Supplementary Appendix

Effectiveness of a second dose of an mRNA vaccine against SARS-CoV-2 Omicron infection in individuals previously infected by other variants

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Supplementary Table 1. Baseline characteristics of all eligible individuals and of the matched study population

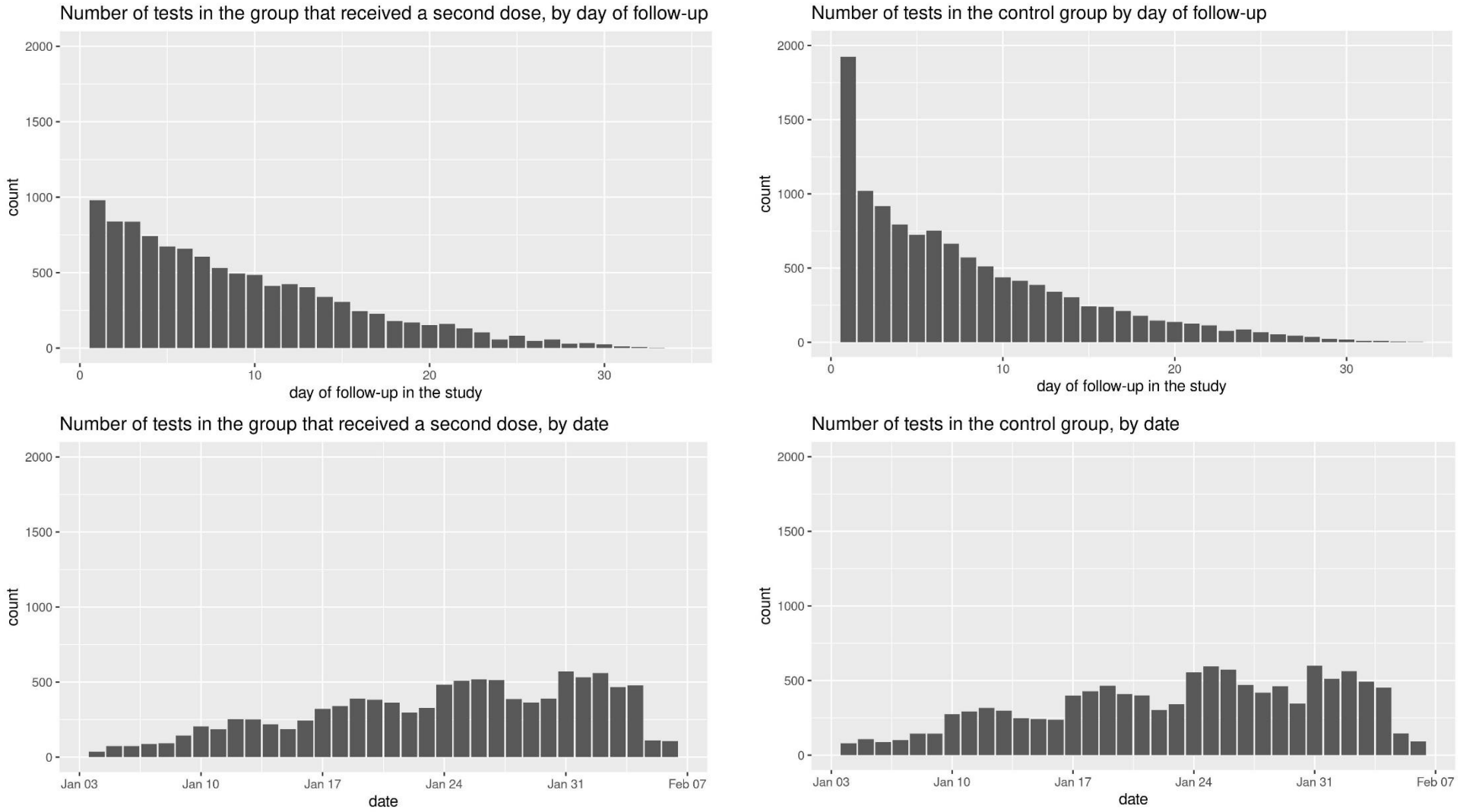
		Eligible (N=1,423,311)	Matched sample (N=778,042)
Age	18-24	325,124 (22.8%)	79,923 (10.3%)
	25-29	181,926 (12.8%)	56,388 (7.2%)
	30-34	164,970 (11.6%)	74,987 (9.6%)
	35-39	147,267 (10.3%)	79,185 (10.2%)
	40-44	169,653 (11.9%)	122,390 (15.7%)
	45-49	149,224 (10.5%)	116,633 (15.0%)
	50-54	147,274 (10.3%)	133,696 (17.2%)
	55-59	103,093 (7.2%)	94,042 (12.1%)
	60-64	34,780 (2.4%)	20,798 (2.7%)
Sex	Male	726,601 (51.1%)	391,114 (50.3%)
	Female	696,710 (48.9%)	386,928 (49.7%)
Number of previous SARS-CoV-2 tests	1	462,851 (32.5%)	258,254 (33.2%)
	2	392,737 (27.6%)	212,316 (27.3%)
	≥ 3	567,723 (39.9%)	307,472 (39.5%)
Type of vaccine first dose	mRNA-1273	362,276 (25.5%)	148,562 (19.1%)
	BNT162b2	1,061,035 (74.5%)	629,480 (80.9%)
Type of vaccine second dose	mRNA-1273	292,661 (20.6%)	268,869 (34.6%)
	BNT162b2	130,075 (9.1%)	120,152 (15.4%)
Period of variant circulation of previous infection	Pre-alpha	828,678 (58.2%)	594,301 (76.4%)
	Alpha	373,166 (26.2%)	146,162 (18.8%)
	Delta	221,467 (15.6%)	37,579 (4.8%)

***** Percentage is over total number of individuals with a second dose

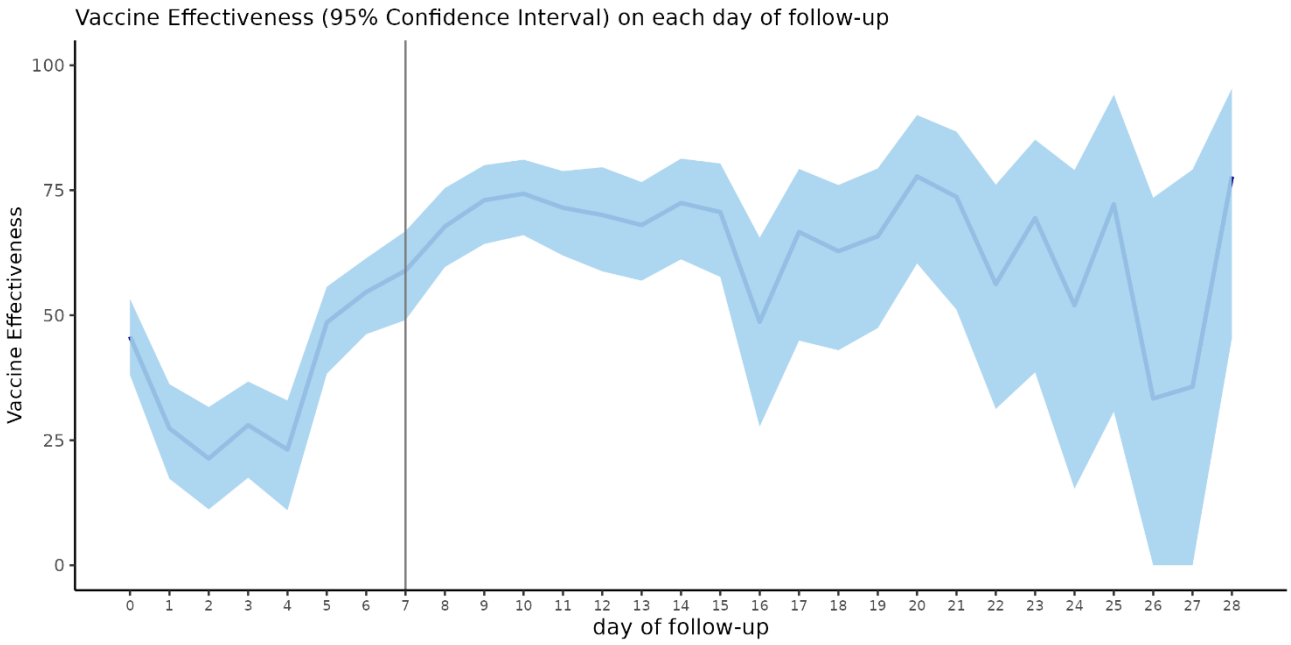
Supplementary Table 2. Sensitivity analyses: Estimated effectiveness in days 7-34 after a second dose in people with previous infection in a period of Omicron variant dominance (3 January – 6 February 2022), under different scenarios

	1 – risk ratio (95% CI)	Risk difference per 1,000 (95% CI)
Main analysis	62.2% (57.9, 66.0)	14.9 (13.4, 16.4)
Restricting to persons with no tests in the 7 days before enrolment	63.2% (58.6, 67.3)	15.0 (13.4, 16.6)
Censoring matched pairs 7 days after the control receives a second dose rather than 0 days	59.8% (55.3, 64.3)	13.3 (11.9, 14.9)
Using date of PCR test result rather than subtracting 2 days	61.8% (57.6, 65.5)	14.4 (13.0, 15.9)
Selecting matched controls without replacement	61.3% (57.1, 65.1)	14.4 (13.0, 15.8)
Restricting to persons without any positive test in the previous 90 days	64.1% (59.9, 67.6)	15.3 (13.9, 16.7)

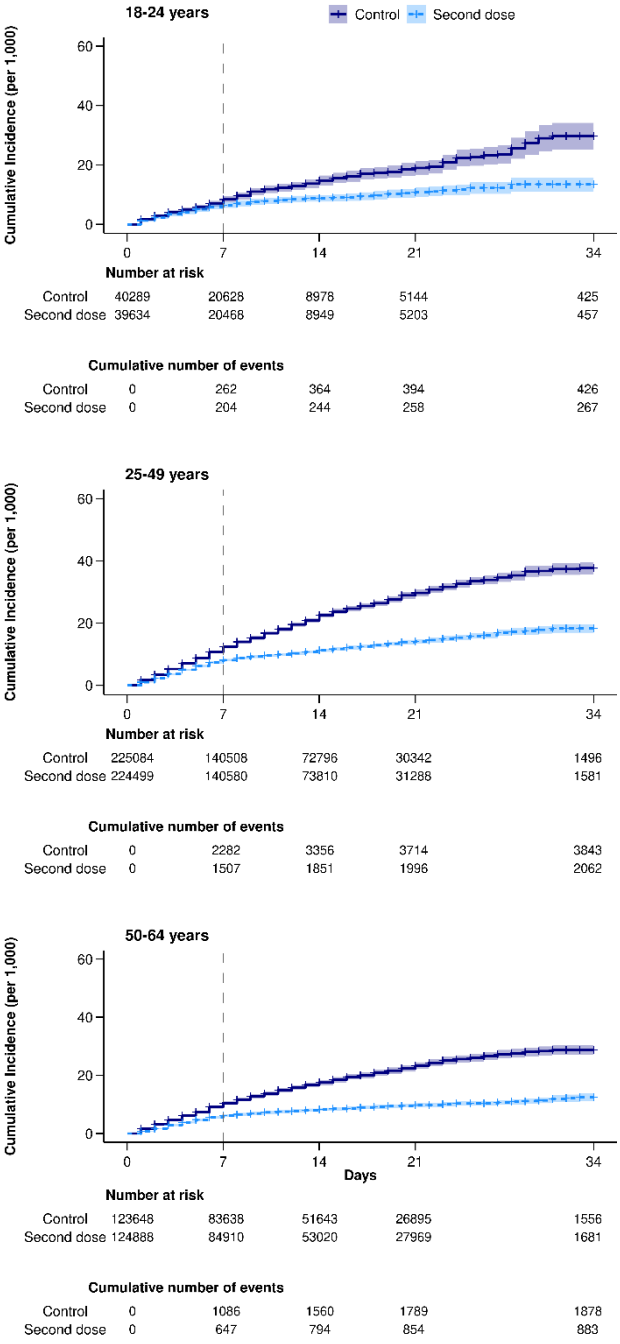
Supplementary Figure 1. Number of laboratory tests in the booster and control groups by day of follow-up and by calendar date.



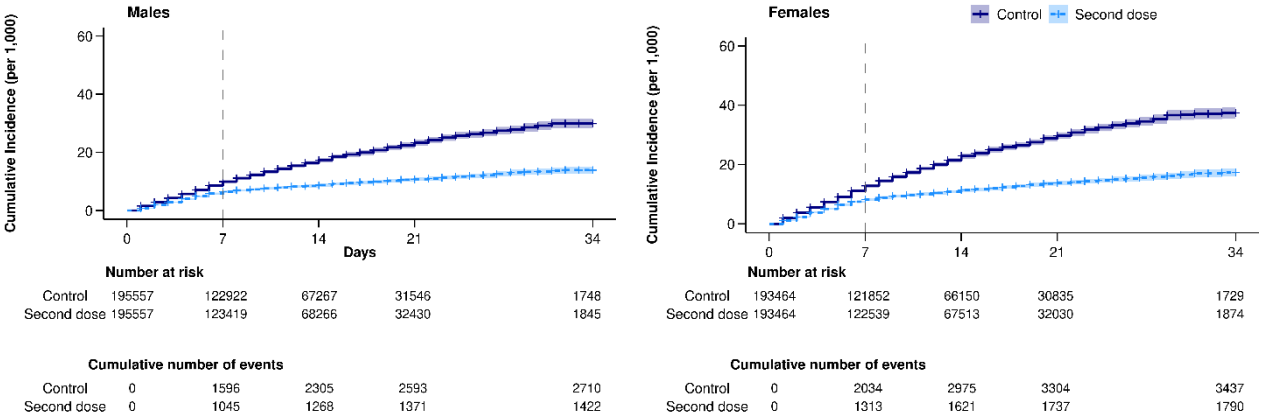
Supplementary Figure 2. Risk ratio (95% confidence interval) in each day of follow-up, estimated using matched pairs who remained under follow-up.



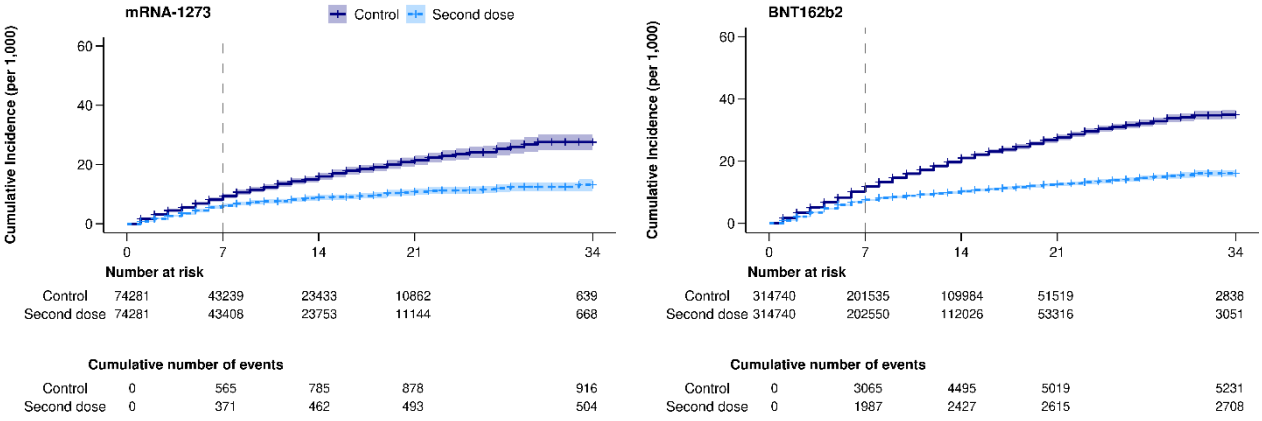
Supplementary Figure 3. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by age, Spain, 3 January to 6 February 2022.



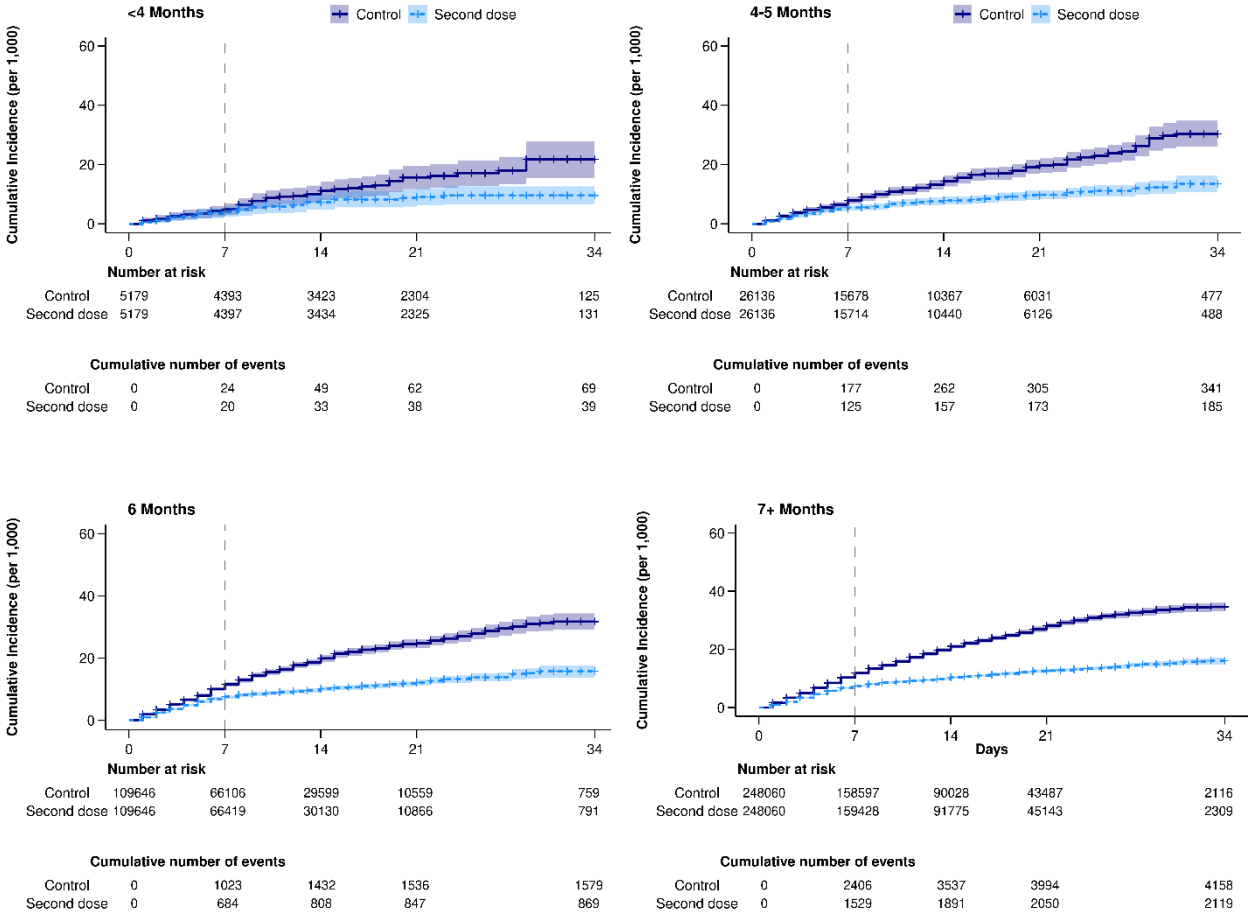
Supplementary Figure 4. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by sex, Spain, 3 January to 6 February 2022.



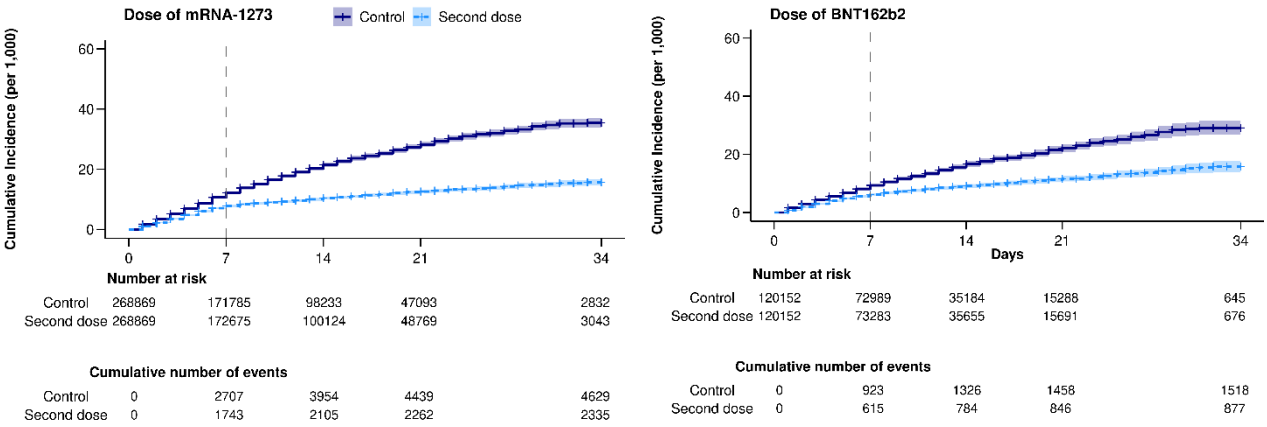
Supplementary Figure 5. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by type of vaccine used as first dose, Spain, 3 January to 6 February 2022.



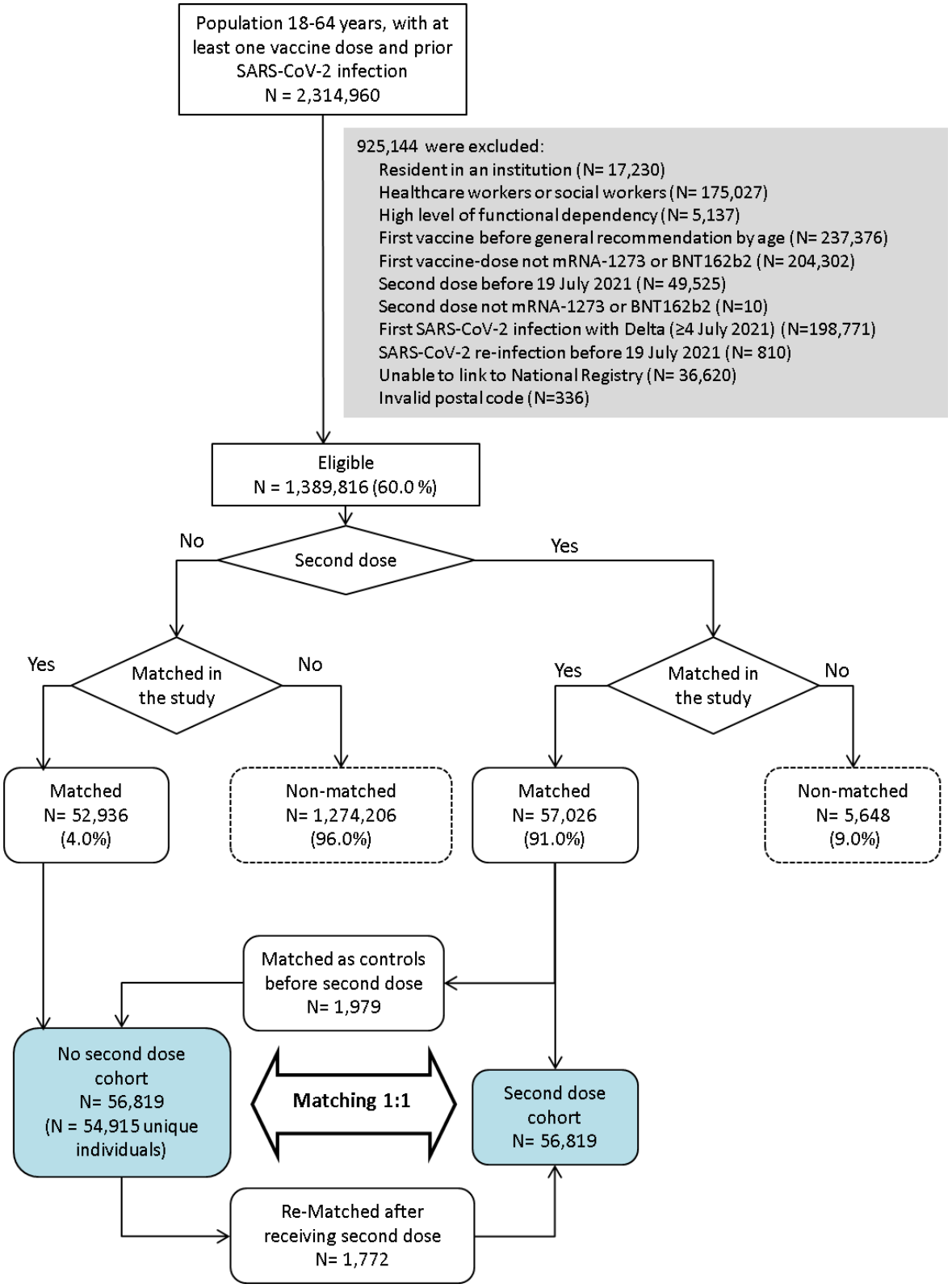
Supplementary Figure 6. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by time between first and second vaccine-dose, Spain, 3 January to 6 February 2022.



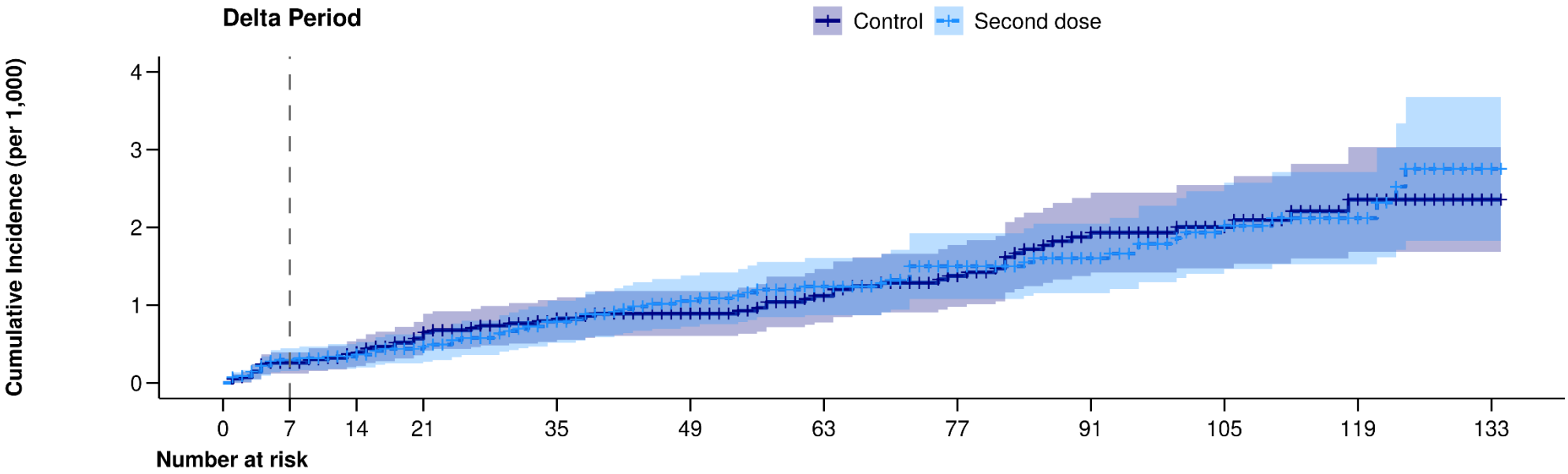
Supplementary Figure 7. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by type of vaccine used as second dose, Spain, 3 January to 6 February 2022.



Supplementary Figure 8. Sample selection flow-chart for estimation of the effectiveness of a second dose in people with previous infection in a period of Delta variant dominance (19 July - 6 November 2021)



Supplementary Figure 9. Risk ratio (95% confidence interval) in each day of follow-up for the analysis of the effectiveness of a second vaccine dose during a period of Delta predominance, estimated using matched pairs who remained under follow-up.



Number at risk

Control	56819	48999	37189	32100	28027	24864	21538	17580	11765	6011	741
Second dose	56819	48999	37192	32097	28011	24849	21524	17571	11749	6000	738

Cumulative number of events

Control	0	14	30	36	38	44	50	61	62	65	65
Second dose	0	16	23	34	42	47	53	55	61	62	65

Supplementary Table 3. Baseline characteristics of the matched study population for the estimation of the effectiveness of a second dose during a period of Delta variant predominance, Spain, 19 July – 30 November 2021

		Administration of second dose (N=56,819)	No second dose (N=56,819)
Age	18-24	9,650 (22.7%)	9,752 (23.0%)
	25-29	7,628 (13.4%)	7,437 (13.1%)
	30-34	8,101 (14.3%)	8,190 (14.4%)
	35-39	6,153 (10.8%)	6,024 (10.6%)
	40-44	6,976 (12.3%)	6,987 (12.3%)
	45-49	5,729 (10.1%)	5,790 (10.2%)
	50-54	6,115 (10.8%)	6,180 (10.9%)
	55-59	4,851 (8.5%)	4,957 (8.7%)
	60-64	1,616 (2.8%)	1,502 (2.6%)
Sex	Female	28,429 (50.0%)	28,429 (50.0%)
	Male	28,390 (50.0%)	28,390 (50.0%)
Number of previous SARS-CoV-2 tests	1	15,807 (27.8%)	15,807 (27.8%)
	2	14,933 (26.3%)	14,933 (26.3%)
	≥ 3	26,079 (45.9%)	26,079 (45.9%)
Type of vaccine used as first dose	mRNA-1273	10,921 (19.2%)	10,921 (19.2%)
	BNT162b2	45,898 (80.8%)	45,898 (80.8%)
Type of vaccine used as second dose	mRNA-1273	11,075 (19.5%)	
	BNT162b2	45,744 (80.5%)	
Interval of time since the first dose	<4 months	33,721 (59.3%)	33,721 (59.3%)
	4-5 months	16,813 (29.6%)	16,813 (29.6%)
	6 months	4,343 (7.6%)	4,343 (7.6%)
	7+ months	1,942 (3.4%)	1,942 (3.4%)
Period of variant circulation of previous infection	Pre-alpha	42,311 (74.5%)	42,458 (74.7%)
	Alpha	14,508 (25.5%)	14,361 (25.3%)

Supplementary Table 4. Sensitivity analyses: Estimated effectiveness in days 7-133 after a second dose people with previous infection in a period of Delta variant dominance (19 July – 30 November, 2021), under different scenarios

	1 – risk ratio (95% CI)	Risk difference per 1,000 (95% CI)
Main analysis	-16.9% (-93.1, 33.8)	-0.4 (-1.6, 0.8)
Restricting to persons with no tests in the 7 days before enrolment	-35.1% (-130.3, 17.4)	-0.7 (-1.8, 0.4)
Censoring matched pairs 7 days after the control receives a second dose rather than 0 days	-4.8% (-136.9, 46.4)	-0.1 (-1.6, 1.8)
Using date of PCR test result rather than subtracting 2 days	-24% (-113.1, 24.9)	-0.5 (-1.8, 0.7)
Selecting matched controls without replacement	3.5% (-63.1, 44.6)	0.1 (-1.2, 1.5)
Restricting to persons without any positive test in the previous 90 days	28.6% (-36, 58.4)	1 (-0.7, 2.8)

Supplementary Table 5. Sensitivity analyses: Estimated effectiveness in days 7-34 after a second dose in people with previous infection in a period of Delta variant dominance (19 July – 30 November, 2021), under different scenarios

	1 – risk ratio (95% CI)	Risk difference per 1,000 (95% CI)
Main analysis	8.8% (-79.8, 54.2)	0.0 (-0.3, 0.4)
Restricting to persons with no tests in the 7 days before enrolment	-5.5% (-110.1, 46.3)	0.0 (-0.4, 0.3)
Censoring matched pairs 7 days after the control receives a second dose rather than 0 days	-50.3% (-288.5, 38.4)	-0.2 (-0.5, 0.2)
Using date of PCR test result rather than subtracting 2 days	4.8% (-82.7, 53.3)	0.0 (-0.3, 0.4)
Selecting matched controls without replacement	-23.7% (-134.7, 39.7)	-0.1 (-0.4, 0.2)
Restricting to persons without any positive test in the previous 90 days	12.1% (-69.2, 49.5)	0.1 (-0.3, 0.4)