ENFORCE

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

Monthly Report

Report number: 3

Date Report: 11th June 2021

Date of data extract: 8th June 2021 (1pm)

Report prepared by: the ENFORCE consortium

Approved by: the ENFORCE scientific steering committee

This report is an edited version of the confidential report generated for distribution and review to the Danish Medicines Agency only. Tables and figures with small numbers (<5 participants per cell) or very specific details and where there is the potential that individual participants could be identified or be able to identify themselves have been removed or edited to maintain participant confidentiality.

Finansieret af
Den Europæiske Union
NextGenerationEU

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

Contents

Summary of key changes from previous report 3
Enrolment 3
Outcomes 3
Methods 4
Data sources 4
Definitions 4
Enrolment 5
Demographics at enrolment 7
Enrolment Progress 8
Withdrawal/Loss to follow-up 9
Outcomes 10
Primary outcome 10
Secondary outcome – data not yet available will be included in future reports 15
Safety Monitoring 17
Local and systemic reactions 17
Adverse and Serious Adverse Events 27
Deaths 28

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

Summary of key changes from previous report

Enrolment

A table outlining the total number of participants who have withdrawn from the study is now included.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 and 2.

The results from the multiantigen serological tests, for the neutralizing antibody titer (NAb) levels for the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid are also included for visits 1 and 2.

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 only on the data stored in REDCap from the case report forms (CRF's) 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.

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.

Definitions

In this version of the report the type of vaccine received is based on self-reports from participants at enrolment into the study which occurs prior to them receiving their first vaccine. In subsequent reports this will be updated using data from the national vaccine registry as the gold standard when this data is available.

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

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.

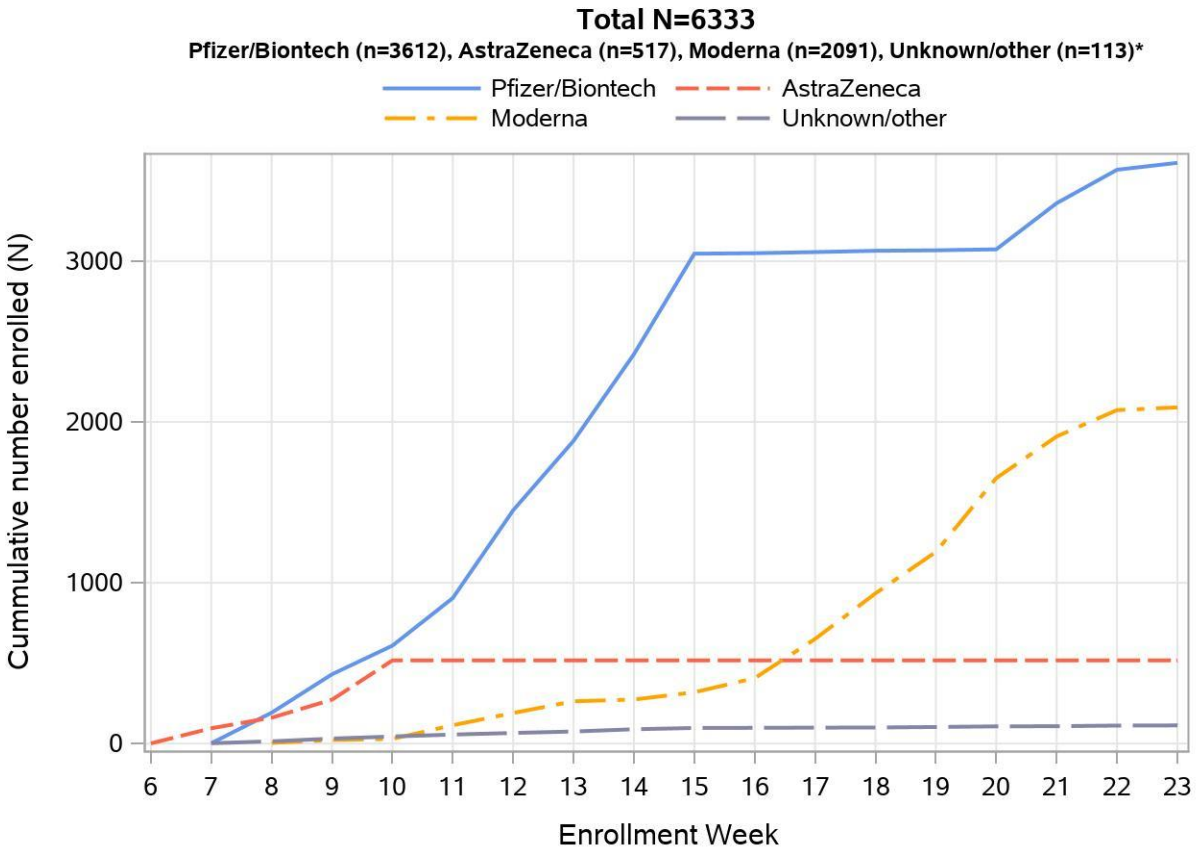
Table 1 Summary of participants enrolled in the study

Total included	*Reason for exclusion*
6345	All patients
6336	Consent withdrawn and requested data deleted
6334	Provided informed consent
6334	Missing enrolment date
6333	Aged under 18
6333	Vaccine not recommended
6333	Vaccinated Previously
6333	Belongs to a vaccine target group
6333	Agrees to follow protocol

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).

A total of 517 participants were enrolled in the AstraZeneca vaccine group prior to 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.

Figure 1 Cumulative number of participants enrolled by vaccine type



*Type of vaccine received is currently based on self-report

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=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Number of persons (%)					
Gender					
Male	2816 (44.5)	1751 (48.5)	81 (15.7)	917 (43.9)	67 (59.3)
Female	3517 (55.5)	1861 (51.5)	436 (84.3)	1174 (56.1)	46 (40.7)
Median (interquartile range, IQR)					
Age at enrolment (years)	65 (56, 75)	71 (56, 78)	45 (31, 56)	64 (59, 69)	71 (61, 79)
Enrolment date	APR21 (MAR21, MAY21)	MAR21 (MAR21, APR21)	MAR21 (FEB21, MAR21)	MAY21 (APR21, MAY21)	MAR21 (MAR21, APR21)

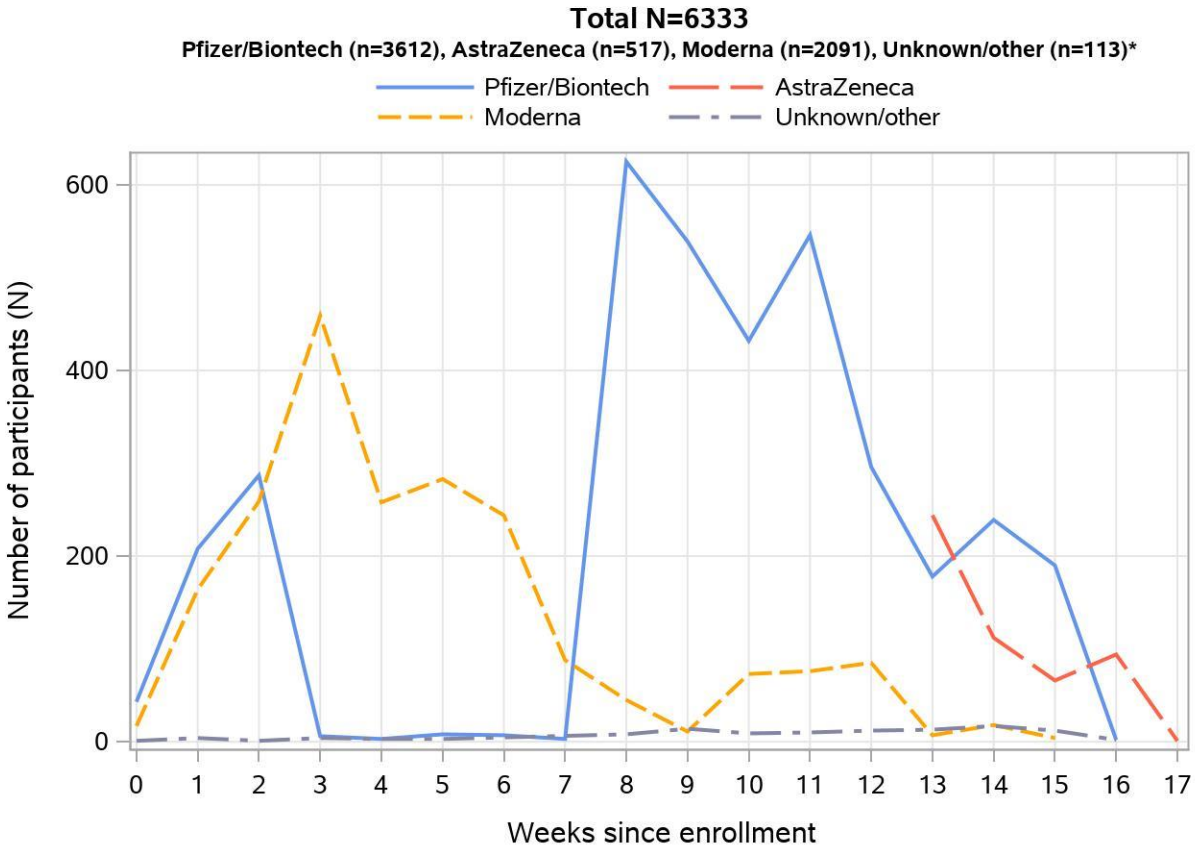
Table 3 Concomitant diseases and medications, overall and by vaccine

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Any concomitant disease N (%)	4296 (67.8)	2729 (75.6)	173 (33.5)	1311 (62.7)	83 (73.5)
Any medications taken in the last 24 hours N (%)	4519 (71.4)	2841 (78.7)	237 (45.8)	1350 (64.6)	91 (80.5)

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 17 weeks ago. The majority of participants in the Pfizer vaccine group have been under follow-up for at least 7 weeks, whereas most of those in the Moderna group have been under follow-up for less than 7 weeks.

Figure 2 Current status of participants



*Type of vaccine received is currently based on self-report

Withdrawal/Loss to follow-up

Table 4 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 4 Number and percent of participants discontinuing in the study, by vaccine type

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Study status (N, % of total)					
Still under follow-up	6237 (98.5)	3549 (98.3)	495 (95.7)	2082 (99.6)	111 (98.2)
Withdrawn	98 (1.5)	63 (1.7)	24 (4.6)	9 (0.4)	2 (1.8)

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), 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 5.

Table 5 Presence of antibodies at study visit, ELISA (Wantai) from SSI

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Number of persons with antibody data at enrolment (% of total)	6275 (99.1)	3573 (98.9)	508 (98.3)	2081 (99.5)	113 (100)
Wantai result at enrolment					
Negative	5981 (95.3)	3441 (96.3)	453 (89.2)	1979 (95.1)	108 (95.6)
Positive	291 (4.6)	131 (3.7)	55 (10.8)	100 (4.8)	5 (4.4)
Inconclusive	3 (0.0)	1 (0.0)	0	2 (0.1)	0
Number of persons with antibody data at visit 2 (% of total)	3899 (61.6)	2877 (79.7)	276 (53.4)	657 (31.4)	89 (78.8)
Wantai result at visit 2					
Negative	915 (23.5)	805 (28.0)	6 (2.2)	68 (10.4)	36 (40.4)
Positive	2933 (75.2)	2028 (70.5)	270 (97.8)	584 (88.9)	51 (57.3)
Inconclusive	51 (1.3)	44 (1.5)	0	5 (0.8)	2 (2.2)
Days from first vaccination (median (IQR))	23 (21, 28)	21 (20, 24)	82 (78, 84)	29 (28, 34)	22 (20, 28)
Number of persons with antibody data at visit 3 (% of total)	388 (6.1)	304 (8.4)	41 (7.9)	26 (1.2)	17 (15.0)
Wantai result at visit 3					
Negative	51 (13.1)	37 (12.2)	3 (7.3)	5 (19.2)	6 (35.3)
Positive	337 (86.9)	267 (87.8)	38 (92.7)	21 (80.8)	11 (64.7)
Days from first vaccination (median (IQR))	90 (87, 92)	90 (87, 92)	90 (89, 94)	87 (83, 90)	89 (87, 91)

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

Table 6 Presence of antibodies at study visit, Receptor-Binding Domain (RBD), Spike antibody and Nucleocapsid

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Number of persons with data at enrolment (% of total)	4480 (70.7)	3037 (84.1)	508 (98.3)	835 (39.9)	100 (88.5)
Number of persons with data at visit 2 (% of total)	2852 (45.0)	2510 (69.5)	13 (2.5)	256 (12.2)	73 (64.6)
CoV-2 Receptor-Binding Domain (SERO)					
GM at enrolment (95%CI)	49 (47, 51)	47 (45, 49)	84 (71, 98)	43 (40, 46)	57 (42, 78)
GM at visit 2 (95%CI)	3064 (2840, 3307)	2839 (2621, 3074)	8387 (4928, 14273)	7617 (5922, 9797)	1458 (801, 2653)
CoV-2 Spike antibody (SERO)					
GM at enrolment (95%CI)	96 (91, 100)	93 (88, 98)	153 (128, 183)	78 (71, 86)	106 (75, 150)
GM at visit 2 (95%CI)	10367 (9641, 11147)	9829 (9108, 10607)	21396 (12970, 35296)	21510 (16975, 27258)	4396 (2380, 8118)
CoV-2 Nucleocapsid (SERO)					
GM at enrolment (95%CI)	253 (240, 267)	252 (237, 269)	354 (293, 427)	208 (186, 234)	260 (175, 385)
GM at visit 2 (95%CI)	243 (228, 259)	244 (228, 262)	345 (157, 759)	223 (183, 272)	243 (155, 381)

GM: Geometric mean

Figure 3 Distribution of CoV-2 Receptor-Binding Domain (RBD) levels at each study visit (see Table 6 for the number included at each time point)

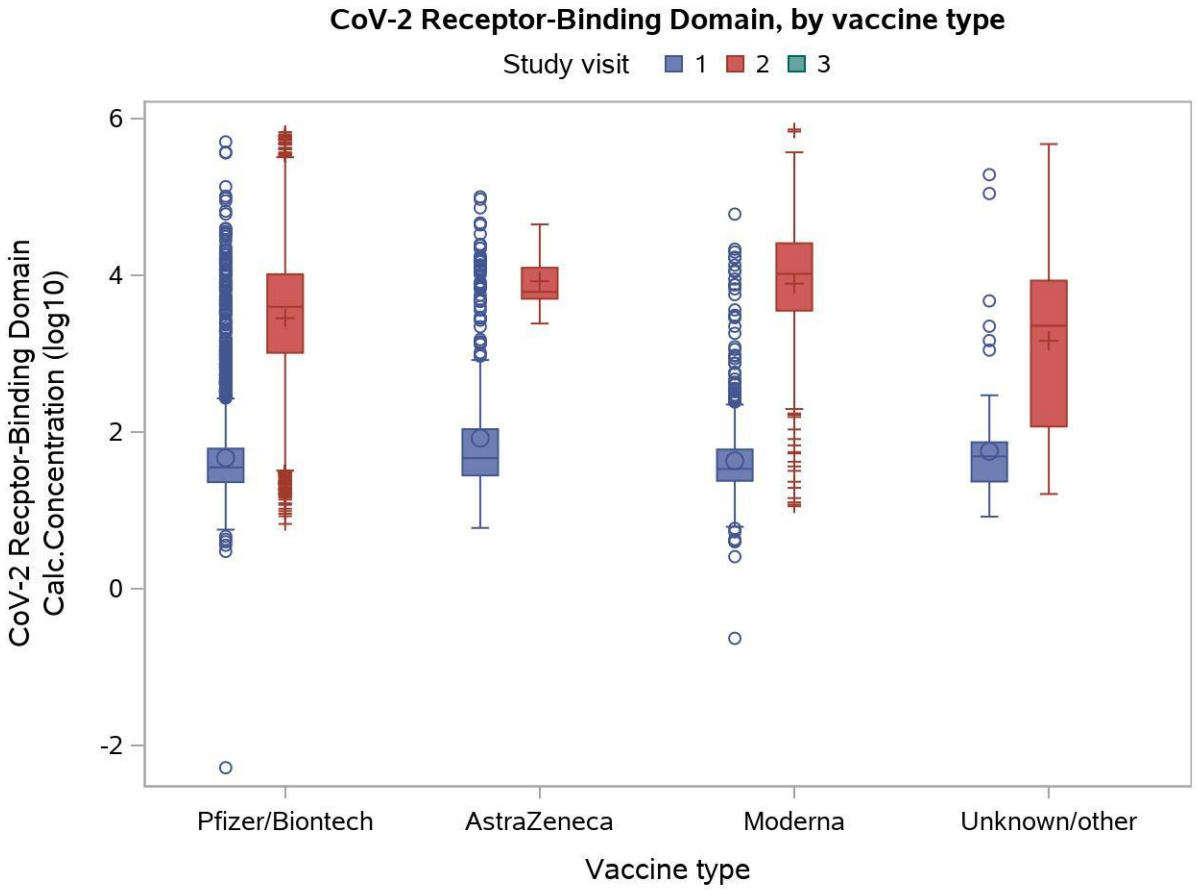


Figure 4 Distribution of CoV-2 Spike antibody levels at each study visit (see Table 6 for the number included at each time point)

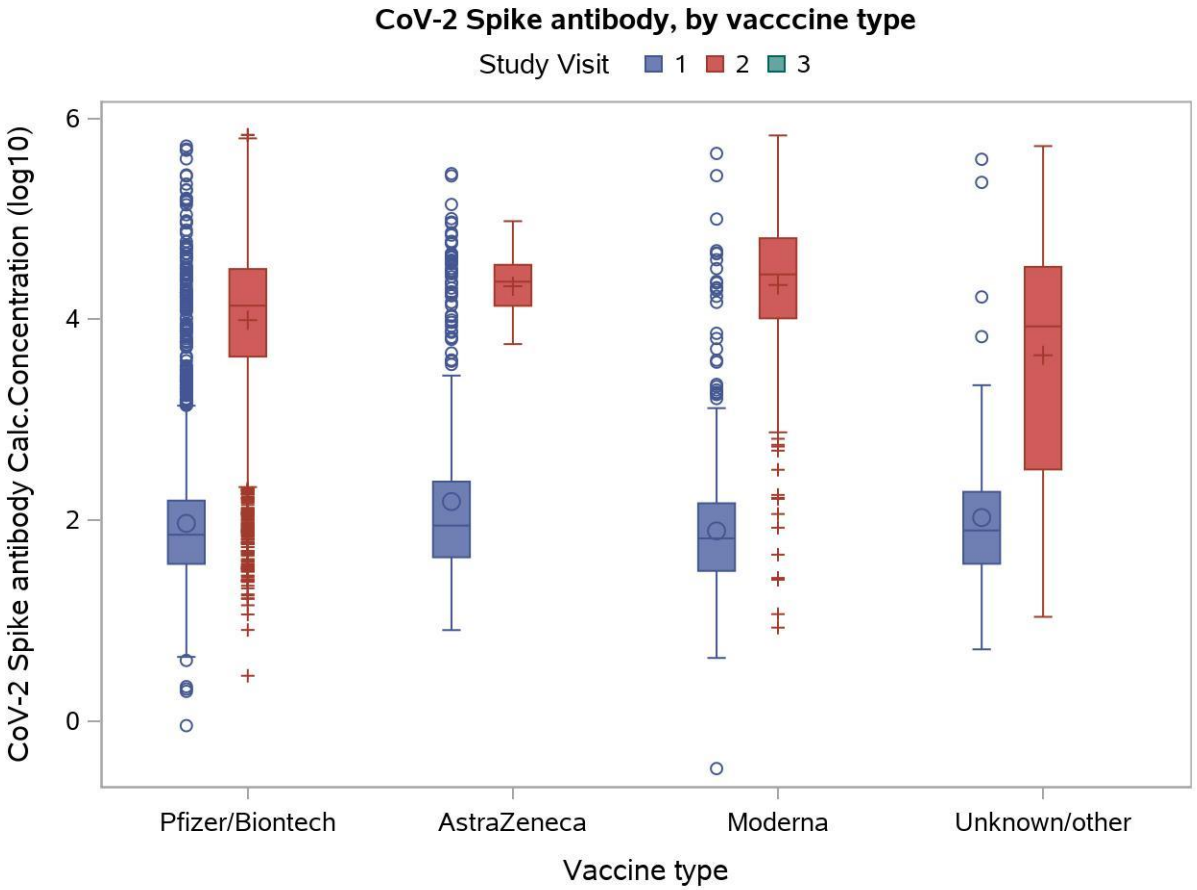
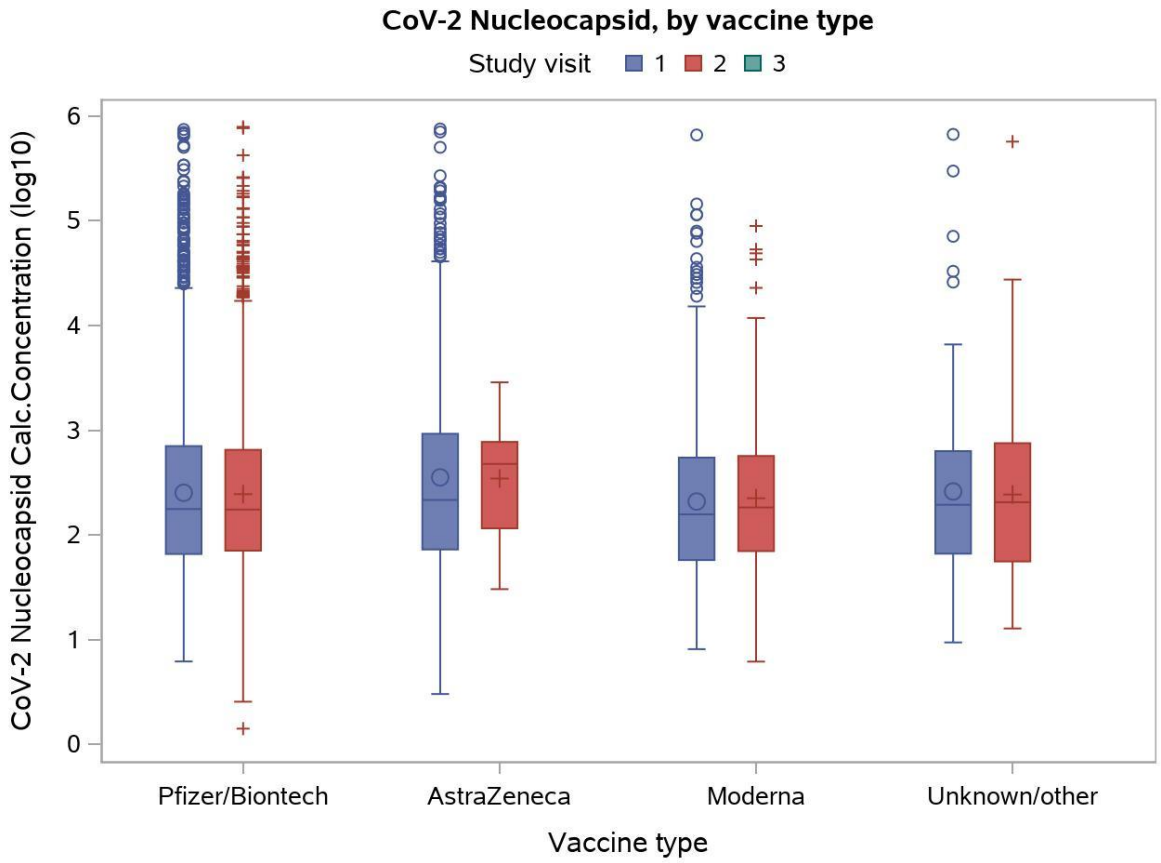


Figure 5 Distribution of CoV-2 Nucleocapsid levels at each study visit (see Table 6 for the number included at each time point)



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 5.

Table 7 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

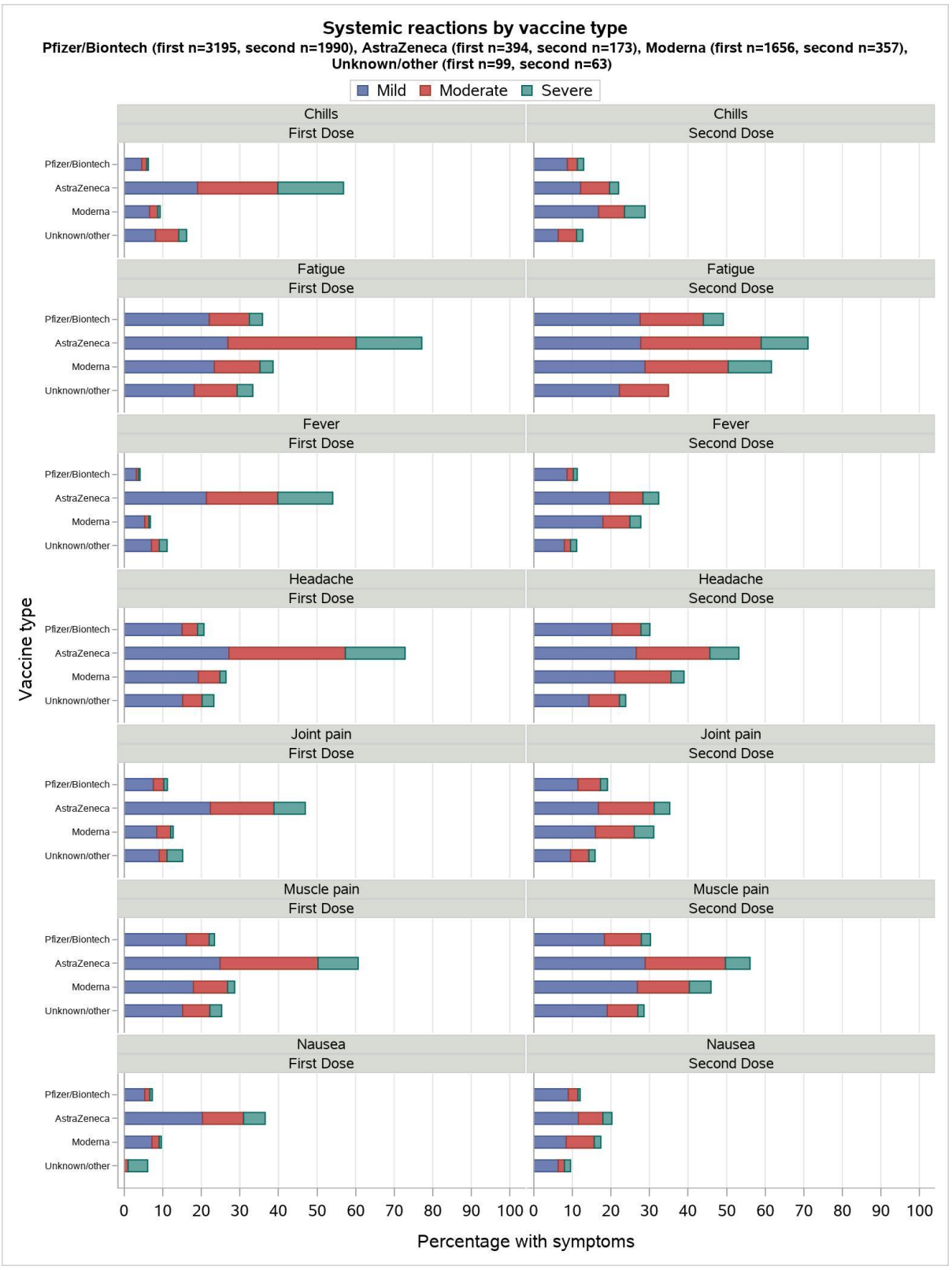
Table 8 outlines the number of participants reporting any local or systemic reactions within 7 days of vaccination. Note that participants can report multiple symptoms. The percentages are out of the total number of participants who had completed the symptoms form at the time of data extraction. All 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 8 Number & percent reporting local/systemic reactions within 7 days post vaccination overall, all and by vaccination

	Total		*Pfizer/Biontech*		*AstraZeneca*		*Moderna*		*Unknown/Other*	
	First (N=5344)	*Second (N=2583)*	*First (N=3195)*	*Second (N=1990)*	*First (N=394)*	*Second (N=173)*	*First (N=1656)*	*Second (N=357)*	*First (N=99)*	*Second (N=63)*
Number of persons (%)										
Any clinical symptoms	3044 (57.0)	1675 (64.8)	1651 (51.7)	1218 (61.2)	358 (90.9)	143 (82.7)	978 (59.1)	280 (78.4)	57 (57.6)	34 (54.0)
Any local symptoms at injection site	4105 (76.8)	1927 (74.6)	2276 (71.2)	1406 (70.7)	346 (87.8)	161 (93.1)	1418 (85.6)	312 (87.4)	65 (65.7)	48 (76.2)

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



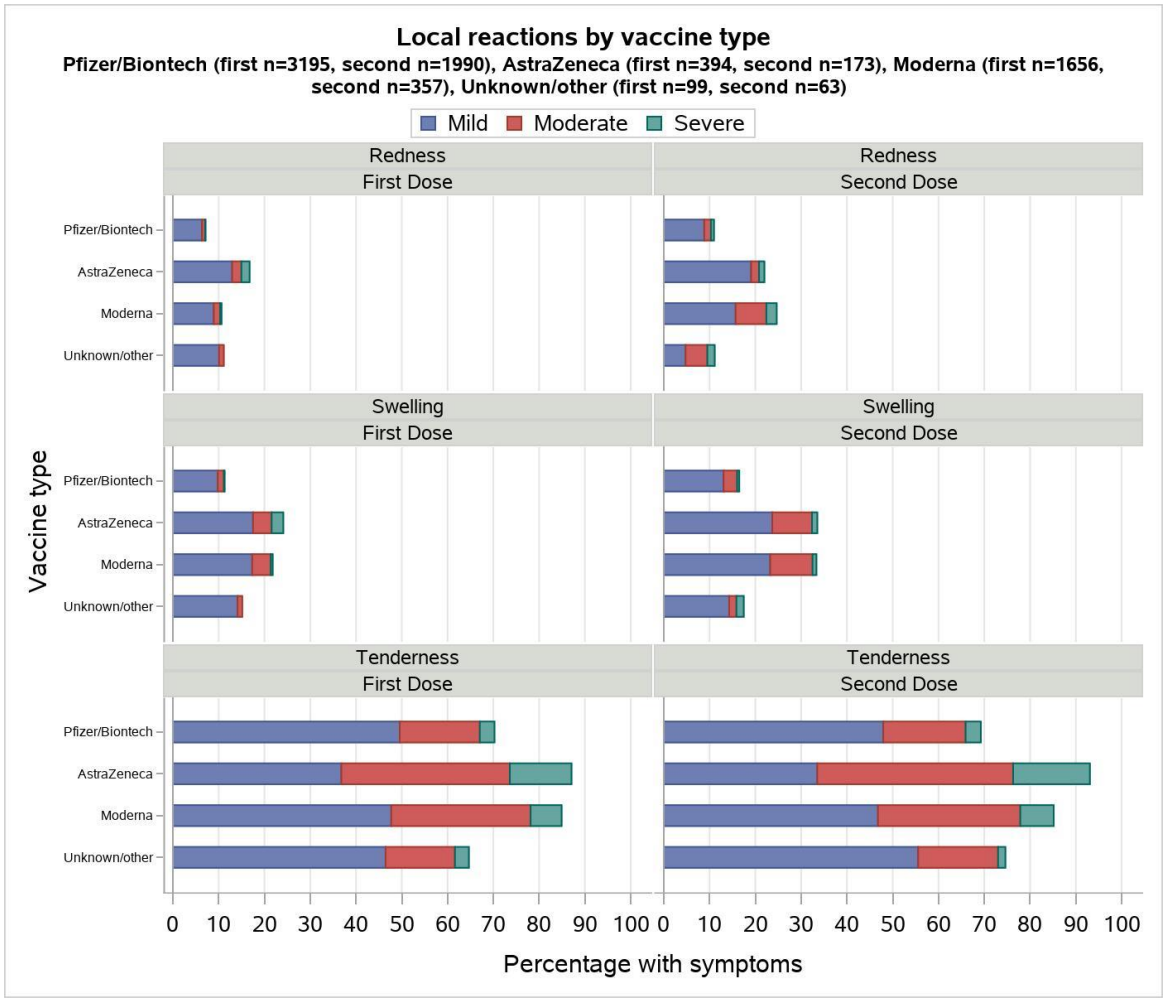

Local reactions by vaccine type
Pfizer/Biontech (first n=3195, second n=1990), AstraZeneca (first n=394, second n=173), Moderna (first n=1656, second n=357), Unknown/other (first n=99, second n=63)
Mild
Moderate
Severe
Redness
First Dose
Redness
Second Dose
Swelling
First Dose
Swelling
Second Dose
Tenderness
First Dose
Tenderness
Second Dose
Vaccine type
Pfizer/Biontech
AstraZeneca
Moderna
Unknown/other
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*

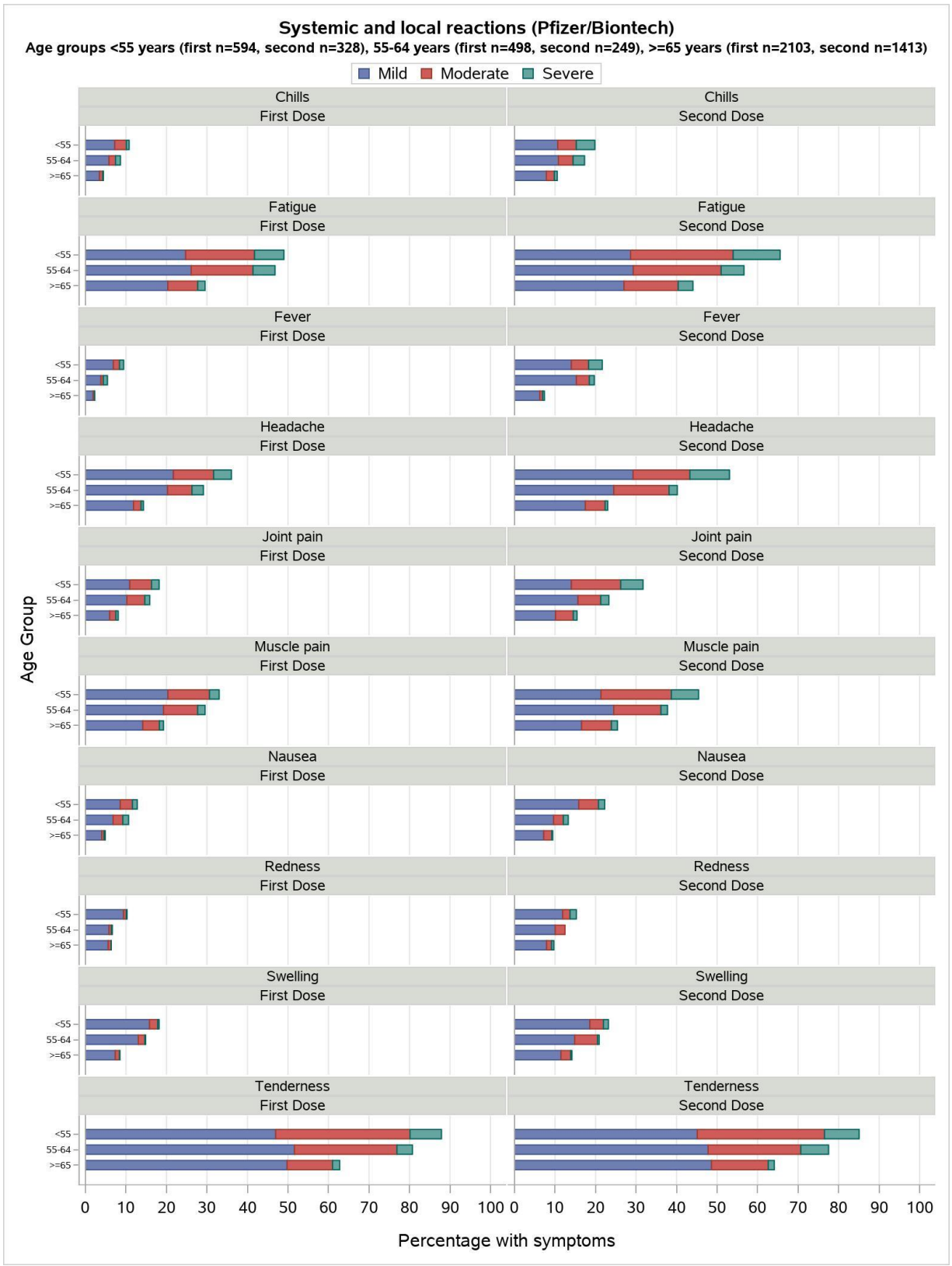


*Figure 8 Percentage of participants reporting systemic and local symptoms following **1st & 2nd dose** of AstraZeneca, by age group. Data in the >65 group not shown due to small numbers.*

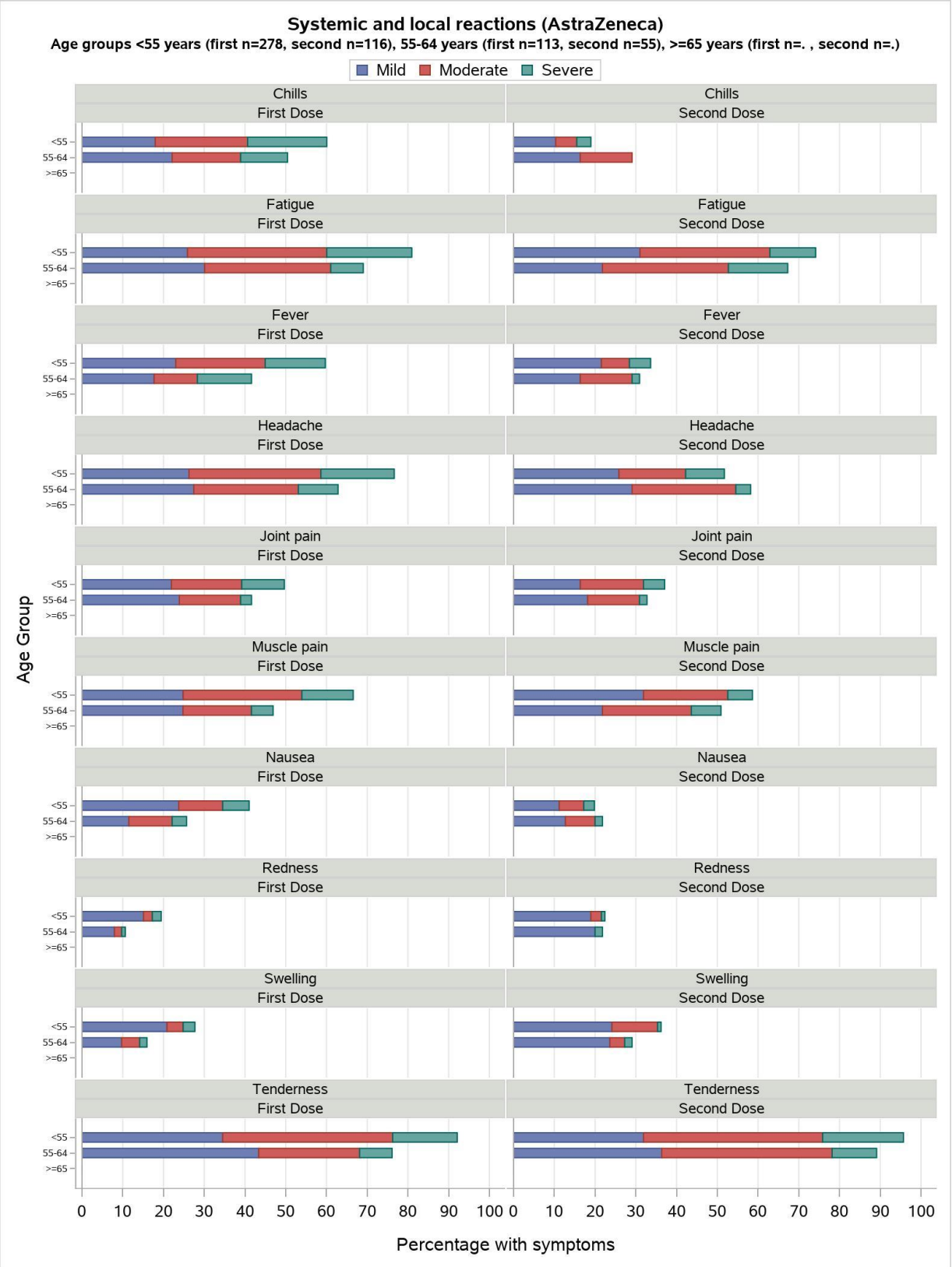


Figure 9 Percentage of participants reporting systemic and local symptoms following 1st dose & 2nd dose of Moderna, by age group

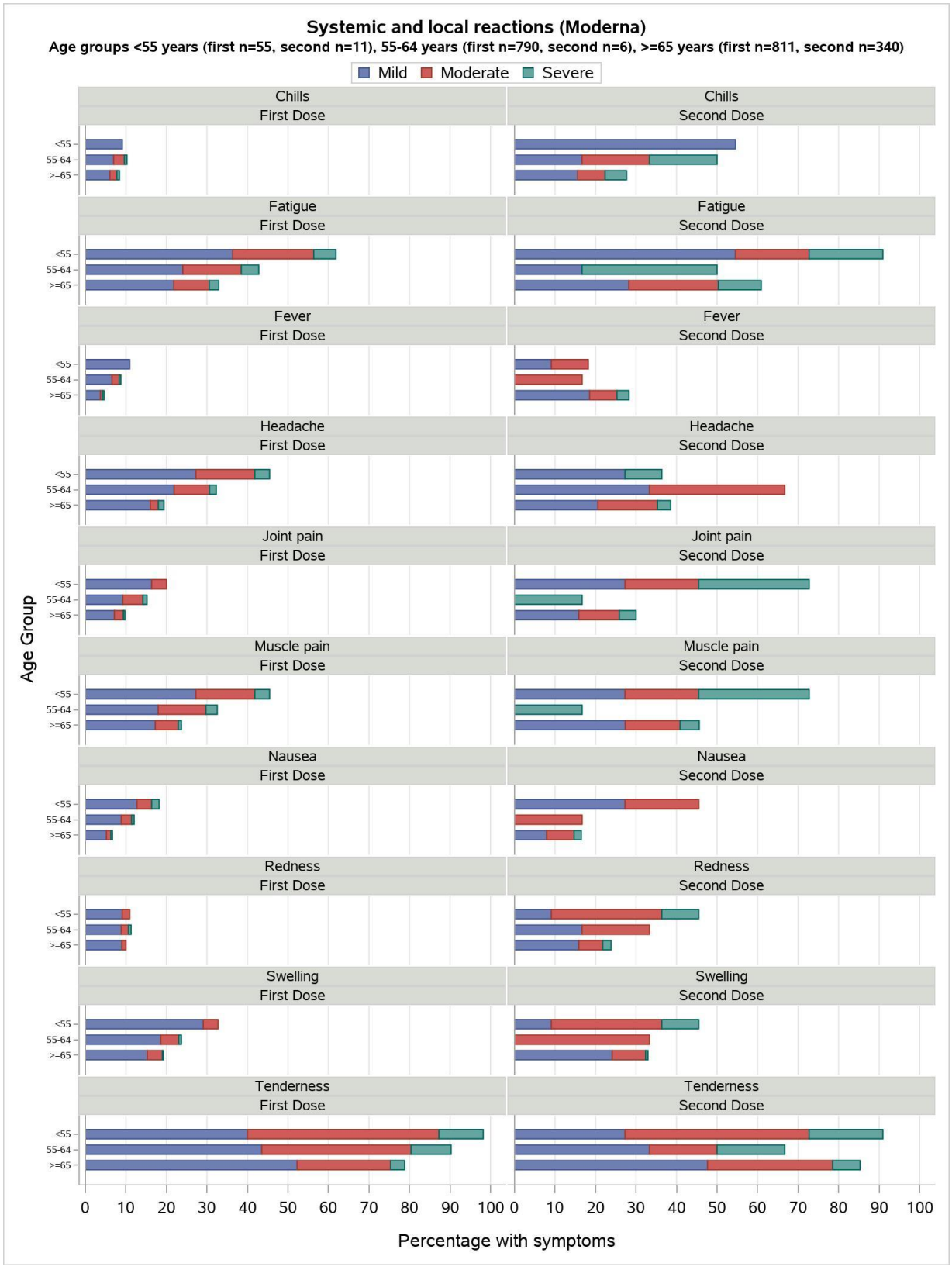


*Figure 10 Percentage of participants reporting systemic and local symptoms following **1st & 2nd dose** of Pfizer/Biontech, by gender*

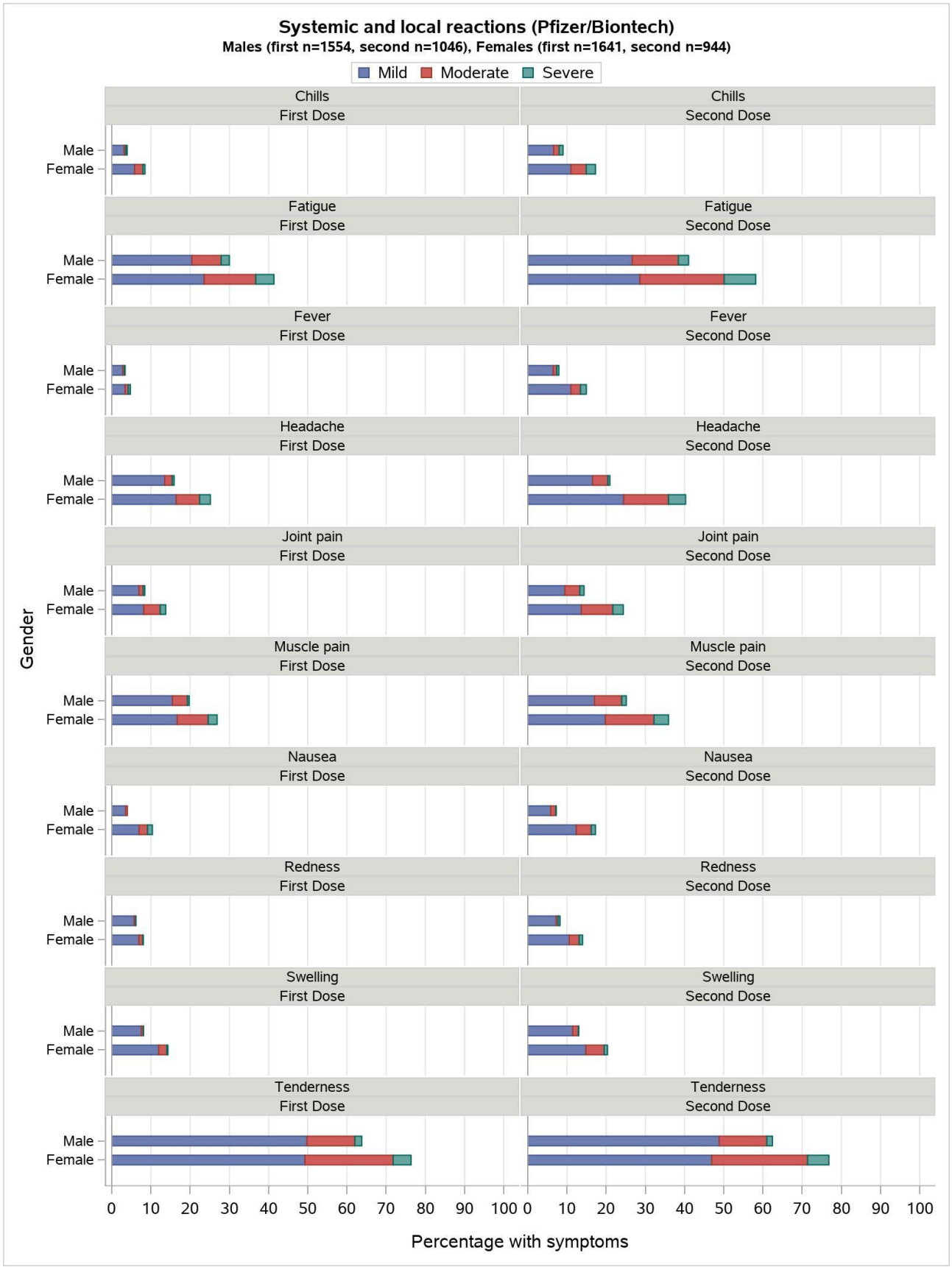


*Figure 11 Percentage of participants reporting systemic and local symptoms following **1st dose and 2nd dose** of AstraZeneca, by gender*

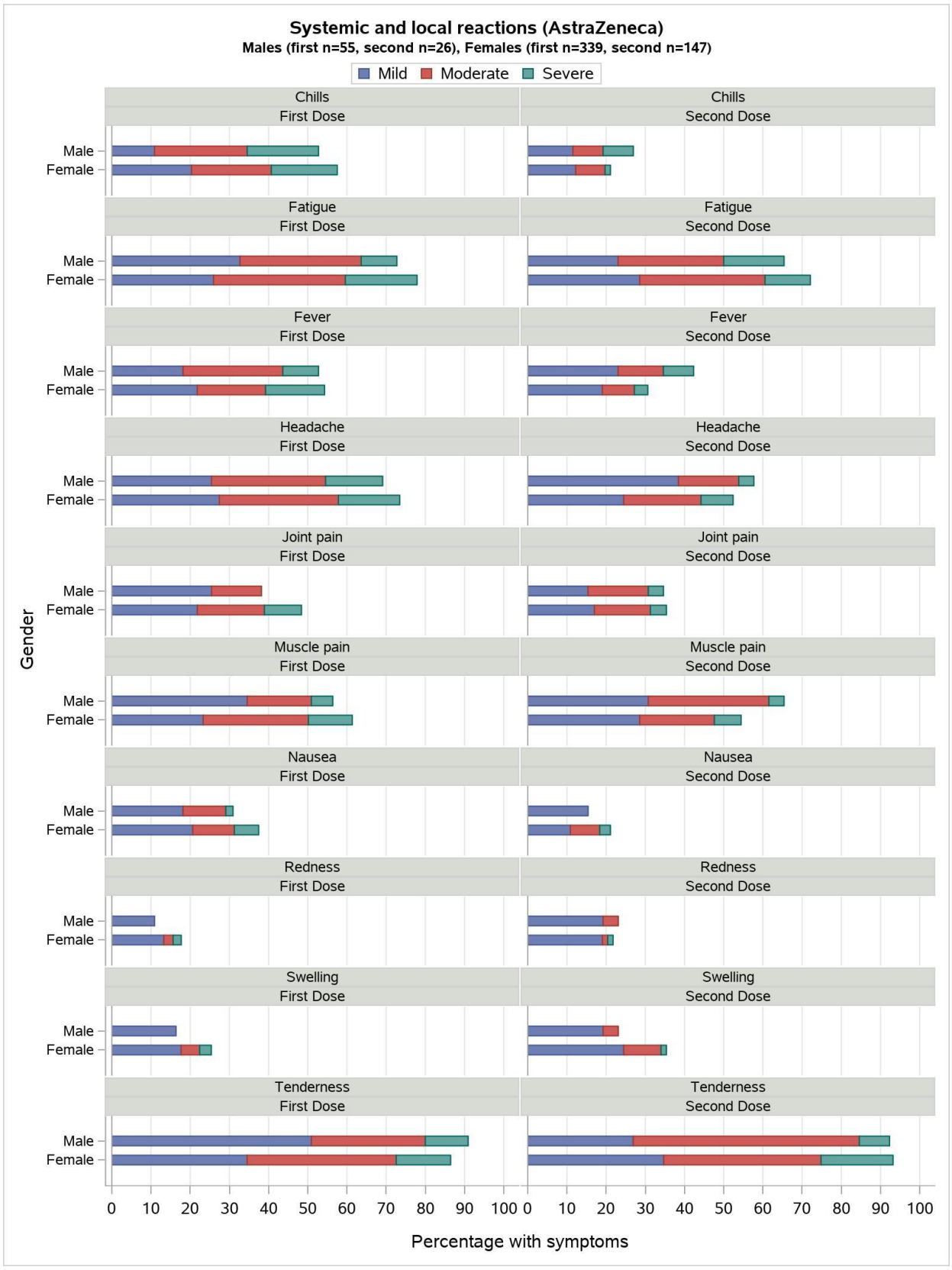
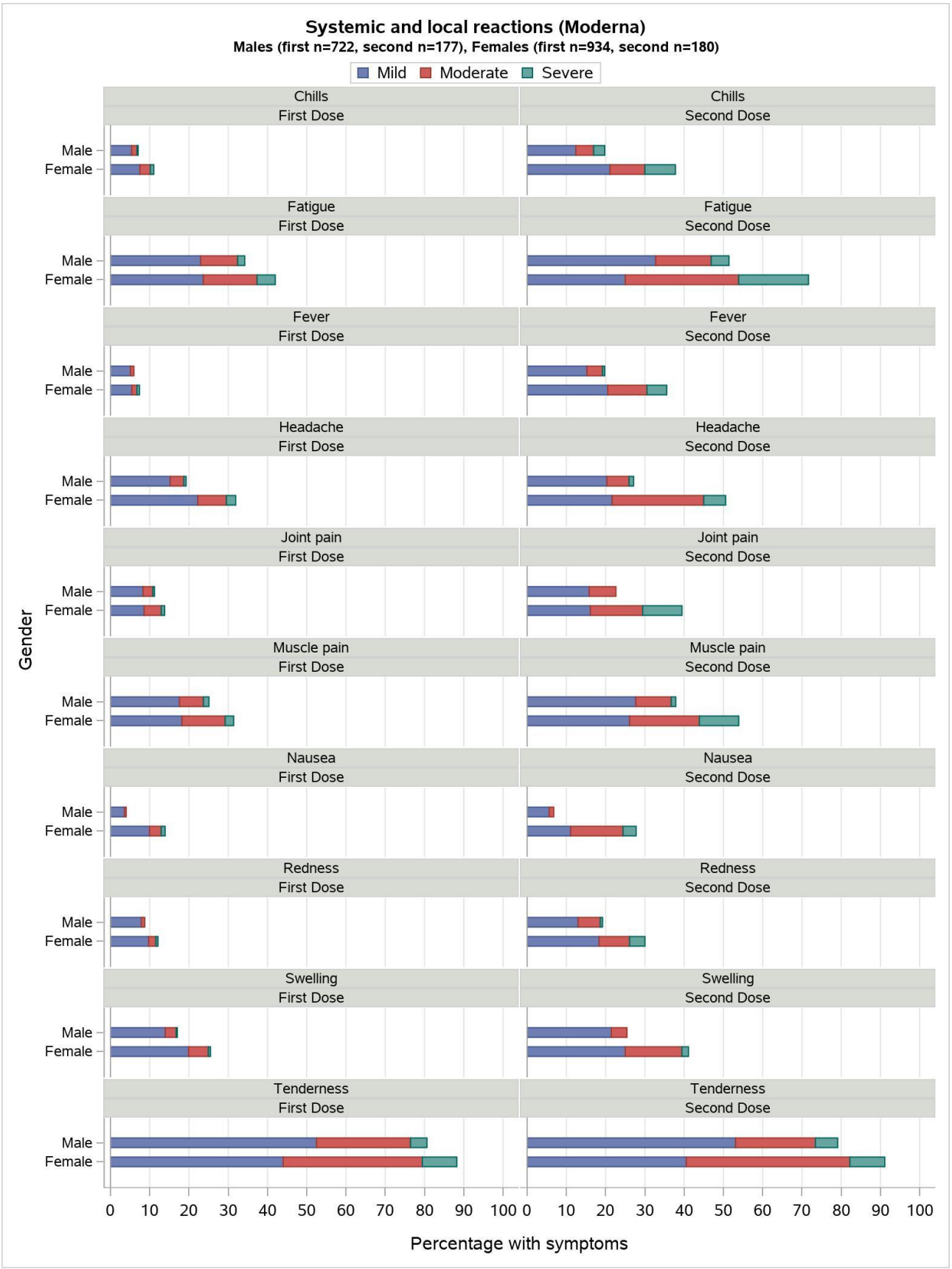


*Figure 12 Percentage of participants reporting systemic and local symptoms following **1st dose and 2nd dose** of Moderna, by gender*



Adverse and Serious Adverse Events

This section gives an overview of the AEs (Table 9) and SAEs (Table 10) reported in the study thus far. The data are first shown overall and by vaccine type.

Table 9 Overview of AEs (grade 3 and 4) reported by vaccine

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Number of persons (%)					
At least one Adverse Event reported	205 (3.2)	134 (3.7)	36 (7.0)	27 (1.3)	8 (7.1)
Number of AE					
Total number of AE reported (N, % of AE)	256 (100)	167 (100)	44 (100)	30 (100)	15 (100)

Table 10 Overview of SAEs reported by vaccine

		Vaccine type			
	Total (N=6333)	*Pfizer/Biontech (N=3612)*	*AstraZeneca (N=517)*	*Moderna (N=2091)*	*Unknown/other (N=113)*
Total number of participants reporting any SAE (N, %)	46 (0.7)	39 (1.1)	<5*	<5*	<5*
Total number of SAE reported (N, % of SAE)	54 (100)	46 (100)	<5*	<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.