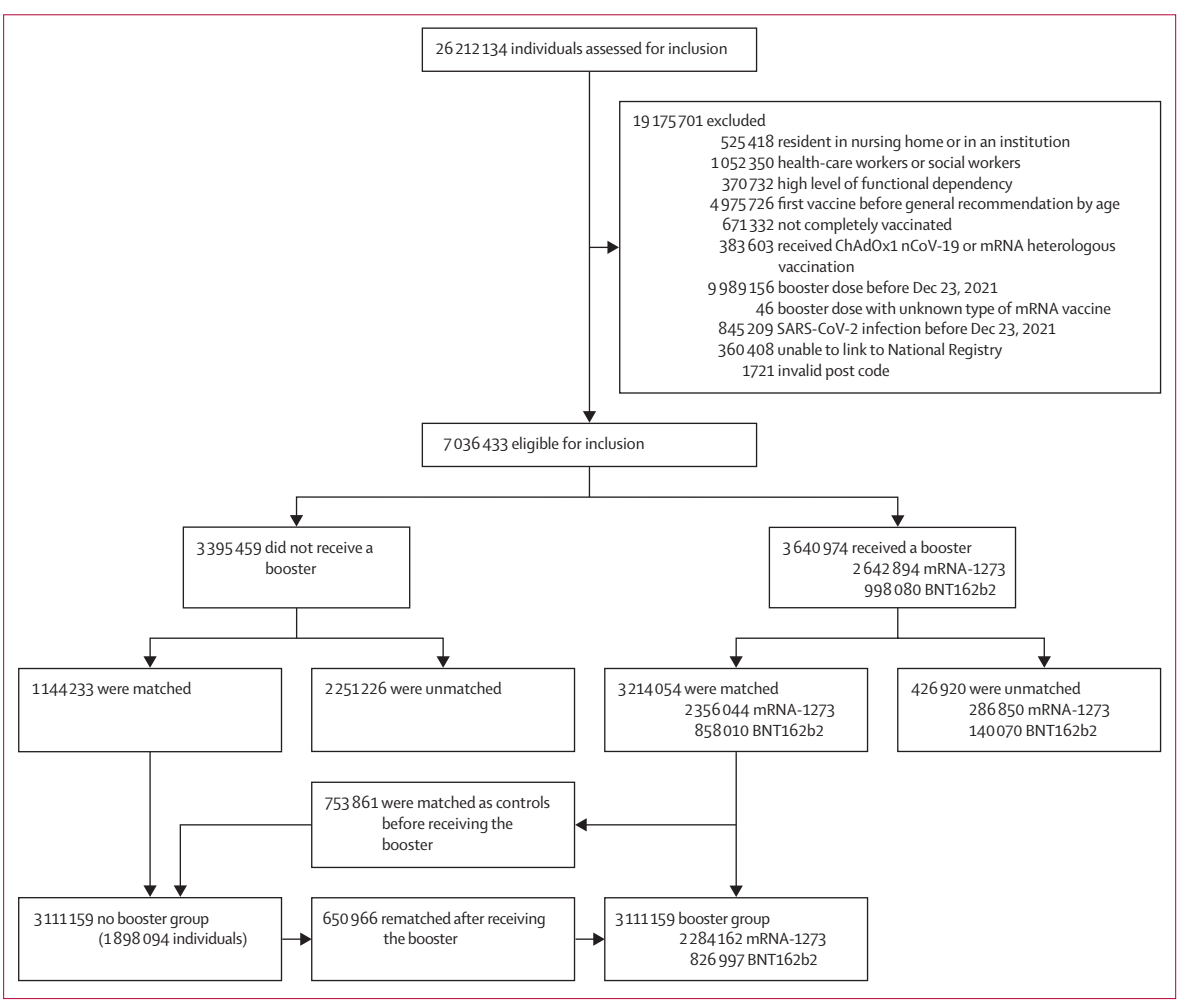

Figure 1: **Study profile**

	Booster group (n=3 111 159)	No booster group (n=3 111 159; 1 898 094 unique individuals)
Age groups (years)		
40–44	542 070 (17·4%)	542 070 (17·4%)
45–49	222 960 (7·2%)	222 960 (7·2%)
50–54	1 045 542 (33·6%)	1 045 542 (33·6%)
55–59	907 251 (29·2%)	907 251 (29·2%)
60–64	182 239 (5·9%)	182 239 (5·9%)
65–69	118 710 (3·8%)	118 710 (3·8%)
70–74	45 328 (1·5%)	45 328 (1·5%)
75–79	25 834 (0·8%)	25 834 (0·8%)
80–84	11 393 (0·4%)	11 393 (0·4%)
85–89	7396 (0·2%)	7396 (0·2%)
≥90	2436 (0·1%)	2436 (0·1%)
Sex		
Male	1 613 610 (51·9%)	1 613 610 (51·9%)
Female	1 497 549 (48·1%)	1 497 549 (48·1%)
Number of previous SARS-CoV-2 tests		
0	1 690 184 (54·3%)	1 690 184 (54·3%)
1	749 466 (24·1%)	749 466 (24·1%)
2	355 249 (11·4%)	355 249 (11·4%)
≥3	316 260 (10·2%)	316 260 (10·2%)
Primary vaccine schedule		
ChAdOx1 nCoV-19	237 193 (7·6%)	237 193 (7·6%)
Ad26.COV2.S	69 208 (2·2%)	69 208 (2·2%)
mRNA-1273	366 023 (11·8%)	366 023 (11·8%)
BNT162b2	2 438 735 (78·4%)	2 438 735 (78·4%)
Booster dose		
mRNA-1273	2 284 162 (73·4%)	NA
BNT162b2	826 997 (26·6%)	NA
Time since completion of primary vaccine schedule		
91–150 days	7383 (0·2%)	7383 (0·2%)
151–180 days	283 958 (9·1%)	283 958 (9·1%)
>180 days	2 819 818 (90·6%)	2 819 818 (90·6%)

Data are n (%). NA=not applicable.

Table 1: **Baseline characteristics of the matched study population**

SARS-CoV-2 tests since the beginning of the pandemic (none, one, two, or three or more). For each matched pair, follow-up started on the day of administration of the booster dose (time zero) and stopped after laboratory-confirmed SARS-CoV-2 infection, death, discontinuation of registration in the NHS population database, receipt of a vaccine-dose by an individual in the non-booster group (with concurrent censoring of the booster member of the pair) or Feb 6, 2022, whichever occurred first.

We also emulated a head-to-head trial of BNT162b2 booster versus mRNA-1273 booster by matching recipients of each type of booster on sex, age group, province, type of vaccine used for primary vaccination, month when the vaccination schedule was completed, and number of SARS-CoV-2 tests since the beginning of the pandemic (none, one, two, or three or more).

Statistical analysis

We computed cumulative incidence (risk) curves of laboratory-confirmed SARS-COV-2 infection in each group using the Kaplan-Meier estimator.[27] We compared the risks 7 or more days after booster administration via differences and ratios, and estimated effectiveness as one minus the risk ratio, using only matched pairs in which both individuals were still at risk 7 days after time zero. To estimate the per-protocol effect under full adherence, we censored both members of a matched pair when the control received an additional vaccine dose. We analysed the entire study population and in subgroups defined by age group, sex, type of vaccine used for primary vaccination, type of mRNA vaccine in the booster, and time interval between complete vaccination and the booster dose.

We did sensitivity analyses restricted to people who had at least one negative test before time zero (to ensure that all individuals had had access to diagnostic services in the past) and to people with no test in the 7 days before time zero (to exclude contacts of cases or other people exposed to SARS-CoV-2 who had tested early in their infection). In another sensitivity analyses, we used dates of laboratory tests as recorded (rather than subtracting 2 days for PCR tests), we censored matched pairs 7 days after the control received a booster (rather than on the date of the booster), we matched without replacement, matched by exact year of age, and restricted events to infections diagnosed by PCR (censoring free of event infections diagnosed by antigenic testing). We computed normal distribution-based 95% CIs using non-parametric bootstrapping with 500 samples. Analyses were done with R (version 4.1.2).

Role of the funding source

There was no funding source.

Results

Between Jan 1, and Feb 6, 2022, 26·2 million people were assessed for inclusion, of whom 7·0 million (26·8%) individuals were eligible (figure 1). 3·6 million (51·7%) people received a booster dose: 2 642 894 (72·6%) received mRNA-1273 and 998 080 (27·4%) received BNT162b2. 3 357 903 (45·7%) had at least one test recorded in SERLAB from the beginning of the pandemic to Jan 3, 2022. We exactly matched 3 111 159 individuals who received a booster to the same number of controls with a median age of 53 years (IQR 50–57; table 1). The characteristics of the matched sample were similar to those of the total eligible population (appendix p 4).

During 82·7 million person-days of follow-up and a maximum follow-up of 34 days, there were 47 104 laboratory-confirmed SARS-CoV-2 infections in the booster group and 93 035 in the no booster group. The risk of infection at 34 days was 2·7% in the booster

	Booster group		No booster group		1–risk ratio (95% CI)	Risk difference per 10 000 individuals (95% CI)
	Events	Risk per 10 000 individuals	Events	Risk per 10 000 individuals		
Overall	21 468	177	42 406	362	51·3% (50·2–52·4)	186 (180–191)
Age group (years)						
40–59	19 035	190	37 090	379	49·9% (48·6–51·3)	189 (183–197)
60–79	2264	119	4998	284	58·0% (55·8–60·4)	165 (154–176)
≥80	169	133	318	286	53·5% (43·9–63·3)	153 (110–194)
Sex						
Male	10 662	170	20 434	338	49·8% (48·1–51·5)	168 (160–177)
Female	10 806	184	21 972	388	52·6% (51·1–54·1)	204 (196–212)
Type of previous vaccination						
ChAdOx1 nCoV-19	1461	125	3264	302	58·6% (55·5–61·6)	177 (162–191)
Ad26.COV2.S	691	181	1280	348	48·0% (42·5–53·7)	167 (140–195)
mRNA-1273	2551	183	5409	410	55·3% (52·3–58·2)	227 (208–245)
BNT162b2	16 765	183	32 453	363	49·7% (48·3–51·1)	181 (174–188)
Time since vaccination completed						
91–150 days	50	131	102	240	45·3% (24·5–67·5)	109 (45, 174)
151–180 days	2450	204	4203	362	43·6% (40·0–47·1)	158 (140–175)
>180 days	18 968	173	38 101	363	52·2% (51·0–53·3)	189 (183–195)
Type of booster						
mRNA-1273	16 700	185	34 123	390	52·5% (51·3–53·7)	204 (198–211)
BNT162b2	4768	152	8283	282	46·2% (43·5–48·7)	130 (120–140)

*Analyses based on 2 083 857 matched pairs who remained under follow-up by day 7 after the booster dose.

Table 2: **Estimated effectiveness of an mRNA COVID-19 vaccine booster in individuals* who had completed primary vaccination schedule against COVID-19**

group and 5·4% in the no booster group. The number of tests per 1000 person-days 7 or more days after the booster (and before a COVID-19 diagnosis) was 1·7 in the booster group and 1·9 in the no booster group, of which 850 (1·2%) of 71 680 tests in the booster group and 756 (0·9%) of 79 752 tests in the no booster group were self-tests.

2 083 857 (67·0%) of 3 111 159 matched pairs remained under follow-up at day 7 and were included in the effectiveness estimation; 562 735 (27·0%) of 2 083 857 matched pairs were censored during the follow-up because the control received a booster. Overall, the estimated effectiveness of the booster was 51·3% (95% CI 50·2–52·4) between day 7 and day 34, and 55·5% (53·8–57·3) between day 14 and day 34. The estimate was stable during most of the period of 27 days (appendix p 7). The estimated number of cases averted between days 7 and 34 was 186 (95% CI 180–191) per 10 000 individuals (table 2; figure 2). Effectiveness estimates were higher for individuals aged 60–79 years (58·0% [95% CI 55·8–60·4) compared with 40–59-year-olds (49·9% [48·6–51·3), and slightly higher for women (52·6% [51·1–54·1) compared with men (49·8% [48·1–51·5]; appendix pp 8–9).

The estimated effectiveness in days 7–34 was 55·3 (95% CI 52·3–58·2) if primary vaccination had been with mRNA-1273, 58·6% (55·5–61·6) if it had been with ChAdOx1 nCoV-19, 48·0% (42·5–53·7) if it had been with Ad26.COV2.S and 49·7% (48·3–51·1) if it had been with BNT162b2 (appendix p 10). The effectiveness estimate increased with time between completed primary vaccination and booster from 43·6% (95% CI 40·0–47·1) for an interval of between 151 days and 180 days to 52·2% (51·0–53·3) for more than 180 days (figure 3).

We estimated an effectiveness for an mRNA-1273 booster of 52·5% (95% CI 51·3–53·7) compared with 46·2% (43·5–48·7) for a BNT162b2 booster (figure 2). A head-to-head comparison including 785 088 matched pairs with follow-up of 7 days or more, estimated a 13% (95% CI 10–16) higher protection for the mRNA-1273 booster compared with the BNT162b2 booster, with little differences in subgroup analyses (appendix p 5). In sensitivity analyses, the estimated effectiveness of an mRNA booster from days 7 to 34 ranged between 47·4% and 52·3% (table 3).

Discussion

Using nationwide data from the Spanish population aged 40 years or older during an era of omicron variant predominance, we estimated a 51% effectiveness of an mRNA booster against laboratory-confirmed SARS-CoV-2 infections up to 34 days after its administration. The boosters were estimated to prevent 186 cases per

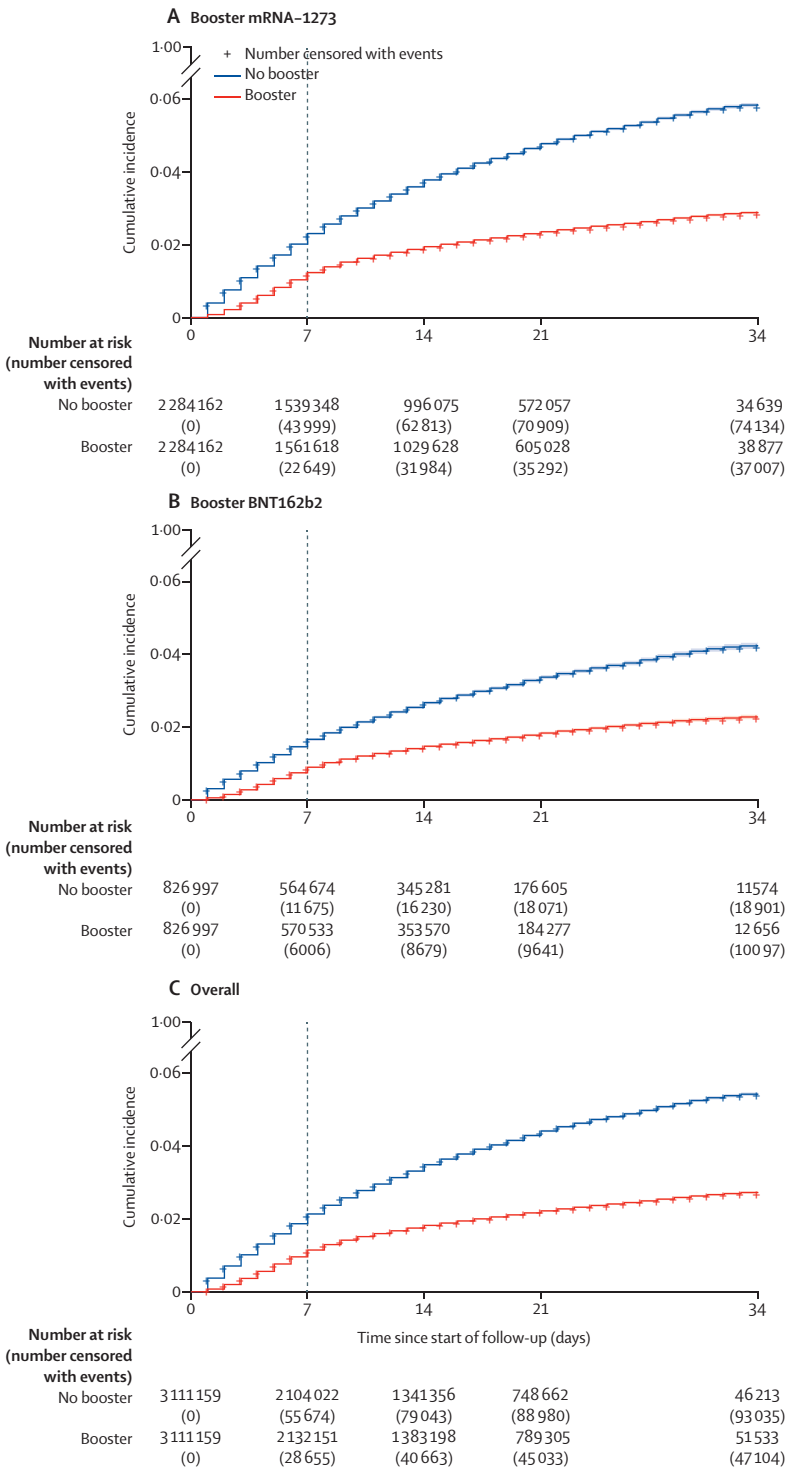

Figure 2: **Estimates of SARS-CoV-2 infection risk by booster status and booster vaccine type**
(A) Pfizer (BNT162b2), (B) Moderna (mRNA-1273), and (C) overall. Shaded areas are 95% CI.

10 000 people during the study, which can be extrapolated to about 1000 cases per 100 000 people per 14 days. This results in one case prevented per 54 people who received a booster dose. mRNA-1273 boosters were estimated to be 13% more effective than BNT162b2 boosters.

The 51% estimated effectiveness we report during a period of omicron variant predominance is lower than estimates obtained during periods of delta variant predominance. Using the same method, nationwide studies in Israel and Qatar estimated a booster effectiveness for infection with the delta variant of 86–88%[6,28] and 49% for the omicron variant.[28] The reduced effectiveness against the omicron variant has also been detected in test-negative designs, but the range of estimates is wide: a study in Scotland estimated effectiveness of boosters against symptomatic omicron infection at 57%[20] and a USA study estimated effectiveness to be 66%,[21] whereas a Canadian study estimated 37% effectiveness against the omicron variant, compared with 93% for the delta variant.[22] In the UK, risk of symptomatic infection was estimated to decrease by 65–75% between 2 weeks and 4 weeks after a booster, but only 50% after 10 weeks.[23]

mRNA-1273 boosters were estimated to be 13% more effective than BNT162b2 boosters. A similar difference was reported in the period of delta variant predominance, for people from a broad range of ages and primed with different vaccines.[29] In our study, the highest effect was in those primed with two doses of mRNA-1273 or ChAdOx1 nCoV-19, and lowest in those primed with two doses of BNT162b2 or one dose of Ad26.COV2.S. A randomised trial reported an increase in the binding antibody concentration after a booster in all groups; however, after the booster, neutralising antibodies titres were highest in those who received mRNA-1273 as their primary schedule, followed by BNT162b2, and then Ad26.COV2.S.[30]

The optimal interval between completing COVID-19 primary vaccination and the administration of a booster dose is not established. In our study, the estimated effectiveness of the booster increased with time since complete vaccination, from about 44% for boosters administered between 151 days and 180 days to 52% for boosters administered after 180 days. Of note, despite the slightly lower effectiveness of boosters at shorter intervals, their administration in the midst of the omicron wave might be justified to reduce transmission as early as possible.

Our study has some limitations. First, like in all observational analyses, our estimates would be affected by confounding bias if booster recipients and non-recipients had a different risk of diagnosis of infection. For example, if booster related side-effects encourage individuals to stay at home, if undiagnosed symptomatic individuals or close contacts of cases defer vaccination, or if the rate of diagnostic tests differ between groups. The increased vaccine effectiveness estimated in the first 2–3 days of follow-up (appendix p 7) mirrors the initial difference in diagnostic intensity between groups (appendix p 6). However, this difference disappeared later, specifically from days 7 to 34 on which our main estimates are based. Second, we could not estimate

	1–risk ratio (95% CI)	Risk difference per 10 000 individuals (95% CI)
Main analysis	51·3% (50·2–52·4)	186 (180–191)
Restricting to people with ≥1 negative lab test at enrolment	51·2% (49·7–52·7)	231 (221–241)
Restricting to persons with no tests in the 7 days before enrolment	50·7% (49·5–51·9)	181 (175–187)
Censoring matched pairs 7 days after the control receives a booster rather than 0 days	47·4% (46·0–48·8)	164 (157–170)
Using date of PCR test result rather than subtracting 2 days	52·3% (51·2–53·4)	224 (217–230)
Selecting matched controls without replacement	52·0% (50·8–53·2)	193 (187–199)
Exact matching by age (year by year *vs* 5-year groups)	50·3% (49·2–51·5)	181 (175–187)
Restricting events to PCR test	50·7% (48·4–53·2)	32 (30–34)

Table 3: **Sensitivity analyses of vaccine effectiveness 7–34 days after an mRNA COVID-19 vaccine booster dose**

booster effectiveness against severe disease and death because this information is not continuously updated in national registries. However, studies during the delta and omicron dominant periods estimated a similar or higher effectiveness against hospitalisation than against infection.[6,24–26,28,29] Therefore, it is expected that effectiveness of the current booster formulations against severe disease caused by the omicron variant will be more than 51%, which makes booster administration the most effective strategy to limit the health effects of omicron epidemics. Third, we could only estimate the effectiveness until day 34 of follow-up. The duration of protection against the omicron variant conferred by the booster will need to be monitored over longer periods of time. Lastly, our study does not include an unknown proportion of positive self-tests that were not consistently recorded in the national registry after Dec 21, 2021, when overload of the laboratory capacity and the primary health-care network led to a policy change that eliminated the requirement to confirm all positive self-tests by PCR. However, the proportion of missing self-tests is expected to be similar in both groups (as supported by the similar numbers of tests and similar proportion of reported self-tests); therefore, it is expected to have little effect on estimates of effectiveness.

In conclusion, in this nationwide follow-up study, we estimated that booster mRNA vaccine-doses were moderately effective at preventing infection with the omicron variant of SARS-CoV-2 up to 34 days after administration. Estimated effectiveness was higher for mRNA-1273 compared with BNT162b2 and increased with time since complete vaccination. These findings suggest that boosters continue to be an effective strategy to limit the health effects of COVID-19 during an omicron-dominated epidemic.

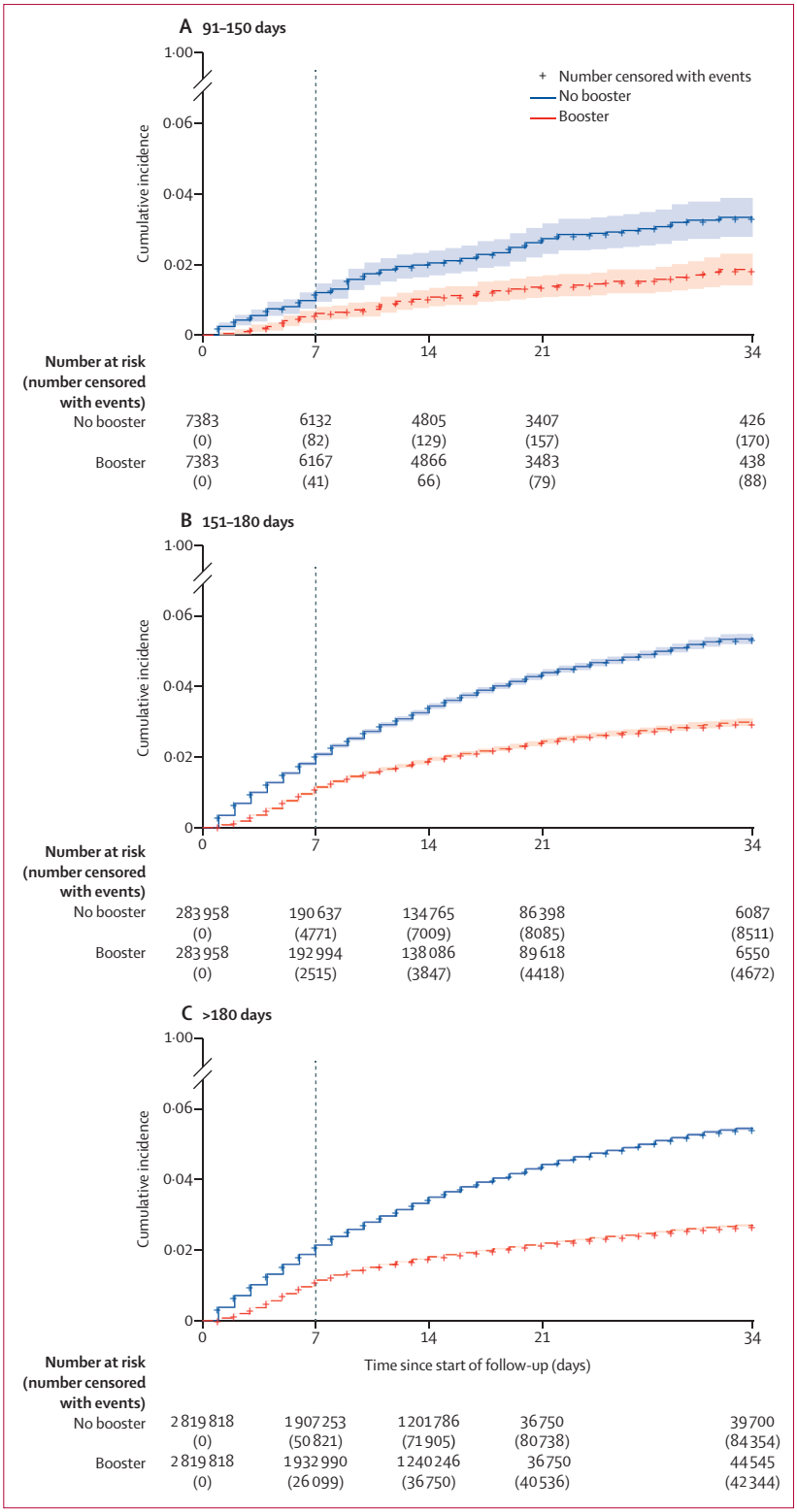

Figure 3: **Estimates of SARS-CoV-2 infection risk by booster status and interval since complete vaccination**
(A) 91–150 days, (B) 151–180 days, and (C) more than 180 days. Shaded areas are 95% CI.

Contributors

SM, MAH, and ALa conceived the study. SM, AR-B, and MAH designed the analysis. SM and AR-B did the analysis. MAH supervised the analysis. Both SM and AR-B had full access and verified the underlying data. SM, AR-B and MAH were responsible for the decision to submit the manuscript. All authors collected the data and critically reviewed study results. All authors participated in the interpretation of results and critically reviewed the content of the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

We declare no competing interest.

Data sharing

The databases used in this study are owned by the Ministry of Health and the Autonomous Communities in Spain, which establish the requirements for their access and use.

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References

1 Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection: test negative design study. *BMJ* 2021; **375:** e067873.

2 Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021; **398:** 1407–16.

3 Thomas SJ, Moreira EDJ Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 2021; **385:** 1761–73.

4 Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* 2021; **398:** 2258–76.

5 Choi A, Koch M, Wu K, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. *Nat Med* 2021; **27:** 2025–31.

6 Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021; **398:** 2093–100.

7 Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *N Engl J Med* 2021; **385:** 1393–400.

8 Ponencia de Programa y Registro de Vacunaciones. Administración de dosis adicionales en personas que han recibido una pauta completa de vacunación frente a COVID-19. Aprobado por la Comisión de Salud Pública del Consejo Interterritorial del SNS, 7 septiembre 2021. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Historico_NotasCOVID-19/docs/Administracion_de_dosis_adicionales_en_personas_que_han_recibido_una_pauta_completa_de_vacunacion_frente_a_COVID-19_7_sept.2021.pdf (accessed May 17, 2022).

9 European Centre for Disease Prevention and Control. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. 2021. https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-vaccination-strategies-and-deployment-plans-Nov-2021.pdf (accessed May 17, 2022).

10 Dosis de recuerdo frente a COVID-19: próximos grupos a vacunar. 2021. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Historico_NotasCOVID-19/docs/Proximos_grupos_dosis_recuerdo.pdf (accessed Dec 16, 2021).

11 Consejo Intererrtorial. Próximos grupos a vacunar con dosis de recuerdo frente a COVID-19. 2022. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/CSP-Proximos_grupos_dosis_de_recuerdo_COVID_19.pdf (accessed May 17, 2022).

12 Ministerio de Sanidad. Estrategia de vacunación frente a COVID-19 en España. Actualización 10. 2021. http://www.mscbs.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Actualizaciones_Estrategia_Vacunacion/docs/COVID-19_Actualizacion10_EstrategiaVacunacion.pdf (accessed May 17, 2022).

13 Minesterio de Sanidad. GIV COVID-19. 2021. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Informe_GIV_comunicacion_20220103.pdf (accessed May 17, 2022).

14 European Centre for Disease Prevention and Control. Data on SARS-CoV-2 variants in the EU/EEA 2022. https://www.ecdc.europa.eu/en/publications-data/data-virus-variants-covid-19-eueea (accessed May 17, 2022).

15 Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 omicron to antibody neutralization. *Nature* 2021; **602:** 671–75.

16 Collie S, Champion J, Moultrie H, Bekker L-G, Gray G. Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. *N Engl J Med* 2022; **386:** 494–96.

17 Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 omicron variant. *Cell* 2022; **185:** 457–66.e4.

18 Gruell H, Vanshylla K, Tober-Lau P, et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 omicron variant. *Nat Med* 2022; **28:** 477–80.

19 Wu M, Wall EC, Carr EJ, et al. Three-dose vaccination elicits neutralising antibodies against omicron. *Lancet* 2022; **399:** 715–17.

20 Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 omicron and delta variants. *JAMA* 2022; **327:** 639–51.

21 Sheikh A, Kerr S, Woolhouse M, McMenamin J, Robertson C. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. 2021. https://www.pure.ed.ac.uk/ws/portalfiles/portal/245818096/Severity_of_Omicron_variant_of_concern_and_vaccine_effectiveness_against_symptomatic_disease.pdf (accessed May 17, 2022).

22 Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes. *medRxiv* 2022; published online Jan 28. https://doi.org/10.1101/2021.12.30.21268565 (preprint).

23 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 34. 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050236/technical-briefing-34-14-january-2022.pdf (accessed May 17, 2022).

24 Thompson M, Natarajan K, Irving S, et al. Effectiveness of a Third Dose 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* 2022; **71:** 139–45.

25 Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. *Nat Med* 2022; published online Feb 21. https://doi.org/10.1038/s41591-022-01753-y.

26 Ferdinands JM, Rao S, Dixon BE, et al. 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* 2022; **71:** 255–63.

27 Kaplan ELMP, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

28 Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Effect of mRNA vaccine boosters against SARS-CoV-2 omicron infection in Qatar. *N Engl J Med* 2022; published online March 9. https://doi.org/10.1056/NEJMoa2200797.

29 Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 booster vaccines against covid-19 related symptoms, hospitalisation and death in England. *Nat Med* 2022; **28:** 831–37.

30 Atmar RL, Lyke KE, Deming ME, et al. Homologous and heterologous Covid-19 booster vaccinations. *N Engl J Med* 2022; **386:** 1046–57.