ENFORCE

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

Monthly Report

Report number: 7

Date Report: 22nd February 2022

Date of data extract: 16th February 2022

Report prepared by: the ENFORCE consortium

Approved by: the ENFORCE scientific steering committee

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

Contents

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Summary of key changes from previous report

Enrolment

Information on the number of individuals who have received a fourth dose and the timing relative to the first vaccination date is now included.

Information on the number of individuals who have had their 5th study visit, which is 1 year after their first vaccine dose, has now been added to the tables. However, as these visits have only just occurred there is no data currently available on their antibody levels at this study visit.

Outcomes

The results of the serum antibody quantification using ELISA (Wantai) performed by Statens Serum Institut (SSI) and from the multiantigen serological tests for antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid are included for those with data up to visit 4 (six months after first vaccination). Results are also shown for those who have received a third dose and had a study visit within 14 days prior to their third vaccination or 28 days following.

The number of breakthrough infections as assessed by a positive SARS-CoV-2 PCR test result after receiving a first dose of vaccine is also included. We are working on incorporating the Nucleocapsid data into this measure.

Safety and Monitoring

Tables summarizing any symptoms reported following the first, second and third dose of the vaccine are included in the report, overall and by vaccine type. Figures showing the severity of the symptoms are also included for all three doses, stratified by vaccine.

Serious adverse events (SAE) and adverse events (AE) (grade 3 & 4) now also include those reported following the third vaccine dose.

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).

Data on deaths are reported from two sources, as a serious adverse events (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 patient 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 predominately based on information provided from the DDV. However, for individuals newly enrolled in the study and where information from the DDV is not yet available the type of vaccine received is based on self-reports from participants at enrolment into the study, prior to them receiving their first 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.

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.

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

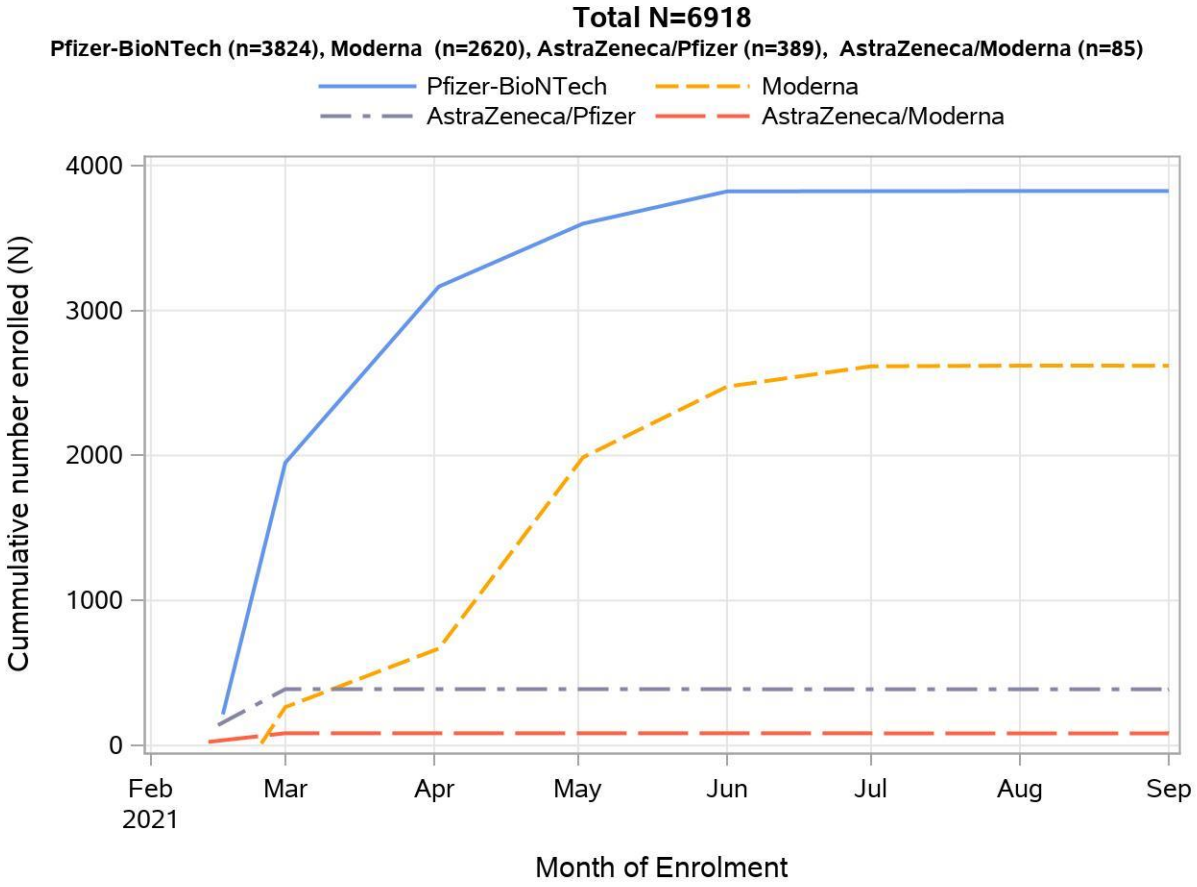
Total included	*Reason for exclusion*
6950	All patients
6927	Consent withdrawn and requested data deleted
6927	Provided informed consent
6927	Missing enrolment date
6926	Aged under 18
6926	Vaccine not recommended
6926	Vaccinated Previously
6926	Agrees to follow protocol
6926	No SSI vaccine data (consent withdrawn) and expected to receive AZ after 10/3/21
6925	No SSI vaccine data (consent withdrawn) and only one study visit (enrolment)
6925	No SSI vaccine data (consent withdrawn) and no study visit after second vaccine
6918	Non-standard vaccine regimen*

*Non-standard regimens included AstraZeneca only, the Janssen COVID-19 vaccine, and a combination of Pfizer-BioNTech and Moderna.

Figure 1 shows the cumulative number of participants enrolled by vaccine type. Enrolment began on the 13th February 2021 when the first patient was enrolled prior to receiving the AstraZeneca vaccine. The first participant enrolled prior to receiving the Pfizer-BioNTech vaccination was on the 16th February 2021, followed by Moderna on the 24th February 2021.

Enrolment into the AstraZeneca vaccine group was stopped following the pausing of AstraZeneca vaccination on 11th March 2021. Enrolment for those receiving Pfizer was paused in week 15, after the target of 2500 participants was reached, but then restarted in week 20. Enrolment in all vaccine groups was competed in August 2021.

Figure 1 Cumulative number of participants enrolled by vaccine type



Demographics at enrolment

Table 2 gives an overview of the participant demographics at the time of enrolment into the study overall and by vaccine. Table 3 gives an overview of the number of participants with concomitant diseases at enrolment and the use of any medications in the 24 hours prior to enrolment.

Table 2 Participant demographics at study enrolment by vaccine

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Number of persons (%)					
Gender					
Male	3000 (43.4)	1841 (48.1)	1085 (41.4)	58 (14.9)	16 (18.8)
Female	3918 (56.6)	1983 (51.9)	1535 (58.6)	331 (85.1)	69 (81.2)
Median (interquartile range, IQR)					
Age at enrolment (years)	64 (54, 75)	71 (55, 78)	61 (54, 69)	45 (31, 56)	45 (33, 56)
Enrolment date	APR21 (MAR21, MAY21)	MAR21 (MAR21, APR21)	MAY21 (APR21, MAY21)	MAR21 (FEB21, MAR21)	MAR21 (FEB21, MAR21)

Table 3 Concomitant diseases and medications, overall and by vaccine

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Any concomitant disease N (%)	4550 (65.8)	2832 (74.1)	1557 (59.4)	147 (37.8)	14 (16.5)
Any medications taken in the last 24 hours N (%)	4781 (69.1)	2956 (77.3)	1606 (61.3)	183 (47.0)	36 (42.4)

Enrolment Progress

Figure 2 shows the current status of participants in the study at the date of most recent data extract. Participants have been in the study from between 7 and 12 months. Table 4 gives the number of participants included in the study who have received each dose of the vaccine and also the number and percentage who have completed each study visit.

Figure 2 Current status of participants

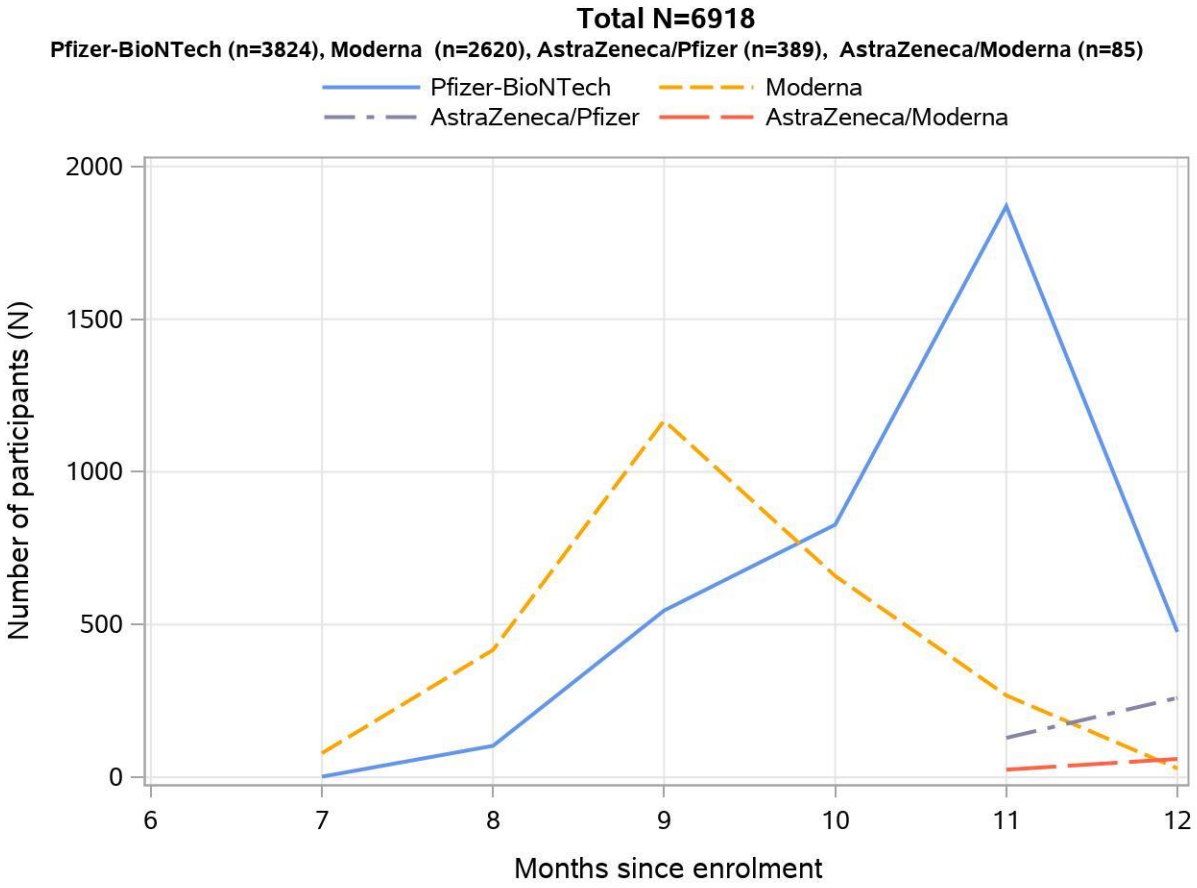


Table 4 Number and percentage of participants completing each study visit

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/Pfizer (N=389)*	*AstraZeneca/Moderna (N=85)*
Received two doses (N, %)	6909 (99.9)	3817 (99.8)	2618 (99.9)	389 (100)	85 (100)
Time between first and second dose (median, IQR)	29 (22, 35)	23 (21, 28)	35 (35, 36)	83 (79, 87)	82 (79, 87)
Visit 2 (prior to second vaccination) (N, %)	6531 (94.4)	3635 (95.1)	2517 (96.1)	329 (84.6)	50 (58.8)
Days from first vaccine to second study visit (median, IQR)	28 (21, 35)	22 (21, 27)	34 (32, 35)	83 (79, 89)	82 (77, 87)
Visit 3 (3 months after first vaccination) (N, %)	6006 (86.8)	3445 (90.1)	2477 (94.5)	64 (16.5)	20 (23.5)
Days from first vaccine to third study visit (median, IQR)	91 (89, 96)	91 (89, 95)	92 (89, 96)	96 (90, 101)	97 (92, 99)
Visit 4 (6 months after first vaccination) (N, %)	5830 (84.3)	3275 (85.6)	2187 (83.5)	311 (79.9)	57 (67.1)
Days from first vaccine to fourth study visit (median, IQR)	182 (179, 186)	183 (179, 186)	182 (177, 186)	182 (179, 186)	182 (180, 189)
Visit 5 (1 year after first vaccination) (N, %)	24 (0.3)	17 (0.4)	<5*	<5*	<5*
Days from first vaccine to fifth study visit (median, IQR)	351 (345, 354)	349 (344, 353)	-	-	-

*Exact numbers not shown due to small numbers

Third and fourth dose progress

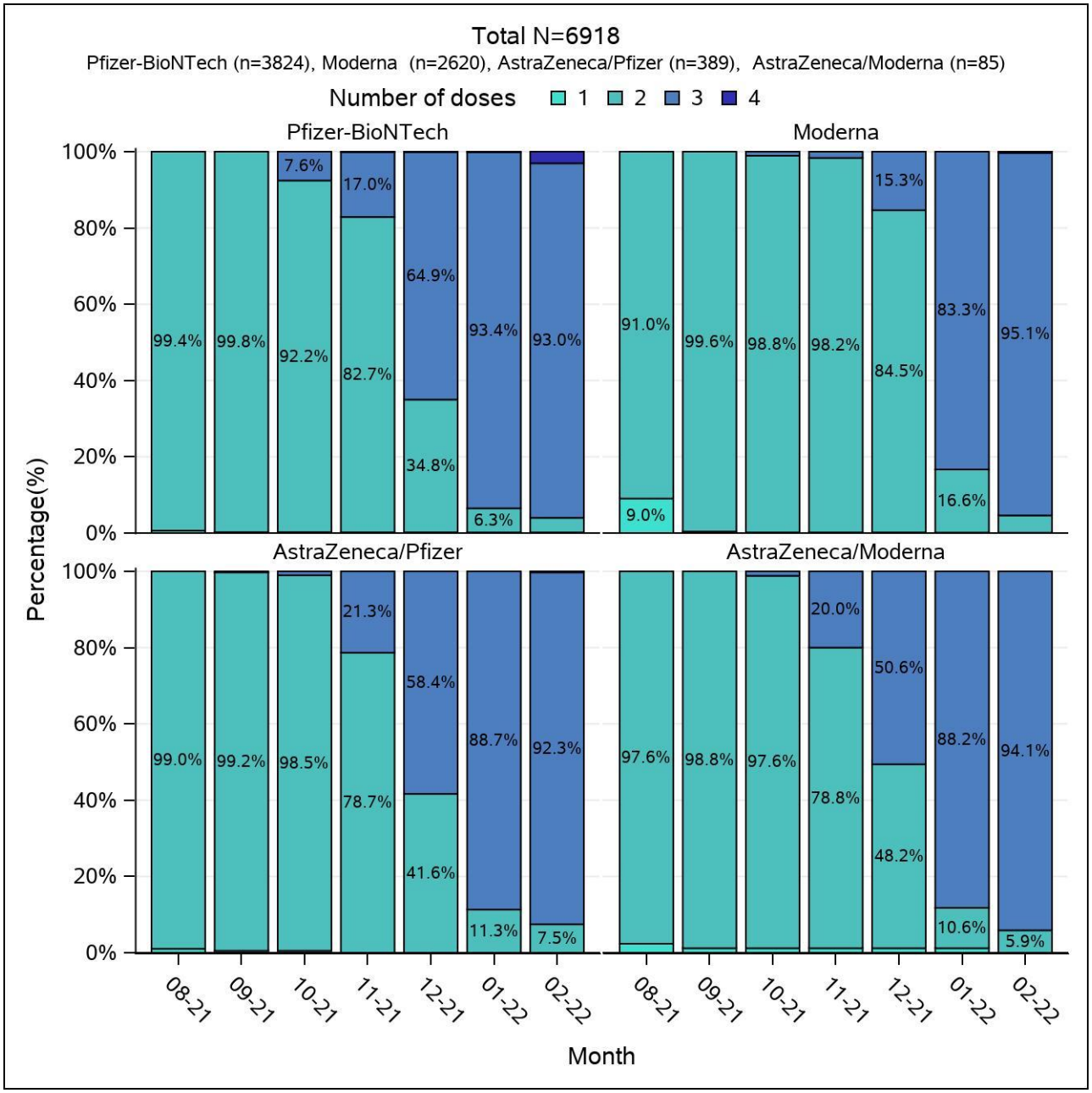
Table 5 gives the number of participants included in the study who have received booster doses of the vaccine and the number and percentage who have completed each booster visit among those who have received a third dose. Figure 3 shows the proportion of participants in each vaccine group who have received each vaccine dose.

Table 5 Number and percentage of participants completing study visits related to their third and fourth doses

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/Pfizer (N=389)*	*AstraZeneca/Moderna (N=85)*
Received a third dose (N, %)	6625 (95.8)	3674 (96.1)	2511 (95.8)	360 (92.5)	80 (94.1)
Time between first and third dose (median, IQR)	225 (210, 236)	229 (216, 238)	216 (204, 224)	266 (246, 280)	274 (244, 283)
Received a fourth dose (N, %)	219 (3.2)	200 (5.2)	18 (0.7)	<5*	<5*
Time between first and fourth dose (median, IQR)	333 (314, 338)	333 (314, 338)	326 (321, 340)	. (., .)	. (., .)
Visit X (0-14 days prior to third dose) (N, %)	2895 (43.7)	1448 (39.4)	1287 (51.3)	133 (36.9)	27 (33.8)
Days from pre-booster visit to third dose (median, IQR)	2 (1, 6)	2 (1, 6)	2 (1, 5)	2 (0, 5)	1 (1, 6)
Visit Xc (28 days after third dose) (N, %)	4535 (68.5)	2411 (65.6)	1840 (73.3)	239 (66.4)	45 (56.3)
Days from third dose to post-booster visit (median, IQR)	28 (26, 32)	28 (26, 32)	29 (27, 32)	29 (25, 34)	29 (27, 33)

* Exact numbers not shown due to small numbers

Figure 3 Percentage of participants receiving each vaccine dose by calendar month



Withdrawal/Loss to follow-up

Table 6 shows the number of participants enrolled in the study who have subsequently withdrawn and no longer wish to be contacted or attend future study visits.

Table 6 Number and percentage of participants discontinuing in the study, by vaccine type

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Study status (N, % of total)					
Still under follow-up	6488 (93.8)	3525 (92.2)	2556 (97.6)	338 (86.9)	69 (81.2)
Total withdrawn	430 (6.2)	299 (7.8)	64 (2.4)	51 (13.1)	16 (18.8)

Outcomes

Primary outcome

Until the threshold for MPNAT has been established we will present the results from both the ELISA (Wantai) and the multiantigen serological test including the Receptor Binding Domain (RBD), the complete Spike (S) protein and the Nucleocapsid (NC).

The data from the ELISA (Wantai) are presented as negative, positive and inconclusive (see methods for categorization) and are shown in Figure 4 and the numbers included at each time point in Table 7.

Figure 4 Presence of antibodies at study visit, ELISA (Wantai) from SSI

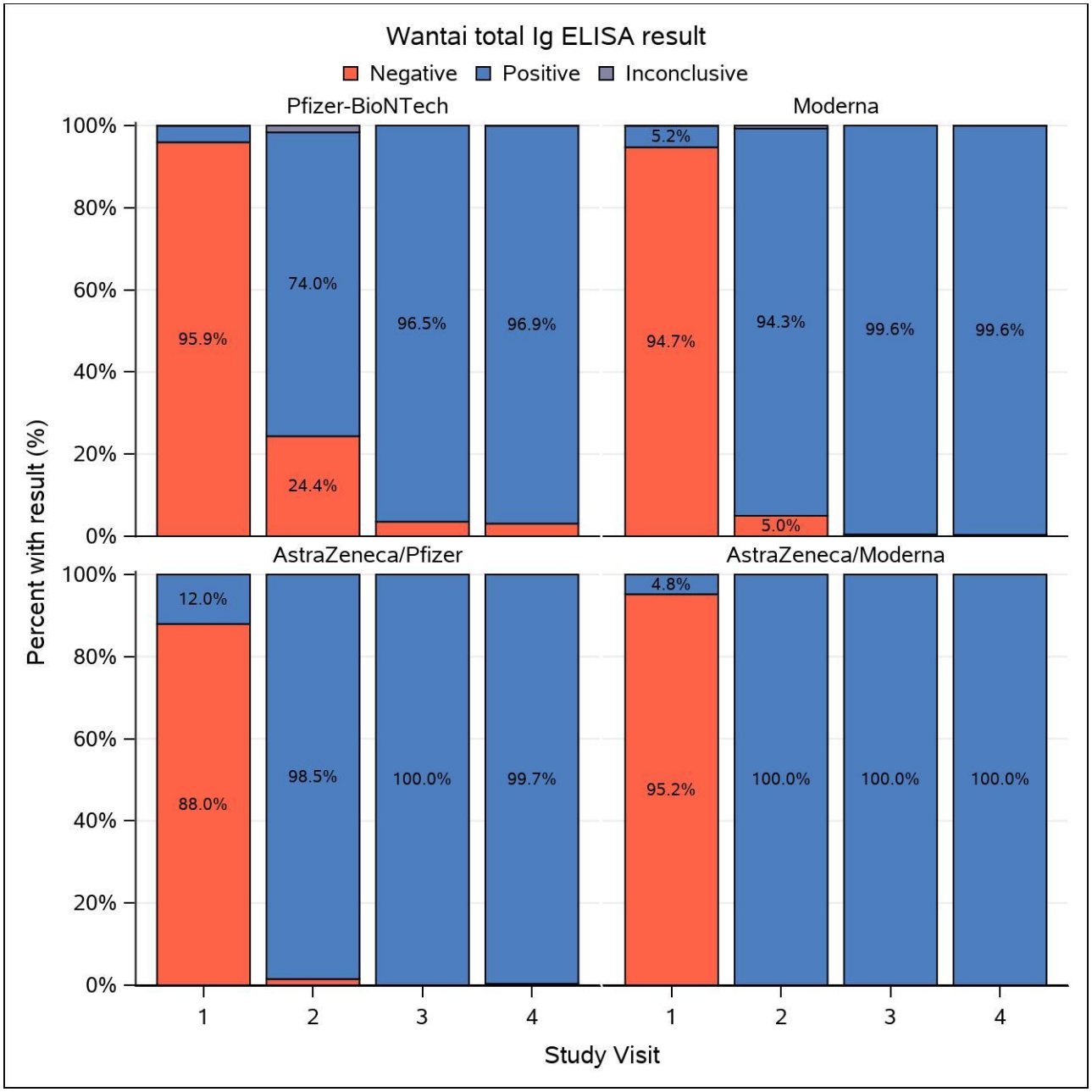


Table 7 Number of individuals with antibody data at each study visit, ELISA (Wantai) from SSI

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
SSI antibody data at visit 1 (enrolment) (N, % of total)	6870 (99.3)	3791 (99.1)	2614 (99.8)	382 (98.2)	83 (97.6)
SSI antibody data at visit 2 (prior to second vaccination) (N, % of total)	6370 (92.1)	3580 (93.6)	2492 (95.1)	260 (66.8)	38 (44.7)
Days from first vaccination (median (IQR))	28 (21, 35)	22 (21, 27)	34 (32, 35)	82 (78, 85)	82 (77, 87)
SSI antibody data at visit 3 (3 months after first vaccination) (N, % of total)	5960 (86.2)	3413 (89.3)	2463 (94.0)	64 (16.5)	20 (23.5)
Days from first vaccination (median (IQR))	91 (89, 96)	91 (89, 95)	92 (89, 96)	96 (90, 101)	97 (92, 99)
SSI antibody data at visit 4 (6 months after first vaccination) (N, % of total)	5712 (82.6)	3200 (83.7)	2148 (82.0)	307 (78.9)	57 (67.1)
Days from first vaccination (median (IQR))	182 (179, 186)	183 (179, 186)	182 (177, 186)	182 (179, 186)	182 (180, 189)

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 at each study visit are reported in Table 8. Figure 5-7 show the distribution of the three assays on the log10 scale, by vaccine type and study visit.

Table 8 Presence of antibodies at study visit, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
AUH antibody data at visit 1 (enrolment) (N, % of total)	6861 (99.2)	3791 (99.1)	2605 (99.4)	382 (98.2)	83 (97.6)
AUH antibody data at visit 2 (prior to second vaccination) (N, % of total)	6302 (91.1)	3574 (93.5)	2490 (95.0)	204 (52.4)	34 (40.0)
AUH antibody data at visit 3 (3 months after first vaccination) (N, % of total)	5957 (86.1)	3411 (89.2)	2462 (94.0)	64 (16.5)	20 (23.5)
AUH antibody data at visit 4 (6 months after first vaccination) (N, % of total)	5925 (85.6)	3225 (84.3)	2338 (89.2)	305 (78.4)	57 (67.1)
CoV-2 Receptor-Binding Domain (SERO)					
GM at enrolment (95%CI)	59 (57, 61)	53 (50, 55)	65 (62, 69)	90 (74, 108)	59 (43, 80)
GM at visit 2 (95%CI)	8843 (8406, 9303)	4086 (3819, 4371)	27498 (25924, 29166)	7504 (6098, 9233)	3466 (2273, 5286)
GM at visit 3 (95%CI)	95324 (91513, 99293)	52088 (49182, 55166)	211776 (203628, 220251)	283372 (235142, 341495)	356061 (274785, 461377)
GM at visit 4 (95%CI)	39858 (38292, 41489)	20100 (19028, 21233)	87932 (84069, 91972)	102976 (91991, 115273)	132483 (102755, 170812)
CoV-2 Spike antibody (SERO)					
GM at enrolment (95%CI)	106 (102, 110)	102 (97, 108)	104 (98, 111)	161 (131, 199)	113 (80, 161)
GM at visit 2 (95%CI)	26884 (25652, 28176)	13665 (12822, 14563)	74112 (70260, 78175)	18555 (15351, 22428)	10907 (6990, 17017)
GM at visit 3 (95%CI)	173430 (167609, 179454)	108485 (103179, 114064)	322683 (313279, 332370)	392880 (350127, 440853)	455735 (407411, 509791)
GM at visit 4 (95%CI)	82810 (79928, 85796)	45631 (43414, 47961)	164395 (158334, 170687)	192840 (176228, 211018)	241303 (201103, 289539)
CoV-2 Nucleocapsid (SERO)					

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
GM at enrolment (95%CI)	263 (251, 275)	268 (252, 284)	243 (226, 261)	361 (288, 452)	292 (201, 423)
GM at visit 2 (95%CI)	299 (286, 313)	283 (267, 300)	316 (295, 340)	427 (314, 581)	218 (134, 354)
GM at visit 3 (95%CI)	412 (394, 430)	376 (354, 399)	462 (433, 493)	637 (394, 1030)	419 (227, 772)
GM at visit 4 (95%CI)	451 (431, 472)	430 (404, 457)	465 (433, 498)	599 (482, 744)	449 (290, 697)

GM: Geometric mean

Figure 5 Distribution of CoV-2 Receptor-Binding Domain (RBD) levels at each study visit (see Table 8 for the number included at each time point)

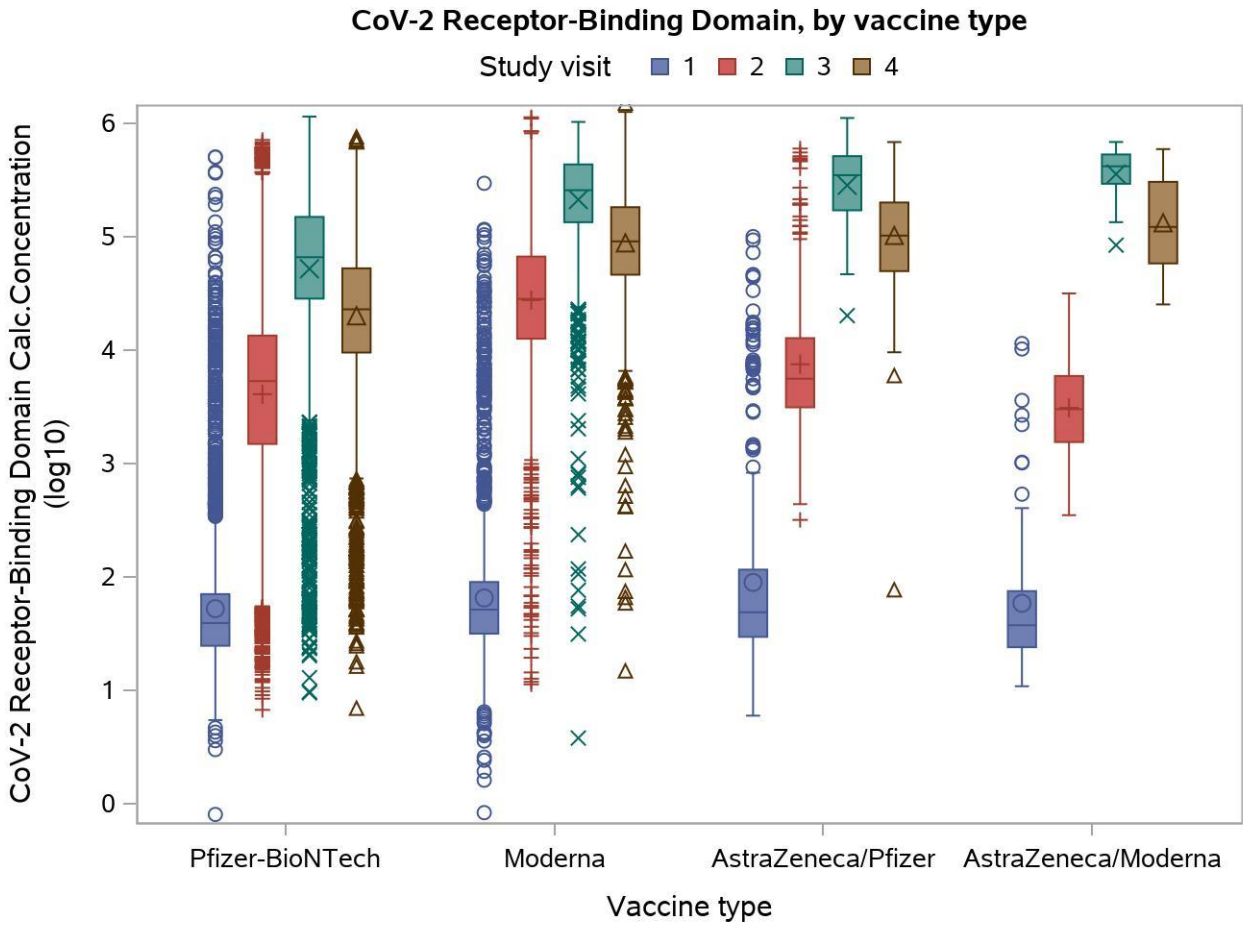


Figure 6 Distribution of CoV-2 Spike antibody levels at each study visit (see Table 8 for the number included at each time point)

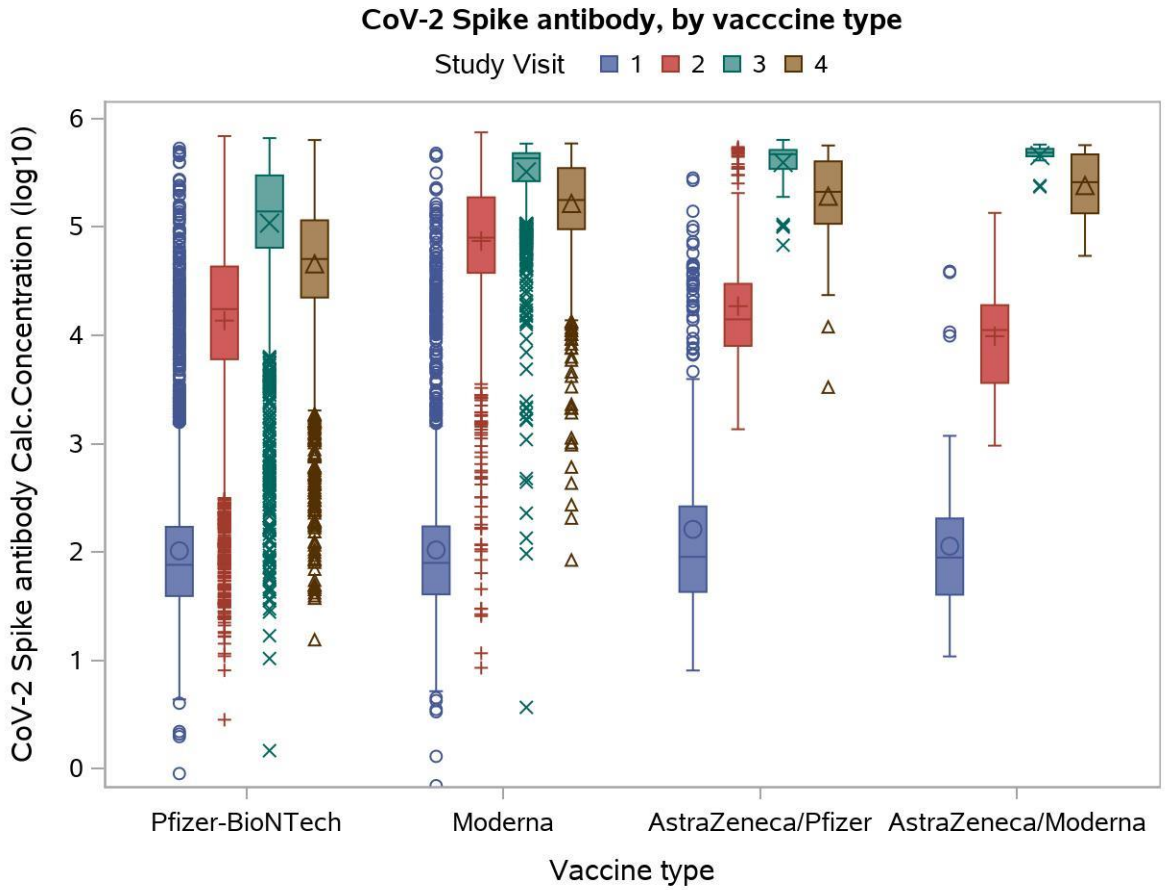
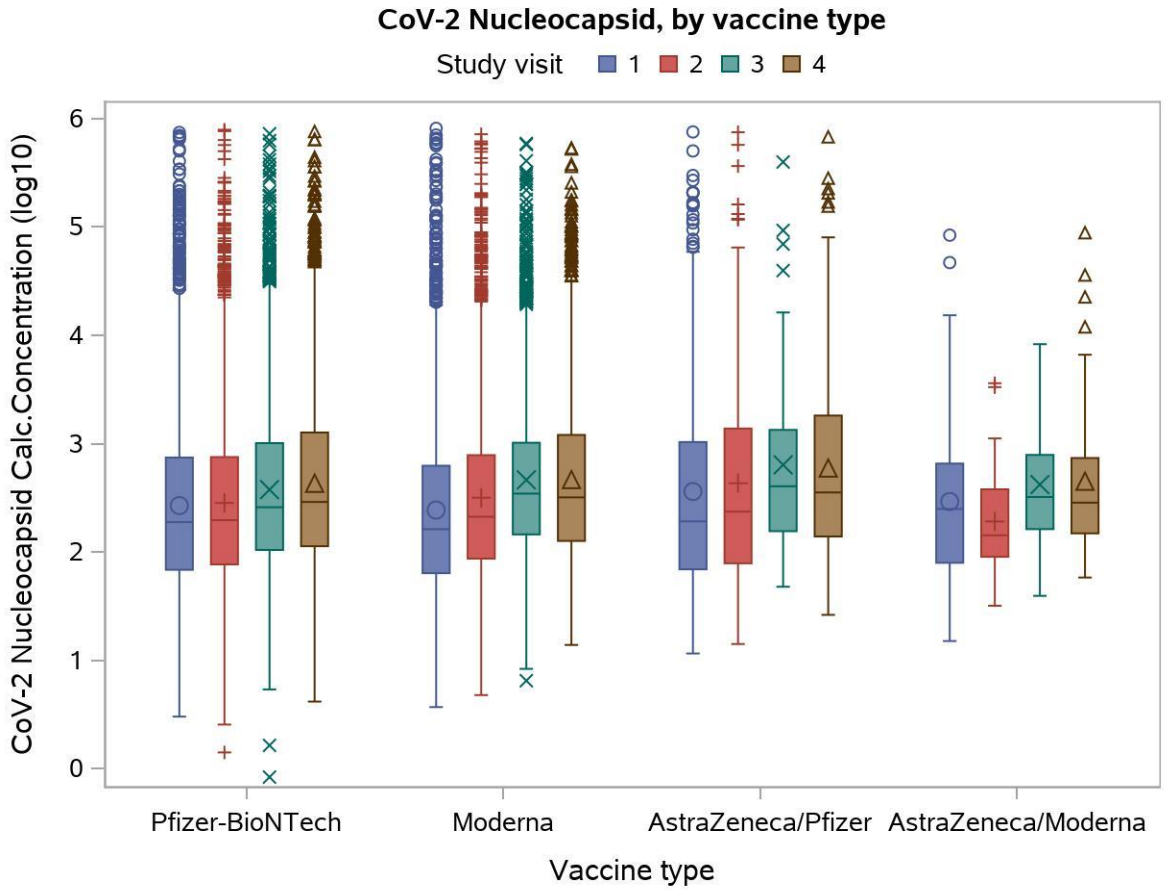


Figure 7 Distribution of CoV-2 Nucleocapsid levels at each study visit (see Table 8 for the number included at each time point)



Primary outcome among those who have received a third dose

The percentage of participants with results from the ELISA (Wantai) assay within 14 days prior to receiving their third dose and 28 days following the vaccination are shown in Table 9.

Table 9 Presence of antibodies at study visit, ELISA (Wantai) from SSI, among participants who have received a third dose

		Vaccine type			
	Total (N=6625)	*Pfizer-BioNTech (N=3674)*	*Moderna (N=2511)*	*AstraZeneca/ Pfizer (N=360)*	*AstraZeneca/ Moderna (N=80)*
SSI antibody data 0-14 days before third dose (N, % of total)	2703 (40.8)	1394 (37.9)	1149 (45.8)	134 (37.2)	26 (32.5)
Wantai result prior to booster (visit X)					
Negative	44 (1.6)	43 (3.1)	<5*	0	0
Positive	2658 (98.3)	1351 (96.9)	1147 (99.8)	134 (100)	26 (100)
Inconclusive	<5*	0	<5*	0	0
Days prior to third dose (median (IQR))	2 (1, 6)	2 (1, 6)	2 (1, 5)	2 (0, 5)	1 (1, 6)
SSI antibody data 28 days after third dose (N, % of total)	4219 (63.7)	2233 (60.8)	1723 (68.6)	220 (61.1)	43 (53.8)
Wantai result after booster (visit Xc)					
Negative	44 (1.0)	38 (1.7)	6 (0.3)	0	0
Positive	4172 (98.9)	2193 (98.2)	1716 (99.6)	220 (100)	43 (100)
Inconclusive	<5*	<5*	<5*	0	0
Days after third dose (median (IQR))	28 (26, 32)	28 (26, 32)	29 (27, 32)	29 (25, 34)	29 (27, 33)

*Exact numbers not shown due to small numbers

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 at the visit prior to the third dose and 28 days following the third dose are reported in Table 10.

Table 10 Presence of antibodies at study visit, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid, among participants who have received a third dose

		Vaccine type			
	Total (N=6625)	*Pfizer-BioNTech (N=3674)*	*Moderna (N=2511)*	*AstraZeneca/ Pfizer (N=360)*	*AstraZeneca/ Moderna (N=80)*
AUH antibody data 0-14 days before third dose (N, % of total)	2868 (43.3)	1446 (39.4)	1262 (50.3)	134 (37.2)	26 (32.5)
AUH antibody data 28 days after third dose (N, % of total)	4066 (61.4)	2263 (61.6)	1535 (61.1)	226 (62.8)	42 (52.5)
CoV-2 Receptor-Binding Domain (SERO)					
GM 0-14 days before third dose (95%CI)	35367 (33420, 37429)	17025 (15674, 18492)	77505 (73132, 82138)	50731 (42556, 60477)	72744 (44788, 118150)
GM 28 days after third dose (95%CI)	344448 (331366, 358047)	277654 (261032, 295335)	463195 (444729, 482428)	375919 (342712, 412343)	473870 (435280, 515883)
CoV-2 Spike antibody (SERO)					
GM 0-14 days before third dose (95%CI)	74030 (70425, 77819)	38731 (35981, 41690)	148353 (141213, 155853)	103353 (88253, 121036)	130904 (87161, 196601)
GM 28 days after third dose (95%CI)	414123 (402316, 426276)	361922 (345307, 379337)	495448 (480895, 510442)	452377 (435507, 469900)	521816 (508257, 535737)
CoV-2 Nucleocapsid (SERO)					
GM 0-14 days before third dose (95%CI)	515 (482, 550)	507 (461, 558)	501 (454, 551)	757 (555, 1033)	618 (300, 1272)
GM 28 days after third dose (95%CI)	799 (760, 840)	721 (673, 773)	893 (826, 967)	1002 (790, 1272)	966 (590, 1582)

Figure 8 and Figure 9 show the distribution of the antibody levels against the Receptor Binding Domain, and the complete Spike protein on the $\log_{10}$ scale, at visit 3 (90 days after the first vaccine dose), 0-14 days prior to receiving the third dose and 28 days after receiving the third dose. Only participants with results at all three visits are included. There are currently 2513 participants with results from all three visits (Pfizer-BioNTech n= 1351, Moderna n=1133, AstraZenca/Pfizer n=24 and AstraZenca/Moderna n=5). Due the small numbers only those in the Pfizer-BioNTech and Moderna groups are shown in the figures.

Figure 8 Distribution of CoV-2 Receptor-Binding Domain (RBD) levels among participants who have received a third dose

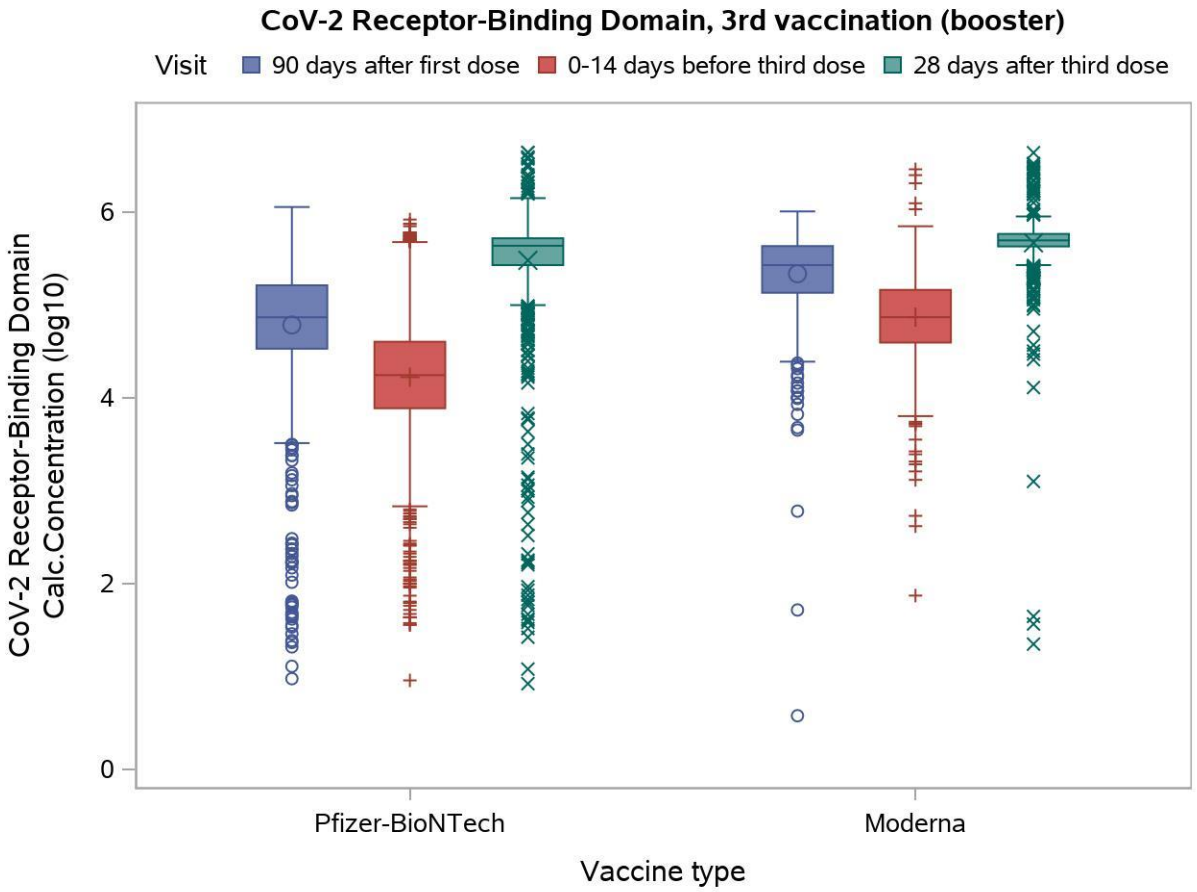
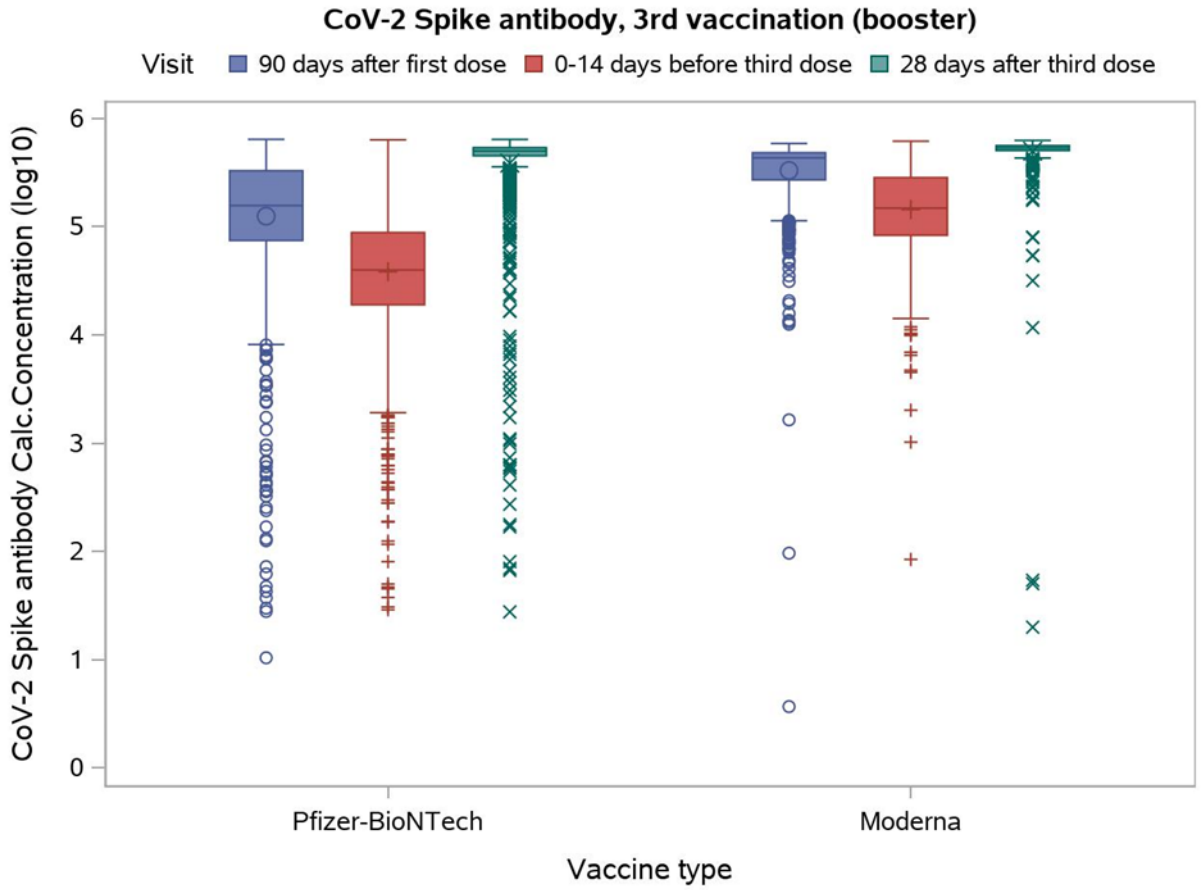


Figure 9 Distribution of CoV-2 Spike antibody levels among participants who have received a third dose



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 11.

Table 11 Number of participants testing positive for SARS-CoV-2

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Number of PCR tests since first vaccine dose (median, IQR)	4 (1, 8)	3 (1, 7)	4 (2, 8)	16 (8, 24)	13 (4, 23)
Number of antigen tests since first vaccine dose (median, IQR)	3 (1, 6)	2 (0, 5)	4 (1, 8)	5 (1, 9)	7 (1, 12)
Number PCR positive for SARS-CoV-2 reported via KIDS (N, % of total)	1664 (24.1)	823 (21.5)	650 (24.8)	169 (43.4)	22 (25.9)
Days from first vaccine dose to SARS-CoV2 positive test (median, IQR)	264 (228, 313)	291 (238, 318)	237 (211, 261)	329 (313, 344)	324 (318, 337)

Safety Monitoring

Local and systemic reactions

Table 12 outlines the number of participants reporting any local or systemic reactions within 7 days of 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. All participants are encouraged to complete the form even if they experience no symptoms. Figure 10 shows the proportion reporting mild, moderate or severe symptoms by vaccine type.

Similarly, Table 13 outlines the number of participants reporting any local or systemic reactions within 0-7 days and 8-14 days of the third vaccine and Figure 11 the proportion reporting mild, moderate or severe symptoms by vaccine type.

Table 12 Number & percentage reporting local/systemic reactions within 0-7 days post vaccination overall, all and by vaccination

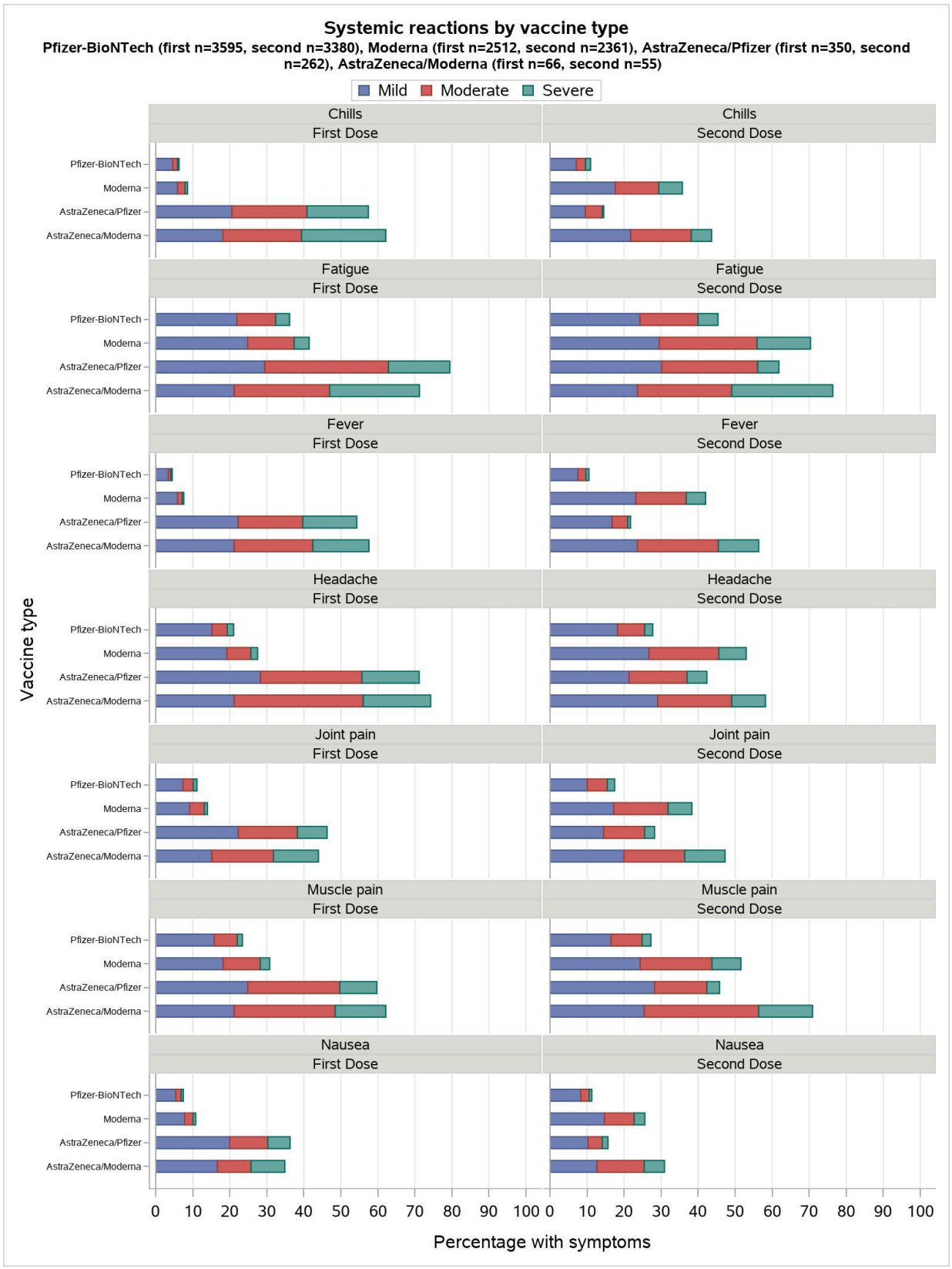
	Total		*Pfizer-BioNTech*		*Moderna*		*AstraZeneca/Pfizer*		*AstraZeneca/Moderna*	
	First (N=6523)	*Second (N=6058)*	*First (N=3595)*	*Second (N=3380)*	*First (N=2512)*	*Second (N=2361)*	*First (N=350)*	*Second (N=262)*	*First (N=66)*	*Second (N=55)*
Number of persons (%)										
Any clinical symptoms	3797 (58.2)	4153 (68.6)	1879 (52.3)	1933 (57.2)	1536 (61.1)	1973 (83.6)	322 (92.0)	198 (75.6)	60 (90.9)	49 (89.1)
Any local symptoms at injection site	5149 (78.9)	4754 (78.5)	2595 (72.2)	2336 (69.1)	2191 (87.2)	2132 (90.3)	306 (87.4)	238 (90.8)	57 (86.4)	48 (87.3)
Symptoms reported										
Muscle pain	1865 (29.1)	2297 (38.9)	842 (23.8)	921 (27.9)	773 (31.4)	1217 (53.4)	209 (60.4)	120 (46.3)	41 (66.1)	39 (70.9)
Joint pain	942 (14.9)	1595 (27.3)	400 (11.4)	590 (18.0)	351 (14.4)	905 (40.1)	162 (48.2)	74 (28.7)	29 (46.0)	26 (49.1)
Fatigue	2665 (41.5)	3398 (57.0)	1299 (36.6)	1533 (46.0)	1041 (42.1)	1661 (71.8)	278 (80.6)	162 (62.3)	47 (74.6)	42 (76.4)
Fever	578 (9.1)	1435 (24.5)	160 (4.6)	355 (10.8)	190 (7.8)	992 (43.5)	190 (55.7)	57 (22.3)	38 (59.4)	31 (57.4)
Headache	1745 (27.3)	2332 (39.5)	756 (21.4)	938 (28.5)	691 (28.1)	1251 (54.4)	249 (71.8)	111 (42.9)	49 (75.4)	32 (58.2)
Nausea	689 (10.9)	1044 (18.0)	268 (7.6)	381 (11.7)	271 (11.2)	605 (27.1)	127 (37.8)	41 (16.1)	23 (36.5)	17 (30.9)
Chills	684 (10.8)	1276 (21.9)	226 (6.5)	370 (11.4)	216 (8.9)	844 (37.5)	201 (58.9)	38 (14.9)	41 (65.1)	24 (44.4)
Local symptoms at injection site										
Redness	619 (9.9)	1015 (17.8)	260 (7.5)	332 (10.3)	290 (12.1)	625 (28.5)	55 (16.7)	41 (16.5)	14 (23.0)	17 (32.7)
Swelling	1055 (17.0)	1417 (25.0)	407 (11.9)	500 (15.6)	552 (23.1)	826 (37.8)	78 (23.9)	74 (30.3)	18 (29.0)	17 (40.5)
Tenderness	5096 (78.6)	4675 (77.8)	2561 (71.8)	2296 (68.5)	2175 (86.9)	2095 (89.5)	304 (87.4)	236 (91.1)	56 (84.8)	48 (87.3)
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)	10 (10, 10)	10 (9, 10)

Table 13 Number & percentage reporting local/systemic reactions within 0-7 days and 8-14 days following a third vaccine dose, overall and by vaccination

	Total		*Pfizer-BioNTech*		*Moderna*		*AstraZeneca/Pfizer*		*AstraZeneca/Moderna*	
	First 7 days (N=4248)	*8-14 days (N=4246)*	*First 7 days (N=2224)*	*8-14 days (N=2254)*	*First 7 days (N=1755)*	*8-14 days (N=1723)*	*First 7 days (N=228)*	*8-14 days (N=229)*	*First 7 days (N=41)*	*8-14 days (N=40)*
Number of persons (%)										
Any clinical symptoms	2302 (54.2)	1002 (23.6)	999 (44.9)	478 (21.2)	1131 (64.4)	460 (26.7)	137 (60.1)	54 (23.6)	35 (85.4)	10 (25.0)
Any local symptoms at injection site	3212 (75.6)	660 (15.5)	1502 (67.5)	336 (14.9)	1492 (85.0)	295 (17.1)	180 (78.9)	20 (8.7)	38 (92.7)	9 (22.5)
Symptoms reported										
Muscle pain	1127 (26.9)	365 (8.7)	454 (20.7)	176 (7.9)	585 (33.7)	173 (10.1)	58 (25.9)	11 (4.8)	30 (73.2)	5 (12.5)
Joint pain	735 (17.7)	293 (7.0)	268 (12.3)	141 (6.3)	402 (23.5)	136 (8.0)	47 (20.9)	11 (4.9)	18 (43.9)	5 (12.5)
Fatigue	1714 (41.0)	733 (17.4)	723 (33.0)	347 (15.5)	852 (49.4)	336 (19.7)	111 (48.7)	41 (18.0)	28 (68.3)	9 (22.5)
Fever	614 (14.8)	127 (3.0)	201 (9.2)	46 (2.1)	360 (21.0)	74 (4.3)	35 (15.6)	6 (2.7)	18 (43.9)	<5*
Headache	1194 (28.6)	489 (11.6)	451 (20.6)	212 (9.5)	637 (37.0)	235 (13.8)	83 (36.6)	33 (14.5)	23 (57.5)	9 (22.5)
Nausea	430 (10.4)	167 (4.0)	179 (8.3)	79 (3.6)	220 (13.0)	69 (4.1)	22 (9.8)	15 (6.6)	9 (22.0)	<5*
Chills	635 (15.3)	166 (3.9)	212 (9.8)	73 (3.3)	380 (22.2)	83 (4.9)	31 (13.8)	7 (3.1)	12 (29.3)	<5*
Local symptoms at injection site										
Redness	539 (13.2)	144 (3.4)	199 (9.3)	61 (2.7)	303 (18.1)	76 (4.5)	25 (11.3)	<5*	12 (29.3)	5 (12.8)
Swelling	772 (19.1)	174 (4.2)	291 (13.6)	72 (3.3)	423 (25.6)	94 (5.6)	44 (20.0)	<5*	14 (35.0)	5 (12.8)
Tenderness	3156 (74.9)	632 (15.1)	1468 (66.5)	322 (14.5)	1470 (84.4)	281 (16.6)	180 (79.3)	20 (8.8)	38 (92.7)	9 (22.5)
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)	10 (10, 10)	10 (10, 10)

*Exact numbers not shown due to small numbers

*Figure 10 Percentage of participants reporting systemic and local symptoms within 0-7 days of their **1st dose and 2nd dose** of the vaccine, by vaccine type*



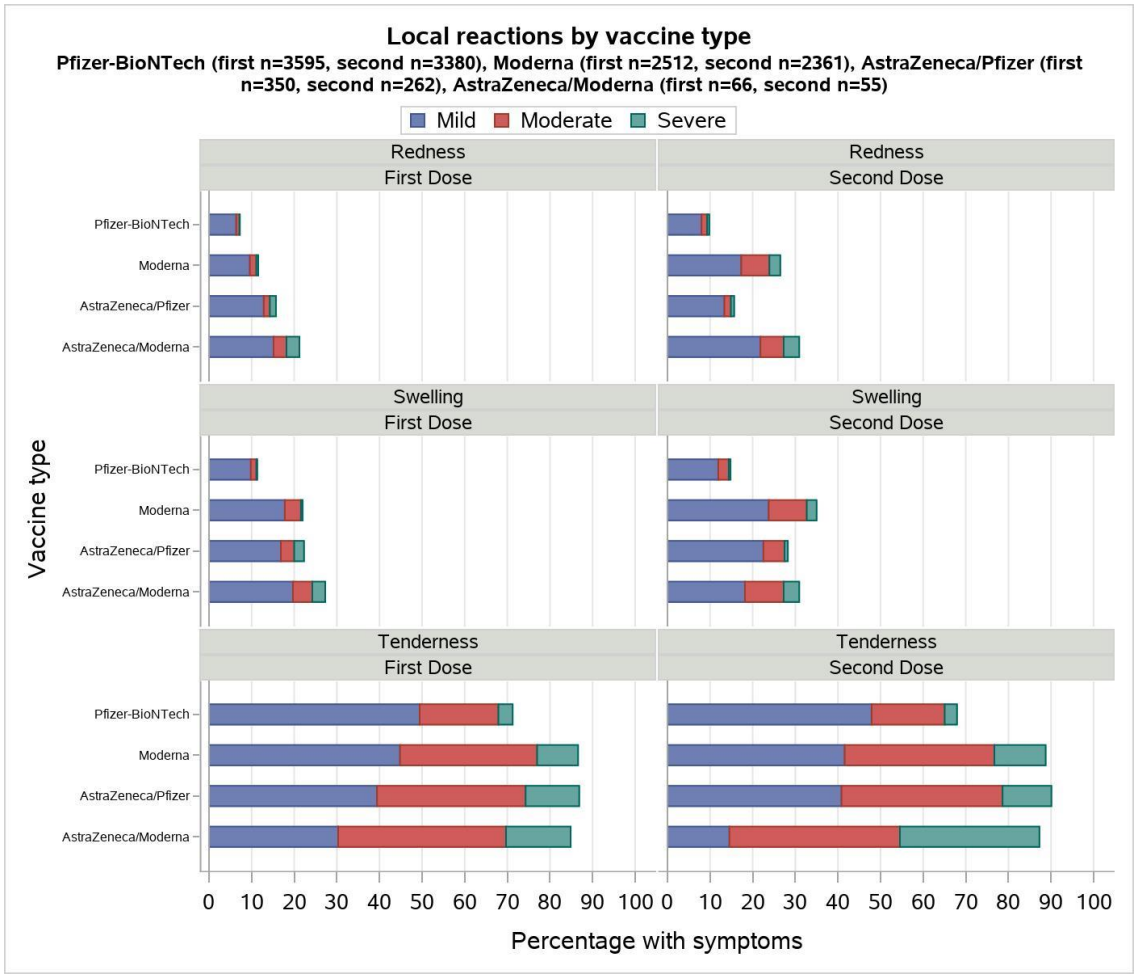
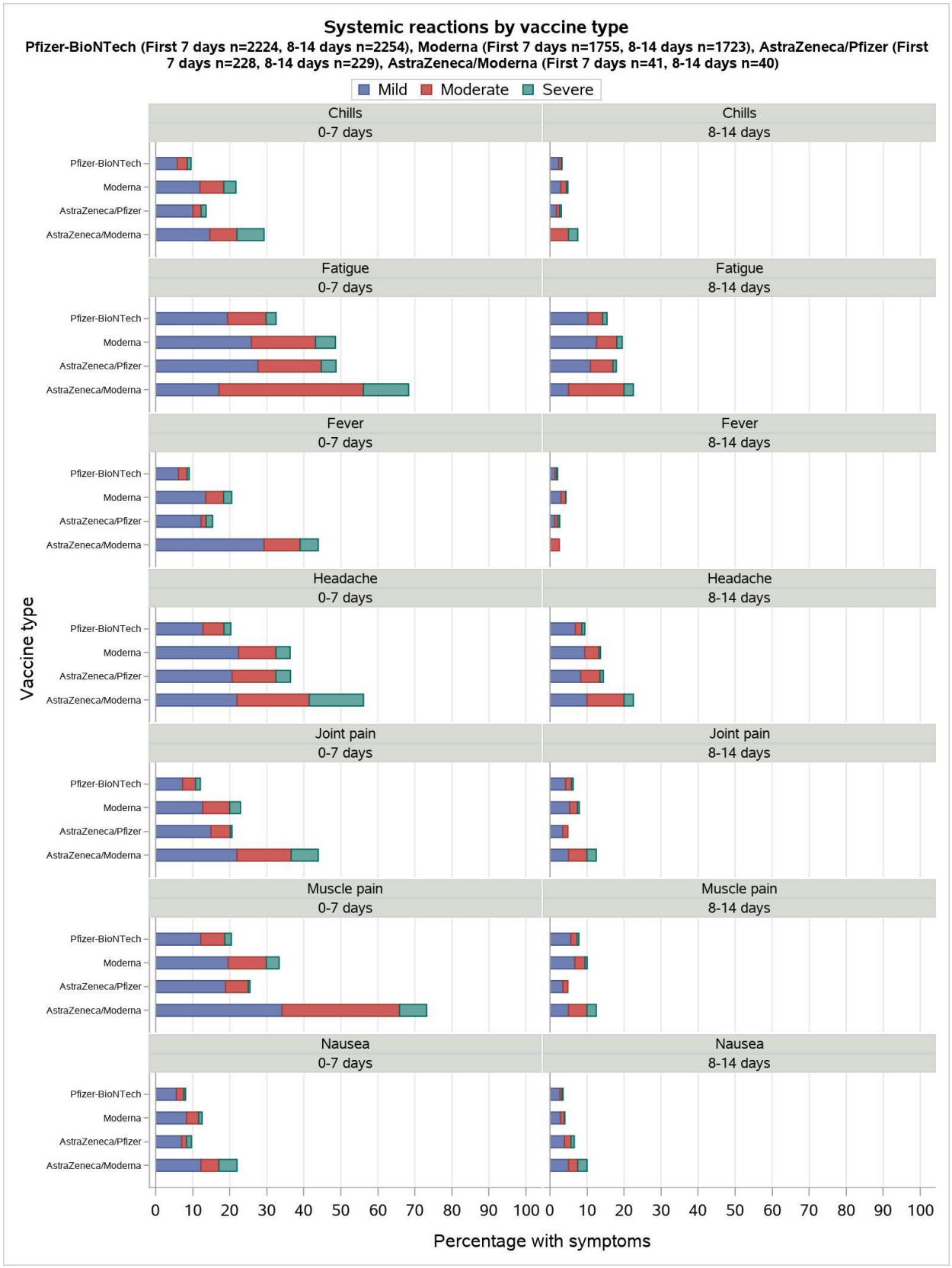
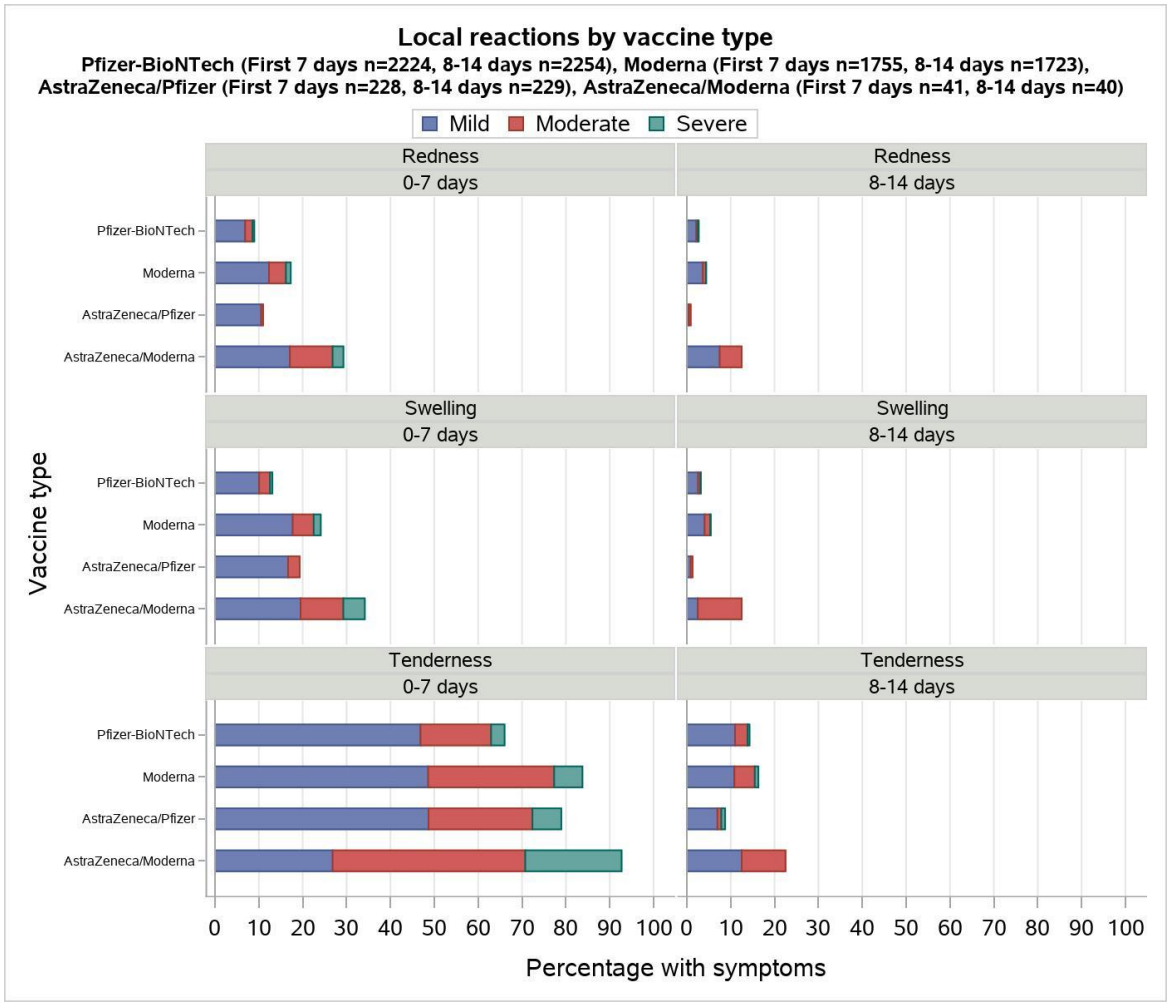

Local reactions by vaccine type
Pfizer-BioNTech (first n=3595, second n=3380), Moderna (first n=2512, second n=2361), AstraZeneca/Pfizer (first n=350, second n=262), AstraZeneca/Moderna (first n=66, second n=55)
Mild
Moderate
Severe
Redness
First Dose
Redness
Second Dose
Swelling
First Dose
Swelling
Second Dose
Tenderness
First Dose
Tenderness
Second Dose
Vaccine type
Pfizer-BioNTech
Moderna
AstraZeneca/Pfizer
AstraZeneca/Moderna
0 10 20 30 40 50 60 70 80 90 100
Percentage with symptoms

*Figure 11 Percentage of participants reporting systemic and local symptoms following the **3rt dose** of the vaccine, by vaccine type*




Local reactions by vaccine type
Pfizer-BioNTech (First 7 days n=2224, 8-14 days n=2254), Moderna (First 7 days n=1755, 8-14 days n=1723), AstraZeneca/Pfizer (First 7 days n=228, 8-14 days n=229), AstraZeneca/Moderna (First 7 days n=41, 8-14 days n=40)
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
Pfizer-BioNTech
Moderna
AstraZeneca/Pfizer
AstraZeneca/Moderna
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 14) and SAEs (Table 15) reported in the study thus far. The data are shown overall and by vaccine type.

Table 14 Overview of AEs (grade 3 and 4) reported by vaccine

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Number of persons (%)					
At least one Adverse Event reported	945 (13.7)	467 (12.2)	387 (14.8)	81 (20.8)	10 (11.8)
Number of AE					
1	693 (73.3)	340 (72.8)	291 (75.2)	57 (70.4)	5 (50.0)
2	168 (17.8)	87 (18.6)	59 (15.2)	18 (22.2)	<5*
3	49 (5.2)	27 (5.8)	19 (4.9)	<5*	0
>=4	35 (3.7)	13 (2.8)	18 (4.7)	<5*	<5*

*Exact numbers not shown due to small numbers

Table 15 Overview of SAEs reported by vaccine

		Vaccine type			
	Total (N=6918)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*AstraZeneca/ Pfizer (N=389)*	*AstraZeneca/ Moderna (N=85)*
Total number of participants reporting any SAE (N, %)	149 (2.2)	111 (2.9)	32 (1.2)	5 (1.3)	<5*
Total number of SAE reported (N, % of SAE)	173 (100)	133 (100)	34 (100)	5 (100)	<5*

*Exact numbers not shown due to small numbers

Deaths

There have been thirty-four 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 26 deaths recorded in the CPR registry that were outside of the period for reporting SAE.