ENFORCE

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

Monthly Report

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

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Summary of key changes from previous report

Enrolment

Information on the type of vaccines received and dates of vaccinations is now available from the Danish Vaccine register (DDV). The vaccination groups have therefore been updated to incorporate this information. With this updated information the number of participants confirmed to have actually received a first dose of the AstraZeneca vaccine is lower than was reported in the earlier reports when this data was based on the information reported at enrolment and prior to their first vaccination.

A table outlining the total number of participants who have completed each study visit and also the number who have received both doses of their vaccine is now included.

Outcomes

The results of the serum antibody quantification using ELISA (Wantai) performed by Statens Serum Institut (SSI) are included for those with data up to visit 3.

The results from the multiantigen serological tests for antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid are also included for visits 1, 2 and 3.

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 through 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.

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 0.9-11). 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.

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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

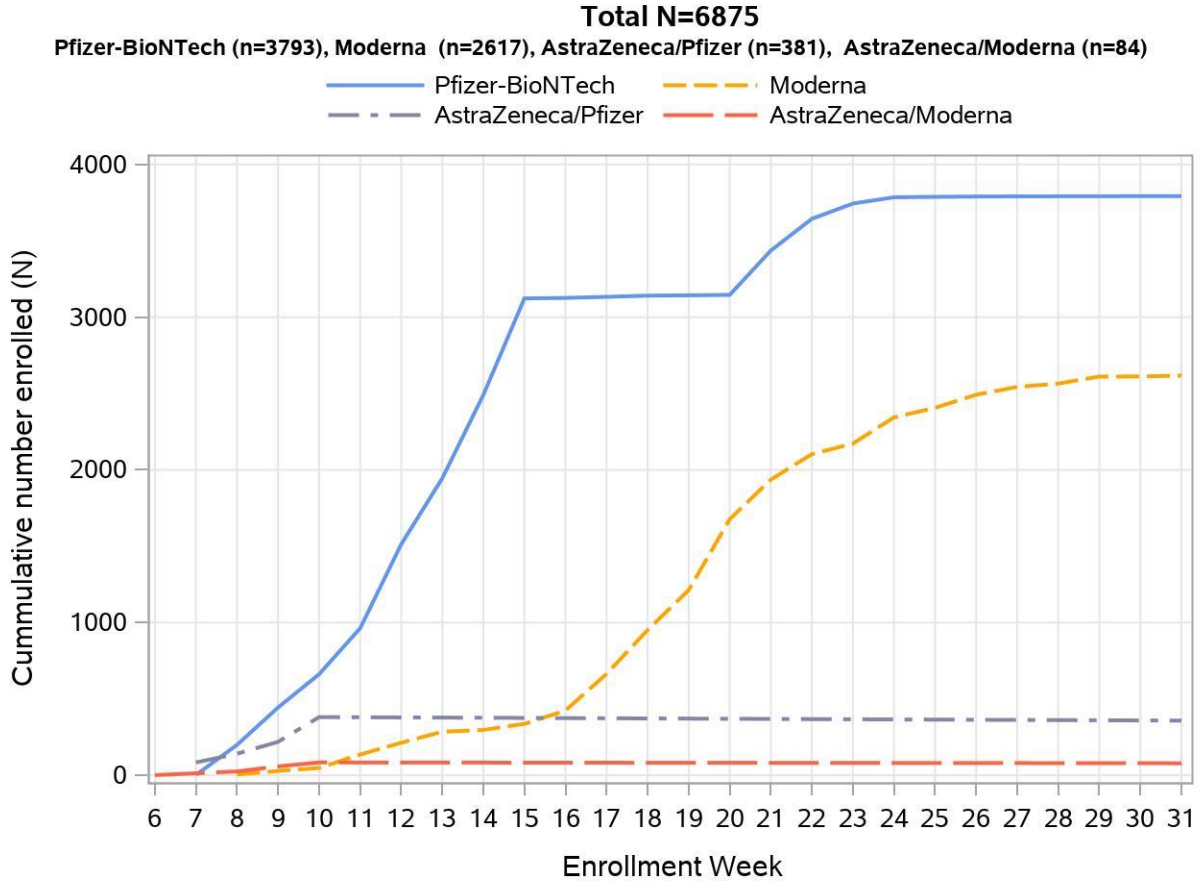
Total included	*Reason for exclusion*
6947	All patients
6931	Consent withdrawn and requested data deleted
6930	Provided informed consent
6930	Missing enrolment date
6929	Aged under 18
6929	Vaccine not recommended
6929	Vaccinated Previously
6929	Agrees to follow protocol
6924	No SSI vaccine data (consent withdrawn) and expected to receive AZ after 10/3/21
6886	No SSI vaccine data (consent withdrawn) and only one study visit (enrolment)
6886	No SSI vaccine data (consent withdrawn) and no study visit after second vaccine
6875	Non-standard vaccine regimen

Enrolment into the AstraZeneca vaccine group was stopped following the pausing of AstraZeneca vaccination in week 10 (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. Enrollment is now complete in all vaccine groups.

Figure 1 shows the cumulative number of participants enrolled by vaccine type. Enrolment began on the 13th February 2021 (Week 6) 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 (week 8).

Enrolment into the AstraZeneca vaccine group was stopped following the pausing of AstraZeneca vaccination in week 10 (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. Enrollment is now complete in all vaccine groups.

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=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca/Pfizer (N=381)*	*AstraZeneca/Moderna (N=84)*
Gender (N,%)					
Male	2982 (43.4)	1825 (48.1)	1085 (41.5)	56 (14.7)	16 (19.0)
Female	3893 (56.6)	1968 (51.9)	1532 (58.5)	325 (85.3)	68 (81.0)
Age at enrolment (Median, IQR))	64 (54, 75)	71 (55, 78)	61 (54, 69)	45 (31, 56)	46 (34, 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=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca/Pfizer (N=381)*	*AstraZeneca/Moderna (N=84)*
Any concomitant disease N (%)	4520 (65.7)	2808 (74.0)	1554 (59.4)	144 (37.8)	14 (16.7)
Any medications taken in the last 24 hours N (%)	4745 (69.0)	2930 (77.2)	1602 (61.2)	178 (46.7)	35 (41.7)

Enrolment Progress

Figure 2 shows the current status of participants in the study at the date of most recent data extract. The first participant was enrolled 27 weeks ago. Table 4 gives the number of participants included in the study who have received both doses of their vaccine and also the number and percentage who have completed each study visit.

Figure 2 Current status of participants

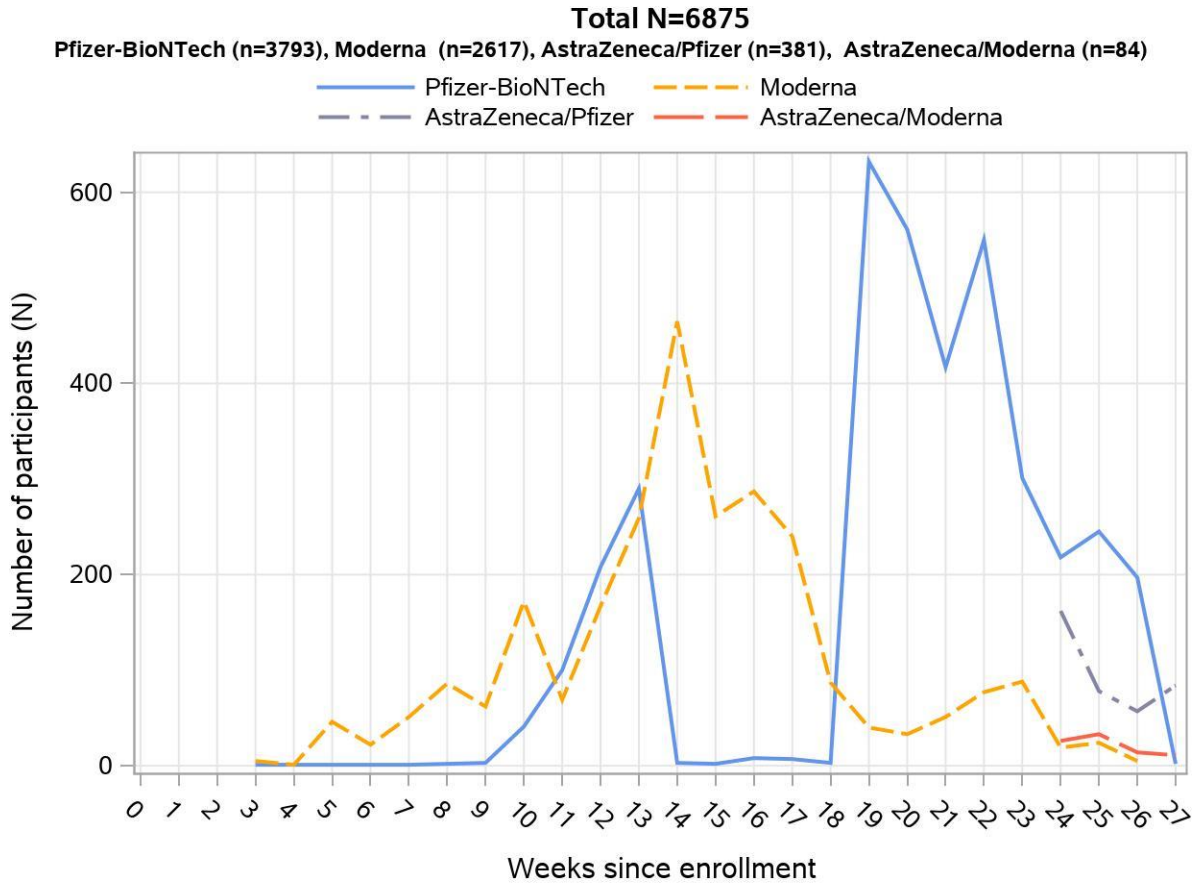


Table 4 Number and percentage of participants completing each study visit

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca /Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
Fully vaccinated (N, %)	6797 (98.9)	3777 (99.6)	2555 (97.6)	381 (100)	84 (100)
Time between first and second dose (median, IQR)	29 (22, 35)	23 (21, 28)	35 (35, 36)	83 (79, 86)	82 (79, 87)
Visit 2 (prior to second vaccination) (N, %)	6388 (92.9)	3568 (94.1)	2446 (93.5)	325 (85.3)	49 (58.3)
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, %)	4061 (59.1)	2832 (74.7)	1145 (43.8)	63 (16.5)	21 (25.0)
Days from first vaccine to third study visit (median, IQR)	91 (88, 94)	91 (89, 94)	91 (87, 94)	96 (90, 101)	97 (92, 99)

Withdrawal/Loss to follow-up

Table 5 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 5 Number and percent of participants discontinuing in the study, by vaccine type

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca/ Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
Study status (N, % of total)					
Still under follow-up	6690 (97.3)	3661 (96.5)	2590 (99.0)	360 (94.5)	79 (94.0)
Withdrawn (N, % of total)	185 (2.7)	132 (3.5)	27 (1.0)	21 (5.5)	5 (6.0)

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), and 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 Table 6.

Table 6 Presence of antibodies at study visit, ELISA (Wantai) from SSI

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca /Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
SSI antibody data at visit 1 (enrolment) (N, % of total)	6507 (94.6)	3594 (94.8)	2480 (94.8)	356 (93.4)	77 (91.7)
Wantai result at enrolment (visit 1)					
Negative	6191 (95.1)	3453 (96.1)	2348 (94.7)	316 (88.8)	74 (96.1)
Positive	311 (4.8)	138 (3.8)	130 (5.2)	40 (11.2)	3 (3.9)
Inconclusive	5 (0.1)	3 (0.1)	2 (0.1)	0	0
SSI antibody data at visit 2 (prior to second vaccination) (N, % of total)	5669 (82.5)	3389 (89.3)	1989 (76.0)	254 (66.7)	37 (44.0)
Wantai result prior to second vaccine (visit 2)					
Negative	960 (16.9)	839 (24.8)	116 (5.8)	5 (2.0)	0
Positive	4642 (81.9)	2493 (73.6)	1863 (93.7)	249 (98.0)	37 (100)
Inconclusive	67 (1.2)	57 (1.7)	10 (0.5)	0	0
Days from first vaccination (median (IQR))	27 (21, 35)	22 (20, 26)	34 (31, 35)	82 (78, 85)	83 (78, 87)
SSI antibody data at visit 3 (3 months after first vaccination) (N, % of total)	3159 (45.9)	2409 (63.5)	680 (26.0)	51 (13.4)	19 (22.6)
Wantai result after second vaccine (visit 3)					
Negative	111 (3.5)	101 (4.2)	10 (1.5)	0	0
Positive	3048 (96.5)	2308 (95.8)	670 (98.5)	51 (100)	19 (100)
Days from first vaccination (median (IQR))	91 (88, 94)	91 (88, 93)	91 (88, 94)	96 (90, 101)	96 (91, 99)

From 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 in Table 7. Figure 3-5 show the distribution of the three assays on the log10 scale, by vaccine type and study visit.

Table 7 Presence of antibodies at study visit, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca/ Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
AUH antibody data at visit 1 (enrolment) (N, % of total)	6098 (88.7)	3554 (93.7)	2111 (80.7)	356 (93.4)	77 (91.7)
AUH antibody data at visit 2 (prior to second vaccination) (N, % of total)	4006 (58.3)	2834 (74.7)	942 (36.0)	196 (51.4)	34 (40.5)
AUH antibody data visit 3 (3 months after first vaccination) (N, % of total)	815 (11.9)	671 (17.7)	84 (3.2)	45 (11.8)	15 (17.9)
CoV-2 Receptor-Binding Domain (SERO)					
GM at enrolment (95%CI)	55 (53, 57)	51 (49, 54)	59 (55, 62)	87 (71, 105)	55 (40, 76)
GM at visit 2 (95%CI)	4447 (4164, 4750)	3056 (2835, 3295)	12673 (11036, 14552)	6919 (5649, 8473)	3317 (2222, 4952)
GM at visit 3 (95%CI)	27022 (22603, 32306)	19906 (16347, 24240)	67672 (43105, 106242)	200895 (106715, 378192)	333482 (235649, 471931)
CoV-2 Spike antibody (SERO)					
GM at enrolment (95%CI)	100 (96, 104)	99 (94, 105)	92 (86, 99)	154 (124, 190)	109 (76, 155)
GM at visit 2 (95%CI)	14376 (13516, 15291)	10459 (9739, 11232)	36469 (32090, 41445)	17287 (14353, 20821)	10239 (6700, 15648)
GM at visit 3 (95%CI)	60491 (51406, 71181)	46907 (39081, 56299)	140360 (97487, 202086)	287969 (159868, 518716)	439244 (379383, 508549)
CoV-2 Nucleocapsid (SERO)					
GM at enrolment (95%CI)	252 (240, 264)	262 (247, 279)	223 (206, 241)	345 (274, 434)	275 (190, 398)
GM at visit 2 (95%CI)	248 (234, 262)	249 (234, 266)	220 (195, 248)	415 (300, 575)	202 (126, 324)
GM at visit 3 (95%CI)	243 (214, 276)	230 (200, 265)	269 (181, 399)	385 (210, 702)	384 (180, 817)

GM: Geometric mean

Figure 3 Distribution of CoV-2 Receptor-Binding Domain (RBD) levels at each study visit (see Table 7 for the number included at each time point)

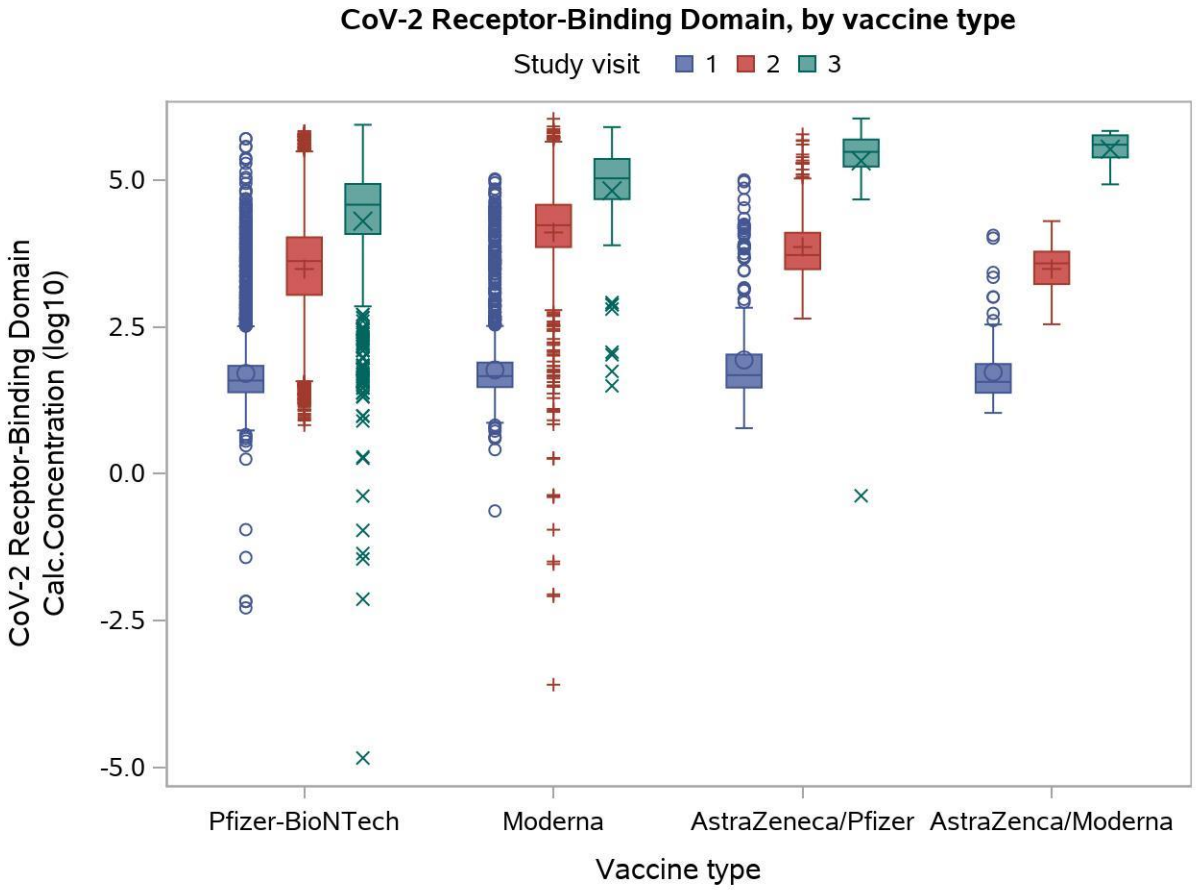


Figure 4 Distribution of CoV-2 Spike antibody levels at each study visit (see Table 7 for the number included at each time point)

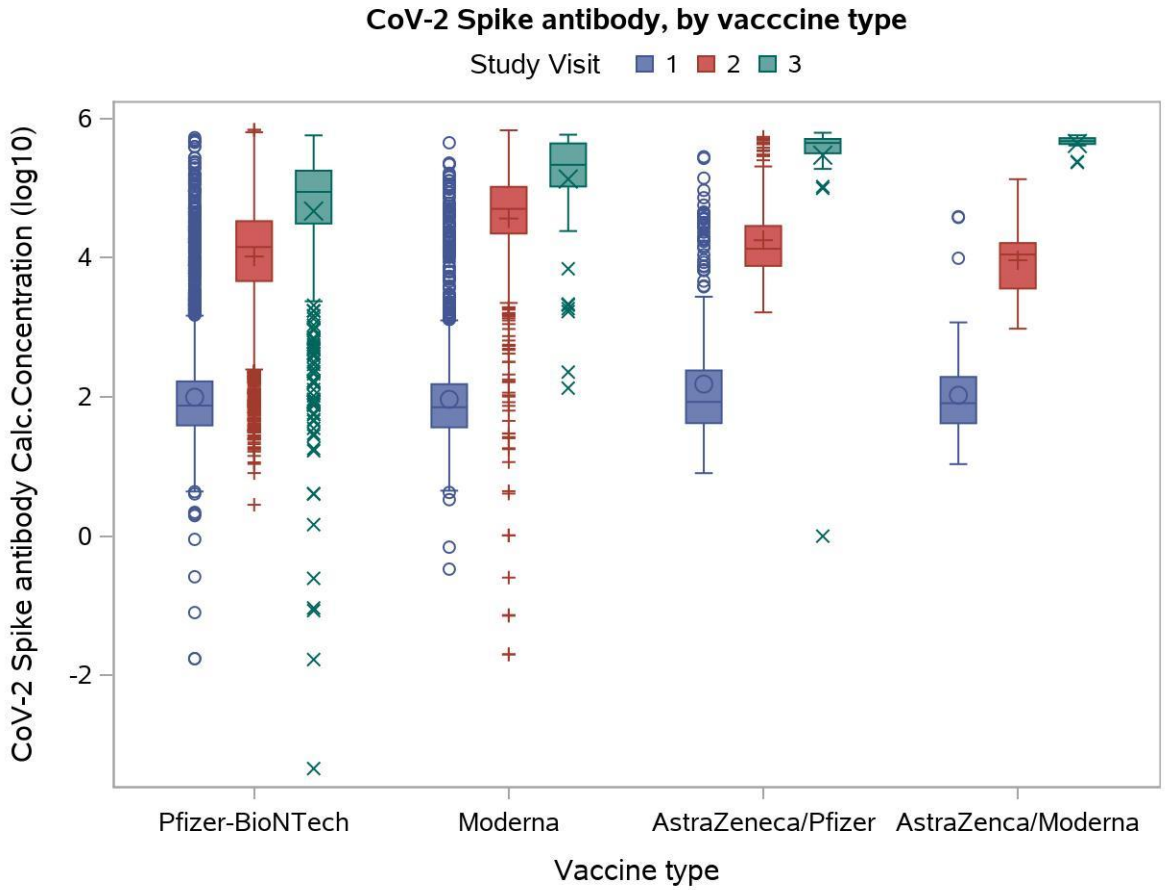
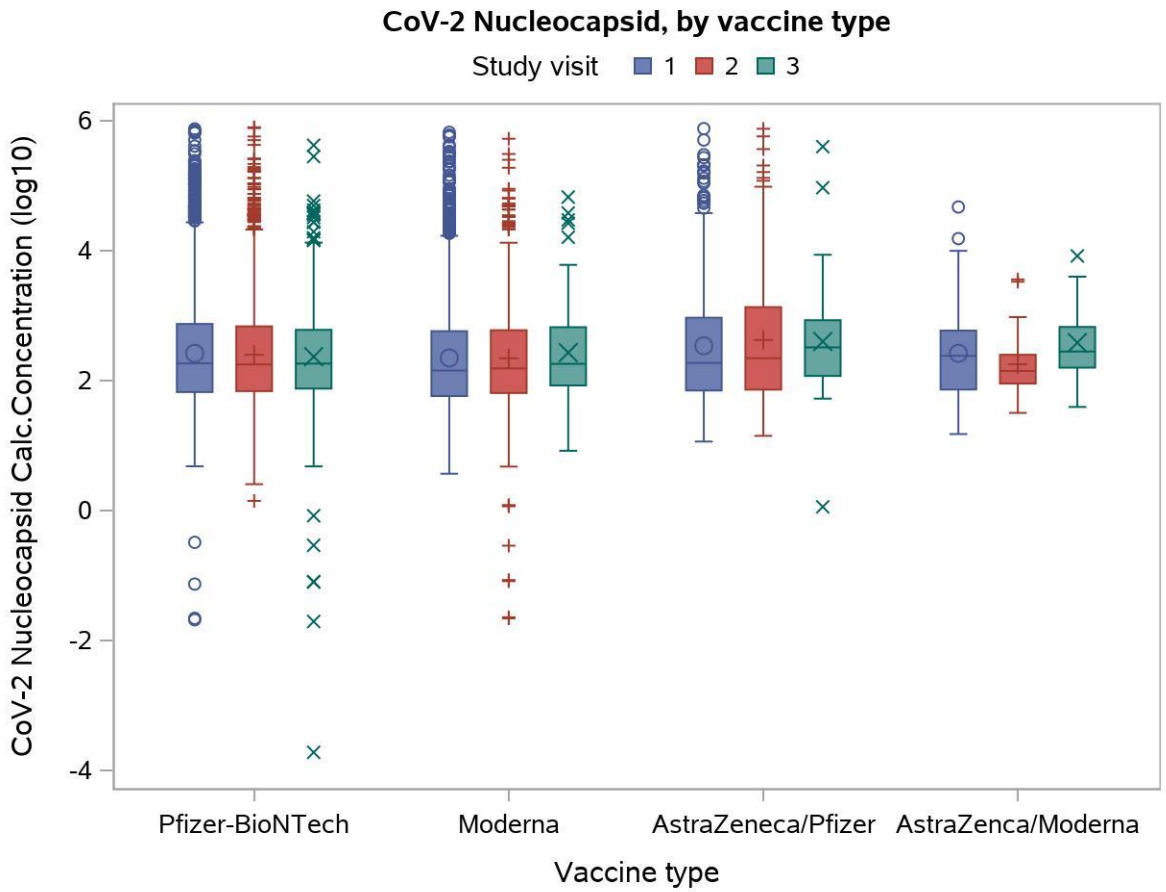


Figure 5 Distribution of CoV-2 Nucleocapsid levels at each study visit (see Table 7 for the number included at each time point)



Secondary outcome – data not yet available will be included in future reports

The secondary outcome of breakthrough infections is monitored in two different ways. The number of participants testing positive for SARS-CoV-19, as reported via MiBa, and by serological monitoring (detection of SARS-CoV-2 nucleocapsid antibodies). The number of participants experiencing these outcomes will be reported in Table 8.

Table 8 Number of participants experiencing breakthrough infection and hospitalisation due to COVID-19

	Overall	**Pfizer/BioNTech**	**Moderna**	**AstraZeneca**	**Other**
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of participants with breakthrough infection					
Number testing positive for SARS-CoV-2 reported via MiBa					
Number with SARS-CoV-2 nucleocapsid antibodies detected					
Time to breakthrough infection (median, IQR)					
Age group					
<65					
65-74					
75-79					
80-84					
≥85					
Sex					
Male					
Female					
Number admitted to hospital due to COVID-19					

Time to hospitalisation (median, IQR)					
Age group					
<65					
65-74					
75-79					
80-84					
≥85					
Sex					
Male					
Female					

Safety Monitoring

Local and systemic reactions

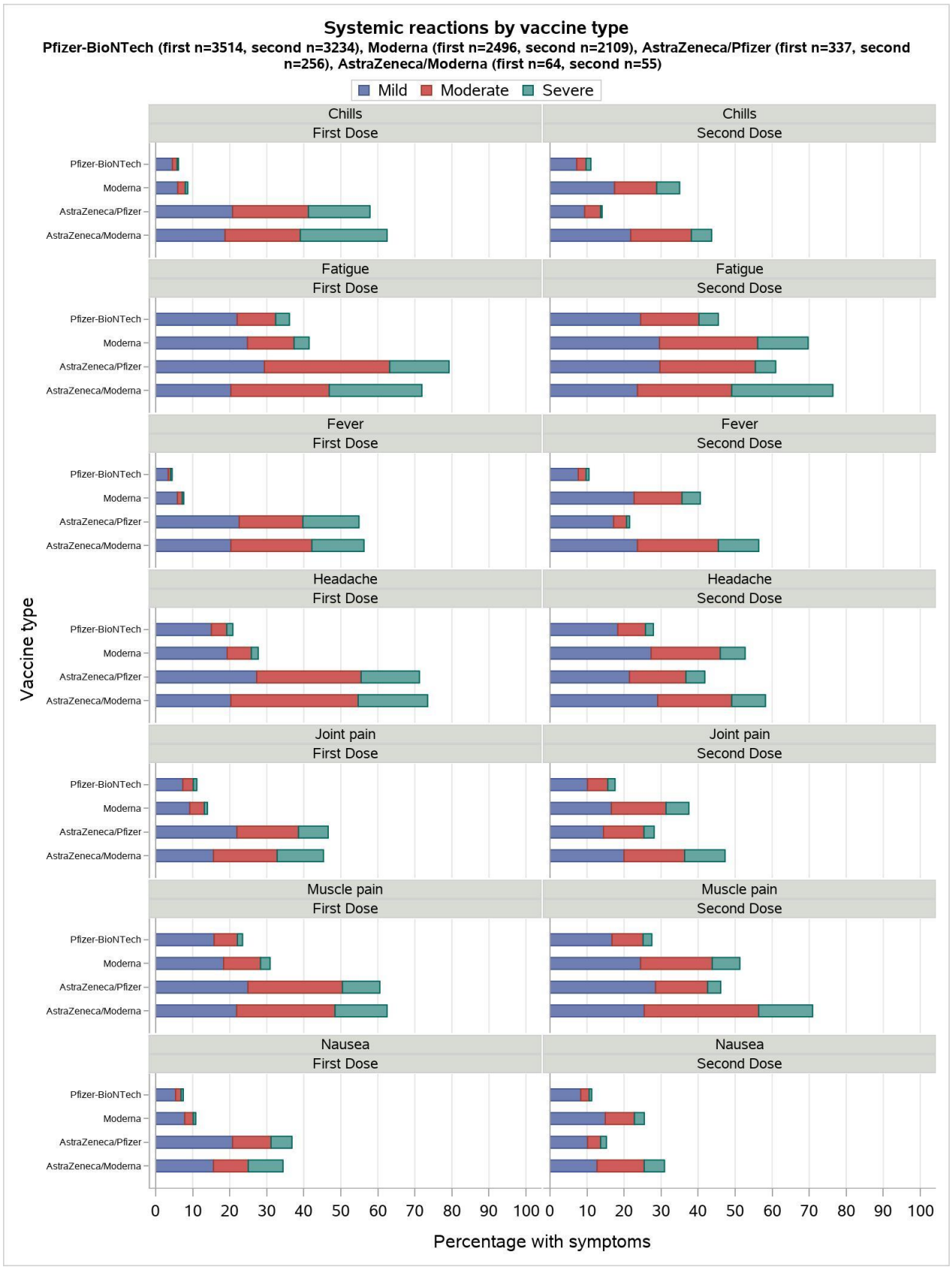
Table 9 outlines the number of participants reporting any local or systemic reactions within 7 days of vaccination. Note that participants can report multiple symptoms. The percentages are out of the total number of participants who had completed the symptoms form at the time of data extraction. All participants are encouraged to complete the form even if they experience no symptoms.

Figure 6 shows the proportion reporting mild, moderate or severe symptoms by vaccine type. To further illustrate the symptoms reported by participant demographics Figure 7-9 show the proportion reporting mild, moderate or severe symptoms by each vaccine separately stratified by age group (<55 years, 55-64 years and ≥65 years) and Figure 10-12 stratified by gender.

Table 9 Number & percent reporting local/systemic reactions within 7 days post vaccination overall, all and by vaccination

	Total		*Pfizer-BioNTech*		*Moderna*		*AstraZeneca/Pfizer*		*AstraZeneca/Moderna*	
	First (N=6411)	*Second (N=5654)*	*First (N=3514)*	*Second (N=3234)*	*First (N=2496)*	*Second (N=2109)*	*First (N=337)*	*Second (N=256)*	*First (N=64)*	*Second (N=55)*
Number of persons (%)										
Any clinical symptoms	3729 (58.2)	3852 (68.1)	1835 (52.2)	1856 (57.4)	1527 (61.2)	1755 (83.2)	309 (91.7)	192 (75.0)	58 (90.6)	49 (89.1)
Any local symptoms at injection site	5076 (79.2)	4425 (78.3)	2543 (72.4)	2237 (69.2)	2182 (87.4)	1908 (90.5)	296 (87.8)	232 (90.6)	55 (85.9)	48 (87.3)

*Figure 6 Percentage of participants reporting systemic and local symptoms following **1st dose and 2nd dose** of the vaccine, by vaccine type*



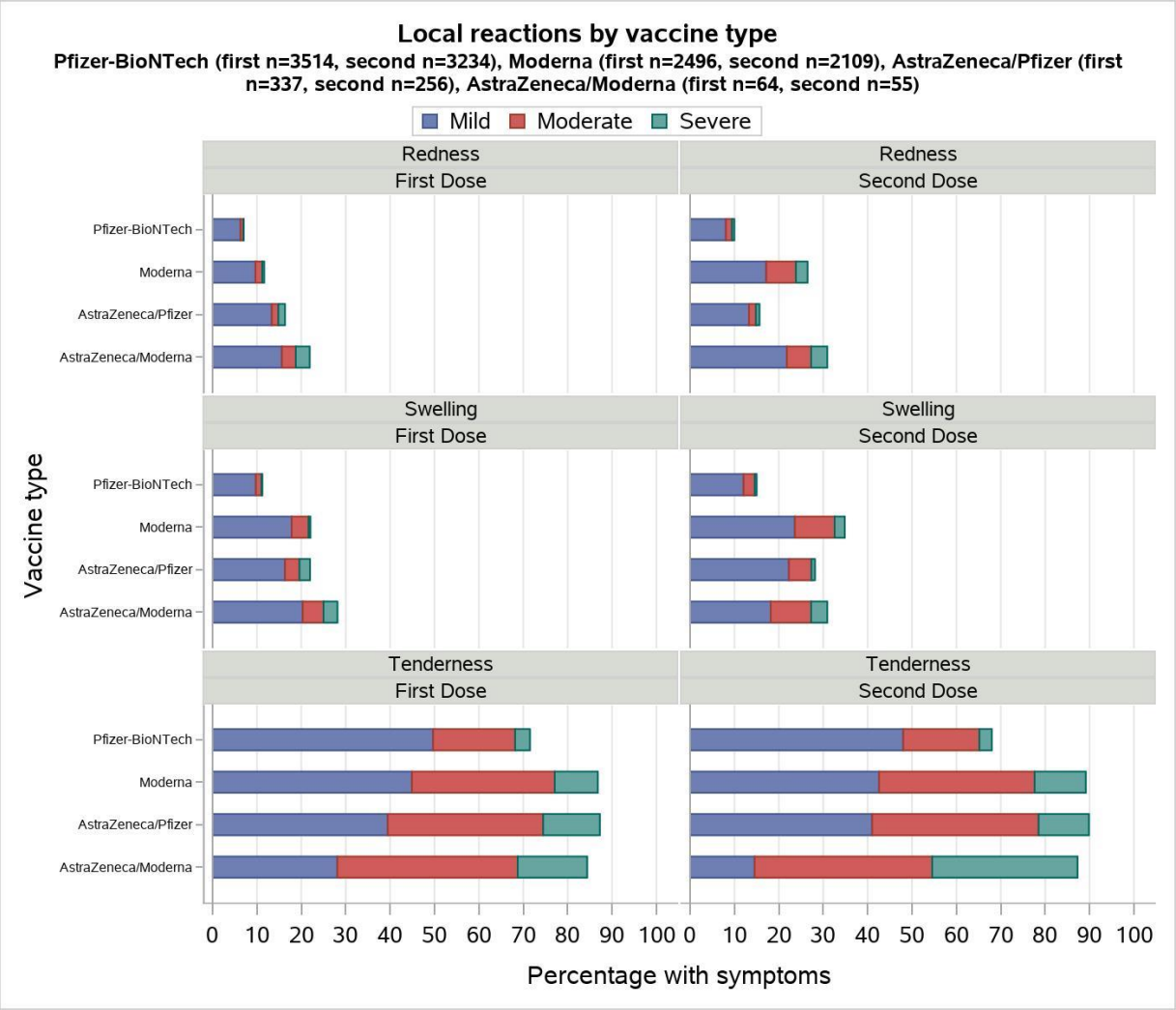

Local reactions by vaccine type
Pfizer-BioNTech (first n=3514, second n=3234), Moderna (first n=2496, second n=2109), AstraZeneca/Pfizer (first n=337, second n=256), AstraZeneca/Moderna (first n=64, second n=55)
Mild
Moderate
Severe
Redness
First Dose
Redness
Second Dose
Swelling
First Dose
Swelling
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 7 Percentage of participants reporting systemic and local symptoms following **1st and 2nd dose** of Pfizer-BioNTech, by age group*

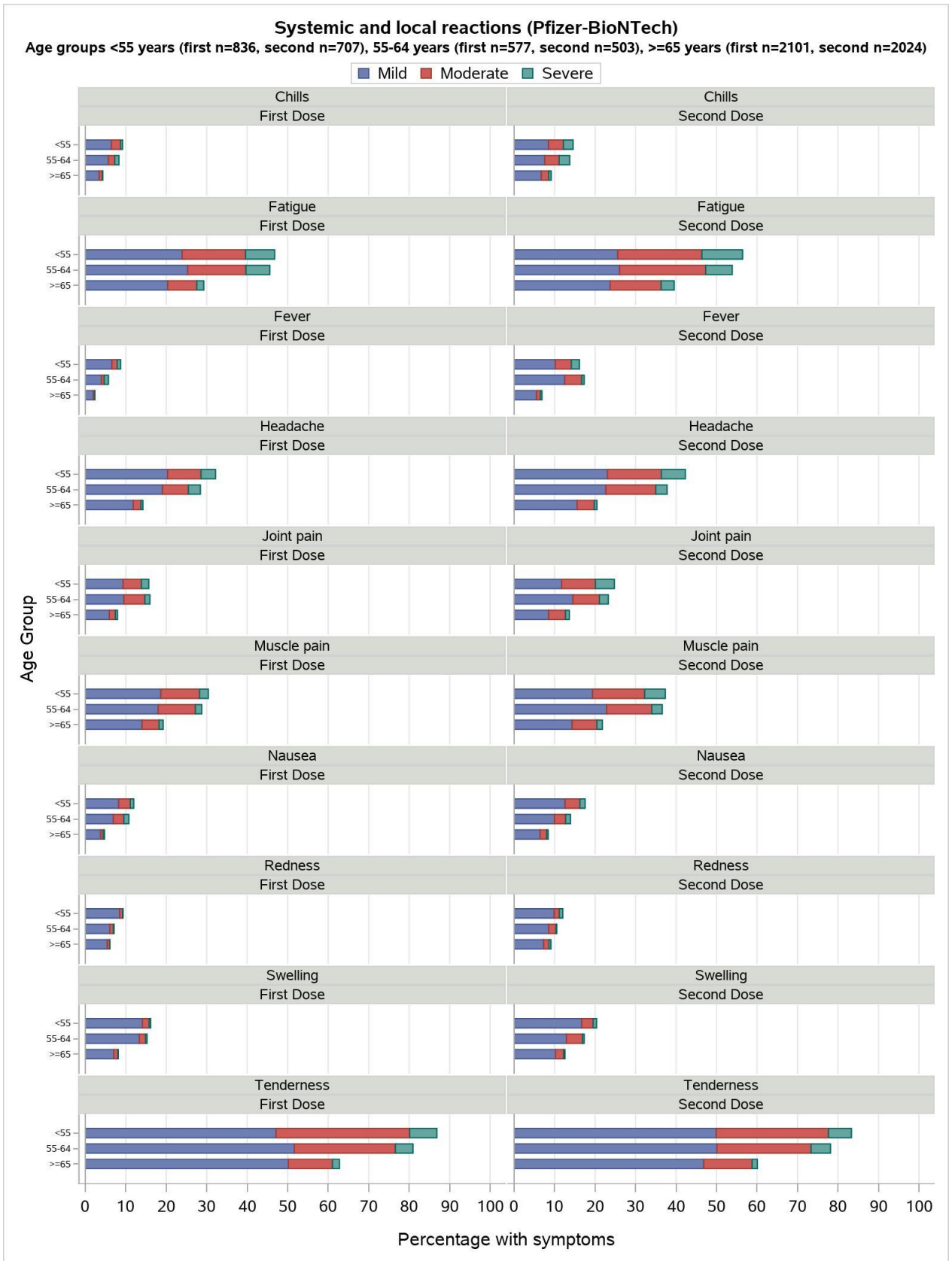


*Figure 8 Percentage of participants reporting systemic and local symptoms following **1st & 2nd dose** of Moderna, by age group*

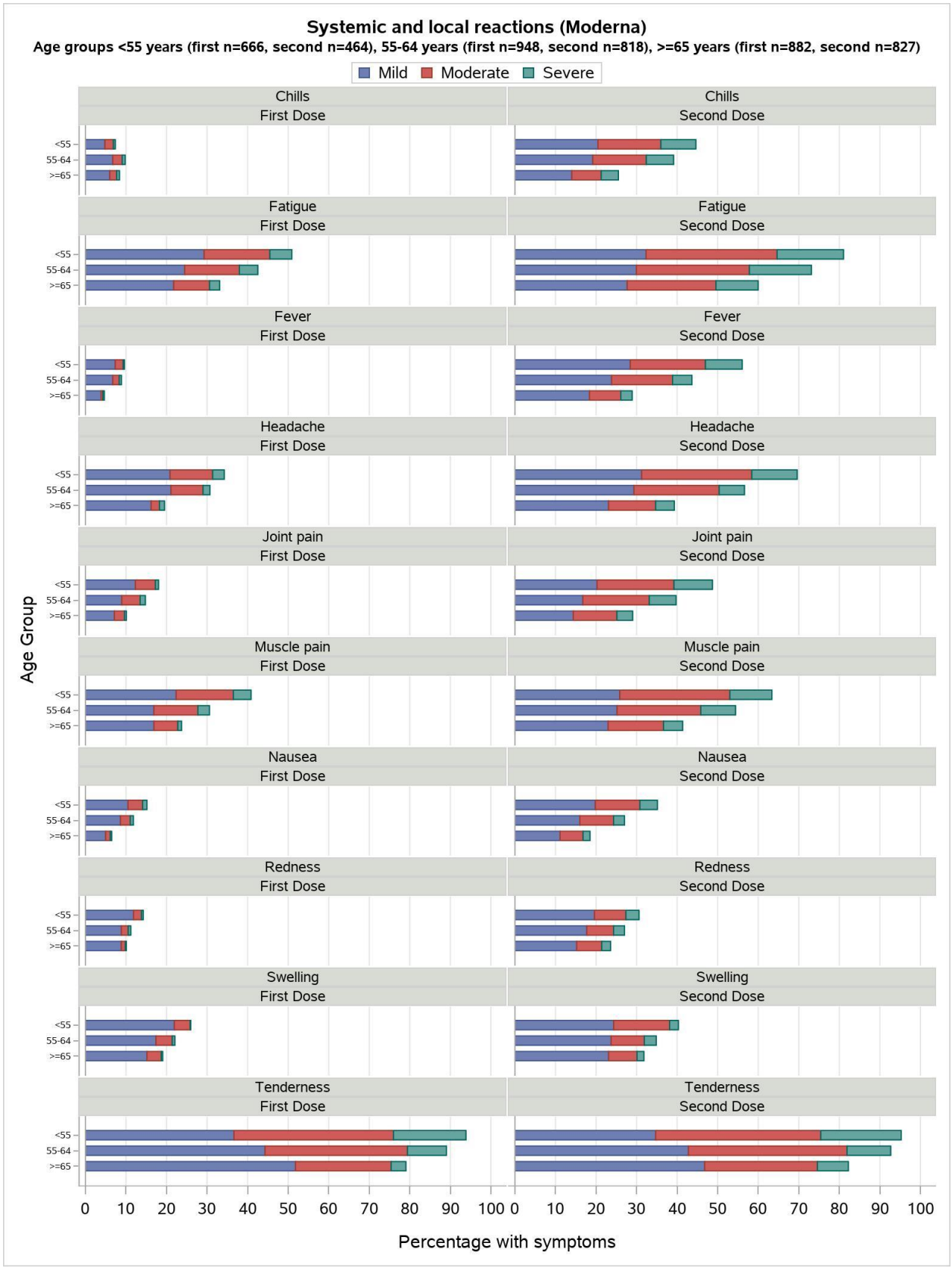


Figure 9 Percentage of participants reporting systemic and local symptoms following 1st dose of AstraZeneca & 2nd dose of Pfizer, by age group. Data on ≥65 years old age group not shown due to small numbers.

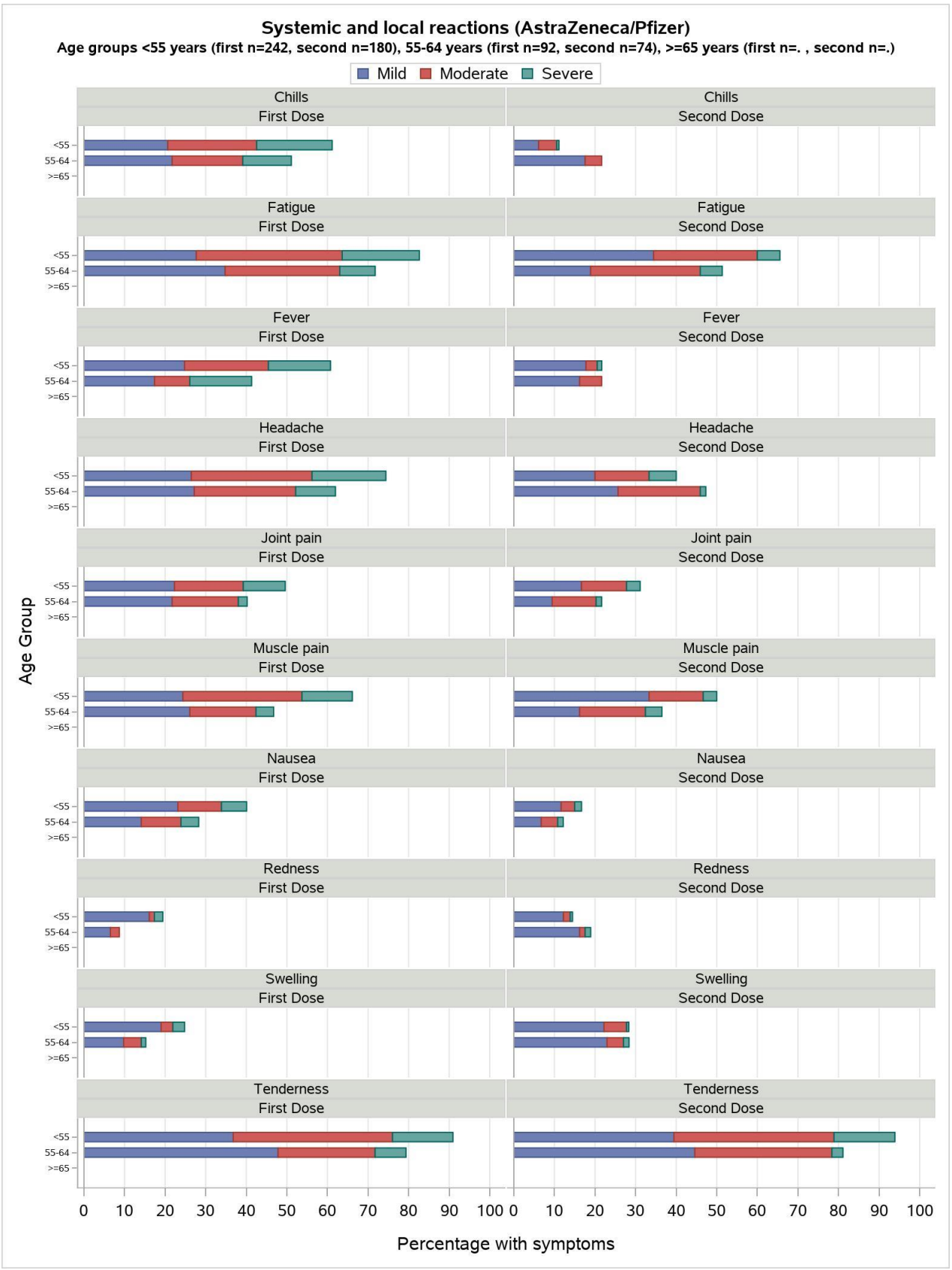


*Figure 10 Percentage of participants reporting systemic and local symptoms following **1st & 2nd dose** of Pfizer-BioNTech, by gender*

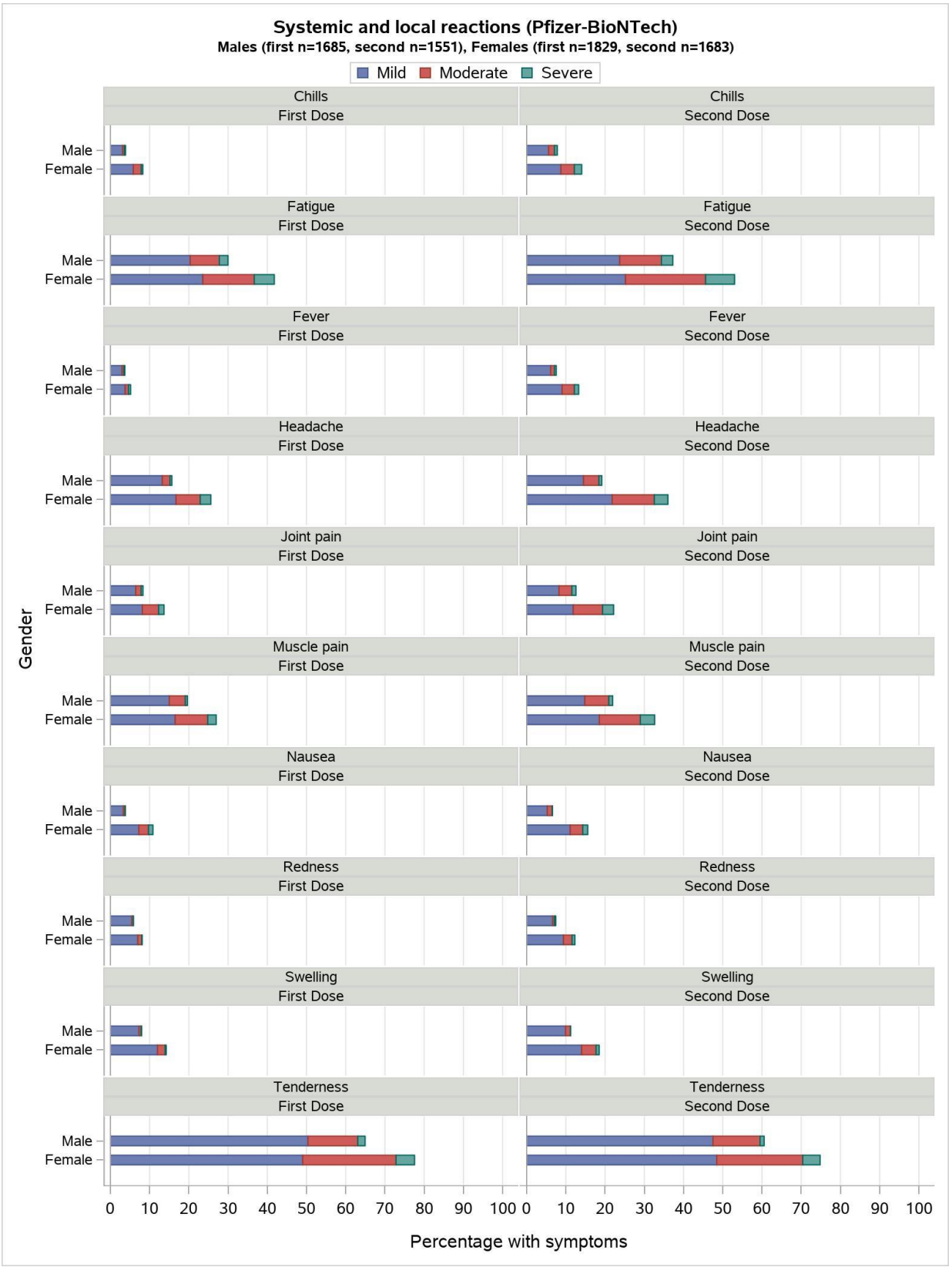


*Figure 11 Percentage of participants reporting systemic and local symptoms following **1st dose and 2nd dose** of Moderna, by gender*

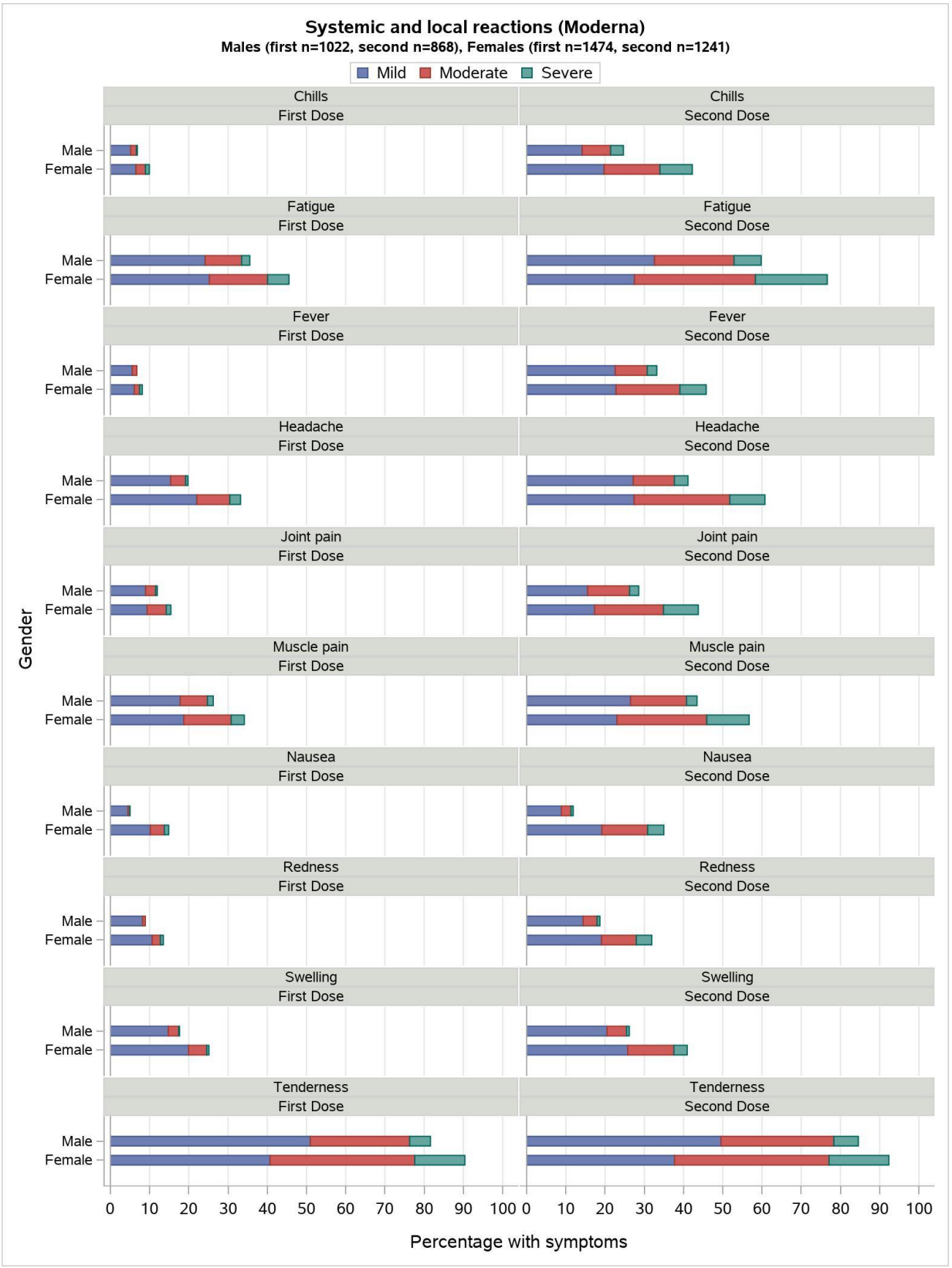
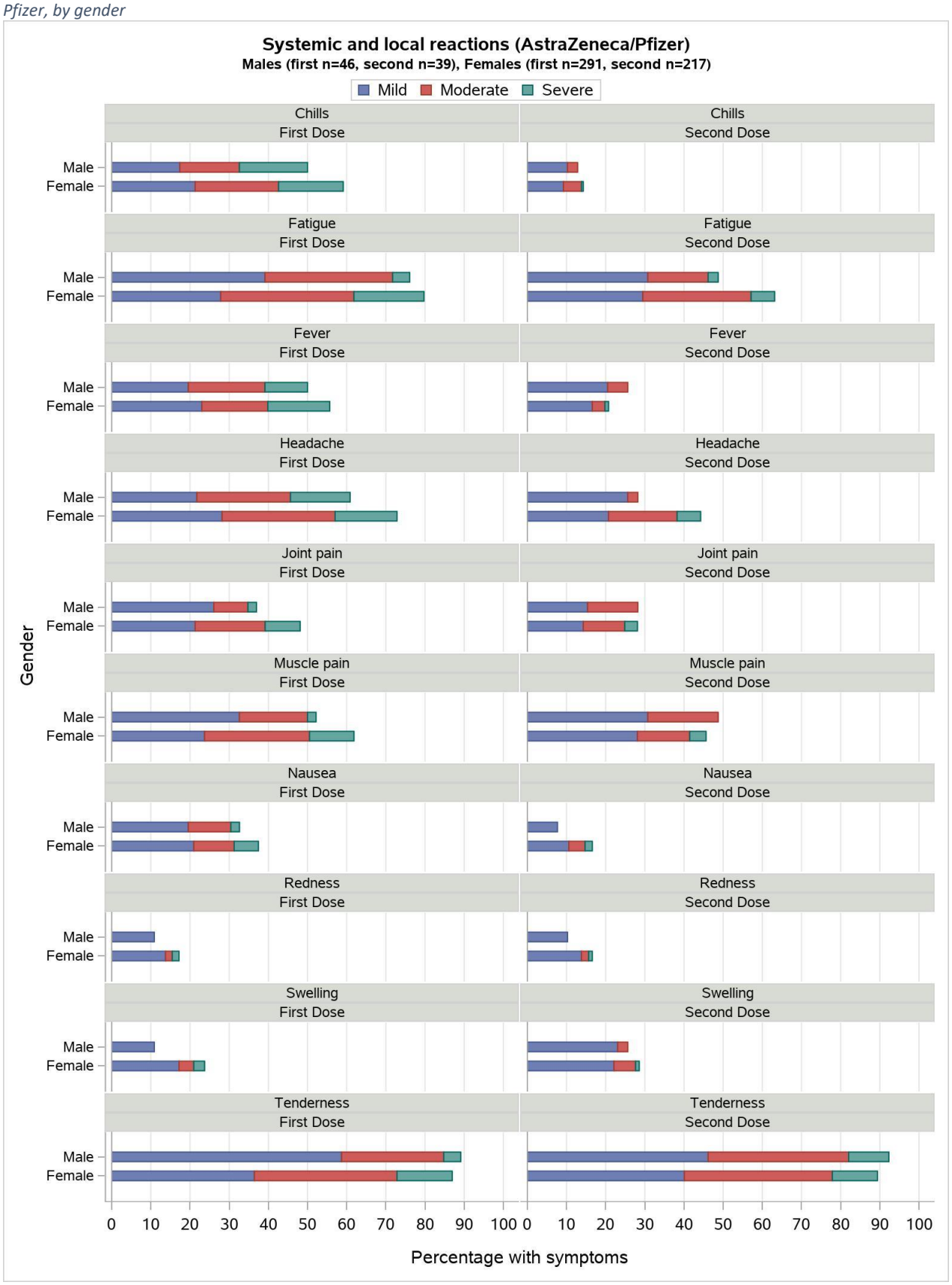


*Figure 12 Percentage of participants reporting systemic and local symptoms following **1st dose of AstraZeneca and 2nd dose** of Pfizer, by gender*



Adverse and Serious Adverse Events

This section gives an overview of the AEs (Table 10) and SAEs (Table 11) reported in the study thus far. The data are first shown overall and by vaccine type.

Table 10 Overview of AEs (grade 3 and 4) reported by vaccine

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca /Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
Number of persons (%)					
At least one Adverse Event reported	587 (8.5)	346 (9.1)	187 (7.1)	48 (12.6)	6 (7.1)
Total number of AE reported (N,% of AE)	766 (100)	451 (100)	240 (100)	64 (100)	11 (100)

Table 11 Overview of SAEs reported by vaccine

		Vaccine type			
	Total (N=6875)	*Pfizer-BioNTech (N=3793)*	*Moderna (N=2617)*	*AstraZeneca/ Pfizer (N=381)*	*AstraZeneca/ Moderna (N=84)*
Total number of participants reporting any SAE (N, %)	102 (1.5)	78 (2.1)	19 (0.7)	<5*	<5*
Total number of SAE reported (N, % of SAE)	118 (100)	92 (100)	21 (100)	<5*	<5*

*Exact numbers not shown due to small numbers

Deaths

There have been <5 deaths reported in the study thus far and none had a reasonable probability of relatedness to vaccination.