

Supplementary Material

Safety of BA.4-5 or BA.1 bivalent mRNA booster vaccines: nationwide cohort study

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Supplementary Table S1. Eligibility criteria and covariates definition.

Variable	Details
Eligibility criteria	
Age of 50 years or older	<i>The Civil Registration System</i> ¹ . Defined by time birthyear and year 2022. Because of national vaccine policy of fourth dose rollout, individuals had to be born in year 1972 or earlier.
Vaccinated with a primary course and one booster Covid-19.	<i>The Danish Vaccination Register</i> ² . Defined as registered received three previous Covid-19 vaccines with the BNT162b2 and/or mRNA-1273 as well as and/or AZD1222 vaccine (the latter as part of the primary vaccination course only). Other vaccine types were rare within our study population. During the national rollout of the primary vaccination course, vaccination with the AZD1222 vaccine was halted in Denmark in early March 2021.
Third vaccine dose not received earlier than 9 September 2021 ^a	<i>The Danish Vaccination Register</i> ² . First day of national rollout of the third (i.e., first booster vaccine dose) to the general Danish population.
Third vaccine dose not received within 90 days of the second dose ^b	<i>The Danish Vaccination Register</i> ² . As vaccination with a third vaccine dose within 90 days of the primary vaccination schedule does not constitute as a booster dose per se, but rather a part of the primary vaccination schedule.
Covariates	
Ethnicity	<i>The Civil Registration System</i> ¹ . Defined by registered place of birth and categorized according Nordic (Denmark, Finland, Norway, or Sweden), Western (rest of Europe, United States, Australia or New Zealand), and non-Western countries (all others).
Region of residency	<i>The Civil Registration System</i> ¹ . Defined by the last registered address at baseline (1 January 2021) and grouped according: Northern Denmark Region, Central Denmark Region, Region of Southern Denmark, Capital Region of Denmark, and Region Zealand.
Vaccination priority groups	<i>The Danish Vaccination Register</i> ² . The Danish Health Agency have provided the governmentally assigned Covid-19 vaccine priority groups that were among other prioritized according to high risk of severe Covid-19 (yes/no; last update 24 May 2021).
Comorbidities	<i>The National Patient Register</i> ³ . Defined as primary diagnoses assigned by the treating physician and registered according to ICD-10 classification system regardless of type of hospital contact registered between 1 January 2018 and baseline (1 January 2021) and included as a categorized sum (0, 1, or ≥ 2 comorbidities).
Asthma	ICD-10 codes: J45, J46
Chronic respiratory disorder	ICD-10 codes: E84, J41-J44, J47, J84
Chronic cardiac disorder	ICD-10 codes: I05-I08, I20-I28, I34-I37, I42-I51
Renal disorder	ICD-10 codes: N03, N05, N07, N18, N19, N25, N26, N27
Diabetes	ICD-10 codes: E10-E14

Autoimmune disorder	ICD-10 codes: D510, D590, D591, D690, D693, D86, E035, E039, E050, E055, E059, E063, E065, E271, E272, E310, G04, G131, G35, G36, G61, G700, H20, I00, I02, K50, K51, K732, K743, K900, L10, L12, L130, L40, L63, L80, M05, M06, M08, M30, M311, M313, M315, M316, M317, M32-M34, M350, M351-M353, M358, M359, M45, M60
Epilepsy	ICD-10 codes: G40, G41
Malignancy	ICD-10 codes: C00-C96 (not C44), D70-D72, D730, D81-D84
Psychiatric disorder	ICD-10 codes: F00-F99

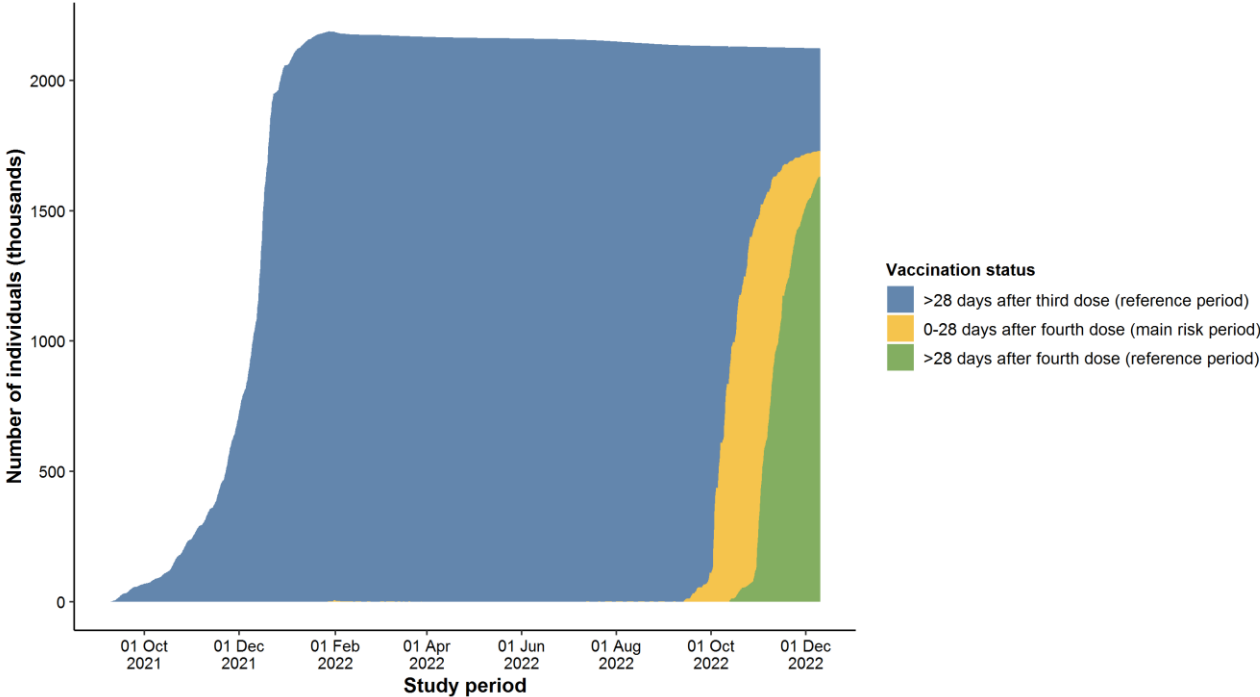
ICD-10 denotes International Classification of Diseases System, version 10. ^aSimilarly, we censored individuals vaccinated with a fourth dose prior to 15 September 2022 (first day of national rollout of the fourth vaccine dose to the general population). ^bSimilarly, we censored individuals receiving a fourth dose within 90 days of the third dose. We also excluded individuals with history of the respective outcome under studied prior to the follow-up period.

Supplementary Table S2. Outcome definitions.

Outcomes	ICD-10 codes
Anaphylaxis	T782, T783, T805, T886
Ischemic cardiac event	I20-I251
Cerebrovascular event	I60-66, G450-G453
Cerebrovascular infarction (incl. TIA) ^b	I63, I64, G450-453
Arterial thromboembolism	I74
Deep venous thrombosis	I80-82 (not I800, I808C, or I821)
Pulmonary embolism	I26
Myocarditis or pericarditis	I300, I308, I309, I328, I401, I408, I409, I418, I514
Myocarditis ^b	I401, I408, I409, I418, I514
Pericarditis ^b	I300, I308, I309, I328
Cerebral venous thrombosis	I636, I676
Thrombocytopenia or coagulative disorders	D65, D683, D686, D688-689, D690, D693-D699 (not D697 or D698A)
Guillain-Barré syndrome	G610
Bell's palsy	G510
Transverse myelitis	G373
Encephalomyelitis or encephalitis	G040, G040A, G048, G049, G058, G361
Narcolepsy	G474
Appendicitis	K35-K37
Aseptic arthritis	M10, M119, M130, M131, M139
Type 1 diabetes mellitus	E10
Subacute thyroiditis	E061
Heart failure	I110, I420, I426-I429, I50, J81,
Arrhythmia	I44-I49
Acute liver failure	K71, K72
Acute kidney failure	D593, I12, I13, N00-N02, N04-N05, N08, N10, N141, N142, N144, N17, N19, R34
Acute pancreatitis	K850, K853, K858, K859
Erythema multiforme	L51
Seizure	G40, G41
Arterial Aneurysm	I71, I72
Uveitis	H20, H30

ICD-10 denotes International Classification of Diseases System, version 10, TIA transient cerebral ischemic attack, and NA not applicable; information on death was gathered from the Danish Civil Registration System. ^aDiagnoses were identified through use of the Danish National Patient Register. Only diagnoses registered as primary diagnoses were included in the outcome definitions, however, secondary diagnoses were included in a sensitivity analysis. Main outcome definition included any hospital contact, whereas in a sensitivity analysis we defined severe adverse events as by hospital contacts with a duration of ≥ 5 hours ^bExamined separately post-hoc.

Supplementary Figure S1. Distribution of follow-up person-time during the studied calendar period by main risk and reference periods.



Supplemental Table S3. Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+-year-olds during 15 September 2022 to 10 December 2022 by sex and age.

Outcome event / subgroup	Number of events / person-years				
	Female	Male	50 to 64 years	65 to 79 years	80 years or older
Anaphylaxis					
Bivalent boosters	14 / 68995	16 / 61165	11 / 53473	14 / 56826	5 / 19860
Reference period	186 / 990447	177 / 901198	140 / 865609	164 / 746874	59 / 279162
Ischemic cardiac event					
Bivalent boosters	231 / 67655	441 / 58541	169 / 52502	373 / 54742	130 / 18953
Reference period	3327 / 972545	6665 / 865900	3089 / 850978	4821 / 720529	2082 / 266938
Cerebrovascular event					
Bivalent boosters	365 / 67597	433 / 59288	132 / 52883	385 / 55219	281 / 18783
Reference period	5229 / 971701	6294 / 876030	2276 / 856918	5200 / 726358	4047 / 264456
Arterial thromboembolism					
Bivalent boosters	10 / 69028	11 / 61174	3 / 53502	12 / 56846	6 / 19854
Reference period	187 / 990873	198 / 901261	88 / 866028	179 / 747045	118 / 279061
Deep vein thrombosis					
Bivalent boosters	111 / 68480	126 / 60508	80 / 53134	113 / 56290	44 / 19564
Reference period	1621 / 983407	1972 / 892241	1170 / 860542	1552 / 739945	871 / 275162
Pulmonary embolism					
Bivalent boosters	107 / 68630	109 / 60748	36 / 53326	110 / 56446	70 / 19606
Reference period	1625 / 985567	1711 / 895550	759 / 863542	1579 / 741886	998 / 275689
Myocarditis or pericarditis					
Bivalent boosters	15 / 69029	14 / 61168	11 / 53482	16 / 56848	2 / 19867
Reference period	130 / 990933	192 / 901182	159 / 865748	122 / 747120	41 / 279247
Cerebral venous thrombosis					
Bivalent boosters	1 / 69067	2 / 61229	1 / 53523	2 / 56892	0 / 19881
Reference period	20 / 991453	17 / 902057	16 / 866393	18 / 747686	3 / 279431

Supplemental Table S3. Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+-year-olds during 15 September 2022 to 10 December 2022 by sex and age.

Outcome event / subgroup	Number of events / person-years				
	Female	Male	50 to 64 years	65 to 79 years	80 years or older
Thrombocytopenia and coagulative disorders					
Bivalent boosters	16 / 68972	14 / 61130	10 / 53452	14 / 56811	6 / 19840
Reference period	234 / 990059	255 / 900620	163 / 865273	200 / 746567	126 / 278839
Guillain-Barré syndrome					
Bivalent boosters	0 / 69066	1 / 61225	1 / 53522	0 / 56890	0 / 19880
Reference period	22 / 991431	26 / 901994	19 / 866363	18 / 747639	11 / 279424
Bell's palsy					
Bivalent boosters	15 / 69003	14 / 61160	11 / 53465	11 / 56835	7 / 19863
Reference period	224 / 990574	225 / 901105	222 / 865526	168 / 746966	59 / 279187
Transverse myelitis					
Bivalent boosters	0 / 69070	0 / 61234	0 / 53526	0 / 56896	0 / 19882
Reference period	9 / 991491	4 / 902106	7 / 866417	4 / 747729	2 / 279451
Encephalomyelitis or encephalitis					
Bivalent boosters	6 / 69061	3 / 61221	4 / 53518	4 / 56885	1 / 19879
Reference period	29 / 991347	38 / 901930	32 / 866291	25 / 747576	10 / 279410
Narcolepsy					
Bivalent boosters	0 / 69066	0 / 61230	0 / 53521	0 / 56893	NE
Reference period	5 / 991426	2 / 902058	5 / 866351	2 / 747695	NE
Appendicitis					
Bivalent boosters	71 / 68714	55 / 60961	46 / 53257	56 / 56623	24 / 19795
Reference period	1067 / 986842	844 / 898443	870 / 862454	766 / 744469	275 / 278362
Aseptic arthritis					
Bivalent boosters	86 / 68542	129 / 60312	64 / 53104	95 / 56207	56 / 19544
Reference period	1169 / 984199	2044 / 889449	1074 / 859993	1381 / 738857	758 / 274798

Supplemental Table S3. Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+-year-olds during 15 September 2022 to 10 December 2022 by sex and age.

Outcome event / subgroup	Number of events / person-years				
	Female	Male	50 to 64 years	65 to 79 years	80 years or older
Type 1 diabetes mellitus					
Bivalent boosters	6 / 68604	18 / 60637	13 / 53018	6 / 56448	5 / 19775
Reference period	221 / 985032	338 / 893587	268 / 859010	225 / 741687	66 / 277921
Subacute thyroiditis					
Bivalent boosters	8 / 69043	8 / 61222	4 / 53500	11 / 56886	1 / 19880
Reference period	90 / 991095	48 / 901951	87 / 866015	42 / 747609	9 / 279422
Heart failure					
Bivalent boosters	193 / 68101	320 / 59476	83 / 53055	230 / 55598	200 / 18925
Reference period	3274 / 978071	5135 / 877652	1376 / 859389	3613 / 730468	3420 / 265866
Arrhythmia					
Bivalent boosters	655 / 65096	875 / 55862	274 / 52072	791 / 52230	465 / 16656
Reference period	9247 / 938393	12395 / 830931	4362 / 845493	10470 / 688849	6810 / 234982
Acute liver failure					
Bivalent boosters	5 / 69028	5 / 61196	3 / 53500	3 / 56856	4 / 19869
Reference period	171 / 990873	204 / 901549	132 / 865997	182 / 747160	61 / 279265
Acute kidney failure					
Bivalent boosters	116 / 68599	120 / 60652	47 / 53306	113 / 56377	76 / 19568
Reference period	1750 / 984823	2069 / 893719	729 / 862895	1763 / 740653	1327 / 274994
Acute pancreatitis					
Bivalent boosters	38 / 68902	39 / 61047	16 / 53409	35 / 56734	26 / 19806
Reference period	593 / 989234	663 / 899594	415 / 864657	521 / 745705	320 / 278466
Erythema multiforme					
Bivalent boosters	0 / 69068	1 / 61231	0 / 53525	1 / 56893	0 / 19880
Reference period	22 / 991455	14 / 902073	8 / 866412	17 / 747691	11 / 279425

Supplemental Table S3. Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+-year-olds during 15 September 2022 to 10 December 2022 by sex and age.

Outcome event / subgroup	Number of events / person-years				
	Female	Male	50 to 64 years	65 to 79 years	80 years or older
Seizure					
Bivalent boosters	47 / 68603	64 / 60713	24 / 53162	67 / 56457	20 / 19698
Reference period	805 / 984905	983 / 894747	583 / 860954	833 / 741864	372 / 276834
Arterial aneurysm					
Bivalent boosters	76 / 68683	222 / 60146	70 / 53285	158 / 56066	70 / 19477
Reference period	1005 / 986383	2561 / 887920	759 / 863051	1972 / 737299	835 / 273952
Uveitis					
Bivalent boosters	19 / 68942	12 / 61136	11 / 53432	12 / 56798	8 / 19848
Reference period	340 / 989707	282 / 900711	272 / 864929	249 / 746478	101 / 279011

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. The sum of person-years within different strata may not equal the total person-years exactly because of rounding. ^aThe corresponding incidence rate ratios with 95% confidence intervals are shown in Figure 3 and 4.

Supplementary Table S4: Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted vaccine as a fourth dose by type of vaccine and reference period in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.^a

Outcome event	Number of events / person-years			
	BNT BA.4-5-containing	BNT BA.1-containing	MOD BA.1-containing	Reference period
Anaphylaxis	22 / 85780.6	7 / 40100.1	1 / 4278.8	363 / 1891644.8
Ischemic cardiac event	425 / 83391.3	227 / 38670.0	20 / 4134.8	9992 / 1838445.5
Cerebrovascular event	468 / 84037.0	305 / 38670.9	25 / 4176.9	11523 / 1847731.6
Arterial thromboembolism	17 / 85808.8	4 / 40112.2	0 / 4280.3	385 / 1892133.7
Deep vein thrombosis	140 / 85065.6	90 / 39674.8	7 / 4247.2	3593 / 1875648.1
Pulmonary embolism	125 / 85349.3	86 / 39774.9	5 / 4253.2	3336 / 1881117.3
Myocarditis or pericarditis	18 / 85799.8	9 / 40116.3	2 / 4280.8	322 / 1892114.4
Cerebral venous thrombosis	2 / 85864.3	1 / 40148.7	0 / 4283.3	37 / 1893510.4
Thrombocytopenia and coagulative disorders	18 / 85748.0	10 / 40077.3	2 / 4277.4	489 / 1890679.3
Guillain-Barré syndrome	1 / 85860.5	0 / 40147.6	0 / 4283.4	48 / 1893425.3
Bell's palsy	19 / 85777.8	9 / 40106.3	1 / 4278.7	449 / 1891679.3
Transverse myelitis	NE	NE	NE	13 / 1893596.9
Encephalomyelitis or encephalitis	6 / 85857.0	2 / 40141.9	1 / 4283.1	67 / 1893277.3
Narcolepsy	NE	NE	NE	7 / 1893483.6
Appendicitis	81 / 85457.2	39 / 39953.9	6 / 4263.6	1911 / 1885284.3
Aseptic arthritis	123 / 85007.9	87 / 39608.3	5 / 4238.1	3213 / 1873648.6
Type 1 diabetes mellitus	13 / 85188.1	10 / 39809.1	1 / 4244.2	559 / 1878618.9
Subacute thyroiditis	10 / 85841.3	6 / 40141.7	0 / 4282.4	138 / 1893045.7
Heart failure	305 / 84375.4	200 / 39005.9	8 / 4196.3	8409 / 1855723.5
Arrhythmia	925 / 80698.5	561 / 36316.3	44 / 3943.1	21642 / 1769323.7
Acute liver failure	7 / 85821.6	3 / 40122.7	0 / 4280.1	375 / 1892421.8
Acute kidney failure	124 / 85300.9	103 / 39704.3	9 / 4245.7	3819 / 1878542.3
Acute pancreatitis	43 / 85654.8	30 / 40021.5	4 / 4272.8	1256 / 1888827.6
Erythema multiforme	1 / 85866.0	0 / 40148.9	0 / 4283.6	36 / 1893528.2

Supplementary Table S4: Number of events and person-years within 28 days after vaccination with a bivalent omicron adapted vaccine as a fourth dose by type of vaccine and reference period in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.^a

Outcome event	Number of events / person-years			
	BNT BA.4-5-containing	BNT BA.1-containing	MOD BA.1-containing	Reference period
Seizure	55 / 85326.4	53 / 39735.5	3 / 4254.2	1788 / 1879652.3
Arterial aneurysm	180 / 85021.6	106 / 39579.0	12 / 4228.2	3566 / 1874302.8
Uveitis	19 / 85722.3	12 / 40077.7	0 / 4277.7	622 / 1890418.3

BNT denotes BNT162b2, MOD mRNA-1273, and NE not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. The sum of person-years within different strata may not equal the total person-years exactly because of rounding. ^aThe corresponding incidence rate ratios with 95% confidence intervals are shown in Figure 5.

Supplementary Table S5: Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 using an alternative analytical approach of a self-controlled case series design.

Outcome event	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Anaphylaxis	30 / 47.6	347 / 673.7	1.05 (0.67 to 1.65)
Ischemic cardiac event	672 / 1354.5	9726 / 18814.4	0.92 (0.84 to 1.01)
Cerebrovascular event	798 / 1329.4	11291 / 19290.0	0.96 (0.89 to 1.05)
Arterial thromboembolism	21 / 38.8	371 / 621.2	1.15 (0.67 to 1.96)
Deep vein thrombosis	237 / 448.4	3460 / 6502.5	1.01 (0.86 to 1.18)
Pulmonary embolism	216 / 369.8	3234 / 5518.4	0.85 (0.72 to 1.00)
Myocarditis or pericarditis	29 / 38.6	314 / 597.8	1.52 (0.94 to 2.45)
Cerebral venous thrombosis	3 / 4.5	36 / 64.3	1.49 (0.31 to 7.10)
Thrombocytopenia or coagulative disorder	30 / 52.9	466 / 834.7	0.87 (0.57 to 1.34)
Guillain-Barré syndrome	1 / 4.4	48 / 71.5	0.20 (0.03 to 1.57)
Bell's palsy	29 / 53.9	435 / 793.4	0.96 (0.62 to 1.51)
Transverse myelitis	0 / 1.9	13 / 26.7	NE
Encephalomyelitis or encephalitis	9 / 7.7	66 / 125.1	1.66 (0.68 to 4.07)
Narcolepsy	0 / 1.0	6 / 14.3	NE
Appendicitis	126 / 260.6	1856 / 3607.4	0.97 (0.78 to 1.21)
Aseptic arthritis	215 / 431.6	3090 / 6130.2	0.92 (0.78 to 1.09)
Type 1 diabetes mellitus	24 / 72.0	538 / 1038.5	0.81 (0.50 to 1.31)
Subacute thyroiditis	16 / 16.6	131 / 257.1	1.97 (0.99 to 3.91)
Heart failure	513 / 921.7	8160 / 13543.2	0.80 (0.72 to 0.89)
Arrhythmia	1530 / 2777.5	20846 / 38150.4	0.93 (0.87 to 0.99)
Acute liver failure	10 / 31.6	368 / 533.3	0.37 (0.19 to 0.74)
Acute kidney failure	236 / 362.7	3736 / 5670.7	0.79 (0.68 to 0.92)
Acute pancreatitis	77 / 146.5	1224 / 2107.8	0.82 (0.63 to 1.07)
Erythema multiforme	1 / 3.7	36 / 59.7	0.43 (0.05 to 3.76)
Seizure	111 / 210.1	1707 / 3053.6	0.89 (0.71 to 1.12)
Arterial aneurysm	298 / 468.9	3429 / 6322.4	0.94 (0.82 to 1.09)
Uveitis	31 / 76.8	600 / 1124.9	0.97 (0.63 to 1.49)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions.

Supplementary Table S6: Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 using an alternative analytical approach of an observed vs expected design.

Outcome event	Number of observed / expected events	Rate ratio (95% CI)
	Bivalent boosters	
Anaphylaxis	30 / 30.3	0.99 (0.67 to 1.41)
Ischemic cardiac event	672 / 801.6	0.84 (0.78 to 0.90)
Cerebrovascular event	798 / 761.0	1.05 (0.98 to 1.12)
Arterial thromboembolism	21 / 33.1	0.63 (0.39 to 0.97)
Deep vein thrombosis	237 / 293.3	0.81 (0.71 to 0.92)
Pulmonary embolism	216 / 230.6	0.94 (0.82 to 1.07)
Myocarditis or pericarditis	29 / 22.6	1.28 (0.86 to 1.84)
Cerebral venous thrombosis	3 / 2.3	1.28 (0.26 to 3.74)
Thrombocytopenia or coagulative disorder	30 / 49.1	0.61 (0.41 to 0.87)
Guillain-Barré syndrome	1 / 3.9	0.26 (0.01 to 1.42)
Bell's palsy	29 / 27.9	1.04 (0.70 to 1.49)
Transverse myelitis	0 / 1.0	NE
Encephalomyelitis or encephalitis	9 / 6.9	1.30 (0.59 to 2.46)
Narcolepsy	0 / 2.2	NE
Appendicitis	126 / 115.5	1.09 (0.91 to 1.30)
Aseptic arthritis	215 / 282.4	0.76 (0.66 to 0.87)
Type 1 diabetes mellitus	24 / 157.5	0.15 (0.10 to 0.23)
Subacute thyroiditis	16 / 6.9	2.31 (1.32 to 3.75)
Heart failure	513 / 610.2	0.84 (0.77 to 0.92)
Arrhythmia	1530 / 1478.1	1.04 (0.98 to 1.09)
Acute liver failure	10 / 33.0	0.30 (0.15 to 0.56)
Acute kidney failure	236 / 231.8	1.02 (0.89 to 1.16)
Acute pancreatitis	77 / 77.0	1.00 (0.79 to 1.25)
Erythema multiforme	1 / 2.9	0.35 (0.01 to 1.95)
Seizure	111 / 168.1	0.66 (0.54 to 0.80)
Arterial aneurysm	298 / 255.5	1.17 (1.04 to 1.31)
Uveitis	31 / 39.9	0.78 (0.53 to 1.10)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. Expected rates were estimated using indirect age- and sex standardization of the historic background rates within the Danish general population from 1 January 2018 to 31 December 2019 (with a washout period of the respective outcome from 1 January 2015 to 31 December 2017),

Supplementary Table S7: Risk of severe adverse events (hospitalization for ≥5 hours) within 28 days after vaccination with a bivalent omicron adapted vaccine as a fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.

Outcome event	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Anaphylaxis	20 / 130178	217 / 1891849	1.16 (0.68 to 2.01)
Ischemic cardiac event	513 / 126464	8188 / 1841576	0.90 (0.81 to 1.00)
Cerebrovascular event	683 / 127072	9990 / 1849868	0.94 (0.86 to 1.03)
Arterial thromboembolism	14 / 130212	271 / 1892266	0.91 (0.49 to 1.70)
Deep vein thrombosis	88 / 129263	1327 / 1878842	0.97 (0.76 to 1.25)
Pulmonary embolism	148 / 129461	2556 / 1882073	0.75 (0.62 to 0.91)
Myocarditis or pericarditis	20 / 130204	263 / 1892203	1.18 (0.69 to 2.03)
Cerebral venous thrombosis	3 / 130297	29 / 1893523	2.10 (0.43 to 10.15)
Thrombocytopenia and coagulative disorders	9 / 130135	220 / 1891056	0.70 (0.33 to 1.48)
Guillain-Barré syndrome	1 / 130292	41 / 1893436	0.23 (0.03 to 1.84)
Bell's palsy	11 / 130193	166 / 1892014	1.16 (0.56 to 2.41)
Transverse myelitis	0 / 130305	5 / 1893609	NE
Encephalomyelitis or encephalitis ^a	9 / 130284	50 / 1893304	2.67 (1.01 to 7.07)
Appendicitis	126 / 129677	1897 / 1885316	1.03 (0.83 to 1.27)
Aseptic arthritis	40 / 129171	786 / 1877282	0.78 (0.54 to 1.12)
Type 1 diabetes mellitus	4 / 129297	133 / 1879275	0.70 (0.23 to 2.16)
Subacute thyroiditis	0 / 130280	6 / 1893231	NE
Heart failure	317 / 127945	5418 / 1859868	0.75 (0.66 to 0.85)
Arrhythmia	904 / 122126	12768 / 1782238	0.90 (0.83 to 0.98)
Acute liver failure	9 / 130238	260 / 1892577	0.45 (0.22 to 0.93)
Acute kidney failure	188 / 129322	3183 / 1879340	0.75 (0.64 to 0.89)
Acute pancreatitis	74 / 129955	1209 / 1888900	0.82 (0.62 to 1.07)
Erythema multiforme	0 / 130300	19 / 1893553	NE
Seizure	59 / 129434	830 / 1881012	0.91 (0.67 to 1.24)
Arterial aneurysm	76 / 129152	1017 / 1877798	1.00 (0.76 to 1.31)
Uveitis	6 / 130142	67 / 1891200	1.35 (0.49 to 3.74)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. ^aThe rate ratio for encephalomyelitis or encephalitis was 1.62 (95% CI 0.74-3.07) and 2.77 (95% CI 0.99-7.75) with use of observed vs. expected and self-controlled case series analysis, respectively.

Supplementary Table S8: Sensitivity analysis of the associated risk of adverse events within 28 days following fourth dose bivalent omicron adapted booster vaccination including both primary and secondary diagnoses in the outcome definitions.

Outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Anaphylaxis	31 / 130156	400 / 1891605	0.92 (0.60 to 1.39)
Ischemic cardiac event	742 / 126093	10864 / 1837213	0.96 (0.88 to 1.04)
Cerebrovascular event	875 / 126740	12807 / 1846000	0.95 (0.88 to 1.03)
Arterial thromboembolism	22 / 130197	425 / 1892073	0.88 (0.54 to 1.45)
Deep vein thrombosis	258 / 128938	4069 / 1875052	0.93 (0.80 to 1.08)
Pulmonary embolism	238 / 129339	3839 / 1880619	0.80 (0.69 to 0.93)
Myocarditis or pericarditis	32 / 130192	379 / 1892054	1.28 (0.83 to 1.97)
Cerebral venous thrombosis	3 / 130296	40 / 1893506	1.58 (0.36 to 6.92)
Thrombocytopenia and coagulative disorders	45 / 130087	700 / 1890477	0.81 (0.57 to 1.14)
Guillain-Barré syndrome	3 / 130291	55 / 1893417	0.64 (0.18 to 2.30)
Bell's palsy	29 / 130160	472 / 1891644	0.94 (0.61 to 1.45)
Transverse myelitis	1 / 130303	14 / 1893595	1.10 (0.10 to 12.18)
Encephalomyelitis or encephalitis	11 / 130280	77 / 1893261	1.80 (0.81 to 4.00)
Narcolepsy	2 / 130295	14 / 1893476	1.05 (0.19 to 5.73)
Appendicitis	129 / 129670	1953 / 1885224	1.01 (0.82 to 1.25)
Aseptic arthritis	251 / 128767	3953 / 1872615	0.85 (0.73 to 0.98)
Type 1 diabetes mellitus	41 / 129197	936 / 1878074	0.80 (0.56 to 1.14)
Subacute thyroiditis	17 / 130265	143 / 1893038	1.60 (0.86 to 2.98)
Heart failure	609 / 127366	10584 / 1853124	0.74 (0.68 to 0.82)
Arrhythmia	1903 / 120307	27536 / 1761569	0.91 (0.87 to 0.96)
Acute liver failure	15 / 130219	498 / 1892336	0.43 (0.25 to 0.75)
Acute kidney failure	386 / 129071	6185 / 1876334	0.81 (0.72 to 0.91)
Acute pancreatitis	83 / 129939	1358 / 1888695	0.80 (0.62 to 1.03)
Erythema multiforme	1 / 130298	41 / 1893522	0.40 (0.05 to 3.36)
Seizure	128 / 129282	2084 / 1879244	0.87 (0.71 to 1.07)
Arterial aneurysm	335 / 128752	4149 / 1873400	0.95 (0.83 to 1.08)
Uveitis	32 / 130073	653 / 1890363	0.85 (0.57 to 1.28)

Supplementary Table S9. Risk of adverse events after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 with use of alternative risk periods.

Alternative risk period/outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Risk period restricted to the first 7 days after fourth vaccine dose			
Anaphylaxis	7 / 33083	398 / 2115427	0.93 (0.43 to 2.00)
Ischemic cardiac event	148 / 32081	11217 / 2055979	0.83 (0.70 to 0.98)
Cerebrovascular event	166 / 32256	12902 / 2066397	0.79 (0.67 to 0.92)
Arterial thromboembolism	6 / 33093	428 / 2115978	1.09 (0.47 to 2.50)
Deep vein thrombosis	60 / 32786	3998 / 2097555	0.97 (0.74 to 1.26)
Pulmonary embolism	35 / 32886	3768 / 2103658	0.55 (0.39 to 0.77)
Myocarditis or pericarditis	9 / 33092	368 / 2115955	1.55 (0.77 to 3.09)
Cerebral venous thrombosis	2 / 33117	43 / 2117512	4.43 (0.89 to 22.12)
Thrombocytopenia or coagulative disorder	9 / 33068	536 / 2114346	0.96 (0.49 to 1.89)
Guillain-Barré syndrome	0 / 33116	56 / 2117417	NE
Bell's palsy	10 / 33084	495 / 2115469	1.36 (0.71 to 2.62)
Transverse myelitis	0 / 33119	13 / 2117610	NE
Encephalomyelitis or encephalitis	1 / 33114	79 / 2117253	0.56 (0.07 to 4.12)
Narcolepsy	0 / 33117	7 / 2117482	NE
Appendicitis	33 / 32960	2118 / 2108328	1.04 (0.73 to 1.48)
Aseptic arthritis	56 / 32752	3616 / 2095306	0.94 (0.71 to 1.23)
Type 1 diabetes mellitus	12 / 32850	611 / 2100857	1.72 (0.94 to 3.15)
Subacute thyroiditis	4 / 33109	162 / 2116997	1.41 (0.50 to 3.96)
Heart failure	127 / 32430	9345 / 2075325	0.82 (0.69 to 0.98)
Arrhythmia	352 / 30760	24219 / 1978552	0.86 (0.77 to 0.95)
Acute liver failure	4 / 33099	404 / 2116300	0.73 (0.27 to 2.01)
Acute kidney failure	45 / 32853	4213 / 2100785	0.61 (0.45 to 0.83)
Acute pancreatitis	19 / 33029	1392 / 2112285	0.84 (0.52 to 1.33)
Erythema multiforme	0 / 33118	42 / 2117532	NE
Seizure	34 / 32869	1985 / 2102039	1.08 (0.76 to 1.54)
Arterial aneurysm	62 / 32748	4025 / 2095996	0.81 (0.62 to 1.04)
Uveitis	4 / 33062	689 / 2114067	0.45 (0.16 to 1.21)
Risk period restricted to the first 14 days after fourth vaccine dose			
Anaphylaxis	14 / 65919	388 / 2040463	0.92 (0.52 to 1.62)
Ischemic cardiac event	319 / 63920	10833 / 1983109	0.89 (0.79 to 1.00)

Supplementary Table S9. Risk of adverse events after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 with use of alternative risk periods.

Alternative risk period/outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Cerebrovascular event	386 / 64268	12436 / 1993146	0.92 (0.83 to 1.03)
Arterial thromboembolism	12 / 65940	415 / 2040993	1.11 (0.60 to 2.06)
Deep vein thrombosis	120 / 65328	3863 / 2023219	0.97 (0.80 to 1.17)
Pulmonary embolism	103 / 65526	3614 / 2029108	0.82 (0.66 to 1.00)
Myocarditis or pericarditis	20 / 65938	351 / 2040972	1.88 (1.13 to 3.11)
Cerebral venous thrombosis	3 / 65988	38 / 2042474	3.78 (0.88 to 16.17)
Thrombocytopenia or coagulative disorder	18 / 65891	516 / 2039421	0.96 (0.58 to 1.58)
Guillain-Barré syndrome	0 / 65986	55 / 2042383	NE
Bell's palsy	15 / 65921	480 / 2040502	1.00 (0.58 to 1.73)
Transverse myelitis	0 / 65992	13 / 2042568	NE
Encephalomyelitis or encephalitis	4 / 65981	76 / 2042224	1.18 (0.40 to 3.47)
Narcolepsy	0 / 65988	7 / 2042446	NE
Appendicitis	68 / 65675	2044 / 2033610	1.08 (0.84 to 1.40)
Aseptic arthritis	109 / 65260	3478 / 2021054	0.90 (0.74 to 1.11)
Type 1 diabetes mellitus	17 / 65455	594 / 2026411	1.20 (0.71 to 2.02)
Subacute thyroiditis	8 / 65972	153 / 2041976	1.46 (0.67 to 3.17)
Heart failure	259 / 64616	9035 / 2001763	0.83 (0.72 to 0.94)
Arrhythmia	744 / 61282	23357 / 1908464	0.90 (0.83 to 0.97)
Acute liver failure	8 / 65952	389 / 2041304	0.72 (0.35 to 1.51)
Acute kidney failure	115 / 65460	4079 / 2026337	0.78 (0.64 to 0.95)
Acute pancreatitis	37 / 65813	1348 / 2037430	0.80 (0.57 to 1.13)
Erythema multiforme	0 / 65989	41 / 2042494	NE
Seizure	53 / 65492	1931 / 2027542	0.82 (0.61 to 1.09)
Arterial aneurysm	147 / 65250	3862 / 2021732	0.97 (0.81 to 1.15)
Uveitis	9 / 65877	672 / 2039147	0.49 (0.25 to 0.96)
Risk period extended to 90 days after fourth vaccine dose			
Anaphylaxis	57 / 262345	272 / 1384066	0.85 (0.56 to 1.29)
Ischemic cardiac event	1381 / 254126	7156 / 1344999	0.92 (0.84 to 1.00)
Cerebrovascular event	1623 / 255346	8439 / 1351895	0.85 (0.78 to 0.92)
Arterial thromboembolism	34 / 262429	291 / 1384423	0.49 (0.30 to 0.81)
Deep vein thrombosis	471 / 259910	2633 / 1372343	0.85 (0.74 to 0.99)

Supplementary Table S9. Risk of adverse events after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 with use of alternative risk periods.

Alternative risk period/outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Pulmonary embolism	462 / 260687	2337 / 1376399	0.76 (0.65 to 0.88)
Myocarditis or pericarditis	47 / 262424	240 / 1384406	0.94 (0.59 to 1.50)
Cerebral venous thrombosis	4 / 262627	28 / 1385436	0.79 (0.18 to 3.56)
Thrombocytopenia or coagulative disorder	65 / 262228	364 / 1383377	0.66 (0.45 to 0.96)
Guillain-Barré syndrome	4 / 262617	41 / 1385374	0.26 (0.08 to 0.86)
Bell's palsy	58 / 262356	358 / 1384079	0.92 (0.61 to 1.40)
Transverse myelitis	0 / 262642	8 / 1385498	NE
Encephalomyelitis or encephalitis	10 / 262596	52 / 1385265	0.48 (0.21 to 1.12)
Narcolepsy	0 / 262626	7 / 1385415	NE
Appendicitis	239 / 261365	1415 / 1379352	0.87 (0.71 to 1.06)
Aseptic arthritis	436 / 259638	2409 / 1370916	0.74 (0.64 to 0.86)
Type 1 diabetes mellitus	51 / 260485	404 / 1374537	0.73 (0.48 to 1.10)
Subacute thyroiditis	21 / 262567	106 / 1385086	0.77 (0.41 to 1.47)
Heart failure	1189 / 256874	6121 / 1357746	0.79 (0.72 to 0.88)
Arrhythmia	3246 / 242808	15767 / 1294964	0.91 (0.85 to 0.96)
Acute liver failure	29 / 262479	262 / 1384634	0.42 (0.26 to 0.69)
Acute kidney failure	507 / 260415	2861 / 1374549	0.64 (0.56 to 0.74)
Acute pancreatitis	159 / 261907	916 / 1381989	0.70 (0.55 to 0.89)
Erythema multiforme	4 / 262630	27 / 1385450	0.83 (0.16 to 4.32)
Seizure	255 / 260574	1278 / 1375293	0.99 (0.80 to 1.22)
Arterial aneurysm	629 / 259535	2547 / 1371468	1.03 (0.90 to 1.19)
Uveitis	68 / 262182	466 / 1383147	1.02 (0.69 to 1.52)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. Day 7, 14, and 90, respectively, was used as the cut-off day to define the respective main risk and reference period for the given analysis (i.e., similar to the application of day 28 for the primary analysis; see Figure 1 for a graphical illustration of the study design for the primary analysis).

Supplementary Table S10. Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 including first SARS-CoV-2 infection as time-varying covariate.

Outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Anaphylaxis	30 / 130159	363 / 1891630	1.01 (0.66 to 1.56)
Ischemic cardiac event	672 / 126196	9992 / 1838431	0.95 (0.87 to 1.04)
Cerebrovascular event	798 / 126885	11523 / 1847717	0.97 (0.89 to 1.05)
Arterial thromboembolism	21 / 130201	385 / 1892119	0.96 (0.57 to 1.61)
Deep vein thrombosis	237 / 128988	3593 / 1875633	0.96 (0.82 to 1.12)
Pulmonary embolism	216 / 129377	3336 / 1881102	0.84 (0.72 to 0.99)
Myocarditis or pericarditis	29 / 130197	322 / 1892099	1.34 (0.85 to 2.13)
Cerebral venous thrombosis	3 / 130296	37 / 1893495	1.61 (0.37 to 7.07)
Thrombocytopenia and coagulative disorders	30 / 130103	489 / 1890664	0.75 (0.49 to 1.13)
Guillain-Barré syndrome	1 / 130291	48 / 1893410	0.19 (0.03 to 1.50)
Bell's palsy	29 / 130163	449 / 1891664	0.98 (0.63 to 1.51)
Transverse myelitis	0 / 130304	13 / 1893582	NE
Encephalomyelitis or encephalitis	9 / 130282	67 / 1893262	1.50 (0.64 to 3.49)
Narcolepsy	0 / 130296	7 / 1893468	NE
Appendicitis	126 / 129675	1911 / 1885269	1.01 (0.82 to 1.25)
Aseptic arthritis	215 / 128854	3213 / 1873634	0.88 (0.75 to 1.03)
Type 1 diabetes mellitus	24 / 129241	559 / 1878604	0.78 (0.49 to 1.23)
Subacute thyroiditis	16 / 130265	138 / 1893031	1.64 (0.86 to 3.11)
Heart failure	513 / 127578	8409 / 1855709	0.79 (0.71 to 0.87)
Arrhythmia	1530 / 120958	21642 / 1769310	0.93 (0.87 to 0.98)
Acute liver failure	10 / 130224	375 / 1892407	0.39 (0.20 to 0.76)
Acute kidney failure	236 / 129251	3819 / 1878527	0.78 (0.67 to 0.91)
Acute pancreatitis	77 / 129949	1256 / 1888813	0.82 (0.63 to 1.07)
Erythema multiforme	1 / 130298	36 / 1893513	0.40 (0.05 to 3.36)
Seizure	111 / 129316	1788 / 1879637	0.85 (0.68 to 1.06)
Arterial aneurysm	298 / 128829	3566 / 1874288	0.99 (0.86 to 1.13)
Uveitis	31 / 130078	622 / 1890403	0.89 (0.59 to 1.35)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. First SARS-CoV-2 infection was defined by the first registered positive PCR test for SARS-CoV-2 and treated as a time-varying covariate classified according to date of testing as uninfected, infected (day 0 to 90), and post infection (>day 90).

Supplementary Table S11. Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 with calendar month adjustment.

Outcome	Number of events / person-years		Incidence rate ratio (95% CI)
	Bivalent boosters	Reference period	
Anaphylaxis	30 / 130159	363 / 1891708	0.94 (0.60 to 1.47)
Ischemic cardiac event	672 / 126196	9992 / 1838509	0.94 (0.86 to 1.04)
Cerebrovascular event	798 / 126885	11523 / 1847796	0.94 (0.86 to 1.02)
Arterial thromboembolism	21 / 130201	385 / 1892197	0.95 (0.55 to 1.61)
Deep vein thrombosis	237 / 128988	3593 / 1875711	0.88 (0.75 to 1.03)
Pulmonary embolism	216 / 129377	3336 / 1881181	0.81 (0.69 to 0.96)
Myocarditis or pericarditis	29 / 130197	322 / 1892178	1.22 (0.76 to 1.97)
Cerebral venous thrombosis	3 / 130296	37 / 1893574	1.31 (0.29 to 5.89)
Thrombocytopenia and coagulative disorders	30 / 130103	489 / 1890743	0.72 (0.47 to 1.11)
Guillain-Barré syndrome	1 / 130291	48 / 1893489	0.18 (0.02 to 1.47)
Bell's palsy	29 / 130163	449 / 1891743	0.98 (0.63 to 1.54)
Transverse myelitis	0 / 130304	13 / 1893660	NE
Encephalomyelitis or encephalitis	9 / 130282	67 / 1893341	1.16 (0.49 to 2.74)
Narcolepsy	0 / 130296	7 / 1893547	NE
Appendicitis	126 / 129675	1911 / 1885347	0.92 (0.74 to 1.15)
Aseptic arthritis	215 / 128854	3213 / 1873713	0.85 (0.72 to 1.01)
Type 1 diabetes mellitus	24 / 129241	559 / 1878682	0.77 (0.48 to 1.23)
Subacute thyroiditis	16 / 130265	138 / 1893109	1.71 (0.88 to 3.32)
Heart failure	513 / 127578	8409 / 1855788	0.78 (0.70 to 0.87)
Arrhythmia	1530 / 120958	21642 / 1769389	0.90 (0.85 to 0.96)
Acute liver failure	10 / 130224	375 / 1892485	0.35 (0.17 to 0.69)
Acute kidney failure	236 / 129251	3819 / 1878607	0.74 (0.64 to 0.87)
Acute pancreatitis	77 / 129949	1256 / 1888891	0.78 (0.60 to 1.03)
Erythema multiforme	1 / 130298	36 / 1893592	0.39 (0.04 to 3.48)
Seizure	111 / 129316	1788 / 1879716	0.83 (0.66 to 1.05)
Arterial aneurysm	298 / 128829	3566 / 1874366	1.03 (0.89 to 1.19)
Uveitis	31 / 130078	622 / 1890482	0.90 (0.58 to 1.39)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions.

Supplemental Table S12. Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 as compared with two reference periods separately.

Outcome event	Number of events / person-years				
	Bivalent boosters (0-28 days of 4th dose)	Reference periods		Incidence rate ratio (95% CI)	
		≥29 days of 3rd dose	≥29 days of 4th dose	vs. ≥29 days of 3rd dose	vs. ≥29 days of 4th dose
Anaphylaxis	30 / 130159	336 / 1759467	27 / 132185	0.90 (0.55 to 1.46)	1.16 (0.69 to 1.96)
Ischemic cardiac event	672 / 126196	9280 / 1710528	709 / 127929	0.91 (0.82 to 1.01)	0.99 (0.89 to 1.10)
Cerebrovascular event	798 / 126885	10697 / 1719283	825 / 128461	0.87 (0.79 to 0.96)	1.06 (0.96 to 1.17)
Arterial thromboembolism	21 / 130201	372 / 1759913	13 / 132227	0.63 (0.36 to 1.10)	1.75 (0.88 to 3.50)
Deep vein thrombosis	237 / 128988	3357 / 1744733	234 / 130922	0.88 (0.74 to 1.04)	1.07 (0.89 to 1.28)
Pulmonary embolism	216 / 129377	3088 / 1749816	246 / 131309	0.74 (0.62 to 0.88)	0.96 (0.80 to 1.15)
Myocarditis or pericarditis	29 / 130197	304 / 1759894	18 / 132228	1.16 (0.70 to 1.94)	1.64 (0.91 to 2.95)
Cerebral venous thrombosis	3 / 130296	36 / 1761187	1 / 132330	1.13 (0.23 to 5.53)	3.08 (0.32 to 29.61)
Thrombocytopenia and coagulative disorders	30 / 130103	454 / 1758561	35 / 132125	0.63 (0.40 to 0.99)	0.91 (0.56 to 1.48)
Guillain-Barré syndrome	1 / 130291	45 / 1761107	3 / 132326	0.13 (0.02 to 1.07)	0.35 (0.04 to 3.41)
Bell's palsy	29 / 130163	420 / 1759493	29 / 132193	0.94 (0.58 to 1.52)	1.02 (0.61 to 1.70)
Transverse myelitis	0 / 130304	13 / 1761266	NE	NE	NE
Encephalomyelitis or encephalitis	9 / 130282	66 / 1760970	1 / 132314	0.84 (0.35 to 2.01)	9.42 (1.19 to 74.37)
Narcolepsy	0 / 130296	7 / 1761160	NE	NE	NE
Appendicitis	126 / 129675	1798 / 1753600	113 / 131691	0.92 (0.73 to 1.17)	1.13 (0.88 to 1.46)
Aseptic arthritis	215 / 128854	2991 / 1742873	221 / 130784	0.75 (0.63 to 0.90)	1.05 (0.87 to 1.26)

Supplemental Table S12. Risk of adverse events within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 as compared with two reference periods separately.

Outcome event	Number of events / person-years			Incidence rate ratio (95% CI)	
	Bivalent boosters (0-28 days of 4th dose)	Reference periods		vs. ≥29 days of 3rd dose	vs. ≥29 days of 4th dose
		≥29 days of 3rd dose	≥29 days of 4th dose		
Type 1 diabetes mellitus	24 / 129241	532 / 1747382	27 / 131243	0.69 (0.42 to 1.14)	0.90 (0.52 to 1.56)
Subacute thyroiditis	16 / 130265	133 / 1760751	5 / 132301	1.18 (0.60 to 2.34)	3.23 (1.18 to 8.82)
Heart failure	513 / 127578	7731 / 1726441	676 / 129297	0.73 (0.65 to 0.82)	0.85 (0.75 to 0.95)
Arrythmia	1530 / 120958	19920 / 1647495	1716 / 121850	0.89 (0.83 to 0.95)	0.97 (0.90 to 1.03)
Acute liver failure	10 / 130224	356 / 1760174	19 / 132254	0.30 (0.15 to 0.61)	0.55 (0.25 to 1.18)
Acute kidney failure	236 / 129251	3548 / 1747386	271 / 131164	0.63 (0.53 to 0.74)	0.97 (0.81 to 1.15)
Acute pancreatitis	77 / 129949	1174 / 1756877	82 / 131958	0.69 (0.52 to 0.92)	1.00 (0.73 to 1.37)
Erythema multiforme	1 / 130298	33 / 1761203	3 / 132332	0.44 (0.04 to 4.64)	0.37 (0.04 to 3.56)
Seizure	111 / 129316	1644 / 1748402	144 / 131258	0.88 (0.68 to 1.13)	0.82 (0.64 to 1.05)
Arterial aneurysm	298 / 128829	3233 / 1743605	331 / 130706	1.02 (0.86 to 1.20)	0.97 (0.83 to 1.13)
Uveitis	31 / 130078	584 / 1758321	37 / 132104	0.96 (0.60 to 1.54)	0.85 (0.53 to 1.37)

NE denotes not estimable. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions.

Supplementary Table S13: Risk of cerebrovascular infarction, myocarditis and/or pericarditis after vaccination with the individual bivalent omicron adapted vaccine types as a fourth dose by sex and age groups within 28 days in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.

Outcome/subgroups	BNT BA.4-5-containing		BNT BA.1-containing		MOD BA.1-containing		Reference period		Incidence rate ratio (95% CI)		
	Events/ PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events/ PYRS	Rate/ 1,000,000	BNT BA.4-5- containing	BNT BA.1- containing	MOD BA.1- containing
Cerebrovascular infarction (including TIA)											
All	377 / 84259	343.0	246 / 38856	485.3	21 / 4189	384.3	9687 / 1853451	400.7	0.97 (0.86 to 1.09)	0.98 (0.85 to 1.12)	0.83 (0.54 to 1.29)
Females	156 / 43643	274.0	118 / 21860	413.8	16 / 2292	535.2	4317 / 974392	339.6	0.92 (0.77 to 1.10)	0.91 (0.74 to 1.11)	1.27 (0.76 to 2.13)
Males	221 / 40616	417.1	128 / 16997	577.3	5 / 1897	202.0	5370 / 879059	468.3	1.01 (0.87 to 1.19)	1.04 (0.86 to 1.26)	0.41 (0.17 to 0.99)
Aged 50 to 64 years	75 / 39699	144.8	21 / 8206	196.2	2 / 1315	116.6	1716 / 806017	163.2	0.89 (0.69 to 1.15)	1.20 (0.77 to 1.87)	0.75 (0.19 to 3.03)
Aged 65 to 79 years	180 / 32245	427.9	110 / 18751	449.7	6 / 1464	314.1	4036 / 690056	448.4	0.95 (0.81 to 1.13)	1.02 (0.83 to 1.25)	0.74 (0.33 to 1.65)
Aged 80 years or older	99 / 7984	950.6	105 / 9726	827.6	12 / 1192	771.5	3351 / 266105	965.4	1.07 (0.86 to 1.33)	0.92 (0.74 to 1.13)	0.94 (0.53 to 1.66)
Myocarditis or pericarditis											
All ^a	18 / 85800	16.1	9 / 40116	17.2	2 / 4281	35.8	322 / 1892114	13.0	1.05 (0.58 to 1.92)	1.29 (0.61 to 2.74)	3.17 (0.77 to 13.11)
Females	8 / 44256	13.9	5 / 22443	17.1	2 / 2331	65.8	130 / 990933	10.1	0.87 (0.33 to 2.33)	1.55 (0.58 to 4.10)	6.45 (1.50 to 27.82)
Males	10 / 41544	18.5	4 / 17673	17.4	0 / 1950	NE	192 / 901182	16.3	1.20 (0.56 to 2.58)	0.99 (0.30 to 3.28)	NE
Aged 50 to 64 years	8 / 40022	15.3	2 / 8313	18.4	1 / 1327	57.8	144 / 812580	13.6	1.30 (0.57 to 2.95)	1.46 (0.34 to 6.23)	5.37 (0.72 to 40.12)
Aged 65 to 79 years	6 / 32993	13.9	4 / 19283	15.9	1 / 1494	51.3	117 / 706700	12.7	0.95 (0.38 to 2.38)	1.04 (0.35 to 3.04)	3.42 (0.46 to 25.70)

Supplementary Table S13: Risk of cerebrovascular infarction, myocarditis and/or pericarditis after vaccination with the individual bivalent omicron adapted vaccine types as a fourth dose by sex and age groups within 28 days in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.

Outcome/subgroups	BNT BA.4-5-containing		BNT BA.1-containing		MOD BA.1-containing		Reference period		Incidence rate ratio (95% CI)		
	Events/ PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events/ PYRS	Rate/ 1,000,000	BNT BA.4-5- containing	BNT BA.1- containing	MOD BA.1- containing
Aged 80 years or older	0 / 8355	NE	2 / 10272	14.9	0 / 1239	NE	41 / 279247	11.3	NE	1.52 (0.31 to 7.38)	NE
Myocarditis											
All	6 / 85859	5.4	2 / 40146	3.8	1 / 4283	17.9	64 / 1893405	2.6	3.74 (1.16 to 12.05)	2.59 (0.52 to 12.94)	12.39 (1.46 to 105.47)
Females	3 / 44278	5.2	2 / 22455	6.8	1 / 2332	32.9	29 / 991433	2.2	7.10 (1.06 to 47.81)	8.50 (1.24 to 58.44)	59.58 (4.97 to 714.53)
Males	3 / 41581	5.5	0 / 17690	NE	0 / 1951	NE	35 / 901972	3.0	2.42 (0.54 to 10.83)	NE	NE
Aged 50 to 64 years	3 / 40050	5.7	0 / 8320	NE	1 / 1327	57.8	25 / 813144	2.4	4.76 (0.80 to 28.37)	NE	50.46 (4.55 to 559.52)
Aged 65 to 79 years	3 / 33017	7.0	1 / 19297	4.0	0 / 1495	NE	26 / 707193	2.8	3.04 (0.62 to 15.00)	1.55 (0.16 to 14.66)	NE
Aged 80 years or older	0 / 8361	NE	1 / 10279	7.5	0 / 1240	NE	7 / 279421	1.9	NE	16.95 (0.62 to 459.83)	NE
Pericarditis											
All	14 / 85811	12.5	7 / 40123	13.4	1 / 4281	17.9	265 / 1892351	10.7	0.85 (0.43 to 1.71)	1.12 (0.48 to 2.64)	1.82 (0.25 to 13.31)
Females	7 / 44260	12.1	3 / 22445	10.2	1 / 2331	32.9	104 / 991018	8.0	0.75 (0.25 to 2.21)	0.99 (0.29 to 3.34)	3.14 (0.42 to 23.64)
Males	7 / 41551	12.9	4 / 17677	17.3	0 / 1951	NE	161 / 901332	13.7	0.96 (0.39 to 2.38)	1.23 (0.37 to 4.13)	NE
Aged 50 to 64 years	6 / 40028	11.5	2 / 8314	18.4	0 / 1327	NE	122 / 812683	11.5	1.09 (0.43 to 2.73)	1.64 (0.38 to 7.07)	NE

Supplementary Table S13: Risk of cerebrovascular infarction, myocarditis and/or pericarditis after vaccination with the individual bivalent omicron adapted vaccine types as a fourth dose by sex and age groups within 28 days in Danish 50+ year-olds during 15 September 2022 to 10 December 2022.

Outcome/subgroups	BNT BA.4-5-containing		BNT BA.1-containing		MOD BA.1-containing		Reference period		Incidence rate ratio (95% CI)		
	Events/ PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events / PYRS	Rate/ 1,000,000	Events/ PYRS	Rate/ 1,000,000	BNT BA.4-5- containing	BNT BA.1- containing	MOD BA.1- containing
Aged 65 to 79 years	4 / 32998	9.3	3 / 19286	11.9	1 / 1494	51.3	92 / 706793	10.0	0.75 (0.25 to 2.25)	0.94 (0.27 to 3.20)	4.09 (0.54 to 31.00)
Aged 80 years or older	0 / 8356	NE	1 / 10274	7.5	0 / 1239	NE	35 / 279276	9.6	NE	0.78 (0.09 to 6.47)	NE

BNT denotes BNT162b2, MOD mRNA-1273, NE not estimable, and PYRS total person-years. Each outcome was studied separately, which is why there may be slight differences in the denominators due to different exclusions. Rate/1,000,000 is the incidence rate per 1,000,000 vaccinated within 28 days. The sum of person-years within different strata may not equal the total person-years exactly because of rounding. ^aThe IRR estimates are identical to those reported in Figure 5.

Supplementary Table S14. Risk of cerebrovascular infarction within 28 days after vaccination with a bivalent omicron adapted mRNA-booster vaccine as the fourth dose in Danish 50+ year-olds during 15 September 2022 to 10 December 2022 by influenza vaccination on the same day.

	Number of events / person-years	Incidence rate ratio (95% CI)
Reference period	9687 / 1853528	(reference)
Influenza vaccinated on same day as bivalent booster vaccination	412 / 66484	0.93 (0.83 to 1.04)
Not influenza vaccinated on same day as bivalent booster vaccination	232 / 60825	1.01 (0.88 to 1.16)

Among the 1740417 individuals who received a fourth dose bivalent booster vaccination, 907731 received an influenza vaccine (predominantly quadrivalent) on the same day (whereof only 783 were high-dose influenza vaccines and no adjuvanted vaccines were identified [consequently, separate analysis not conducted]).

Supplementary references

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