

## 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**

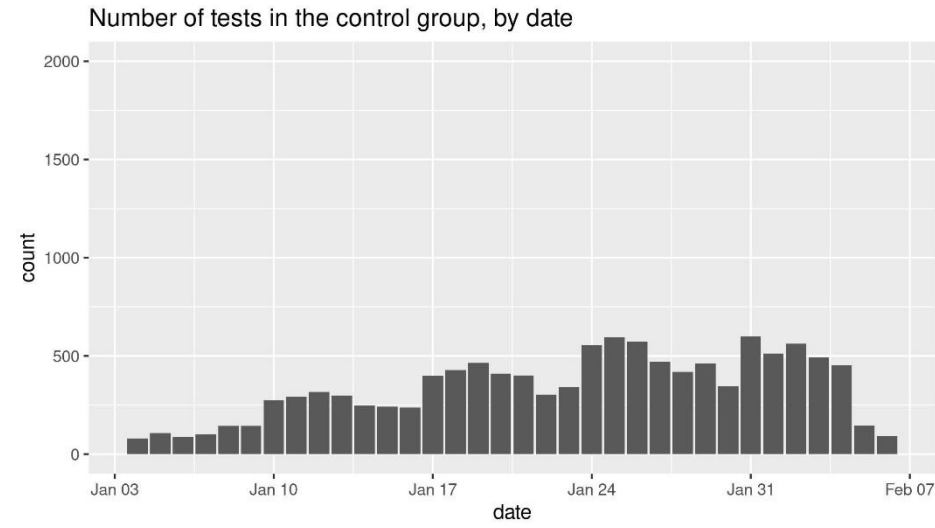
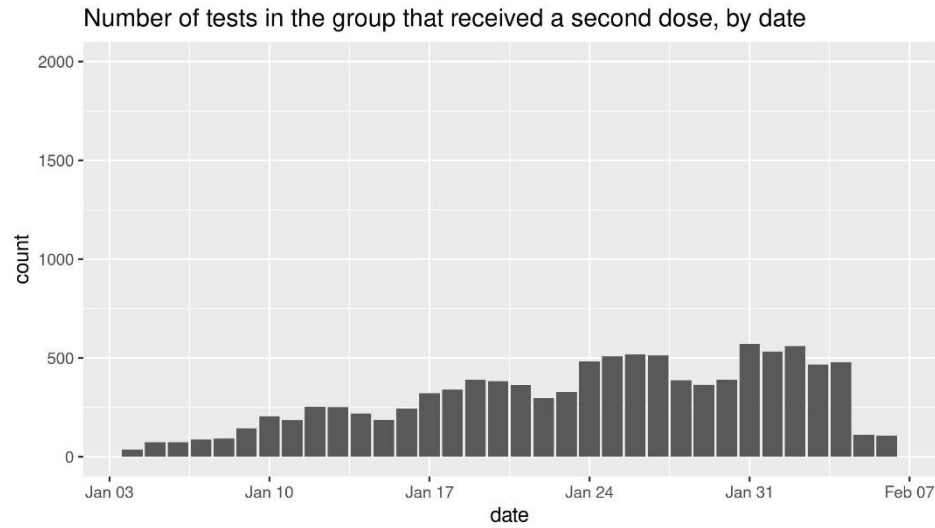
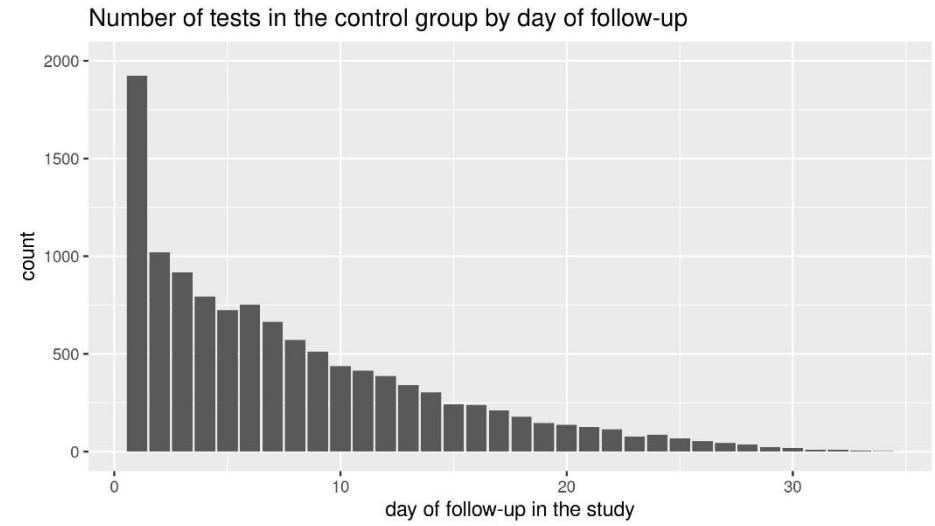
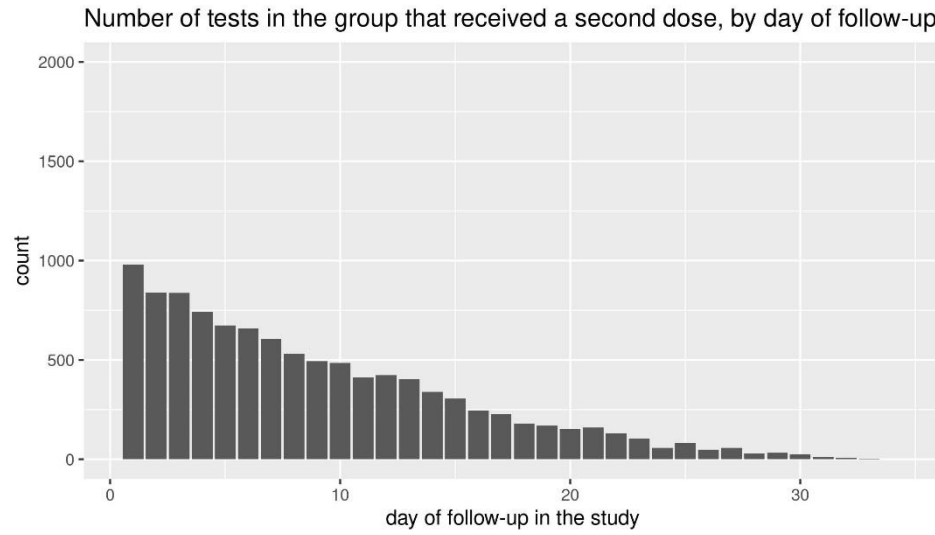
		<b>Eligible (N=1,423,311)</b>	<b>Matched sample (N=778,042)</b>
Age	18-24	325,124 (22.8%)	79,923 (10.3%)
	25-29	181,926 (12.8%)	56,388 (7.2%)
	30-34	164,970 (11.6%)	74,987 (9.6%)
	35-39	147,267 (10.3%)	79,185 (10.2%)
	40-44	169,653 (11.9%)	122,390 (15.7%)
	45-49	149,224 (10.5%)	116,633 (15.0%)
	50-54	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

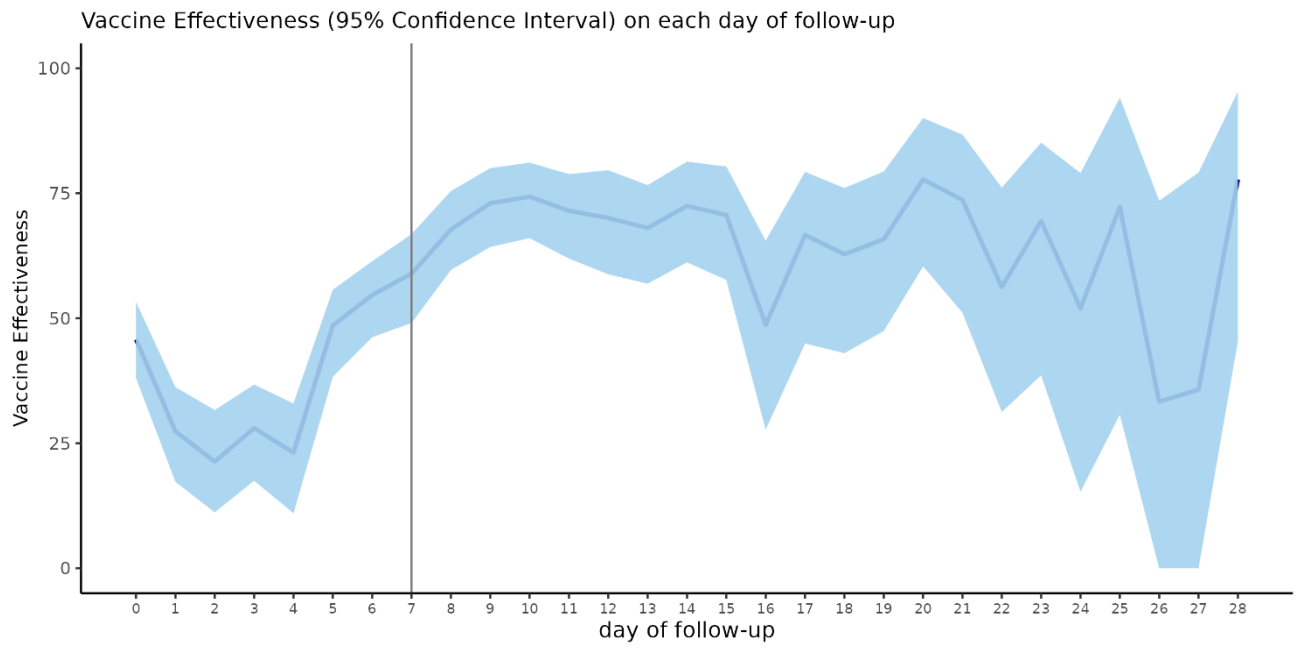
**Supplementary Table 2. Sensitivity analyses: Estimated effectiveness in days 7-34 after a second dose in people with previous infection in a period of Omicron variant dominance (3 January – 6 February 2022), under different scenarios**

	<b>1 – risk ratio (95% CI)</b>	<b>Risk difference per 1,000 (95% CI)</b>
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)

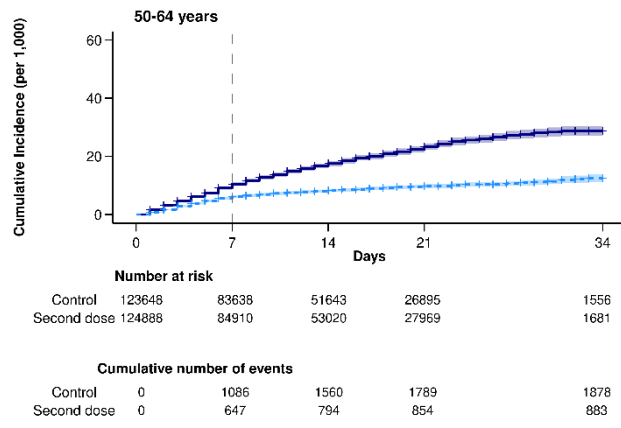
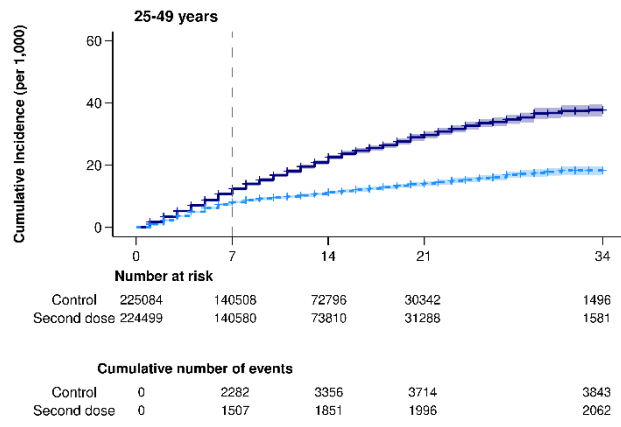
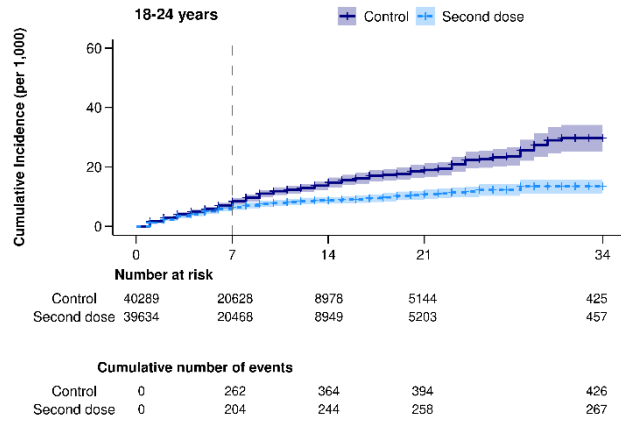
**Supplementary Figure 1. Number of laboratory tests in the booster and control groups by day of follow-up and by calendar date.**



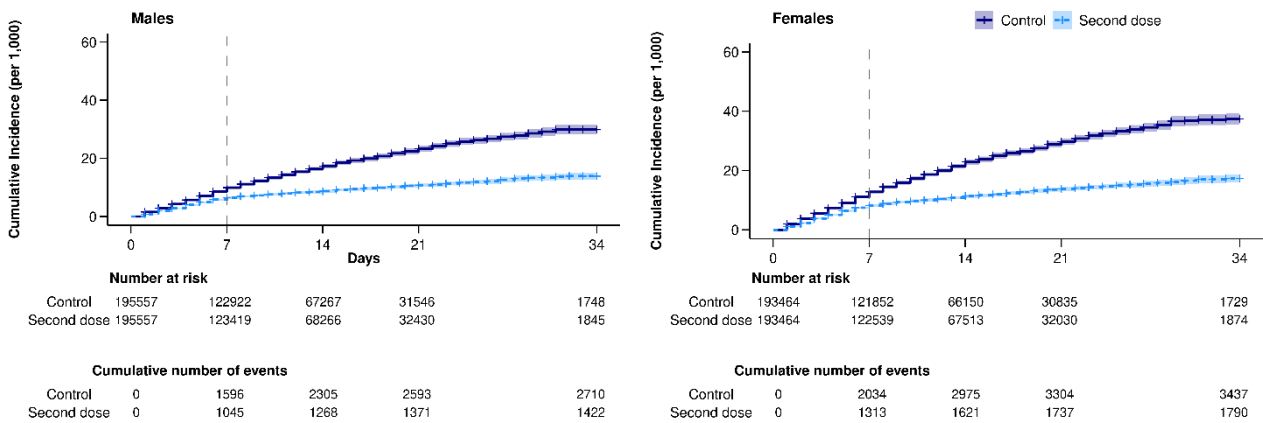
**Supplementary Figure 2. Risk ratio (95% confidence interval) in each day of follow-up, estimated using matched pairs who remained under follow-up.**



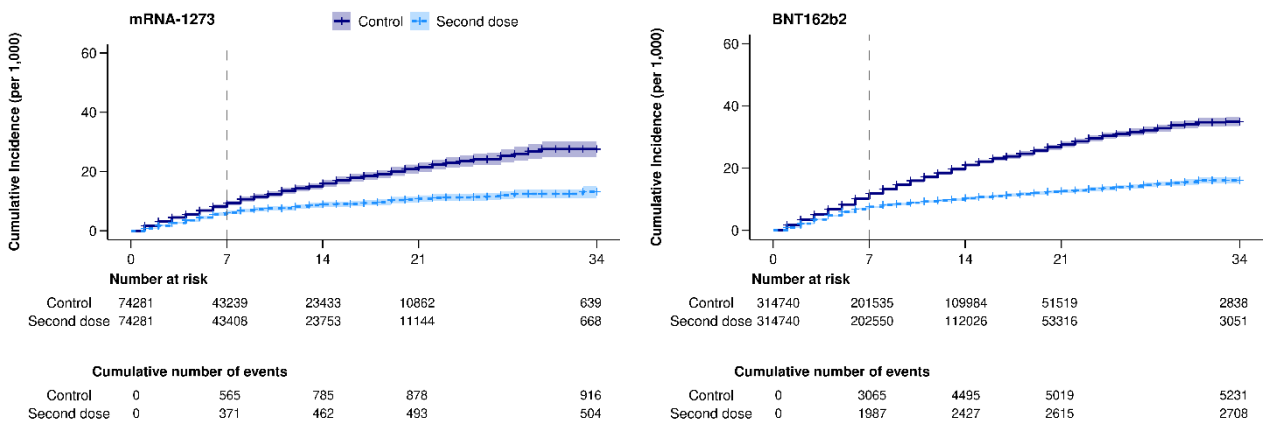
**Supplementary Figure 3. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by age, Spain, 3 January to 6 February 2022.**



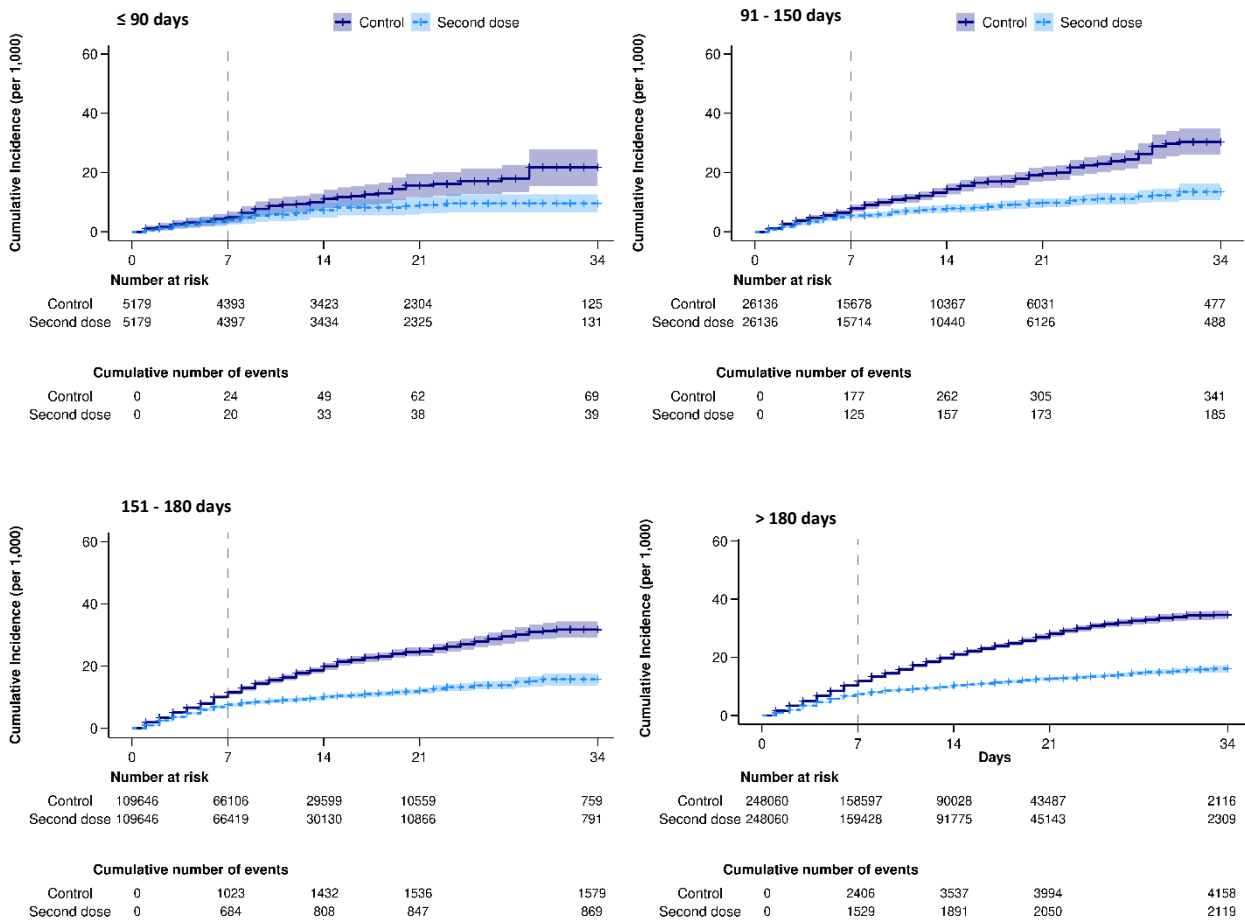
**Supplementary Figure 4. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by sex, Spain, 3 January to 6 February 2022.**



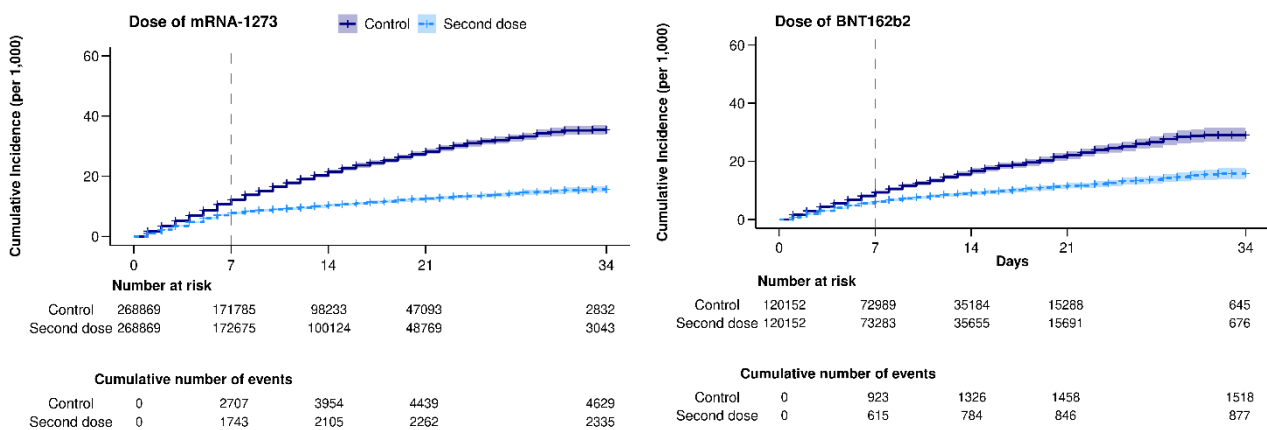
**Supplementary Figure 5. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by type of vaccine used as first dose, Spain, 3 January to 6 February 2022.**



**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.**

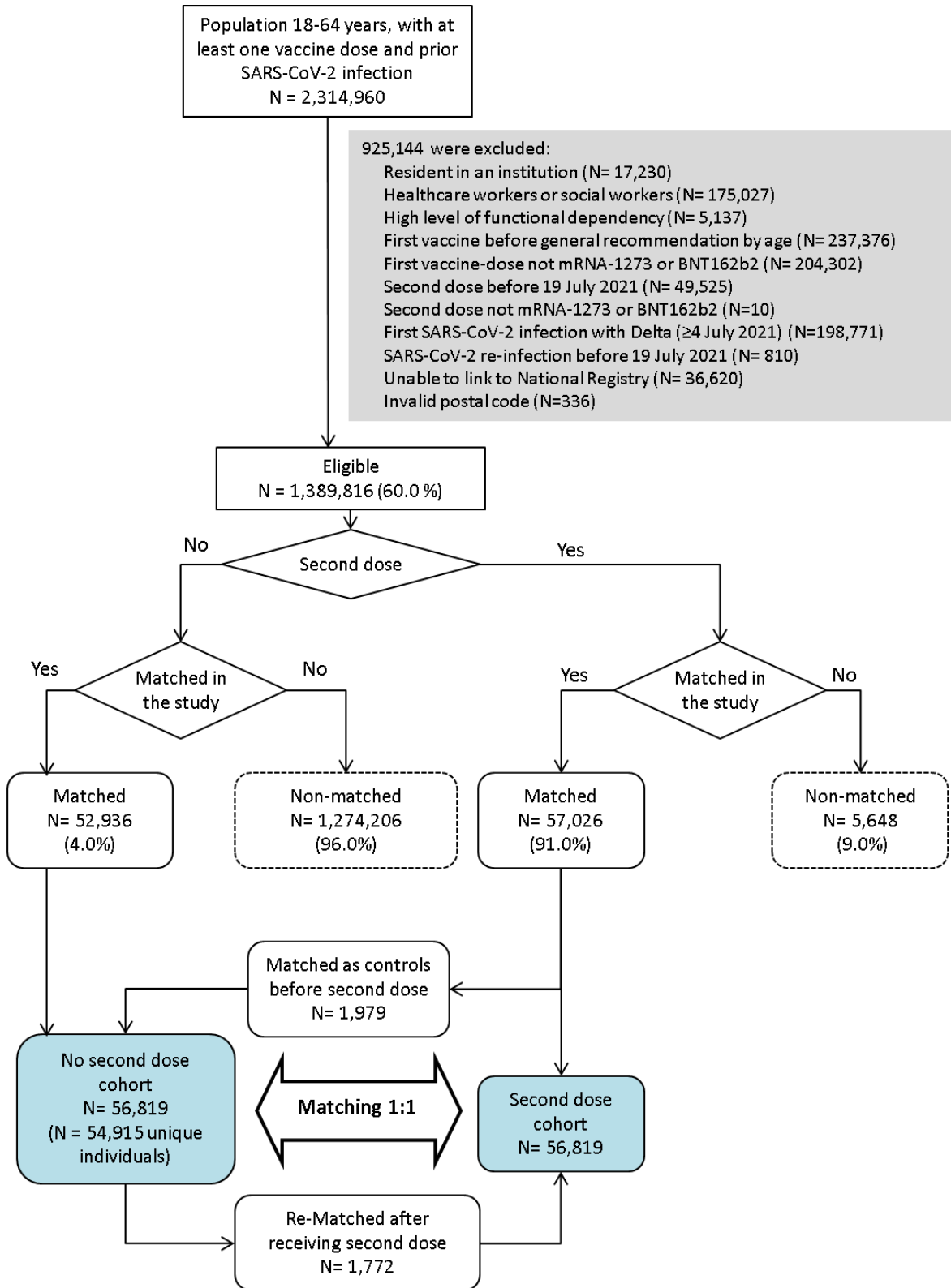


**Supplementary Figure 7. Estimates of Covid-19 risk by administration of a second vaccine-dose in individuals with infection, by type of vaccine used as second dose, Spain, 3 January to 6 February 2022.**

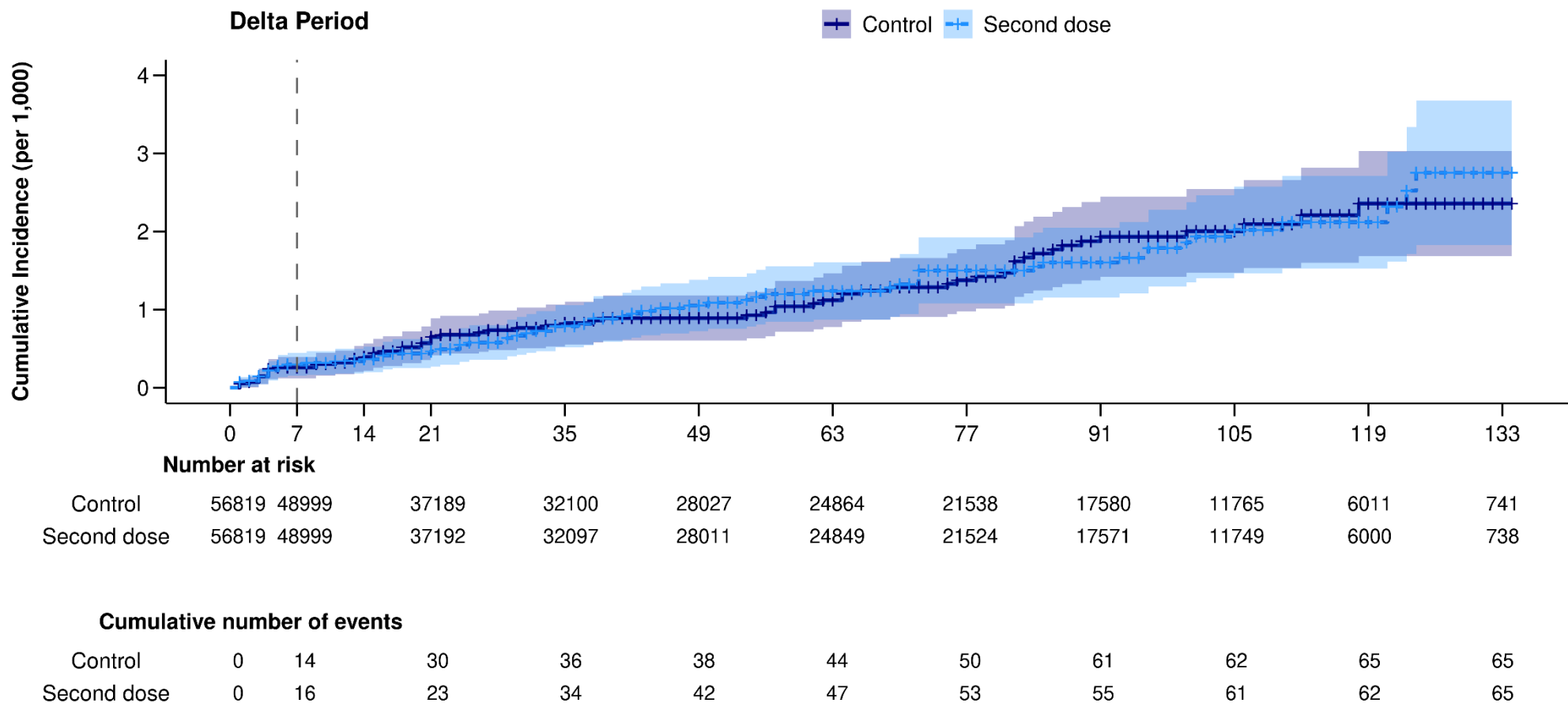




**Supplementary Figure 8. Sample selection flow-chart for estimation of the effectiveness of a second dose in people with previous infection in a period of Delta variant dominance (19 July - 6 November 2021)**



**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.**



**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**

	<b>1 – risk ratio (95% CI)</b>	<b>Risk difference per 1,000 (95% CI)</b>
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**

	<b>1 – risk ratio (95% CI)</b>	<b>Risk difference per 1,000 (95% CI)</b>
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)