ENFORCE

Danish National Cohort Study of Effectiveness and Safety of SARS-CoV-2 Vaccines

Monthly Report

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Contents

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Summary of key changes from previous report

This report focuses on individuals who have received either a 4th or 5th dose of a SARS-CoV-2 vaccine.

The data presented in this report are presented either by the number of vaccine doses a participant has received or by the type of vaccine received when considering specific doses.

For the 4th and subsequent doses, the vaccine types have been split into three groups:

1. Original: This includes the wild-type Original Pfizer-BioNTech and Original Moderna vaccines
2. Bivalent BA.1: This includes the bivalent vaccines Pfizer-BioNTech Original/Omicron BA.1, and Moderna Original/Omicron BA.1
3. Bivalent BA.4-5: This includes the bivalent vaccines Pfizer-BioNTech Original/Omicron BA.4-5

Enrolment

The characteristics of individuals enrolled in the study are presented by the number of vaccine doses they had received at the time this report was generate.

Outcomes

The results of the X and Xc study visits for individuals receiving a 4th or 5th dose on SARS-CoV-2 vaccine are presented in this report. In addition to the original mesoscale assay, this report also contains results from the Meso Scale Serology Omicron assay which quantifies total IgG to six SARS-CoV-2 antigens: Spike (wildtype), Spike (B.1.1.529: BA.1), Spike (B.1.1.529: BA.2), Spike (B.1.1.529: BA.3), Spike (B.1.1.529: BA.4) and Spike (B.1.1.529: BA.5). These results are available for individuals having a study visit from October 2022 onwards.

Safety and Monitoring

Local and systemic reactions reported after the 4th and 5th vaccine doses are included in this report. This report also includes all SAEs and AE's reported following receipt of either a 4th or 5th vaccine dose. To shorten the report, the summary tables and overview of all AEs and SAEs occurring from the first 3 doses and reported previously are not included in this report. These can be found in the previous reports and can also be added back into future reports as required. It should also be noted that a number of participants may have received influenza and pneumococcal vaccines at the same time as their 4th and 5th vaccine doses. We are currently unable to identify how many participants this relates to and so the safety outcomes reported here are potentially confounded by simultaneous vaccinations.

Methods

The data presented in this report are descriptive. A detailed statistical analysis plan will be developed prior to any formal analysis being conducted.

Data sources

The data used to generate this report are currently based on the data stored in REDCap from the case report forms (CRFs) and online symptoms form. Data on serum antibody quantification using ELISA (Wantai) was provided by the SSI and the multiantigen serological tests by Aarhus University Hospital.

Information on the type of vaccines received and the dates of vaccinations were initially collected and reported though the study CRFs. This has now been validated via data from the Danish Vaccine Register (DDV), with the DDV considered the gold standard where discrepancies have arisen.

Data on any SARS-CoV-2 PCR-tests or SARS-CoV-2 antibody measurements were extracted from the surveillance system Key Infectious Diseases System (KIDS) (Statens Serum Institut, Copenhagen, Denmark).

Data on deaths are reported from two sources, as a serious adverse event (SAE) on the CRF and recorded in REDCap or through the Danish Civil Registration System (CPR). The CPR registry is a national register containing basic personal information, including dates of the deaths for all persons in Denmark who have a CPR number.

Definitions

In this version of the report the type of vaccine received, and date of vaccination is based on information provided from the DDV. Participants who received a first dose of Janssen were classed as having received a booster dose if they had at least one subsequent dose of an mRNA vaccine.

Results from the ELISA detection of total serum Ig to the Receptor Binding Domain (Wantai) were recorded as Negative (ratio <0.9), Positive (ratio >1.1), or inconclusive (ratio between 0.9-1.1). The ratio was calculated as the OD value/cut-off, where the cut-off= average of the negative controls +0.16. If the average is below 0.03 then the cut-off is set to 0.16 + 0.03. For manual execution the cut-off will almost always be 0.19.

For the multiantigen serological tests, the geometric mean and 95% confidence intervals (CI) for the antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid at each study visit are reported. The calibration curve used to calculate antibody concentrations are performed by fitting the signals from the calibrators in a 4-parameter sigmoidal dose-response model. Antibody concentrations can then be determined from their ECL signals by backfitting to the calibration curve. To better evaluate the response to the bivalent vaccines, in addition to the original mesoscale assay, this report also contains results from the Meso Scale Serology Omicron assay which quantifies total IgG to six SARS-CoV-2 antigens: Spike (wildtype), Spike (B.1.1.529: BA.1), Spike (B.1.1.529: BA.2), Spike (B.1.1.529: BA.3), Spike (B.1.1.529: BA.4) and Spike (B.1.1.529: BA.5). These results are available for individuals having a study visit X or Xc from October 2022.

Breakthrough infection was defined as a positive SARS-CoV-2 PCR test result reported in the KIDS dataset after the date of first vaccination. The timing of the infection was based on the date of first positive test.

A complete list of the AEs and SAEs reported after the 4th and 5th vaccine doses is provided. All SAEs and AEs are coded using MedDRA and are presented using the preferred terms and ordered alphabetically by system organ class.

Enrolment

The section gives an overview of the current enrolment status of participants in the study. Table 1 outlines the number of participants currently enrolled in the study and reasons for exclusion.

Table 1 Summary of participants enrolled in the study

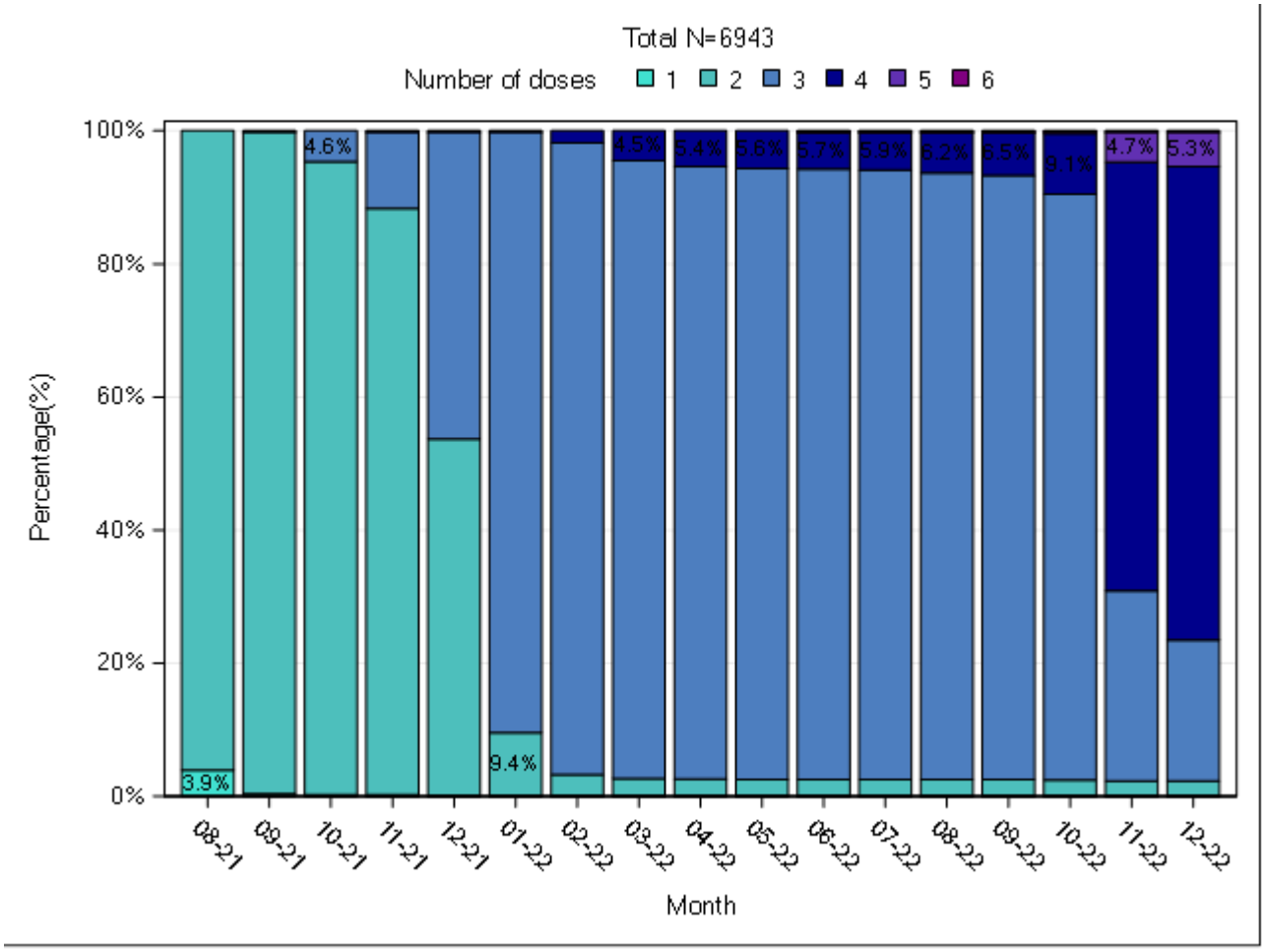
Total included	*Reason for exclusion*
6972	All patients
6949	Consent withdrawn and requested data deleted
6949	Provided informed consent
6949	Missing enrolment date
6948	Aged under 18
6948	Vaccine not recommended
6948	Vaccinated Previously
6948	Agrees to follow protocol
6948	No SSI vaccine data (consent withdrawn) and expected to receive AZ after 10/3/21
6947	No SSI vaccine data (consent withdrawn) and only one study visit (enrolment)
6947	No SSI vaccine data (consent withdrawn) and no study visit after second vaccine
6943	Non-standard vaccine regimen*

*Non-standard regimens included AstraZeneca only, and a combination of Pfizer-BioNTech and Moderna for the first and second dose.

Demographics by number of vaccine doses received

All participants have now been under follow-up for between 15 and 22 months. Figure 1 shows the number of vaccine doses participants have received over time. Table 2 gives an overview of the participant demographics by the number of vaccine doses received at the time of most recent data extraction. The majority of the cohort, 5312 (76%) participants, have now received at least four doses of vaccine, with most receiving their fourth dose between October and December 2022.

Figure 1 Number of vaccine doses participants have received over time



From Table 2 , individuals who have received at least 5 doses of vaccine are those at increased risk and mainly aged ≥ 65 years old. Those who have only received 2 or 3 doses are mainly younger individuals (aged <55 years old).

Table 2 Participant demographics at study enrolment by number of vaccine doses received

		Current vaccine status			
	Total (N=6943)	*2/3 doses (N=1631)*	*4 doses (N=4941)*	*5+ doses (N=371)*	*p-value*
Age at enrolment (median, IQR)	64 (53, 75)	46 (39, 57)	68 (59, 76)	67 (58, 73)	.
Age Group (N, %)					<.0001
<55	1972 (28.4)	1161 (71.2)	739 (15.0)	72 (19.4)	.
55-64	1762 (25.4)	282 (17.3)	1401 (28.4)	79 (21.3)	.
>=65	3209 (46.2)	188 (11.5)	2801 (56.7)	220 (59.3)	.
Gender (N, %)					<.0001
Male	3014 (43.4)	579 (35.5)	2236 (45.3)	199 (53.6)	.
Female	3929 (56.6)	1052 (64.5)	2705 (54.7)	172 (46.4)	.
Original Vaccine type (N,%)					<.0001
Pfizer-BioNTech	3824 (55.1)	639 (39.2)	2857 (57.8)	328 (88.4)	.
Moderna	2620 (37.7)	725 (44.5)	1853 (37.5)	42 (11.3)	.
AstraZeneca/mRNA	499 (7.2)	267 (16.4)	231 (4.7)	<5*	.
Vaccine priority group (N,%)					<.0001
1. Individuals at increased risk	1599 (23.0)	312 (19.1)	968 (19.6)	319 (86.0)	.
2. Health care workers	590 (8.5)	282 (17.3)	299 (6.1)	9 (2.4)	.
3. General population	4754 (68.5)	1037 (63.6)	3674 (74.4)	43 (11.6)	.

*Exact number not show due to small numbers

Withdrawal/Loss to follow-up

The number and percentage of participants discontinuing in the study is give in Table 3. A little under 10% have withdrawn from the study. However, we are still able to collect registry data from the majority of these participants.

Table 3 Number and percentage of participants discontinuing in the study

	Total (N=6943)
Study status (N, % of total)	
Still under follow-up	6284 (90.5)
Total withdrawn (N, % of total)	659 (9.5)

Outcomes

Primary outcome

From the multiantigen serological tests, the geometric mean (GM) and 95% confidence intervals (CI) for the antibody levels against the Receptor Binding Domain, and the complete Spike at each main study visit are reported in Table 4 (1st year of follow-up).

Table 4 Presence of antibodies at study visit, Receptor-Binding Domain (RBD) and Spike antibody

	Total (N=6943)
AUH antibody data at visit 1 (enrolment) (N, % of total)	6862 (98.8)
AUH antibody data at visit 2 (prior to second vaccination) (N, % of total)	6301 (90.8)
AUH antibody data at visit 3 (3 months after first vaccination) (N, % of total)	5957 (85.8)
AUH antibody data at visit 4 (6 months after first vaccination) (N, % of total)	5931 (85.4)
AUH antibody data at visit 5 (1 year after first vaccination) (N, % of total)	5603 (80.7)
CoV-2 Receptor-Binding Domain (SERO)	
GM at enrolment (95%CI)	59 (57, 61)
GM at visit 2 (95%CI)	8839 (8402, 9299)
GM at visit 3 (95%CI)	95324 (91513, 99293)
GM at visit 4 (95%CI)	39921 (38352, 41554)
GM at visit 5 (95%CI)	313661 (305650, 321881)
CoV-2 Spike antibody (SERO)	
GM at enrolment (95%CI)	106 (102, 110)
GM at visit 2 (95%CI)	26873 (25641, 28164)
GM at visit 3 (95%CI)	173430 (167609, 179454)
GM at visit 4 (95%CI)	82900 (80016, 85888)
GM at visit 5 (95%CI)	401105 (393787, 408559)

GM: Geometric Mean

Secondary outcome

The secondary outcome of breakthrough infections is monitored in two different ways. The number of participants testing positive for SARS-CoV-2, as reported via KIDS, and by serological monitoring (detection of SARS-CoV-2 nucleocapsid antibodies). The number of participants experiencing a positive PCR test following their first vaccination is reported in Table 5.

We are still developing the definition for breakthrough infection based on SARS-CoV-2 nucleocapsid antibodies. However, Table 6 shows the number and percentage with nucleocapsid titers >3000 U/mL at each main study visit.

Table 5 Number of participants testing positive for SARS-CoV-2

	Total (N=6943)
Ever tested for SARS-CoV-2 reported via KIDS (N, % of total)	6644 (95.7)
Number of PCR tests since first vaccine dose (median, IQR)	5 (2, 10)
Number of antigen tests since first vaccine dose (median, IQR)	3 (1, 7)
Number PCR positive for SARS-CoV-2 reported via KIDS (N, % of total)	3326 (47.9)
Days from first vaccine dose to SARS-CoV2 positive test (median, IQR)	310 (257, 349)
Age Group (n, % in category)	
<55	1255 (63.6)
55-64	853 (48.4)
>=65	1218 (38.0)
Gender (n, % in category)	
Male	1369 (45.4)
Female	1957 (49.8)

Table 6 Number of participants with nucleocapsid titers >3000 U/mL at each main study visit

	Total (N=6943)
CoV-2 Nucleocapsid (SERO)	
Enrolment (n, %)	
<=3000	6157 (89.8)
>3000	697 (10.2)
Visit 2 (n, %)	
<=3000	5620 (89.3)
>3000	676 (10.7)
Visit 3 (n, %)	
<=3000	5193 (87.2)
>3000	765 (12.8)
Visit 4 (n, %)	
<=3000	5062 (85.4)
>3000	864 (14.6)
Visit 5 (n, %)	
<=3000	2591 (46.2)
>3000	3012 (53.8)

Fourth Vaccine Dose

Demographics

Table 7 gives an overview of the participant demographics among individuals who have received a 4th vaccine dose, stratified by the type of vaccine they received.

The majority have received a bivalent vaccine for their 4th dose, with 51% (n=2738) receiving the bivalent omicron BA4/5 and 38% (n=2005) receiving the bivalent omicron BA1 (either Moderna n=776, or Pfizer n=1229). Individuals who did not receive a bivalent vaccine for their 4th dose were those in the increased risk vaccine priority group who received their 4th dose earlier before the bivalent vaccines were available.

*Table 7 Participant demographics among those who received a 4th dose, by **4th** vaccine type*

		4th Vaccine type		
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
Number of persons (%)				
Age Group				
<55	811 (15.3)	137 (24.1)	147 (7.3)	527 (19.2)
55-64	1480 (27.9)	120 (21.1)	480 (23.9)	880 (32.1)
>=65	3021 (56.9)	312 (54.8)	1378 (68.7)	1331 (48.6)
Gender				
Male	2435 (45.8)	288 (50.6)	941 (46.9)	1206 (44.0)
Female	2877 (54.2)	281 (49.4)	1064 (53.1)	1532 (56.0)
Vaccine priority group				
1. Individuals at increased risk	1287 (24.2)	433 (76.1)	349 (17.4)	505 (18.4)
2. Health care workers	308 (5.8)	13 (2.3)	54 (2.7)	241 (8.8)
3. General population	3717 (70.0)	123 (21.6)	1602 (79.9)	1992 (72.8)
Vaccine group				
Pfizer-BioNTech	3185 (60.0)	472 (83.0)	1130 (56.4)	1583 (57.8)
Moderna	1895 (35.7)	84 (14.8)	838 (41.8)	973 (35.5)
AstraZeneca/mRNA	232 (4.4)	13 (2.3)	37 (1.8)	182 (6.6)
Median (interquartile range, IQR)				
Age at enrolment (years)	68 (58, 76)	66 (55, 74)	71 (63, 79)	64 (57, 74)
Enrolment date	APR21 (MAR21, MAY21)	MAR21 (MAR21, MAR21)	APR21 (MAR21, MAY21)	APR21 (MAR21, MAY21)

Study visits

Of the 5312 participants who have received a 4th vaccine dose, 2702 (51%) had a study visit prior to their 4th dose and 3243 (61%) have had a study visit a median of 29 days after their 4th dose, 2485 (76%) had both a pre and post vaccine visit.

*Table 8 Number and percentage of participants completing **4th** dose study visits*

			Vaccine type	
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
Received a fourth dose (N, %)	5312 (100)	569 (100)	2005 (100)	2738 (100)
Time between first and fourth dose (median, IQR)	542 (512, 563)	346 (333, 476)	544 (522, 559)	547 (520, 572)
Visit 4X (0-14 days prior to fourth dose) (N, %)	2702 (50.9)	109 (19.2)	1000 (49.9)	1593 (58.2)
Days from pre-fourth dose visit to fourth dose (median, IQR)	4 (1, 8)	3 (1, 6)	4 (1, 7)	4 (1, 8)
Visit 4Xc (28 days after fourth dose) (N, %)	3253 (61.2)	381 (67.0)	1198 (59.8)	1674 (61.1)
Days from fourth dose to post-booster visit(median, IQR)	29 (26, 32)	28 (26, 33)	29 (25, 33)	29 (26, 32)
Total withdrawn (N, % of total)	388 (7.3)	69 (12.1)	154 (7.7)	165 (6.0)

Outcomes

Primary outcome

The data from the ELISA (Wantai) before and after the 4th vaccine dose are shown in Table 9.

Table 9 Presence of antibodies before and after the 4th vaccine dose, ELISA (Wantai) from SSI

		4th Vaccine type		
	Total (N=5312)	*Original (N=563)*	*Bivalent/Omicron BA1 (N=2011)*	*Bivalent/Omicron BA4/5 (N=2738)*
SSI antibody data 0-14 days before fourth dose (N, % of total)	2568 (48.3)	109 (19.4)	935 (46.5)	1524 (55.7)
Wantai result prior to 4th dose (visit 4X)				
Positive	2558 (99.6)	106 (97.2)	932 (99.7)	1520 (99.7)
Days prior to fourth dose (median (IQR))	4 (1, 8)	3 (1, 6)	4 (1, 7)	4 (1, 8)
SSI antibody data 28 days after fourth dose (N, % of total)	2884 (54.3)	384 (68.2)	1067 (53.1)	1433 (52.3)
Wantai result after 4th dose (visit 4Xc)				
Positive	2787 (96.6)	357 (93.0)	1022 (95.8)	1408 (98.3)
Days after fourth dose (median (IQR))	29 (26, 32)	28 (26, 33)	29 (25, 33)	29 (26, 32)

From the multiantigen serological tests, the geometric mean (GM) and 95% confidence intervals (CI) for the antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid before and after the 4th vaccine dose are reported in Table 10 from the original mesoscale assay and Table 11 from the omicron specific assay.

*Table 10 Presence of antibodies before and after the **4th** dose, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid (original Mesoscale assay)*

			4th Vaccine type	
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
AUH antibody data 0-14 days before fourth dose (N, % of total)	2595 (48.9)	119 (20.9)	932 (46.5)	1544 (56.4)
AUH antibody data 28 days after fourth dose (N, % of total)	2687 (50.6)	381 (67.0)	1110 (55.4)	1196 (43.7)
CoV-2 Receptor-Binding Domain (SERO)				
GM 0-14 days before fourth dose (95%CI)	240777 (230691, 251304)	116165 (76569, 176237)	237627 (221616, 254794)	256723 (244729, 269305)
GM 28 days after fourth dose (95%CI)	445074 (428772, 461996)	181331 (144676, 227272)	522070 (509225, 535239)	510911 (500837, 521187)
CoV-2 Spike antibody (SERO)				
GM 0-14 days before fourth dose (95%CI)	334948 (324347, 345896)	183907 (131666, 256877)	336874 (320825, 353724)	349579 (337023, 362603)
GM 28 days after fourth dose (95%CI)	485398 (472364, 498790)	260080 (218054, 310205)	533928 (528977, 538926)	542020 (537454, 546625)
CoV-2 Nucleocapsid (SERO)				
GM 0-14 days before fourth dose (95%CI)	5274 (4831, 5757)	3641 (2322, 5710)	4709 (4064, 5457)	5810 (5193, 6499)
GM 28 days after fourth dose (95%CI)	5092 (4713, 5502)	1764 (1413, 2203)	5976 (5324, 6709)	6153 (5505, 6878)

GM: Geometric mean

*Table 11 Presence of omicron specific antibodies before and after the **4th** dose, by 4th vaccine type*

		4th Vaccine type		
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
AUH omicron antibody data before fourth dose (N, % of total)	2586 (48.7)	50 (8.8)	979 (48.8)	1557 (56.9)
AUH omicron antibody data after fourth dose (N, % of total)	2360 (44.4)	68 (12.0)	1104 (55.1)	1188 (43.4)
Spike (wildtype)				
GM 0-14 days before fourth dose (95%CI)	798262 (757717, 840978)	732328 (474615, 1129978)	793991 (726325, 867960)	803181 (752851, 856875)
GM 28 days after fourth dose (95%CI)	2949902 (2848248, 3055184)	2070462 (1613917, 2656154)	3100271 (2946342, 3262241)	2874366 (2737105, 3018510)
Spike (B.1.1.529: BA.1)				
GM 0-14 days before fourth dose (95%CI)	181234 (171789, 191197)	165122 (104134, 261828)	180376 (164718, 197523)	182320 (170560, 194890)
GM 28 days after fourth dose (95%CI)	966982 (927774, 1007847)	610073 (455907, 816370)	1034903 (974881, 1098620)	932065 (879517, 987753)
Spike (B.1.1.529: BA.2)				
GM 0-14 days before fourth dose (95%CI)	240223 (226652, 254607)	231110 (144159, 370506)	233163 (211215, 257392)	245076 (227930, 263511)
GM 28 days after fourth dose (95%CI)	1104120 (1059985, 1150092)	733145 (552766, 972386)	1095257 (1033064, 1161193)	1138800 (1074828, 1206580)
Spike (B.1.1.529: BA.3)				
GM 0-14 days before fourth dose (95%CI)	136735 (129526, 144344)	129101 (81988, 203285)	137984 (125847, 151292)	136205 (127319, 145710)
GM 28 days after fourth dose (95%CI)	742337 (710623, 775467)	506878 (371907, 690831)	802517 (752770, 855552)	705981 (664626, 749909)
Spike (B.1.1.529: BA.4)				
GM 0-14 days before fourth dose (95%CI)	238127 (225046, 251968)	216012 (136959, 340694)	232913 (211719, 256228)	242222 (225659, 260001)
GM 28 days after fourth dose (95%CI)	1187141 (1141039, 1235107)	735950 (551352, 982354)	1170351 (1105729, 1238750)	1236338 (1169318, 1307199)
Spike (B.1.1.529: BA.5)				
GM 0-14 days before fourth dose (95%CI)	255361 (241434, 270091)	234363 (149050, 368507)	249794 (227274, 274546)	259638 (241983, 278582)
GM 28 days after fourth dose (95%CI)	1257642 (1208658, 1308612)	776550 (582920, 1034498)	1247513 (1177953, 1321180)	1302585 (1232139, 1377058)

Figure 2-Figure 7 show the distribution of the omicron specific assays on the log10 scale before and after the 4th vaccine dose. See Table 11 for the number of participants contributing data to each figure.

*Figure 2 Distribution of CoV-2 Spike **(Wildtype)** antibody levels before and after the **4th** vaccine dose*

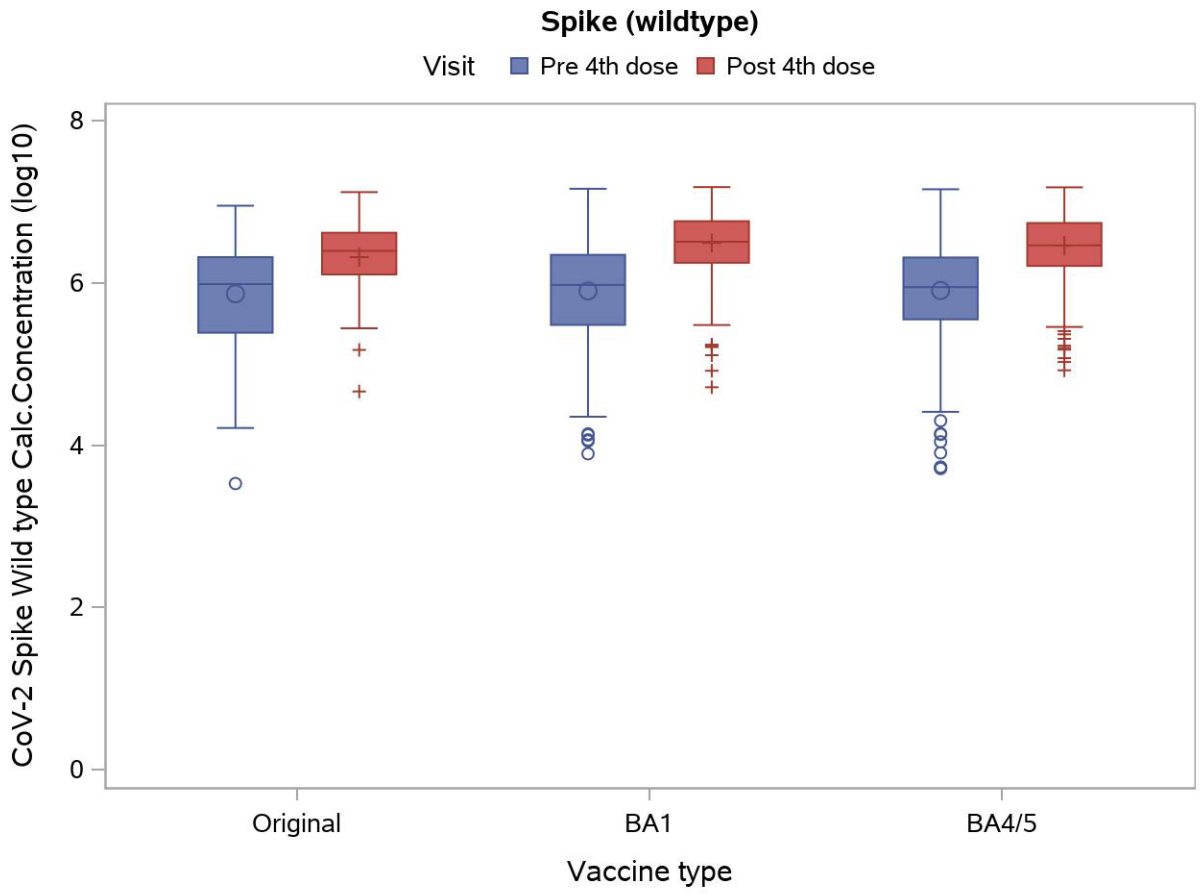


*Figure 3 Distribution of CoV-2 Spike **(B.1.1.528: BA1)** antibody levels before and after the **4th** vaccine dose*

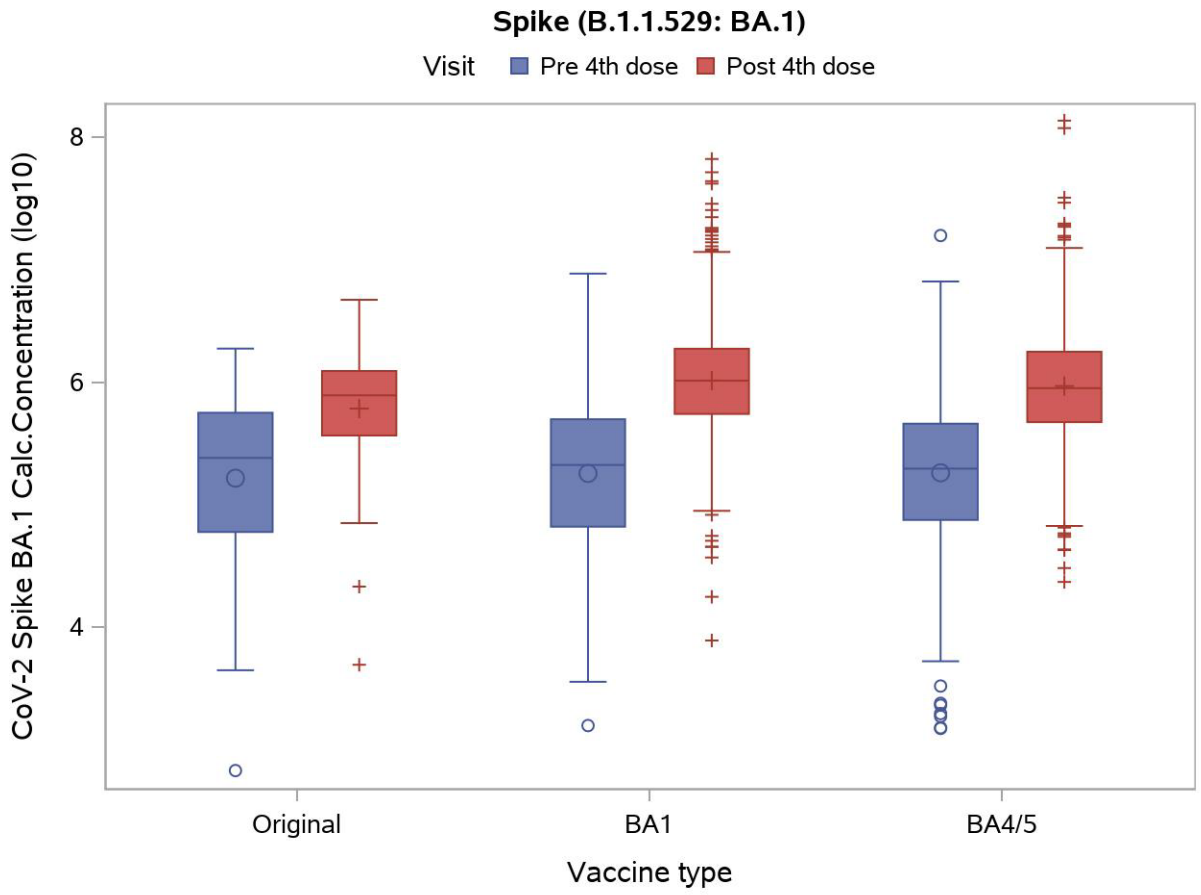


*Figure 4 Distribution of CoV-2 Spike **(B.1.1.528: BA2)** antibody levels before and after the **4th** vaccine dose*

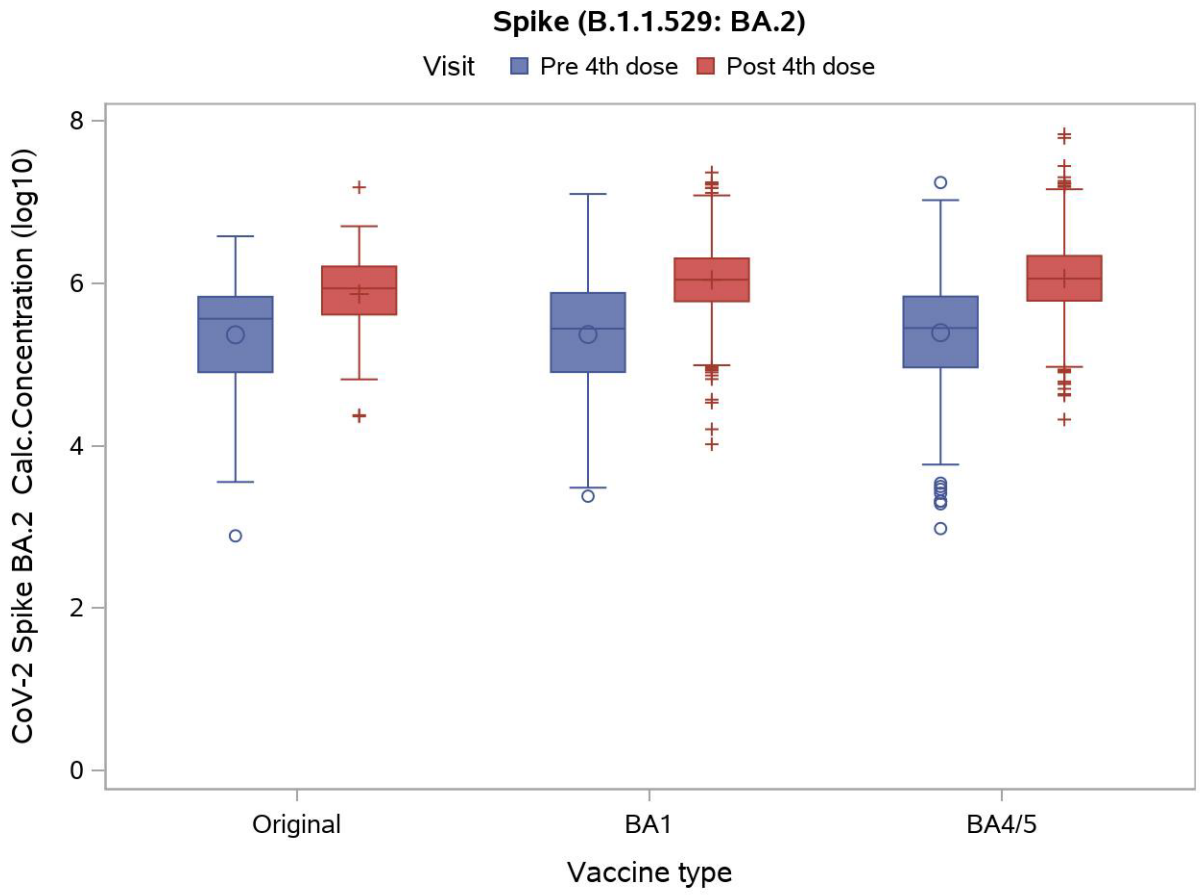


*Figure 5 Distribution of CoV-2 Spike **(B.1.1.528: BA3)** antibody levels before and after the **4th** vaccine dose*

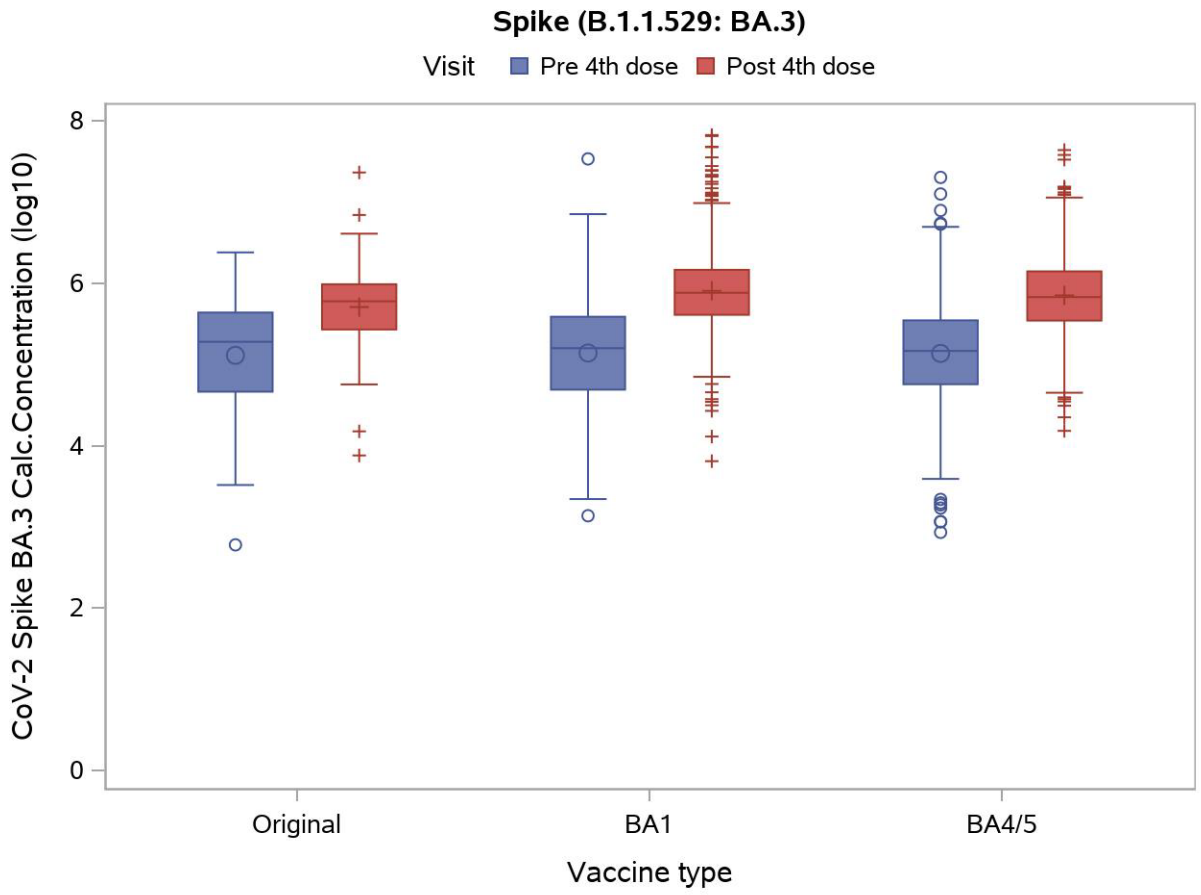


*Figure 6 Distribution of CoV-2 Spike **(B.1.1.528: BA4)** antibody levels before and after the **4th** vaccine dose*

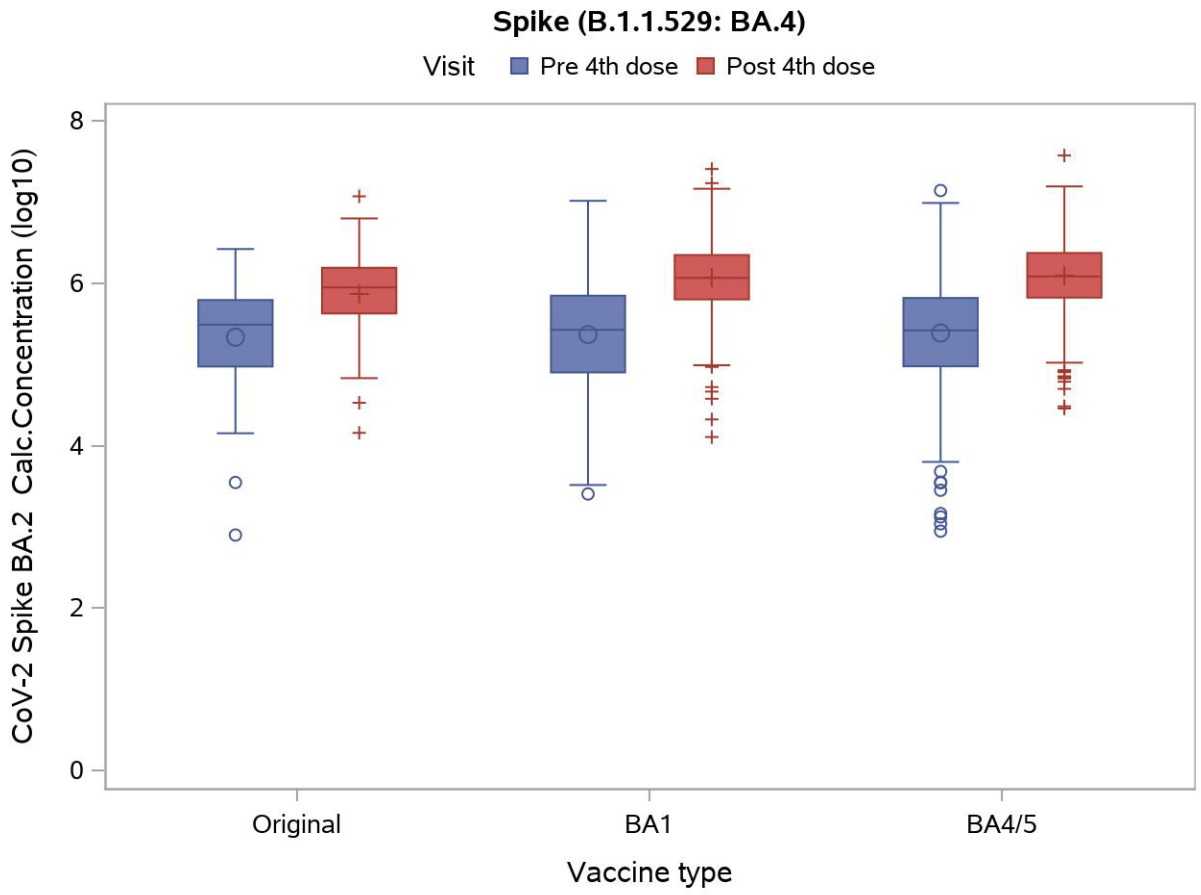
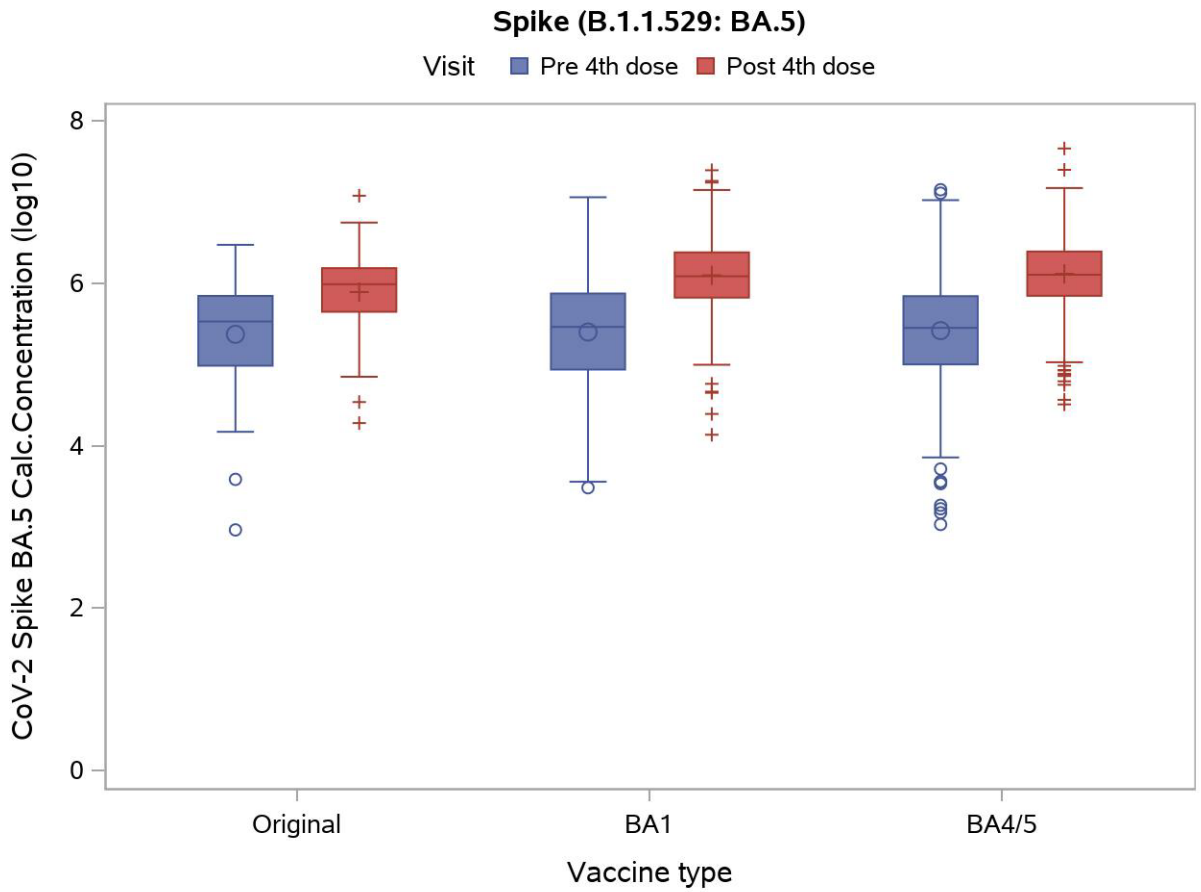


*Figure 7 Distribution of CoV-2 Spike **(B.1.1.528: BA5)** antibody levels before and after the **4th** vaccine dose*



Safety and Monitoring

It should be noted that a number of participants may have received influenza and pneumococcal vaccines at the same time as their 4th vaccine dose. We are currently unable to identify how many participants this relates to and so the safety outcomes reported here are potentially confounded by simultaneous vaccinations.

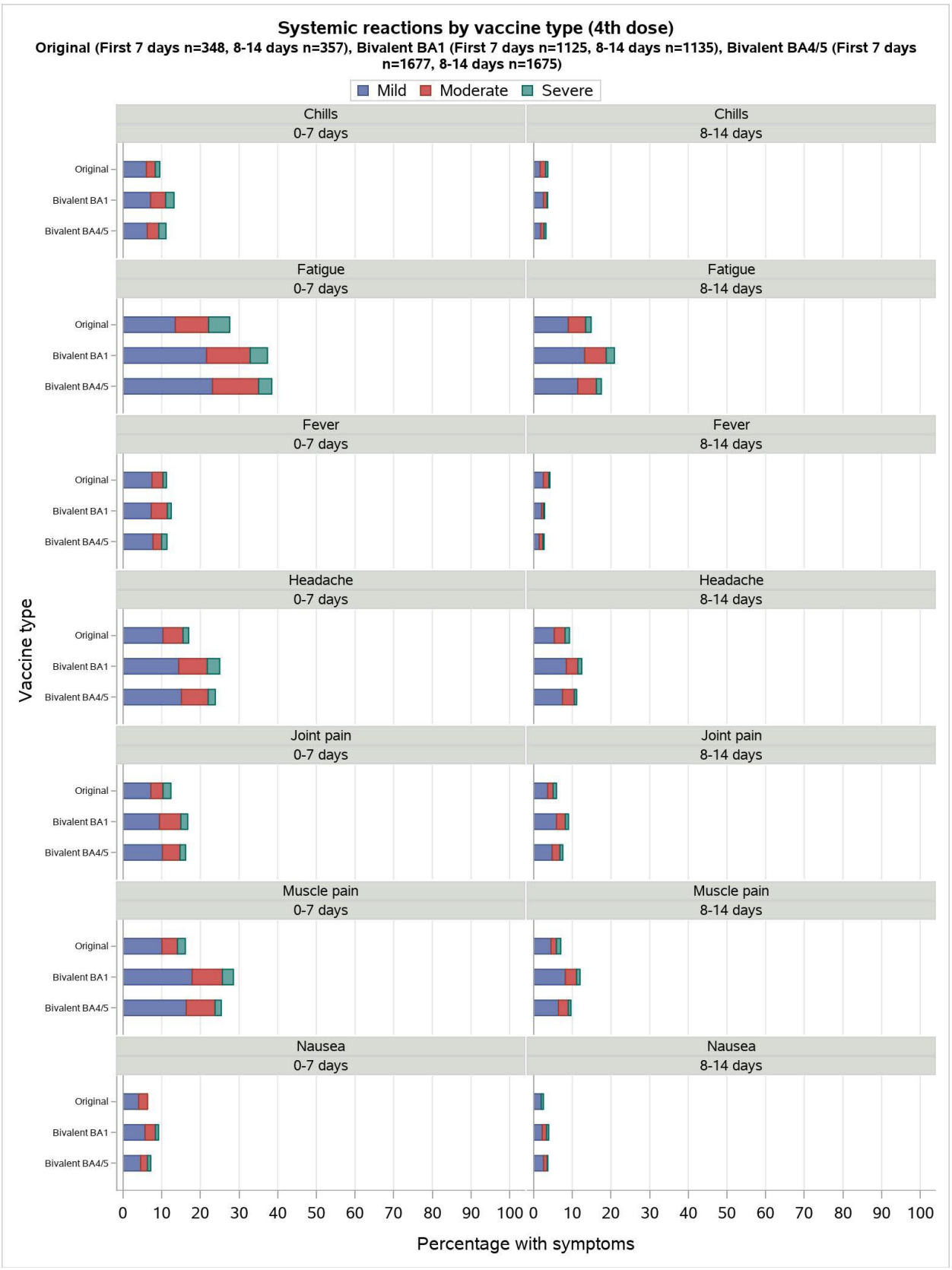
Local and systemic reactions

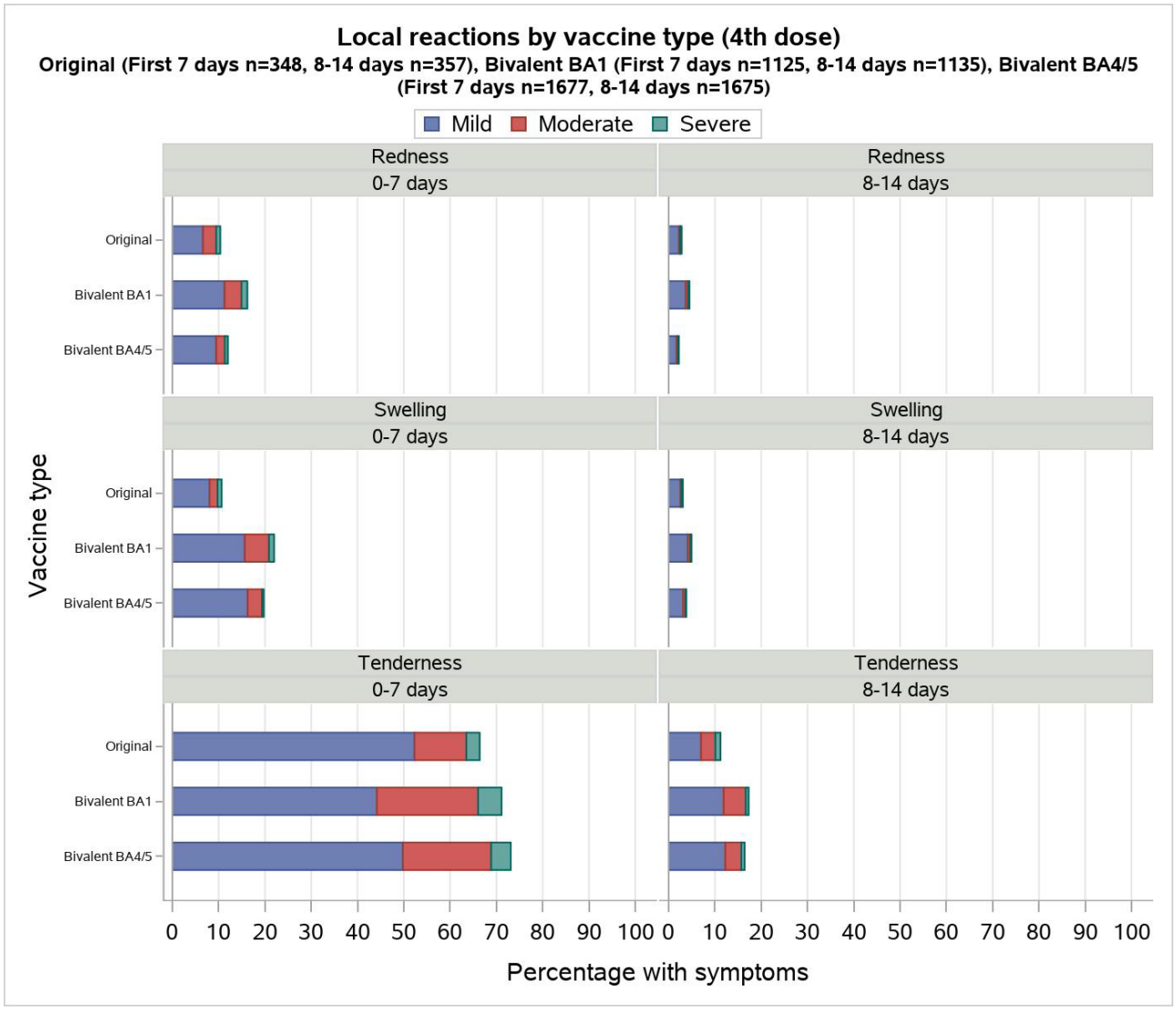
Table 12 outlines the number of participants reporting any local or systemic reactions within 2 weeks of their 4th vaccination. The total number of participants experiencing any symptoms are reported as well as the number experiencing each individual symptom. Note that participants can report multiple symptoms. The percentages are out of the total number of participants who had completed the symptoms form at the time of data extraction. Figure 8 Percentage of participants reporting systemic and local symptoms within 0-7 days of their **4th** dose of the vaccine, by 4th vaccine type shows the proportion reporting mild, moderate or severe symptoms by vaccine type.

Table 12 Number & percentage reporting local/systemic reactions within 0-7 days and 8-14 days following a 4th vaccine dose, overall and by 4th vaccine type

	Total		*Original*		*Bivalent BA1*		*Bivalent BA4/5*	
	First 7 days (N=3158)	*8-14 days (N=3176)*	*First 7 days (N=348)*	*8-14 days (N=357)*	*First 7 days (N=1125)*	*8-14 days (N=1135)*	*First 7 days (N=1677)*	*8-14 days (N=1675)*
Number of persons (%)								
Any clinical symptoms	1574 (49.8)	781 (24.6)	128 (36.8)	68 (19.0)	587 (52.2)	314 (27.7)	858 (51.2)	397 (23.7)
Any local symptoms at injection site	2309 (73.1)	536 (16.9)	235 (67.5)	42 (11.8)	820 (72.9)	210 (18.5)	1251 (74.6)	282 (16.8)
Symptoms reported								
Muscle pain	803 (25.9)	324 (10.3)	56 (16.3)	25 (7.1)	321 (29.1)	136 (12.1)	426 (25.9)	161 (9.7)
Joint pain	502 (16.4)	249 (8.0)	43 (12.6)	21 (5.9)	188 (17.3)	102 (9.1)	271 (16.6)	126 (7.6)
Fatigue	1162 (37.3)	585 (18.6)	96 (27.9)	53 (14.9)	420 (37.9)	237 (21.1)	645 (38.9)	293 (17.7)
Fever	369 (12.0)	93 (3.0)	39 (11.4)	15 (4.2)	140 (12.8)	32 (2.9)	190 (11.6)	45 (2.7)
Headache	740 (24.0)	362 (11.6)	59 (17.3)	33 (9.3)	281 (25.7)	141 (12.7)	400 (24.4)	186 (11.2)
Nausea	245 (8.0)	115 (3.7)	22 (6.4)	9 (2.5)	103 (9.5)	44 (3.9)	120 (7.4)	61 (3.7)
Chills	368 (12.0)	108 (3.5)	33 (9.7)	13 (3.7)	148 (13.6)	41 (3.7)	186 (11.4)	53 (3.2)
Local symptoms at injection site								
Redness	419 (13.9)	98 (3.1)	36 (10.6)	10 (2.8)	182 (17.0)	51 (4.6)	201 (12.6)	37 (2.2)
Swelling	615 (20.5)	131 (4.2)	37 (10.9)	11 (3.1)	247 (23.1)	56 (5.1)	331 (20.8)	64 (3.9)
Tenderness	2260 (72.3)	513 (16.4)	231 (66.6)	40 (11.4)	800 (72.1)	196 (17.6)	1226 (73.8)	275 (16.6)
Median (interquartile range, IQR)								
Number of symptom boxes completed	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)

*Figure 8 Percentage of participants reporting systemic and local symptoms within 0-7 days of their **4th** dose of the vaccine, by 4th vaccine type*




Local reactions by vaccine type (4th dose)
Original (First 7 days n=348, 8-14 days n=357), Bivalent BA1 (First 7 days n=1125, 8-14 days n=1135), Bivalent BA4/5 (First 7 days n=1677, 8-14 days n=1675)
Mild
Moderate
Severe
Redness
0-7 days
Redness
8-14 days
Swelling
0-7 days
Swelling
8-14 days
Tenderness
0-7 days
Tenderness
8-14 days
Vaccine type
Original
Bivalent BA1
Bivalent BA4/5
0 10 20 30 40 50 60 70 80 90 100
Percentage with symptoms

Adverse and Serious Adverse Events

This section gives an overview of the AEs (Table 13) and SAEs (

Table 14) reported following the 4th vaccine dose.

*Table 13 Overview of AEs reported (grade 3 and grade 4) following the 4th dose, by **4th** vaccine*

		4th Vaccine type		
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
Number of persons (%)				
At least one Adverse Event reported	171 (3.2)	28 (4.9)	60 (3.0)	83 (3.0)

*Table 14 Overview and current status of SAEs reported following the 4th dose, by **4th** vaccine*

		4th Vaccine type		
	Total (N=5312)	*Original (N=569)*	*Bivalent BA1 (N=2005)*	*Bivalent BA4/5 (N=2738)*
Total number of participants reporting any SAE (N, %)	21 (0.4)	7 (1.2)	5 (0.2)	9 (0.3)
Total number of SAE reported (N, % of SAE)	21 (100)	7 (100)	5 (100)	9 (100)

Fifth Vaccine Dose

Demographics

Table 15 gives an overview of the participant demographics among individuals who have received a 5th vaccine dose, stratified by the type of vaccine they received.

The majority 94% (n=348) have received a bivalent vaccine for their 5th dose.

*Table 15 Participant demographics among those who received a 5th dose, by **5th** vaccine type*

		5th Vaccine type		
	Total (N=371)	*Original (N=23)*	*Bivalent BA1 (N=136)*	*Bivalent BA4/5 (N=212)*
Number of persons (%)				
Age Group				
<55	72 (19.4)	5 (21.7)	16 (11.8)	51 (24.1)
55-64	79 (21.3)	5 (21.7)	26 (19.1)	48 (22.6)
>=65	220 (59.3)	13 (56.5)	94 (69.1)	113 (53.3)
Gender				
Male	199 (53.6)	13 (56.5)	82 (60.3)	104 (49.1)
Female	172 (46.4)	10 (43.5)	54 (39.7)	108 (50.9)
Vaccine priority group				
1. Individuals at increased risk	319 (86.0)	20 (87.0)	120 (88.2)	179 (84.4)
2. Health care workers	9 (2.4)	<5*	<5*	<5*
3. General population	43 (11.6)	<5*	13 (9.6)	27 (12.7)
Original Vaccine group				
Pfizer-BioNTech	328 (88.4)	19 (82.6)	119 (87.5)	190 (89.6)
Moderna	42 (11.3)	<5*	17 (12.5)	21 (9.9)
AstraZeneca/mRNA	<5*	<5*	<5*	<5*
Median (interquartile range, IQR)				
Age at enrolment (years)	67 (58, 73)	67 (58, 72)	70 (60, 76)	66 (55, 73)
Enrolment date	MAR21 (FEB21, MAR21)	MAR21 (MAR21, MAR21)	MAR21 (FEB21, MAR21)	MAR21 (FEB21, MAR21)

*Exact number not shown due to small numbers

Study visits

Of the 371 participants who have received a 5th vaccine dose, 156 (42%) had a study visit prior to their 5th dose and 217 (59%) have had a study visit a median of 29 days after their 5th dose, 143 (38%) had both a pre and post vaccine visit.

*Table 16 Number and percentage of participants completing **5th** dose study visits*

		Vaccine type		
	Total (N=371)	*Original (N=23)*	*Bivalent BA1 (N=136)*	*Bivalent BA4/5 (N=212)*
Received a fifth dose (N, %)	371 (100)	23 (100)	136 (100)	212 (100)
Time between first and fifth dose (median, IQR)	583 (568, 594)	528 (487, 570)	579 (565, 585)	589 (574, 600)
Visit 5X (0-14 days prior to fifth dose) (N, %)	156 (42.0)	6 (26.1)	48 (35.3)	102 (48.1)
Days from pre-fifth dose visit to fifth dose (median, IQR)	4 (1, 9)	4 (1, 7)	4 (1, 7)	6 (1, 10)
Visit 5Xc (28 days after fifth dose) (N, %)	217 (58.5)	14 (60.9)	80 (58.8)	123 (58.0)
Days from fifth dose to post-booster visit(median, IQR)	29 (26, 33)	29 (27, 33)	29 (24, 33)	29 (26, 33)
Total withdrawn (N, % of total)	40 (10.8)	4 (17.4)	14 (10.3)	22 (10.4)

Outcomes

Primary outcome

From the multiantigen serological tests, the geometric mean (GM) and 95% confidence intervals (CI) for the antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid before and after the 5th vaccine dose are reported in Table 17 from the original mesoscale assay. Fewer than 5 participants with a pre and 9 participants with a post vaccine visit had samples analyzed by the omicron specific assay, so this data is not shown.

*Table 17 Presence of antibodies before and after the **5th dose**, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid (original Mesoscale assay)*

		5th Vaccine type		
	Total (N=371)	*Original (N=23)*	*Bivalent BA1 (N=136)*	*Bivalent BA4/5 (N=212)*
AUH antibody data 0-14 days before fifth dose (N, % of total)	150 (40.4)	6 (26.1)	46 (33.8)	98 (46.2)
AUH antibody data 28 days after fifth dose (N, % of total)	173 (46.6)	13 (56.5)	76 (55.9)	84 (39.6)
CoV-2 Receptor-Binding Domain (SERO)				
GM 0-14 days before fifth dose (95%CI)	96836 (67838, 138228)	175005 (43010, 712086)	102210 (54890, 190325)	91052 (57335, 144595)
GM 28 days after fifth dose (95%CI)	167541 (120601, 232752)	147175 (31102, 696423)	150058 (87940, 256056)	188859 (122240, 291783)
CoV-2 Spike antibody (SERO)				
GM 0-14 days before fifth dose (95%CI)	170274 (128802, 225100)	291618 (133899, 635115)	192773 (124670, 298078)	155433 (106611, 226614)
GM 28 days after fifth dose (95%CI)	267133 (209209, 341094)	216592 (63161, 742740)	264186 (185050, 377164)	278728 (195213, 397973)
CoV-2 Nucleocapsid (SERO)				
GM 0-14 days before fifth dose (95%CI)	2317 (1645, 3264)	1208 (445, 3279)	1902 (1018, 3556)	2645 (1708, 4096)
GM 28 days after fifth dose (95%CI)	2790 (2054, 3791)	2192 (721, 6662)	2075 (1349, 3191)	3788 (2359, 6080)

Safety and Monitoring

It should be noted that a number of participants may have received influenza and pneumococcal vaccines at the same time as their 5th vaccine dose. We are currently unable to identify how many participants this relates to and so the safety outcomes reported here are potentially confounded by simultaneous vaccinations.

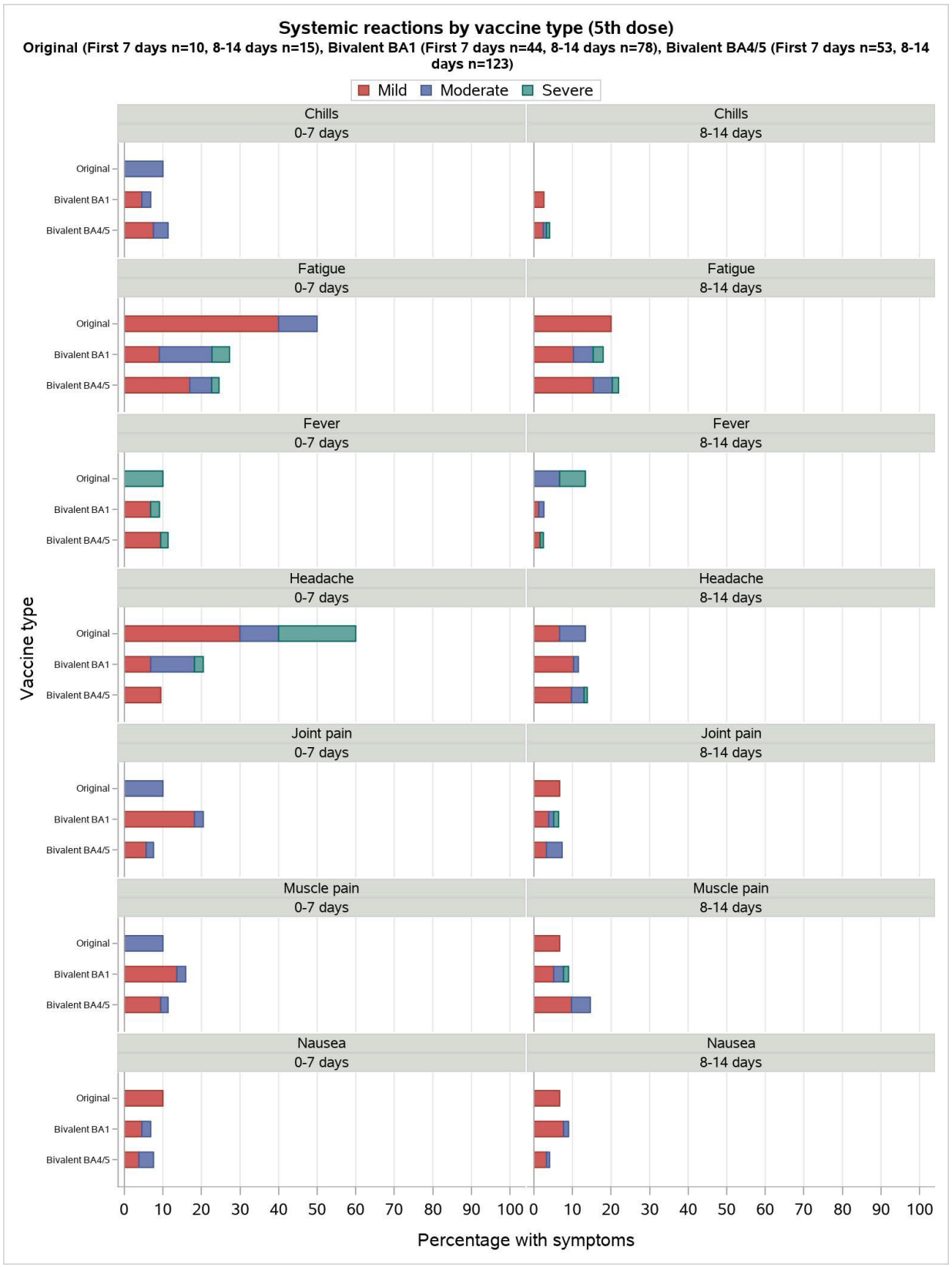
Local and systemic reactions

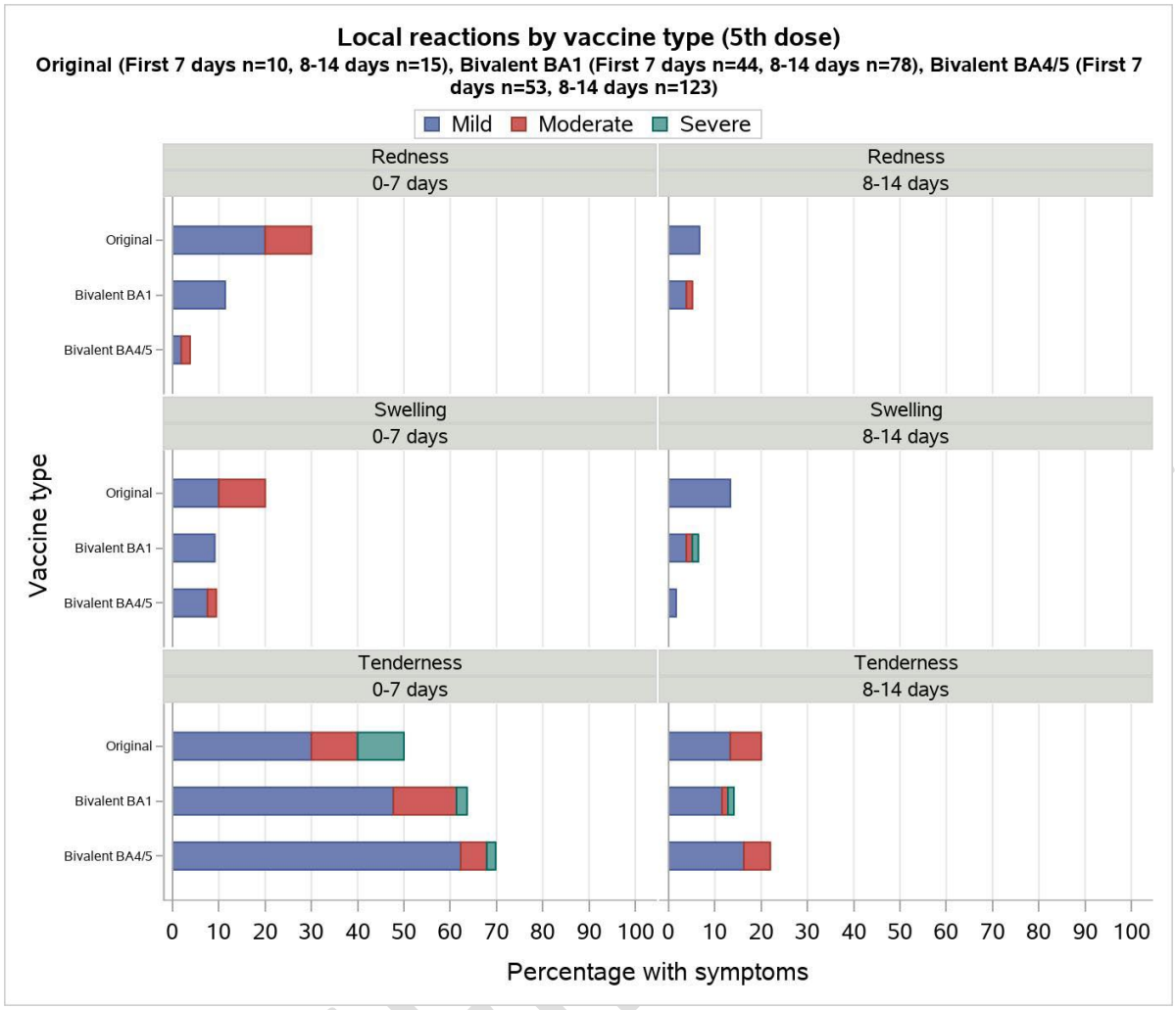
Table 18 outlines the number of participants reporting any local or systemic reactions within 7 days of their 5th vaccination. The total number of participants experiencing any symptoms are reported as well as the number experiencing each individual symptom. Figure 9 shows the proportion reporting mild, moderate or severe symptoms by vaccine type.

Table 18 Number & percentage reporting local/systemic reactions within 0-7 days and 8-14 days following a 5th vaccine dose, overall and by 5th vaccine type

	Total		*Original*		*Bivalent BA1*		*Bivalent BA4/5*	
	First 7 days (N=107)	*8-14 days (N=216)*	*First 7 days (N=10)*	*8-14 days (N=15)*	*First 7 days (N=44)*	*8-14 days (N=78)*	*First 7 days (N=53)*	*8-14 days (N=123)*
Number of persons (%)								
Any clinical symptoms	42 (39.3)	58 (26.9)	7 (70.0)	4 (26.7)	16 (36.4)	16 (20.5)	19 (35.8)	38 (30.9)
Any local symptoms at injection site	70 (65.4)	41 (19.0)	5 (50.0)	3 (20.0)	28 (63.6)	11 (14.1)	37 (69.8)	27 (22.0)

*Figure 9 Percentage of participants reporting systemic and local symptoms within 0-7 days of their **5th dose** of the vaccine, by vaccine type*




Local reactions by vaccine type (5th dose)
Original (First 7 days n=10, 8-14 days n=15), Bivalent BA1 (First 7 days n=44, 8-14 days n=78), Bivalent BA4/5 (First 7 days n=53, 8-14 days n=123)
Mild
Moderate
Severe
Redness
0-7 days
Redness
8-14 days
Swelling
0-7 days
Swelling
8-14 days
Tenderness
0-7 days
Tenderness
8-14 days
Vaccine type
Original
Bivalent BA1
Bivalent BA4/5
0 10 20 30 40 50 60 70 80 90 100
Percentage with symptoms

Adverse and Serious Adverse Events

This section gives an overview of the AEs (Table 19) and SAEs (Table 20) reported following 5th vaccine dose.

Table 19 Overview of AEs reported (grade 3 and grade 4) by 5th vaccine

		5th Vaccine type		
	Total (N=371)	*Original (N=23)*	*Bivalent BA1 (N=136)*	*Bivalent BA4/5 (N=212)*
Number of persons (%)				
At least one Adverse Event reported	25 (6.7)	<5*	5 (3.7)	18 (8.5)

*Exact numbers not shown due to small numbers

Table 20 Overview and current status of SAEs reported by 5th vaccine

		5th Vaccine type		
	Total (N=371)	*Original (N=23)*	*Bivalent BA1 (N=136)*	*Bivalent BA4/5 (N=212)*
Total number of participants reporting any SAE (N, %)	6 (1.6)	<5*	<5*	<5*
Total number of SAE reported (N, % of SAE)	6 (100)	<5*	<5*	<5*

*Exact numbers not shown due to small numbers

Deaths

There have been 80 deaths reported in the study thus far. Eight were reported as a SAE but none had a reasonable probability of relatedness to vaccination nor were reported as a SUSAR. There were an additional 72 deaths recorded in the CPR registry that were outside of the period for reporting SAE (

Table 21).

Table 21 Characteristics of participants who have died

	Total (N=80)
Number of persons (%)	
Age Group	
<55	7 (8.8)
55-64	15 (18.8)
>=65	58 (72.5)
Gender	
Male	42 (52.5)
Female	38 (47.5)
Death reported as an SAE	
Yes	8 (10.0)
No	72 (90.0)
Reasonable probability of relatedness to vaccination	
No	8 (100)
Median (interquartile range, IQR)	
Age at enrolment (years)	74 (64, 80)
Time from first vaccine dose (days)	346 (246, 487)