Supplementary material

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Supplementary Tables

Table S1. Start dates of the data collection period, per study site.

Country	Study site	Number of hospitals, n	Data collection start date	Test-positive cases/Test-negative controls included in analytical dataset (N=1425) N
Belgium	Le Centre Hospitalier Universitaire St Pierre, Brussels	1	1 December 2023	1/4
	Universitair Ziekenhuis Antwerpen (UZA), Antwerp	1	1 December 2023	1/4
Germany	University Hospital Frankfurt, Frankfurt	1	2 October 2023	1/1
	University Hospital Ulm, Ulm	1	2 October 2023	3/10
Italy	Inter-university Research Centre on Influenza and Other Transmissible Infections (CIRI-IT):	6		45/101
	Hospitals: Genoa, Rome, Milan, Bari		2 October 2023	
	Hospitals: Siena and Pisa		18 December 2023	
Spain	Valencia Hospital Network for the Study of Infectious Diseases (VAHNSI), Valencia	5	1 December 2023	160/640
	Hospital Universitari Germans Trias i Pujol (GTPUH), Badalona, Barcelona	1	1 December 2023	37/139
	Hospital Universitari Vall d'Hebron, Barcelona	1	1 December 2023	60/218

Abbreviations: N, Number.

Table S2. Definition of chronic conditions.

Chronic condition	Definition
Asthma	• Any of the following diagnostic codes (ICD-10): J45, J46 • INCLUDING: predominantly allergic asthma, nonallergic asthma, status asthmaticus, acute severe asthma • EXCLUDING: acute severe asthma, chronic asthmatic (obstructive) bronchitis, chronic obstructive asthma, eosinophilic asthma, lung diseases due to external agents
Lung disease	• Any of the following diagnostic codes (ICD-10): A15-16, A19, A31.0, B33.4, E84.0, J40-44, J47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 • INCLUDING: tuberculosis (pulmonary, miliary, but not that of other systems), atypical mycobacteria, cystic fibrosis, chronic obstructive pulmonary disease (COPD), bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure • EXCLUDING: acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax
Cardiovascular disease	• Any of the following diagnostic codes (ICD- 10): A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-25, I26-28, I30-43, I44- 46, I48, I49.0, I49.5, I50-52, I70-71, Q20-Q28 • INCLUDING: all conditions of heart and large vessels that are chronic or likely to have chronic sequelae, cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms & dissecation, other heart diseases and their complications • EXCLUDING: uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization
Hypertension	• Any of the following diagnostic codes (ICD-10): I10, I11.9, I12, I13.1, I13.9, I15 • INCLUDING: essential (primary) hypertension, secondary hypertension • EXCLUDING: hypertensive heart/renal disease with (congestive) heart failure
Liver disease	• Any of the following diagnostic codes (ICD- 10): B18, B19, K70.1-4, K70.9, K71.1, K71.3, K71.4, K71.6-9, K72.1, K72.9, K73, K74, K75.2, K75.4, K75.8, K75.9, K76.1, K76.2, K76.5, K76.6, K76.9 • INCLUDING: all conditions of the liver that are chronic or likely to have chronic sequelae • EXCLUDING: acute liver disease, liver cancer/metastasis, liver transplant
Renal disease	• Any of the following diagnostic codes (ICD- 10): I12-13, M10.30, N00-19, N20.0, N25-27, N28.0, N28.9, Q63.9, Z90.5 • EXCLUDING: clinically nonsignificant kidney cysts
Type 2 diabetes	• Any of the following diagnostic codes (ICD-10): E11 • INCLUDING: non-insulin dependent diabetes mellitus (adult-onset, maturity-onset, nonketotic, stable, type II, non-insulin-dependent diabetes of the young)
Cancer	• Any of the following diagnostic codes (ICD- 10): C00-97, D37-48, Z85, Z92.3, Z92.6 • INCLUDING: all malignant neoplasms (both solid and hematologic) with potential to metastasize, either in treatment, active follow-up, or <5 years post curative treatment • EXCLUDING: benign & in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent & in complete remission for ≥5 years
Immunodeficiency	• Any of the following diagnostic codes (ICD-10): B20-B24, D80–84, D89, Z94 • INCLUDING: human immunodeficiency virus (HIV) infections, immunodeficiencies and organ transplants, iatrogenic immunodeficiencies (systemic treatment of more than two weeks duration, in the three months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, tumor necrosis factor alpha (TNF-α) blockers and other biological or cytostatic drugs with immunosuppressive effect) • EXCLUDING: disorders of the immune system which do not lead to immunosuppression (e.g. some autoimmune conditions)

Table S3. Characteristics of study participants, according to receipt of BNT162b2 XBB.1.5-adapted vaccine and SARS-CoV-2 case classification, using various prior vaccination categories as reference groups.

		Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
	Total, N (col %)	Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Total	861	120	561	63	117
Sex					
Female	424 (49.2)	52 (43.3)	283 (50.4)	31 (49.2)	58 (49.6)
Male	437 (50.8)	68 (56.7)	278 (49.6)	32 (50.8)	59 (50.4)
Age, years					
Median (IQR)	80.0 (72.0, 87.0)	84.0 (76.0, 88.0)	80.0 (73.0, 87.0)	76.0 (67.0, 84.5)	77.0 (66.0, 86.0)
18-49	18 (2.1)	0 (0.0)	6 (1.1)	6 (9.5)	6 (5.1)
50-64	83 (9.6)	9 (7.5)	45 (8.0)	8 (12.7)	21 (17.9)
≥65	760 (88.3)	111 (92.5)	510 (90.9)	49 (77.8)	90 (76.9)
Symptom onset, month					
Dec 2023	442 (51.3)	58 (48.3)	278 (49.6)	38 (60.3)	68 (58.1)
Jan 2024	348 (40.4)	50 (41.7)	239 (42.6)	22 (34.9)	37 (31.6)
Feb 2024	67 (7.8)	12 (10.0)	41 (7.3)	2 (3.2)	12 (10.3)
Mar 2024	4 (0.5)	0 (0.0)	3 (0.5)	1 (1.6)	0 (0.0)
Country of hospitalization					
Belgium	5 (0.6)	1 (0.8)	4 (0.7)	0 (0.0)	0 (0.0)
Germany	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Italy	46 (5.3)	12 (10.0)	19 (3.4)	5 (7.9)	10 (8.5)
Spain	810 (94.1)	107 (89.2)	538 (95.9)	58 (92.1)	107 (91.5)
Body mass index (BMI), kg/m^2 [1]					
Median (IQR)	25.9 (23.1, 29.7)	25.4 (22.6, 29.2)	26.0 (23.3, 30.0)	25.2 (23.8, 27.4)	26.4 (23.6, 31.8)
Underweight (BMI <18.5)	22 (3.6)	7 (8.2)	10 (2.4)	1 (2.5)	4 (6.5)
Normal weight (BMI ≥18.5 to <25.0)	227 (37.6)	33 (38.8)	161 (38.7)	16 (40.0)	17 (27.4)
Overweight (BMI ≥25.0 to <30.0)	193 (32.0)	25 (29.4)	132 (31.7)	17 (42.5)	19 (30.6)
Obese (BMI ≥30.0)[2]	161 (26.7)	20 (23.5)	113 (27.2)	6 (15.0)	22 (35.5)
Missing	258	35	145	23	55
Number of chronic conditions					
0-1[3]	207 (24.0)	26 (21.7)	126 (22.5)	21 (33.3)	34 (29.1)
2	242 (28.1)	35 (29.2)	157 (28.0)	15 (23.8)	35 (29.9)
≥3	412 (47.9)	59 (49.2)	278 (49.6)	27 (42.9)	48 (41.0)
Type of chronic condition					
Asthma	82 (9.5)	8 (6.7)	56 (10.0)	6 (9.5)	12 (10.3)
Lung disease	336 (39.0)	45 (37.5)	224 (39.9)	23 (36.5)	44 (37.6)
Cardiovascular disease	439 (51.0)	64 (53.3)	297 (52.9)	25 (39.7)	53 (45.3)
Hypertension	609 (70.7)	88 (73.3)	408 (72.7)	39 (61.9)	74 (63.2)

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Renal disease	50 (5.8)	7 (5.8)	28 (5.0)	3 (4.8)	12 (10.3)
Liver disease	164 (19.0)	27 (22.5)	105 (18.7)	13 (20.6)	19 (16.2)
Type 2 diabetes	280 (32.5)	45 (37.5)	195 (34.8)	15 (23.8)	25 (21.4)
Immunodeficiency or cancer[4]	173 (20.1)	24 (20.0)	103 (18.4)	15 (23.8)	31 (26.5)
Level of SARI severity[1]					
Hospital admission without intensive care unit (ICU) admission and without in-hospital death	775 (90.4)	104 (88.1)	507 (90.5)	62 (98.4)	102 (87.9)
ICU admission without in-hospital death	1 (0.8)	14 (2.5)	0 (0.0)	3 (2.6)	1 (0.8)
In-hospital death	13 (11.0)	39 (7.0)	1 (1.6)	11 (9.5)	13 (11.0)
Missing	4	2	1	0	1
Length of hospital stay, days[1]					
Median (IQR)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	6.0 (4.0, 9.5)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)
1–3	150 (17.6)	20 (17.1)	98 (17.5)	12 (19.0)	20 (17.4)
4–6	296 (34.7)	44 (37.6)	183 (32.7)	24 (38.1)	45 (39.1)
7–13	294 (34.4)	40 (34.2)	200 (35.8)	20 (31.7)	34 (29.6)
14–27	104 (12.2)	11 (9.4)	70 (12.5)	7 (11.1)	16 (13.9)
28–41	8 (0.9)	2 (1.7)	6 (1.1)	0 (0.0)	0 (0.0)
≥42	2 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Missing	7	3	2	0	2
Pregnancy[1,5]					
Yes	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
No	422 (99.8)	52 (100.0)	282 (99.6)	30 (100.0)	58 (100.0)
Missing	1	0	0	1	0
Reported prior SARS-CoV-2 infection[1]					
Yes	183 (25.3)	22 (21.8)	131 (27.0)	9 (18.4)	21 (24.1)
No	540 (74.7)	79 (78.2)	355 (73.0)	40 (81.6)	66 (75.9)
Missing	138	19	75	14	30
Influenza vaccination within 12 months prior to hospitalization[1]					
Yes	698 (81.2)	112 (93.3)	528 (94.3)	23 (36.5)	35 (29.9)
No	162 (18.8)	8 (6.7)	32 (5.7)	40 (63.5)	82 (70.1)
Missing	1	0	1	0	0
Pneumococcal vaccination[1]					
Yes	454 (53.0)	66 (55.0)	298 (53.4)	32 (50.8)	58 (50.0)
No	403 (47.0)	54 (45.0)	260 (46.6)	31 (49.2)	58 (50.0)
Missing	4	0	3	0	1
Smoking history[1]					

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Never-smoker	379 (47.1)	52 (48.6)	254 (47.7)	24 (40.7)	49 (46.2)
Ex-smoker	319 (39.7)	43 (40.2)	210 (39.5)	30 (50.8)	36 (34.0)
Occasional smoker	13 (1.6)	2 (1.9)	10 (1.9)	1 (1.7)	0 (0.0)
Daily smoker	93 (11.6)	10 (9.3)	58 (10.9)	4 (6.8)	21 (19.8)
Missing	57	13	29	4	11
Long-term care facility resident[1]					
Yes	41 (4.8)	7 (6.0)	29 (5.2)	1 (1.6)	4 (3.5)
No	808 (95.2)	110 (94.0)	527 (94.8)	61 (98.4)	110 (96.5)
Missing	12	3	5	1	3
Total	928	119	505	84	220
Sex					
Female	473 (51.0)	51 (42.9)	260 (51.5)	54 (64.3)	108 (49.1)
Male	455 (49.0)	68 (57.1)	245 (48.5)	30 (35.7)	112 (50.9)
Age, years					
Median (IQR)	79.0 (70.0, 86.0)	84.0 (76.0, 88.0)	81.0 (74.0, 88.0)	78.0 (58.8, 85.2)	70.0 (56.0, 80.0)
18-49	54 (5.8)	0 (0.0)	6 (1.2)	10 (11.9)	38 (17.3)
50-64	112 (12.1)	9 (7.6)	37 (7.3)	18 (21.4)	48 (21.8)
≥65	762 (82.1)	110 (92.4)	462 (91.5)	56 (66.7)	134 (60.9)
Symptom onset, month					
Dec 2023	441 (47.5)	57 (47.9)	241 (47.7)	32 (38.1)	111 (50.5)
Jan 2024	376 (40.5)	50 (42.0)	214 (42.4)	40 (47.6)	72 (32.7)
Feb 2024	109 (11.7)	12 (10.1)	49 (9.7)	11 (13.1)	37 (16.8)
Mar 2024	2 (0.2)	0 (0.0)	1 (0.2)	1 (1.2)	0 (0.0)
Country of hospitalization					
Belgium	2 (0.2)	1 (0.8)	1 (0.2)	0 (0.0)	0 (0.0)
Germany	7 (0.8)	0 (0.0)	2 (0.4)	2 (2.4)	3 (1.4)
Italy	114 (12.3)	12 (10.1)	20 (4.0)	25 (29.8)	57 (25.9)
Spain	805 (86.7)	106 (89.1)	482 (95.4)	57 (67.9)	160 (72.7)
Body mass index (BMI), kg/m^2 [1]					
Median (IQR)	25.8 (22.7, 29.5)	25.4 (22.6, 29.2)	26.1 (23.0, 29.8)	24.9 (22.6, 28.4)	25.9 (22.5, 29.6)
Underweight (BMI <18.5)	24 (3.5)	7 (8.2)	11 (2.9)	3 (5.0)	3 (1.8)
Normal weight (BMI ≥18.5 to <25.0)	267 (39.1)	33 (38.8)	143 (38.2)	26 (43.3)	65 (39.6)
Overweight (BMI ≥25.0 to <30.0)	215 (31.5)	25 (29.4)	119 (31.8)	17 (28.3)	54 (32.9)
Obese (BMI ≥30.0)[2]	177 (25.9)	20 (23.5)	101 (27.0)	14 (23.3)	42 (25.6)
Missing	245	34	131	24	56
Number of chronic conditions					
0-1[3]	260 (28.0)	26 (21.8)	118 (23.4)	29 (34.5)	87 (39.5)
2	276 (29.7)	35 (29.4)	151 (29.9)	27 (32.1)	63 (28.6)

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
≥3	392 (42.2)	58 (48.7)	236 (46.7)	28 (33.3)	70 (31.8)
Type of chronic condition					
Asthma	91 (9.8)	8 (6.7)	48 (9.5)	6 (7.1)	29 (13.2)
Lung disease	330 (35.6)	45 (37.8)	195 (38.6)	22 (26.2)	68 (30.9)
Cardiovascular disease	438 (47.2)	63 (52.9)	260 (51.5)	44 (52.4)	71 (32.3)
Hypertension	632 (68.1)	87 (73.1)	376 (74.5)	50 (59.5)	119 (54.1)
Renal disease	54 (5.8)	7 (5.9)	28 (5.5)	7 (8.3)	12 (5.5)
Liver disease	149 (16.1)	26 (21.8)	85 (16.8)	10 (11.9)	28 (12.7)
Type 2 diabetes	284 (30.6)	44 (37.0)	167 (33.1)	19 (22.6)	54 (24.5)
Immunodeficiency or cancer[4]	175 (18.9)	23 (19.3)	91 (18.0)	20 (23.8)	41 (18.6)
Level of SARI severity[1]					
Hospital admission without intensive care unit (ICU) admission and without in-hospital death	854 (92.7)	103 (88.0)	463 (91.9)	79 (96.3)	209 (95.9)
ICU admission without in-hospital death	19 (2.1)	1 (0.9)	12 (2.4)	2 (2.4)	4 (1.8)
In-hospital death	48 (5.2)	13 (11.1)	29 (5.8)	1 (1.2)	5 (2.3)
Missing	7	2	1	2	2
Length of hospital stay, days[1]					
Median (IQR)	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	6.5 (4.0, 9.8)	6.0 (4.0, 11.0)	6.0 (4.0, 9.0)
1–3	172 (18.9)	20 (17.2)	88 (17.5)	17 (21.5)	47 (22.0)
4–6	304 (33.4)	44 (37.9)	163 (32.5)	24 (30.4)	73 (34.1)
7–13	322 (35.3)	39 (33.6)	186 (37.1)	26 (32.9)	71 (33.2)
14–27	101 (11.1)	11 (9.5)	60 (12.0)	12 (15.2)	18 (8.4)
28–41	9 (1.0)	2 (1.7)	4 (0.8)	0 (0.0)	3 (1.4)
≥42	3 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.9)
Missing	17	3	3	5	6
Pregnancy[1,5]					
Yes	2 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.9)
No	469 (99.6)	51 (100.0)	259 (99.6)	54 (100.0)	105 (99.1)
Missing	2	0	0	0	2
Reported prior SARS-CoV-2 infection[1]					
Yes	208 (26.7)	22 (21.8)	108 (25.0)	22 (34.4)	56 (30.9)
No	570 (73.3)	79 (78.2)	324 (75.0)	42 (65.6)	125 (69.1)
Missing	150	18	73	20	39
Influenza vaccination within 12 months prior to hospitalization[1]					
Yes	644 (69.5)	111 (93.3)	476 (94.4)	22 (26.2)	35 (15.9)
No	283 (30.5)	8 (6.7)	28 (5.6)	62 (73.8)	185 (84.1)
Missing	1	0	1	0	0

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Pneumococcal vaccination[1]					
Yes	399 (43.2)	65 (54.6)	268 (53.4)	19 (22.9)	47 (21.5)
No	524 (56.8)	54 (45.4)	234 (46.6)	64 (77.1)	172 (78.5)
Missing	5	0	3	1	1
Smoking history[1]					
Never-smoker	385 (44.9)	51 (48.1)	225 (46.9)	35 (53.0)	74 (35.9)
Ex-smoker	320 (37.3)	43 (40.6)	193 (40.2)	18 (27.3)	66 (32.0)
Occasional smoker	28 (3.3)	2 (1.9)	7 (1.5)	2 (3.0)	17 (8.3)
Daily smoker	125 (14.6)	10 (9.4)	55 (11.5)	11 (16.7)	49 (23.8)
Missing	70	13	25	18	14
Long-term care facility resident[1]					
Yes	42 (4.6)	7 (6.0)	24 (4.8)	2 (2.4)	9 (4.1)
No	875 (95.4)	109 (94.0)	478 (95.2)	80 (97.6)	208 (95.9)
Missing	11	3	3	2	3
Total	649	120	467	18	44
Sex					
Female	326 (50.2)	52 (43.3)	237 (50.7)	9 (50.0)	28 (63.6)
Male	323 (49.8)	68 (56.7)	230 (49.3)	9 (50.0)	16 (36.4)
Age, years					
Median (IQR)	81.0 (72.0, 88.0)	84.0 (76.0, 88.0)	81.0 (73.0, 88.0)	73.5 (60.0, 82.8)	71.0 (48.0, 80.0)
18-49	19 (2.9)	0 (0.0)	5 (1.1)	2 (11.1)	12 (27.3)
50-64	56 (8.6)	9 (7.5)	36 (7.7)	4 (22.2)	7 (15.9)
≥65	574 (88.4)	111 (92.5)	426 (91.2)	12 (66.7)	25 (56.8)
Symptom onset, month					
Dec 2023	316 (48.7)	58 (48.3)	220 (47.1)	12 (66.7)	26 (59.1)
Jan 2024	279 (43.0)	50 (41.7)	208 (44.5)	6 (33.3)	15 (34.1)
Feb 2024	54 (8.3)	12 (10.0)	39 (8.4)	0 (0.0)	3 (6.8)
Country of hospitalization					
Belgium	5 (0.8)	1 (0.8)	4 (0.9)	0 (0.0)	0 (0.0)
Germany	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Italy	36 (5.5)	12 (10.0)	20 (4.3)	1 (5.6)	3 (6.8)
Spain	608 (93.7)	107 (89.2)	443 (94.9)	17 (94.4)	41 (93.2)
Body mass index (BMI), kg/m^2 [1]					
Median (IQR)	25.6 (22.9, 29.8)	25.4 (22.6, 29.2)	25.9 (23.0, 29.8)	25.0 (20.8, 27.3)	25.0 (22.3, 31.0)
Underweight (BMI <18.5)	18 (3.8)	7 (8.2)	8 (2.3)	1 (7.7)	2 (6.2)
Normal weight (BMI ≥18.5 to <25.0)	189 (39.5)	33 (38.8)	137 (39.3)	6 (46.2)	13 (40.6)
Overweight (BMI ≥25.0 to <30.0)	147 (30.7)	25 (29.4)	110 (31.5)	4 (30.8)	8 (25.0)

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Obese (BMI ≥30.0)[2]	125 (26.1)	20 (23.5)	94 (26.9)	2 (15.4)	9 (28.1)
Missing	170	35	118	5	12
Number of chronic conditions					
0-1[3]	160 (24.7)	26 (21.7)	103 (22.1)	8 (44.4)	23 (52.3)
2	180 (27.7)	35 (29.2)	135 (28.9)	3 (16.7)	7 (15.9)
≥3	309 (47.6)	59 (49.2)	229 (49.0)	7 (38.9)	14 (31.8)
Type of chronic condition					
Asthma	58 (8.9)	8 (6.7)	45 (9.6)	0 (0.0)	5 (11.4)
Lung disease	250 (38.5)	45 (37.5)	186 (39.8)	7 (38.9)	12 (27.3)
Cardiovascular disease	334 (51.5)	64 (53.3)	252 (54.0)	7 (38.9)	11 (25.0)
Hypertension	458 (70.6)	88 (73.3)	338 (72.4)	9 (50.0)	23 (52.3)
Renal disease	32 (4.9)	7 (5.8)	22 (4.7)	1 (5.6)	2 (4.5)
Liver disease	113 (17.4)	27 (22.5)	79 (16.9)	2 (11.1)	5 (11.4)
Type 2 diabetes	223 (34.4)	45 (37.5)	161 (34.5)	5 (27.8)	12 (27.3)
Immunodeficiency or cancer[4]	120 (18.5)	24 (20.0)	86 (18.4)	4 (22.2)	6 (13.6)
Level of SARI severity[1]					
Hospital admission without intensive care unit (ICU) admission and without in-hospital death	580 (89.8)	104 (88.1)	422 (90.6)	15 (83.3)	39 (88.6)
ICU admission without in-hospital death	16 (2.5)	1 (0.8)	13 (2.8)	0 (0.0)	2 (4.5)
In-hospital death	50 (7.7)	13 (11.0)	31 (6.7)	3 (16.7)	3 (6.8)
Missing	3	2	1	0	0
Length of hospital stay, days[1]					
Median (IQR)	6.0 (4.0, 10.0)	6.0 (4.0, 9.0)	7.0 (4.0, 10.0)	7.0 (4.2, 11.0)	6.0 (3.0, 9.0)
1–3	114 (17.7)	20 (17.1)	78 (16.8)	4 (22.2)	12 (27.3)
4–6	211 (32.8)	44 (37.6)	150 (32.3)	4 (22.2)	13 (29.5)
7–13	231 (35.9)	40 (34.2)	172 (37.1)	6 (33.3)	13 (29.5)
14–27	77 (12.0)	11 (9.4)	58 (12.5)	3 (16.7)	5 (11.4)
28–41	9 (1.4)	2 (1.7)	5 (1.1)	1 (5.6)	1 (2.3)
≥42	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Missing	6	3	3	0	0
Pregnancy[1,5]					
Yes	1 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
No	325 (99.7)	52 (100.0)	236 (99.6)	9 (100.0)	28 (100.0)
Missing	0	0	0	0	0
Reported prior SARS-CoV-2 infection[1]					
Yes	137 (24.8)	22 (21.8)	106 (26.5)	1 (6.2)	8 (22.2)
No	416 (75.2)	79 (78.2)	294 (73.5)	15 (93.8)	28 (77.8)
Missing	96	19	67	2	8

	Total, N (col %)	Received BNT162b2 XBB.1.5-adapted vaccine in 2023–2024 season, (N, col %)		Received ≥ 1 BA.4/5 bivalent dose, (N, col %)	
		Test-positive cases	Test-negative controls	Test-positive cases	Test-negative controls
Influenza vaccination within 12 months prior to hospitalization[1]					
Yes	553 (86.0)	112 (93.3)	439 (94.2)	1 (6.2)	1 (2.4)
No	90 (14.0)	8 (6.7)	27 (5.8)	15 (93.8)	40 (97.6)
Missing	6	0	1	2	3
Pneumococcal vaccination[1]					
Yes	321 (50.0)	66 (55.0)	246 (52.9)	3 (18.8)	6 (14.6)
No	321 (50.0)	54 (45.0)	219 (47.1)	13 (81.2)	35 (85.4)
Missing	7	0	2	2	3
Smoking history[1]					
Never-smoker	293 (48.0)	52 (48.6)	208 (47.1)	9 (52.9)	24 (54.5)
Ex-smoker	232 (38.0)	43 (40.2)	177 (40.0)	4 (23.5)	8 (18.2)
Occasional smoker	13 (2.1)	2 (1.9)	7 (1.6)	1 (5.9)	3 (6.8)
Daily smoker	72 (11.8)	10 (9.3)	50 (11.3)	3 (17.6)	9 (20.5)
Missing	39	13	25	1	0
Long-term care facility resident[1]					
Yes	29 (4.5)	7 (6.0)	22 (4.7)	0 (0.0)	0 (0.0)
No	612 (95.5)	110 (94.0)	442 (95.3)	17 (100.0)	43 (100.0)
Missing	8	3	3	1	1

[1] Percentages exclude subjects with missing values.

[2] Obese classification was based on both BMI ≥30.0 kg/m^2 and obesity as a categorical variable (yes/no).

[3] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions, based on the list of chronic conditions provided in Supplementary Table S2. Here, the cell counts among participants having "0–1" chronic conditions are provided as a composite.

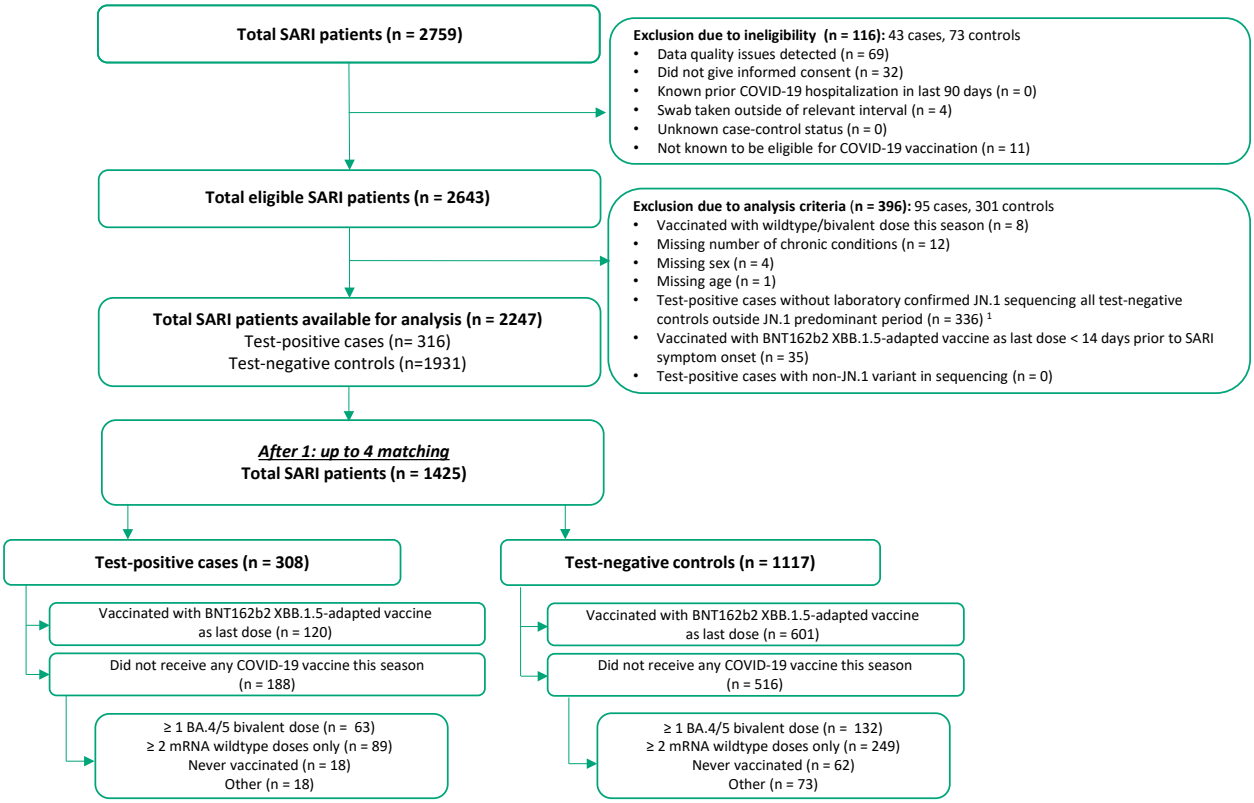
[4] The categories "Cancer" and "Immunodeficiency" among chronic conditions are identified as separate types of chronic conditions, as presented in Supplementary Table S2. Here, the cell counts among participants having "Immunodeficiency or cancer" are provided as a composite.

[5]Pregnancy status counts and percentages were counted in female patients.

[6] 246 patients out of the 310 (79.4%) who did not receive any COVID-19 vaccine in 2023-2024 season and had previously received ≥2 mRNA wildtype doses only, in this matched dataset, had received ≥3 mRNA wildtype doses only.

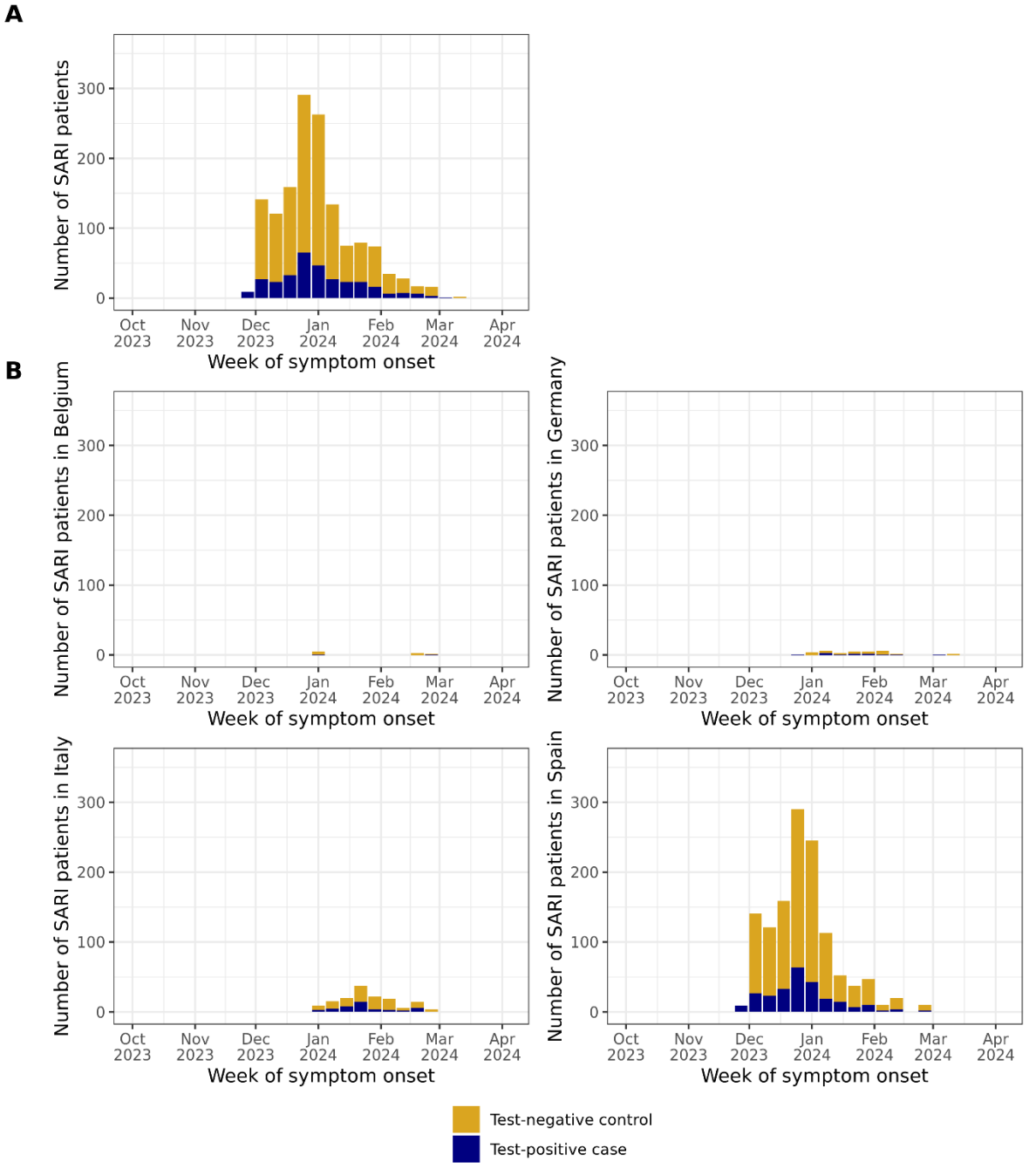
Supplementary Figures

Figure S1 Flow diagram of study population



[1] 14 patients infected with JN.1 outside of the JN.1 predominant period were included in the analysis.

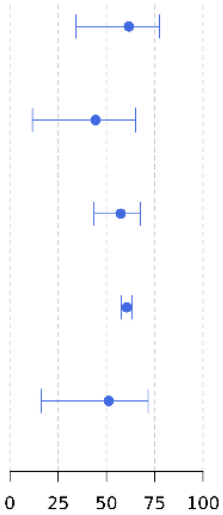
Figure S2. Number of SARI patients enrolled according to SARS-CoV-2 case status over time A) overall and B) by country.



JN.1 variant predominance started on: 29 December 2023 in Belgium, 31 December 2023 in Germany, 1 January 2024 in Italy and 3 December 2023 in Spain. Vaccination campaigns began: 15 September 2023 in Belgium, 18 September 2023 in Germany, 25 September 2023 in Italy, 16 October 2023 in the Valencia region of Spain, and 26 September 2023 in the Catalonian region of Spain.

Figure S3. Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season, by time since last dose, among adults ≥65 years.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Weeks since XBB.1.5-adapted vaccine dose						
Age group: ≥65y						
2 to <4 wks	Yes	32	4 (12%)	28 (88%)	23 (22; 26)	61.6% (34.2; 77.6)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
4 to <8 wks	Yes	201	38 (19%)	163 (81%)	46 (38; 50)	44.4% (11.7; 65.0)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
8 to <12 wks	Yes	306	50 (16%)	256 (84%)	68 (62; 75)	57.4% (43.7; 67.7)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
12 to <16 wks	Yes	102	16 (16%)	86 (84%)	90 (86; 98)	60.5% (57.7; 63.2)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
16 to <22 wks	Yes	17	3 (18%)	14 (82%)	125 (119; 135)	51.2% (16.1; 71.6)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).

Statistical Analyses Supplementary Material

A.1. General framework for the COVID-19 vaccine effectiveness analysis

To address potential intra-cluster correlation among subjects from the same study site, Generalized Estimating Equations (GEE) were employed for analyzing subject-level data. In this context, a study site is regarded as a distinct cluster. Heterogeneity between study sites may exist due to the differences in recruitment, local differences in the intensity of the epidemic and healthcare practices.

A.1.1. Analysis overview

VE against hospitalization due to laboratory-confirmed COVID-19 was estimated as:

$$VE = (1 - OR) \text{ x } 100\%$$

where OR denotes the odds ratio calculated as the ratio of the odds of vaccination among SARS-CoV-2 test-positive cases to the odds of vaccination among SARS-CoV-2 test-negative controls.

Let K denote the number of clusters (study sites), n_k represent the number of included patients from study site k ($k = 1, \dots, K$) (from now will be referred to as cluster). We denote Y_{ik} the variable representing the infection status of subject i from cluster k, $Y_{ik} = 1$ [if positive-case] and $Y_{ik} = 0$ [if negative-control]. X_1 is the variable representing the vaccination status of subject i from cluster k, $X_{1ik} = 1$ [if vaccinated] and $X_{1ik} = 0$ [if unvaccinated or other exposure definition depending on the analyses].

Assuming that Y_{ik} follow a binomial distribution with $\pi_{ik} = P(Y_{ik} = 1|X_{1ik})$, the probability of being a COVID-19 positive case by laboratory-confirmed RT-PCR test or other equivalent tests (from now on, we will just refer to it as a COVID-19 positive case). Conditionally on the vaccination status and using a logit-function, we can relate:

$$\text{logit}\,(\pi_{ik}) = \log\left(\frac{\pi_{ik}}{1-\pi_{ik}}\right) = \beta_0 + \beta_1 X_{1ik} \quad [1]$$

Hence, the odds of having COVID-19 in the vaccinated group (i.e. $X_1 = 1$) is $\pi_{vaccinated}/(1 - \pi_{vaccinated}) = \exp(\beta_0 + \beta_1)$ while the odds of having COVID-19 in the reference group (either unvaccinated this season, or unvaccinated group depending on the objective, i.e., $X_1 = 0$) is $\pi_{reference}/(1 - \pi_{reference}) = \exp(\beta_0)$. Consequently, the odds ratio (OR) of having COVID-19 in the vaccinated group compared to the reference group is estimated as:

$$OR = \frac{\pi_{vaccinated}/(1-\pi_{vaccinated})}{\pi_{reference}/(1-\pi_{reference})} = \frac{\exp(\beta_0+\beta_1)}{\exp(\beta_0)} = \exp(\beta_1).$$

Finally, the VE is calculated as follows:

$$VE = \left(1 - \exp(\beta_1)\right) \times 100\%$$

The GEE approach was used to obtain the population-averaged estimate (over study sites) of the parameter of interest (in this case, β_1), adjusting for other covariates when appropriate, depending on the analyses. We computed 95% Wald CIs, assuming normal sampling distributions of the estimates. For each VE estimate and the corresponding 95% CI, the median and IQR of time since last dose (measured in days) for the exposed subjects contributing to the estimate was calculated and reported.

A.1.2. Confounder adjustment

The estimated VE was adjusted for the symptom onset date, and other covariates [confounder-adjusted VE estimate].

The confounder-adjusted VE estimate was obtained from a logistic regression model that included the following covariates: vaccination status, symptom onset date, age, sex, and the number of chronic conditions. Date of symptom onset was included in the model to adjust for potential confounding due to changes in SARS-CoV-2 incidence as well as time-varying vaccination coverage. The effects of symptom onset date and patient age were modeled using cubic regression splines. The number of chronic conditions was modelled as a categorical variable, taking values 0 (no chronic condition present), 1 (only one chronic condition present), 2 (two chronic conditions present), or ≥3 (at least three chronic conditions present) and were based on the presence of the chronic conditions.

A.1.3. Generalized Estimating Equations (GEE) approach

A.1.3.1. Overview of the approach

Generalized Estimating Equations (GEE), initially proposed by [2,3] is a widely used approach for analyzing clustered data. GEE employ a marginal logistic regression model to address potential intra-cluster correlation, particularly in cases where outcomes of subjects from a study site may exhibit greater relatedness compared to subjects from other study sites. Treating a study site as a cluster, with the cluster size equal to the number of subjects from the corresponding study site included in the analysis, GEE models provide population-averaged results. Notably, GEE avoids the need to specify the full joint likelihood function while doing model fitting, a challenge in cases of discrete response variables, requiring only the specification of the first two marginal moments – the mean vector and the variance-covariance matrix.

In the GEE approach, the robust sandwich estimator, which relies on a working correlation matrix, yields a consistent and asymptotically normal estimator [3]. A working correlation matrix is a matrix presenting an assumed correlation structure between observations from the same cluster. The clusters are assumed to be independent of each other. If the assumed working correlation structure is close to the truth, some efficiency might be gained. However, the estimates from GEE are consistent even if the working correlation structure is mis-specified. Exchangeable, independent, and first-order autoregressive structures are examples of commonly used working correlation structures [2].

A1.3.2. Model fitting procedure

For all analyses, we assumed an independent working correlation among outcomes of subjects within the same cluster. Seaman et al and Kahan et al [4, 5] have shown that using an exchangeable working correlation structure might lead to biased estimates in case there are cluster based confounding (CBC) and/or informative cluster sizes (ICS) present, hence an independent working correlation structure is recommended. GEE models were fit using the PGEE package in R [6]. The PGEE package implements a penalized GEE procedure, as proposed by GEE procedure, as proposed by Wang et al. (2012) [7], designed for the analysis of correlated data with high-dimensional covariates. This method accommodates situations with the diverging number of parameters to be estimated. In our analyses, however, we slightly modified the written package to allow for a "ridge" penalty term. The inclusion of the ridge penalty term is useful to handle difficulty in model fitting when there is multicollinearity present [8]. Multicollinearity may be present when there is strong correlation among predictor variables which might lead to unstable and biased standard errors [9].

There are additional challenges in the process of model fitting. One common issue is complete separation which occurs when one of the cells in the 2x2 table [outcome by exposure] is 0 [10]. As a result, the estimated odds ratio is either 0 or infinity. Using logistic regression for odds ratio estimation often generates very extreme estimates (1e-8 or 1e8, for example, depending on specific data) corresponding to unrealistic VE estimates (approximately 100% or -1e-10). This problem may remain undetected when examining the 2x2 table of outcome and exposure in the absence of relevant covariate information, referred to as quasi-complete separation. It is quite probable that, for certain covariate values, the 2x2 table [outcome x exposure] contains a 0 cell, while the overall 2x2 table does not. Our analysis likely had sparse data due to relatively small sample sizes when incorporating covariates in the model. Consequently, if any entries in the 2x2 table of exposure and outcome have a 0 count, then the VE estimate was reported as NE (non-estimable) due to the presence of complete or quasi-complete separation and to avoid running a model fitting procedure that would yield nonsensical estimates for the VE coefficient.

GEE routines typically obtain initial coefficient estimates from corresponding generalized linear models (GLM) and update these parameters iteratively until convergence. However, in the presence of separation, utilizing a regular (i.e., unpenalized) GLM routine can result in infinite estimates of the odds ratio (on the log scale). To circumvent these issues, the initial coefficients are obtained from ridge regression (i.e., a GLM with a ridge penalty) using the glmnet package [11], and these coefficients are subsequently utilized in the PGEE call. The use of glmnet also facilitates obtaining an approximate estimate of the penalty parameter used in the penalized GEE model. This penalty parameter is selected by minimizing out-of-sample binomial deviance through five-fold cross-validation, employing the one-standard error rule. This procedure is achieved by using the glmnet package [12]. The initial coefficient associated with the penalty parameter determined by the one-standard error rule is chosen as the coefficient for the PGEE fitting procedure.

To ensure reproducibility in all analyses, the seed number 23 was employed by calling set.seed (23) before the glmnet function was called. The variables passed to the glmnet call were not necessary to be standardized (i.e., not rescaled

to have 0 mean and unit variance). This is because the function itself already implements data processing procedures to ensure that the included covariates (either categorical variables or B-spline bases of the continuous variables) are on the same scale. An intercept column should be added if it is not present in the model matrix. It is worth noting that only the spline terms are penalized in the glmnet package and the PGEE calls.

Finally, it is crucial to ensure that the data passed to glmnet and PGEE for model fitting are ordered by study site to guarantee accurate results produced by PGEE. Additionally, the scale parameter (scale.fix) for the PGEE model should be set to TRUE, which corresponds to a scale.value of 1 for binomial data [13]. To guarantee reliable VE estimates, the GEE analysis was only conducted if there were a minimum of 2 subjects in each cell of the 2x2 table (exposure x outcome) without considering stratification for other covariates. This condition leads to the requirement of a total sample size of at least 8 subjects. It is essential to highlight that, depending on the analysis with the inclusion of different sets of covariates, a sample size as modest as 8 could still pose challenges in model fitting or result in VE estimates with very wide confidence intervals.

Confounder adjusted VE estimate

For the confounder adjusted VE estimate, the effects of symptom onset date (X_2), patient age in years (X_3), patient gender assigned at birth (X_4), and number of chronic conditions (X_5) were included in the GEE models. Formula [1] is extended to:

$$\text{logit}\,(\pi_{ik}) = \beta_0 + \beta_1 X_{1ik} + s_2(X_{2ik}) + s_3(X_{3ik}) + \beta_4 X_{4ik} + \beta_5 X_{5ik} \quad [1a]$$

Here, X_2 and X_3 are treated as continuous variables. s_2 and s_3 are (cubic spline) smooth functions of the variables representing symptom onset date (X_2) and patient age (X_3). The use of a smooth function allows capture of a flexible relationship between the odds of having COVID-19 and symptom onset date as well as patient age. For symptom onset date, we defined 2 knots corresponding to 2024-01-15 and 2024-02-15 for the cubic spline capturing the effect of symptom onset date. This assumption corresponds to a cubic spline term with 5 degrees of freedom. For the effect of age, we performed the analysis using 2 knots (at age 50 and 65 years) for its spline term, corresponding to 5 degrees of freedom. In any analysis with less than 10% of subjects younger than 50 years old, we performed the analysis using only 1 knot (at age 65 years) instead of the spline term of age, leading to a total number of degrees of freedom equal to 4.

A.1.4. Missing data

When a subject lacked data on outcome, exposure, or specific covariates (dependent on the model), that specific subject was excluded from the analysis. This method, referred to as complete case analysis (CCA), uses only subjects with complete information for all variables included in the analysis. When data is missing completely at random (MCAR), CCA yields unbiased estimates. Under the assumption that missingness happens completely at random (MCAR mechanism), the set of complete observations is considered a random sample from the population. Thus, CCA will not produce biased estimates [14].

Given that COVID-19 status was part of the primary data collection, it was anticipated that case status (test-positive or test-negative) should be available for nearly all subjects. On the other hand, data on exposure status and, in particular, potential confounders may be missing for a portion of subjects. These details are typically obtained from pre-existing medical records, vaccine registries, or other records, which existed before the SARI episode. Consequently, it is reasonable to assume that the MCAR mechanism holds. However, the CCA approach, which utilizes a subset of the whole sample when missingness occurs, can lead to loss of precision, especially when the number of subjects with missing data is relatively high. Consequently, if the CCA makes use of a dataset with more than 10% loss in sample size in comparison with the full dataset, techniques such as multiple imputation should be implemented to generate imputed datasets for subsequent analysis.

In the current study, there was no subject excluded because of missingness of test results. In total, 0·6% (17/2711) of SARI patients were excluded from analyses due to missing data on number of chronic conditions (n=12), sex (n=4) and age (n=1). Consequently, we did not perform any (multiple) imputation. Results reported in the main manuscript are considered to be reasonable with respect to the handling approach of missing data.

A.2 SAMPLE SIZE CALCULATIONS, TECHNICAL SPECIFICATIONS

A.2.1. Sample size calculation

The goal of the sample size calculations was to determine the minimum sample size necessary to ensure desirable properties of the VE estimates. An example of a desirable property is the width of the 95% CI. The 95% CI width is defined as the difference between the upper and lower values of the CI and can be viewed as a measure of the precision around the VE estimate.

Simulation-based methods to determine sample sizes were developed to closely mimic the actual study design and proposed analytical approaches at the cost of requiring additional parameter assumptions and computational burden.

A.2.2. Simulation-based approach

A.2.2.1. Data generation workflow

Notation

Before describing the data generation workflow, the following parameters which act as input for the model have to be defined:

$VE_{x,overall}$: the overall VE of exposure x, the corresponding odds ratio is $OR_{x,overall} = 1 - \frac{VE_{x,overall}}{100}$.

$c = P(unexposed|control)$: proportion of unexposed subjects among the controls

$P_x = P(exposure\ x|exposed, control)$: brand share of exposure x among the exposed

r: ratio of cases to control (that is, number of cases per one control)

General set-up

In each simulation run, a dataset is constructed by combining data generated for a number of individual sites. We will denote the total number of study sites as k and the total sample size as N. Additionally, it is assumed that each site contributes the same number of subjects ($\frac{N}{k}$). In order to allow for variability in the underlying vaccine effects across study sites, the VE can be different from site to site. In the next section, it is described how data for one site is generated given the study site-specific VEs for all exposures. The subsequent section describes how VE is varied across the study sites to introduce between-site variability.

A.2.3. Simulating data at the site level

For each site, $\frac{N}{k} \times \frac{r}{1+r}$ cases and $\frac{N}{k} \times \frac{1}{1+r}$ controls are simulated.

Vaccine exposure status for the controls is generated from a multinomial distribution with the probability of being unexposed equal to c and the probability of being exposed to brand x equal to $(1-c)P_x$ (with $\sum_x P_x = 1$).

For each $\frac{N}{k} \times \frac{r}{1+r}$ of the cases, the vaccine exposure status is then generated from a multinomial distribution with the probability of being unexposed $P(unexposed|case) = \frac{1}{1+\sum_x \mathrm{OR}_x * \frac{(1-c)P_x}{c}}$ and the probability of being exposed to brand x equal to $P(exposure\ x|case) = \mathrm{OR}_x * \frac{(1-c)P_x}{c} * P(unexposed|case)$, where

$$\frac{\frac{P(exposure\ x|case)}{P(unexposed|case)}}{\frac{P(exposure\ x|control)}{P(unexposed|control)}} = OR_{x,site}$$

A.2.4. Simulating study site-specific VE

A.2.4.1. Effect of vaccination

To incorporate the expected between-site heterogeneity, for each study site a site-specific odds ratio ($OR_{x,site}$) was generated from a log-normal distribution with a median of $1 - \frac{VE_{x,overall}}{100}$ and variance on the log scale of 0.05. The value of the variance parameter on the log scale was selected to be 0.05 as it introduced an amount of between-site heterogeneity and was in line with the heterogeneity seen in a previous database study [1]. Note that decreasing the value of this parameter leads to a decrease in the sample size requirements. The expected value of the VE over the sites is then equal to $100 \times \left(1 - \exp\left(\log\left(1 - \frac{VE_{x,overall}}{100}\right) + \frac{0.05}{2}\right)\right)$.

A.2.4.2. Estimates and data obtained for each simulation

For each simulated dataset, an estimate of the VE and the corresponding 95% CI was obtained using the generalized estimating equations (GEE) method:

- The expected OR on the log-scale of the treatment effect was estimated using a logistic regression model with the disease status as the outcome and the exposure as a covariate. The estimates were obtained using the GEE method in which the sites were considered clusters and the variances were calculated using a robust sandwich estimator.
- The estimated log OR and the corresponding CI were then back-transformed to obtain an estimate of the mean overall VE and its 95% CI.
- The overall VE estimate and the width of the CI are stored for each simulation.

A.2.5. Number of simulations performed

For each combination of parameter settings, a total of 100 – 200 simulations are recommended. On an empirical basis, this number of simulation runs leads to stable Monte Carlo CIs while limiting the computational burden.

A.2.6. Summary measures of the simulation study

For each combination of study characteristics, the measure of interest is obtained from all simulations, which is:

- The expected range of the 95% CI is defined as the mean range of the CI obtained from all simulations.

For each measure, 95% Monte Carlo CIs were constructed based on the respective Monte Carlo standard errors observed in the simulations.

A.2.7. Sample size calculations for the study reported in this manuscript

The sample size of the number of SARI patients in the autumn/winter 2023-2024 season required to obtain a VE estimate for the primary objective with an expected width of the 95% CI meeting a prespecified expectation relied on the following assumptions: An overall vaccination coverage of 40%, a proportion among vaccinated subjects vaccinated with at least one dose of BNT162b2 Omicron XBB.1.5-adapted vaccine in the autumn/winter 2023-2024 season of 90% (scenario 1) or 95% (scenario 2), an anticipated VE of 70% (scenario 1) or 40% (scenario 2) for BNT162b2 Omicron XBB.1.5-adapted vaccine [15], and a control-case ratio of 2:1 (scenario 1) or 4:1 (scenario 2). Sample size calculations were simulation-based, assuming data collection from 10 study sites and a GEE analysis. 10 study sites corresponds to the number of study sites that were anticipated to take part in the study (as of prior to study launch).

Targeting a VE estimate with a corresponding 95% CI width of ≤50% and given the assumptions specified above, a sample size of at least 410 SARI patients was calculated (Table 4). Since the sample size calculation applied for crude VE estimates (not adjusting for any covariates), we conservatively inflated the obtained sample size by a factor of 1.2 to obtain the required sample sizes for adjusted estimates. Consequently, a size of at least 410 x 1.2 = 492 SARI patients (with (410-82) x 1.2 = 394 controls, 82 x 1.2 = 98 COVID-19 cases) included in the analysis was targeted. This sample size allows estimation of adjusted VE with a 95% CI width ≤50%, assuming VE for BNT162b2 Omicron

XBB.1.5-adapted vaccine of 70%, an overall vaccination coverage of 40%, and a BNT162b2 Omicron XBB.1.5-adapted vaccine proportion of 90%, with a control:case ratio of 4:1.

Table 1. The required number of SARI patients and COVID-19 cases to allow estimation of VE with an expected 95% CI width ≤50% based on a study including 10 sites, and overall vaccination coverage of 40%.

Anticipated VE for BNT162b2 Omicron XBB.1.5-adapted vaccine	Anticipated VE for all other vaccine brands	Proportion of vaccinated with at least one dose of BNT162b2 Omicron XBB.1.5-adapted vaccine among vaccinated in the autumn/winter 2023-2024 season	Control-case ratio	SARI patients	COVID-19 cases		
					All	Not vaccinated in the autumn/winter 2023-2024 season	Exposed to BNT162b2 Omicron XBB.1.5-adapted vaccine in the autumn/winter 2023-2024 season
40%	40%	90%	2:1	420	140	100	36
40%	40%	90%	4:1	710	142	101	37
40%	40%	95%	2:1	100	33	24	9
40%	40%	95%	4:1	410	82	59	22
70%	70%	90%	2:1	170	57	47	9
70%	**70%**	**90%**	**4:1**	**410**	**82**	**68**	**12**
70%	70%	95%	2:1	120	40	33	6
70%	70%	95%	4:1	270	54	45	9

Abbreviations: CI, confidence interval; VE, vaccine effectiveness; SARI, severe acute respiratory infection

A.2.6. Adjusted sample size taking into account matching of cases and controls

Matching of COVID-19 cases and controls by study site and temporal proximity of symptom onset (2 weeks) was performed to mitigate potential selection bias and confounding by time trends. The matching process, however, was anticipated to result in a reduction of the sample size for analysis by approximately 40% based on observations from data for the autumn/winter 2022-2023 season (hospital admission between 02 October 2022 – 31 May 2023), given a matching ratio of 1 (positive) case to a maximum of 4 (negative) controls. Consequently, to achieve a sample size of 492 SARI patients for the estimation of VE for the primary objective, 492 ÷ (1 – 0.4) = 820 SARI patients were required.

A.2.7. References

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A.3. Matching cases and controls

Up to 4 test-negative controls were exact matched to each case, based on

- Study site (and thus, Country)
- Temporal proximity of symptom onset (2 weeks)

Matching was conducted in R with an exact matching methodology. The number of controls matched to each case was examined. When more than 4 controls were available to match to 1 case, we selected controls based on distance between symptom onset dates between the controls and the case, with the rule that shorter distance had priority.

Matching was performed separately for each VE analysis. For example, for the analysis of the primary objective, only cases and controls who met the definitions of "vaccinated with at least one dose of BNT162b2 XBB vaccine" or "had not been vaccinated against COVID-19 during the 2023–2024 season" were matched. In the end, for the primary objective analyses, 8 test- positive cases were removed due to no matched controls found. There were 814 test-negative controls removed to reduce the case:control ratio from 1:6 to 1:4 at most.

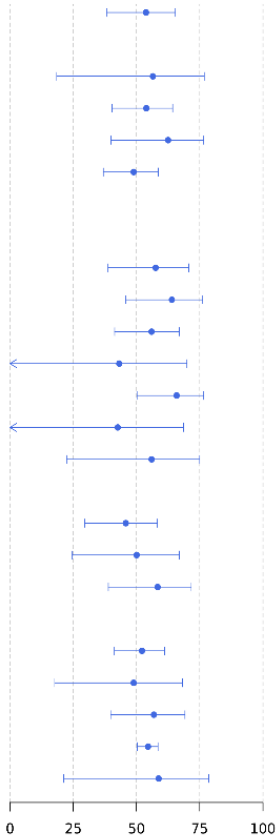
A.4. Sensitivity analysis results

In this section, we provide results from various sensitivity analyses for all VE estimates reported in Figure 1 in the main manuscript.

A.4.1 Sensitivity analysis with regard to location and number of knots applied to symptom onset dates

Figure A.4.1a [Sensitivity analysis 1a] Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season. The location of knots for symptom onset dates were placed at 10Jan2024, 31Jan2024, and 21Feb2024 (in increments of 3 weeks).

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.2; 65.4)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	56.5% (18.5; 76.8)
	No	251	60 (24%)	191 (76%)	725 (587; 781)[2]	
≥65y	Yes	658	111 (17%)	547 (83%)	64 (49; 79)	53.9% (40.3; 64.3)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
65-79y	Yes	255	28 (11%)	227 (89%)	59 (44; 73)	62.5% (40.0; 76.6)
	No	235	57 (24%)	178 (76%)	708 (426; 758)[2]	
≥80y	Yes	403	83 (21%)	320 (79%)	67 (52; 81)	48.9% (36.9; 58.6)
	No	218	71 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	
	No	69	12 (17%)	57 (83%)	725 (447; 777)[2]	
Lung disease	Yes	288	45 (16%)	243 (84%)	62 (46; 76)	57.6% (38.8; 70.7)
	No	221	60 (27%)	161 (73%)	707 (424; 766)[2]	
Cardiovascular disease	Yes	382	64 (17%)	318 (83%)	64 (48; 79)	64.0% (45.7; 76.2)
	No	251	84 (33%)	167 (67%)	712 (430; 775)[2]	
Hypertension	Yes	527	88 (17%)	439 (83%)	64 (49; 78)	56.0% (41.4; 67.0)
	No	383	110 (29%)	273 (71%)	713 (425; 776)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	43.2% (-7.6; 70.0)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	65.9% (50.2; 76.6)
	No	86	31 (36%)	55 (64%)	654 (425; 780)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	42.6% (-4.7; 68.6)
	No	157	44 (28%)	113 (72%)	722 (428; 774)[2]	
Immunodeficiency or cancer [3]	Yes	133	24 (18%)	109 (82%)	58 (41; 71)	56.0% (22.4; 75.0)
	No	145	48 (33%)	97 (67%)	674 (427; 775)[2]	
Number of chronic conditions						
0-1[4]	Yes	158	26 (16%)	132 (84%)	64 (48; 81)	45.8% (29.5; 58.3)
	No	286	67 (23%)	219 (77%)	716 (485; 763)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	50.1% (24.7; 66.9)
	No	177	48 (27%)	129 (73%)	726 (429; 780)[2]	
≥3	Yes	350	59 (17%)	291 (83%)	63 (46; 78)	58.4% (38.9; 71.7)
	No	241	73 (30%)	168 (70%)	694 (424; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	52.2% (41.3; 61.1)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	48.9% (17.7; 68.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
8 to <12 wks	Yes	327	53 (16%)	274 (84%)	68 (62; 76)	56.9% (39.8; 69.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
12 to <16 wks	Yes	112	19 (17%)	93 (83%)	91 (87; 98)	54.6% (50.3; 58.5)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	58.8% (21.2; 78.5)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.

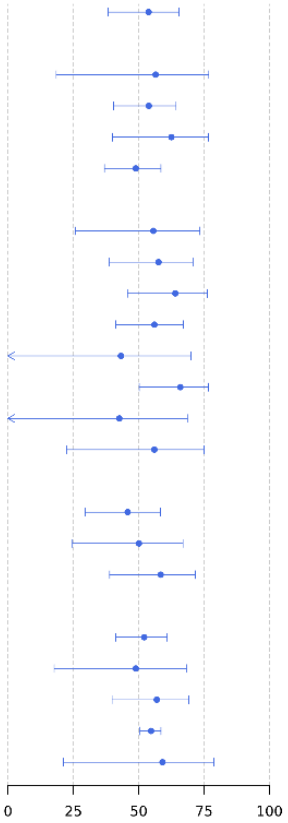
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).

[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.

[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

Figure A.4.1b [Sensitivity analysis 1b] Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season. The location of knots for symptom onset dates were placed at 15Jan2024, 31Jan2024, and 15Feb2024.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.3; 65.4)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	56.5% (18.5; 76.8)
	No	251	60 (24%)	191 (76%)	725 (587; 781)[2]	
≥65y	Yes	658	111 (17%)	547 (83%)	64 (49; 79)	53.9% (40.3; 64.3)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
65-79y	Yes	255	28 (11%)	227 (89%)	59 (44; 73)	62.5% (40.0; 76.6)
	No	235	57 (24%)	178 (76%)	708 (426; 758)[2]	
≥80y	Yes	403	83 (21%)	320 (79%)	67 (52; 81)	48.9% (36.9; 58.5)
	No	218	71 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	55.6% (25.7; 73.4)
	No	69	12 (17%)	57 (83%)	725 (447; 777)[2]	
Lung disease	Yes	288	45 (16%)	243 (84%)	62 (46; 76)	57.6% (38.8; 70.7)
	No	221	60 (27%)	161 (73%)	707 (424; 766)[2]	
Cardiovascular disease	Yes	382	64 (17%)	318 (83%)	64 (48; 79)	64.0% (45.7; 76.2)
	No	251	84 (33%)	167 (67%)	712 (430; 775)[2]	
Hypertension	Yes	527	88 (17%)	439 (83%)	64 (49; 78)	56.0% (41.3; 67.0)
	No	383	110 (29%)	273 (71%)	713 (425; 776)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	43.2% (-7.6; 70.0)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	65.9% (50.2; 76.6)
	No	86	31 (36%)	55 (64%)	654 (425; 780)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	42.6% (-4.7; 68.6)
	No	157	44 (28%)	113 (72%)	722 (428; 774)[2]	
Immunodeficiency or cancer [3]	Yes	133	24 (18%)	109 (82%)	58 (41; 71)	56.0% (22.4; 75.0)
	No	145	48 (33%)	97 (67%)	674 (427; 775)[2]	
Number of chronic conditions						
0-1[4]	Yes	158	26 (16%)	132 (84%)	64 (48; 81)	45.8% (29.5; 58.3)
	No	286	67 (23%)	219 (77%)	716 (485; 763)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	50.1% (24.7; 66.9)
	No	177	48 (27%)	129 (73%)	726 (429; 780)[2]	
≥3	Yes	350	59 (17%)	291 (83%)	63 (46; 78)	58.4% (38.9; 71.7)
	No	241	73 (30%)	168 (70%)	694 (424; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	52.1% (41.3; 60.9)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	48.9% (17.7; 68.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
8 to <12 wks	Yes	327	53 (16%)	274 (84%)	68 (62; 76)	56.9% (39.8; 69.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
12 to <16 wks	Yes	112	19 (17%)	93 (83%)	91 (87; 98)	54.7% (50.5; 58.5)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	59.1% (21.3; 78.8)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.

[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).

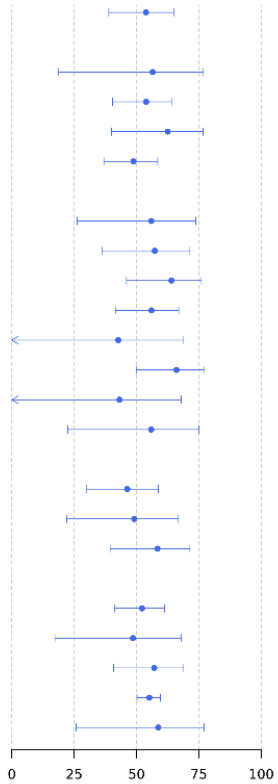
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.

[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.2 Sensitivity analysis with regard to number and location of knots for age

Figure A.4.2a [Sensitivity analysis 2a] Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season. The location of knots for age were placed at 60 and 75 years.

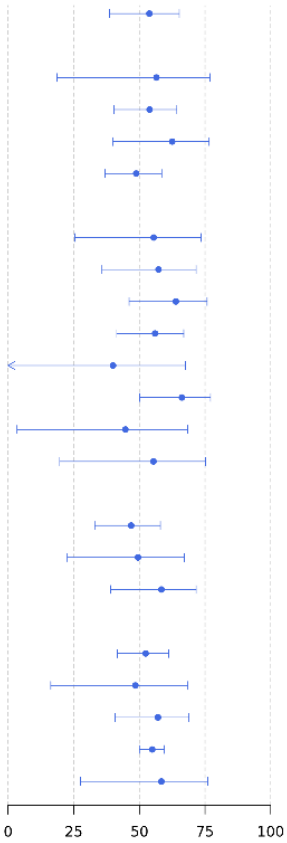
Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.9; 65.1)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	56.5% (18.6; 76.8)
	No	251	60 (24%)	191 (76%)	725 (587; 781)[2]	
≥65y	Yes	658	111 (17%)	547 (83%)	64 (49; 79)	53.9% (40.4; 64.3)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
65-79y	Yes	255	28 (11%)	227 (89%)	59 (44; 73)	62.5% (40.0; 76.6)
	No	235	57 (24%)	178 (76%)	708 (426; 758)[2]	
≥80y	Yes	403	83 (21%)	320 (79%)	67 (52; 81)	48.8% (36.9; 58.5)
	No	218	71 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	55.9% (26.2; 73.7)
	No	69	12 (17%)	57 (83%)	725 (447; 777)[2]	
Lung disease	Yes	288	45 (16%)	243 (84%)	62 (46; 76)	57.3% (36.1; 71.4)
	No	221	60 (27%)	161 (73%)	707 (424; 766)[2]	
Cardiovascular disease	Yes	382	64 (17%)	318 (83%)	64 (48; 79)	64.0% (46.0; 76.0)
	No	251	84 (33%)	167 (67%)	712 (430; 775)[2]	
Hypertension	Yes	527	88 (17%)	439 (83%)	64 (49; 78)	56.0% (41.5; 66.9)
	No	383	110 (29%)	273 (71%)	713 (425; 776)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	42.7% (-5.6; 68.9)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	66.0% (50.1; 76.9)
	No	86	31 (36%)	55 (64%)	654 (425; 780)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	43.2% (-0.3; 67.9)
	No	157	44 (28%)	113 (72%)	722 (428; 774)[2]	
Immunodeficiency or cancer [3]	Yes	133	24 (18%)	109 (82%)	58 (41; 71)	55.9% (22.5; 74.9)
	No	145	48 (33%)	97 (67%)	674 (427; 775)[2]	
Number of chronic conditions						
0-1[4]	Yes	158	26 (16%)	132 (84%)	64 (48; 81)	46.3% (30.1; 58.7)
	No	286	67 (23%)	219 (77%)	716 (485; 763)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	49.1% (22.0; 66.8)
	No	177	48 (27%)	129 (73%)	726 (429; 780)[2]	
≥3	Yes	350	59 (17%)	291 (83%)	63 (46; 78)	58.4% (39.4; 71.4)
	No	241	73 (30%)	168 (70%)	694 (424; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	52.2% (41.1; 61.3)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	48.6% (17.3; 68.0)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
8 to <12 wks	Yes	327	53 (16%)	274 (84%)	68 (62; 76)	57.1% (40.8; 68.9)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
12 to <16 wks	Yes	112	19 (17%)	93 (83%)	91 (87; 98)	55.1% (50.2; 59.5)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	58.7% (25.8; 77.0)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

Figure A.4.2b [Sensitivity analysis 2b] Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season. The location of knots for age were placed at 50, 65, and 80 years.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.7; 65.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	56.5% (18.6; 76.8)
	No	251	60 (24%)	191 (76%)	725 (587; 781)[2]	
≥65y	Yes	658	111 (17%)	547 (83%)	64 (49; 79)	53.9% (40.4; 64.3)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
65-79y	Yes	255	28 (11%)	227 (89%)	59 (44; 73)	62.5% (40.0; 76.6)
	No	235	57 (24%)	178 (76%)	708 (426; 758)[2]	
≥80y	Yes	403	83 (21%)	320 (79%)	67 (52; 81)	48.8% (36.9; 58.5)
	No	218	71 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	55.5% (25.4; 73.5)
	No	69	12 (17%)	57 (83%)	725 (447; 777)[2]	
Lung disease	Yes	288	45 (16%)	243 (84%)	62 (46; 76)	57.3% (35.8; 71.6)
	No	221	60 (27%)	161 (73%)	707 (424; 766)[2]	
Cardiovascular disease	Yes	382	64 (17%)	318 (83%)	64 (48; 79)	63.9% (46.1; 75.8)
	No	251	84 (33%)	167 (67%)	712 (430; 775)[2]	
Hypertension	Yes	527	88 (17%)	439 (83%)	64 (49; 78)	56.0% (41.4; 66.9)
	No	383	110 (29%)	273 (71%)	713 (425; 776)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	40.0% (-11.2; 67.6)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	66.2% (50.1; 77.1)
	No	86	31 (36%)	55 (64%)	654 (425; 780)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	44.7% (3.5; 68.4)
	No	157	44 (28%)	113 (72%)	722 (428; 774)[2]	
Immunodeficiency or cancer [3]	Yes	133	24 (18%)	109 (82%)	58 (41; 71)	55.4% (19.7; 75.2)
	No	145	48 (33%)	97 (67%)	674 (427; 775)[2]	
Number of chronic conditions						
0-1[4]	Yes	158	26 (16%)	132 (84%)	64 (48; 81)	46.9% (33.0; 58.0)
	No	286	67 (23%)	219 (77%)	716 (485; 763)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	49.5% (22.6; 67.1)
	No	177	48 (27%)	129 (73%)	726 (429; 780)[2]	
≥3	Yes	350	59 (17%)	291 (83%)	63 (46; 78)	58.4% (39.0; 71.6)
	No	241	73 (30%)	168 (70%)	694 (424; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	52.4% (41.6; 61.1)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	48.5% (16.3; 68.3)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
8 to <12 wks	Yes	327	53 (16%)	274 (84%)	68 (62; 76)	57.1% (40.8; 68.9)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
12 to <16 wks	Yes	112	19 (17%)	93 (83%)	91 (87; 98)	54.9% (50.0; 59.4)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	58.4% (27.6; 76.0)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	

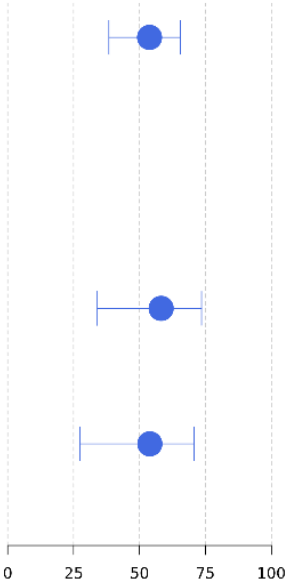


[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.3 Sensitivity analysis with regard to VE estimates stratified by history of prior COVID-19 infection

Figure A.4.3 Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season. Results for VE estimates stratified by history of prior COVID-19 infection are presented.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.4; 65.4)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Prior COVID-19 infection history						
Prior COVID-19 infection	Yes	162	22 (14%)	140 (86%)	68 (49; 81)	58.2% (34.0; 73.5)
	No	138	34 (25%)	104 (75%)	709 (424; 778)[2]	
No prior COVID-19 infection	Yes	464	79 (17%)	385 (83%)	63 (49; 79)	53.9% (27.5; 70.7)
	No	416	112 (27%)	304 (73%)	717 (433; 770)[2]	

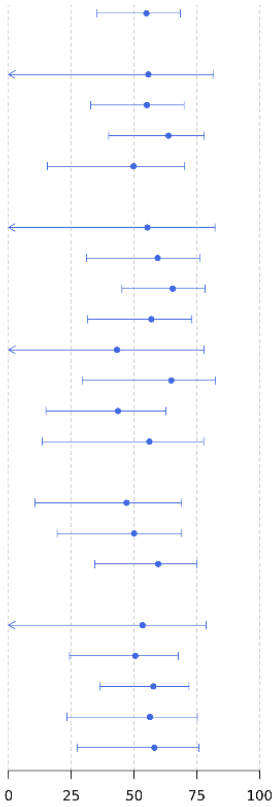


[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).

A.4.4 Sensitivity analysis with regard to VE estimates obtained from a matched analysis with matched units as cluster

Figure A.4.4 Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season, adjusted for cluster covariate matching

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	724	121 (17%)	603 (83%)	63 (48; 79)	54.9% (35.3; 68.5)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	55.7% (-7.5; 81.7)
	No	260	62 (24%)	198 (76%)	725 (580; 789)[2]	
≥65y	Yes	661	112 (17%)	549 (83%)	64 (49; 79)	55.1% (32.8; 69.9)
	No	461	133 (29%)	328 (71%)	698 (425; 767)[2]	
65-79y	Yes	257	29 (11%)	228 (89%)	59 (44; 73)	63.7% (39.9; 78.0)
	No	242	61 (25%)	181 (75%)	708 (425; 761)[2]	
≥80y	Yes	404	83 (21%)	321 (79%)	67 (52; 81)	49.8% (15.5; 70.2)
	No	219	72 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	55.3% (-12.6; 82.2)
	No	71	12 (17%)	59 (83%)	726 (449; 781)[2]	
Lung disease	Yes	289	46 (16%)	243 (84%)	62 (46; 76)	59.4% (31.0; 76.1)
	No	230	65 (28%)	165 (72%)	705 (419; 766)[2]	
Cardiovascular disease	Yes	384	65 (17%)	319 (83%)	64 (48; 79)	65.4% (45.2; 78.2)
	No	264	91 (34%)	173 (66%)	710 (429; 776)[2]	
Hypertension	Yes	529	89 (17%)	440 (83%)	64 (49; 79)	56.9% (31.6; 72.8)
	No	395	116 (29%)	279 (71%)	712 (425; 777)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	43.2% (-45.5; 77.8)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	64.8% (29.3; 82.5)
	No	90	31 (34%)	59 (66%)	661 (426; 786)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	43.6% (14.9; 62.6)
	No	159	45 (28%)	114 (72%)	724 (429; 776)[2]	
Immunodeficiency or cancer [3]	Yes	136	25 (18%)	111 (82%)	58 (41; 72)	56.1% (13.5; 77.7)
	No	152	51 (34%)	101 (66%)	676 (428; 776)[2]	
Number of chronic conditions						
0-1[4]	Yes	159	26 (16%)	133 (84%)	64 (48; 82)	47.0% (10.5; 68.7)
	No	289	68 (24%)	221 (76%)	716 (491; 764)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	50.0% (19.4; 69.0)
	No	179	48 (27%)	131 (73%)	726 (429; 780)[2]	
≥3	Yes	352	60 (17%)	292 (83%)	63 (46; 78)	59.6% (34.4; 75.1)
	No	253	79 (31%)	174 (69%)	694 (421; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	53.4% (-1.4; 78.6)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	50.5% (24.3; 67.7)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	
8 to <12 wks	Yes	329	54 (16%)	275 (84%)	68 (62; 76)	57.7% (36.3; 71.9)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	
12 to <16 wks	Yes	113	19 (17%)	94 (83%)	91 (87; 98)	56.3% (23.3; 75.2)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	58.1% (27.5; 75.8)
	No	721	195 (27%)	526 (73%)	716 (431; 773)[2]	

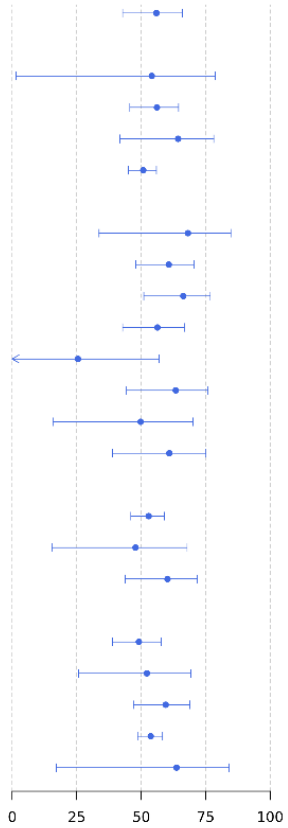


[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.5 Sensitivity analysis with regard to VE estimates obtained from Spanish data only

Figure A.4.5 Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season in Spain.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	685	107 (16%)	578 (84%)	63 (48; 79)	55.9% (42.8; 66.0)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	
Age group (years)						
18-64y	Yes	57	8 (14%)	49 (86%)	54 (37; 76)	54.1% (1.6; 78.6)
	No	211	50 (24%)	161 (76%)	718 (543; 792)[2]	
≥65y	Yes	628	99 (16%)	529 (84%)	64 (49; 79)	56.1% (45.6; 64.5)
	No	358	100 (28%)	258 (72%)	661 (416; 760)[2]	
65-79y	Yes	249	27 (11%)	222 (89%)	59 (44; 72)	64.3% (41.8; 78.1)
	No	192	48 (25%)	144 (75%)	698 (416; 756)[2]	
≥80y	Yes	379	72 (19%)	307 (81%)	67 (52; 81)	50.8% (45.0; 55.9)
	No	166	52 (31%)	114 (69%)	458 (416; 765)[2]	
Type of chronic condition						
Asthma	Yes	65	6 (9%)	59 (91%)	63 (48; 80)	68.1% (33.7; 84.7)
	No	52	8 (15%)	44 (85%)	724 (456; 782)[2]	
Lung disease	Yes	274	39 (14%)	235 (86%)	62 (46; 76)	60.7% (47.9; 70.4)
	No	183	48 (26%)	135 (74%)	696 (410; 763)[2]	
Cardiovascular disease	Yes	360	53 (15%)	307 (85%)	64 (48; 78)	66.3% (51.0; 76.8)
	No	191	61 (32%)	130 (68%)	706 (420; 772)[2]	
Hypertension	Yes	508	78 (15%)	430 (85%)	64 (49; 78)	56.3% (42.8; 66.7)
	No	309	84 (27%)	225 (73%)	703 (414; 771)[2]	
Chronic liver disease	Yes	36	7 (19%)	29 (81%)	62 (46; 73)	25.5% (-29.0; 57.0)
	No	48	13 (27%)	35 (73%)	704 (415; 776)[2]	
Renal disease	Yes	130	24 (18%)	106 (82%)	66 (52; 81)	63.4% (44.3; 75.9)
	No	78	27 (35%)	51 (65%)	602 (425; 784)[2]	
Type 2 diabetes	Yes	243	42 (17%)	201 (83%)	63 (46; 78)	49.8% (16.0; 70.0)
	No	137	39 (28%)	98 (72%)	724 (420; 774)[2]	
Immunodeficiency or cancer [3]	Yes	122	21 (17%)	101 (83%)	58 (41; 70)	60.9% (38.8; 75.1)
	No	114	40 (35%)	74 (65%)	649 (420; 761)[2]	
Number of chronic conditions						
0-1[4]	Yes	146	23 (16%)	123 (84%)	64 (48; 81)	52.9% (46.0; 58.9)
	No	228	56 (25%)	172 (75%)	709 (434; 751)[2]	
2	Yes	206	32 (16%)	174 (84%)	66 (50; 77)	47.8% (15.4; 67.8)
	No	145	37 (26%)	108 (74%)	711 (416; 772)[2]	
≥3	Yes	333	52 (16%)	281 (84%)	63 (46; 76)	60.2% (43.8; 71.8)
	No	196	57 (29%)	139 (71%)	679 (413; 773)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	39	6 (15%)	33 (85%)	23 (22; 26)	49.1% (38.9; 57.7)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	
4 to <8 wks	Yes	210	34 (16%)	176 (84%)	45 (37; 50)	52.2% (25.7; 69.2)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	
8 to <12 wks	Yes	315	47 (15%)	268 (85%)	68 (62; 76)	59.5% (47.2; 68.9)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	
12 to <16 wks	Yes	108	18 (17%)	90 (83%)	90 (87; 98)	53.7% (48.6; 58.3)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	
16 to <22 wks	Yes	13	2 (15%)	11 (85%)	120 (116; 126)	63.7% (17.2; 84.1)
	No	569	150 (26%)	419 (74%)	709 (423; 764)[2]	

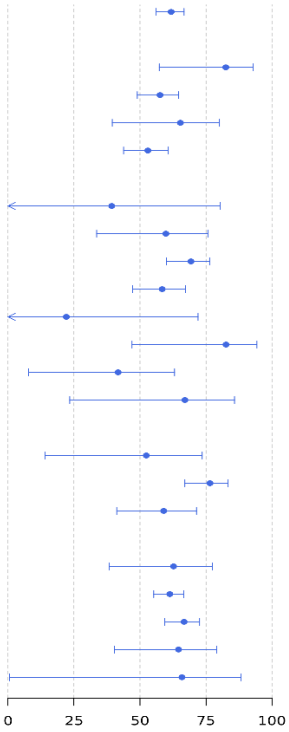


[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.6 Sensitivity analysis with regard to VE estimates while accounting additionally for influenza vaccination

Figure A.4.6. Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season, adjusted additionally for 2023-2024 influenza vaccination status.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	660	108 (16%)	552 (84%)	64 (49; 80)	61.8% (56.1; 66.7)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	
Age group (years)						
18-64y	Yes	55	8 (15%)	47 (85%)	57 (40; 80)	82.5% (57.3; 92.8)
	No	238	56 (24%)	182 (76%)	726 (643; 782)[2]	
≥65y	Yes	605	100 (17%)	505 (83%)	65 (50; 80)	57.6% (49.0; 64.7)
	No	430	122 (28%)	308 (72%)	703 (425; 766)[2]	
65-79y	Yes	239	27 (11%)	212 (89%)	60 (44; 75)	65.3% (39.5; 80.1)
	No	225	55 (24%)	170 (76%)	712 (425; 762)[2]	
≥80y	Yes	366	73 (20%)	293 (80%)	68 (53; 82)	53.0% (43.8; 60.7)
	No	205	67 (33%)	138 (67%)	676 (425; 770)[2]	
Type of chronic condition						
Asthma	Yes	63	8 (13%)	55 (87%)	61 (48; 80)	39.3% (-87.8; 80.4)
	No	66	11 (17%)	55 (83%)	726 (452; 778)[2]	
Lung disease	Yes	258	41 (16%)	217 (84%)	63 (47; 77)	59.8% (33.6; 75.7)
	No	211	57 (27%)	154 (73%)	710 (423; 768)[2]	
Cardiovascular disease	Yes	340	54 (16%)	286 (84%)	65 (51; 79)	69.3% (60.0; 76.4)
	No	241	80 (33%)	161 (67%)	717 (430; 777)[2]	
Hypertension	Yes	484	79 (16%)	405 (84%)	65 (49; 79)	58.4% (47.2; 67.2)
	No	361	103 (29%)	258 (71%)	717 (425; 777)[2]	
Chronic liver disease	Yes	32	6 (19%)	26 (81%)	66 (54; 80)	22.1% (-116.5; 72.0)
	No	49	13 (27%)	36 (73%)	719 (417; 782)[2]	
Renal disease	Yes	116	23 (20%)	93 (80%)	67 (52; 81)	82.6% (47.0; 94.3)
	No	78	27 (35%)	51 (65%)	661 (425; 780)[2]	
Type 2 diabetes	Yes	224	38 (17%)	186 (83%)	64 (48; 79)	41.7% (7.8; 63.1)
	No	147	41 (28%)	106 (72%)	722 (428; 772)[2]	
Immunodeficiency or cancer [3]	Yes	103	19 (18%)	84 (82%)	60 (46; 75)	67.0% (23.4; 85.8)
	No	132	43 (33%)	89 (67%)	689 (428; 777)[2]	
Number of chronic conditions						
0-1[4]	Yes	150	24 (16%)	126 (84%)	65 (48; 82)	52.4% (14.1; 73.6)
	No	273	65 (24%)	208 (76%)	716 (490; 764)[2]	
2	Yes	204	34 (17%)	170 (83%)	66 (51; 78)	76.5% (67.0; 83.3)
	No	171	46 (27%)	125 (73%)	724 (428; 779)[2]	
≥3	Yes	306	50 (16%)	256 (84%)	64 (48; 79)	59.0% (41.2; 71.4)
	No	224	67 (30%)	157 (70%)	713 (425; 775)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	34	5 (15%)	29 (85%)	24 (21; 26)	62.7% (38.4; 77.4)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	
4 to <8 wks	Yes	192	33 (17%)	159 (83%)	46 (38; 50)	61.3% (55.2; 66.6)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	
8 to <12 wks	Yes	307	49 (16%)	258 (84%)	69 (62; 76)	66.7% (59.4; 72.6)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	
12 to <16 wks	Yes	108	18 (17%)	90 (83%)	92 (87; 99)	64.6% (40.3; 79.1)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	65.9% (0.5; 88.3)
	No	668	178 (27%)	490 (73%)	717 (432; 773)[2]	

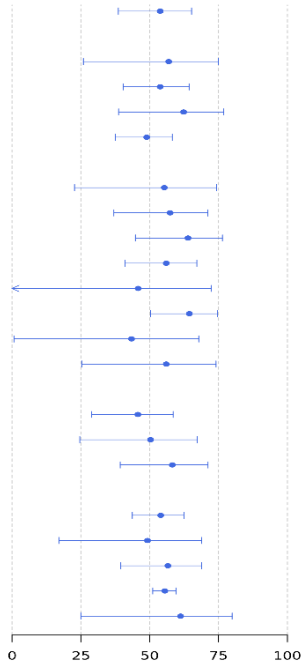


[1] Vaccine effectiveness estimates are adjusted for 2023-2024 influenza vaccination status, date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.7 Sensitivity analysis with regard to VE estimates where we separately adjusted for hypertension condition

Figure A.4.7. Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season, adjusted separately for hypertension condition.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	721	120 (17%)	601 (83%)	63 (48; 79)	53.8% (38.6; 65.2)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
Age group (years)						
18-64y	Yes	63	9 (14%)	54 (86%)	56 (38; 78)	56.9% (25.9; 74.9)
	No	251	60 (24%)	191 (76%)	725 (587; 781)[2]	
≥65y	Yes	658	111 (17%)	547 (83%)	64 (49; 79)	53.8% (40.3; 64.3)
	No	453	128 (28%)	325 (72%)	698 (425; 765)[2]	
65-79y	Yes	255	28 (11%)	227 (89%)	59 (44; 73)	62.3% (38.7; 76.9)
	No	235	57 (24%)	178 (76%)	708 (426; 758)[2]	
≥80y	Yes	403	83 (21%)	320 (79%)	67 (52; 81)	48.9% (37.5; 58.2)
	No	218	71 (33%)	147 (67%)	676 (425; 772)[2]	
Type of chronic condition						
Asthma	Yes	69	8 (12%)	61 (88%)	61 (48; 80)	55.3% (22.7; 74.2)
	No	69	12 (17%)	57 (83%)	725 (447; 777)[2]	
Lung disease	Yes	288	45 (16%)	243 (84%)	62 (46; 76)	57.4% (37.0; 71.1)
	No	221	60 (27%)	161 (73%)	707 (424; 766)[2]	
Cardiovascular disease	Yes	382	64 (17%)	318 (83%)	64 (48; 79)	63.9% (44.8; 76.4)
	No	251	84 (33%)	167 (67%)	712 (430; 775)[2]	
Hypertension	Yes	527	88 (17%)	439 (83%)	64 (49; 78)	56.0% (41.1; 67.1)
	No	383	110 (29%)	273 (71%)	713 (425; 776)[2]	
Chronic liver disease	Yes	39	7 (18%)	32 (82%)	63 (48; 76)	45.8% (-6.0; 72.3)
	No	53	15 (28%)	38 (72%)	713 (424; 775)[2]	
Renal disease	Yes	134	27 (20%)	107 (80%)	66 (52; 81)	64.4% (50.3; 74.5)
	No	86	31 (36%)	55 (64%)	654 (425; 780)[2]	
Type 2 diabetes	Yes	247	45 (18%)	202 (82%)	63 (46; 78)	43.4% (0.7; 67.8)
	No	157	44 (28%)	113 (72%)	722 (428; 774)[2]	
Immunodeficiency or cancer [3]	Yes	133	24 (18%)	109 (82%)	58 (41; 71)	56.0% (25.3; 74.1)
	No	145	48 (33%)	97 (67%)	674 (427; 775)[2]	
Number of chronic conditions						
0-1[4]	Yes	158	26 (16%)	132 (84%)	64 (48; 81)	45.7% (29.0; 58.5)
	No	286	67 (23%)	219 (77%)	716 (485; 763)[2]	
2	Yes	213	35 (16%)	178 (84%)	66 (50; 77)	50.3% (24.6; 67.2)
	No	177	48 (27%)	129 (73%)	726 (429; 780)[2]	
≥3	Yes	350	59 (17%)	291 (83%)	63 (46; 78)	58.2% (39.3; 71.2)
	No	241	73 (30%)	168 (70%)	694 (424; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	54.0% (43.7; 62.4)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
4 to <8 wks	Yes	223	39 (17%)	184 (83%)	45 (37; 50)	49.2% (17.1; 68.8)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
8 to <12 wks	Yes	327	53 (16%)	274 (84%)	68 (62; 76)	56.6% (39.5; 68.8)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
12 to <16 wks	Yes	112	19 (17%)	93 (83%)	91 (87; 98)	55.5% (51.1; 59.5)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	
16 to <22 wks	Yes	19	3 (16%)	16 (84%)	126 (120; 140)	61.2% (25.0; 79.9)
	No	704	188 (27%)	516 (73%)	716 (431; 772)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, number of chronic conditions, and hypertension condition. For this specific analyses, we counted the number of chronic conditions based on the list specified in the manuscript without hypertension as this condition is added as an additional (binary) covariate into the model.

[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).

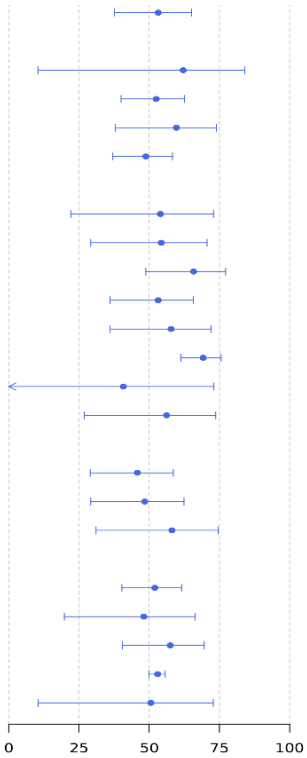
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.

[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.

A.4.8 Sensitivity analysis with regard to VE estimates obtained using stricter criteria (symptom onset within 7 days)

Figure A.4.8.1 Vaccine effectiveness[1] against COVID-19 hospitalization in SARI patients who received at least one dose of BNT162b2 XBB.1.5-adapted vaccine compared to patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season, whose symptom onset date was within 7 days prior to and up to 72 hours after the hospital admission date.

Strata	Exposure	Total, N	Test-positive cases: N (%)	Test-negative controls: N (%)	Days since last vaccine dose: Median (Q1; Q3)	VE (95% CI)
Overall						
Overall	Yes	659	110 (17%)	549 (83%)	63 (47; 79)	53.2% (37.6; 65.0)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	
Age group (years)						
18-64y	Yes	58	8 (14%)	50 (86%)	54 (37; 76)	62.1% (10.4; 84.0)
	No	224	56 (25%)	168 (75%)	725 (577; 777)[2]	
≥65y	Yes	601	102 (17%)	499 (83%)	63 (49; 79)	52.5% (40.0; 62.5)
	No	418	117 (28%)	301 (72%)	697 (428; 768)[2]	
65-79y	Yes	231	26 (11%)	205 (89%)	58 (42; 72)	59.7% (38.0; 73.9)
	No	216	51 (24%)	165 (76%)	708 (431; 761)[2]	
≥80y	Yes	370	76 (21%)	294 (79%)	67 (52; 81)	48.8% (37.1; 58.3)
	No	202	66 (33%)	136 (67%)	613 (426; 772)[2]	
Type of chronic condition						
Asthma	Yes	67	7 (10%)	60 (90%)	61 (48; 80)	54.0% (22.1; 72.9)
	No	63	10 (16%)	53 (84%)	728 (452; 778)[2]	
Lung disease	Yes	264	44 (17%)	220 (83%)	62 (46; 76)	54.3% (29.2; 70.6)
	No	197	54 (27%)	143 (73%)	707 (425; 768)[2]	
Cardiovascular disease	Yes	351	56 (16%)	295 (84%)	63 (48; 78)	65.8% (48.8; 77.2)
	No	235	78 (33%)	157 (67%)	710 (431; 774)[2]	
Hypertension	Yes	481	83 (17%)	398 (83%)	64 (49; 78)	53.2% (36.1; 65.7)
	No	345	99 (29%)	246 (71%)	711 (428; 776)[2]	
Chronic liver disease	Yes	37	6 (16%)	31 (84%)	62 (47; 76)	57.8% (36.0; 72.1)
	No	45	14 (31%)	31 (69%)	698 (431; 766)[2]	
Renal disease	Yes	122	23 (19%)	99 (81%)	65 (52; 81)	69.2% (61.2; 75.6)
	No	79	29 (37%)	50 (63%)	609 (425; 782)[2]	
Type 2 diabetes	Yes	222	42 (19%)	180 (81%)	62 (46; 77)	40.8% (-29.7; 73.0)
	No	144	41 (28%)	103 (72%)	725 (432; 780)[2]	
Immunodeficiency or cancer [3]	Yes	121	23 (19%)	98 (81%)	58 (41; 71)	56.2% (26.9; 73.7)
	No	136	47 (35%)	89 (65%)	663 (428; 768)[2]	
Number of chronic conditions						
0-1[4]	Yes	146	24 (16%)	122 (84%)	63 (48; 82)	45.8% (29.0; 58.6)
	No	263	63 (24%)	200 (76%)	716 (468; 760)[2]	
2	Yes	196	33 (17%)	163 (83%)	66 (51; 77)	48.4% (29.2; 62.4)
	No	159	43 (27%)	116 (73%)	722 (430; 779)[2]	
≥3	Yes	317	53 (17%)	264 (83%)	62 (45; 76)	58.1% (31.1; 74.5)
	No	220	67 (30%)	153 (70%)	696 (427; 774)[2]	
Weeks since XBB.1.5-adapted vaccine dose						
2 to <4 wks	Yes	40	6 (15%)	34 (85%)	24 (22; 26)	52.0% (40.3; 61.5)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	
4 to <8 wks	Yes	206	36 (17%)	170 (83%)	45 (37; 50)	48.1% (19.8; 66.4)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	
8 to <12 wks	Yes	294	47 (16%)	247 (84%)	68 (62; 75)	57.5% (40.5; 69.6)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	
12 to <16 wks	Yes	103	18 (17%)	85 (83%)	90 (86; 98)	53.0% (50.0; 55.7)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	
16 to <22 wks	Yes	16	3 (19%)	13 (81%)	128 (120; 140)	50.6% (10.5; 72.8)
	No	642	173 (27%)	469 (73%)	714 (432; 772)[2]	



[1] Vaccine effectiveness estimates are adjusted for date of symptom onset, age, sex, and number of chronic conditions.
[2] 'Never vaccinated' subjects were excluded when calculating the median (IQR) of time since last vaccine dose in the unexposed group (patients who did not receive any dose of a COVID-19 vaccine in the 2023–2024 autumn/winter season).
[3] The categories "Cancer" and "Immunodeficiency" among chronic conditions are counted as separate types of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "Immunodeficiency or cancer" is provided as a composite.
[4] The categories "0" and "1" among the number of chronic conditions are counted as separate categories of number of chronic conditions in all adjusted VE estimates. Here, the VE estimate among participants having "0–1"chronic conditions is provided as a composite.