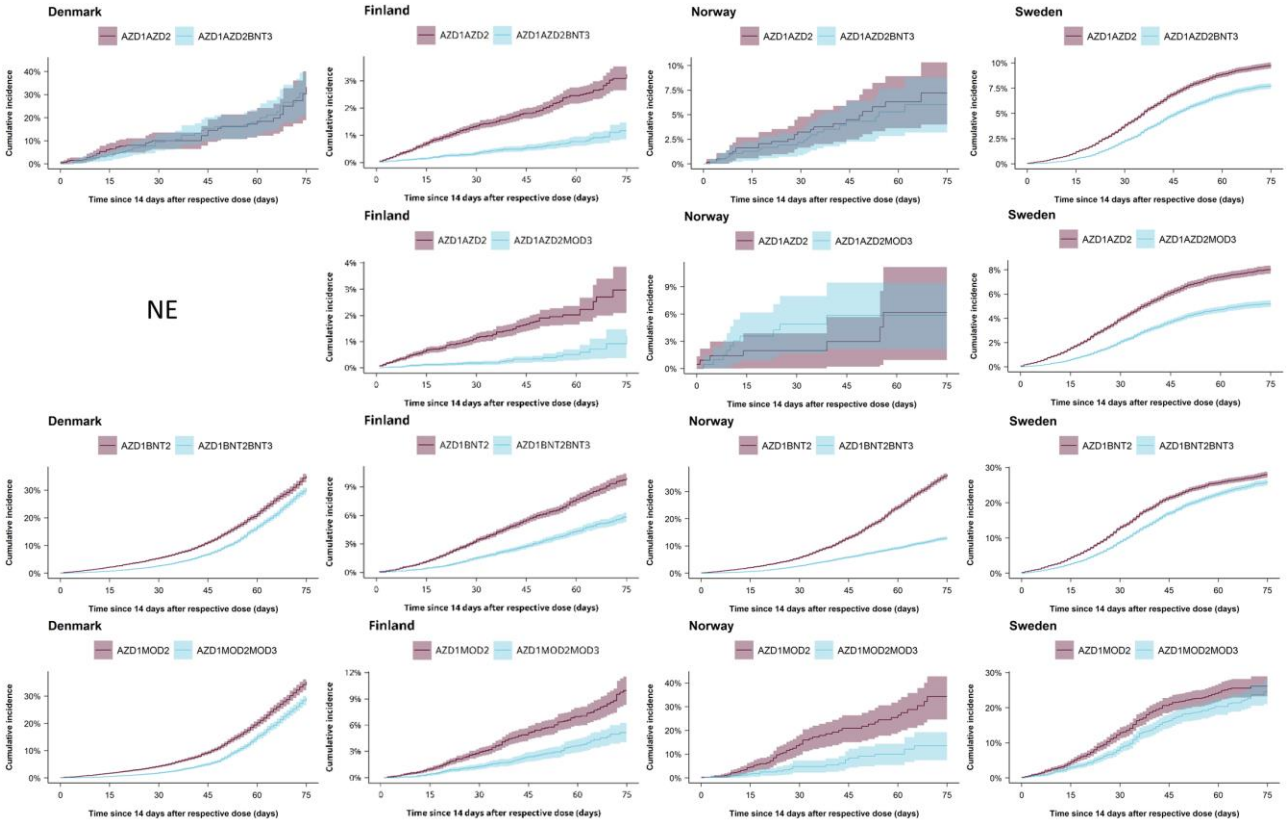
10.2.2 Comparative vaccine effectiveness of booster vs. primary schedules (objective 2; i.e. 3- vs. 2-dose)

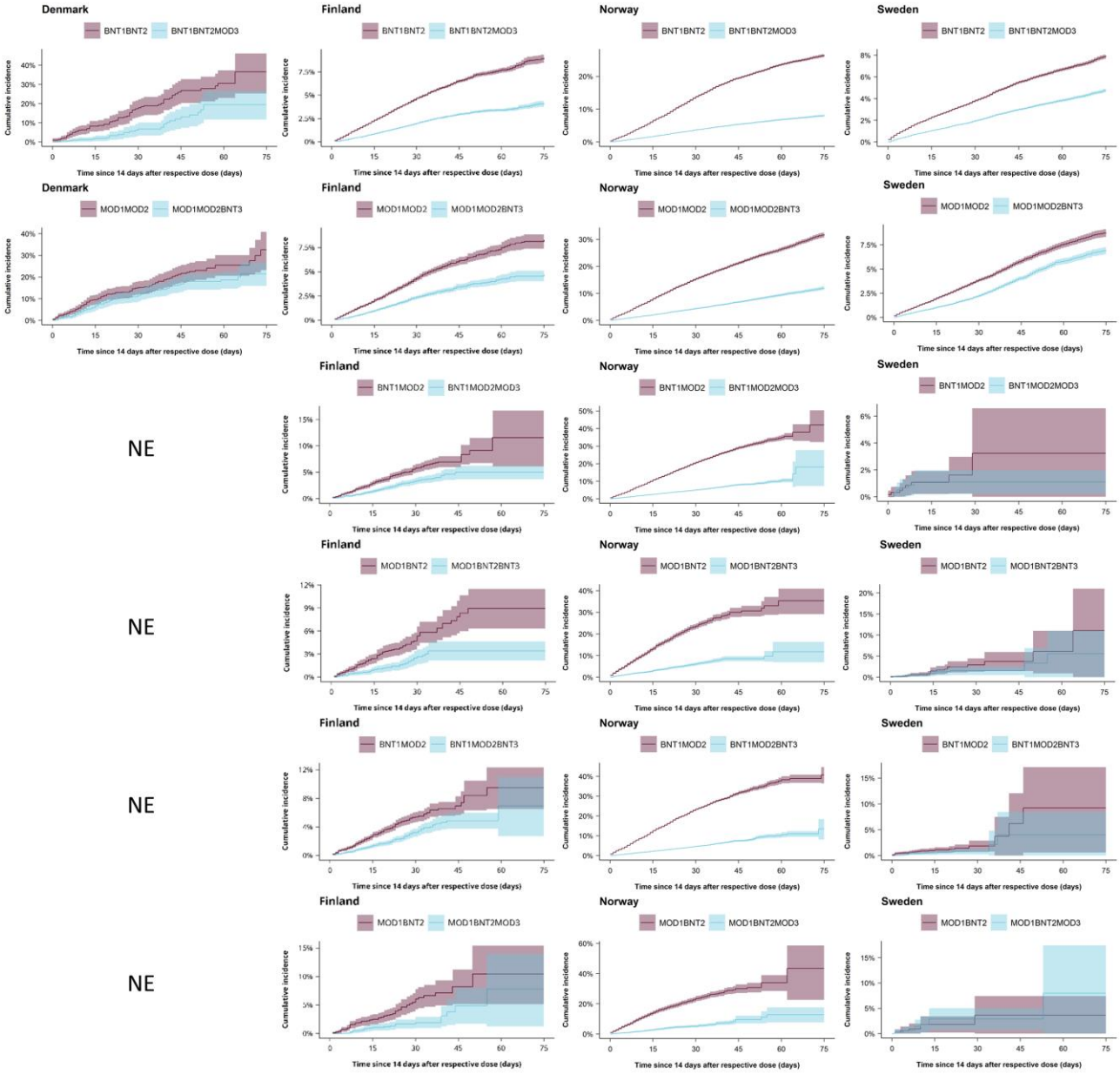
Figures 21 to 23 present the cumulative incidence curves of documented covid-19 infection for the matched booster vs. primary schedule comparisons (i.e. 3- vs. 2-dose). As few to no events of covid-19 related hospitalisation, ICU admission, or death occurred across the majority of comparisons in all countries, only those county-specific comparisons that yielded a sufficient number of cases for data analysis are presented in Figures 24 and 25.

Figure 21. Country-specific cumulative incidence curves of documented covid-19 infection for matched analyses comparing heterologous AZD-mRNA booster schedules with the primary schedule counterpart.



NE denotes not estimated.

Figure 22. Country-specific cumulative incidence curves of documented covid-19 infection for matched analyses comparing heterologous mRNA booster schedules with the primary schedule counterpart.



NE denotes not estimated.

Figure 23. Country-specific cumulative incidence curves of documented covid-19 infection for matched analyses comparing homologous mRNA booster schedules with the primary schedule counterpart.

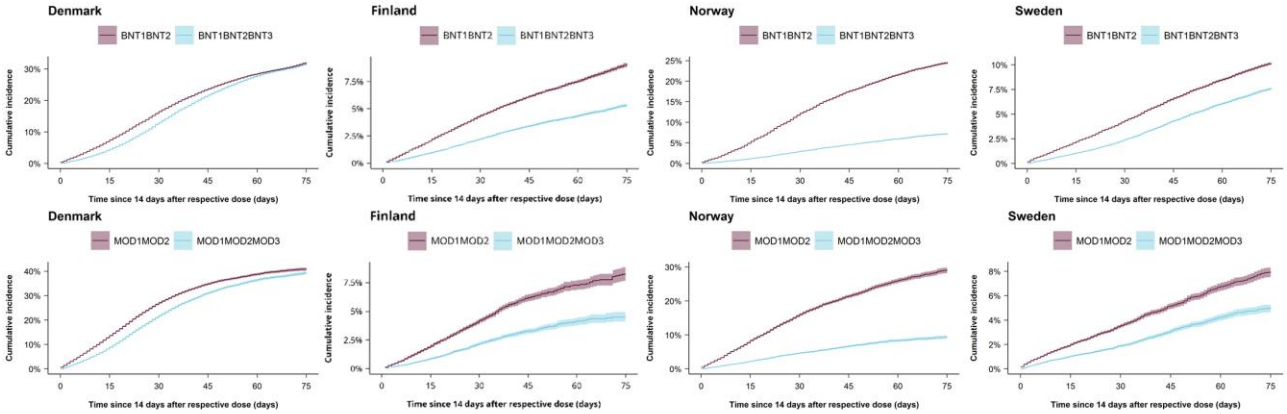
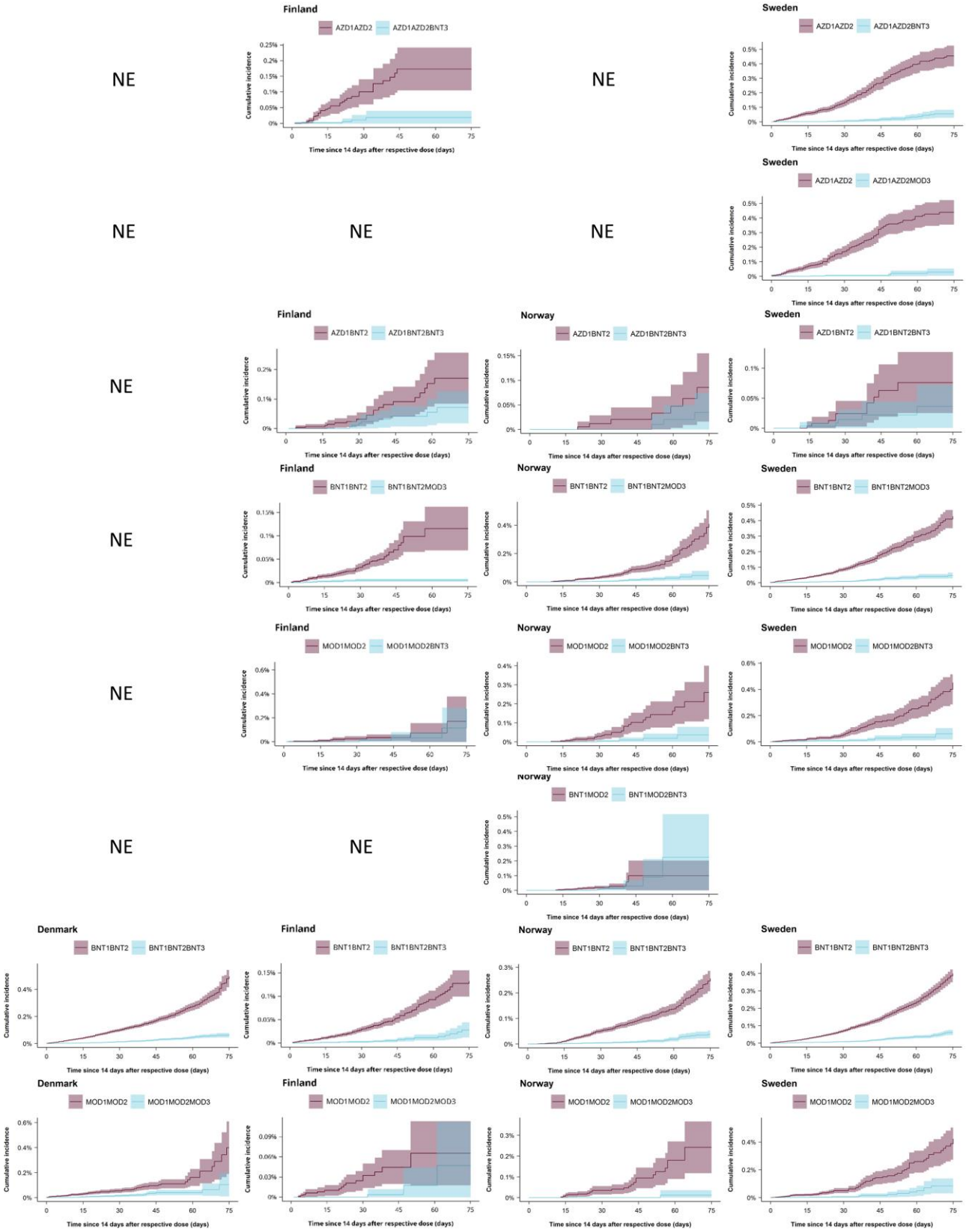
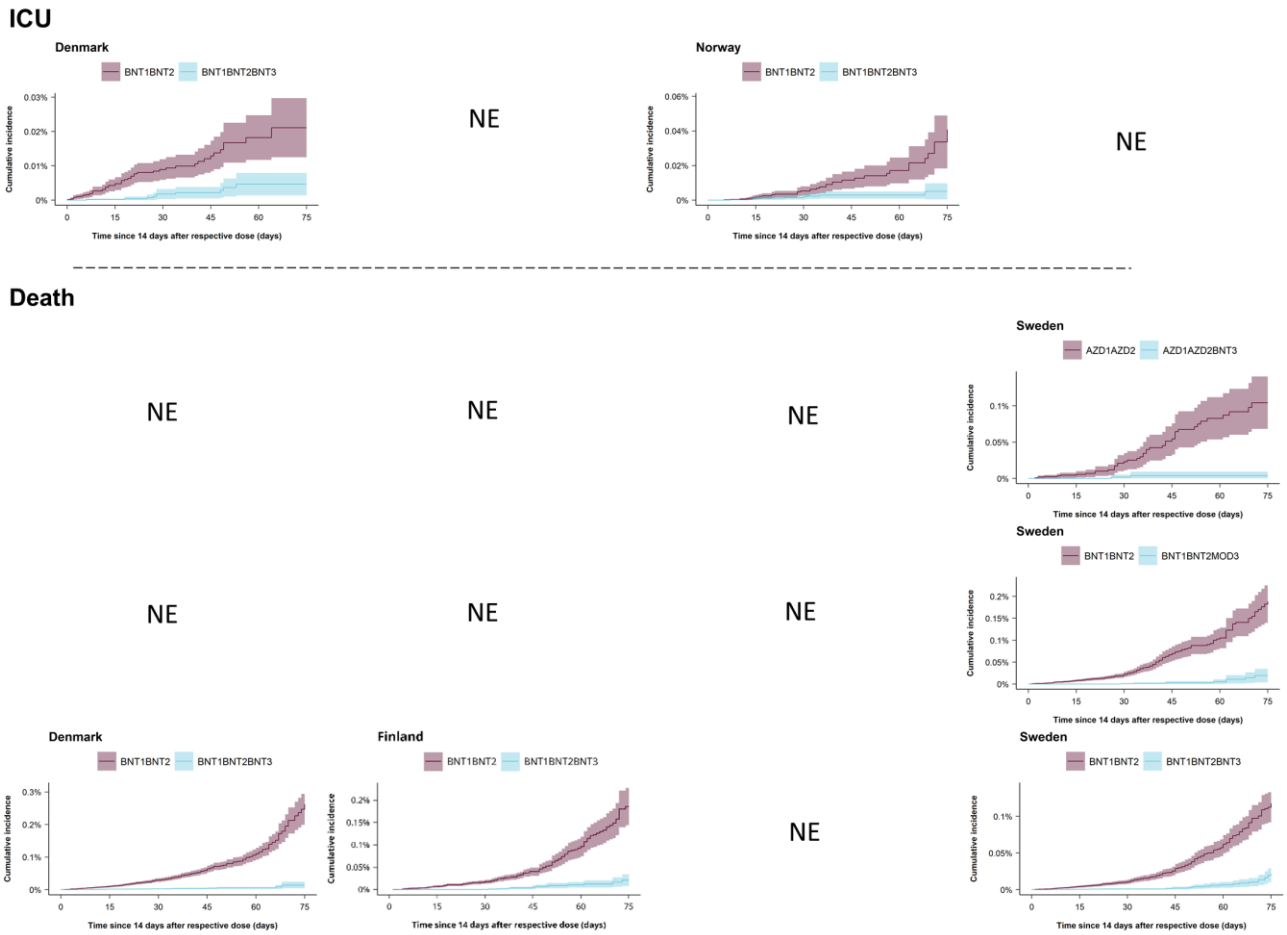


Figure 24. Country-specific cumulative incidence curves of covid-19 hospitalisation for matched analyses comparing heterologous or homologous booster schedules with the primary schedule counterpart.



NE denotes not estimated.

Figure 25. Country-specific cumulative incidence curves of covid-19 related intensive care unit admission and death for matched analyses comparing heterologous and homologous booster schedules with the primary schedule counterpart.



ICU denotes intensive care unit and NE not estimated.

Table 5 presents the number of endpoint events, total person-years, and measures of association for each booster vs. primary schedule comparison across countries. Country-combined results for documented covid-19 infection and hospitalisation are presented in Table 6.

Table 5. Country-specific associations between covid-19 endpoints and studied heterologous and homologous booster vaccine schedules as compared with the matched primary schedule counterpart.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
AZD1AZD2BNT3 vs AZD1AZD2				
Documented infection				
Denmark	46 / 33.9	46 / 32.7	-2.8% (-17.8% - 12.2%)	5.4% (-40.9% - 51.6%)
Finland	157 / 3413.4	550 / 3392.7	-2.1% (-2.6% - -1.5%)	63.8% (52.8% - 74.8%)
Norway	21 / 64.0	25 / 64.0	-1.2% (-5.2% - 2.8%)	12.6% (-44.3% - 69.6%)
Sweden	3380 / 10951.1	4851 / 10673.7	-2.0% (-2.4% - -1.6%)	20.6% (17.1% - 24.1%)
Hospitalisation				
Denmark				
Finland	<5 / 3477.4	37 / 3419.6	-0.2% (-0.2% - -0.1%)	88.4% (75.0% - 100%)
Norway				
Sweden	18 / 11160.6	213 / 10866.9	-0.4% (-0.5% - -0.3%)	87.8% (81.2% - 94.3%)
ICU admission				
Denmark				
Finland	<5 / 3478.5	8 / 3420.7	0.0% (0.0% - 0.0%)	29.5% (-139.4% - 100%)
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 3539.6	16 / 3470.4	-0.1% (-0.2% - 0.0%)	91.8% (72.2% - 100%)
Norway				
Sweden	<3 / 11331.5	41 / 11094.5	-0.1% (-0.1% - -0.1%)	96.1% (90.6% - 100%)
AZD1AZD2MOD3 vs AZD1AZD2				
Documented infection				
Denmark	3 / 4.8	3 / 4.7		
Finland	47 / 1613.3	236 / 1593.6	-1.7% (-3.0% - -0.4%)	56.8% (23.3% - 90.2%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	10 / 21.7	7 / 21.7	-0.2% (-6.5% - 6.1%)	-24.9% (-224.1% - 100%)
Sweden	1604 / 6455.9	2782 / 6268.3	-2.8% (-3.2% - -2.4%)	34.6% (30.2% - 38.9%)
Hospitalisation				
Denmark				
Finland	0 / 1652.5	23 / 1606.5		
Norway				
Sweden	6 / 6576.8	139 / 6387.2	-0.4% (-0.5% - -0.3%)	93.3% (87.2% - 99.5%)
ICU admission				
Denmark				
Finland	0 / 1653.3	5 / 1607.2		
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 1702.9	10 / 1638.0	-0.1% (-0.2% - 0.0%)	73.4% (15.5% - 100%)
Norway				
Sweden				
AZD1BNT2BNT3 vs AZD1BNT2				
Documented infection				
Denmark	2115 / 2992.7	2778 / 2820.3	-4.4% (-6.4% - -2.5%)	12.6% (7.4% - 17.8%)
Finland	727 / 3390.0	1435 / 3347.4	-4.1% (-4.9% - -3.3%)	41.3% (35.4% - 47.3%)
Norway	1433 / 2888.3	3680 / 2681.8	-23.3% (-24.5% - -22.1%)	64.4% (62.2% - 66.5%)
Sweden	3807 / 2952.2	4518 / 2789.9	-2.0% (-3.2% - -0.7%)	7.0% (2.8% - 11.3%)
Hospitalisation				
Denmark	<3 / 3124.1	<3 / 2936.8	0.0% (0.0% - 0.0%)	
Finland	8 / 3464.2	21 / 3405.7	-0.1% (-0.2% - 0.0%)	55.1% (10.4% - 99.9%)
Norway	<5 / 3096.8	7 / 2821.7	-0.1% (-0.1% - 0.0%)	
Sweden	5 / 3140.1	10 / 2987.5	0.0% (-0.1% - 0.0%)	45.3% (-60.5% - 100%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
ICU admission				
Denmark				
Finland	<5 / 3464.7	<5 / 3406.2	0.0% (0.0% - 0.0%)	-35.8% (-34878238451366668.0% - 100%)
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 3522.9	6 / 3478.9		
Norway				
Sweden				
AZD1MOD2MOD3 vs AZD1MOD2				
Documented infection				
Denmark	1037 / 1664.4	1424 / 1582.5	-5.8% (-8.5% - -3.2%)	16.5% (9.6% - 23.4%)
Finland	126 / 690.4	265 / 683.5	-4.8% (-6.8% - -2.8%)	47.7% (32.9% - 62.5%)
Norway	24 / 39.7	61 / 35.9	-20.7% (-30.7% - -10.7%)	59.9% (40.7% - 79.2%)
Sweden	293 / 245.8	362 / 231.9	-1.6% (-5.8% - 2.6%)	5.8% (-10.0% - 21.5%)
Hospitalisation				
Denmark	<3 / 1719.1	<3 / 1634.9	-0.1% (-0.2% - 0.1%)	
Finland	0 / 702.4	5 / 693.7		
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 702.4	<5 / 693.8		
Norway				
Sweden				
Death				
Denmark				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Finland	0 / 713.2	<5 / 706.2		
Norway				
Sweden				
BNT1BNT2MOD3 vs BNT1BNT2				
Documented infection				
Denmark	28 / 30.7	72 / 31.8		
Finland	4565 / 19549.9	11043 / 19336.8	-4.9% (-5.5% - -4.3%)	54.4% (50.0% - 58.7%)
Norway	7349 / 16624.8	26432 / 15427.7	-18.3% (-18.9% - -17.7%)	69.0% (67.6% - 70.4%)
Sweden	8768 / 35105.9	17118 / 34112.7	-3.2% (-3.4% - -2.9%)	39.7% (37.1% - 42.3%)
Hospitalisation				
Denmark				
Finland	11 / 20564.9	89 / 19857.1	-0.1% (-0.2% - -0.1%)	95.2% (91.2% - 99.1%)
Norway	17 / 18061.9	106 / 16625.1	-0.4% (-0.5% - -0.2%)	88.4% (79.4% - 97.4%)
Sweden	53 / 37614.4	441 / 35709.8	-0.4% (-0.4% - -0.3%)	89.3% (84.7% - 93.9%)
ICU admission				
Denmark				
Finland	<5 / 20568.1	9 / 19859.9	0.0% (0.0% - 0.0%)	80.2% (25.3% - 100%)
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 21989.5	44 / 20850.0	-0.2% (-0.3% - 0.0%)	98.7% (96.4% - 100%)
Norway				
Sweden	9 / 41120.9	151 / 38859.8	-0.2% (-0.2% - -0.1%)	89.8% (81.1% - 98.4%)
MOD1MOD2BNT3 vs MOD1MOD2				
Documented infection				
Denmark	88 / 63.2	116 / 58.1	-11.1% (-21.8% - -0.4%)	32.6% (6.6% - 58.6%)
Finland	811 / 3029.6	1532 / 2990.0	-3.6% (-4.6% - -2.6%)	42.9% (33.7% - 52.1%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	2756 / 4865.2	8885 / 4453.9	-19.8% (-20.9% - -18.7%)	62.3% (59.9% - 64.6%)
Sweden	2438 / 8042.2	3823 / 7846.7	-1.8% (-2.3% - -1.3%)	20.6% (15.4% - 25.8%)
Hospitalisation				
Denmark				
Finland	5 / 3149.2	11 / 3055.5	0.1% (-0.3% - 0.5%)	
Norway	<5 / 5456.8	27 / 4878.9	-0.2% (-0.4% - -0.1%)	84.4% (63.3% - 100%)
Sweden	15 / 8496.0	85 / 8160.8	-0.4% (-0.5% - -0.3%)	86.2% (75.6% - 96.9%)
ICU admission				
Denmark				
Finland	0 / 3149.7	0 / 3055.8	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 3285.6	11 / 3161.5	-0.3% (-0.7% - 0.1%)	70.6% (-21.5% - 100%)
Norway				
Sweden				
BNT1MOD2MOD3 vs BNT1MOD2				
Documented infection				
Denmark	<3 / 0.3	<3 / 0.3		
Finland	146 / 378.4	263 / 371.3	-6.6% (-12.1% - -1.0%)	54.4% (31.1% - 77.7%)
Norway	2448 / 3821.4	9691 / 3481.8		
Sweden	6 / 27.9	8 / 27.4	-2.1% (-5.8% - 1.6%)	47.7% (-57.5% - 100%)
Hospitalisation				
Denmark				
Finland	0 / 402.2	0 / 383.3	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
ICU admission				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Denmark				
Finland	0 / 402.2	0 / 383.3	0.0% (0.0% - 0.0%)	
Norway	<5 / 4378.5	<5 / 3957.7	0.0% (-0.1% - 0.0%)	
Sweden				
Death				
Denmark				
Finland	0 / 425.1	0 / 403.4	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
MOD1BNT2BNT3 vs MOD1BNT2				
Documented infection				
Denmark	4 / 0.9	3 / 1.0		
Finland	41 / 156.8	96 / 153.7	-5.5% (-8.3% - -2.7%)	61.0% (43.6% - 78.3%)
Norway	341 / 440.3	1306 / 391.5		
Sweden	14 / 61.8	21 / 60.9	-5.5% (-16.1% - 5.2%)	38.1% (-51.8% - 100%)
Hospitalisation				
Denmark				
Finland	0 / 163.2	<5 / 157.6		
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 163.2	0 / 157.6	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 170.2	0 / 163.7	0.0% (0.0% - 0.0%)	
Norway				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden				
BNT1MOD2BNT3 vs BNT1MOD2				
Documented infection				
Denmark				
Finland	157 / 421.6	279 / 415.4	-2.5% (-7.4% - 2.4%)	24.6% (-24.5% - 73.7%)
Norway	4362 / 7567.4	22129 / 6865.5	-27.3% (-34.1% - -20.5%)	66.9% (53.5% - 80.4%)
Sweden	13 / 90.8	26 / 89.9	-5.0% (-14.6% - 4.6%)	38.7% (-96.3% - 100%)
Hospitalisation				
Denmark				
Finland	0 / 444.6	0 / 427.8	0.0% (0.0% - 0.0%)	
Norway	7 / 8631.4	17 / 7877.6	0.1% (-0.2% - 0.4%)	
Sweden				
ICU admission				
Denmark				
Finland	0 / 444.6	0 / 427.8	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 469.9	0 / 448.2	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
MOD1BNT2MOD3 vs MOD1BNT2				
Documented infection				
Denmark				
Finland	23 / 89.5	59 / 87.4	-2.7% (-11.3% - 5.9%)	20.4% (-64.1% - 100%)
Norway	170 / 244.2	705 / 212.9	-30.6% (-49.3% - -12.0%)	69.4% (52.6% - 86.3%)
Sweden	8 / 16.9	6 / 16.8	4.6% (-6.7% - 15.8%)	

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Hospitalisation				
Denmark				
Finland	0 / 94.7	0 / 90.2	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 94.7	0 / 90.2	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 99.5	0 / 94.7	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
BNT1BNT2BNT3 vs BNT1BNT2				
Documented infection				
Denmark	74627 / 44918.4	84594 / 41590.3	-0.5% (-0.8% - -0.1%)	1.4% (0.4% - 2.5%)
Finland	13007 / 48445.0	25523 / 48168.5	-3.7% (-4.0% - -3.5%)	41.0% (39.1% - 43.0%)
Norway	15227 / 43287.1	58630 / 40260.9	-17.3% (-17.6% - -17.0%)	70.5% (69.8% - 71.1%)
Sweden	23226 / 72261.7	38516 / 70079.1	-2.6% (-2.7% - -2.4%)	25.1% (23.5% - 26.7%)
Hospitalisation				
Denmark	113 / 52784.9	656 / 45990.7	-0.4% (-0.5% - -0.4%)	86.5% (82.2% - 90.8%)
Finland	28 / 51088.2	205 / 49417.1	-0.1% (-0.1% - -0.1%)	78.2% (64.8% - 91.7%)
Norway	40 / 46327.7	289 / 42735.9	-0.2% (-0.3% - -0.2%)	85.0% (78.8% - 91.2%)
Sweden	122 / 75966.6	796 / 72832.4	-0.3% (-0.4% - -0.3%)	84.3% (80.4% - 88.2%)
ICU admission				
Denmark	10 / 52820.0	51 / 46001.5	0.0% (0.0% - 0.0%)	77.0% (57.9% - 96.0%)
Finland	0 / 51097.2	20 / 49423.4		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	10 / 46324.9	38 / 42740.0	0.0% (-0.1% - 0.0%)	86.6% (71.8% - 100%)
Sweden				
Death				
Denmark	23 / 60800.4	273 / 52568.1	-0.2% (-0.3% - -0.2%)	94.6% (90.7% - 98.6%)
Finland	17 / 53948.7	206 / 51666.5	-0.2% (-0.2% - -0.1%)	88.2% (80.3% - 96.0%)
Norway				
Sweden	26 / 80260.1	188 / 77206.2	-0.1% (-0.1% - -0.1%)	81.4% (71.7% - 91.1%)
MOD1MOD2MOD3 vs MOD1MOD2				
Documented infection				
Denmark	19949 / 7338.4	23129 / 6637.5	-1.7% (-2.6% - -0.7%)	4.1% (1.8% - 6.3%)
Finland	1293 / 5137.7	2525 / 5056.3	-3.7% (-4.5% - -2.9%)	45.0% (38.1% - 51.9%)
Norway	2532 / 4619.0	8391 / 4190.4	-19.8% (-20.7% - -18.8%)	67.8% (65.8% - 69.8%)
Sweden	1923 / 7653.4	3440 / 7457.3	-2.9% (-3.4% - -2.4%)	36.9% (31.9% - 41.9%)
Hospitalisation				
Denmark	22 / 9219.0	69 / 7859.2	-0.3% (-0.5% - -0.1%)	72.4% (42.8% - 100%)
Finland	<5 / 5372.0	18 / 5172.0	0.0% (-0.1% - 0.1%)	15.7% (-123.2% - 100%)
Norway	<5 / 5189.6	26 / 4597.5	-0.2% (-0.4% - -0.1%)	94.7% (83.3% - 100%)
Sweden	14 / 8078.0	79 / 7736.0	-0.3% (-0.5% - -0.2%)	80.1% (66.0% - 94.1%)
ICU admission				
Denmark	<3 / 9236.0	<3 / 7861.5	0.0% (0.0% - 0.0%)	
Finland	0 / 5372.5	0 / 5172.6	0.0% (0.0% - 0.0%)	
Norway	<5 / 5178.3	6 / 4591.0	-0.1% (-0.2% - 0.0%)	
Sweden				
Death				
Denmark	<3 / 11163.5	19 / 9494.2	-0.1% (-0.3% - 0.0%)	95.4% (85.1% - 100%)
Finland	<5 / 5590.4	22 / 5360.2	-0.2% (-0.4% - 0.1%)	62.7% (-32.4% - 100%)
Norway				
Sweden	<3 / 8646.4	19 / 8277.5	-0.1% (-0.2% - -0.1%)	90.0% (67.7% - 100%)

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).

Table 6. Meta-analysis of the country-specific results for the associations between documented covid-19 infection and covid-19 related hospitalisation and studied heterologous or homologous booster vaccine schedules as compared with the matched primary schedule counterpart

Studied schedule	Compared schedule	Studied schedule events	Compared schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
Outcome: Documented infection							
AZD1AZD2BNT3	AZD1AZD2	3604	5472	-2.0% (-2.3%--1.7%)	30.8% (1.8%-59.8%)	0.9773	DK, FI, SE, NO
AZD1BNT2BNT3	AZD1BNT2	8082	12411	-8.5% (-18.2%-1.3%)	31.4% (5.2%-57.6%)	<0.0001	DK, FI, SE, NO
AZD1AZD2MOD3	AZD1AZD2	1661	3025	-2.4% (-3.4%--1.4%)	38.1% (22.4%-53.9%)	0.227	FI, NO, SE
AZD1MOD2MOD3	AZD1MOD2	1480	2112	-7.0% (-13.5%--0.5%)	31.9% (7.3%-56.4%)	0.0061	DK, FI, SE, NO
BNT1BNT2MOD3	BNT1BNT2	20682	54593	-8.8% (-18.1%-0.6%)	54.4% (37.7%-71.0%)	<0.0001	FI, NO, SE
MOD1MOD2BNT3	MOD1MOD2	6093	14356	-8.9% (-17.6%--0.2%)	40.3% (21.4%-59.2%)	<0.0001	DK, FI, SE, NO
BNT1MOD2MOD3	BNT1MOD2	152	271	-3.8% (-8.1%-0.4%)	54.1% (31.3%-76.9%)	0.1871	FI, SE
MOD1BNT2BNT3	MOD1BNT2	55	117	-5.5% (-8.2%--2.8%)	60.1% (43.1%-77.2%)	0.9891	FI, SE
BNT1MOD2BNT3	BNT1MOD2	4532	22434	-11.6% (-27.2%-4.0%)	52.9% (18.4%-87.3%)	<0.0001	FI, NO, SE

MOD1BNT2MOD3	MOD1BNT2	193	764	-15.4% (-42.7%-11.9%)	63.2% (31.1%-95.3%)	0.0077	FI, NO
BNT1BNT2BNT3	BNT1BNT2	126087	207263	-6.0% (-13.5%-1.5%)	34.5% (6.1%-62.9%)	<0.0001	DK, FI, SE, NO
MOD1MOD2MOD3	MOD1MOD2	25697	37485	-7.0% (-15.4%-1.3%)	38.4% (12.4%-64.4%)	<0.0001	DK, FI, SE, NO
Outcome: Hospitalisation							
AZD1AZD2BNT3	AZD1AZD2	<23	250	-0.3% (-0.6%-0.0%)	87.9% (82.0%-93.7%)	<0.0001	FI, SE
AZD1AZD2MOD3	AZD1AZD2	6	139	-0.4% (-6.6%-5.8%)	93.3% (84.6%-102.0%)	1	SE
AZD1BNT2BNT3	AZD1BNT2	13	31	-0.1% (-0.1%-0.0%)	53.7% (12.5%-94.8%)	0.3504	FI, SE
BNT1BNT2MOD3	BNT1BNT2	81	636	-0.3% (-0.5%--0.1%)	91.7% (87.1%-96.2%)	<0.0001	FI, NO, SE
MOD1MOD2BNT3	MOD1MOD2	<25	123	-0.2% (-0.5%-0.0%)	85.8% (76.3%-95.3%)	0.0406	FI, NO, SE
BNT1BNT2BNT3	BNT1BNT2	303	1946	-0.3% (-0.4%--0.1%)	85.0% (82.4%-87.6%)	<0.0001	DK, FI, SE, NO
MOD1MOD2MOD3	MOD1MOD2	<46	192	-0.2% (-0.4%--0.1%)	85.0% (72.1%-97.9%)	0.0001	DK, FI, SE, NO

CI denotes confidence interval, CVE comparative vaccine effectiveness, DK Denmark, FI Finland, NO Norway, RD risk difference, and SE Sweden. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

Similar to 3- vs. 3-dose comparisons (objective 1; weighted analysis), we observed substantial variation in the cumulative incidences of documented covid-19 infection at day 75 of the booster vs. primary schedule comparisons (3- vs. 2-dose) across countries and vaccine schedules (again, likely due to the observed differences in calendar months for the respective studied schedules that were highly correlated to the emergence of the omicron variant, differences in the country-specific background infection rates, and differences in testing strategies). The cumulative incidences of documented covid-19 infection ranged from ≈ 15% to 40% in Denmark, in Finland ≈ 1% to 10%, in Norway ≈ 5% to 40%, and in Sweden ≈ <1% to 30%.

Overall, proportionally fewer booster vaccinated acquired documented infection than the primary schedules vaccinated. However, the comparative VE of the distinct booster schedules varied between countries. Across examined booster schedules, the protective effect of a booster dose against documented infection was generally smaller in Denmark and Sweden, while more pronounced in Finland and Norway. The incidence of severe covid-19 related endpoints (covid-19 related hospitalisation, ICU admission, and death) were low to none for both heterologous and homologous booster vaccinated across all compared schedules and countries. Receiving a booster dose, however, was largely associated with a reduced risk of severe covid-19 related endpoints across all countries.

In Denmark, risk differences of documented infection where heterologous booster schedules were compared with the primary vaccine schedule counterpart ranged from -11.0% to -2.8%, with corresponding cVEs ranging between 5.4% and 32.6%. CVEs for severe covid-19 related outcomes could not be estimated in Denmark.

In Denmark, the risk differences of documented infection where homologous mRNA booster schedules were compared with the primary vaccine schedule counterpart was -0.5% for BNT (cVE of 1.5%) and 1.7% for MOD (cVE of 4.1%). However, cVEs for severe covid-19 related outcomes ranged between 72.4% and 95.4%.

In Finland, risk differences of documented infection where heterologous booster schedules were compared with the primary vaccine schedule counterpart ranged from -6.2% to -2.0 %, with corresponding cVEs ranging between 27.9% and 63.6%. CVEs for severe covid-19 related outcomes ranged between 24.0% and 98.2%.

In Finland, the risk differences of documented infection where homologous mRNA booster schedules were compared with the primary vaccine schedule counterpart was -4.0% for BNT (cVE of 44.0%) and -3.7% for MOD (cVE of 46.2%). CVEs for severe covid-19 related outcomes ranged between 38.2% and 86.4%.

In Norway, risk differences of documented infection where heterologous booster schedules were compared with the primary vaccine schedule counterpart ranged from -30.6% to -0.2%,

with corresponding cVEs ranging between 12.6% and 69.0%. CVEs for severe covid-19 related outcomes ranged between 84.4% and 88.4% (only calculated for two comparisons of hospitalisation risk).

In Norway, the risk differences of documented infection where homologous mRNA booster schedules were compared with the primary vaccine schedule counterpart was -17.3% for BNT (cVE of 70.4%) and -19.8% for MOD (cVE of 67.8%). CVEs for severe covid-19 related outcomes ranged between 85.0% and 94.7%.

In Sweden, risk differences of documented infection where heterologous booster schedules were compared with the primary vaccine schedule counterpart ranged from -5.5% to -1.6% (except one risk difference of 4.6% for MOD1BNT2MOD3 vs MOD1BNT2, but numbers were small [364 vs 364 vaccinated and 8 vs. 6 events, respectively]), with corresponding cVEs ranging between 5.8% and 47.7%. CVEs for severe covid-19 related outcomes ranged between 45.3% and 96.1%.

In Sweden, the risk differences of documented infection where homologous mRNA booster schedules were compared with the primary vaccine schedule counterpart was -2.6% for BNT (cVE of 25.1%) and -2.9% for MOD (cVE of 36.9%). CVEs for severe covid-19 related outcomes ranged between 80.1% and 90.0%.

In meta-analyses, combining country-specific estimates for documented infection where heterologous booster schedules were compared with the primary vaccine schedule counterpart for each country, risk differences ranged from -15.4% to -2.0%, with corresponding cVEs ranging between 30.8% and 63.2%. For hospitalisation, risk differences ranged from -0.4% to -0.1% with cVEs from 53.7% to 91.7%.

In meta-analyses, combining country-specific estimates for documented infection where homologous mRNA booster schedules were compared with the primary vaccine schedule counterpart for each country, risk differences were -6.0% for BNT and -7.0% for MOD, with corresponding cVEs of 34.5% and 38.4%, respectively. For hospitalisation, risk differences were -0.3% for BNT (cVE 85.0%) and -0.2 for MOD (cVE 85.0%).

However, between countries the results were heterogeneous (statistically significant tests of heterogeneity).

10.3 Other analyses

10.3.1 Assessment of comparative vaccine effectiveness for selected schedules in the periods of specific covid-19 variants of concern (objective 3)

Our pre-specified analysis plan in the study protocol aimed at assessing the comparative effectiveness against different covid-19 variants of predominance. However, because of the strong correlation between calendar time and variant of predominance, and calendar time and period of use of the specific vaccination schedules, we were not able to conduct covid-19 variant stratified analyses of the heterologous booster schedule comparisons with 1) homologous booster schedules as well as 2) primary schedules. The booster schedules were primarily administered during the period of omicron predominance. To increase the specificity of the results even further in terms of capturing the omicron variant covid-19 endpoints, we conducted stratified analyses where we only included follow-up time after the country-specific dates where the omicron variant was estimated to account for at least 90% of all covid-19 infections in the country. Figures 26 to 31 present the cumulative incidence curves for the covid-19 endpoints for the weighted analyses (3-dose vs. 3-dose) and Figures 32 to 36 present the curves the matched analysis (3- vs. 2-dose). The results are provided in Tables 7 to 11: Table 7 and 8 show the country-specific results for the weighted and matched analyses, respectively, while the meta-analysis results are presented in Table 9 and 10.

Figure 26. Country-specific adjusted cumulative incidence curves of documented covid-19 infection for weighted analysis comparing heterologous AZD-mRNA booster and homologous mRNA booster vaccine schedules during period of omicron predominance

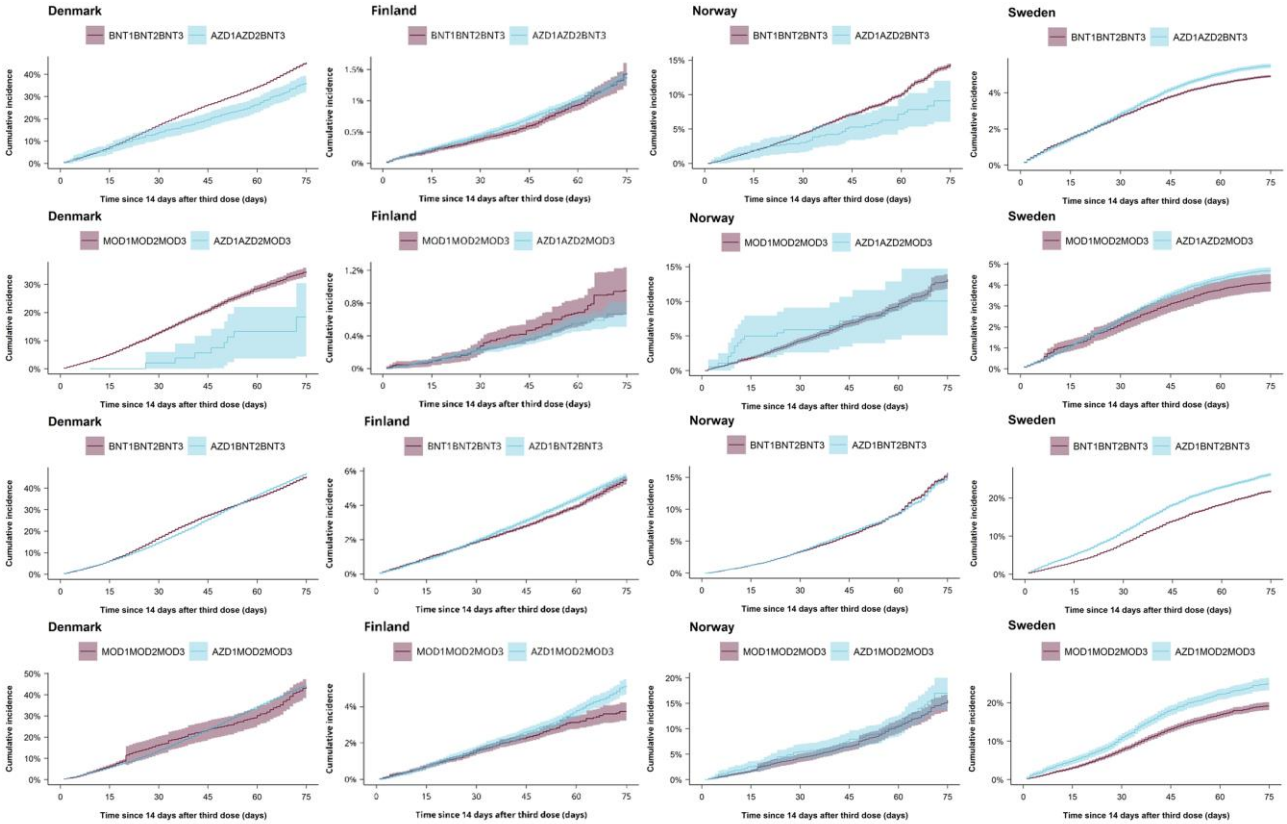
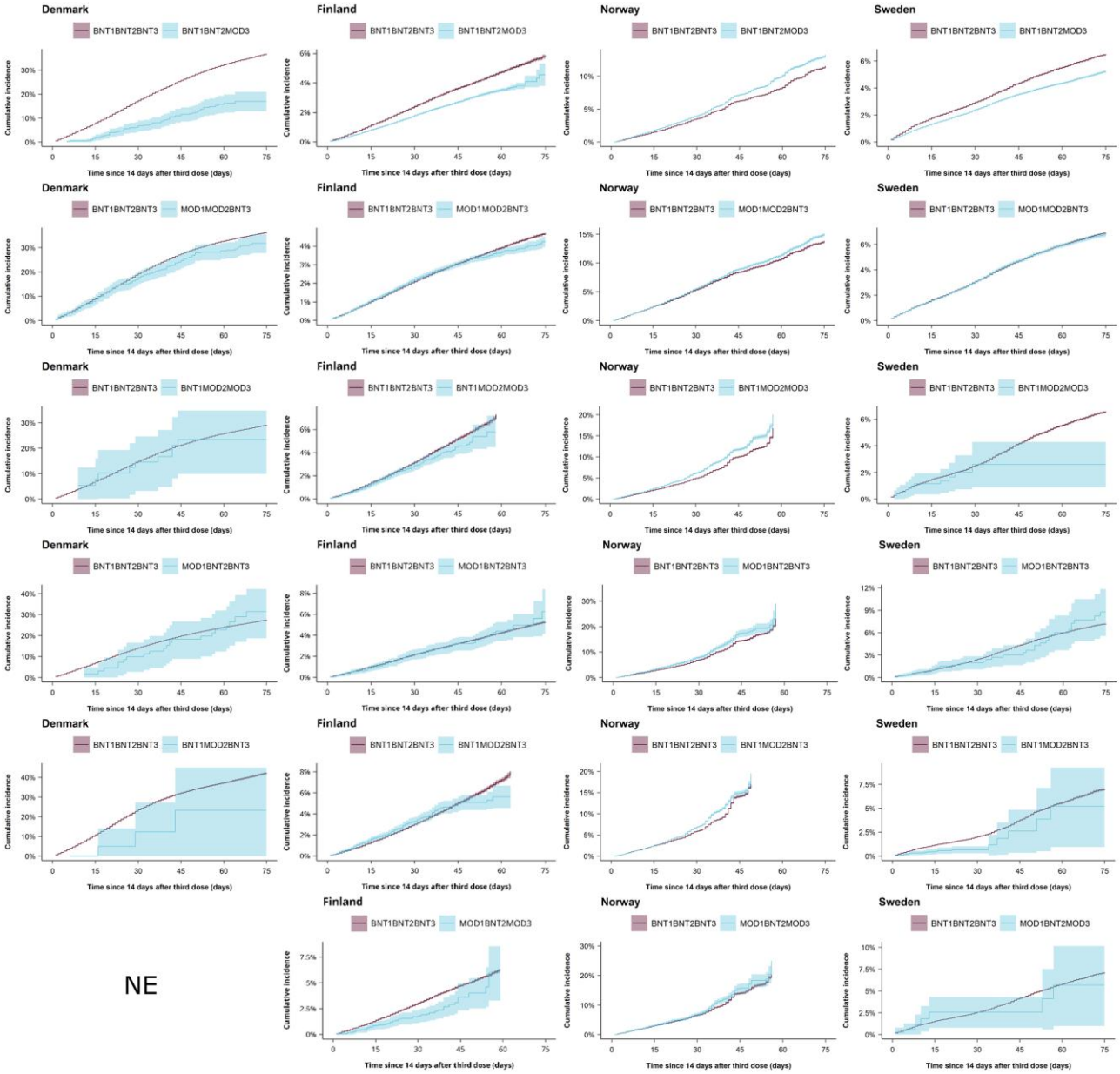
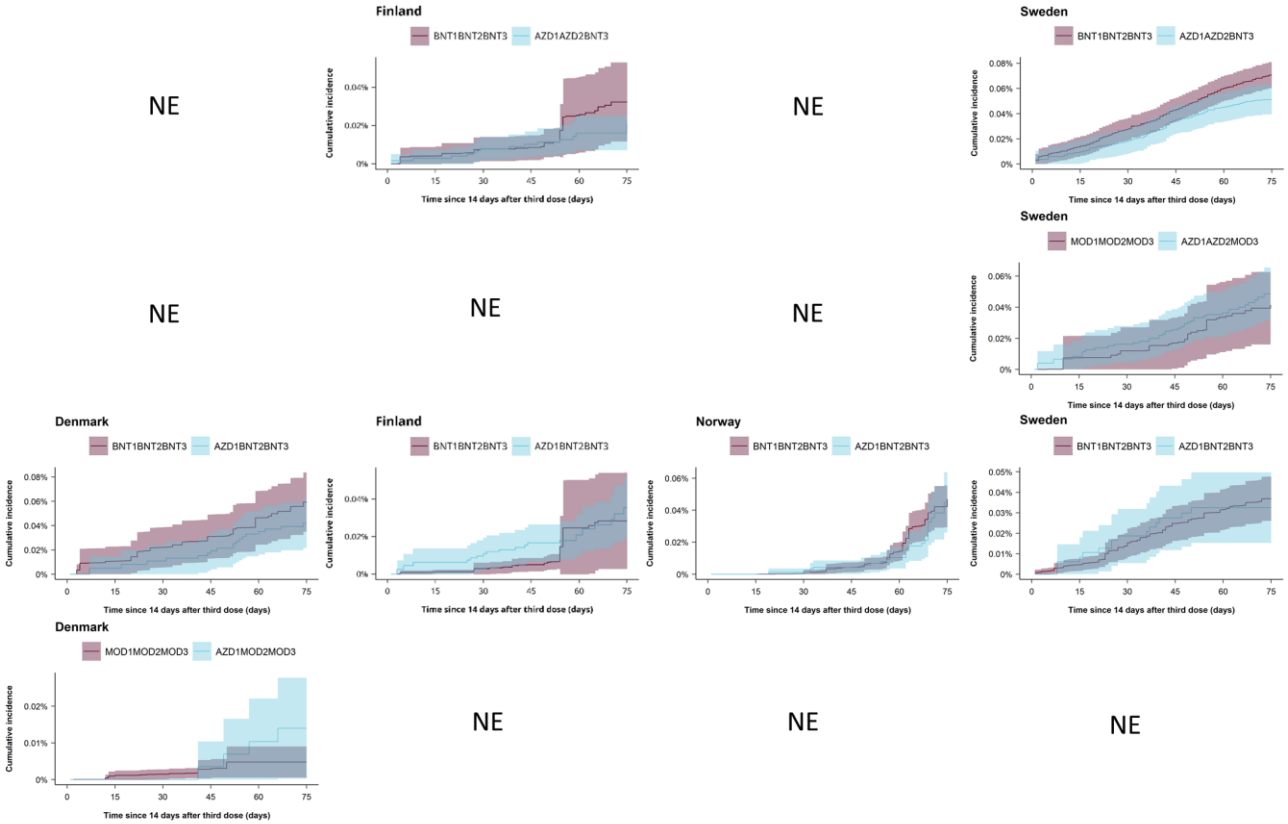


Figure 27. Country-specific adjusted cumulative incidence curves of documented covid-19 infection for weighted analysis comparing heterologous and homologous mRNA booster vaccine schedules during period of omicron predominance



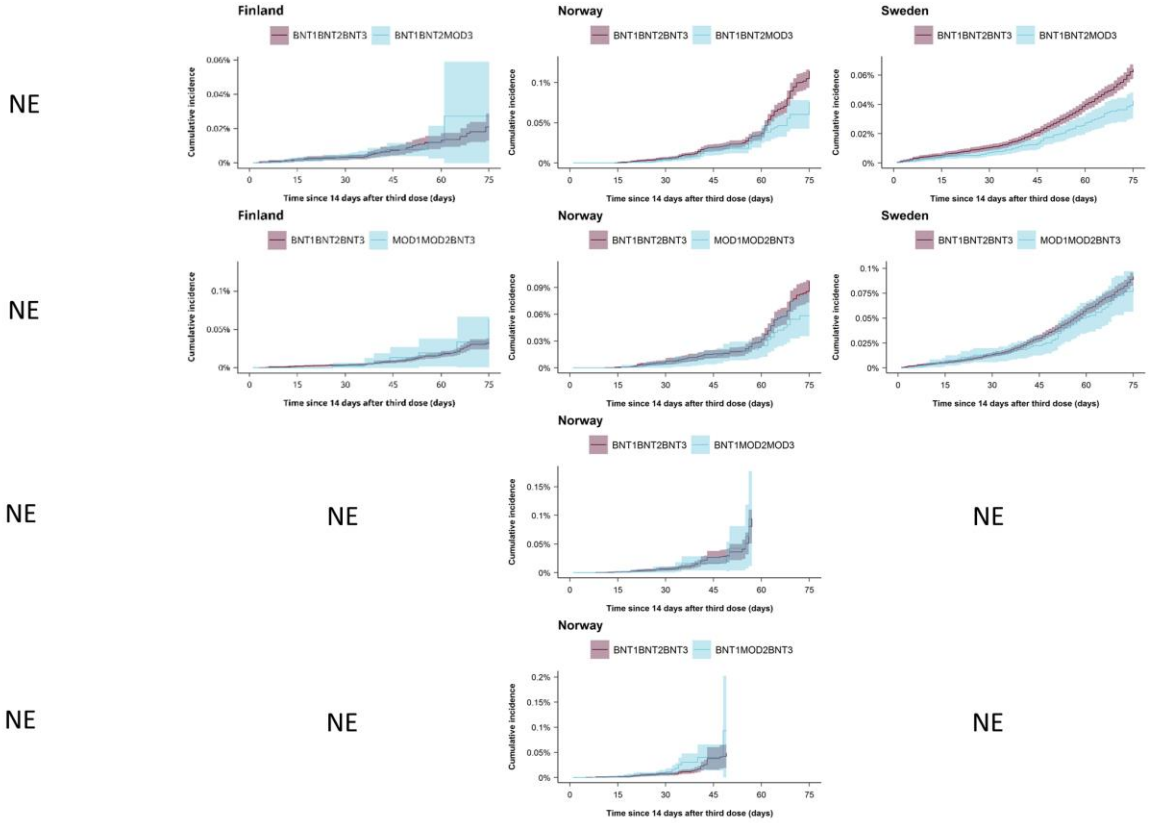
NE denotes not estimated.

Figure 28. Country-specific adjusted cumulative incidence curves of covid-19 hospitalisation for weighted analysis comparing heterologous AZD-mRNA booster and homologous mRNA booster vaccine schedules during period of omicron predominance



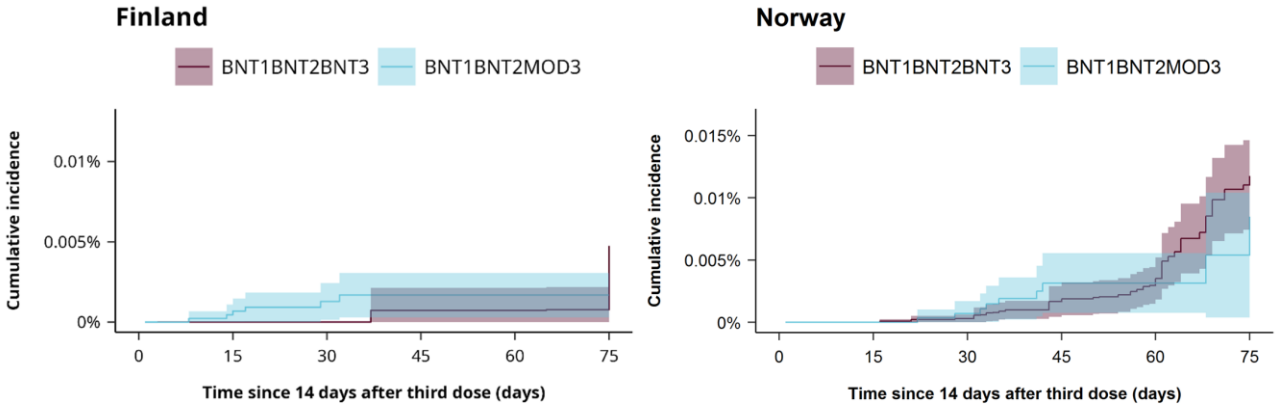
NE denotes not estimated.

Figure 29. Country-specific adjusted cumulative incidence curves of covid-19 hospitalisation for weighted analysis comparing heterologous and homologous mRNA booster vaccine schedules during period of omicron predominance



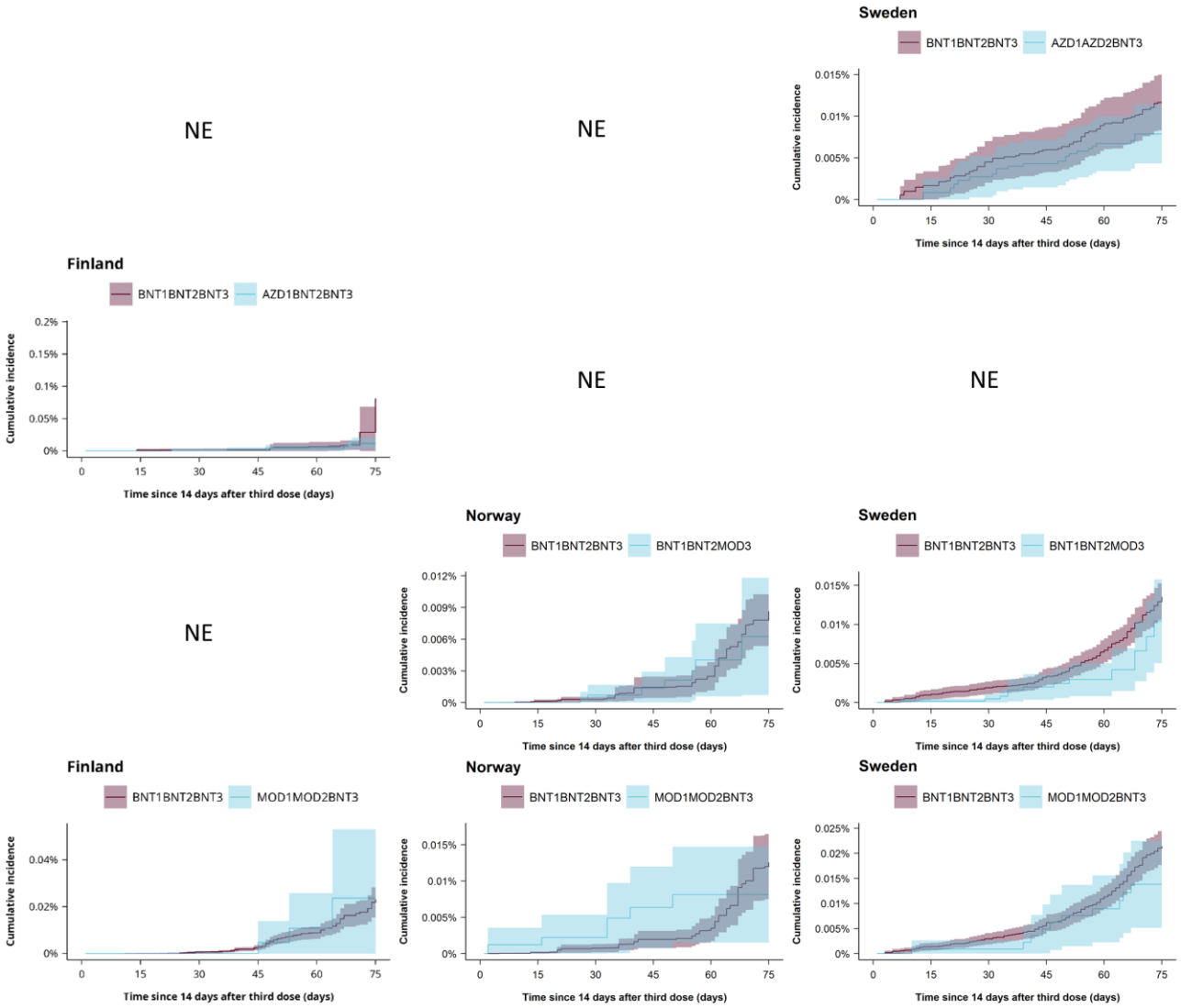
NE denotes not estimated.

Figure 30. Country-specific adjusted cumulative incidence curves of covid-19 related intensive care unit admission for weighted analysis comparing heterologous and homologous booster vaccine schedules during period of omicron predominance



NE denotes not estimated.

Figure 31. Country-specific adjusted cumulative incidence curves of covid-19 related death for weighted analysis comparing heterologous and homologous booster vaccine schedules during period of omicron predominance



NE denotes not estimated.

Figure 32. Country-specific cumulative incidence curves of documented covid-19 infection for matched analysis comparing heterologous AZD-mRNA booster schedules with the primary schedule counterpart during period of omicron predominance

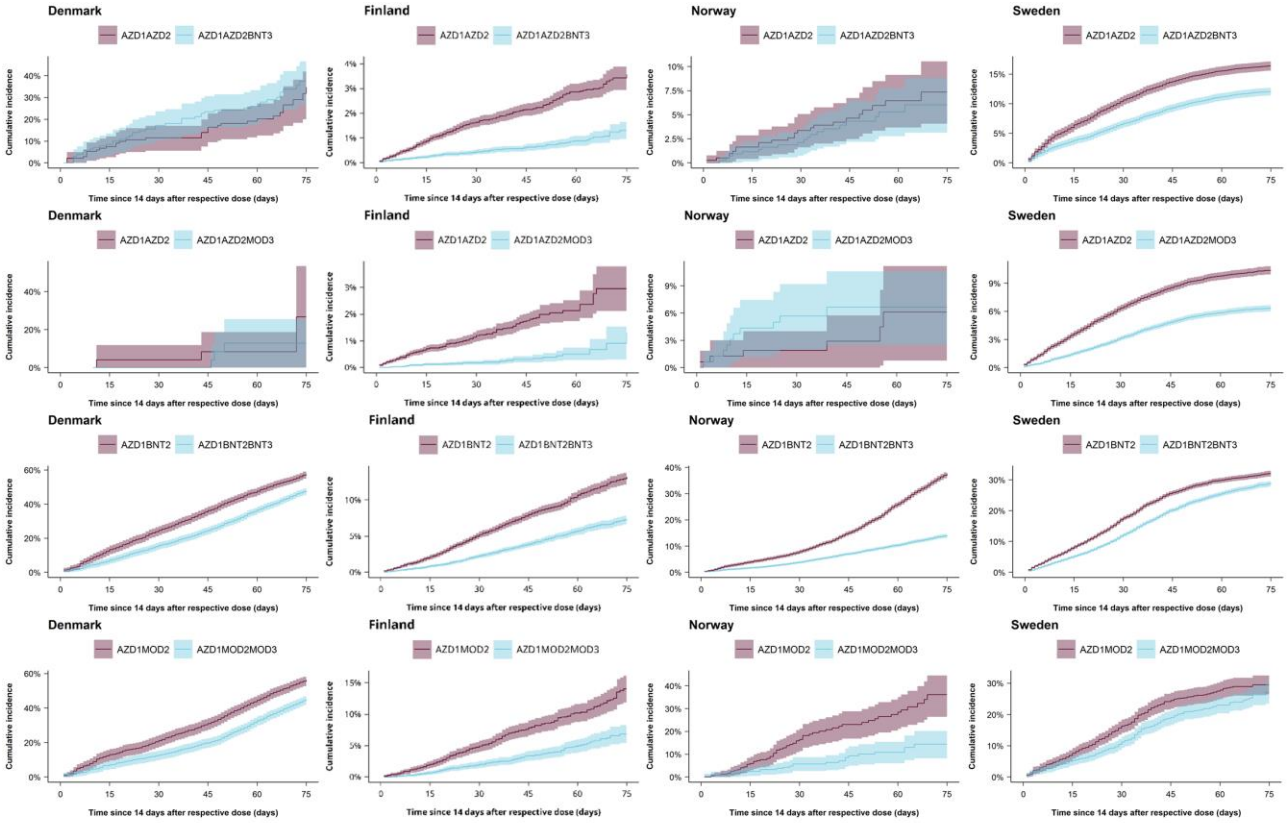
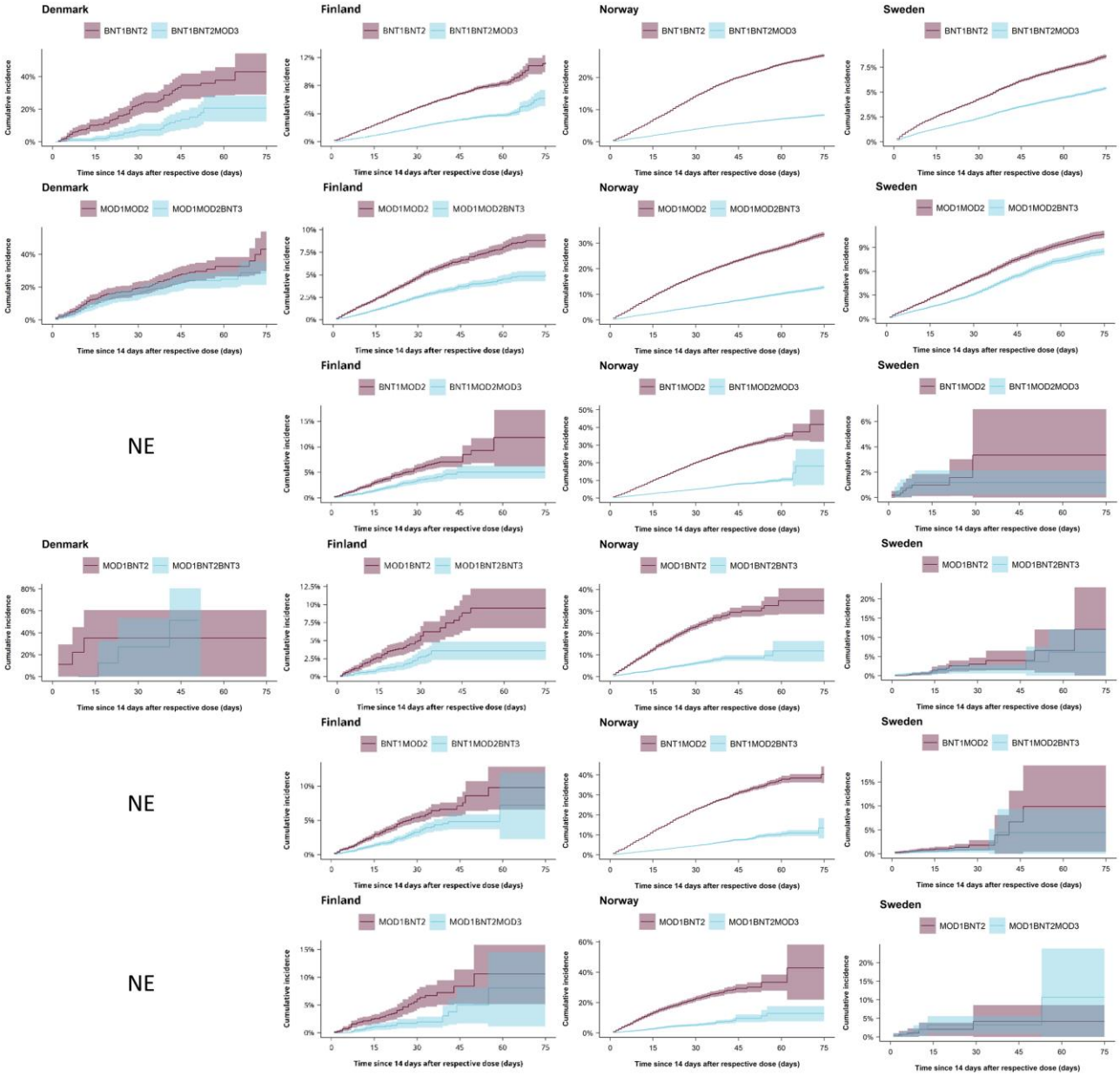


Figure 33. Country-specific cumulative incidence curves of documented covid-19 infection for matched analysis comparing heterologous mRNA booster schedules with the primary schedule counterpart during period of omicron predominance



NE denotes not estimated.

Figure 34. Country-specific cumulative incidence curves of documented covid-19 infection for matched analysis comparing homologous mRNA booster schedules with the primary schedule counterpart during period of omicron predominance

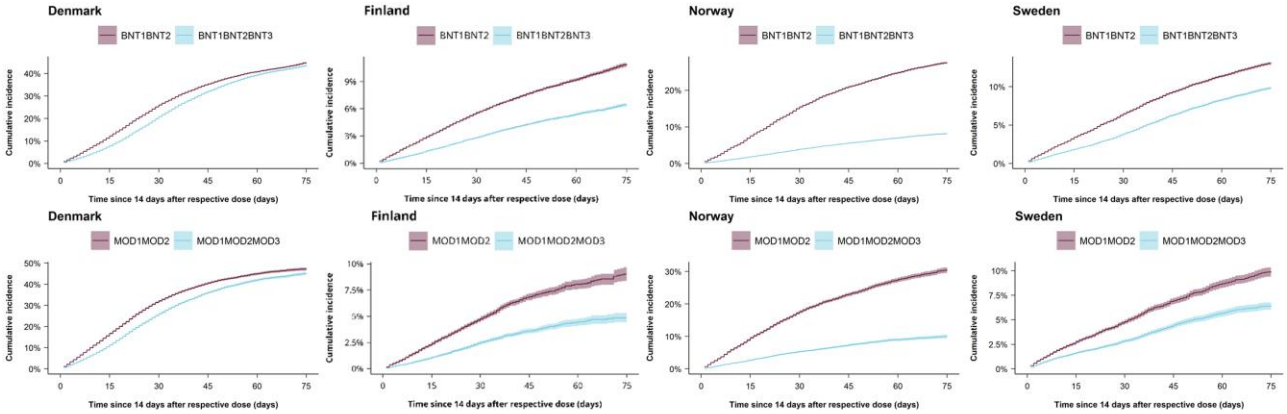
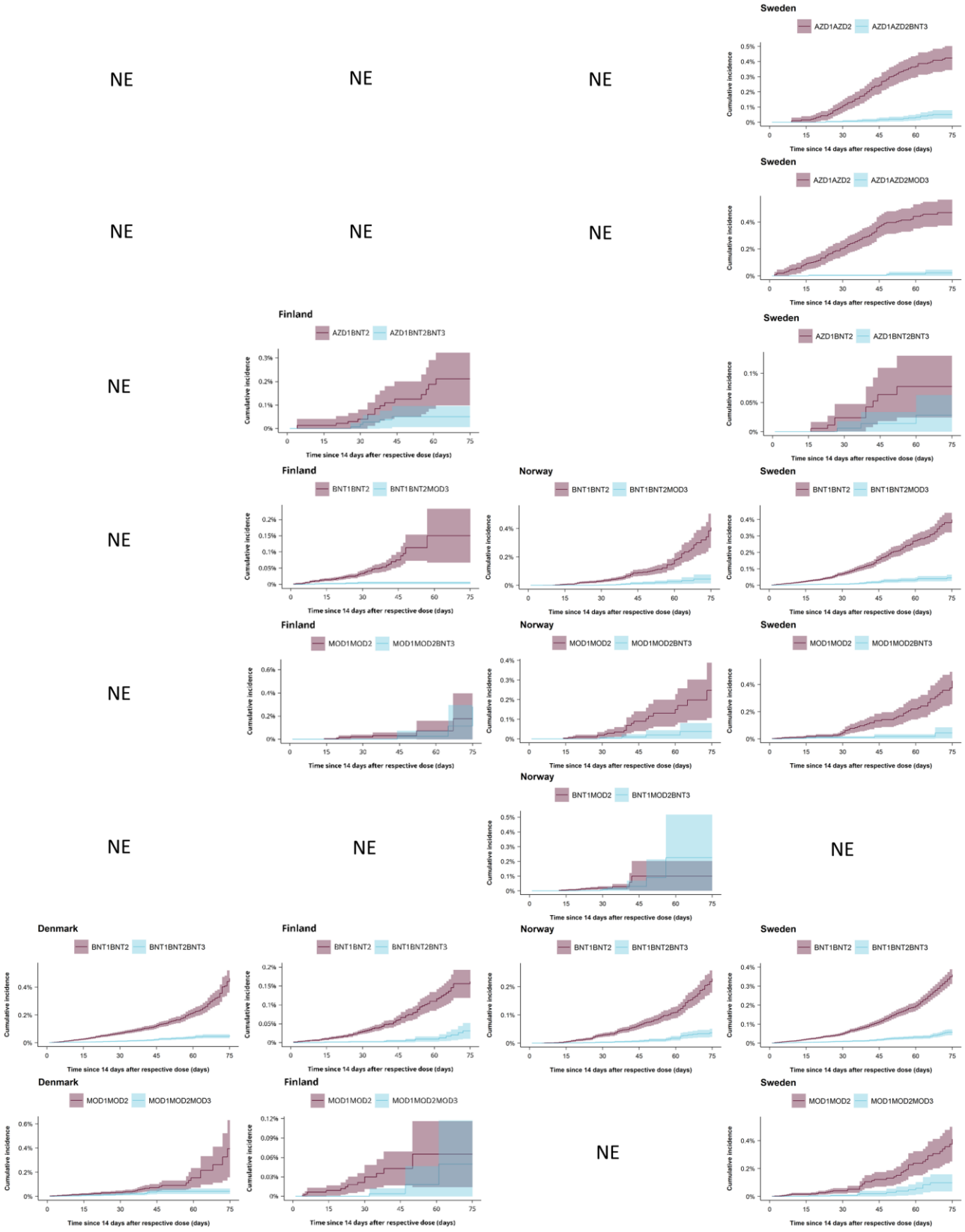
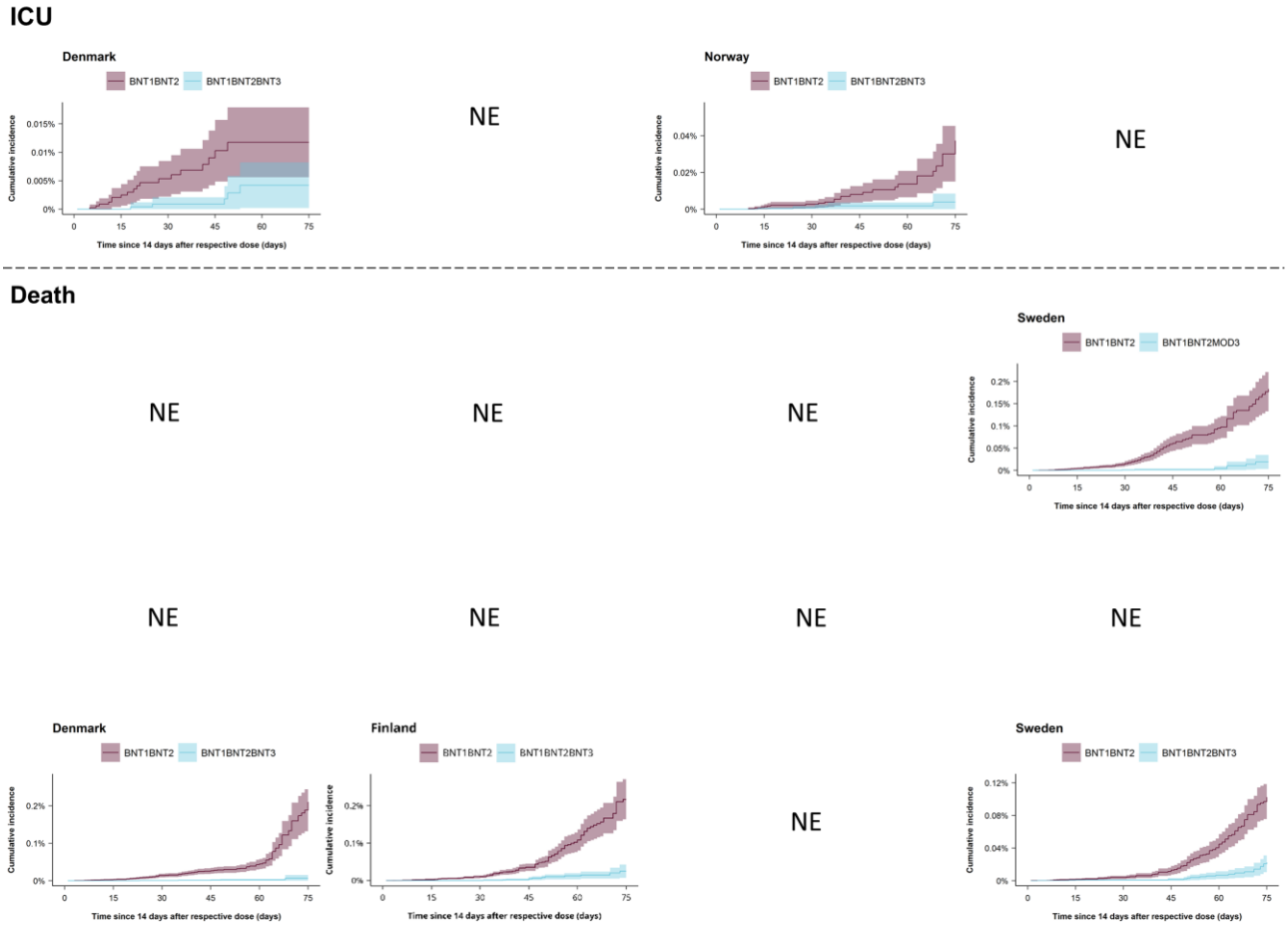


Figure 35. Country-specific cumulative incidence curves of covid-19 hospitalisation for matched analysis comparing heterologous or homologous booster schedules with the primary schedule counterpart during period of omicron predominance



NE denotes not estimated.

Figure 36. Country-specific cumulative incidence curves of covid-19 related intensive care unit admission and death for matched analysis comparing homologous booster schedules with the primary schedule counterpart during period of omicron predominance



NE denotes not estimated.

Table 7. Country-specific associations between covid-19 endpoints and studied heterologous booster vaccine schedules compared with the homologous booster schedules during period of omicron predominance.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
AZD1AZD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	229 / 106.7	517302 / 210481.9	-9.1% (-12.9% - -5.3%)	20.0% (11.7% - 28.4%)
Finland	984 / 15450.9	2361 / 47961.4	-0.1% (-0.3% - 0.2%)	4.0% (-10.1% - 18.0%)
Norway	41 / 92.0	68585 / 166278.5	-5.4% (-8.4% - -2.4%)	37.2% (16.6% - 57.8%)
Sweden	12843 / 48515.0	58756 / 152425.3	0.6% (0.4% - 0.7%)	-11.8% (-14.8% - -8.9%)
Hospitalisation				
Denmark	0 / 114.4	506 / 227582.4		
Finland	14 / 15484.5	51 / 48041.1	0.0% (0.0% - 0.0%)	35.5% (-21.8% - 92.8%)
Norway	<5 / 92.3	497 / 162461.8	0.3% (-0.5% - 1.2%)	
Sweden	129 / 49118.2	459 / 155561.6	0.0% (0.0% - 0.0%)	27.5% (7.6% - 47.4%)
ICU admission				
Denmark	0 / 114.4	39 / 227596.7		
Finland	<5 / 15484.9	<5 / 48042.4	0.0% (0.0% - 0.0%)	-44.7% (-3736045837.7% - 100%)
Norway	0 / 92.3	58 / 162462.5		
Sweden	0 / 49123.0	0 / 155578.0	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 120.2	46 / 241932.7		
Finland	0 / 15512.4	25 / 48107.7		
Norway	0 / 93.5	55 / 164026.8		
Sweden				
AZD1AZD2MOD3 vs MOD1MOD2MOD3				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Documented infection				
Denmark	8 / 8.3	75144 / 24196.7	-16.1% (-29.2% - -3.0%)	46.7% (9.0% - 84.4%)
Finland	175 / 5651.2	186 / 4701.5	-0.3% (-0.6% - 0.0%)	30.1% (3.6% - 56.6%)
Norway	17 / 29.3	10959 / 16424.1	-3.1% (-8.1% - 1.8%)	23.8% (-13.2% - 60.7%)
Sweden	3915 / 16218.7	3707 / 12528.7	0.6% (0.1% - 1.0%)	-13.8% (-25.9% - -1.7%)
Hospitalisation				
Denmark	0 / 8.7	44 / 27090.6		
Finland	<5 / 5656.8	<5 / 4707.3	0.0% (-0.1% - 0.0%)	59.4% (-37.9% - 100%)
Norway	0 / 29.8	31 / 16743.8		
Sweden	38 / 16375.9	28 / 12723.0	0.0% (0.0% - 0.0%)	-17.3% (-95.7% - 61.1%)
ICU admission				
Denmark	0 / 8.7	3 / 27091.9		
Finland	0 / 5656.8	0 / 4707.3	0.0% (0.0% - 0.0%)	
Norway	0 / 29.8	<5 / 16743.9		
Sweden	0 / 16377.1	0 / 12723.9	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 8.9	6 / 29320.2		
Finland	<5 / 5661.2	0 / 4711.4	0.0% (0.0% - 0.0%)	
Norway	0 / 30.2	<5 / 17046.7		
Sweden				
AZD1BNT2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	23844 / 7275.4	414234 / 156233.3	1.5% (0.9% - 2.1%)	-3.3% (-4.6% - -2.0%)
Finland	4043 / 14032.0	30960 / 90433.8	0.2% (-0.1% - 0.5%)	-3.1% (-8.7% - 2.4%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	10967 / 14713.4	54798 / 94786.2	-0.4% (-0.8% - 0.0%)	2.4% (-0.1% - 4.8%)
Sweden	10752 / 6894.9	63323 / 145842.6	4.4% (3.8% - 4.9%)	-20.0% (-22.6% - -17.4%)
Hospitalisation				
Denmark	18 / 8111.6	366 / 173397.9	0.0% (0.0% - 0.0%)	29.4% (-15.4% - 74.2%)
Finland	21 / 14169.2	41 / 91381.4	0.0% (0.0% - 0.0%)	-24.4% (-150.6% - 100%)
Norway	25 / 15023.1	258 / 96272.8	0.0% (0.0% - 0.0%)	4.4% (-45.8% - 54.6%)
Sweden	14 / 7315.4	281 / 148817.3	0.0% (0.0% - 0.0%)	11.7% (-41.8% - 65.1%)
ICU admission				
Denmark	0 / 8112.1	23 / 173408.0		
Finland	<5 / 14169.6	<5 / 91382.5	0.0% (0.0% - 0.0%)	
Norway	<5 / 15023.1	26 / 96273.2	0.0% (0.0% - 0.0%)	28.7% (-77.7% - 100%)
Sweden	0 / 7316.0	0 / 148827.9	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 8712.8	25 / 185154.5		
Finland	7 / 14277.2	14 / 91951.7	-0.1% (-0.2% - 0.0%)	85.9% (63.7% - 100%)
Norway	<5 / 15281.9	16 / 97568.4	0.0% (0.0% - 0.0%)	21.9% (-162.6% - 100%)
Sweden				
AZD1MOD2MOD3 vs MOD1MOD2MOD3				
Documented infection				
Denmark	13053 / 4220.7	54891 / 18868.7	0.9% (-3.6% - 5.4%)	-2.1% (-12.6% - 8.4%)
Finland	625 / 2531.7	2851 / 11105.1	1.4% (0.8% - 2.1%)	-38.1% (-59.9% - -16.4%)
Norway	119 / 149.9	10078 / 12448.1	1.4% (-2.2% - 4.9%)	-8.8% (-32.0% - 14.4%)
Sweden	846 / 563.9	4155 / 11813.5	5.8% (3.8% - 7.7%)	-30.2% (-41.3% - -19.1%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Hospitalisation				
Denmark	4 / 4662.1	29 / 21889.2	0.0% (0.0% - 0.0%)	
Finland	0 / 2551.5	<5 / 11186.8		
Norway	0 / 153.2	18 / 12746.5		
Sweden	<3 / 596.5	19 / 12040.3	0.0% (-0.1% - 0.1%)	26.4% (-141.5% - 100%)
ICU admission				
Denmark	0 / 4662.1	3 / 21890.1		
Finland	0 / 2551.5	0 / 11186.9	0.0% (0.0% - 0.0%)	
Norway	0 / 153.2	0 / 12746.5		
Sweden	0 / 596.5	0 / 12041.1	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 4952.2	3 / 23537.1		
Finland	<5 / 2565.6	0 / 11228.2	0.0% (0.0% - 0.0%)	
Norway	0 / 156.1	0 / 13031.0		
Sweden				
BNT1BNT2MOD3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	67 / 68.1	580653 / 285991.3	-19.8% (-23.9% - -15.8%)	53.8% (42.8% - 64.8%)
Finland	9059 / 41126.9	35063 / 135419.5	-1.3% (-2.1% - -0.5%)	22.0% (9.0% - 35.0%)
Norway	22855 / 37121.8	61454 / 165998.0	1.7% (1.5% - 1.9%)	-14.7% (-16.7% - -12.6%)
Sweden	17858 / 63874.3	66697 / 186663.1	-1.3% (-1.4% - -1.1%)	19.3% (17.8% - 20.8%)
Hospitalisation				
Denmark	0 / 70.4	936 / 306929.8		
Finland	23 / 41378.8	95 / 136474.5	0.0% (0.0% - 0.0%)	-32.1% (-191.8% - 100%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	63 / 37745.2	544 / 167469.0	0.0% (-0.1% - 0.0%)	33.6% (12.9% - 54.4%)
Sweden	95 / 64907.4	709 / 189673.1	0.0% (0.0% - 0.0%)	34.0% (18.1% - 49.8%)
ICU admission				
Denmark	0 / 70.4	70 / 306955.7		
Finland	6 / 41379.1	<5 / 136476.7	0.0% (0.0% - 0.0%)	64.5% (-1.5% - 100%)
Norway	8 / 37745.2	59 / 167469.5	0.0% (0.0% - 0.0%)	27.8% (-42.9% - 98.5%)
Sweden	0 / 64911.7	0 / 189697.0	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 72.2	127 / 322585.7		
Finland	0 / 41487.2	36 / 137098.2		
Norway	7 / 38310.9	67 / 168860.0	0.0% (0.0% - 0.0%)	27.5% (-40.5% - 95.5%)
Sweden				
MOD1MOD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	215 / 103.1	586998 / 304529.9	-4.6% (-8.4% - -0.7%)	12.6% (1.9% - 23.2%)
Finland	1534 / 6296.0	37771 / 154446.1	-0.4% (-0.7% - -0.1%)	9.0% (2.6% - 15.3%)
Norway	10124 / 13306.3	70657 / 190310.5	1.3% (0.9% - 1.6%)	-9.3% (-11.9% - -6.8%)
Sweden	5744 / 16309.7	74728 / 202021.2	-0.1% (-0.3% - 0.0%)	2.0% (-0.6% - 4.6%)
Hospitalisation				
Denmark	0 / 111.2	1211 / 325568.4		
Finland	7 / 6338.8	144 / 155579.4	0.0% (0.0% - 0.1%)	-88.5% (-2053305166.0% - 100%)
Norway	28 / 13598.5	656 / 192172.3	0.0% (-0.1% - 0.0%)	39.9% (14.3% - 65.6%)
Sweden	58 / 16586.0	785 / 205396.6	0.0% (0.0% - 0.0%)	12.0% (-12.0% - 36.1%)
ICU admission				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Denmark	0 / 111.2	82 / 325602.1		
Finland	0 / 6338.8	5 / 155582.9		
Norway	<5 / 13598.6	69 / 192172.9	0.0% (0.0% - 0.0%)	10.8% (-104.1% - 100%)
Sweden	0 / 16588.0	0 / 205422.8	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 117.7	228 / 341336.0		
Finland	<5 / 6358.6	90 / 156256.1	0.0% (0.0% - 0.0%)	-2.7% (-133.7% - 100%)
Norway	6 / 13863.7	105 / 193789.7	0.0% (0.0% - 0.0%)	35.3% (-22.2% - 92.8%)
Sweden				
BNT1MOD2MOD3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	10 / 6.4	573968 / 297012.1	-5.8% (-18.2% - 6.6%)	19.9% (-22.6% - 62.4%)
Finland				
Norway	6995 / 7980.9	30755 / 47764.3	3.2% (2.2% - 4.3%)	-19.3% (-25.6% - -13.0%)
Sweden	12 / 48.2	66067 / 177793.9	-4.0% (-5.7% - -2.3%)	60.4% (34.4% - 86.3%)
Hospitalisation				
Denmark	<3 / 6.8	1169 / 321102.9	2.3% (-2.5% - 7.2%)	
Finland				
Norway	12 / 8184.6	92 / 48607.2	0.0% (-0.1% - 0.1%)	-0.2% (-94.5% - 94.2%)
Sweden	0 / 48.9	534 / 179785.9		
ICU admission				
Denmark	0 / 6.8	79 / 321135.3		
Finland				
Norway	<5 / 8184.6	5 / 48607.5	0.0% (0.0% - 0.0%)	75.6% (15.1% - 100%)
Sweden	0 / 48.9	0 / 179804.6	0.0% (0.0% - 0.0%)	

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Death				
Denmark	0 / 6.9	216 / 336846.8		
Finland				
Norway	0 / 8365.2	<5 / 49348.5		
Sweden				
MOD1BNT2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	20 / 11.1	595378 / 306951.1	3.9% (-7.8% - 15.6%)	-14.1% (-56.5% - 28.3%)
Finland	119 / 443.9	37192 / 146823.3	1.0% (-1.1% - 3.1%)	-19.1% (-59.5% - 21.2%)
Norway	1064 / 930.9	38236 / 55002.8	6.2% (0.3% - 12.1%)	-27.0% (-52.8% - -1.2%)
Sweden	41 / 119.7	74260 / 200193.9	1.5% (-1.6% - 4.7%)	-21.3% (-64.7% - 22.2%)
Hospitalisation				
Denmark	0 / 11.7	1220 / 328308.9		
Finland	0 / 447.3	114 / 147934.3		
Norway	0 / 964.2	99 / 56077.6		
Sweden	0 / 121.9	731 / 203560.9		
ICU admission				
Denmark	0 / 11.7	83 / 328342.9		
Finland	0 / 447.3	<5 / 147937.0		
Norway	0 / 964.2	7 / 56078.0		
Sweden	0 / 121.9	0 / 203585.6	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 12.0	228 / 344332.5		
Finland	0 / 449.2	58 / 148591.5		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	0 / 995.1	5 / 57024.6		
Sweden				
BNT1MOD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	3 / 2.3	584116 / 294224.6	-19.0% (-44.5% - 6.5%)	44.9% (-15.5% - 100%)
Finland				
Norway	10660 / 12518.7	32303 / 43862.6	1.4% (-0.1% - 2.9%)	-7.8% (-16.0% - 0.4%)
Sweden	19 / 142.3	52427 / 123389.4	-1.8% (-6.0% - 2.3%)	26.0% (-33.1% - 85.2%)
Hospitalisation				
Denmark	0 / 2.5	1062 / 315280.9		
Finland				
Norway	21 / 12837.2	69 / 44793.7	0.0% (-0.1% - 0.2%)	-92.4% (-336.5% - 100%)
Sweden	0 / 143.7	161 / 123056.9		
ICU admission				
Denmark	0 / 2.5	73 / 315310.5		
Finland				
Norway	<5 / 12837.3	5 / 44794.0	0.0% (0.0% - 0.0%)	91.3% (69.0% - 100%)
Sweden	0 / 143.7	0 / 123063.7	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 2.7	168 / 331071.9		
Finland				
Norway	<5 / 13113.8	<5 / 45628.6	0.0% (0.0% - 0.0%)	-6.6% (-248.1% - 100%)
Sweden				
MOD1BNT2MOD3 vs BNT1BNT2BNT3				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Documented infection				
Denmark	0 / 1.6	564709 / 296644.2		
Finland				
Norway	649 / 612.5	32573 / 50075.2	2.9% (-2.4% - 8.1%)	-12.9% (-36.6% - 10.7%)
Sweden	10 / 27.2	67166 / 184851.6	-1.4% (-6.0% - 3.1%)	20.1% (-44.2% - 84.4%)
Hospitalisation				
Denmark	0 / 1.6	1157 / 316793.1		
Finland				
Norway	<5 / 638.1	100 / 51983.6	-0.1% (-0.1% - 0.0%)	74.6% (22.5% - 100%)
Sweden	0 / 27.7	655 / 187889.6		
ICU admission				
Denmark	0 / 1.6	78 / 316825.1		
Finland				
Norway	0 / 638.1	7 / 51983.9		
Sweden	0 / 27.7	0 / 187911.9	0.0% (0.0% - 0.0%)	
Death				
Denmark	0 / 1.6	195 / 331931.8		
Finland				
Norway	0 / 659.0	6 / 52791.9		
Sweden				

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).

Table 8. Country-specific associations between covid-19 endpoints and studied heterologous and homologous booster vaccine schedules as compared with the matched primary schedule counterpart during period of omicron predominance.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
AZD1AZD2BNT3 vs AZD1AZD2				
Documented infection				
Denmark	41 / 19.3	30 / 19.0	1.4% (-1.3% - 4.1%)	
Finland	121 / 2141.5	400 / 2115.1	-2.3% (-2.9% - -1.6%)	63.1% (51.9% - 74.2%)
Norway	19 / 57.5	23 / 57.5		
Sweden	2906 / 4788.4	3676 / 4546.3	0.7% (0.4% - 1.0%)	
Hospitalisation				
Denmark				
Finland	<5 / 2200.2	31 / 2137.6	-0.2% (-0.3% - -0.1%)	93.7% (83.8% - 100%)
Norway				
Sweden	14 / 4952.1	119 / 4700.0	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark				
Finland	0 / 2201.2	8 / 2138.5		
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 2256.8	16 / 2182.7		
Norway				
Sweden	<3 / 5089.5	26 / 4877.4	0.0% (0.0% - 0.0%)	
AZD1AZD2MOD3 vs AZD1AZD2				
Documented infection				
Denmark	3 / 3.7	3 / 3.7	0.0% (0.0% - 0.0%)	
Finland	39 / 1385.8	208 / 1363.8	-1.7% (-3.0% - -0.3%)	54.8% (16.9% - 92.8%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	10 / 20.0	6 / 20.0		
Sweden	1426 / 3938.8	2258 / 3765.0	0.3% (0.1% - 0.4%)	
Hospitalisation				
Denmark				
Finland	0 / 1424.2	21 / 1376.0		
Norway				
Sweden	4 / 4036.6	102 / 3863.4	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark				
Finland	0 / 1425.0	5 / 1376.6		
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 1473.9	10 / 1406.5	-0.1% (-0.2% - 0.0%)	74.6% (20.2% - 100%)
Norway				
Sweden				
AZD1BNT2BNT3 vs AZD1BNT2				
Documented infection				
Denmark	1477 / 427.5	1346 / 317.8	-5.0% (-13.8% - 3.7%)	28.7% (4.8% - 52.7%)
Finland	566 / 1601.0	1049 / 1536.7	-5.9% (-6.9% - -4.9%)	44.6% (39.0% - 50.2%)
Norway	1341 / 1896.6	3278 / 1699.2	3.8% (1.3% - 6.3%)	
Sweden	3529 / 1989.0	3976 / 1830.9	2.0% (1.3% - 2.6%)	
Hospitalisation				
Denmark	<3 / 506.3	0 / 372.8	0.0% (0.0% - 0.1%)	
Finland	5 / 1665.2	15 / 1584.6	-0.2% (-0.3% - 0.0%)	73.1% (42.3% - 100%)
Norway	<5 / 2074.0	7 / 1816.1	0.0% (0.0% - 0.0%)	
Sweden	3 / 2163.2	9 / 2013.8	0.0% (0.0% - 0.0%)	
ICU admission				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Denmark				
Finland	<5 / 1665.6	<5 / 1585.0	0.0% (-0.1% - 0.0%)	12.4% (-162.5% - 100%)
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 1717.0	5 / 1647.3		
Norway				
Sweden				
AZD1MOD2MOD3 vs AZD1MOD2				
Documented infection				
Denmark	820 / 261.2	840 / 205.7	-5.4% (-16.7% - 5.9%)	-13.9% (-80.2% - 52.3%)
Finland	110 / 351.4	230 / 338.6	-7.2% (-9.9% - -4.6%)	51.0% (37.6% - 64.4%)
Norway	23 / 31.1	58 / 27.4		
Sweden	272 / 173.9	323 / 160.5	2.1% (0.6% - 3.5%)	
Hospitalisation				
Denmark	<3 / 301.8	<3 / 240.2	0.0% (0.0% - 0.0%)	
Finland	0 / 362.0	5 / 347.6		
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 362.0	<5 / 347.7		
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 371.5	<5 / 358.5		
Norway				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden				
BNT1BNT2MOD3 vs BNT1BNT2				
Documented infection				
Denmark	26 / 24.4	63 / 21.5		
Finland	4539 / 18387.7	10703 / 18020.4	-5.1% (-6.9% - -3.3%)	44.8% (32.7% - 57.0%)
Norway	7300 / 15397.6	25150 / 14215.5	0.7% (0.4% - 1.1%)	
Sweden	8376 / 27887.1	14613 / 26970.2	0.6% (0.4% - 0.8%)	
Hospitalisation				
Denmark				
Finland	10 / 19397.4	88 / 18528.0	-0.1% (-0.2% - -0.1%)	96.4% (92.9% - 99.8%)
Norway	15 / 16801.8	101 / 15388.7	0.0% (0.0% - 0.1%)	
Sweden	42 / 30368.9	306 / 28544.3	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark				
Finland	<5 / 19400.6	9 / 18530.8	0.0% (0.0% - 0.0%)	81.2% (26.2% - 100%)
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 20817.5	44 / 19506.8	-0.6% (-1.1% - 0.0%)	99.5% (97.6% - 100%)
Norway				
Sweden	8 / 33844.0	107 / 31655.8	0.0% (0.0% - 0.0%)	
MOD1MOD2BNT3 vs MOD1MOD2				
Documented infection				
Denmark	88 / 45.1	106 / 40.3	-7.6% (-20.7% - 5.6%)	56.7% (10.6% - 100%)
Finland	797 / 2687.6	1508 / 2645.3	-3.9% (-5.0% - -2.9%)	43.8% (34.8% - 52.8%)
Norway	2710 / 4143.9	8270 / 3741.7	1.0% (0.6% - 1.4%)	
Sweden	2286 / 5474.8	3263 / 5298.7	0.9% (0.5% - 1.3%)	

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Hospitalisation				
Denmark				
Finland	<5 / 2806.5	8 / 2710.2	0.1% (-0.3% - 0.5%)	
Norway	<5 / 4722.3	22 / 4158.8	0.0% (0.0% - 0.0%)	
Sweden	9 / 5925.5	56 / 5610.2	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark				
Finland	0 / 2806.9	0 / 2710.4	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	<5 / 2942.0	9 / 2815.4	-0.3% (-0.7% - 0.1%)	70.4% (-29.6% - 100%)
Norway				
Sweden				
BNT1MOD2MOD3 vs BNT1MOD2				
Documented infection				
Denmark	<3 / 0.2	<3 / 0.1		
Finland	146 / 372.9	262 / 365.7	-6.8% (-12.6% - -1.0%)	54.8% (31.2% - 78.4%)
Norway	2447 / 3816.8	9242 / 3477.1		
Sweden	6 / 25.9	7 / 25.4		
Hospitalisation				
Denmark				
Finland	0 / 396.7	0 / 377.8	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 396.7	0 / 377.8	0.0% (0.0% - 0.0%)	

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	<5 / 4373.6	<5 / 3952.8		
Sweden				
Death				
Denmark				
Finland	0 / 419.6	0 / 397.9	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
MOD1BNT2BNT3 vs MOD1BNT2				
Documented infection				
Denmark	4 / 0.8	3 / 0.7		
Finland	39 / 141.5	93 / 138.3	-5.9% (-8.9% - -3.0%)	61.6% (44.3% - 78.8%)
Norway	341 / 437.8	1234 / 389.0		
Sweden	14 / 56.6	18 / 55.7	0.5% (-0.5% - 1.6%)	
Hospitalisation				
Denmark				
Finland	0 / 148.0	<5 / 142.2		
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 148.0	0 / 142.2	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 155.0	0 / 148.3	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
BNT1MOD2BNT3 vs BNT1MOD2				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Documented infection				
Denmark				
Finland	156 / 413.1	278 / 406.8	-2.5% (-8.1% - 3.1%)	23.6% (-31.5% - 78.6%)
Norway	4360 / 7556.4	20965 / 6854.6		
Sweden	13 / 88.0	23 / 87.1	1.4% (-1.4% - 4.2%)	
Hospitalisation				
Denmark				
Finland	0 / 436.1	0 / 419.1	0.0% (0.0% - 0.0%)	
Norway	7 / 8620.6	17 / 7866.9		
Sweden				
ICU admission				
Denmark				
Finland	0 / 436.1	0 / 419.1	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 461.3	0 / 439.5	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
MOD1BNT2MOD3 vs MOD1BNT2				
Documented infection				
Denmark				
Finland	23 / 88.1	59 / 86.0	-2.7% (-11.7% - 6.3%)	19.4% (-67.9% - 100%)
Norway	170 / 243.4	661 / 212.1		
Sweden	8 / 14.6	6 / 14.6	0.0% (0.0% - 0.0%)	
Hospitalisation				
Denmark				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Finland	0 / 93.3	0 / 88.8	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
ICU admission				
Denmark				
Finland	0 / 93.3	0 / 88.8	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
Death				
Denmark				
Finland	0 / 98.1	0 / 93.3	0.0% (0.0% - 0.0%)	
Norway				
Sweden				
BNT1BNT2BNT3 vs BNT1BNT2				
Documented infection				
Denmark	72537 / 26043.4	75846 / 23124.2	-0.8% (-1.7% - 0.1%)	22.1% (-15.7% - 59.9%)
Finland	12478 / 36198.6	23870 / 35633.7	-4.4% (-4.7% - -4.2%)	40.7% (38.6% - 42.7%)
Norway	14817 / 32856.9	54493 / 29978.4	0.6% (0.4% - 0.8%)	
Sweden	21284 / 42924.2	31553 / 41025.8	1.0% (0.8% - 1.1%)	
Hospitalisation				
Denmark	65 / 33544.7	303 / 27226.2	-0.2% (-0.6% - 0.2%)	44.9% (-41.0% - 100%)
Finland	19 / 38789.6	167 / 36833.2	-0.1% (-0.2% - -0.1%)	79.9% (65.6% - 94.1%)
Norway	32 / 35721.9	183 / 32333.0	0.0% (0.0% - 0.1%)	
Sweden	81 / 46479.5	449 / 43618.1	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark	5 / 33575.0	18 / 27229.5	0.0% (0.0% - 0.0%)	
Finland	0 / 38796.7	16 / 36838.3		
Norway	5 / 35723.1	24 / 32336.3	0.0% (0.0% - 0.0%)	
Sweden				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Death				
Denmark	6 / 41254.8	94 / 33414.0	-0.1% (-0.3% - 0.1%)	
Finland	15 / 41604.8	147 / 39027.1	-0.2% (-0.2% - -0.1%)	87.7% (79.1% - 96.4%)
Norway				
Sweden	21 / 50681.0	99 / 47870.1	0.0% (0.0% - 0.0%)	
MOD1MOD2MOD3 vs MOD1MOD2				
Documented infection				
Denmark	19826 / 5850.0	21869 / 5172.7	-1.4% (-3.1% - 0.3%)	23.9% (-13.8% - 61.6%)
Finland	1274 / 4412.1	2483 / 4330.0	-4.2% (-5.0% - -3.4%)	46.0% (39.4% - 52.7%)
Norway	2505 / 4067.9	7866 / 3646.4	1.2% (0.5% - 2.0%)	
Sweden	1818 / 5044.4	2901 / 4868.4	0.8% (0.5% - 1.1%)	
Hospitalisation				
Denmark	18 / 7706.6	41 / 6373.4	-0.2% (-0.5% - 0.2%)	94.7% (84.2% - 100%)
Finland	<5 / 4644.5	15 / 4444.4	0.0% (-0.1% - 0.1%)	8.9% (-147.4% - 100%)
Norway	<5 / 4623.0	24 / 4041.3	0.0% (0.0% - 0.0%)	
Sweden	12 / 5476.1	52 / 5153.7	0.0% (0.0% - 0.0%)	
ICU admission				
Denmark	<3 / 7721.5	0 / 6372.1	0.0% (0.0% - 0.0%)	
Finland	0 / 4645.0	0 / 4444.8	0.0% (0.0% - 0.0%)	
Norway	<5 / 4614.0	5 / 4036.2	0.0% (0.0% - 0.0%)	
Sweden				
Death				
Denmark	<3 / 9633.6	7 / 7986.6	-0.1% (-0.2% - 0.1%)	
Finland	<5 / 4861.1	18 / 4630.6	-0.2% (-0.4% - 0.1%)	62.2% (-36.3% - 100%)
Norway				
Sweden	<3 / 6031.7	13 / 5681.4	0.0% (0.0% - 0.0%)	

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).

Table 9. Meta-analysis of the country-specific weighted adjusted results for the associations between documented covid-19 infection and covid-19 related hospitalisation and studied heterologous booster vaccine schedules compared with homologous booster schedules during period of omicron predominance.

Studied schedule	Compared schedule	Studied schedule events	Compa-rative schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
Outcome: documented infection							
AZD1AZD2BNT3	BNT1BNT2BNT3	14097	647004	-3.2% (-7.6%-1.2%)	11.0% (-9.3%-31.3%)	<0.0001	DK, FI, SE, NO
AZD1AZD2MOD3	MOD1MOD2MOD3	4115	89996	-0.1% (-1.0%-0.9%)	18.3% (-9.6%-46.2%)	0.0008	DK, FI, SE, NO
AZD1BNT2BNT3	BNT1BNT2BNT3	49606	563315	1.4% (-0.7%-3.5%)	-6.1% (-15.7%-3.6%)	<0.0001	DK, FI, SE, NO
AZD1MOD2MOD3	MOD1MOD2MOD3	14643	71975	2.6% (0.1%-5.1%)	-19.3% (-36.3%--2.3%)	0.0005	DK, FI, SE, NO
BNT1BNT2MOD3	BNT1BNT2BNT3	49839	743867	-5.0% (-14.5%-4.5%)	19.7% (-7.8%-47.3%)	<0.0001	DK, FI, SE, NO
MOD1MOD2BNT3	BNT1BNT2BNT3	17617	770154	-0.2% (-1.6%-1.2%)	2.8% (-6.7%-12.2%)	<0.0001	DK, FI, SE, NO
BNT1MOD2MOD3	BNT1BNT2BNT3	22	640035	-4.0% (-5.7%--2.3%)	43.8% (4.8%-82.8%)	0.7738	DK, SE
MOD1BNT2BNT3	BNT1BNT2BNT3	180	706830	1.2% (-0.5%-3.0%)	-18.1% (-42.4%-6.1%)	0.871	DK, FI, SE
BNT1MOD2BNT3	BNT1BNT2BNT3	22	636543	-5.6% (-19.5%-8.3%)	35.3% (-7.0%-77.6%)	0.1935	DK, SE
MOD1BNT2MOD3	BNT1BNT2BNT3	10	67166	-1.4% (-9.1%-6.3%)	20.1% (-44.5%-84.7%)	1	SE

Studied schedule	Compared schedule	Studied schedule events	Compa-rative schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
Outcome: hospitalisation							
AZD1AZD2BNT3	BNT1BNT2BNT3	<148	1007	0.0% (0.0%-0.0%)	28.2% (9.4%-47.0%)	0.5993	FI, NO, SE
AZD1AZD2MOD3	MOD1MOD2MOD3	<43	<33	0.0% (0.0%-0.0%)	15.4% (-58.9%-89.8%)	0.4528	FI, SE
AZD1BNT2BNT3	BNT1BNT2BNT3	78	946	0.0% (0.0%-0.0%)	14.5% (-13.1%-42.2%)	0.7492	DK, FI, SE, NO
AZD1MOD2MOD3	MOD1MOD2MOD3	<7	48	0.0% (0.0%-0.0%)	-11.2% (-172.8%-100.0%)	0.5781	DK, SE
BNT1BNT2MOD3	BNT1BNT2BNT3	181	1348	0.0% (0.0%-0.0%)	33.4% (20.9%-46.0%)	0.1006	FI, NO, SE
MOD1MOD2BNT3	BNT1BNT2BNT3	93	1585	0.0% (0.0%-0.0%)	25.6% (-1.7%-52.9%)	0.1144	FI, NO, SE
BNT1MOD2MOD3	BNT1BNT2BNT3	<3	1169	2.3% (-5.5%-10.2%)	NE	1	DK

CI denotes confidence interval, CVE comparative vaccine effectiveness, DK Denmark, FI Finland, NO Norway, RD risk difference, and SE Sweden. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

Table 10. Meta-analysis of the country-specific results for the associations between documented covid-19 infection and covid-19 related hospitalisation and studied heterologous or homologous booster vaccine schedules as compared with the matched primary schedule counterpart during period of omicron predominance.

Studied schedule	Compared schedule	Studied schedule events	Compa-rative schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
Outcome: documented infection							
AZD1AZD2BNT3	AZD1AZD2	3027	4076	-0.8% (-3.7%-2.1%)	62.9% (39.9%-86.0%)	<0.0001	FI, SE
AZD1AZD2MOD3	AZD1AZD2	39	208	-1.7% (-8.0%-4.7%)	54.8% (16.4%-93.3%)	1	FI
AZD1BNT2BNT3	AZD1BNT2	2043	2395	-5.9% (-6.9%--4.9%)	41.1% (28.4%-53.9%)	0.8504	DK, FI
AZD1MOD2MOD3	AZD1MOD2	930	1070	-7.1% (-9.7%--4.5%)	27.0% (-34.4%-88.4%)	0.7615	DK, FI
BNT1BNT2MOD3	BNT1BNT2	12915	25316	-2.2% (-7.8%-3.4%)	-268.6% (-1092.7%-555.4%)	<0.0001	FI, SE
MOD1MOD2BNT3	MOD1MOD2	885	1614	-4.0% (-5.0%--2.9%)	44.3% (35.5%-53.1%)	0.5925	DK, FI
BNT1MOD2MOD3	BNT1MOD2	146	262	-6.8% (-15.3%-1.7%)	54.8% (30.4%-79.2%)	1	FI
MOD1BNT2BNT3	MOD1BNT2	39	93	-5.9% (-12.8%-0.9%)	61.6% (43.3%-79.9%)	1	FI
BNT1MOD2BNT3	BNT1MOD2	156	278	-2.5% (-10.8%-5.9%)	23.6% (-31.9%-79.0%)	1	FI
MOD1BNT2MOD3	MOD1BNT2	23	59	-2.7% (-13.6%-8.3%)	19.4% (-68.1%-106.9%)	1	FI

Studied schedule	Compared schedule	Studied schedule events	Compa-rative schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
BNT1BNT2BNT3	BNT1BNT2	121116	185762	-0.9% (-3.4%-1.5%)	-326.9% (-951.5%-297.7%)	<0.0001	DK, FI, SE, NO
MOD1MOD2MOD3	MOD1MOD2	21100	24352	-2.9% (-5.6%--0.1%)	43.1% (28.3%-57.8%)	0.0035	DK, FI
Outcome: hospitalisation							
AZD1AZD2BNT3	AZD1AZD2	<5	31	-0.2% (-6.4%-6.0%)	93.7% (82.0%-105.3%)	1	FI
AZD1BNT2BNT3	AZD1BNT2	5	15	-0.2% (-6.4%-6.0%)	73.1% (41.7%-104.5%)	1	FI
BNT1BNT2MOD3	BNT1BNT2	10	88	-0.1% (-6.3%-6.1%)	96.4% (89.3%-103.5%)	1	FI
BNT1BNT2BNT3	BNT1BNT2	84	470	-0.1% (-0.2%--0.1%)	78.9% (64.8%-93.0%)	0.7165	DK, FI
MOD1MOD2MOD3	MOD1MOD2	<23	56	0.0% (-0.1%-0.1%)	88.8% (46.2%-131.3%)	0.3662	DK, FI

CI denotes confidence interval, CVE comparative vaccine effectiveness, DK Denmark, FI Finland, NO Norway, RD risk difference, and SE Sweden. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

Overall, results of the omicron period specific results were very similar to the results of our main analyses (that is, weighted analyses for objective 1 and matched analyses for objective 2). Heterologous booster schedules provided largely comparable effectiveness against covid-19 outcomes to that of the compared homologous booster schedules in all countries. However, estimates, particularly for documented infections, varied across comparisons and schedules. The number of cases of severe covid-19 outcomes were generally low to none for both the heterologous and homologous booster schedules in all countries, and therefore not all comparisons yielded sufficient number of cases for analyses. However, among those comparison where analyses were feasible, we observed comparable effectiveness of heterologous and homologous booster schedules. Meta-analyses for infection showed risk differences ranging between -5.6% and 2.6% (corresponding CVE of -19.3% to 43.8). For hospitalisation, risk differences were lower than 0.1%, CVE ranged between -11.2% and 33.4%. Of note, the majority of meta-analysed comparisons showed significant heterogeneity.

When compared with matched primary schedules, heterologous booster schedules were largely associated with lower risk of covid-19 outcomes, but estimates varied across countries and compared schedules, in particular for the outcome of documented infection. The low cumulative incidences of severe covid-19 outcomes compared better across comparisons and countries than for infection. However, only few heterologous booster schedules vs. primary schedules comparisons for the risk of covid-19 related ICU admission and death could be conducted owing to few to no cases. Meta-analyses for infection showed risk differences ranging between -7.1% and -0.8% for heterologous booster schedules vs. primary schedules (corresponding cVE of 27.0% to 62.9; except for BNT1BNT2MOD3 vs BNT1BNT2 where cVE was -268.6%, the 95% CI was very wide [-1092.7%-555.4%] and the p-value for heterogeneity was <0.0001). For homologous booster schedules vs primary schedules, risk differences were -0.9% for BNT booster schedules (cVE of -326.9% with wide 95% CI [-951.5%-297.7%] with significant heterogeneity, p-value of <0.0001) and -2.9% (corresponding cVE of 43.1%; p-value of 0.0035 for heterogeneity) for MOD. For hospitalisation, meta-analyses could not be conducted for the heterologous booster schedules vs. primary schedules, but for homologous booster schedules vs primary schedules the cVE was 78.9% for the BNT schedule and 88.8% for the MOD schedule.

10.3.2 Assessment of comparative waning immunity between heterologous and homologous primary vaccine schedules and waning within heterologous primary schedules (objective 4)

We assessed waning immunity in relation to risk of documented infection within the primary schedule comparisons in Denmark and Finland. The cumulative incidence curves, extending follow-up to 180 days are presented in Figure 37. Table 11 presents the comparative measures of waning; an increase/decrease in risk difference at a later time-point is suggestive of more/less comparative waning on the absolute scale and an increase/decrease in cVE at a later time-point is suggestive of less/more comparative waning on the relative scale.

Overall, the risk differences of documented infection between heterologous and homologous primary vaccine schedules remained consistent throughout later endpoints of 120, 150 and 180 days in both countries. In Denmark, at day 180, the risk difference ranged from -1.6 to 0.01% with cVEs between -0.4% and 19.6%. In Finland, at day 180, the risk difference ranged from -1.1 to 0.1% with cVEs between -12.3% and 24.3%. Results did not suggest that the risk of infection was higher for heterologous primary schedules compared with homologous primary schedules when extending follow-up to 180 days.

Table 12 presents the measures of waning within the heterologous primary vaccine schedules in Denmark, that is, risk differences comparing cumulative incidences at later- to earlier time-points in the same schedule. A difference between risk differences of 0.0% is suggestive of no waning and a difference >0.0% is suggestive of waning.

For both AZD1BNT2 and AZD1MOD2, the cumulative incidence was relative constant up to 150 days since start of follow-up with little waning (risk differences between 0.2% and 0.6%). From day 150 to day 180 the incidences increased suggesting waning (risk differences were 2.3% and 1.8%, respectively). However, these increases at day 180 also fits well with the start of the omicron wave in December 2021 in Denmark, as the index dates for the AZD1mRNA2 schedules were around May and June 2021 (se Figure 5 for density plots of the distributions of index date by calendar time).

The majority of BNT1MOD2 schedules were administered in August and September 2021 while the administration of the MOD1BNT2 schedules were generally well-distributed from April 2021 to January 2022. As such, the cumulative incidence for the BNT1MOD2 was increased at day 150 compared with day 120 (RD of 8.6% as compared with 3.7% for day 120 vs. day 75) and day 180 (RD of 8.1%), corresponding to the timing of meeting the omicron wave for the majority of vaccinated individuals in this schedule group. For the MOD1BNT2 schedules (where the index dates were more well-distributed across calendar time) the cumulative incidence increases were close to similar at all assessed time points (risk differences were 5.3% at day 120 vs. day 75, 4.9% at day 150 vs. day 120, 4.9% at day 180 vs. day 150. Given the

differences in the distribution of index date across calendar time and thus the infection rates, indirect comparisons of waning immunity is difficult.

Figure 37. Adjusted cumulative incidence curves of documented covid-19 infection for weighted analysis comparing heterologous and homologous primary vaccine schedules with follow-up of 180 days.

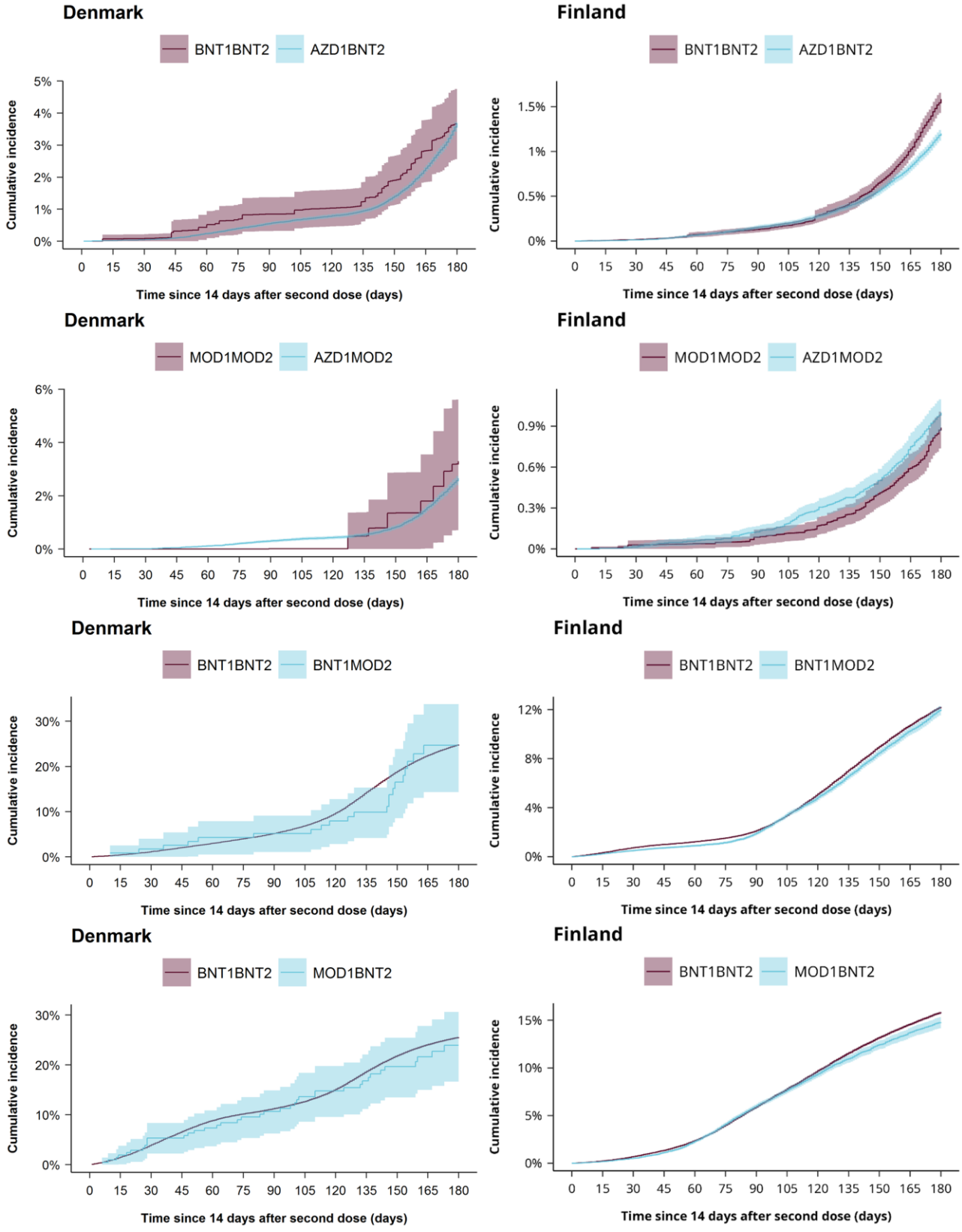


Table 11. Association between documented covid-19 infection and heterologous primary vaccine schedules as compared with homologous schedules in Denmark and Finland with 180 days of follow-up.

Days of follow-up	Studied schedule	Comparison schedule	Studied schedule event / PYRS	Comparison schedule event / PYRS	RD (95% CI)	CVE (95 CI)
Country: Denmark						
75	AZD1BNT2	BNT1BNT2	325 / 16652.06	561 / 40789.53	-0.29% (-0.75% - 0.18%)	41.69% (1.76% - 81.62%)
120	AZD1BNT2	BNT1BNT2	641 / 26562.94	1499 / 65009.79	-0.24% (-0.82% - 0.33%)	23.54% (-19.17% - 66.24%)
150	AZD1BNT2	BNT1BNT2	1070 / 32586.28	4429 / 80801.09	-0.5% (-1.27% - 0.27%)	26.25% (-3.78% - 56.28%)
180	AZD1BNT2	BNT1BNT2	2185 / 36717.15	8542 / 89897.69	0.01% (-1.09% - 1.12%)	-0.35% (-30.55% - 29.84%)
75	AZD1MOD2	MOD1MOD2	95 / 9204.29	64 / 8266.34	0.21% (0.17% - 0.25%)	
120	AZD1MOD2	MOD1MOD2	193 / 14699.84	161 / 13205.49	0.42% (0.36% - 0.48%)	
150	AZD1MOD2	MOD1MOD2	349 / 18050.84	514 / 16473.89	-0.52% (-2.06% - 1.01%)	38.6% (-31.17% - 100%)
180	AZD1MOD2	MOD1MOD2	842 / 20361.63	1091 / 18343.13	-0.65% (-3.12% - 1.83%)	19.58% (-40.74% - 79.91%)

Days of follow-up	Studied schedule	Comparison schedule	Studied schedule event / PYRS	Comparison schedule event / PYRS	RD (95% CI)	CVE (95 CI)
75	BNT1MOD2	BNT1BNT2	5 / 23.36	35543 / 582502.95	0.26% (-3.4% - 3.93%)	-6.52% (-97.89% - 84.85%)
120	BNT1MOD2	BNT1BNT2	9 / 36.21	101570 / 922349.02	-1.77% (-6.75% - 3.22%)	18.19% (-33.19% - 69.56%)
150	BNT1MOD2	BNT1BNT2	16 / 42.89	212083 / 1111112.28	-2.36% (-9.99% - 5.27%)	12.48% (-27.86% - 52.82%)
180	BNT1MOD2	BNT1BNT2	21 / 46.19	272841 / 1210064.67	-0.15% (-9.85% - 9.54%)	0.61% (-38.4% - 39.63%)
75	MOD1BNT2	BNT1BNT2	19 / 38.91	36673 / 573402.74	-0.64% (-4.73% - 3.46%)	6.27% (-33.95% - 46.48%)
120	MOD1BNT2	BNT1BNT2	28 / 57.41	102618 / 907589.2	-0.3% (-5.4% - 4.8%)	1.99% (-31.78% - 35.76%)
150	MOD1BNT2	BNT1BNT2	35 / 67.2	212978 / 1092605.34	-2.17% (-8.13% - 3.79%)	9.92% (-17.34% - 37.19%)
180	MOD1BNT2	BNT1BNT2	39 / 73.14	273641 / 1188050.23	-1.59% (-8.56% - 5.38%)	6.21% (-21.08% - 33.5%)
Country: Finland						
75	AZD1BNT2	BNT1BNT2	130 / 25256.94	3565 / 315645.85	0.0% (0.0% - 0.0%)	-3.8% (-39.9% - 32.2%)

Days of follow-up	Studied schedule	Comparison schedule	Studied schedule event / PYRS	Comparison schedule event / PYRS	RD (95% CI)	CVE (95 CI)
120	AZD1BNT2	BNT1BNT2	345 / 40349.01	21001 / 503632.02	0.0% (-0.1% - 0.1%)	3.3% (-23.0% - 29.7%)
150	AZD1BNT2	BNT1BNT2	699 / 50377.75	66467 / 626233.22	-0.1% (-0.2% - 0.0%)	13.7% (0.7% - 26.7%)
180	AZD1BNT2	BNT1BNT2	1469 / 60344.96	109459 / 737658.54	-0.4% (-0.5% - -0.3%)	24.3% (17.6% - 31.0%)
75	AZD1MOD2	MOD1MOD2	21 / 5579.24	337 / 42976.45		
120	AZD1MOD2	MOD1MOD2	83 / 8914.08	2736 / 68581.27	0.1% (0.0% - 0.2%)	-78.5% (-155.9% - -1.0%)
150	AZD1MOD2	MOD1MOD2	136 / 11130.71	7819 / 85311.03	0.1% (0.0% - 0.2%)	-21.6% (-56.7% - 13.6%)
180	AZD1MOD2	MOD1MOD2	270 / 13333.76	12511 / 99526.88	0.1% (-0.1% - 0.3%)	-12.3% (-33.9% - 9.4%)
75	BNT1MOD2	BNT1BNT2	510 / 8952.27	20300 / 377334.35	-0.4% (-0.5% - -0.3%)	24.3% (17.3% - 31.2%)
120	BNT1MOD2	BNT1BNT2	1968 / 13691.02	72759 / 587769.02	-0.3% (-0.5% - -0.1%)	5.4% (1.1% - 9.6%)
150	BNT1MOD2	BNT1BNT2	3284 / 16473.66	136088 / 710911.45	-0.5% (-0.8% - -0.2%)	5.5% (2.3% - 8.8%)
180	BNT1MOD2	BNT1BNT2	3891 / 17743.07	177384 / 801810.31	-0.2% (-0.6% - 0.2%)	1.6% (-1.7% - 4.9%)
75	MOD1BNT2	BNT1BNT2	1548 / 7822.31	21038 / 452653.34	0.1% (-0.1% - 0.3%)	-2.7% (-8.1% - 2.7%)
120	MOD1BNT2	BNT1BNT2	3095 / 11191.09	75848 / 707585.6	-0.3% (-0.7% - 0.0%)	3.6% (0.1% - 7.1%)

Days of follow-up	Studied schedule	Comparison schedule	Studied schedule event / PYRS	Comparison schedule event / PYRS	RD (95% CI)	CVE (95 CI)
150	MOD1BNT2	BNT1BNT2	3437 / 11986.22	141351 / 859712.12	-0.8% (-1.2% - -0.3%)	5.7% (2.1% - 9.3%)
180	MOD1BNT2	BNT1BNT2	3585 / 12431.05	189685 / 978626.88	-1.1% (-1.6% - -0.5%)	6.7% (2.9% - 10.4%)

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated.

Table 12. Comparison of waning immunity within the heterologous primary vaccine schedules in Denmark.

Studied schedule	Comparison (time 2 vs time 1)	Number of cases for time 2	PYRS for time 2	Number of cases for time 1	PYRS for time 1	RD (95% CI)
AZD1BNT2	Day 120 vs day 75	641	26562.94	325	16652.06	0.4% (0.3% - 0.5%)
AZD1BNT2	Day 150 vs day 120	1070	32586.28	641	26562.94	0.6% (0.5% - 0.7%)
AZD1BNT2	Day 180 vs day 150	2185	36717.15	1070	32586.28	2.3% (2.1% - 2.5%)
AZD1MOD2	Day 120 vs day 75	193	14699.84	95	9204.29	0.2% (0.1% - 0.3%)
AZD1MOD2	Day 150 vs day 120	349	18050.84	193	14699.84	0.4% (0.3% - 0.5%)
AZD1MOD2	Day 180 vs day 150	842	20361.63	349	18050.84	1.8% (1.6% - 2.0%)
BNT1MOD2	Day 120 vs day 75	9	36.21	5	23.36	3.7% (-2.5% - 9.9%)
BNT1MOD2	Day 150 vs day 120	16	42.89	9	36.21	8.6% (-0.5% - 17.7%)
BNT1MOD2	Day 180 vs day 150	21	46.19	16	42.89	8.1% (-4.2% - 20.5%)
MOD1BNT2	Day 120 vs day 75	28	57.41	19	38.91	5.3% (-1.3% - 11.8%)
MOD1BNT2	Day 150 vs day 120	35	67.2	28	57.41	4.9% (-3.0% - 12.7%)
MOD1BNT2	Day 180 vs day 150	39	73.14	35	67.2	4.3% (-4.9% - 13.4%)

CI denotes confidence interval, PYRS person-years, and RD risk difference.

10.3.3 Vaccine effectiveness in a child-adolescent population of individuals aged 5 to 17 years (objective 5)

Descriptive country-specific results for our analyses of VE among children and adolescents are presented in Table 13 and 14 and density plots for age and index date distributions in Figure 38 to 42.

Denmark and Finland had the largest number of included children aged 5 to 11 years, while vaccination of this age group was less common in Norway and Sweden (a total of ≈1600 vaccinated with one dose in both countries); mean ages were ≈ 9 to 11 years across countries and comparisons. In Denmark and Norway, children aged 5 to 11 years were mainly homologous primary schedule (i.e. 2-dose) vaccinated with BNT during December 2021 and January 2022 (period of omicron variant predominance in both countries). In Finland and Sweden, most BNT vaccination of 5- to 11-year olds occurred in January 2022 (period of omicron variant predominance in both countries).

For children and adolescents aged 12 to 17 years, most included individuals were vaccinated in the months of the autumn 2021 (period of delta predominance in all countries) across the four countries, although vaccination with BNT in Denmark for this age group started earlier (in June 2021); mean ages were ≈ 14 to 17 years across countries and comparisons. The homologous schedule with BNT was the most used schedules in all countries, and Denmark and Sweden had the largest number of individuals vaccinated with the BNT schedules. Finland and Sweden contributed with the most MOD homologous primary vaccinated children in this age group (> 23,000 vaccinated; Denmark and Norway had <900 vaccinated with MOD1MOD2).

Table 13. Descriptive results for matched comparison of primary schedule vaccinated with mRNA vaccines vs. unvaccinated children aged 5 to 11 years.

	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)[a]	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)[a]	Female sex (%)	Calendar period (min-max)
BNT1 vs unvaccinated								
Denmark	135925	9 (2.1)	48.4%	15/03/21 - 28/02/22	135925	8.9 (2.1)	48.7%	15/03/21 - 28/02/22
Finland	100238	9.3 (2.0)	48.9%	28/06/21-27/02/22	100238	9.2 (1.9)	48.8%	28/06/21-27/02/22
Norway	1570	10.3 (1.5)	47.1%	20/04/21 - 28/02/22	1570	10.3 (1.5)	47.1%	20/04/21 - 28/02/22
Sweden	1623	10.3 (1.6)	47.6%	23/02/21 - 28/02/22	1623	10.3 (1.6)	49.6%	23/02/21 - 28/02/22
BNT1BNT2 vs unvaccinated								
Denmark	79000	9.3 (2.1)	48.2%	05/04/21 - 28/02/22	79000	9.2 (2.1)	48.8%	05/04/21 - 28/02/22
Finland	14920	11.2 (1.3)	47.6%	07/09/21-27/02/22	14920	10.9 (1.3)	48.8%	07/09/21-27/02/22
Norway	368	10.0 (1.7)	49.2%	01/06/21 - 28/02/22	368	10.0 (1.7)	44.6%	01/06/21 - 28/02/22
Sweden	153	10.9 (0.8)	51.6%	05/04/21 - 28/02/22	153	10.9 (0.8)	44.4%	05/04/21 - 28/02/22

SD denotes standard deviation.

Table 14. Descriptive results for matched comparison of primary schedule vaccinated with mRNA vaccines vs. unvaccinated children or adolescents aged 12 years or older.

	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
BNT1 vs unvaccinated								
Denmark	184138	14.8 (1.7)	49.1%	09/01/21 - 28/02/22	184138	14.7 (1.7)	48.3%	09/01/21 - 28/02/22
Finland	147113	15.2 (1.8)	50.5%	28/06/21-27/02/22	147113	15.2 (1.8)	46.2%	28/06/21-27/02/22
Norway	55234	16.1 (1.2)	51.2%	21/12/20 - 28/02/22	55234	16.1 (1.2)	48.5%	21/12/20 - 28/02/22
Sweden	307906	14.3 (1.7)	49.8%	21/01/21 - 28/02/22	307906	14.3 (1.7)	46.9%	21/01/21 - 28/02/22
MOD1 vs unvaccinated								
Denmark	785	15.0 (1.7)	44.7%	31/12/20 - 28/02/22	785	15.0 (1.7)	45.2%	31/12/20 - 28/02/22
Finland	72687	14.3 (1.4)	49.6%	28/06/21-27/02/22	72687	14.3 (1.5)	48.1%	28/06/21-27/02/22
Norway	4478	16.3 (0.8)	48.1%	08/04/21 - 28/02/22	4478	16.3 (0.8)	45.7%	08/04/21 - 28/02/22
Sweden	37867	16.5 (0.6)	49.3%	04/04/21 - 28/02/22	37867	16.5 (0.6)	44.9%	04/04/21 - 28/02/22
BNT1BNT2 vs unvaccinated								
Denmark	108287	14.5 (1.7)	49.1%	31/01/21 - 28/02/22	108287	14.4 (1.7)	48.2%	31/01/21 - 28/02/22
Finland	84681	14.9 (1.8)	51.4%	23/07/21-27/02/22	84681	14.9 (1.8)	44.5%	23/07/21-27/02/22
Norway	16340	16.5 (1.1)	52.8%	18/02/21 - 28/02/22	16340	16.5 (1.1)	47.1%	18/02/21 - 28/02/22
Sweden	216438	14.3 (1.7)	48.1%	11/02/21 - 28/02/22	216438	14.3 (1.7)	47.5%	11/02/21 - 28/02/22
MOD1MOD2 vs unvaccinated								
Denmark	691	14.9 (1.7)	44.3%	20/04/21 - 28/02/22	691	14.8 (1.7)	44.9%	20/04/21 - 28/02/22
Finland	31949	14.3 (1.4)	66.6%	17/08/21-27/02/22	31949	14.3 (1.4)	66.5%	17/08/21-27/02/22
Norway	870	16.8 (0.6)	51.4%	06/05/21 - 28/02/22	870	16.8 (0.6)	41.3%	06/05/21 - 28/02/22
Sweden	23295	16.5 (0.5)	51.0%	03/05/21 - 28/02/22	23295	16.5 (0.5)	44.3%	03/05/21 - 28/02/22
BNT1MOD2 vs unvaccinated								

	Studied schedule				Comparison schedule			
	Total individuals	**Age (mean, SD)**	**Female sex (%)**	**Calendar period (min-max)**	**Total individuals**	**Age (mean, SD)**	**Female sex (%)**	**Calendar period (min-max)**
Denmark	3	14.7 (1.2)	66.7%	02/09/21 - 24/10/21	3	14.8 (1.1)	66.7%	02/09/21 - 24/10/21
Finland	4565	16.0 (1.6)	58.4%	08/08/21-27/02/22	4565	16.0 (1.6)	53.8%	08/08/21-27/02/22
Norway	6062	16.9 (0.4)	52.0%	04/08/21 - 28/02/22	6062	16.9 (0.4)	45.2%	04/08/21 - 28/02/22
Sweden	839	16.4 (0.9)	50.5%	11/08/21 - 28/02/22	839	16.4 (0.9)	43.5%	11/08/21 - 28/02/22
MOD1BNT2 vs unvaccinated								
Denmark	6	16.0 (1.3)	33.3%	21/06/21 - 21/12/21	6	16.1 (1.4)	50.0%	21/06/21 - 21/12/21
Finland	38631	14.2 (1.4)	28.1%	01/09/21-27/02/22	38631	14.2 (1.4)	28.2%	01/09/21-27/02/22
Norway	1543	16.2 (0.8)	47.1%	14/07/21 - 28/02/22	1543	16.2 (0.8)	39.5%	14/07/21 - 28/02/22
Sweden	12443	16.4 (0.6)	47.3%	14/07/21 - 28/02/22	12443	16.4 (0.6)	44.4%	14/07/21 - 28/02/22

SD denotes standard deviation. [a]Age was defined by birth year in Norway and Sweden (the specific birthdates for individuals younger than 18 years were not available in these countries).

Figure 38. Density plots for distribution of age and index date for matched analysis of children aged 5 to 11 years by country.

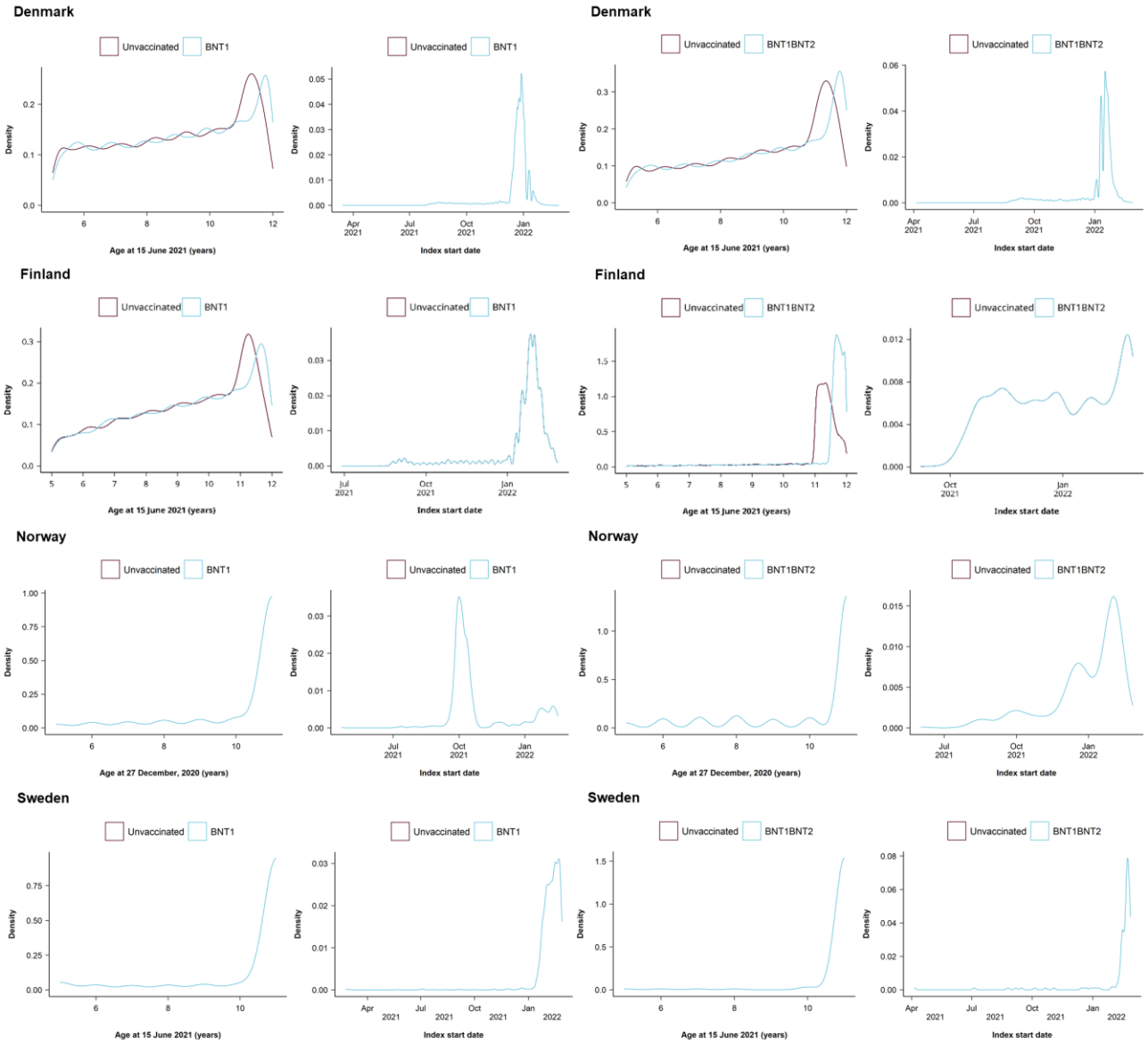


Figure 39. Density plots for distribution of age and index date for matched analysis of children aged 12 to 17 years by vaccine schedule in Denmark.

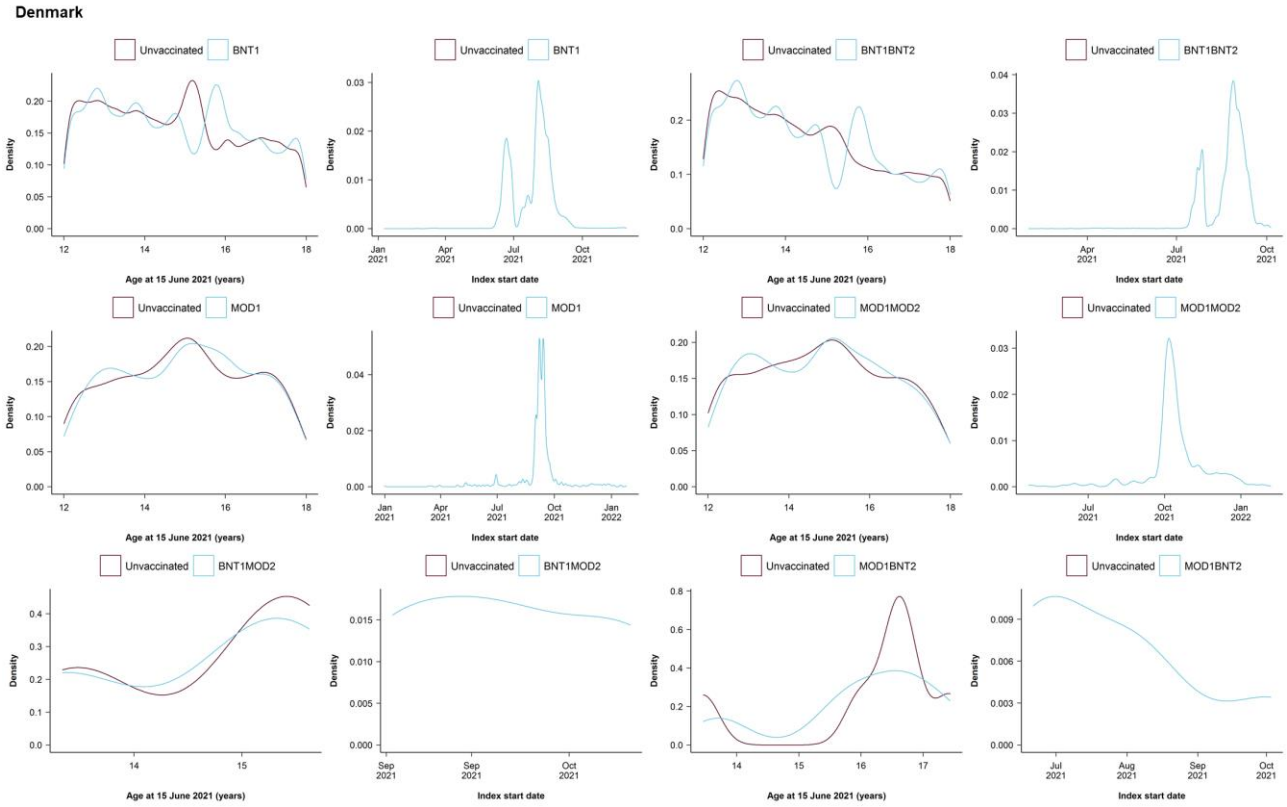


Figure 40. Density plots for distribution of age and index date for matched analysis of children aged 12 to 17 years by vaccine schedule in Finland.

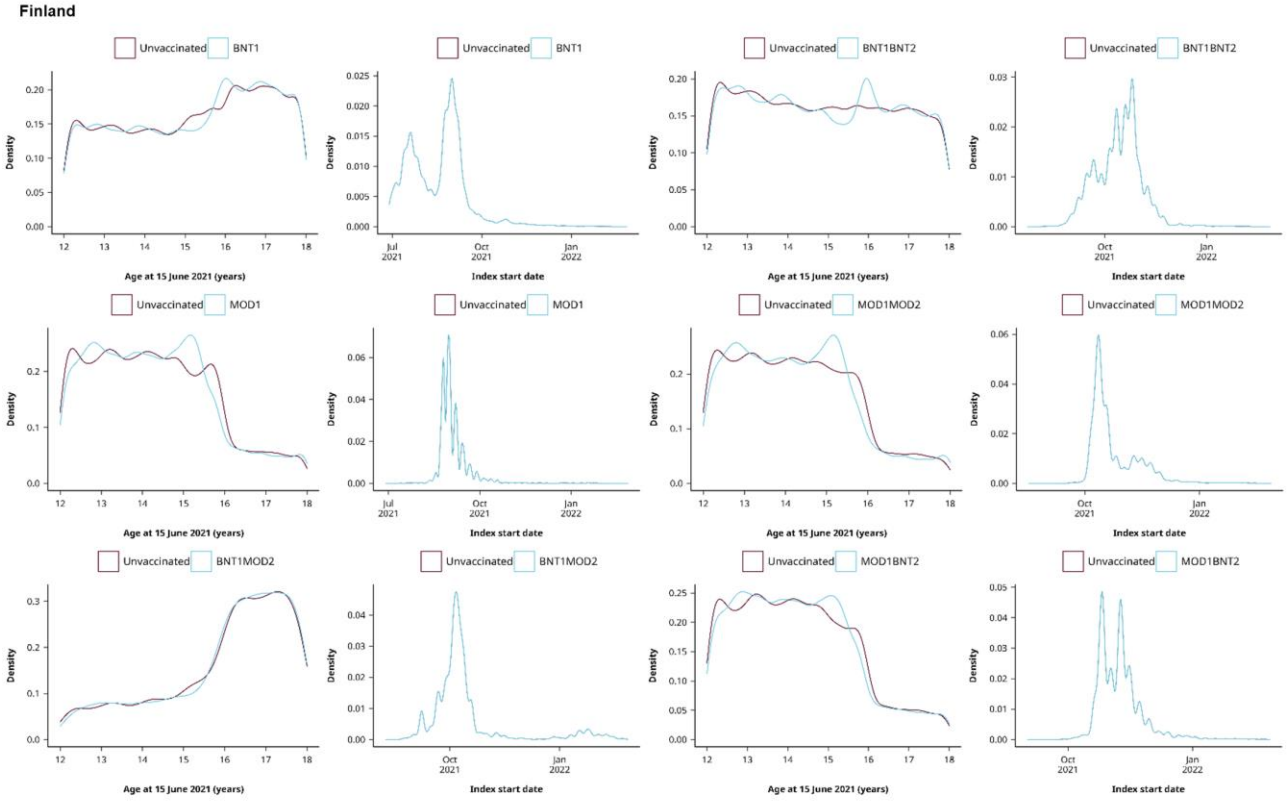


Figure 41. Density plots for distribution of age and index date for matched analysis of children aged 12 to 17 years by vaccine schedule in Norway.

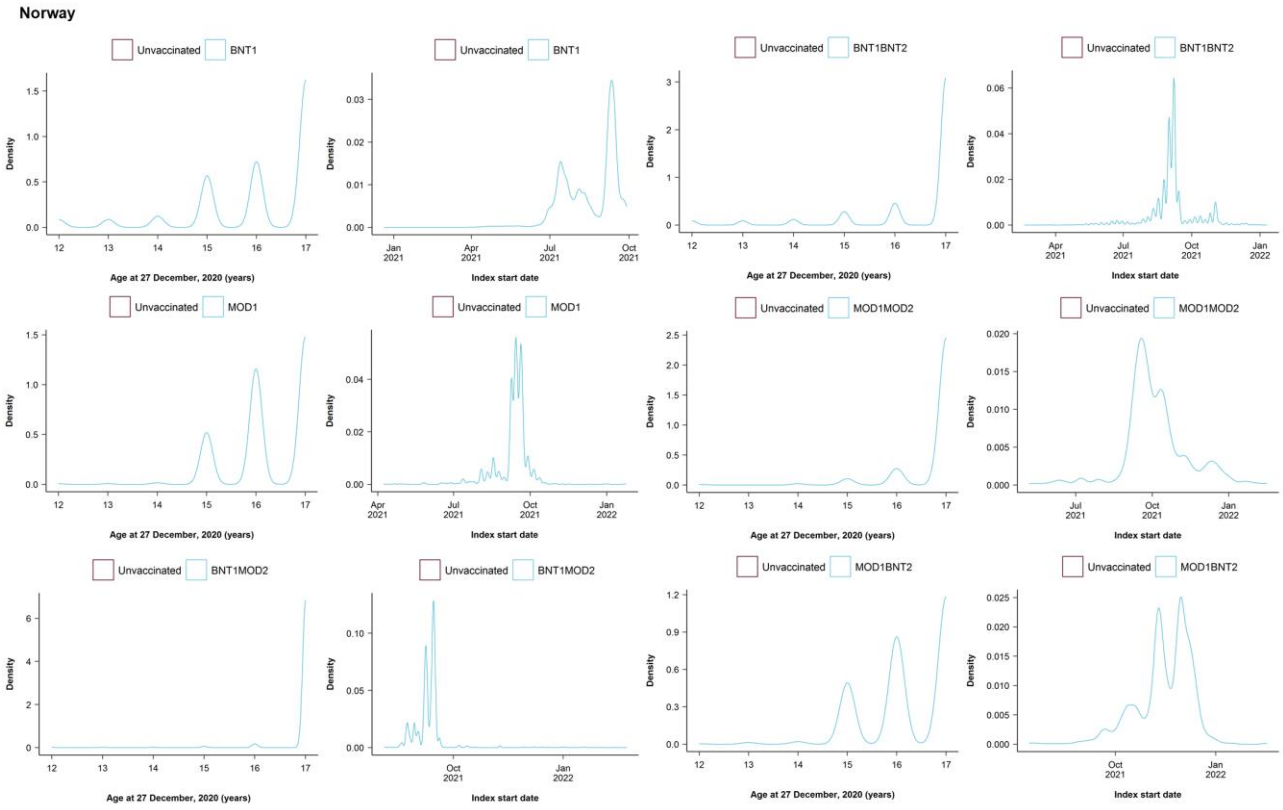


Figure 42. Density plots for distribution of age and index date for matched analysis of children aged 12 to 17 years by vaccine schedule in Sweden.

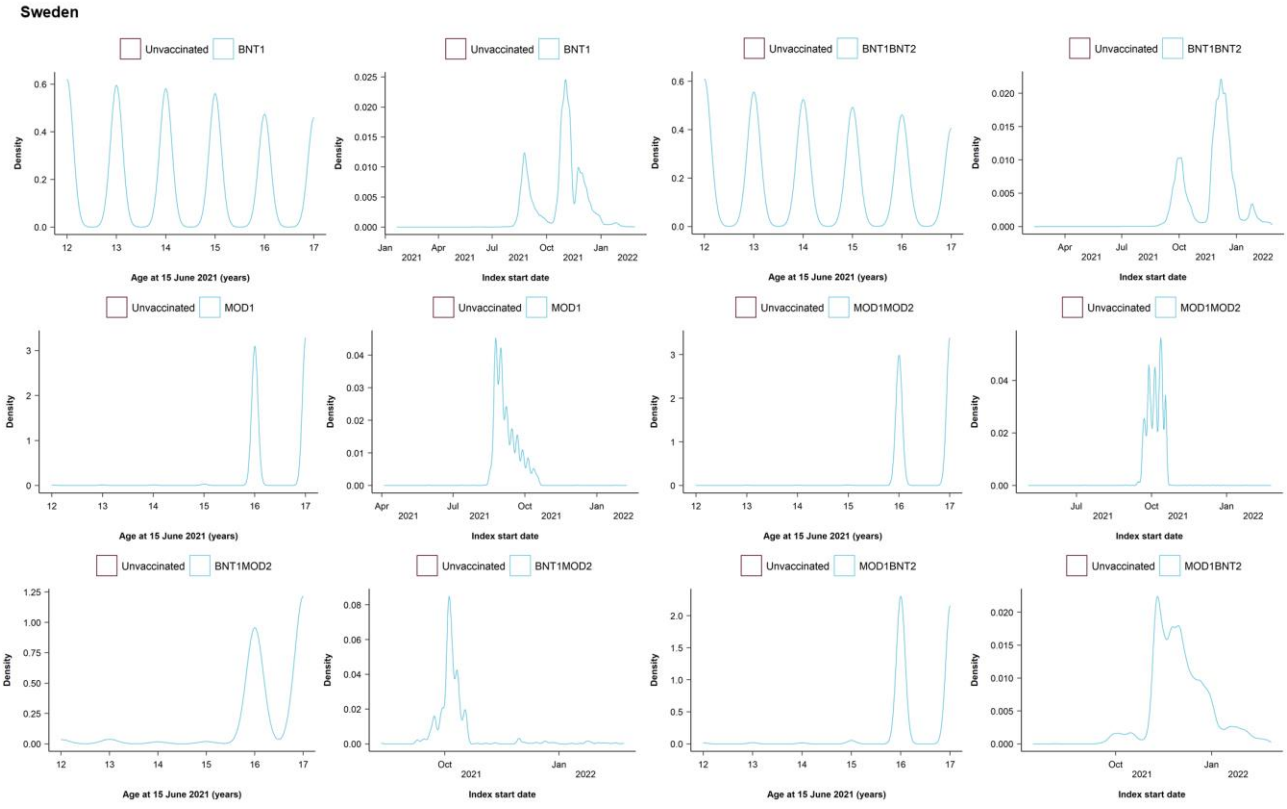
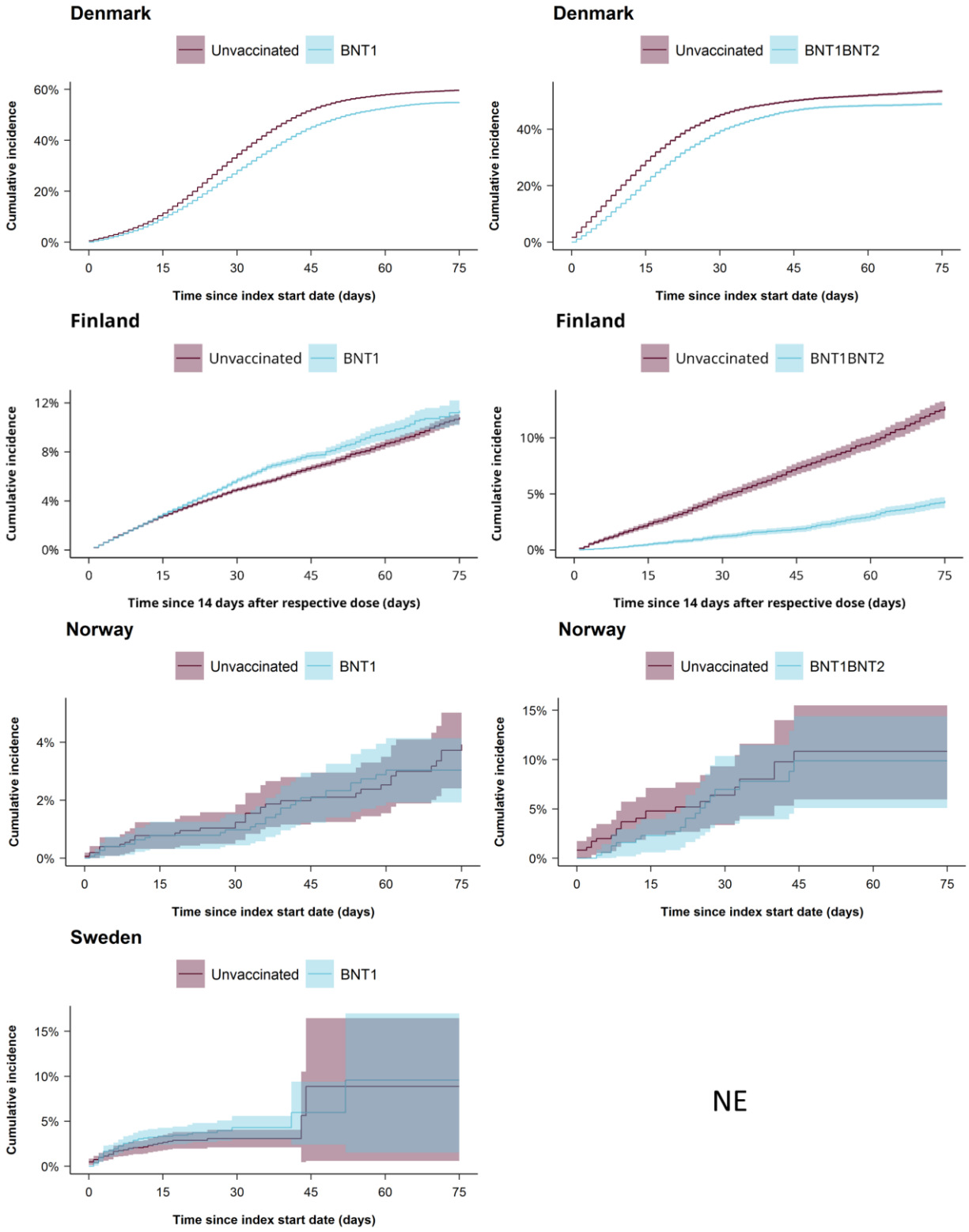
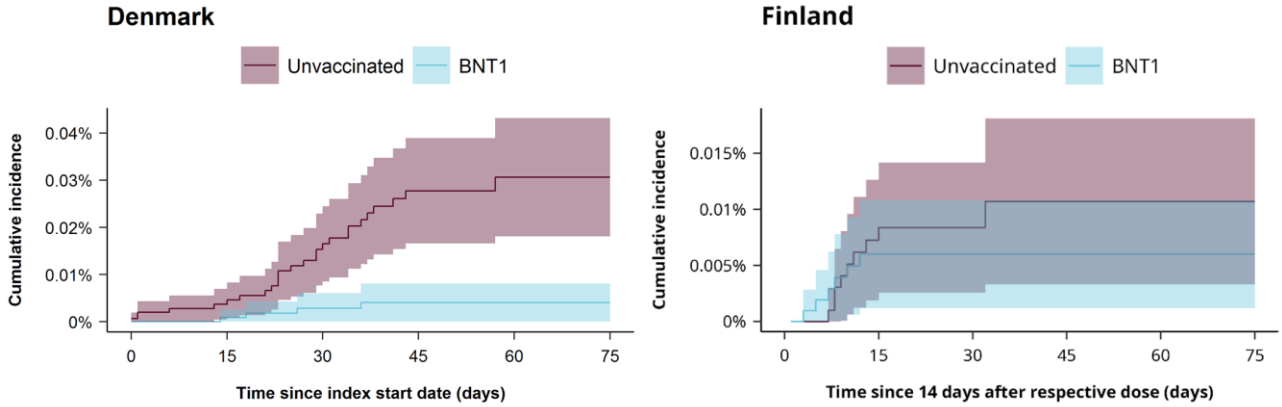


Figure 43. Country-specific cumulative incidence curves of documented covid-19 infection for matched analysis comparing homologous BNT primary schedule with unvaccinated among children aged 5 to 11 years.



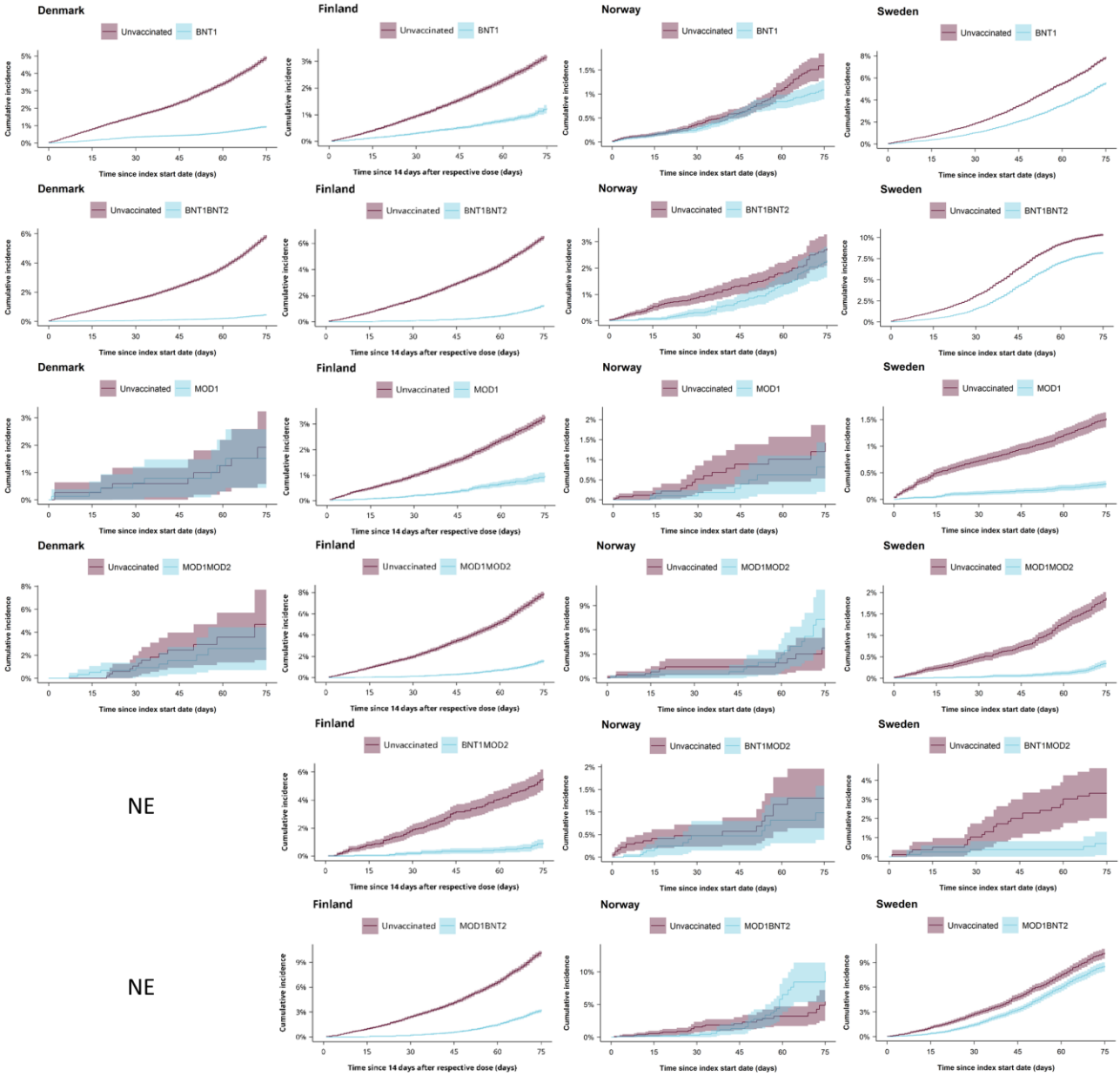
NE denotes not estimated.

Figure 44. Country-specific cumulative incidence curves of covid-19 related hospitalisation for matched analysis comparing homologous BNT primary schedule with unvaccinated among children aged 5 to 11 years.



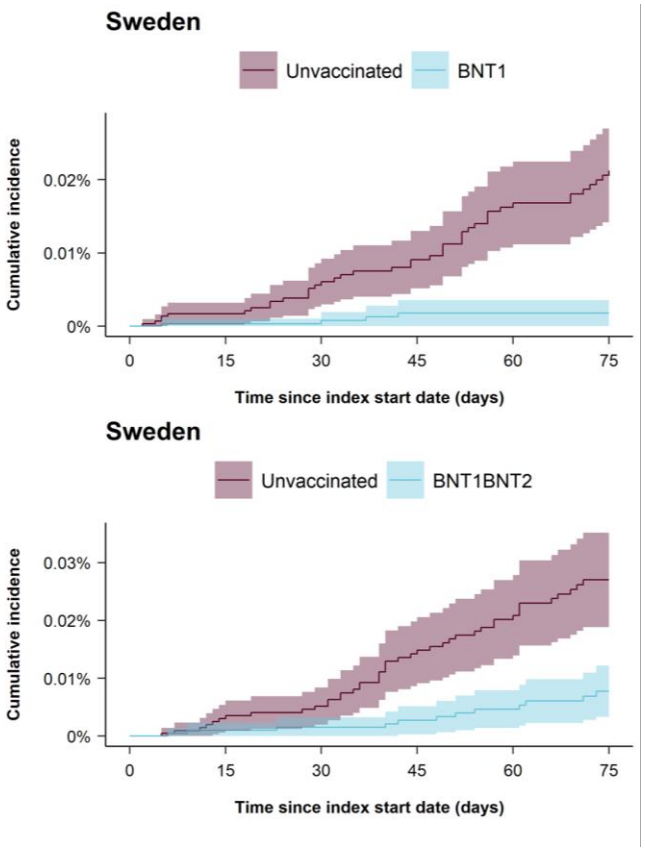
Cumulative incidence curves of covid-19 related hospitalisation could not be estimated for BNT1 vs. unvaccinated in Norway and Sweden and BNT1BNT2 vs. unvaccinated for all four countries.

Figure 45. Country-specific cumulative incidence curves of documented covid-19 infection for matched analysis comparing homologous BNT primary schedule with unvaccinated among children and adolescents aged 12 years or older.



NE denotes not estimated.

Figure 46. Country-specific cumulative incidence curves of covid-19 related hospitalisation for matched analysis comparing homologous BNT primary schedule with unvaccinated among children and adolescents aged 12 years or older.



Cumulative incidence curves of covid-19 related hospitalisation could not be estimated in Denmark, Finland, and Norway.

Table 15. Association between covid-19 outcomes in matched comparison of primary schedule vaccinated vs. unvaccinated children aged 5 to 11 years.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	VE (95% CI)
Outcome: documented infection				
BNT vs Unvaccinated				
Denmark	49901 / 12066.2	54587 / 11213.0	-4.8% (-5.2% - -4.3%)	8.0% (7.3% - 8.8%)
Finland	5080 / 7253.4	5893 / 9642.2	0.5% (-0.6% - 1.7%)	-5.1% (-16.0% - 5.8%)
Norway	30 / 190.5	35 / 189.0	-0.9% (-2.6% - 0.8%)	19.9% (-21.2% - 60.9%)
Sweden	54 / 79.8	42 / 80.3	0.7% (-5.6% - 7.0%)	-19.2% (-115.7% - 77.4%)
BNT1BNT2 vs Unvaccinated				
Denmark	31459 / 6123.8	34683 / 5601.6	-4.7% (-5.4% - -4.0%)	8.8% (7.5% - 10.0%)
Finland	323 / 1675.3	1262 / 1880.2	-8.4% (-9.3% - -7.5%)	65.6% (61.4% - 69.9%)
Norway	19 / 28.9	23 / 28.0	-1.0% (-7.3% - 5.4%)	4.7% (-57.6% - 67.1%)
Sweden	<3 / 5.3	<3 / 5.2	-0.9% (-23.0% - 21.3%)	
Outcome: hospitalisation[b]				
BNT vs Unvaccinated				
Denmark	4/15091,76	26/14024,27	0.0% (-0.0%- -0.0%)	85.7% (70.5%-100.0%)
Finland	6/7747,13	10/10095,11	0.0% (-0.0%- -0.0%)	34.0% (-57.8%-100.0%)
BNT1BNT2 vs Unvaccinated				
Denmark	<3/8595,74	19/7788,31	-0.0% (-0.0%- -0.0%)	91.2% (72.4%-100.0%)
Finland	0/1718,21	<5/1937,28	0.0% (-0.0%- -0.0%)	
Outcome: MIS-C[b]				
BNT vs Unvaccinated				
Denmark	<3/21442,88	13/20333,2	-0.0% (-0.0%- 0.0%)	88.4% (63.4%-100.0%)
BNT1BNT2 vs Unvaccinated				
Denmark	<3/13059,38	6/12102,73	-0.0% (-0.0%- 0.0%)	

CI denotes confidence interval, MIS-C multisystem inflammatory syndrome in children, PYRS person-years, RD risk difference, and VE vaccine effectiveness. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).[b]For severe outcomes only those country-specific comparisons where analyses were accomplished are presented.

Table 16. Association between covid-19 outcomes in matched comparison of primary schedule vaccinated vs. unvaccinated children or adolescents aged 12 years or older.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	VE (95% CI)
Outcome: documented infection				
BNT vs Unvaccinated				
Documented infection				
Denmark	969 / 21649.2	5029 / 21211.3	-4.0% (-4.1% - -3.9%)	80.8% (79.5% - 82.1%)
Finland	671 / 15031.1	13457 / 36952.9	-2.0% (-2.1% - -1.8%)	61.1% (56.0% - 66.2%)
Norway	179 / 3777.4	228 / 3759.4	-0.5% (-0.8% - -0.2%)	31.0% (14.0% - 48.0%)
Sweden	10923 / 43317.0	15874 / 42803.7	-2.3% (-2.5% - -2.2%)	29.3% (27.6% - 31.0%)
MOD vs Unvaccinated				
Documented infection				
Denmark	8 / 107.3	9 / 106.9	-0.4% (-2.1% - 1.4%)	5.0% (-134.0% - 100%)
Finland	228 / 7196.5	8666 / 20537.2	-2.3% (-2.6% - -2.1%)	70.7% (64.1% - 77.3%)
Norway	8 / 273.8	17 / 272.0	-0.6% (-1.6% - 0.4%)	37.5% (-27.8% - 100%)
Sweden	83 / 5782.6	443 / 5741.3	-1.2% (-1.4% - -1.1%)	80.5% (75.9% - 85.0%)
BNT1BNT2 vs Unvaccinated				
Documented infection				
Denmark	376 / 17866.1	4957 / 17469.4	-5.4% (-5.6% - -5.3%)	92.2% (91.3% - 93.0%)
Finland	842 / 14671.9	12133 / 22495.8	-5.3% (-5.5% - -5.1%)	80.2% (78.8% - 81.7%)
Norway	67 / 958.7	118 / 946.6	-0.5% (-1.3% - 0.3%)	16.3% (-11.6% - 44.3%)
Sweden	13491 / 33844.4	17504 / 33303.9	-2.1% (-2.3% - -1.9%)	20.6% (18.9% - 22.3%)
BNT1MOD2 vs Unvaccinated				
Documented infection				
Denmark				
Finland	31 / 747.0	609 / 1162.4	-4.6% (-5.5% - -3.7%)	83.1% (76.6% - 89.6%)
Norway	13 / 303.0	25 / 299.9	-0.3% (-1.2% - 0.6%)	18.3% (-48.9% - 85.5%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	VE (95% CI)
Sweden	5 / 148.0	24 / 146.1	-2.7% (-4.1% - -1.2%)	78.5% (57.2% - 99.8%)
MOD1BNT2 vs Unvaccinated				
Documented infection				
Denmark				
Finland	1017 / 6804.9	5788 / 9128.0	-7.0% (-7.4% - -6.6%)	68.1% (66.0% - 70.2%)
Norway	34 / 132.1	26 / 130.8	4.7% (0.2% - 9.2%)	
Sweden	819 / 2035.8	995 / 2012.9	-1.5% (-2.4% - -0.7%)	15.2% (7.3% - 23.0%)
MOD1MOD2 vs Unvaccinated				
Documented infection				
Denmark	9 / 71.0	13 / 70.4	-2.1% (-5.6% - 1.4%)	38.0% (-33.9% - 100%)
Finland	411 / 5591.3	5419 / 8165.6	-6.3% (-6.7% - -6.0%)	79.6% (77.4% - 81.7%)
Norway	16 / 72.5	12 / 72.1	3.4% (-0.7% - 7.5%)	
Sweden	67 / 4177.4	371 / 4151.1	-1.5% (-1.7% - -1.3%)	80.9% (75.8% - 86.0%)
Outcome: hospitalisation[b]				
BNT vs Unvaccinated				
Sweden	4/43849,16	42/43450,59	-0.0% (-0.0%- -0.0%)	91.1% (81.6%-100.0%)
BNT1BNT2 vs Unvaccinated				
Sweden	12/34566,5	43/33989,23	-0.0% (-0.0%- -0.0%)	71.0% (51.9%-90.0%)

CI denotes confidence interval, PYRS person-years, RD risk difference, and VE vaccine effectiveness. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date). [b]For severe outcomes only those country-specific comparisons where analyses were accomplished are presented.

Table 17. Meta-analysis for documented infection comparing vaccinated children with the BNT vaccine with unvaccinated of age 5 to 11 years.

Studied schedule	Compared schedule	Studied schedule events	Comparative schedule events	RD (95% CI)	VE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
BNT1	Unvaccinated	55065	60557	-1.5% (-4.3%-1.3%)	3.7% (-7.3%-14.7%)	<0.0001	DK, FI, SE, NO
BNT1BNT2	Unvaccinated	31801	35968	-5.5% (-9.2%--1.9%)	30.3% (-11.7%-72.2%)	<0.0001	DK, FI, NO

CI denotes confidence interval, DK Denmark, FI Finland, NO Norway, RD risk difference, SE Sweden, and VE vaccine effectiveness. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

Table 18. Meta-analysis for documented infection comparing vaccinated children with unvaccinated of age 12 to 17 years.

Studied schedule	Compared schedule	Studied schedule events	Comparative schedule events	RD (95% CI)	VE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
MOD1	Unvaccinated	327	9135	-1.3% (-2.2%--0.4%)	74.7% (65.0%-84.4%)	<0.0001	DK, FI, SE, NO
BNT1	Unvaccinated	12742	34588	-2.2% (-3.6%--0.8%)	51.1% (26.5%-75.6%)	<0.0001	DK, FI, SE, NO
MOD1MOD2	Unvaccinated	503	5815	-2.0% (-5.8%-1.9%)	79.7% (77.7%-81.7%)	<0.0001	DK, FI, SE, NO
BNT1BNT2	Unvaccinated	14776	34712	-3.3% (-5.7%--1.0%)	53.4% (14.9%-92.0%)	<0.0001	DK, FI, SE, NO
BNT1MOD2	Unvaccinated	49	658	-2.5% (-5.0%-0.0%)	82.2% (76.0%-88.3%)	<0.0001	FI, SE, NO
MOD1BNT2	Unvaccinated	1870	6809	-1.6% (-8.0%-4.8%)	19.4% (-50.0%-88.9%)	<0.0001	FI, SE, NO

CI denotes confidence interval, DK Denmark, FI Finland, NO Norway, RD risk difference, SE Sweden, and VE vaccine effectiveness. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

Cumulative incidence curves are presented in Figure 43 to 46 and country-specific results are presented in Table 15 and 16; meta-analyses for documented infection in Table 16 and 18. For both vaccinated and unvaccinated the cumulative incidences of documented covid-19 infection at day 75 varied across schedules and comparisons (from ≈ <1% to 50%), although the cumulative incidences across the comparisons of children and adolescents aged 12 years or older were more similar (from ≈ <1% to 10%).

In Denmark, comparing vaccinated (both one and two dose vaccinated with BNT) children aged 5 to 11 years with unvaccinated, the risk differences were approximately -5% for both vaccinated groups, corresponding to a VE of 8% for one-dose vaccinated and a VE of 9% for two-dose vaccinated. The absolute risk reduction of vaccination for this age category was not similarly observed in the other countries; however, having received a full primary vaccine schedule in Finland was associated with a risk difference of -8.4% with a corresponding VE of 65.4%. Of note, few children in this age group were included for analysis in Norway and Sweden (thus, these are most likely selected high-risk individuals); BNT1BNT2 vs unvaccinated was associated with risk differences of -1.0% (VE 4.7%) and -0.9% (VE not estimated) in the two countries. The meta-analyses showed significant heterogeneity with p-values <0.001 (VE of 4% and 30% for one and two doses of BNT as compared with unvaccinated).

Only Denmark and Finland could contribute with analyses for the outcome of hospitalisation among children aged 5 to 11 years and only Denmark assessed the risk of MIS-C. BNT vaccination schedules were associated with a lower risk of severe outcomes in these analysis; VE against hospitalisation of 85.7% and 34% for 1 dose in Denmark and Finland, respectively, and 91.2% for 2-dose BNT in Denmark (not estimable in Finland). One dose BNT lowered the risk of MIS-C in Denmark, VE of 88.4% (not estimable for the 2-dose BNT schedule).

Among children and adolescents aged 12 years or older, receiving a primary vaccine schedule was more clearly associated with a reduced risk of documented infection across schedules and countries than in the younger age category. In Denmark, risk differences ranged from -5.4% to -0.4% with corresponding VEs between 5.0% and 92.2%. In Finland, risk differences ranged from -14.9% to -2.0% with corresponding VEs between 60.4% and 84.1%. In Norway, risk differences ranged from -0.5% to 4.7% with corresponding VEs between -114.9% and 37.5%. In Sweden, risk differences ranged from -2.7% to -1.2% with corresponding VEs between 15.2% and 80.9%. The meta-analyses showed significant heterogeneity with p-values <0.001 (VE ranged from 19.4% and 82.2%).

No hospitalisations occurred in Denmark (nor for MIS-C), Finland, and Norway for any of the vaccinated children age 12 to 17 years; therefore, analyses could not be conducted. Analysis

of risk of hospitalisation was possible for the BNT-vaccinated only in Sweden: one dose of BNT was associated with a VE of 91%, and two doses with a VE of 71.0% compared with unvaccinated. Again, please note that comparing these two VEs from Sweden needs to take differences in calendar period of observation for the respective schedules (i.e. one dose: mainly prior omicron period [November 2021] and two doses: mainly during the period of emergence of omicron in Sweden [December 2021], Figure 42) into account, and therefore estimates cannot be directly compared.

10.3.4 Subgroup analyses by age for selected schedules in Denmark

Subgroup analyses according to age groups were conducted in Denmark comparing 1) heterologous with homologous booster schedules, and 2) heterologous or homologous booster schedules with the primary schedules counterpart. Results from these subgroup analyses are presented in Figure 38 to 41 and Table 15.

In the weighted analyses, comparing 3- vs. 3-dose schedules (i.e. heterologous with homologous booster schedules), we did not observe any major differences in the comparative vaccine effectiveness across age groups; the cumulative incidences of infection were highest for the younger age groups for both heterologous and homologous booster schedules. Risk differences of documented infection ranged between -10.8% and 6.5%, -15.6% and 5.8%, and -8.1% and 7.0% for the age group of 18 to 39 years, 40 to 59 years, and 60 years of older, respectively. Similarly, risk differences for covid-19 hospitalisation was around 0.0% for all age groups in the comparison of AZD1BNT2BNT3 vs BNT1BNT2BNT3 (that is, the one comparison that yielded sufficient number of cases for analysis of this outcome). In the matched analyses, comparing 3- vs. 2-dose schedules (i.e. heterologous or homologous booster schedules with the primary schedules counterpart), for which the homologous mRNA schedules could primarily be examined, risk differences were small in all age groups. However, the relative benefit of receiving a booster dose was proportionally greater among older individuals than younger individuals. E.g. the cVE for documented infection was >40% for individuals aged 75 years or older, whereas the cVE ranged between -9.5% and 6.1% for the younger age groups. Moreover, the benefit of a booster dose was more apparent for the severe covid-19 endpoints (covid-19 related hospitalisation, ICU admission, and death; could only be examined by age groups for the BNT 3- vs. 2- dose comparison) for all age groups. E.g. receiving a booster dose was associated with cVE of >76% for all age groups. The cVEs were generally higher across these severe outcomes among older individuals (cVE >90% for individuals age 75 years or older). Notably, the corresponding 95% CIs for the younger age groups were generally wider.

Figure 47. Cumulative incidence curves of documented covid-19 infection for weighted analysis comparing heterologous with homologous booster schedules by age groups in Denmark.

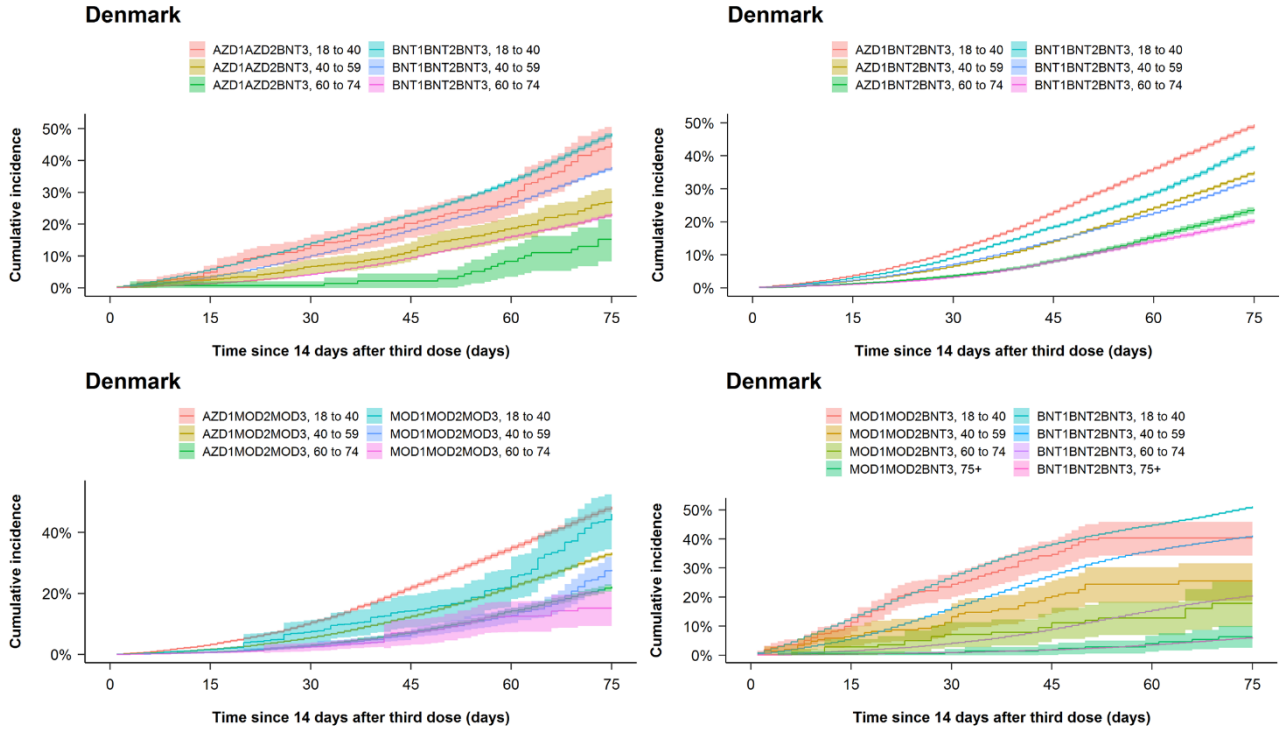


Figure 48. Cumulative incidence curves of covid-19 hospitalisation for weighted analysis comparing heterologous with homologous booster schedules by age groups in Denmark.

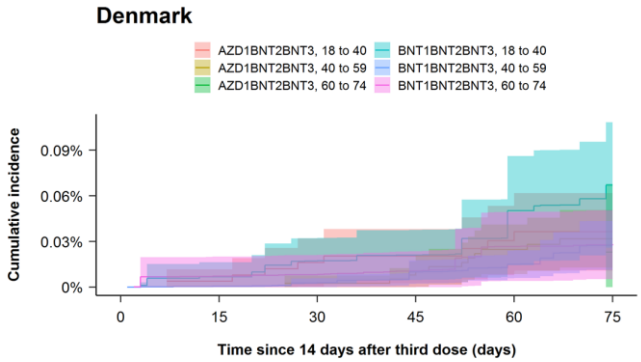


Figure 49. Cumulative incidence curves of documented covid-19 infection for matched analysis comparing heterologous or homologous booster schedules with the primary schedule counterpart by age groups in Denmark.

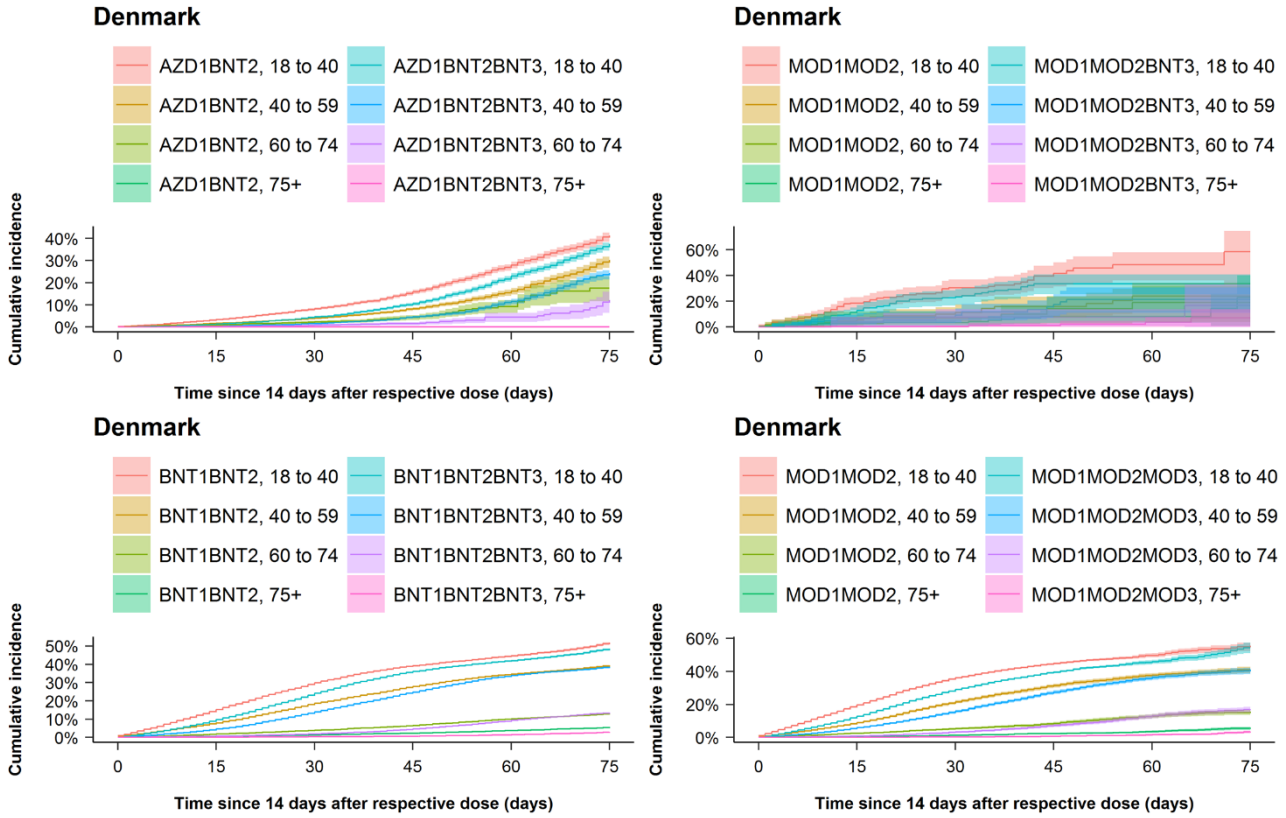


Figure 50. Cumulative incidence curves of severe covid-19 endpoints for matched analysis comparing heterologous or homologous booster schedules with the primary schedule counterpart by age groups in Denmark.

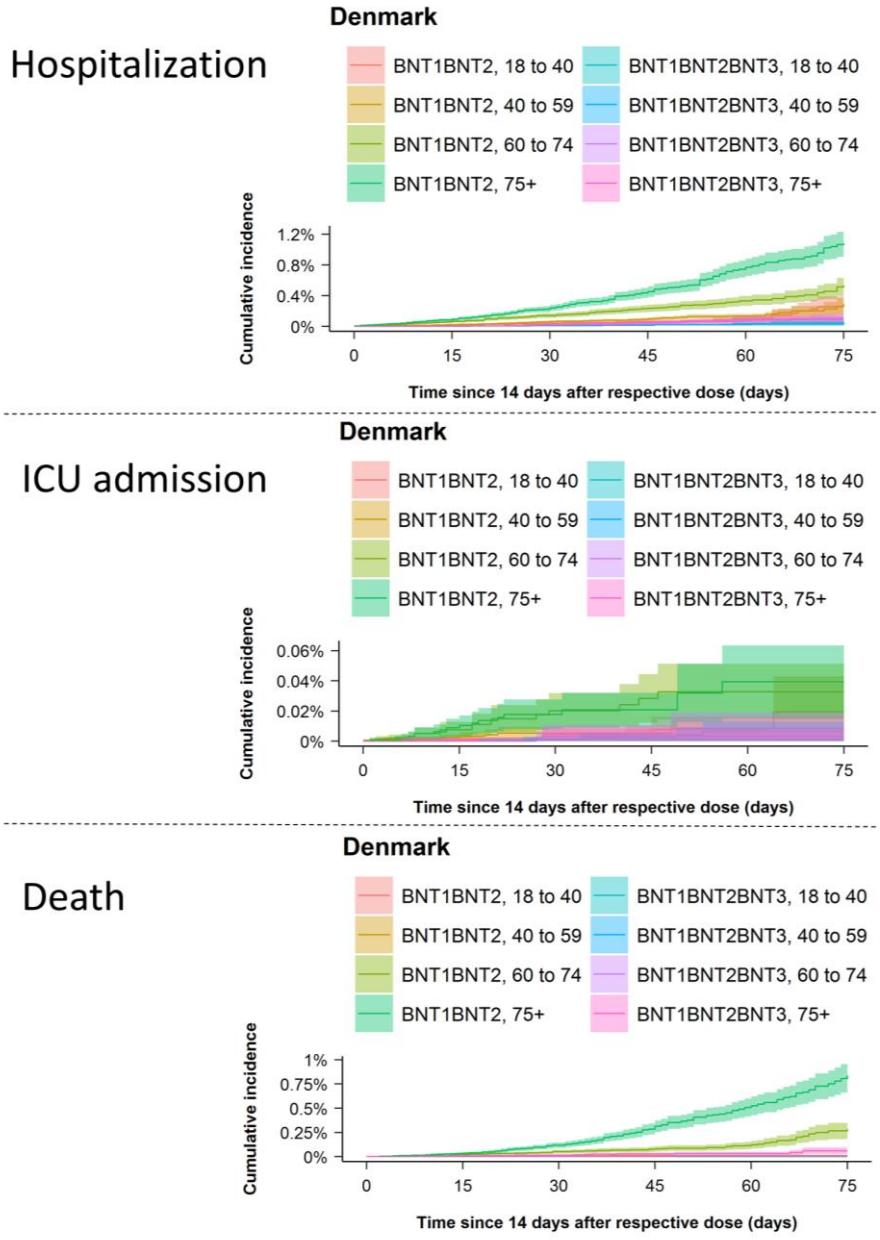


Table 19. Associations between covid-19 endpoints comparing heterologous with homologous booster vaccine schedules by age groups in Denmark.

Age group (years)	Studied schedule events / PYRS	Comparison schedule events / PYRS	RD (95% CI)	CVE (95 CI)
Outcome: documented infection				
AZD1AZD2BNT3 vs BNT1BNT2BNT3				
18 to 39	115 / 48.81	126076 / 33602.48	-2.76% (-9.61% - 4.1%)	5.7% (-8.46% - 19.85%)
40 to 59	108 / 77.6	307646 / 120162.61	-10.69% (-15.26% - -6.13%)	28.2% (16.19% - 40.21%)
60 to 74	18 / 25.94	88312 / 69804.95	-8.09% (-14.72% - -1.47%)	34.7% (6.38% - 63.02%)
AZD1BNT2BNT3 vs BNT1BNT2BNT3				
18 to 39	11436 / 3945.64	88010 / 26465.85	6.53% (5.57% - 7.5%)	-15.19% (-17.62% - -12.75%)
40 to 59	13166 / 6903.21	294487 / 121366.67	2.19% (1.54% - 2.85%)	-6.64% (-8.67% - -4.6%)
60 to 74	1618 / 1334.45	37654 / 25604.02	3.16% (1.86% - 4.46%)	-15.3% (-21.96% - -8.65%)
AZD1MOD2MOD3 vs MOD1MOD2MOD3				
18 to 39	5206 / 1858.31	28765 / 7181.52	2.45% (-6.69% - 11.59%)	-5.33% (-26.24% - 15.58%)
40 to 59	7677 / 4317.99	21444 / 8704.05	5.75% (0.98% - 10.52%)	-20.79% (-41.55% - -0.03%)
60 to 74	984 / 879.14	4885 / 3512.56	6.99% (1.22% - 12.76%)	-46.02% (-100.84% - 8.8%)
MOD1MOD2BNT3 vs BNT1BNT2BNT3				
18 to 39	136 / 40.62	133472 / 37821	-10.8% (-16.6% - -5%)	21.11% (9.78% - 32.43%)
40 to 59	48 / 29.98	312924 / 128822.57	-15.62% (-22.03% - -9.22%)	38% (22.43% - 53.58%)
60 to 74	20 / 22.28	126310 / 131383.62	-2.77% (-10.48% - 4.94%)	13.45% (-24% - 50.89%)
75+	<14 / 39.39	26375 / 77009.61	0.19% (-3.56% - 3.94%)	-3.08% (-64.26% - 58.1%)
Outcome: hospitalisation				
AZD1BNT2BNT3 vs BNT1BNT2BNT3				
18 to 39	<10 / 4351.7	63 / 30999.52	-0.03% (-0.08% - 0.02%)	45.8% (-4.67% - 96.27%)
40 to 59	11 / 7340.02	246 / 132875.77	0% (-0.02% - 0.03%)	-15.57% (-112.07% - 80.92%)
60 to 74	<10 / 1381.23	80 / 26856.78	-0.01% (-0.06% - 0.05%)	18.62% (-153.8% - 100%)

Table 20. Associations between covid-19 endpoints comparing heterologous and homologous booster vaccine schedules with the primary vaccine schedule counterpart by age groups in Denmark.

Age groups (years)	Studied schedule (3rd dose) event / PYRS	Compared schedule (2rd dose) event / PYRS	RD (95% CI)	CVE (95 CI)
Outcome: documented infection				
AZD1BNT2BNT3 vs AZD1BNT2				
18 to 39	1427 / 1235.39	1699 / 1143.11	-3.78% (-6.34% - -1.22%)	9.12% (3.19% - 15.05%)
40 to 59	641 / 1463.24	977 / 1391.62	-5.81% (-8.99% - -2.64%)	19.11% (9.72% - 28.51%)
60 to 74	47 / 292.94	102 / 284.42		
75+	0 / 1.11	0 / 1.11	0% (0% - 0%)	
MOD1MOD2BNT3 vs MOD1MOD2				
18 to 39	59 / 19.36	74 / 16.96		
40 to 59	18 / 12.65	18 / 12.3		
60 to 74	6 / 8.47	10 / 7.85		
75+	5 / 22.74	14 / 21.01		
BNT1BNT2BNT3 vs BNT1BNT2				
18 to 39	41629 / 12904.18	46567 / 11558.72	-3.17% (-4.15% - -2.2%)	6.13% (4.31% - 7.95%)
40 to 59	28726 / 14428.8	31636 / 13123.33	-0.7% (-1.49% - 0.09%)	1.77% (-0.22% - 3.76%)
60 to 74	3643 / 8927.12	4726 / 8576.36	0.63% (-0.08% - 1.34%)	-4.89% (-10.44% - 0.67%)
75+	629 / 8658.32	1665 / 8331.92	-2.72% (-3.18% - -2.26%)	48.04% (42.17% - 53.91%)
MOD1MOD2MOD3 vs MOD1MOD2				
18 to 39	16798 / 4313.09	19515 / 3797.36		
40 to 59	2638 / 1179.59	2904 / 1072.47	0.3% (-2.53% - 3.12%)	-0.77% (-7.7% - 6.15%)
60 to 74	427 / 713.76	503 / 680.22	1.43% (-0.91% - 3.77%)	-9.46% (-25.32% - 6.39%)

Age groups (years)	Studied schedule (3rd dose) event / PYRS	Compared schedule (2rd dose) event / PYRS	RD (95% CI)	CVE (95 CI)
75+	86 / 1131.94	207 / 1087.45	-2.36% (-3.7% - -1.02%)	39.92% (21.58% - 58.27%)
Outcome: hospitalisation				
BNT1BNT2BNT3 vs BNT1BNT2				
18 to 39	25 / 17177.5	72 / 14065.16	-0.21% (-0.36% - -0.05%)	76.52% (49.69% - 100%)
40 to 59	29 / 17306.33	113 / 14676.22	-0.23% (-0.38% - -0.09%)	78.81% (56.5% - 100%)
60 to 74	31 / 9505.7	168 / 8828.41	-0.42% (-0.55% - -0.29%)	78.96% (68.8% - 89.11%)
75+	28 / 8795.33	303 / 8420.88	-0.99% (-1.15% - -0.82%)	91.59% (87.69% - 95.49%)
Outcome: ICU admission				
BNT1BNT2BNT3 vs BNT1BNT2				
18 to 39	<3 / 17197.52	5 / 14063.72	-0.01% (-0.02% - 0%)	
40 to 59	4 / 17313.47	10 / 14678.27	-0.01% (-0.04% - 0.01%)	44.95% (-93.75% - 100%)
60 to 74	3 / 9514.44	18 / 8838	-0.02% (-0.05% - 0%)	71.66% (32.1% - 100%)
75+	<3 / 8794.54	18 / 8421.54	-0.04% (-0.06% - -0.01%)	90.4% (71.8% - 100%)
Outcome: Death				
BNT1BNT2BNT3 vs BNT1BNT2				
18 to 39	0 / 21798.1	3 / 17639.81	0% (0% - 0%)	
40 to 59	<3 / 20122.48	12 / 17076.8	-0.01% (-0.02% - 0%)	81.16% (47.73% - 100%)
60 to 74	<3 / 9987.66	70 / 9309.67	-0.28% (-0.38% - -0.19%)	98.6% (95.79% - 100%)
75+	20 / 8892.2	188 / 8541.78	-0.78% (-0.93% - -0.62%)	92.77% (88.44% - 97.11%)

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated.

10.3.5 Homologous primary schedules vs unvaccinated for risk of documented covid-19 in Denmark (quality control analysis number 1)

We conducted two sets of quality control analyses with use of the Danish study cohort. First, we examined the VE of homologous primary vaccine schedules with the BNT vaccine as compared with matched unvaccinated in relation to the risk of documented covid-19 infection among individuals age 18 years or older. Results are presented in Table 21 to 22 and Figure 51 to 52.

Table 21. Descriptive characteristics for matched comparison of homologous primary schedule vaccinated with mRNA vaccines vs. unvaccinated.

	Studied schedule				Unvaccinated			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
BNT1BNT2 vs. unvaccinated								
Denmark	959,820	47.7 (19.7)	53.4	22/01/21 - 28/02/22	959,820	47.4 (19.4)	52.8	22/01/21 - 28/02/22
MOD1MOD2 vs. unvaccinated								
Denmark	414,820	42.1 (17.1)	48.4	17/02/21 - 28/02/22	414,820	42 (17)	47.9	17/02/21 - 28/02/22

SD denotes standard deviation.

The individuals included for this analysis were vaccinated from 22 January 2021 to 28 February 2022 (variants of predominance during this period were alpha/beta from 15 March to 30 June 2021, delta from 15 July to 15 November 2021, and omicron from 28 December 2021 to 28 February 2022).

Figure 51. Cumulative incidence curves of documented infection and density plots for matched comparison of homologous primary schedule vaccinated with mRNA vaccines vs. unvaccinated.

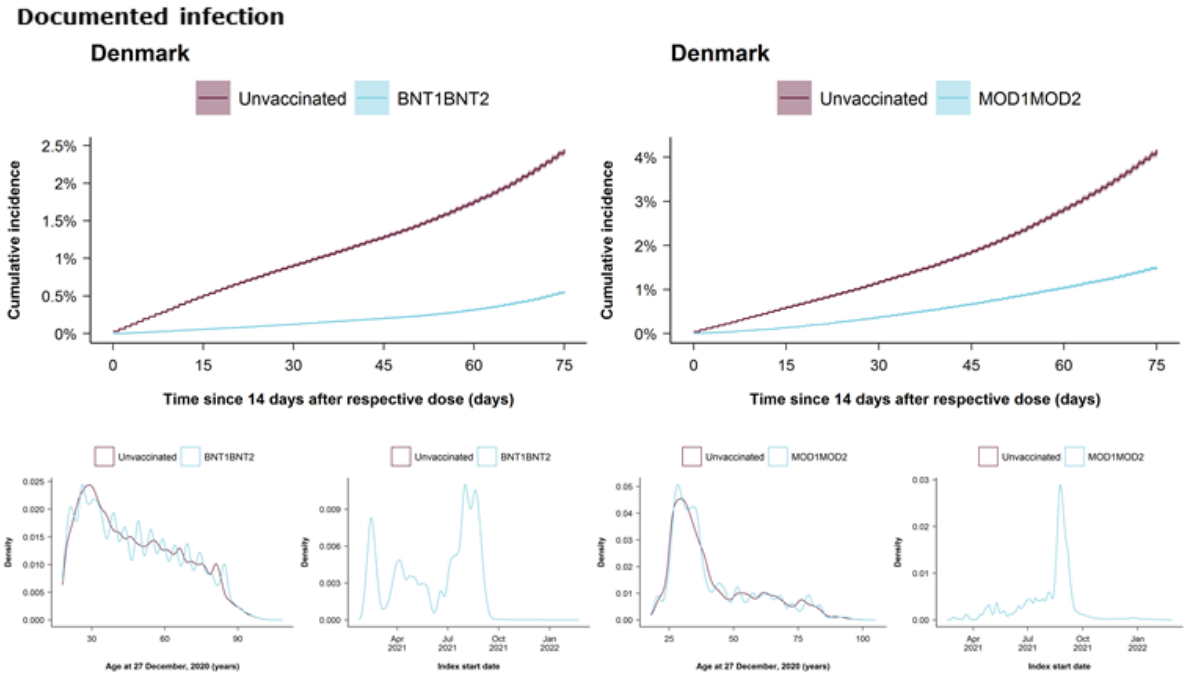
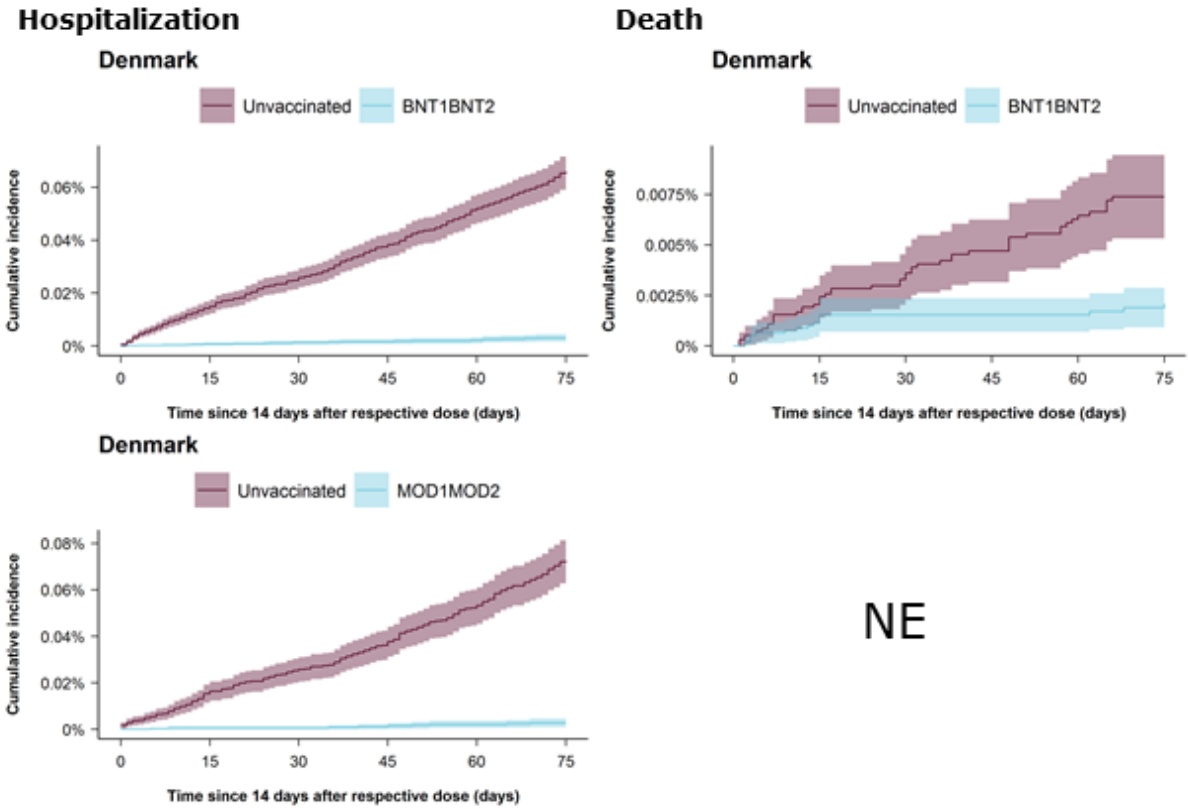


Figure 52. Cumulative incidence curves of severe covid-19 endpoints for matched comparison of homologous primary schedule vaccinated with mRNA vaccines vs. unvaccinated.



NE denotes not estimated. Cumulative incidence curves for ICU admission were not applicable.

Table 22. Association between covid-19 outcomes for matched comparison of homologous primary schedule vaccinated with mRNA vaccines vs. unvaccinated in Denmark.

Covid-19 outcome	Studied schedule	Unvaccinated	Measures of association at day 75 since start of follow-up	
	Events/PYRS	Events/PYRS	RD (95% CI)	VE (95% CI)
BNT1BNT2 vs. unvaccinated				
Documented infection	3451/135,195	15,948/133,548	-1.88% (-1.93%- -1.84%)	76.9% (76.1%-77.7%)
Hospitalisation	20/135971.2	434/134174.7	-0.06% (-0.07%- -0.06%)	95.5% (93.3% - 97.6%)
ICU admission	<3/135987.8	46/134194.2	-0.01% (-0.01%-0%)	97.8% (93.1% - 100%)
Death	16/136735.7	51/134690.3	-0.01% (-0.01%-0%)	71.3% (54.0%-88.5%)
MOD1MOD2 vs. unvaccinated				
Documented infection	4851/67,716	13,455/66,835	-2.66% (-2.74%- -2.59%)	63.8% (62.6%-64.9%)
Hospitalisation	9/68038.6	235/67080.18	-0.07% (-0.08%- -0.06%)	96.2% (93.6%-98.7%)
ICU admission				
Death				

CI denotes confidence interval, CVE comparative vaccine effectiveness, NE not estimable, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated.

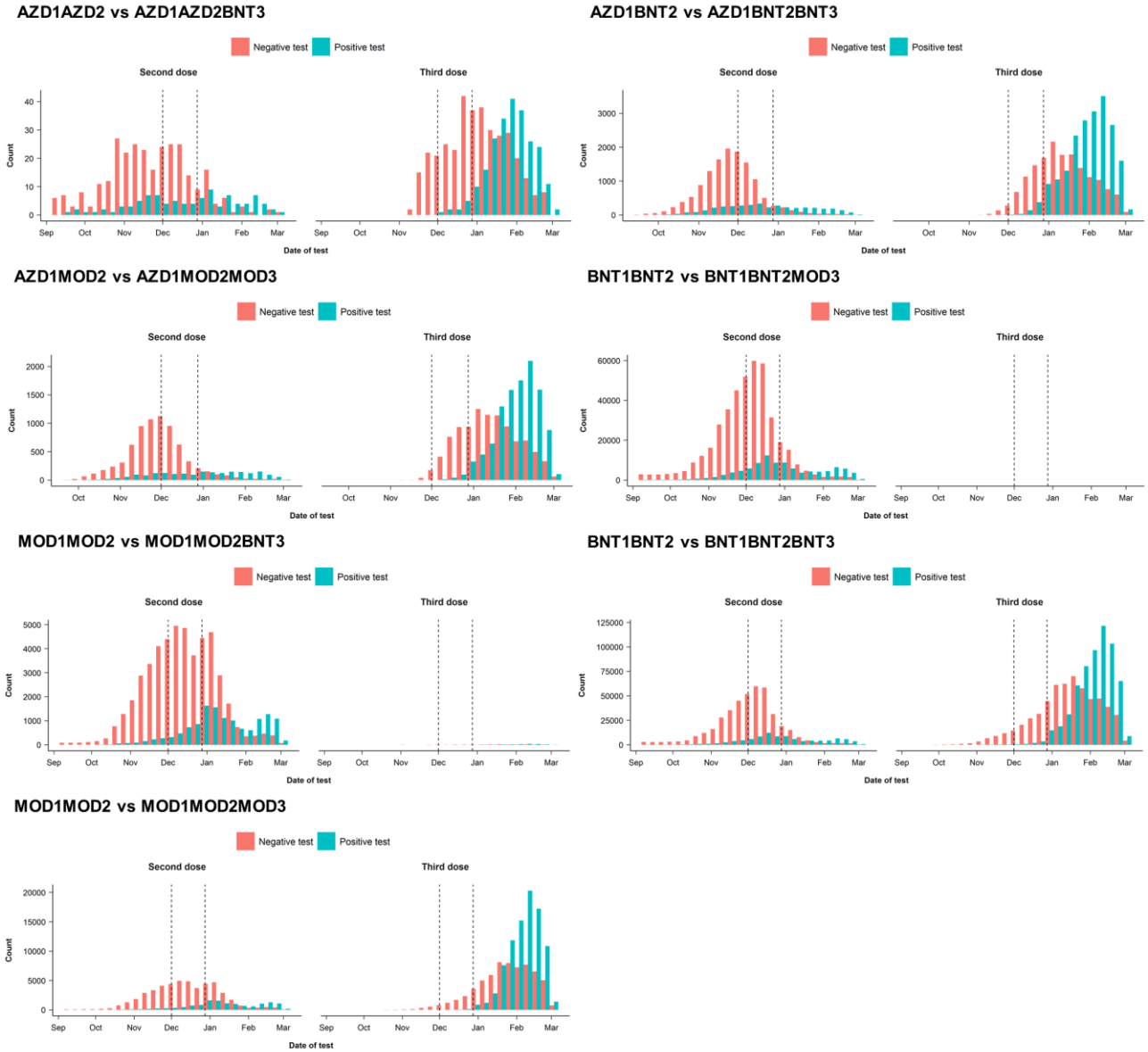
Fewer vaccinated individuals with BNT1BNT2 or MOD1MOD2 acquired covid-19 infection compared with unvaccinated during the 75 days of follow-up (RD of -1.9% and -2.7%, respectively), which corresponded to VEs of 77% and 64%, respectively. The cumulative incidence of covid-19 related hospitalisations was low for both vaccinated and unvaccinated groups; however, the risk was significantly reduced among vaccinated individuals (VE > 95%). In the comparison that included BNT1BNT2 vaccinated, VEs for covid-19 related ICU admission and death was 98% and 71%, respectively.

10.3.6 Comparative vaccine effectiveness of heterologous and homologous booster vs. primary schedule in Denmark with use of a test-negative case-control design (quality control analysis number 2)

In the second quality control analysis, we used a test-negative case-control design to compare the vaccine effectiveness of booster dose schedules from day 14 since day of receiving the booster dose and 75 days onwards with primary schedules. The distribution of positive and negative tests by calendar period are presented in Figure 53. Table 23 presents the main results and Table 24 presents the results stratified by calendar period (together with the main results). In the main analysis the cVEs ranged from -24% to 65%; the negative cVE estimate was found in the comparison of MOD1MOD2MOD3 vs. MOD1MOD2 (and similarly when comparing BNT1BNT2BNT3 vs. MOD1MOD2). Given the distribution of tests among primary and booster schedules by calendar period, we considered if the cVE estimates were dependent on if the booster dose was received primarily during the period of the omicron wave in Denmark. E.g. individuals who had received primary vaccination schedules including AZD, in general received their booster dose earlier (i.e. to a greater extent prior to the omicron wave) than the mRNA-only-based schedules, and comparative VE estimates for the AZD-including schedules were relatively higher (cVE ranged from 44% to 49%). As such, when stratifying by calendar period, we found that the cVEs were between 55% and 84% in the calendar periods before the Omicron wave (including >76% for the MOD1MOD2MOD3 vs. MOD1MOD2) while the estimates were generally lowered for all booster schedules during the omicron wave (for MOD1MOD2MOD3 vs. MOD1MOD2 the comparative VE was -34% in this period). As such, among individuals tested for covid-19 infection, those individuals who had received a booster dose were less likely to be cases (i.e. having covid-19 infection) compared with test-negative controls, in particular in the period prior to the omicron wave in Denmark. Thus, findings overall indicated that having received a booster dose was associated with an improved protection against documented covid-19 infection, relative to having received a primary vaccine schedule. However, during the omicron wave results were likely biased and findings were imprecise. In addition, we did not observe lower cVE among heterologous booster vaccinated as compared (indirectly) with homologous booster vaccinated. Moreover, in another pre-planned analysis (Table 25), we compared the effectiveness against documented infection with day 2 to 6 since the booster dose (at which time the booster dose is not considered to have had an effect on the protection against covid-19 yet; furthermore, this analysis would likely be less affected by calendar period and differences in test/risk behaviour). For the majority of comparisons, cVE ranged from 43% to 78%, however 95% CIs were wide, and the AZD1AZD2BNT3 showed a cVE of -24.2% (-328.7%-64%; few positive and negative test for the day 2 to 6 period; most likely due to relative lower infection rates in the population at this time for the majority of these included individuals [that is, primarily November and early December 2021]). For the larger-sized comparisons (AZD1BNT2BNT3, AZD1MOD2MOD3,

BNT1BNT2BNT3, and MOD1MOD2MOD3 [ie, with narrower 95% CIs]), the cVEs were between 43% and 51%.

Figure 53. Distribution of positive and negative tests for covid-19 during the study period by compared primary (2 dose) and booster (3 dose) schedules.



The dashed lines denotes (from left to right) 1 December 2021 and 28 December 2022. The period from 28 December and onwards throughout the study period was characterized by omicron predominance and very high covid-19 infection rates in Denmark.

Table 23. Results from comparative vaccine effectiveness of documented covid-19 infection comparing booster schedules with primary vaccine schedules counterpart with use of a test-negative case-control design during study period 6 September 2021 to 28 February 2022.

Primary schedule (2 doses)	Booster schedule (3 doses)	Total no. of tests	Primary schedule (2 doses)		Booster schedule (3 doses)		CVE (95% CI)
			Negative test N (%)	Positive test N (%)	Negative test N (%)	Positive test N (%)	
AZD1AZD2	AZD1AZD2BNT3	989	294 (29.7%)	97 (9.8%)	360 (36.4%)	238 (24.1%)	49.7% (18.7%-68.9%)
AZD1BNT2	AZD1BNT2BNT3	53077	13024 (24.5%)	3977 (7.5%)	16116 (30.4%)	19960 (37.6%)	44.2% (39.9%-48.3%)
AZD1MOD2	AZD1MOD2MOD3	30166	7272 (24.1%)	1996 (6.6%)	10005 (33.2%)	10893 (36.1%)	48.0% (42.4%-53.0%)
BNT1BNT2	BNT1BNT2MOD3	522163	423064 (81.0%)	98952 (19.0%)	86 (0.0%)	61 (0.0%)	64.7% (49.4%-75.4%)
MOD1MOD2	MOD1MOD2BNT3	63043	49177 (78.0%)	13514 (21.4%)	175 (0.3%)	177 (0.3%)	15.5% (-7.7%-33.7%)
BNT1BNT2	BNT1BNT2BNT3	1723791	423064 (24.5%)	98952 (5.7%)	592585 (34.4%)	609190 (35.3%)	16.0% (14.9%-17.1%)
MOD1MOD2	MOD1MOD2MOD3	217462	49177 (22.6%)	13514 (6.2%)	65160 (30.0%)	89611 (41.2%)	-23.6% (-27.7%--19.5%)
MOD1MOD2	BNT1BNT2BNT3	1264466	49177 (3.9%)	13514 (1.1%)	592585 (46.9%)	609190 (48.2%)	-16.9% (-19.9%--14.0%)
BNT1BNT2	MOD1MOD2MOD3	676787	423064 (62.5%)	98952 (14.6%)	65160 (9.6%)	89611 (13.2%)	13.8% (12.0%-15.6%)

CVE denotes comparative vaccine effectiveness. CVE was calculated as 1 – adjusted OR; OR was adjusted for calendar week of testing, number of positive PCR for covid-19 per day (spline with 5 knots), age, sex, region of residence, vaccine priority group, and comorbidities.

Table 24. Results from comparative vaccine effectiveness of documented covid-19 infection comparing booster schedules with primary vaccine schedules counterpart with use of a test-negative case-control design during study period 6 September 2021 to 28 February 2022 by calendar periods.

	Total no. of tests	Primary schedule (2 doses)		Booster schedule (3 doses)		CVE (95% CI)
		Negative test N (%)	Positive test N (%)	Negative test N (%)	Positive test N (%)	
AZD1AZD2 vs AZD1AZD2BNT3						
Whole study period[a]	989	294 (29.7%)	97 (9.8%)	360 (36.4%)	238 (24.1%)	49.7% (18.7%-68.9%)
Before 1 December 2021	259	177 (68.3%)	34 (13.1%)	48 (18.5%)	0	
1 December to 28 December 2021	213	75 (35.2%)	18 (8.5%)	109 (51.2%)	11 (5.2%)	84.3% (19.6%-96.9%)
After 28 December 2021	517	42 (8.1%)	45 (8.7%)	203 (39.3%)	227 (43.9%)	8.4% (-64.7%-49.1%)
AZD1BNT2 vs AZD1BNT2BNT3						
Whole study period[a]	53077	13024 (24.5%)	3977 (7.5%)	16116 (30.4%)	19960 (37.6%)	44.2% (39.9%-48.3%)
Before 1 December 2021	9210	7785 (84.5%)	1166 (12.7%)	251 (2.7%)	8 (0.1%)	79.5% (58.2%-90%)
1 December to 28 December 2021	9996	4390 (43.9%)	1122 (11.2%)	3770 (37.7%)	714 (7.1%)	55.1% (48.9%-60.7%)
After 28 December 2021	33871	849 (2.5%)	1689 (5.0%)	12095 (35.7%)	19238 (56.8%)	36.4% (30.1%-42.2%)
AZD1MOD2 vs AZD1MOD2MOD3						
Whole study period[a]	30166	7272 (24.1%)	1996 (6.6%)	10005 (33.2%)	10893 (36.1%)	48% (42.4%-53%)
Before 1 December 2021	4568	3986 (87.3%)	481 (10.5%)	101 (2.2%)	0	
1 December to 28 December 2021	5697	2657 (46.6%)	431 (7.6%)	2394 (42.0%)	215 (3.8%)	65.1% (56.8%-71.8%)
After 28 December 2021	19901	629 (3.2%)	1084 (5.4%)	7510 (37.7%)	10678 (53.7%)	39% (31.4%-45.8%)
BNT1BNT2 vs BNT1BNT2MOD3						
Whole study period[a]	522163	423064 (81.0%)	98952 (19.0%)	86 (0.0%)	61 (0.0%)	64.7% (49.4%-75.4%)
Before 1 December 2021	197308	180146 (91.3%)	17153 (8.7%)	8 (0.0%)	<3 (0.0%)	-27.9% (-935.2%-84.2%)
1 December to 28 December 2021	226425	190418 (84.1%)	36005 (15.9%)	<3 (0.0%)	0	
After 28 December 2021	98430	52500 (53.3%)	45794 (46.5%)	76 (0.1%)	60 (0.1%)	62% (45.1%-73.6%)

MOD1MOD2 vs MOD1MOD2BNT3						
Whole study period[a]	63043	49177 (78.0%)	13514 (21.4%)	175 (0.3%)	177 (0.3%)	15.5% (-7.7%-33.7%)
Before 1 December 2021	17433	16413 (94.1%)	1001 (5.7%)	19 (0.1%)	0	
1 December to 28 December 2021	19956	17284 (86.6%)	2641 (13.2%)	31 (0.2%)	0	
After 28 December 2021	25654	15480 (60.3%)	9872 (38.5%)	125 (0.5%)	177 (0.7%)	0.1% (-28.9%-22.5%)
BNT1BNT2 vs BNT1BNT2BNT3						
Whole study period[a]	1723791	423064 (24.5%)	98952 (5.7%)	592585 (34.4%)	609190 (35.3%)	16.0% (14.9%-17.1%)
Before 1 December 2021	237600	180146 (75.8%)	17153 (7.2%)	39419 (16.6%)	882 (0.4%)	79.5% (77.8%-81.2%)
1 December to 28 December 2021	329462	190418 (57.8%)	36005 (10.9%)	94900 (28.8%)	8139 (2.5%)	68.6% (67.1%-70.1%)
After 28 December 2021	1156729	52500 (4.5%)	45794 (4.0%)	458266 (39.6%)	600169 (51.9%)	-3.9% (-5.5%--2.3%)
MOD1MOD2 vs MOD1MOD2MOD3						
Whole study period[a]	217462	49177 (22.6%)	13514 (6.2%)	65160 (30.0%)	89611 (41.2%)	-23.6% (-27.7%--19.5%)
Before 1 December 2021	18823	16413 (87.2%)	1001 (5.3%)	1392 (7.4%)	17 (0.1%)	79.1% (64.9%-87.5%)
1 December to 28 December 2021	26464	17284 (65.3%)	2641 (10.0%)	6218 (23.5%)	321 (1.2%)	75.8% (70.7%-80.1%)
After 28 December 2021	172175	15480 (9.0%)	9872 (5.7%)	57550 (33.4%)	89273 (51.9%)	-33.9% (-38.7%--29.3%)
MOD1MOD2 vs BNT1BNT2BNT3						
Whole study period[a]	1264466	49177 (3.9%)	13514 (1.1%)	592585 (46.9%)	609190 (48.2%)	-16.9% (-19.9%--14%)
Before 1 December 2021	57715	16413 (28.4%)	1001 (1.7%)	39419 (68.3%)	882 (1.5%)	65.7% (57.7%-72.1%)
1 December to 28 December 2021	122964	17284 (14.1%)	2641 (2.1%)	94900 (77.2%)	8139 (6.6%)	56.9% (52.0%-61.2%)
After 28 December 2021	1083787	15480 (1.4%)	9872 (0.9%)	458266 (42.3%)	600169 (55.4%)	-48.6% (-53.1%--44.3%)
BNT1BNT2 vs MOD1MOD2MOD3						
Whole study period[a]	676787	423064 (62.5%)	98952 (14.6%)	65160 (9.6%)	89611 (13.2%)	13.8% (12.0%-15.6%)
Before 1 December 2021	198708	180146 (90.7%)	17153 (8.6%)	1392 (0.7%)	17 (0.0%)	88.0% (80.5%-92.6%)
1 December to 28 December 2021	232962	190418 (81.7%)	36005 (15.5%)	6218 (2.7%)	321 (0.1%)	80.9% (78.3%-83.2%)
After 28 December 2021	245117	52500 (21.4%)	45794 (18.7%)	57550 (23.5%)	89273 (36.4%)	7.3% (5.2%-9.4%)

CVE denotes comparative vaccine effectiveness. Grey-colored cells denotes not estimated. CVE was calculated as 1 – adjusted OR; OR was adjusted for calendar week of testing, number of previous PCR test for covid-19, age, sex, region of residence, vaccine priority group, and comorbidities. By 28 December 2021 omicron accounted for

>90% of all document covid-19 infections in Denmark. [a] Whole study period includes the calendar period 6 September 2021 to 28 February 2022 and these results are also presented in Table 23.

Table 25. Results from comparative vaccine effectiveness of documented covid-19 infection comparing booster schedules day 14 to 89 with day 2 to 6 after the date of the booster vaccine with use of a test-negative case-control design during 6 September 2021 to 28 February 2022.

Booster schedules	Total number of tests	Number of tests 2-6 days after 3rd dose		Number of tests during 14 to 14+75 days after 3rd dose		CVE (95% CI)
		Negative test	Positive test	Negative test	Positive test	
AZD1AZD2BNT3	626	23 (3.7%)	5 (0.8%)	360 (57.5%)	238 (38.0%)	-24.2% (-328.7%-64.0%)
AZD1BNT2BNT3	38476	1789 (4.6%)	611 (1.6%)	16116 (41.9%)	19960 (51.9%)	48.7% (41.8%-54.8%)
AZD1MOD2MOD3	22143	996 (4.5%)	249 (1.1%)	10005 (45.2%)	10893 (49.2%)	50.9% (40.4%-59.6%)
BNT1BNT2MOD3	155	5 (3.2%)	3 (1.9%)	86 (55.5%)	61 (39.4%)	78.4% (-523.3%-99.3%)
MOD1MOD2BNT3	378	13 (3.4%)	13 (3.4%)	175 (46.3%)	177 (46.8%)	75.3% (9.9%-93.2%)
BNT1BNT2BNT3	1299752	62978 (4.8%)	34999 (2.7%)	592585 (45.6%)	609190 (46.9%)	48.4% (47.4%-49.3%)
MOD1MOD2MOD3	171355	8323 (4.9%)	8261 (4.8%)	65160 (38.0%)	89611 (52.3%)	42.8% (40.3%-45.2%)

10.4 Adverse events and adverse reactions

Not applicable. Secondary use of data.

11. DISCUSSION

11.1 Key results

This study compared the effectiveness of 1) heterologous primary- and booster covid-19 vaccination schedules with corresponding homologous schedules and 2) heterologous or homologous booster schedules with primary vaccination schedules in the Nordic countries. Additional secondary objectives included examining the (comparative) vaccine effectiveness according to covid-19 variant, waning immunity, and age groups including children and adolescents.

Across the four countries and included comparisons, our results largely support that heterologous primary and booster schedules with the AZD, BNT, and/or MOD vaccines provided protection against covid-19 outcomes that was not inferior to the vaccine effectiveness of homologous schedules (objective 1).

Similarly, our findings largely support that both heterologous and homologous booster dose schedules in the Nordic countries improved the protection against covid-19 outcomes as compared to primary schedules (objective 2). However, while booster dose schedules improved the protection against severe covid-19 outcomes, the effectiveness against documented infection was less distinct for some country-specific comparisons, particularly in Denmark.

Given the high correlation between calendar period and the respective vaccination schedules, and calendar period and the covid-19 variant of predominance, our results within the individual comparisons were primarily variant specific (objective 3). This was supported by results from the omicron-specific booster schedules analyses that were compatible to the main findings.

The analyses of waning immunity, where extending the follow-up from 75 days to 180 days for the primary schedules, were not suggestive of an inferior longer-term protection of the heterologous schedules as compared with the homologous schedules (objective 4).

Our analyses of the vaccine effectiveness of primary schedules among children and adolescents aged 5 to 11 and 12 years or older found high protection against covid-19 endpoints as compared with unvaccinated (objective 5); this includes risk of hospitalisation and MIS-C for those schedules, countries, and age groups where these severe endpoints could be examined.

Age-stratified analysis of the main (adult) study cohorts in Denmark did not suggest that effectiveness of heterologous booster schedules performed differently across age groups as compared with homologous booster schedules. The assessment of the protective benefit of receiving a third (booster) dose as opposed to not receiving a third dose according to age

groups was mainly possible for the homologous mRNA-vaccine schedules (specifically BNT; as the subdividing the individual heterologous schedules by age resulted in too small subgroups for adequate age-stratified analyses). In this analysis, we found that the effectiveness of a booster dose schedule increased with increasing age and this observation was most likely due to differences in the underlying calendar periods. However, the booster dose schedules provided consistent improved protection against severe covid-19 outcomes across all age groups.

The quality control analysis that assessed the effectiveness of homologous primary schedules with the BNT or MOD vaccine compared with unvaccinated individuals in Denmark, was able to reproduce the high vaccine effectiveness estimated reported in previous studies. Finally, the results of the quality control analysis with use of a test-negative case-control design to compare VE between booster vs. primary schedule vaccinated in Denmark were comparable to our main findings (objective 2). Also the effectiveness of heterologous and homologous booster schedules was overall similar in these analyses. However, at the time that the majority of the homologous mRNA schedule vaccinated individuals received a booster dose, the infection rates were very high due to the omicron surge in Denmark, which affected the results during this period. See further discussion below in subsection '*Interpretation'* on limitations to the test-negative design.

11.2 Limitations

Our results should be interpreted in light of potential limitations.

As represented by our descriptive results, the compared vaccine schedules were strongly correlated with specific calendar periods and thus also correlated with the covid-19 variant of predominance at this time. This means that our results are primarily variant-specific.

Similarly, our results in terms of absolute numbers of the studied covid-19 endpoints (primarily the outcome of documented infection) were correlated to the country-specific background infection rates at time of the distinct comparisons. E.g. the majority of the Danish booster schedule analyses were conducted during a period where the infection rates were very high (i.e. cumulative incidences for these analyses were around 40%, due to the marked omicron surge in Denmark) relative to the lower incidence rates observed in the other countries such as in Finland. Likewise and as also observed in our results, the omicron wave during December 2021 to February 2022 in our study period resulted in proportionally more individuals infected in Denmark followed by Norway and Sweden, and lastly, Finland where the outbreaks were relatively smaller. While this potentially provides means for assessing the (comparative) vaccine effectiveness given different outbreak scenarios and infection rates, this also weakens the opportunity to directly compare the absolute risk differences between compared groups across countries. Of note, any absolute difference would produce proportionally larger relative

effect sizes (that is, the vaccine effectiveness measure) when the absolute rates are low relative to being higher, and we observed much variation in the cumulative incidences of infection across countries. As such, indirect comparisons of schedules and specific country estimates, in particular for the outcome of infection, is in general made difficult, and also highlights the need for both absolute and relative measures to properly interpret effectiveness estimates.

In addition, we utilised a comparative study design and controlled for calendar time to mitigate biases from temporal differences in the covid-19 endpoints ascertainment for each individual comparison. However, the adjustment for calendar time in our weighted analysis was defined by monthly intervals, which could potentially have been too unrefined for periods with rapid increases in the infection rates, such as the omicron wave; thus, bias, particularly of relevance to the endpoint of documented infection, could have been introduced. E.g. if differences in calendar time was not sufficiently controlled for between the compared schedules, the schedule that contributed with most time at risk during the calendar period with a relative higher infection rate would inherently have relatively higher observed incidence rates to the compared schedule.

In addition, another limitation to the studied outcome documented infection was its dependency on secondary use of national microbiology PCR test results. Therefore we did not have complete registration of all infected individuals in the populations but only those who tested positive.

Similarly, differences in national testing strategies and capacities and over-time changes hereto also likely influenced our results for documented infection. E.g. compared to the other Nordic countries, Denmark had proportionally higher recorded use of PCR tests for covid-19 during the study period and had implemented an open public testing policy where PCR tests were made freely available to anyone, regardless of symptoms or being in certain key/risk groups. During the omicron period, daily covid-19 tests peaked at approximately 40.2, 8.6, 6.6, and 5.3 per 1000 individuals in Denmark, Finland, Norway, and Sweden, respectively (as of 1 March 2022 the total number of covid-19 tests per 1000 individuals was 10,808.7, 1803.9, 1976.0, and 1772.1, in the four countries, respectively).(50) Also, whereas at-home antigen-self-tests (i.e. tests that would not be registered in our utilised national registers) were not incorporated into the national testing strategy in Denmark, these were made widely available and part of the testing strategies for more rural regions in Finland. Moreover, after the emergence of omicron in Finland, home-testing was made part of common practice in all regions (not just rural regions) due to smaller testing capacity. Given, these differences in testing strategies across countries, the proportion of captured individuals with this test positive outcome likely differed on whether having symptoms, reason for testing (e.g. contact tracing, routine screening) and proportion of accidental findings, which again also varied within each

country across the studied calendar period. We did not have individual-level data on symptoms or specific indications for being tested. These considerations on outcome ascertainment further highlight limitations for comparing the individual schedule comparisons across countries as well as schedule comparisons within the same country during different calendar periods. As highlighted our comparative design mitigates these concerns within the individual country-specific comparisons. Figure 54 to 57 below presents country-specific test data and positive test data from the publicly available source information ourworldindata.org (50) and the table below presents the overall testing strategies for each country.

Figure 54. Daily tests with 7 day-rolling average for covid-19 per thousand individuals by country (source: ourworlddata.org(50)).

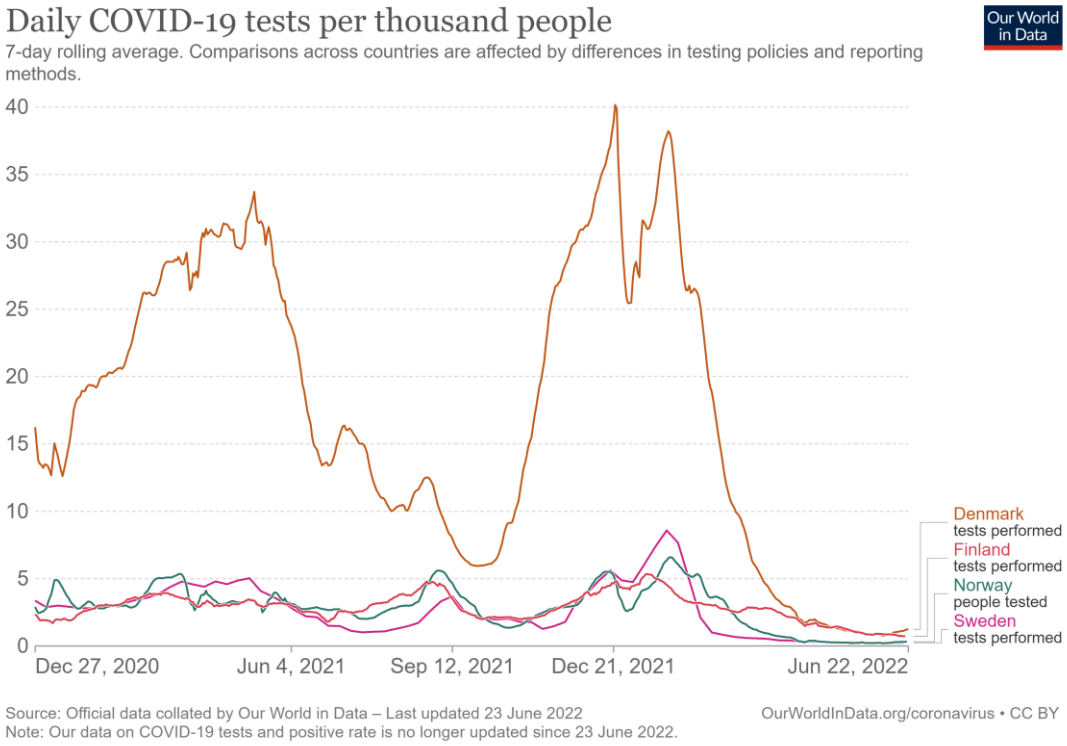


Figure 55. Country-specific covid-19 test positive rates with a 7 day-rolling average (source: ourworlddata.org(50)).

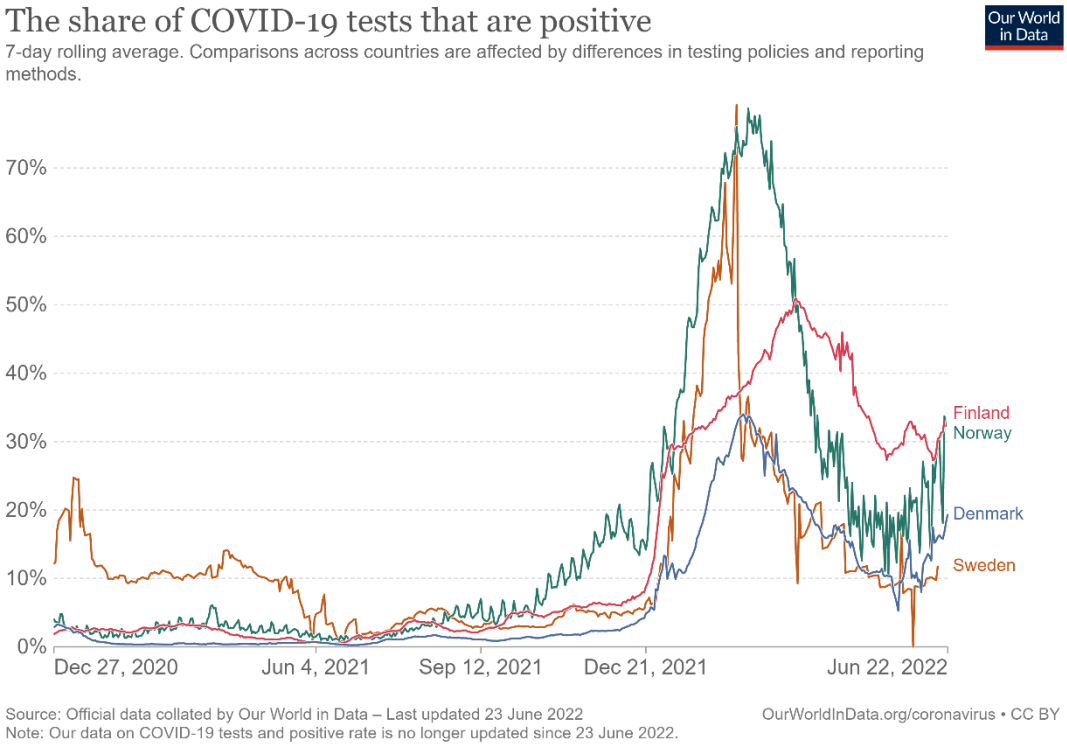


Figure 56. Total number of test performed for covid-19 per thousand individuals by country (source: ourworlddata.org(50)).

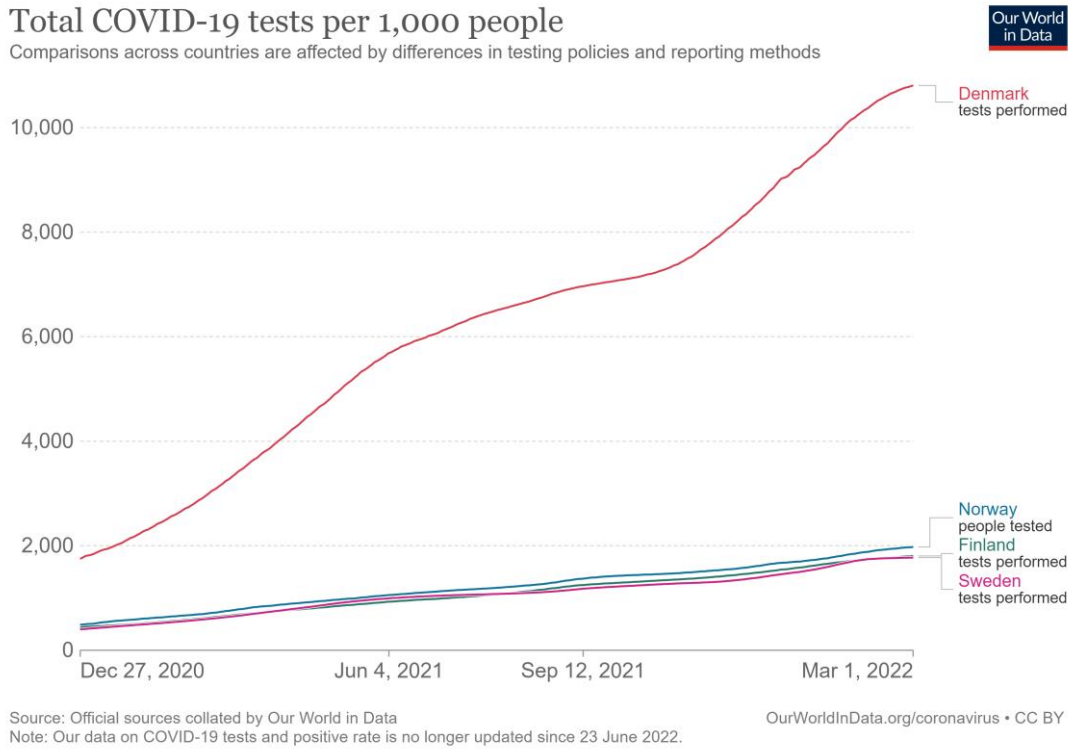
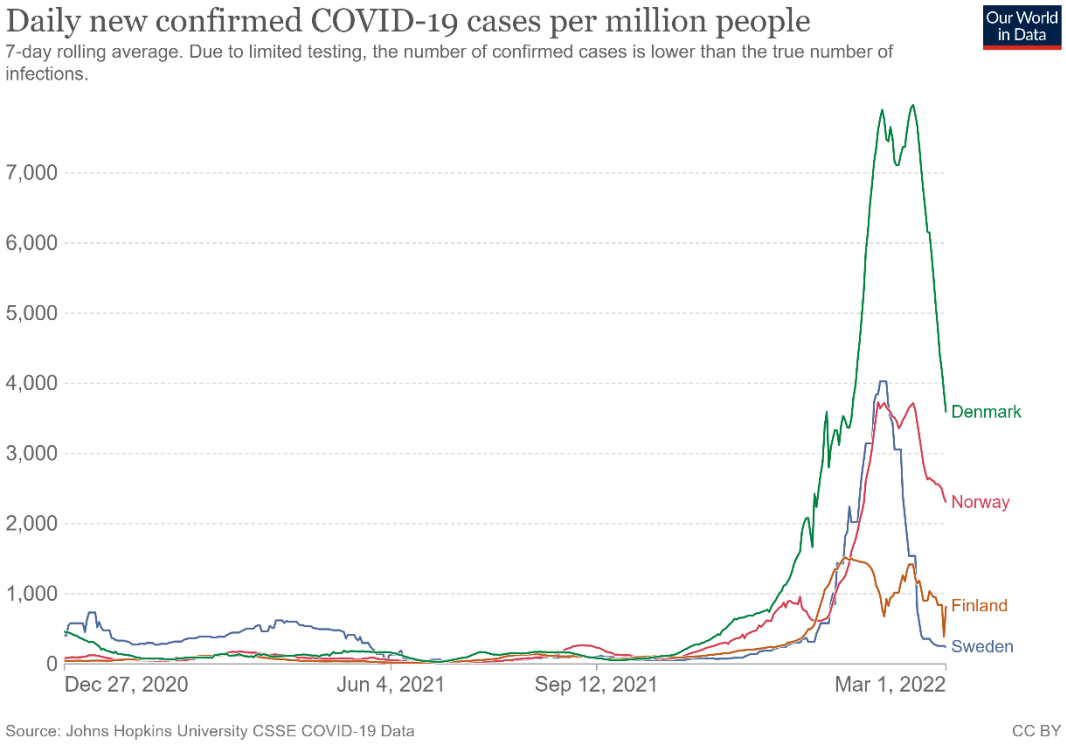


Figure 57. Number of test positive individuals for covid-19 per million individuals with a 7 day-rolling average by country (source: ourworlddata.org(50)).



Country	Main points in testing strategies
Denmark	Overall, testing was easily accessible, free of charge, and available to everyone regardless of symptoms or close contact tracing. Close contact tracing was recommend throughout the study period and included testing on days 4 and 6 (primarily) after the last contact incident; however, governmental assistance with active contact tracing diminished during the period of Omicron predominance. Routine screening tests were performed in certain groups such as among health care and social care workers, in workplaces, in relation to in-/outpatient contacts, and in primary schools. The test capacity was very high in Denmark, with one of the world's highest amount of test performed per capita. Hence, at most time points during the study period, 15-25% of the population were PCR tested at least once a week.(50) Besides PCR testing, an extensive antigen-testing programme (with an even higher weekly test frequency) supplemented the Danish testing strategy and was primarily intended for asymptomatic individuals (e.g. for contact tracing) whereas symptomatic individuals were recommended PCR testing. Likewise, individuals with a positive antigen test were recommended a confirmatory PCR test. In December 2021, self-administered antigen home tests became more widely available and used (however, during the omicron wave, PCR-test was widely used with a national test capacity of 200.000 daily tests). By 1 February 2022, covid-19 was no longer considered a societally critical disease, and the PCR testing capacity and its use subsequently descaled until end of study period.
Finland	All symptomatic individuals were recommended testing until 10 February 2021. From hereafter to 13 September 2021, testing was recommended for individuals with severe symptoms, risk groups, pregnant, health care workers, and to the extent that the national testing capacity allowed it, all symptomatic individuals (regardless of severity; in principle all symptomatic were tested during this time window). From hereafter to December 2021 testing was recommended for all symptomatic unvaccinated, those with prior SARS-Cov-2 over 6 months ago or one dose vaccinated and two dose vaccinated if they were either: in hospital emergency, SARS-CoV-2 exposed individuals, risk groups, individuals with suspected decreased vaccination protection, health care workers or in long-term-care units. From mid-December, Finland was unable to PCR test all symptomatic that wanted to be tested due to increasing number of Omicron cases. On 10

	February 2022 testing strategy was officially changed and PCR testing was made recommended for individuals with severe symptoms, risk groups, pregnant, and health care workers; however, in principal this change happened during December 2021.
Norway	During 2021 and 2022 testing was available to more or less anyone regardless of symptoms, in close contact with covid-19 infected individuals, vaccination status etc.. Close contacts were recommended testing on day 3 and 7 (this recommendation was suspended between 27 September – 29 November 2021), and; however, since May 2021, fully vaccinated or individuals with previous recorded infection were excepted for this recommendation. Since 19 October 2021 more use of rapid test was introduced and subsequent confirmation with PCR testing was recommended. From 23 January 2022, PCR tests were no longer recommended for those who had received a booster dose. From 12 February 2022, testing was only recommended for adults with symptoms.
Sweden	Until 1 November 2021 (during the study period), testing was available for all symptomatic individuals regardless of vaccination status. From hereafter, PCR testing was recommended for unvaccinated symptomatic people and vaccinated individuals in certain key/risk groups/environments, and for groups and situations at risk of severe covid-19 and transmission. On 22 November 2021 testing recommendations were adjusted to include all symptomatic individuals regardless of vaccination status. On 9 February 2022, PCR testing and contact tracing recommendations were changed to aim at protecting people in health care and elderly care (being staff, patients, and care recipients) who have an increased risk of severe covid-19.

Another consideration when interpreting the results for documented infection is that differences in individuals' self-seeking testing behaviour or general risk behaviour could also affect the results for this study endpoint. E.g. if one comparison group relative to the other compared group had greater testing or risk behaviour (e.g. higher among 3-dose compared with 2-dose vaccinated) this would lead to bias in the results due to likely higher incidences in documented infections for this respective group.

As mentioned, the various sources of ascertainment bias described above are of particular interest when interpreting the results of our analyses for the risk of documented infection. However, our severe endpoints of covid-19 related hospitalisation, ICU admission, and death

would not be expected to be influenced by these type of biases (or at least, to a minor extent). A limitation to these severe endpoints is, however, that given the relative rarity (which is also ascribed to the protection provided by the covid-19 vaccines) the proportional number of cases among the included vaccinated groups were low to none in many of our comparisons. Although our results indicated comparative effectiveness of the heterologous and homologous schedules (objective 1) and that receiving either a heterologous or homologous booster dose provided improved protection against these severe outcomes (objective 2), this means that the statistical precision of our reported estimates were low for some of these comparisons, and likewise, that statistical association analyses could not be conducted for many of these comparisons. In addition, as noted in the '*Variables*' subsection, the utilised definitions for the severe endpoints (covid-19 related hospitalisation, ICU admission, and death) may potentially have captured individuals with an outcome not directly related to covid-19 but where covid-19 was a contributing factor or co-occurred. Similarly, we may not have captured all possible severe events (e.g. covid-19 related deaths occurring later than 30 days after testing positive for SARS-CoV-2). Given the comparative design, however, these potential misclassifications of the severe outcomes are unlikely to be different between the compared groups.

11.3 Interpretation

Immunogenicity and reactogenicity data support that heterologous primary and booster covid-19 vaccine schedules produce a non-inferior immunogenic response to homologous schedules.(51) Data to inform on the comparative effectiveness – that is, how these immunogenic findings translate into preventing covid-19 infection and severe outcomes – of heterologous vaccine schedules, however, are sparse. A few previous studies have reported results for the vaccine effectiveness on heterologous primary schedules (i.e. 2-doses) with AZD in combination with mRNA vaccines compared with unvaccinated; vaccine effectiveness estimates against infections have ranged between 61% and >95%.(9–11,52–55) Although the heterologous primary schedules were not directly compared with homologous schedules, the vaccine effectiveness estimates were similar to those of the homologous schedules.(51) A few studies have also reported results on the risk of hospitalisation for heterologous primary schedules with effectiveness findings similar to those for the homologous schedules, but again as when indirectly compared through the comparisons to unvaccinated individuals.(52,54,56)

One observational study from Spain and one from the US have previously directly compared heterologous vs. homologous booster (i.e. 3-dose) schedules; however, the studies only examined MOD1MOD2BNT3 vs. MOD1MOD2MOD3 and BNT1BNT2MOD3 vs. BNT1BNT2BNT3 of relevance to our results and did not include the AZD vaccine.(57,58) Although, the risk of documented infection (as assessed between day 7 to 34 after the booster dose) was very similar in the study from Spain, the authors reported that those boosted with MOD, regardless

of being in a heterologous or homologous schedules (i.e. MOD1MOD2BNT3 vs MOD1MOD2MOD3 and BNT1BNT2BNT3 vs. BNT1BNT2MOD3), had fewer cases of documented infections (a difference of 20 and 25 cases per 10,000 individuals, respectively; the results are provided in the appendix of the study).(57) The study from Spain did not assess the risk of severe covid-19 outcomes (i.e. covid-19 related hospitalisation, ICU admission, and death) but only the risk of documented infection. The US study (conducted during a period of delta predominance) found no significant differences in the risk of infection or severe outcomes when comparing matched heterologous and homologous mRNA booster vaccinated; however, the numbers of cases with severe outcomes were small, and thus, the statistical power to assess differences between groups was limited.(58) Moreover, a recent community-based study based on self-reported data through an app, found similar vaccine effectiveness against covid-19 infection of heterologous- (vaccine effectiveness of 88.5%) and homologous booster (92.5%) schedules, both compared with unvaccinated.(59) Of note, since a still increasing number of individuals receive vaccination for covid-19, those who choose to remain unvaccinated are increasingly less representative of the general population and thus less suitable as comparisons. This indeed include the Nordic countries where covid-19 vaccine coverages are very high (approximately >85% of the populations for primary schedules). Furthermore, given the many potential sources of biases that could affect the outcome of documented infection (as described above under subsection *'Limitations'*) indirect comparison of different booster schedules by use of a common unvaccinated comparison group is most likely an inadequate approach.

As such, our analyses contribute with a substantial expansion to the body of literature examining the (direct) comparative vaccine effectiveness between heterologous and homologous primary and booster vaccine schedules. In our weighted analyses comparing heterologous vs. homologous primary and booster schedules (i.e. 2- vs. 2-dose and 3- vs. 3-dose) for the outcome of documented covid-19 infection, we generally observed only small differences in absolute numbers between compared heterologous and homologous schedules. Of note, our results for documented infection should be interpreted while appreciating the potential limitations to this outcome (see subsection '*Limitations*') where in particular different sources of ascertainment bias could have influenced these associations as opposed to associations with the severe outcomes. Complementing, the main results for documented infection, extending the follow-up to 180 days (i.e. the waning immunity analyses), increases in risk differences beyond day 75 were not observed. Hence, the heterologous vs. homologous weighted comparisons did not support any noteworthy discrepancies in effectiveness against acquiring covid-19 infection. Additionally, the results suggested that the protection provided against severe outcomes from heterologous primary and booster schedules was not inferior to the compared homologous schedules. However, it should be noted that the number of cases was generally low and therefore analyses could not be conducted for many of the individual

pre-planned comparisons in all countries. Moreover, the heterologous vs. homologous primary schedule comparisons were assessed in the period prior to omicron predominance (mainly during the period of delta predominance) while our booster schedule comparisons were conducted primarily during the period of omicron predominance.

While previous data to inform on the effectiveness of heterologous booster schedules are limited, evidence to support the protective benefit of a homologous mRNA booster schedules (as opposed to unvaccinated and primary [2-dose] vaccination) is more well-documented.(15,17,19,60) Observational studies have shown that homologous mRNA booster vaccines improve protection against covid-19 outcomes compared with homologous mRNA primary vaccine schedules during periods predominated by the delta variant.(15,17,19,61) An increasing number of studies suggest that the vaccine effectiveness of primary and booster schedules against covid-19 are reduced with the omicron variant compared with delta.(21,60,62–67) However, data support that receiving a booster dose increases the vaccine effectiveness against the omicron variant compared to primary schedules and that the protection against severe covid-19 outcomes remains relatively high with omicron. Our matched analyses comparing the risk of covid-19 outcomes among individuals receiving a booster dose with those who had not (yet) received a booster dose (i.e. 3- vs. 2-dose) were primarily conducted during a period of omicron predominance. Therefore, we were unable to assess the comparative vaccine effectiveness of a booster dose by other covid-19 variants (as also reflected by our results from the omicron stratified analyses that were very similar to our main analyses [for both objective 1 and 2]). The results from our comparisons of homologous booster schedules with the mRNA vaccines vs. primary schedules found (similar to previous studies) an increased protection against covid-19 outcomes associated with receiving a booster dose and in particular against severe outcomes. In Denmark, however, magnitudes of the relative effectiveness estimates for documented covid-19 infection were lower. This finding was observed across most-to-all of the Danish booster vs. primary schedule comparisons for risk of documented infection.

Previous studies that have assessed the relative effect of heterologous booster schedules are sparse and mainly limited to studies conducted during periods of delta variant predominance and/or as compared with unvaccinated.(19,21,59,68–72) To our knowledge no studies have reported the effectiveness of the individual heterologous booster schedules with the AZD, BNT, and MOD vaccines compared with primary schedules during a period of omicron variant predominance. Studies that have assessed the effectiveness of booster doses against covid-19 during a period of omicron predominance as compared with unvaccinated found similar levels of protection of heterologous and homologous (when indirectly compared) for symptomatic infection(21) and severe outcomes(69). However, as noted, comparisons to unvaccinated hold concerns of healthy vaccinee bias and fundamental differences in testing and risk behaviour

between vaccinated and unvaccinated groups, in particular when assessing the effectiveness of booster schedules and the exchangeability between compared groups is reduced. Also, as the vast majority of the population have received a primary vaccination schedule, those who choose to remain unvaccinated is unlikely to be a proper representative sample of the general population and these comparisons provide little evidence to inform vaccination strategies in the current setting. Studies conducted during periods of delta variant predominance overall found improved protection of heterologous boosters compared with primary schedules that was comparable to that observed for homologous booster schedules.(19,70–72) A cohort study from Chile found that among individuals primary schedule vaccinated with CoronaVac (Sinovac Biotech), both those who received a homologous booster and a heterologous AZD or BNT booster had a high level of protection against the delta variant (including severe outcomes) as compared with unvaccinated, and that both heterologous schedules offered greater protection than the homologous schedule (when indirectly compared).(56) For most of these studies, however, the effectiveness against severe outcomes was not analysed or the numbers of cases were very low precluding statistical precision.

Our results from the heterologous booster vs. primary schedule comparisons, which primarily were conducted during a period of omicron predominance, indicated that receiving a booster dose increased the protection against all outcomes but that the gained protection against severe covid-19 outcomes was more pronounced overall. Similar to the observed pattern among homologous schedules, variations in the effectiveness measures were observed across schedules and countries; in particular, we observed cross-country differences in the association with documented covid-19 infection, where the relative estimates in Denmark had lower magnitude. The effect sizes for severe outcomes were more stable across countries and schedules. As previously noted, assessing the vaccine effectiveness against documented infection brings several methodological challenges as these estimates are dependent on various factors such as national testing strategies, individual-level testing and risk behaviour, immunity status of the population, and community infection rates etc.. We believe that these factors likely contributed to the observed differences for documented infection (e.g. rather than true differences in the effectiveness of the same vaccine schedule in different countries). In addition, the results from the quality control analysis with the test-negative design, were largely compatible with the results from the main analyses. While a key feature of the test-negative design is that unmeasured confounding due to differences in health care-seeking behaviour may be reduced (e.g. those who are more likely to actively chose to get vaccinated may also be more likely to seek medical care in general and testing) through the restriction to a population with similar access to and uptake of medical care testing resources, this is offset by other limitations. A number of assumptions must be fulfilled for the test-negative study design to produce unbiased estimates of vaccination effectiveness. First, the decision to vaccinate should not influence the susceptibility or exposure to infection and symptoms, and

second, vaccination should confer no- or full protection.(73,74) In particular in the omicron period, the second assumption is unlikely to be fulfilled, and may bias the vaccination effectiveness estimate downwards.

Our analyses of waning immunity was restricted to 180 days after primary vaccination. Only primary vaccination was evaluated since the short follow-up for the booster schedules (due to the study period ending on 28 February 2022) hampered the possibility for adequate analyses of waning for booster schedules. We observed no differences in the risk of documented covid-19 infection comparing heterologous and homologous primary schedules at day 180 since start of follow-up. Previous work have shown substantial decrease in the humoral immune response after 6 months of receipt of homologous primary vaccination(75); however, declines in antibodies may not directly translate into the effectiveness against covid-19 infection and severe outcomes. Previous observational studies have provided diverging findings in the duration of protection against covid-19 infection, with vaccine effectiveness estimates for homologous mRNA or AZD primary schedules at 5 to 6 months up to around 80% and as low as around 20%.(12,76–79) A Swedish study reported a VE of 66% for heterologous primary schedules of AZD1mRNA2 at 4 months and onwards as compared with matched unvaccinated, which was similar to that observed for the homologous primary schedules with the mRNA vaccines.(80) Although the homologous and heterologous primary vaccine schedules were not directly compared in this study, their findings are somewhat in concert with our results of no major differences in the duration of protection between heterologous and homologous primary vaccine schedules up to 6 months. Of note, the individual comparisons were highly influenced by the time of vaccination and by period changes in population infection rates. As such the results were likely influenced by the impact of the omicron wave on infection rates. While this makes the interpretation of vaccine effectiveness changes within schedules difficult, it also hampers our ability to indirectly compare the comparative waning results across the respective comparisons.

In our subgroups analyses, stratifying the studied Danish population by age, our results were not suggestive of differences in the comparative effectiveness of heterologous vs. homologous booster schedules by age. However, when we compared receiving a booster dose schedule with those primary vaccinated who had not (yet) received a booster dose, we found an increasing protective effect of a booster dose with increasing age. While we cannot exclude a true age effect on the effectiveness of a booster dose, the results most likely reflect different calendar periods of observation for the older and younger age group which also implies different variants of predominance (delta comparisons vs. omicron comparisons, respectively) and different population infection rates. In Denmark, vaccination roll-out were prioritised and administered according to decreasing age groups (i.e. older individuals were vaccinated relative earlier; as well as key/risk groups were prioritised) and initiation of booster doses

started in early September 2021 (i.e. delta period), while booster schedules were administered to the majority of the general population during December 2021 through February 2022 (i.e. omicron period and the population infection rate was high). We did not conduct variant-specific or calendar-specific age-stratified analyses. Additionally, no major age differences have been identified in other studies including when assessing delta- and omicron-specific effectiveness.(19,21,78)

For our analyses of vaccine effectiveness among children and adolescents, only few were vaccinated in Norway in both the younger and older children and adolescent age group, and likewise, few children aged 5 to 11 years were vaccinated in Sweden. The incidence rates of documented infection ranged widely across country and age groups, where particularly in Denmark the incidence rates for children age 5 to 11 years were very high (>50% acquired an infection) due to the extensive omicron surge in Denmark at time of vaccination of this younger age group, whereas the children age 12 to 17 years were predominantly vaccinated in the autumn 2021 (i.e. delta period with lower population incidence rates). Overall, we found a significant reduction in the risk of acquiring covid-19 infection associated with receiving a primary vaccine schedule as compared with being unvaccinated across countries and for both age groups. However, the relative effect estimates were smaller in Denmark for the children age 5 to 11 where incidence rates were very high compared to the other countries. The risk of covid-19 related hospitalisation was also reduced among vaccinated in both age groups as compared with unvaccinated (note, that not all countries nor schedules had sufficient number of cases for these analyses).

Our findings of a reduced risk of infection among children aged 5 to 11 and 12 to 17 years are in line with previous findings. A recent study from Israel found an absolute risk difference of 1.9% (95% CI 1.3% to 2.4%; corresponding to a vaccine effectiveness of 51%) for omicron infection among children aged 5 to 11 years, BNT1BNT2 vaccinated at day 7 to 21 after vaccination as compared with unvaccinated.(81) Similarly, a study from the US found a vaccine effectiveness of BNT1BNT2 of 31% against omicron infection in children aged 5 to 11 years old during day 14 to 149 after vaccination as compared with unvaccinated.(82) Among children aged 12 years or older, the same study found a vaccine effectiveness of 87% against delta infection and a vaccine effectiveness of 59% against omicron.(82) Another US study, based on data from New York state during November 2021 to January 2022, found an increased risk of infection for unvaccinated as compared with vaccinated children aged 5 to 11 and 12 to 17 years, but the protection provided by the vaccines declined as omicron became more prevalent as well as when time since vaccination increased (more pronounced for the younger than the older age group).(83) Also, a test-negative case-control study during a period of omicron predominance found a VE of 60% against infection among both children aged 5 to 11 and 12 to 17 years at week 2 to 4 after vaccination that, however, quickly

declined: at 2 months since vaccination, the vaccine effectiveness was 29% and 17% respectively.(84) Lastly, prior studies on the protection against severe covid-19 outcomes among children and adolescents are sparse. However, a test-negative case-control study from the US found a vaccine effectiveness against hospitalisation of 68% among children aged 5 to 11 years during the omicron period.(85) Among adolescents aged 12 to 18 years, the vaccine effectiveness against hospitalisation for covid-19 was >92% during the delta-predominant period, while during the omicron-predominant period the vaccine effectiveness was 40% against hospitalisation for covid-19 but 79% against critical covid-19 and 20% against noncritical covid-19.(85) Although, not all countries could contribute with analyses for severe covid-19 outcomes and not all schedules could be examined because of no events among vaccinated individuals, we found that the risk of covid-19 hospitalisation was lower for both children aged 5 to 11 years (vaccine effectiveness of 86% and 34% for 1 dose, and 91% for 2 doses of BNT; during the omicron period) and 12 to 17 years (91% for 1 dose and 71% for 2 doses; mainly conducted during the period of delta). Moreover, 1 dose of BNT lowered the risk of MIS-C in Denmark, vaccine effectiveness of 88.4% (not estimable in other countries nor for 2-dose BNT schedule in any countries due to no events among vaccinated). As such our results provides an important contribution of the vaccine effectiveness of primary vaccine schedules among children and adolescents. Among others, this include results in relation to the effectiveness against different variants of predominance, the effectiveness of heterologous schedules for children and adolescents aged 12 to 17 years, and the effectiveness in relation to severe outcomes for which currently available data are particularly sparse.

11.4 Generalisability

Our study results have a high degree of generalisability to other similar populations. However, as our objective was to provide comparative vaccine effectiveness analyses from study cohorts that had high resemblances to the general populations vaccinated with ADZ, BNT and/or MOD in the Nordic countries, this also means that some subgroups were not included in our study. As per study design we for example did not include individuals who had received the Ad26.CoV2-S vaccine, individuals who had received 3 vaccine doses as part of the primary schedule (these were most likely individuals with immunocompromised conditions), and individuals with previous documented covid-19 infection. Therefore, our results cannot be directly used to help evaluate the effectiveness of vaccine schedules or in subgroups not included. In addition and as noted above under the subsection *'11.2 Limitations'*, our results, in particular for the outcome of documented infection, should be interpreted in the context of the given background infection rates and covid-19 variant of predominance during the respective calendar periods the individual schedule comparisons were examined, and in

relation to the differences in national testing strategies across countries as well as over time. Therefore, indirect comparisons of the respective comparative results across schedules and countries are limited hereby. Lastly, for some of the individual pre-planned comparisons, we had insufficient statistical power to conduct analysis, in particular for severe covid-19 outcomes in all countries. Although, we were unable to provide results for these specific comparisons, given that we observed no significant discrepancies in the effectiveness across the different heterologous schedules, results from the comparisons where analyses were feasible, may indirectly help inform on the effectiveness of those where analyses were not feasible.

12. OTHER INFORMATION

None.

13. CONCLUSION

This study compared the effectiveness of 1) heterologous primary- and booster covid-19 vaccination schedules to the corresponding homologous primary- and booster covid-19 vaccination schedules and 2) heterologous or homologous booster schedules to primary schedules in the Nordic countries. Additional sub objectives included examining the (comparative) vaccine effectiveness according to covid-19 variant, waning immunity, and age groups including children and adolescents.

Our results largely support that heterologous primary and booster schedules with the AZD, BNT, and/or MOD vaccines provided protection against covid-19 endpoints that was not inferior to the vaccine effectiveness of homologous schedules (objective 1). Similarly, our findings largely support that both heterologous and homologous booster doses in the Nordic countries increased the protection against covid-19 outcomes as compared to primary schedules (objective 2). Although booster dose schedules improved the protection against severe covid-19 outcomes, the effectiveness against documented infection was less apparent for some comparisons, particularly in Denmark. However, these observed differences in the protection against acquiring infection, were most likely due to differences in national population testing strategies, in background population infection rates, and in testing- and risk behaviour across countries.

Our results within the individual comparisons were primarily variant specific. As such, the administration of booster doses in the Nordic countries occurred at a time of omicron variant predominance; thus, analyses stratified by different covid-19 variants (objective 3) were not feasible. When we increased the specificity of the analyses to the omicron variant (by

restricting to specific calendar periods of omicron predominance) we found similar results to our main findings.

Our results were not suggestive of an inferior longer-term protection of the heterologous primary vaccine schedules as compared with the homologous primary vaccine schedules (objective 4).

Lastly, our analyses of the vaccine effectiveness of primary schedules among children and adolescents showed an increased protection against covid-19 endpoints as compared with unvaccinated (objective 5). This includes increased protection against severe covid-19 endpoints for both children and adolescent aged 5 to 11 and 12 to 17 years among those schedules that could be analysed for these severe outcomes.

14. REFERENCES

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APPENDIX A. OVERVIEW OF TABLES AND FIGURES.