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

The data presented in this report are presented stratified by three vaccine groups:

1. Pfizer-BioNTech, which includes all individuals who received a first dose of Pfizer-BioNTech.
2. Moderna, which includes all individuals who received a first dose of Moderna.
3. Adenoviral Vector/mRNA, which include participants who received a first dose of AstraZeneca followed by a subsequent dose of either Pfizer-BioNTech or Moderna, and those who were enrolled in ENFORCE Plus and received Janssen as their first vaccine.

Enrolment

Over 80% of those initially enrolled in the cohort have returned for their 5th study visit, which is 1 year after their first vaccine dose. This report contains details of the number of individuals who have completed their 5th study visit, and the timing of the visits. Information on the number of individuals who have received their 4th and 5th doses of vaccine is also included.

Outcomes

Visit 5 (1 year after first vaccination) 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 have now been analyzed for almost all (99%) of those who have returned for their 1-year study visit and are included in this report.

Results are also shown for those who have received a fourth vaccine dose and had a subsequent study visit.

Safety and Monitoring

There have been no additional SAE or AE reported since the previous report (31st May 2022). However, it should be noted that very few individuals (≈50) received a new vaccine dose during this period and thus had the possibility of reporting them. The summary tables of all SAE and AE's occurring previously remain included in this report and are presented for the three vaccine groups outlined above.

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. The "Adenoviral Vector/mRNA" vaccine group includes participants who received a first dose of either AstraZeneca followed by a subsequent dose of either Pfizer-BioNTech or Moderna, and those who were enrolled in ENFORCE Plus and received Janssen as their first vaccine. Participants who received a first dose of Janssen were classed as having received a booster dose if that 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.

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*
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.

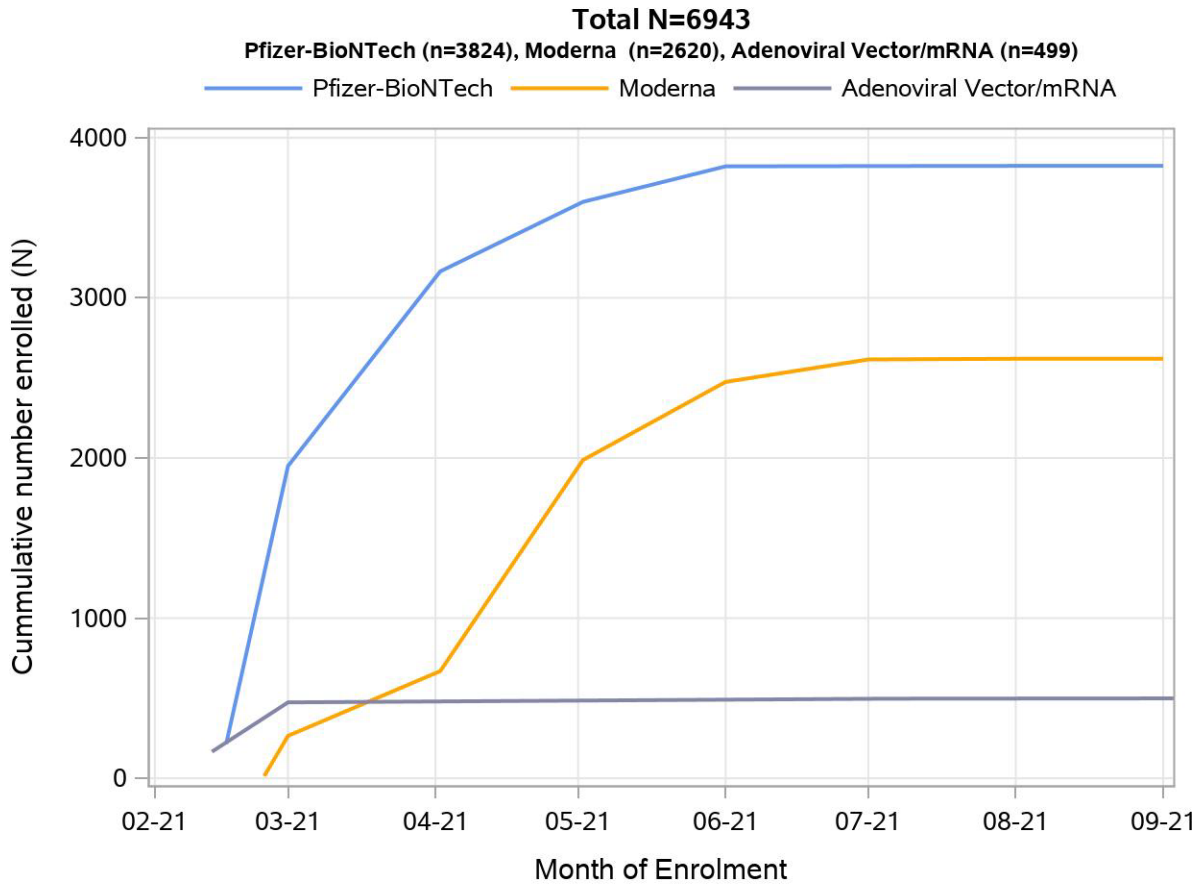
Figure 1 shows the cumulative number of participants enrolled by vaccine type. Enrolment began on the 13th February 2021 when the first patient was enrolled prior to receiving the AstraZeneca vaccine. Enrolment into this group was stopped following the pausing of AstraZeneca vaccination on 11th March 2021.

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 for those receiving Pfizer was paused in week 15, after the target of 2500 participants was reached, but then restarted in week 20.

Individuals who received a first dose of the Janssen vaccine were initially enrolled in the ENFORCE Plus study during July 2021 and are now included together with those who received a first dose of AstraZeneca in the Adenoviral Vector/mRNA vaccine group.

Enrolment in all vaccine groups was completed 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=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Number of persons (%)				
Gender				
Male	3014 (43.4)	1841 (48.1)	1085 (41.4)	88 (17.6)
Female	3929 (56.6)	1983 (51.9)	1535 (58.6)	411 (82.4)
Median (interquartile range, IQR)				
Age at enrolment (years)	64 (53, 75)	71 (55, 78)	61 (54, 69)	45 (31, 55)
Enrolment date	APR21 (MAR21, MAY21)	MAR21 (MAR21, APR21)	MAY21 (APR21, MAY21)	MAR21 (FEB21, MAR21)

Table 3 Concomitant diseases and medications, overall and by vaccine

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Any concomitant disease N (%)	4554 (65.6)	2832 (74.1)	1557 (59.4)	165 (33.1)
Any medications taken in the last 24 hours N (%)	4788 (69.0)	2956 (77.3)	1606 (61.3)	226 (45.3)

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 11 and 18 months. Almost all the participants still under follow-up have now had their 5th scheduled study visit at 1 year after their first vaccine dose. 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

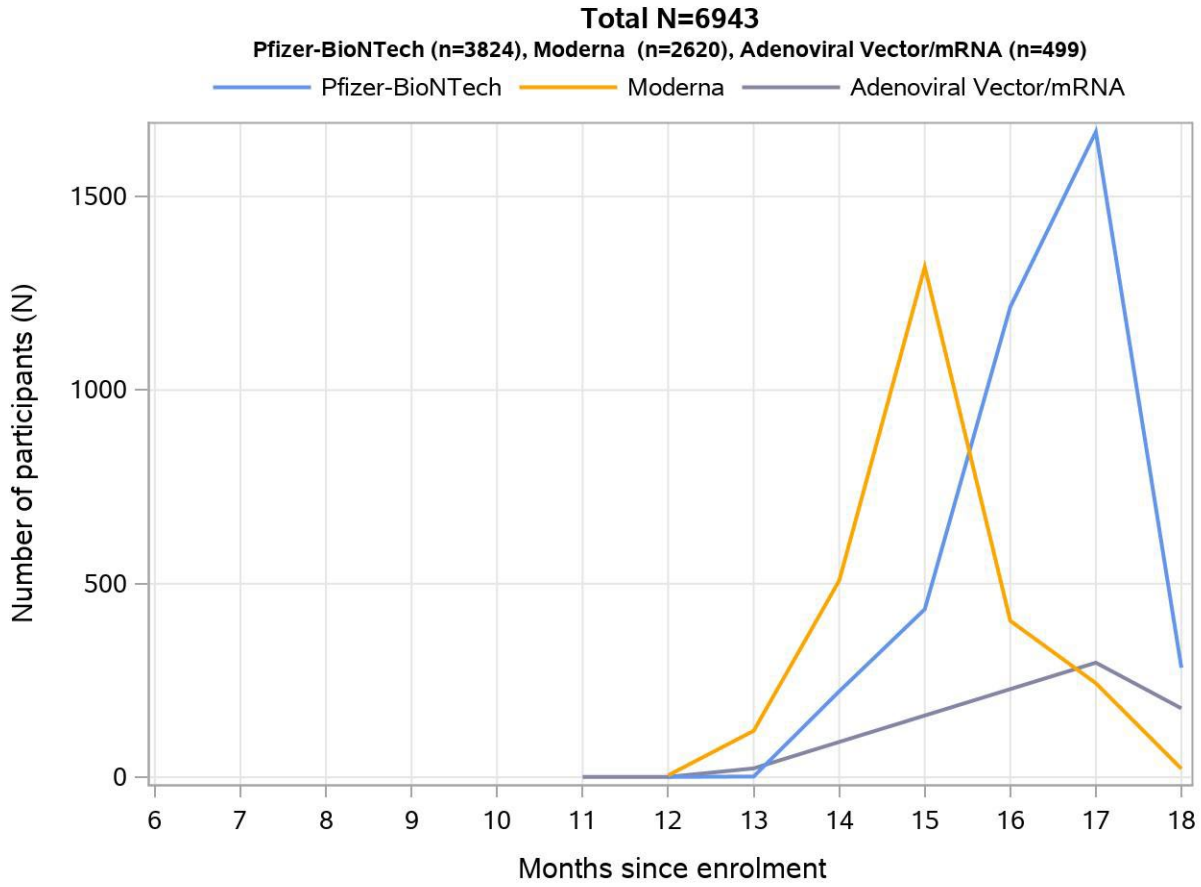


Table 4 Number and percentage of participants completing each study visit

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Received two doses (N, %)	**6935 (99.9)**	**3818 (99.8)**	**2618 (99.9)**	**499 (100)***
Time between first and second dose (median, IQR)	29 (22, 35)	23 (21, 28)	35 (35, 36)	83 (79, 87)†
Visit 2 (prior to second vaccination) (N, %)	**6535 (94.1)**	**3636 (95.1)**	**2518 (96.1)**	**381 (76.4)**
Days from first vaccine to second study visit (median, IQR)	28 (21, 35)	22 (21, 27)	34 (32, 35)	83 (79, 89)
Visit 3 (3 months after first vaccination) (N, %)	**6031 (86.9)**	**3448 (90.2)**	**2478 (94.6)**	**105 (21.0)**
Days from first vaccine to third study visit (median, IQR)	92 (89, 96)	91 (89, 95)	92 (89, 96)	95 (90, 99)
Visit 4 (6 months after first vaccination) (N, %)	**6069 (87.4)**	**3305 (86.4)**	**2374 (90.6)**	**390 (78.2)**
Days from first vaccine to fourth study visit (median, IQR)	182 (179, 186)	183 (179, 186)	182 (177, 186)	182 (179, 187)
Visit 5 (1 year after first vaccination) (N, %)	**5623 (81.0)**	**2957 (77.3)**	**2306 (88.0)**	**360 (72.1)**
Days from first vaccine to fifth study visit (median, IQR)	365 (361, 370)	365 (360, 371)	364 (361, 369)	369 (364, 373)

*including 25 participants who received 1 dose of Janssen, †excludes the 25 participants who received a first dose of Janssen.

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

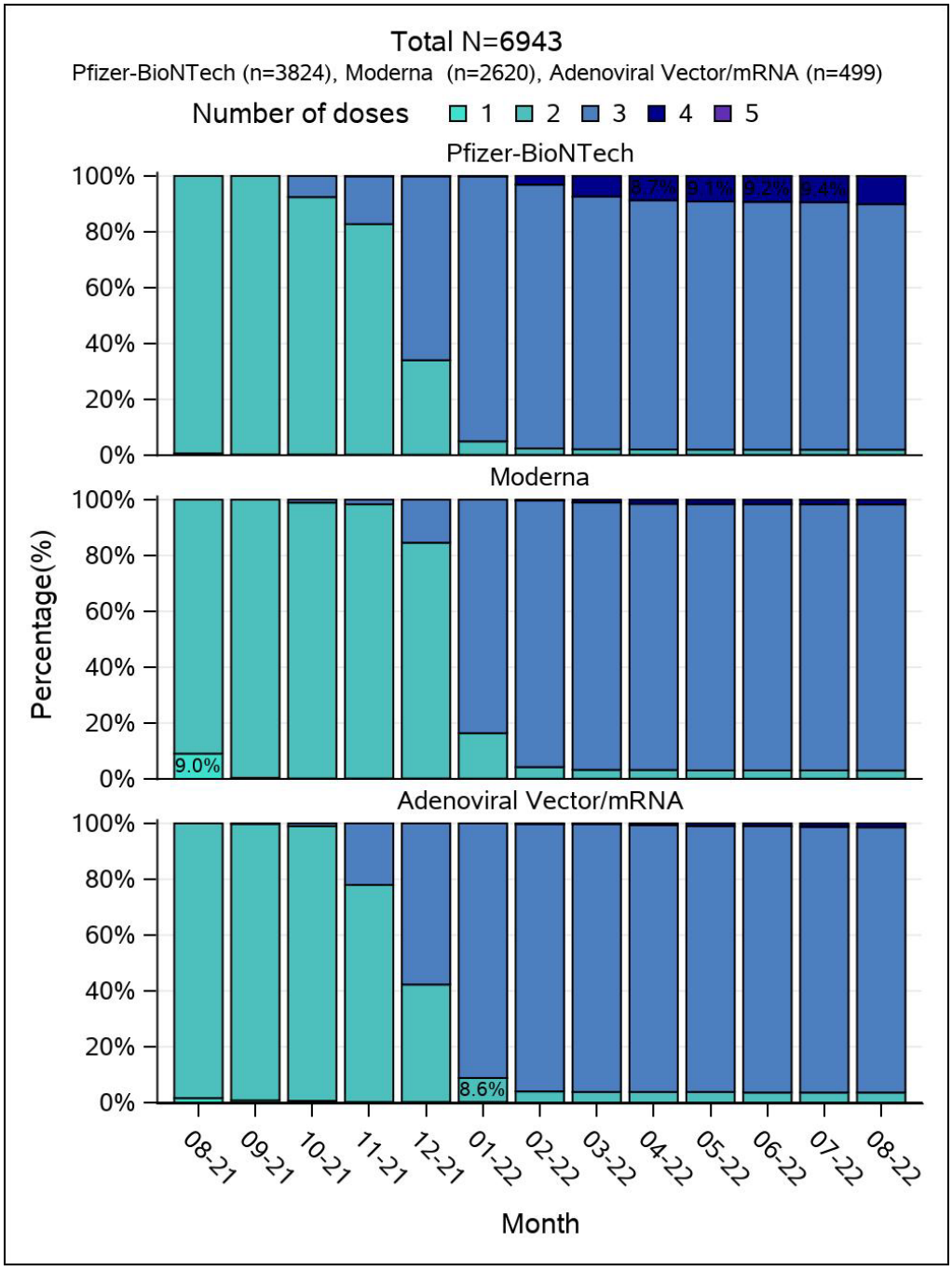
		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Received a third dose (N, %)	**6771 (97.5)**	**3749 (98.0)**	**2541 (97.0)**	**481 (96.4)***
Time between first and third dose (median, IQR)	225 (210, 236)	229 (217, 238)	216 (204, 224)	266 (244, 281)
Visit X (0-14 days prior to third dose) (N, %)	2923 (42.1)	1454 (38.0)	1303 (49.7)	166 (33.3)
Days from pre-third dose visit to third dose (median, IQR)	2 (1, 6)	2 (1, 6)	2 (1, 5)	2 (0, 5)
Visit Xc (28 days after third dose) (N, %)	4662 (67.1)	2439 (63.8)	1931 (73.7)	292 (58.5)
Days from third dose to post-booster visit (median, IQR)	29 (26, 32)	28 (26, 32)	29 (27, 32)	29 (25, 34)
Received a fourth dose (N, %)	**448 (6.5)**	**394 (10.3)**	**47 (1.8)**	**7 (1.4)†**
Time between first and fourth dose (median, IQR)	225 (210, 237)	229 (217, 238)	216 (204, 224)	268 (246, 282)
Visit 4X (0-14 days prior to fourth dose) (N, %)	61 (0.9)	56 (1.5)	5 (0.2)	0
Days from pre-fourth dose visit to third dose (median, IQR)	3 (1, 6)	3 (1, 6)	3 (0, 7)	. (., .)
Visit 4Xc (28 days after fourth dose) (N, %)	297 (4.3)	262 (6.9)	33 (1.3)	<5‡
Days from fourth dose to post-booster visit (median, IQR)	29 (26, 34)	28 (26, 33)	33 (28, 38)	36 (27, 44)

* includes 22 participants who received a first dose of Janssen followed by a booster dose of either Pfizer-BioNTech or Moderna

†includes 5 participants who received a first dose of Janssen followed by two subsequent doses of either Pfizer-BioNTech or Moderna

‡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=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Study status (N, % of total)				
Still under follow-up	6342 (91.3)	3427 (89.6)	2495 (95.2)	420 (84.2)
Total withdrawn (N, % of total)	601 (8.7)	397 (10.4)	125 (4.8)	79 (15.8)

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

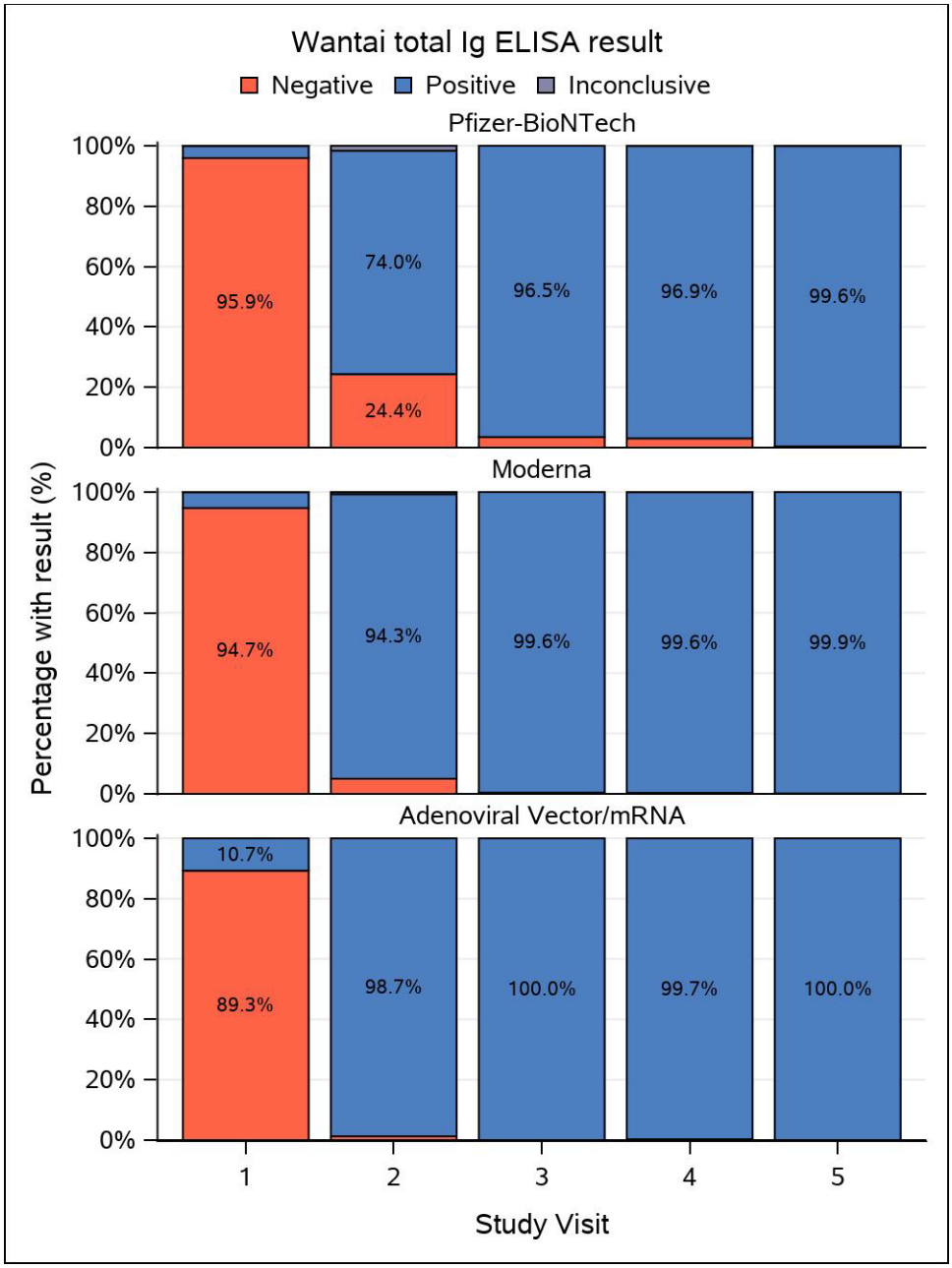


Table 7 Number of individuals with antibody data at each study visit, ELISA (Wantai) from SSI

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
SSI antibody data at visit 1 (enrolment) (N, % of total)	6894 (99.3)	3791 (99.1)	2614 (99.8)	489 (98.0)
SSI antibody data at visit 2 (prior to second vaccination) (N, % of total)	6370 (91.7)	3580 (93.6)	2492 (95.1)	298 (59.7)
Days from first vaccination (median (IQR))	28 (21, 35)	22 (21, 27)	34 (32, 35)	82 (78, 85)
SSI antibody data at visit 3 (3 months after first vaccination) (N, % of total)	5981 (86.1)	3413 (89.3)	2463 (94.0)	105 (21.0)
Days from first vaccination (median (IQR))	91 (89, 96)	91 (89, 95)	92 (89, 96)	95 (90, 99)
SSI antibody data at visit 4 (6 months after first vaccination) (N, % of total)	5736 (82.6)	3202 (83.7)	2150 (82.1)	384 (77.0)
Days from first vaccination (median (IQR))	182 (179, 186)	183 (179, 186)	182 (177, 186)	182 (179, 187)
SSI antibody data at visit 5 (1 year after first vaccination) (N, % of total)	5567 (80.2)	2931 (76.6)	2277 (86.9)	359 (71.9)
Days from first vaccination (median (IQR))	365 (361, 370)	365 (360, 371)	364 (361, 369)	369 (364, 373)

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=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
AUH antibody data at visit 1 (enrolment) (N, % of total)	6862 (98.8)	3791 (99.1)	2605 (99.4)	466 (93.4)
AUH antibody data at visit 2 (prior to second vaccination) (N, % of total)	6301 (90.8)	3574 (93.5)	2490 (95.0)	237 (47.5)
AUH antibody data at visit 3 (3 months after first vaccination) (N, % of total)	5957 (85.8)	3411 (89.2)	2462 (94.0)	84 (16.8)
AUH antibody data at visit 4 (6 months after first vaccination) (N, % of total)	5931 (85.4)	3227 (84.4)	2342 (89.4)	362 (72.5)
AUH antibody data at visit 5 (1 year after first vaccination) (N, % of total)	5570 (80.2)	2953 (77.2)	2274 (86.8)	343 (68.7)
CoV-2 Receptor-Binding Domain (SERO)				
GM at enrolment (95%CI)	59 (57, 61)	53 (50, 55)	65 (62, 69)	83 (70, 98)
GM at visit 2 (95%CI)	8839 (8402, 9299)	4086 (3819, 4371)	27498 (25924, 29166)	6634 (5492, 8013)
GM at visit 3 (95%CI)	95324 (91513, 99293)	52088 (49182, 55166)	211776 (203628, 220251)	299205 (256515, 348999)
GM at visit 4 (95%CI)	39921 (38352, 41554)	20106 (19034, 21238)	88182 (84306, 92236)	107144 (96648, 118778)
GM at visit 5 (95%CI)	313866 (305819, 322123)	265193 (254546, 276285)	394853 (383522, 406518)	292321 (265010, 322447)
CoV-2 Spike antibody (SERO)				
GM at enrolment (95%CI)	106 (102, 110)	102 (97, 108)	104 (98, 111)	151 (126, 182)
GM at visit 2 (95%CI)	26873 (25641, 28164)	13665 (12822, 14563)	74112 (70260, 78175)	16979 (14270, 20202)
GM at visit 3 (95%CI)	173430 (167609, 179454)	108485 (103179, 114064)	322683 (313279, 332370)	407010 (371340, 446108)

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
GM at visit 4 (95%CI)	82900 (80016, 85888)	45639 (43423, 47968)	164698 (158629, 170998)	199769 (184177, 216681)
GM at visit 5 (95%CI)	401168 (393823, 408650)	362476 (351553, 373739)	457645 (449400, 466041)	401151 (376778, 427101)
CoV-2 Nucleocapsid (SERO)				
GM at enrolment (95%CI)	263 (251, 275)	268 (252, 284)	243 (226, 261)	348 (286, 423)
GM at visit 2 (95%CI)	299 (286, 313)	283 (267, 300)	316 (295, 340)	382 (291, 501)
GM at visit 3 (95%CI)	412 (394, 430)	376 (354, 399)	462 (433, 493)	576 (390, 851)
GM at visit 4 (95%CI)	451 (431, 472)	430 (404, 457)	465 (434, 499)	572 (471, 695)
GM at visit 5 (95%CI)	4023 (3763, 4302)	3432 (3127, 3766)	4426 (4000, 4898)	8410 (6311, 11207)

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)

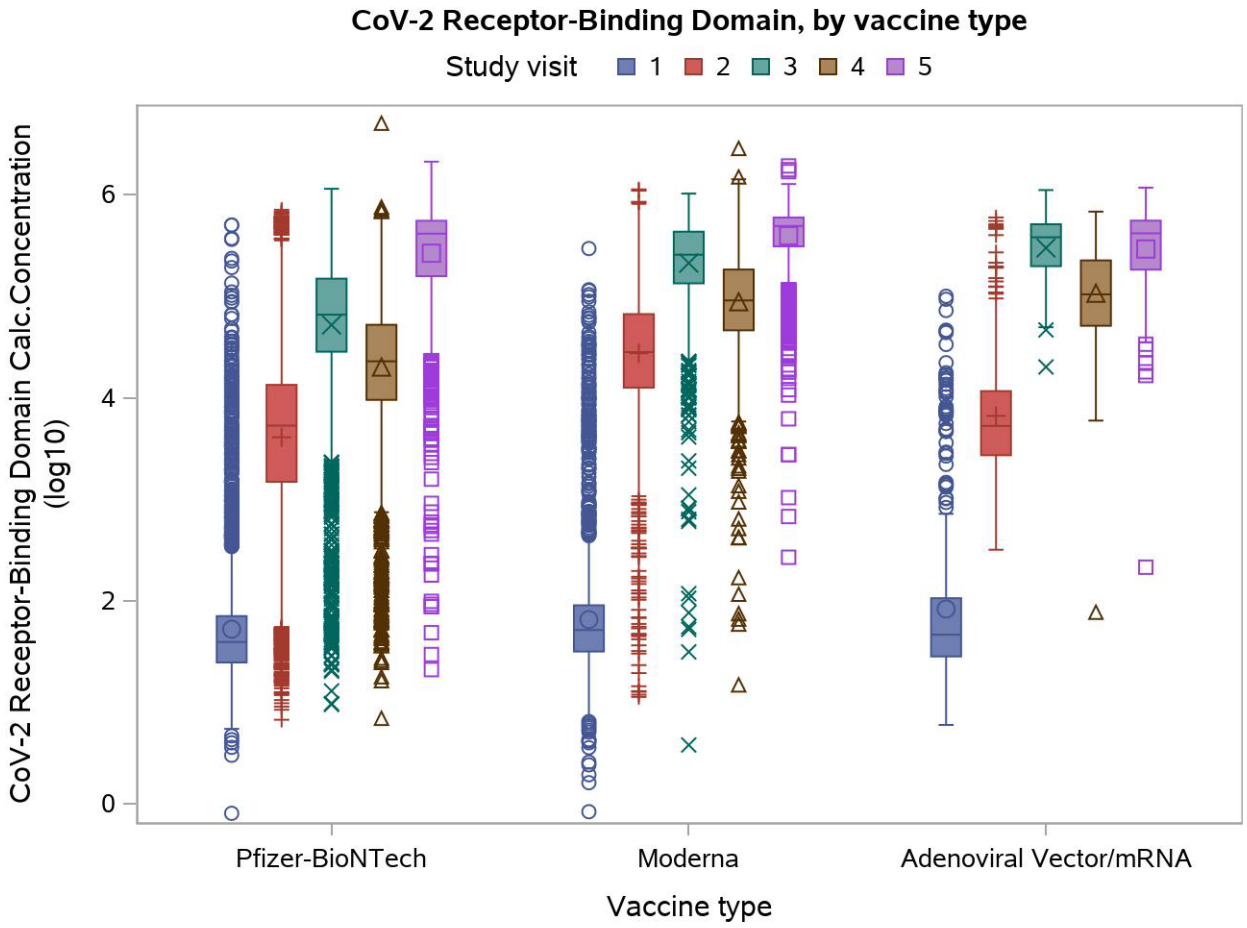


Figure 6 Distribution of CoV-2 Spike antibody levels at each study visit (see Table 8 for the number included at each time point)

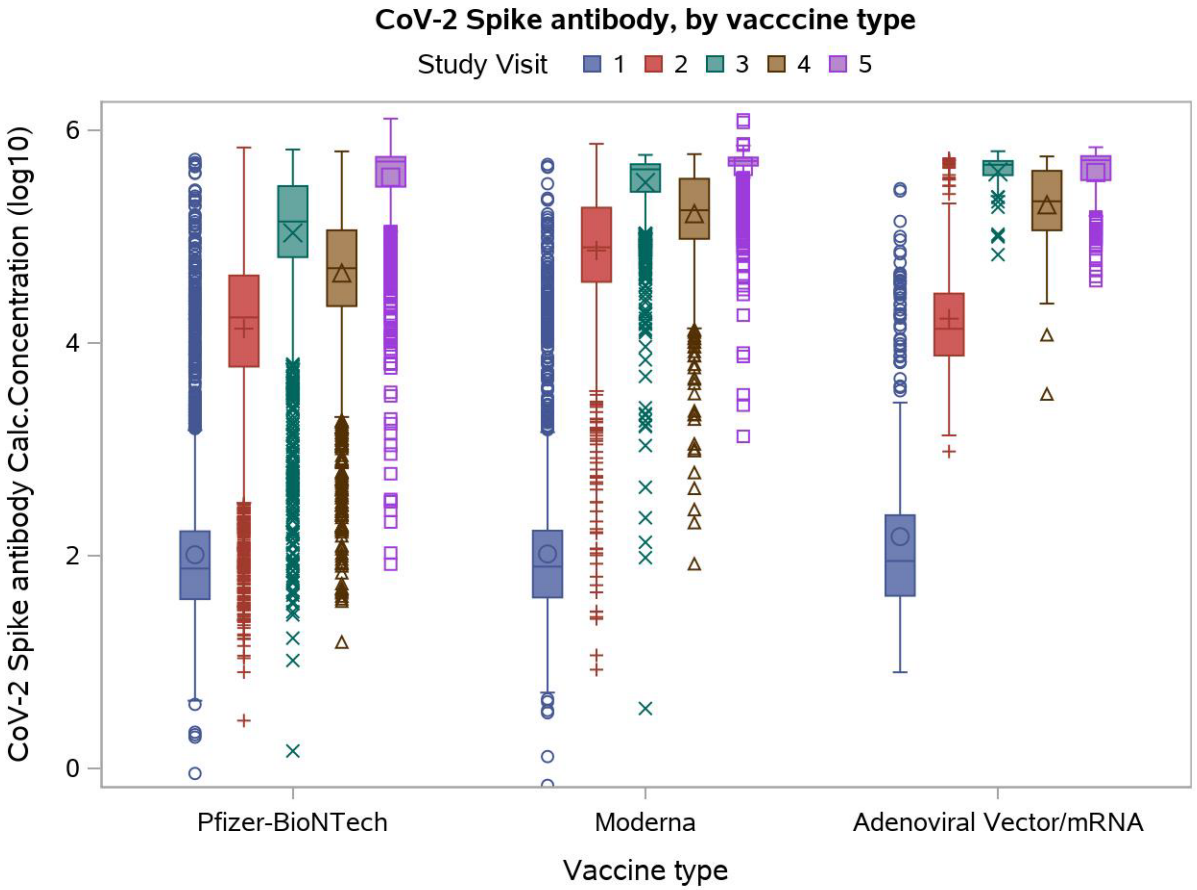
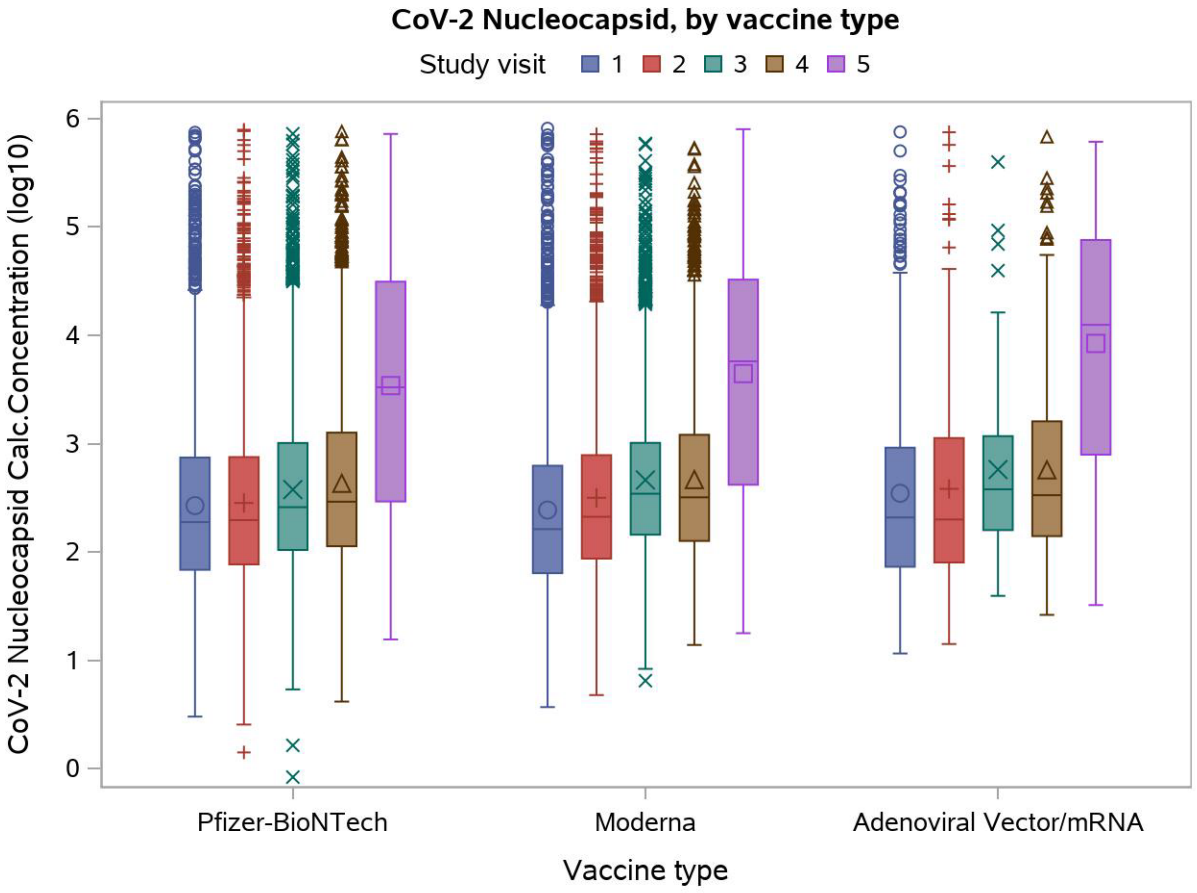


Figure 7 Distribution of CoV-2 Nucleocapsid levels at each study visit (see Table 8 for the number included at each time point)



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=6771)	*Pfizer-BioNTech (N=3749)*	*Moderna (N=2541)*	*Adenoviral Vector/mRNA (N=481)*
SSI antibody data 0-14 days before third dose (N, % of total)	2720 (40.2)	1395 (37.2)	1165 (45.8)	160 (33.3)
Wantai result prior to booster (visit X)				
Negative	44 (1.6)	43 (3.1)	1 (0.1)	0
Positive	2675 (98.3)	1352 (96.9)	1163 (99.8)	160 (100)
Inconclusive	1 (0.0)	0	1 (0.1)	0
Days prior to third dose (median (IQR))	2 (1, 6)	2 (1, 6)	2 (1, 5)	2 (0, 5)
SSI antibody data 28 days after third dose (N, % of total)	4421 (65.3)	2269 (60.5)	1883 (74.1)	269 (55.9)
Wantai result after booster (visit Xc)				
Negative	47 (1.1)	40 (1.8)	7 (0.4)	0
Positive	4371 (98.9)	2227 (98.1)	1875 (99.6)	269 (100)
Inconclusive	3 (0.1)	2 (0.1)	1 (0.1)	0
Days after third dose (median (IQR))	29 (26, 32)	28 (26, 32)	29 (27, 32)	29 (25, 34)

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 protein 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), and Spike antibody, among participants who have received a third dose

		Vaccine type		
	Total (N=6771)	*Pfizer-BioNTech (N=3749)*	*Moderna (N=2541)*	*Adenoviral Vector/mRNA (N=481)*
AUH antibody data 0-14 days before third dose (N, % of total)	2897 (42.8)	1448 (38.6)	1289 (50.7)	160 (33.3)
AUH antibody data 28 days after third dose (N, % of total)	4619 (68.2)	2419 (64.5)	1915 (75.4)	285 (59.3)
CoV-2 Receptor-Binding Domain (SERO)				
GM 0-14 days before third dose (95%CI)	36190 (34172, 38328)	17132 (15752, 18633)	79802 (75192, 84694)	53863 (45608, 63613)
GM 28 days after third dose (95%CI)	363054 (350363, 376204)	282833 (266424, 300253)	491117 (474395, 508428)	396934 (367817, 428356)
CoV-2 Spike antibody (SERO)				
GM 0-14 days before third dose (95%CI)	75174 (71482, 79055)	38866 (36069, 41879)	150859 (143500, 158596)	107602 (92880, 124657)
GM 28 days after third dose (95%CI)	425932 (414767, 437397)	364926 (348570, 382050)	510630 (498263, 523304)	467635 (453091, 482645)

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), 28 days after receiving the third dose, and at visit 5 (1 year after the first vaccine dose). Only participants with results at all three visits are included. There are currently 4018 participants with results from all three visits (Pfizer-BioNTech n= 2151, Moderna n=1820, Adenoviral Vector/mRNA n=47). 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

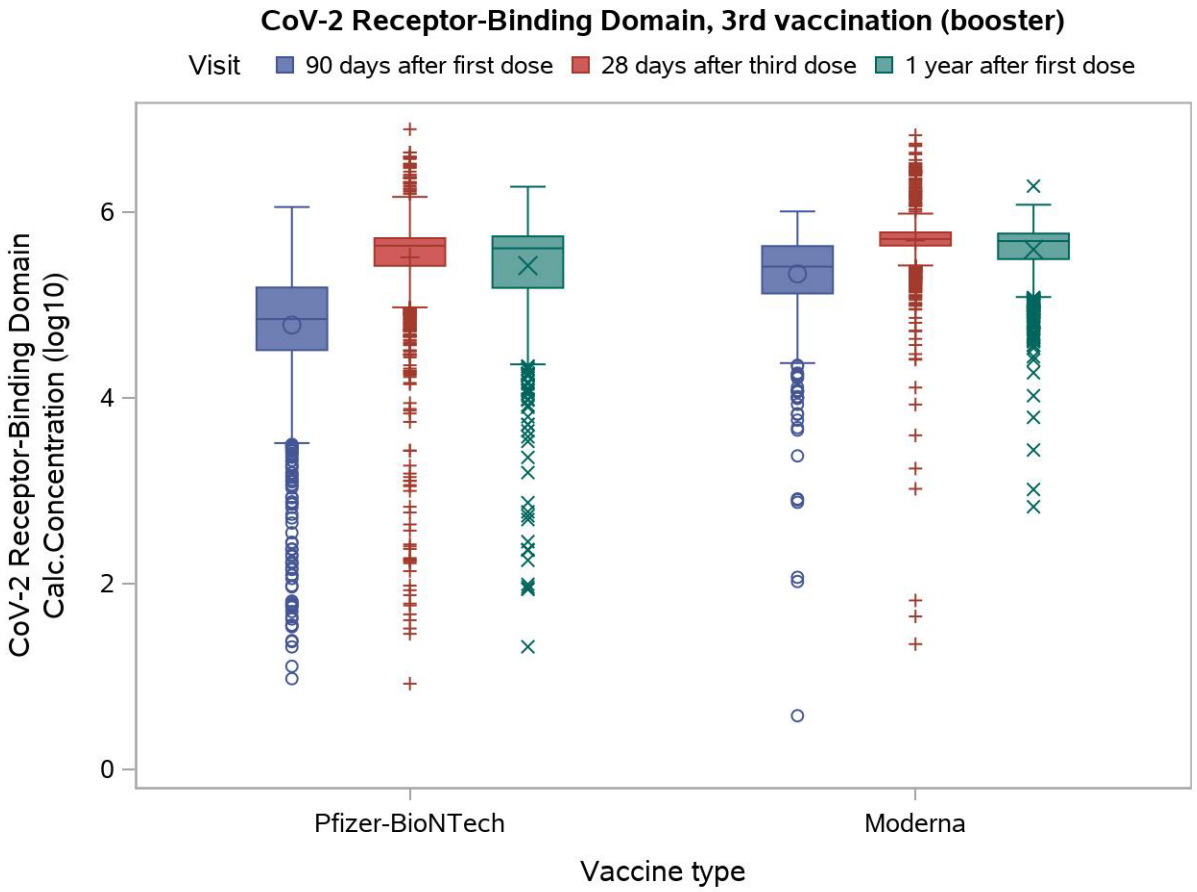
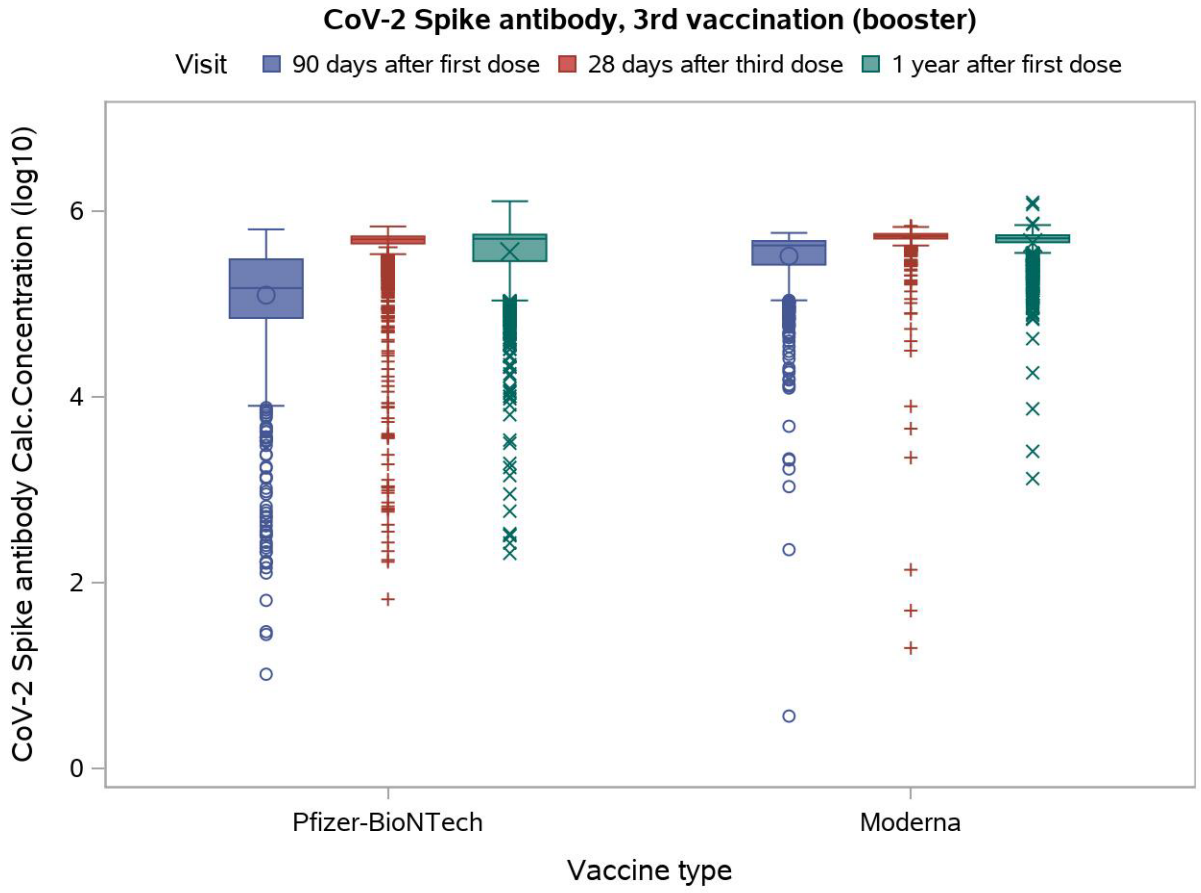


Figure 9 Distribution of CoV-2 Spike antibody levels among participants who have received a third dose



Primary outcome among those who received a fourth dose

The percentage of participants with results from the ELISA (Wantai) assay within 14 days prior to receiving their fourth dose and 28 days following the vaccination are shown in Table 11.

Table 11 Presence of antibodies at study visit, ELISA (Wantai) from SSI, among participants who have received a fourth dose

		Vaccine type		
	Total (N=448)	*Pfizer-BioNTech (N=394)*	*Moderna (N=47)*	*Adenoviral Vector/mRNA (N=7)*
SSI antibody data 0-14 days before fourth dose (N, % of total)	64 (14.3)	58 (14.7)	6 (12.8)	0
Wantai result prior to fourth dose (visit 4X)				
Negative	<5*	<5*	0	0
Positive	61 (95.3)	55 (94.8)	6 (100)	0
Inconclusive	<5*	<5*	0	0
Days prior to fourth dose (median (IQR))	3 (1, 6)	3 (1, 6)	3 (0, 7)	. (., .)
SSI antibody data 28 days after fourth dose (N, % of total)	304 (67.9)	269 (68.3)	33 (70.2)	<5*
Wantai result after fourth dose (visit 4Xc)				
Negative	19 (6.3)	17 (6.3)	<5*	0
Positive	285 (93.8)	252 (93.7)	31 (93.9)	<5*
Days after fourth dose (median (IQR))	29 (26, 34)	28 (26, 33)	33 (28, 38)	. (., .)

*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, and the complete Spike protein at the visit prior to the fourth dose and 28 days following the fourth dose are reported in Table 12.

Table 12 Presence of antibodies at study visit, Receptor-Binding Domain (RBD), and Spike antibody, among participants who have received a fourth dose

		Vaccine type		
	Total (N=448)	*Pfizer-BioNTech (N=394)*	*Moderna (N=47)*	*Adenoviral Vector/mRNA (N=7)*
AUH antibody data 0-14 days before fourth dose (N, % of total)	74 (16.5)	68 (17.3)	6 (12.8)	0
AUH antibody data 28 days after fourth dose (N, % of total)	300 (67.0)	265 (67.3)	33 (70.2)	<5*
CoV-2 Receptor-Binding Domain (SERO)				
GM 0-14 days before fourth dose (95%CI)	70240 (37719, 130800)	67382 (34418, 131917)	112473 (29327, 431341)	. (., .)
GM 28 days after fourth dose (95%CI)	143724 (109425, 188773)	137082 (102475, 183375)	193595 (82152, 456211)	. (., .)
CoV-2 Spike antibody (SERO)				
GM 0-14 days before fourth dose (95%CI)	124671 (75588, 205626)	119329 (69521, 204823)	204783 (70742, 592803)	. (., .)
GM 28 days after fourth dose (95%CI)	218189 (175792, 270811)	210713 (167147, 265634)	273049 (141710, 526114)	. (., .)
CoV-2 Nucleocapsid (SERO)				
GM 0-14 days before fourth dose (95%CI)	2689 (1500, 4818)	2843 (1544, 5238)	1425 (94, 21592)	. (., .)
GM 28 days after fourth dose (95%CI)	1474 (1155, 1883)	1413 (1087, 1836)	1823 (953, 3488)	. (., .)

*Exact numbers not shown due to small numbers

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 13. We are still developing the definition for breakthrough infection based on SARS-CoV-2 nucleocapsid antibodies. However, Table 14 shows the number and percentage with nucleocapsid titers >3000 U/mL at each study visit.

Table 13 Number of participants testing positive for SARS-CoV-2

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Ever tested for SARS-CoV-2 reported via KIDS (N, % of total)	6632 (95.5)	3599 (94.1)	2537 (96.8)	496 (99.4)
Number of PCR tests since first vaccine dose (median, IQR)	5 (2, 10)	4 (2, 8)	5 (2, 9)	16 (9, 25)
Number of antigen tests since first vaccine dose (median, IQR)	3 (1, 7)	2 (0, 6)	4 (1, 8)	6 (2, 10)
Number PCR positive for SARS-CoV-2 reported via KIDS (N, % of total)	3106 (44.7)	1594 (41.7)	1195 (45.6)	317 (63.5)
Days from first vaccine dose to SARS-CoV2 positive test (median, IQR)	304 (253, 341)	320 (272, 345)	268 (231, 305)	340 (317, 360)

Table 14 Number of participants with nucleocapsid titers >3000 U/mL at each study visit

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
CoV-2 Nucleocapsid (SERO)				
Enrolment (n, %)				
<=3000	6157 (89.8)	3406 (89.9)	2348 (90.3)	403 (86.5)
>3000	697 (10.2)	383 (10.1)	251 (9.7)	63 (13.5)
Visit 2 (n, %)				
<=3000	5620 (89.3)	3202 (89.7)	2215 (89.0)	203 (85.7)
>3000	676 (10.7)	368 (10.3)	274 (11.0)	34 (14.3)
Visit 3 (n, %)				
<=3000	5193 (87.2)	2976 (87.2)	2148 (87.2)	69 (82.1)
>3000	765 (12.8)	435 (12.8)	315 (12.8)	15 (17.9)
Visit 4 (n, %)				
<=3000	5062 (85.4)	2755 (85.4)	2011 (86.0)	296 (81.8)
>3000	864 (14.6)	471 (14.6)	327 (14.0)	66 (18.2)
Visit 5 (n, %)				
<=3000	2580 (46.3)	1453 (49.2)	997 (43.8)	130 (37.9)
>3000	2990 (53.7)	1500 (50.8)	1277 (56.2)	213 (62.1)

Safety Monitoring

Local and systemic reactions

Table 15 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 16 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.

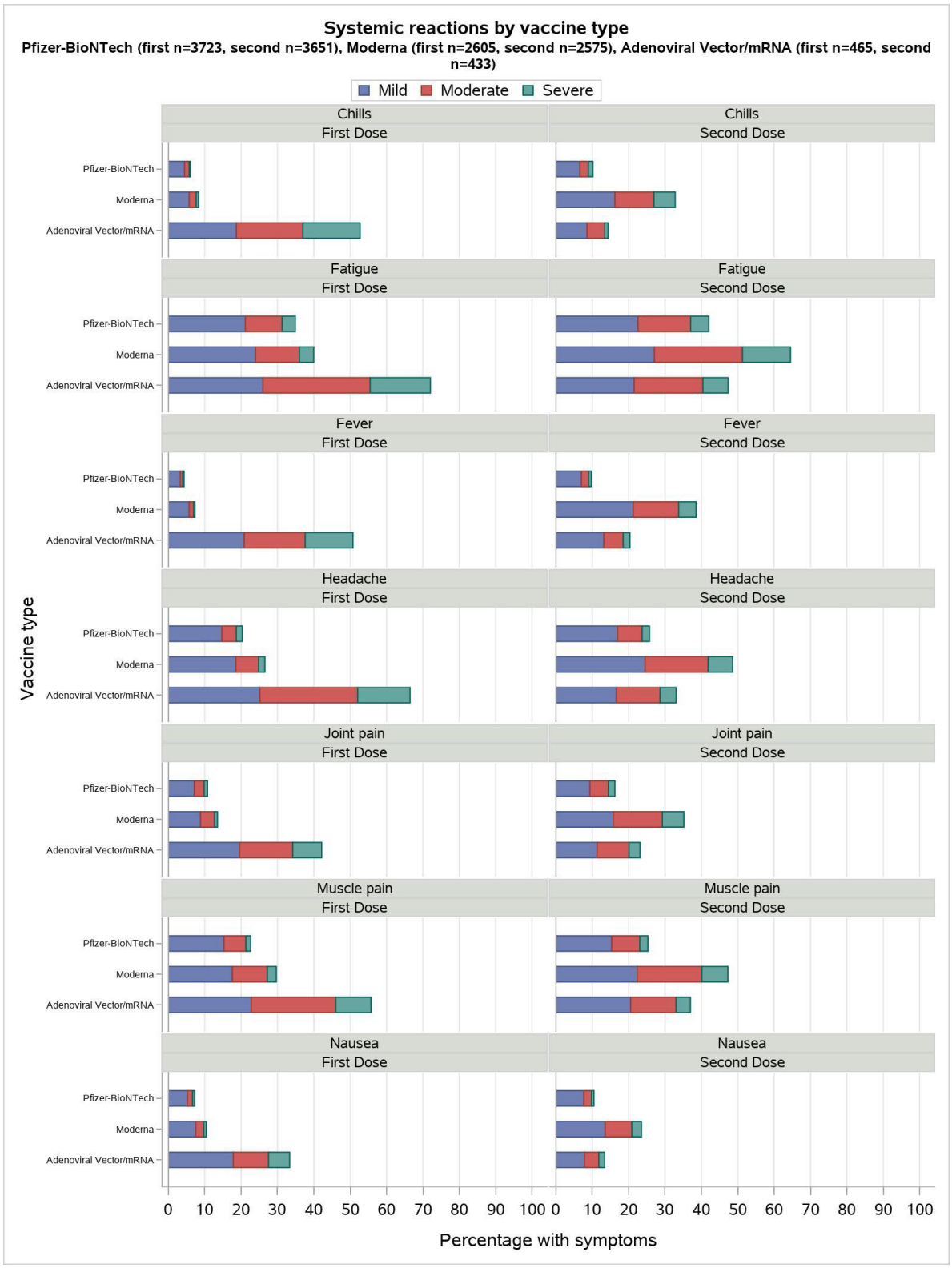
Table 15 Number & percentage reporting local/systemic reactions within 0-7 days post vaccination overall, all and by vaccination

	Total		*Pfizer-BioNTech*		*Moderna*		*Adenoviral Vector/mRNA*	
	First (N=6793)	*Second (N=6659)*	*First (N=3723)*	*Second (N=3651)*	*First (N=2605)*	*Second (N=2575)*	*First (N=465)*	*Second (N=433)*
Number of persons (%)								
Any clinical symptoms	3811 (56.1)	4155 (62.4)	1879 (50.5)	1934 (53.0)	1536 (59.0)	1973 (76.6)	396 (85.2)	248 (57.3)
Any local symptoms at injection site	5164 (76.0)	4757 (71.4)	2594 (69.7)	2338 (64.0)	2191 (84.1)	2132 (82.8)	379 (81.5)	287 (66.3)
Symptoms reported								
Muscle pain	1874 (28.1)	2299 (35.4)	842 (23.0)	922 (25.8)	773 (30.3)	1217 (48.8)	259 (56.8)	160 (37.2)
Joint pain	947 (14.3)	1596 (24.8)	400 (11.0)	591 (16.7)	351 (13.9)	905 (36.7)	196 (43.8)	100 (23.4)
Fatigue	2675 (39.9)	3400 (51.9)	1299 (35.4)	1534 (42.6)	1041 (40.6)	1661 (65.8)	335 (73.3)	205 (47.6)
Fever	586 (8.9)	1435 (22.2)	160 (4.4)	355 (10.0)	190 (7.5)	992 (39.8)	236 (52.0)	88 (20.7)
Headache	1756 (26.4)	2332 (35.9)	756 (20.7)	938 (26.3)	691 (27.1)	1251 (49.9)	309 (67.0)	143 (33.3)
Nausea	694 (10.5)	1044 (16.3)	268 (7.4)	381 (10.8)	271 (10.8)	605 (24.7)	155 (34.6)	58 (13.6)
Chills	687 (10.4)	1276 (19.9)	226 (6.2)	370 (10.5)	216 (8.6)	844 (34.3)	245 (54.1)	62 (14.6)
Local symptoms at injection site								
Redness	623 (10.0)	1015 (17.7)	260 (7.5)	332 (10.3)	290 (12.1)	625 (28.5)	73 (17.9)	58 (19.1)
Swelling	1060 (17.1)	1422 (24.9)	407 (11.9)	501 (15.6)	552 (23.1)	828 (37.7)	101 (25.0)	93 (31.1)
Tenderness	5111 (78.7)	4678 (77.8)	2560 (71.8)	2298 (68.5)	2175 (86.9)	2095 (89.5)	376 (87.4)	285 (89.9)
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 (7, 10)

Table 16 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*		*Adenoviral Vector/mRNA*	
	First 7 days (N=4301)	*8-14 days (N=4306)*	*First 7 days (N=2237)*	*8-14 days (N=2268)*	*First 7 days (N=1794)*	*8-14 days (N=1767)*	*First 7 days (N=270)*	*8-14 days (N=271)*
Number of persons (%)								
Any clinical symptoms	2340 (54.4)	1021 (23.7)	1010 (45.1)	484 (21.3)	1158 (64.5)	472 (26.7)	172 (63.7)	65 (24.0)
Any local symptoms at injection site	3257 (75.7)	672 (15.6)	1511 (67.5)	338 (14.9)	1527 (85.1)	303 (17.1)	219 (81.1)	31 (11.4)
Symptoms reported								
Muscle pain	1139 (26.8)	370 (8.7)	458 (20.8)	178 (7.9)	593 (33.5)	176 (10.0)	88 (33.1)	16 (6.0)
Joint pain	745 (17.7)	300 (7.0)	270 (12.3)	143 (6.4)	410 (23.4)	141 (8.1)	65 (24.3)	16 (6.0)
Fatigue	1741 (41.1)	747 (17.5)	729 (33.1)	349 (15.5)	873 (49.5)	347 (19.8)	139 (51.5)	51 (18.9)
Fever	629 (15.0)	130 (3.0)	205 (9.4)	46 (2.0)	371 (21.2)	76 (4.3)	53 (19.9)	8 (3.0)
Headache	1213 (28.7)	494 (11.6)	455 (20.7)	214 (9.5)	652 (37.0)	237 (13.6)	106 (39.6)	43 (16.0)
Nausea	434 (10.4)	169 (4.0)	179 (8.2)	80 (3.6)	224 (12.9)	70 (4.0)	31 (11.7)	19 (7.1)
Chills	643 (15.3)	168 (3.9)	215 (9.8)	73 (3.2)	385 (22.0)	84 (4.8)	43 (16.1)	11 (4.1)
Local symptoms at injection site								
Redness	545 (13.2)	146 (3.4)	198 (9.2)	62 (2.8)	310 (18.1)	77 (4.4)	37 (14.0)	7 (2.6)
Swelling	786 (19.2)	176 (4.2)	292 (13.6)	73 (3.3)	436 (25.7)	95 (5.5)	58 (22.2)	8 (3.0)
Tenderness	3201 (75.0)	644 (15.1)	1478 (66.6)	324 (14.5)	1504 (84.4)	289 (16.6)	219 (81.4)	31 (11.5)
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)

*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*



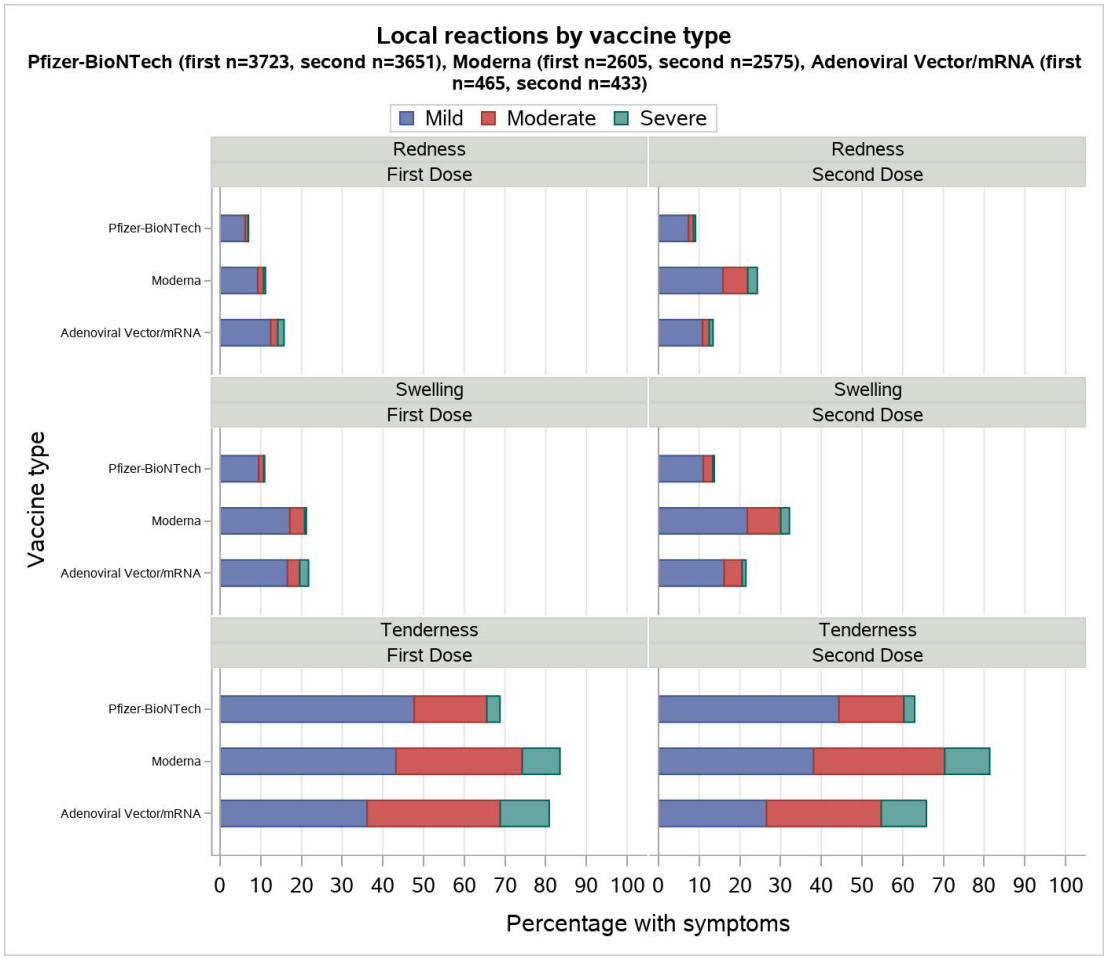
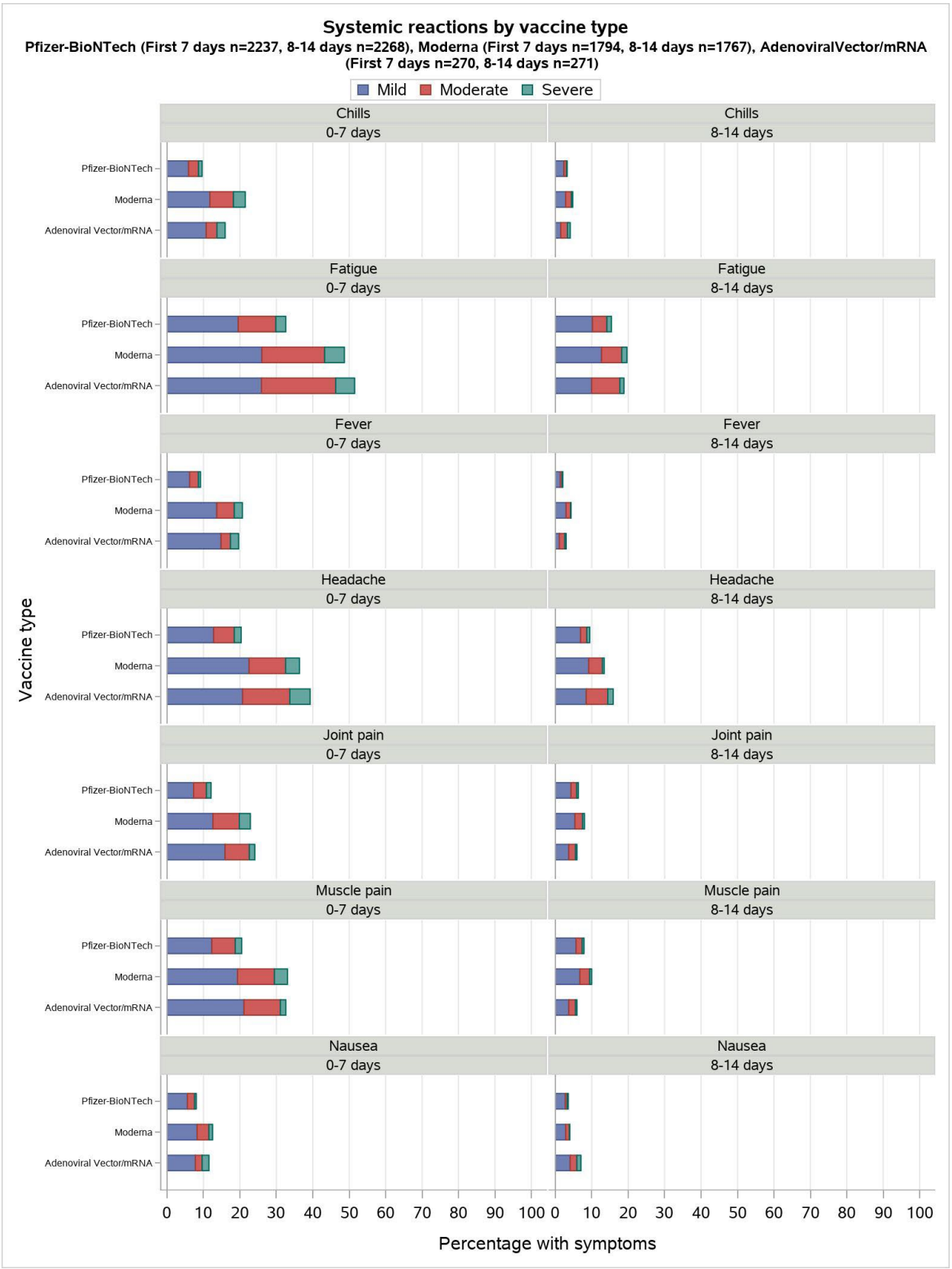
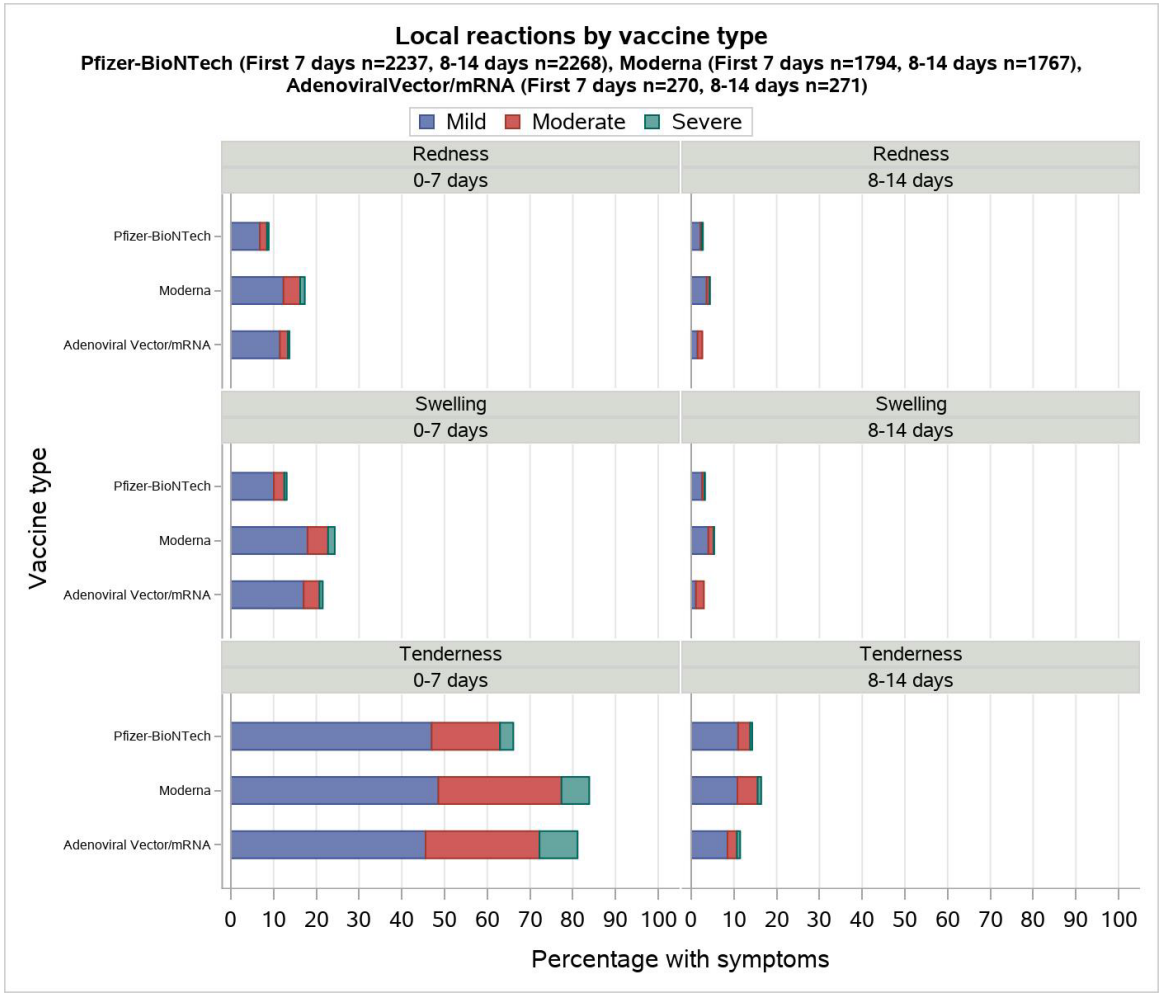

Local reactions by vaccine type
Pfizer-BioNTech (first n=3723, second n=3651), Moderna (first n=2605, second n=2575), Adenoviral Vector/mRNA (first n=465, second n=433)
Mild
Moderate
Severe
Redness
First Dose
Redness
Second Dose
Swelling
First Dose
Swelling
Second Dose
Tenderness
First Dose
Tenderness
Second Dose
Vaccine type
Pfizer-BioNTech
Moderna
Adenoviral Vector/mRNA
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 **3rd dose** of the vaccine, by vaccine type*




Local reactions by vaccine type
Pfizer-BioNTech (First 7 days n=2237, 8-14 days n=2268), Moderna (First 7 days n=1794, 8-14 days n=1767),
AdenoviralVector/mRNA (First 7 days n=270, 8-14 days n=271)
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
Pfizer-BioNTech
Moderna
Adenoviral Vector/mRNA
Vaccine type
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 17) and SAEs (Table 18) reported in the study thus far. The data are shown overall and by vaccine type.

Table 17 Overview of AEs (grade 3 and 4) reported by vaccine

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Number of persons (%)				
At least one Adverse Event reported	976 (14.1)	487 (12.7)	395 (15.1)	94 (18.8)
Number of AE				
1	717 (73.5)	357 (73.3)	295 (74.7)	65 (69.1)
2	175 (17.9)	90 (18.5)	63 (15.9)	22 (23.4)
3	48 (4.9)	27 (5.5)	18 (4.6)	<5*
>=4	36 (3.7)	13 (2.7)	19 (4.8)	<5*

*Exact numbers not shown due to small numbers

Table 18 Overview of SAEs reported by vaccine

		Vaccine type		
	Total (N=6943)	*Pfizer-BioNTech (N=3824)*	*Moderna (N=2620)*	*Adenoviral Vector/mRNA (N=499)*
Total number of participants reporting any SAE (N, %)	150 (2.2)	112 (2.9)	32 (1.2)	6 (1.2)
Total number of SAE reported (N, % of SAE)	176 (100)	136 (100)	34 (100)	6 (100)
Reasonable probability of relatedness to vaccination				
No	166 (94.3)	130 (95.6)	31 (91.2)	<5*
Yes	10 (5.7)	6 (4.4)	<5*	<5*

*Exact numbers not shown due to small numbers

Deaths

There have been 53 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 45 deaths recorded in the CPR registry that were outside of the period for reporting SAE (Table 19).

Table 19 Characteristics of participants who have died

		Vaccine type		
	Total (N=53)	*Pfizer-BioNTech (N=41)*	*Moderna (N=12)*	*Adenoviral Vector/mRNA (N=0)*
Median (interquartile range, IQR)				.
Age at enrolment (years)	75 (69, 80)	73 (69, 79)	80 (67, 84)	0
Time from first vaccine dose (days)	299 (177, 345)	305 (212, 367)	262 (84, 324)	0