ENFORCE

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

Monthly Report

Report number: 12

Date Report: 2nd November 2023

Date of data extract: 30th October 2023

Report prepared by: The ENFORCE Consortium

Approved by: ENFORCE Scientific Steering Committee

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Summary of key changes from previous report

This report is split into two parts, the first looks at participant outcomes 2 years after receiving their first vaccine dose and the second reports on the individuals who have agreed to remain in the study beyond the initial two year period.

Overview of 2 year antibody responses

This section provides an overview of the antibody responses for individuals enrolled in ENFORCE who returned for their 2 year study visit. The data included in this report are presented by the number of vaccine doses a participant had received prior to their 2 year study visit. Information in also provided on the number of participants experiencing breakthrough infection during the study period and the number of deaths which have occurred.

Study continuation beyond 2 years

The characteristics of individuals who consented to remain in the study beyond the initial 2 year study period are presented and compared to those who have withdrawn.

This report also provides an overview of the number of participants who have received a new SARS-CoV-2 vaccine dose in the autumn of 2023 and how many have had an X or Xc study visit corresponding to the new vaccine dose. Further, an overview of any local or systemic reactions for vaccines received during autumn 2023 are included in this report. This report also includes all SAEs and AE's reported following receipt a new vaccine dose in autumn 2023.

The serology results of the X and Xc study visits occurring in autumn of this year are not included in this report but will be included in subsequent reports.

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 based on the data stored in REDCap from the case report forms (CRFs) and online symptoms forms. Data on serum antibody quantification using ELISA (Wantai) were provided by the SSI and the multiantigen serological tests by Aarhus University Hospital.

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

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

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

Definitions

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

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

For the multiantigen serological tests, the geometric mean and 95% confidence intervals (CI) for the antibody levels against the Receptor Binding Domain, the complete Spike protein and the Nucleocapsid at each study visit are reported. The calibration curve used to calculate antibody concentrations are performed by fitting the signals from the calibrators in a 4-parameter sigmoidal dose-response model. Antibody concentrations can then be determined from their ECL signals by backfitting to the calibration curve.

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

A complete list of the AEs and SAEs reported for all new vaccine doses received from September 2023 onwards is provided. All SAEs and AEs are coded using MedDRA and are presented using the preferred terms and ordered alphabetically by system organ class.

Overview of 2 year antibody responses

The section gives an overview of the participants in the study who returned for their 2 year study visit.

Participant demographics

Of the 6943 initially enrolled in ENFORCE and contributing to previous reports 5202 (75%) returned for their study visit 2 years after receiving their first vaccine dose. Table 1 gives an overview of the characteristics of the initial cohort and the sub-group who returned for the 2 year visit. Characteristics were similar in those with a 2 year visit compared to the cohort overall.

Table 1 Participant characteristics of the initial cohort and the sub-group who returned for the 2 year visit

	Enrolled (N=6943)	*2 year visit (N=5202)*
Age at enrolment (median, IQR)	64 (53, 75)	64 (55, 75)
Age Group (N, %)		
<55	1972 (28.4)	1297 (24.9)
55-64	1762 (25.4)	1364 (26.2)
>=65	3209 (46.2)	2541 (48.8)
Gender (N, %)		
Male	3014 (43.4)	2265 (43.5)
Female	3929 (56.6)	2937 (56.5)
Original Vaccine type (N,%)		
Pfizer-BioNTech	3824 (55.1)	2740 (52.7)
Moderna	2620 (37.7)	2136 (41.1)
AstraZeneca/mRNA	499 (7.2)	326 (6.3)
Vaccine priority group (N,%)		
1. Individuals at increased risk	1599 (23.0)	1102 (21.2)
2. Health care workers	590 (8.5)	392 (7.5)
3. General population	4754 (68.5)	3708 (71.3)

Table 2 gives an overview of the participant demographics by the number of vaccine doses received prior to their 2 year study visit. The majority (77%) of the 5202 participants with a 2 year study visits had received 4 doses of vaccine. Individuals who have received at least 5 doses of vaccine were more likely to be those at increased risk and mainly aged ≥ 65 years old. Those who had only received 3 doses were mainly younger individuals (aged <55 years old).

Table 2 Participant demographics by number of vaccine doses received at 2 year visit

		Vaccine status at 2 year visit			
	Total (N=5202)*	*3 doses (N=809)*	*4 doses (N=4004)*	*5 doses (N=310)*	*p-value*
Age at enrolment (median, IQR)	64 (55, 75)	45 (40, 54)	68 (59, 76)	67 (57, 73)	.
Age Group (N, %)					<.0001
<55	1297 (24.9)	626 (77.4)	568 (14.2)	64 (20.6)	.
55-64	1364 (26.2)	122 (15.1)	1154 (28.8)	64 (20.6)	.
>=65	2541 (48.8)	61 (7.5)	2282 (57.0)	182 (58.7)	.
Gender (N, %)					<.0001
Male	2265 (43.5)	272 (33.6)	1808 (45.2)	153 (49.4)	.
Female	2937 (56.5)	537 (66.4)	2196 (54.8)	157 (50.6)	.
Original Vaccine type (N,%)					<.0001
Pfizer-BioNTech	2740 (52.7)	239 (29.5)	2198 (54.9)	272 (87.7)	.
Moderna	2136 (41.1)	437 (54.0)	1627 (40.6)	36 (11.6)	.
AstraZeneca/mRNA	326 (6.3)	133 (16.4)	179 (4.5)	2 (0.6)	.
Vaccine priority group (N,%)					<.0001
1. Individuals at increased risk	1102 (21.2)	121 (15.0)	702 (17.5)	258 (83.2)	.
2. Health care workers	392 (7.5)	147 (18.2)	234 (5.8)	7 (2.3)	.
3. General population	3708 (71.3)	541 (66.9)	3068 (76.6)	45 (14.5)	.
Days from last vaccine dose (median, IQR)	194 (166, 227)	519 (489, 538)	187 (164, 210)	146 (132, 164)	.

*Note individuals who had received <3 doses (n= 67) and those who had received > 5 doses (n=12) are included in the overall characteristics but due to small numbers their characteristics are not presented separately.

Outcomes

Primary outcome

From the multiantigen serological tests, the geometric mean (GM) and 95% confidence intervals (CI) for the antibody levels against the complete Spike protein IgG and the Receptor Binding Domain (RBD) at each main study visit are reported in Table 3 for individuals who completed their 2 year study visit.

Table 3 Presence of antibodies at study visit, Receptor-Binding Domain (RBD) and Spike antibody

		Vaccine status at 2 year visit		
	Total (N=5202)*	*3 doses (N=809)*	*4 doses (N=4004)*	*5 doses (N=310)*
Study visit data (N, % of total)				
Visit 1 (enrolment)	5171 (99.4)	804 (99.4)	3982 (99.5)	306 (98.7)
Visit 2 (prior to second vaccination)	4975 (95.6)	741 (91.6)	3873 (96.7)	296 (95.5)
Visit 3 (3 months after first vaccination)	4853 (93.3)	699 (86.4)	3778 (94.4)	303 (97.7)
Visit 4 (6 months after first vaccination)	4958 (95.3)	732 (90.5)	3900 (97.4)	252 (81.3)
Visit 5 (1 year after first vaccination)	4923 (94.6)	780 (96.4)	3923 (98.0)	152 (49.0)
Visit 6 (2 years after first vaccination)	4846 (93.2)	757 (93.6)	3723 (93.0)	296 (95.5)
Total spike IgG (GM, 95% CI)				
Enrolment	103 (99, 108)	124 (111, 140)	101 (96, 106)	81 (67, 97)
Visit 2	28309 (26889, 29804)	66432 (60030, 73516)	29251 (27772, 30809)	2154 (1585, 2927)
Visit 3	178212 (171768, 184898)	286175 (268411, 305114)	192875 (186713, 199241)	25732 (19066, 34728)
Visit 4	85508 (82287, 88855)	147046 (136085, 158891)	86832 (83575, 90215)	14263 (10679, 19050)
Visit 5	403457 (395841, 411219)	430223 (412861, 448316)	411776 (404487, 419197)	230908 (175125, 304460)
Visit 6	437837 (430204, 445605)	378424 (360605, 397123)	473602 (467043, 480252)	269392 (229284, 316515)
CoV-2 Receptor-Binding Domain (GM, 95% CI)				
Enrolment	58 (56, 60)	76 (68, 83)	55 (53, 58)	47 (40, 56)
Visit 2	9300 (8794, 9835)	23430 (20892, 26276)	9533 (8999, 10100)	649 (480, 878)
Visit 3	97986 (93729, 102435)	183114 (168069, 199506)	106259 (102044, 110649)	9730 (6992, 13538)
Visit 4	41213 (39449, 43056)	78071 (71058, 85775)	41828 (40044, 43690)	5076 (3714, 6936)

		Vaccine status at 2 year visit		
	Total (N=5202)*	*3 doses (N=809)*	*4 doses (N=4004)*	*5 doses (N=310)*
Visit 5	314970 (306491, 323685)	355889 (335516, 377499)	320792 (312154, 329669)	151515 (107306, 213938)
Visit 6	408164 (397444, 419172)	336612 (314595, 360170)	456907 (446211, 467860)	195335 (157650, 242027)

GM: Geometric Mean

*Note individuals who had received < 3 doses (n= 67) and those who had received > 5 doses (n=12) are included in the overall results but due to small numbers they are not presented separately.

Figure 1 and Figure 2 show the distribution of the antibodies against the complete Spike protein IgG and the RBD respectively. Data are presented at each of the key study visits, including study visits which occurred 28 days after the 3rd and 4th vaccine doses (where available) and stratified by the number of vaccine doses received prior to the 2 year study visit. Similarly, Figure 3 and Figure 4 show the distribution of the Spike and RBD ACE2 receptor binding antibodies at each study visit by the number of vaccine doses received prior to the 2 year study visit.

Figure 1 Distribution of CoV-2 Spike antibody levels at each study visit, by number of doses received prior to the 2 year study visit

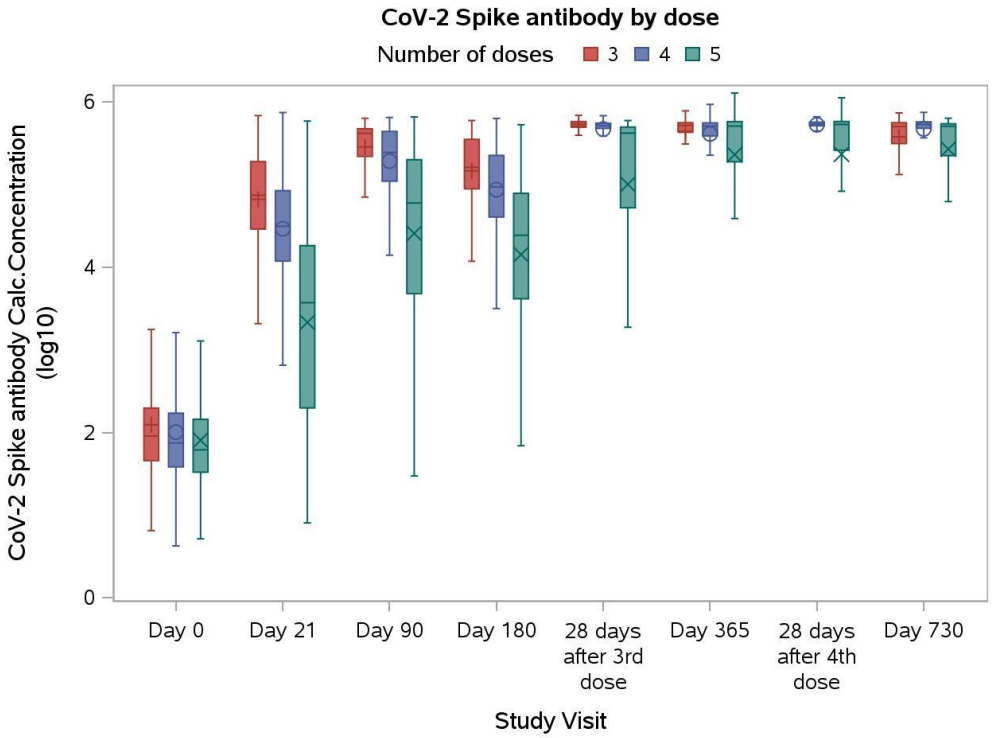


Figure 2 Distribution of CoV-2 CoV-2 Receptor-Binding Domain (RBD) antibody levels at each study visit, by number of doses received prior to the 2 year study visit

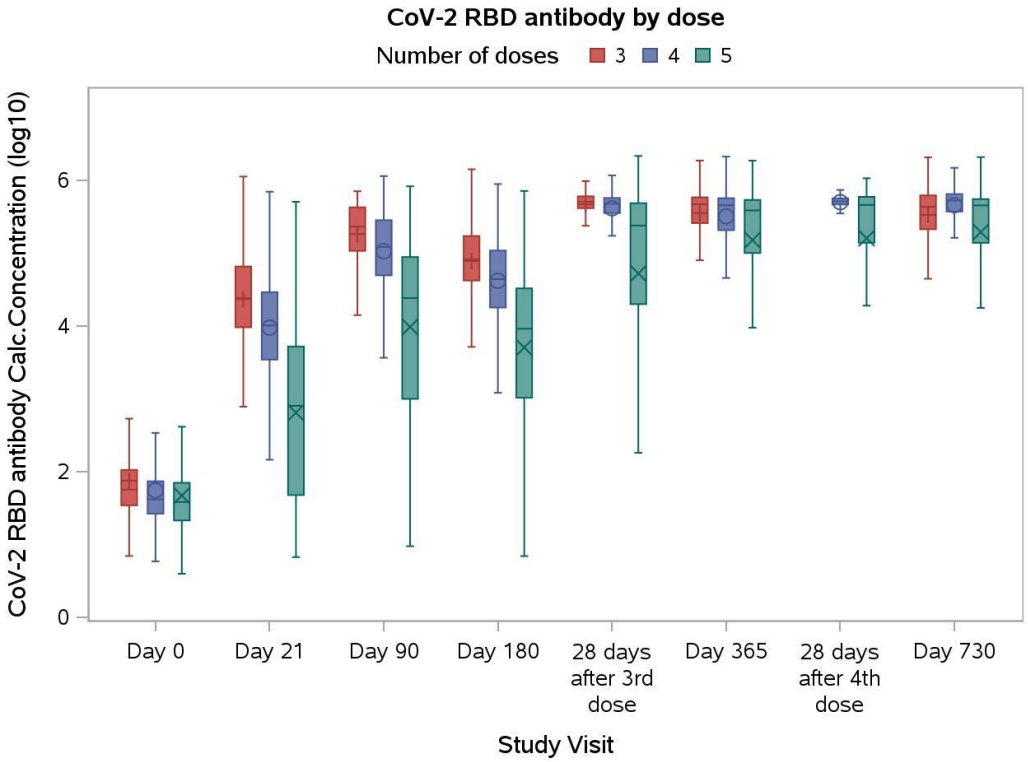


Figure 3 Distribution of spike ACE2 receptor blocking antibodies at each study visit, by number of doses received prior to the 2 year study visit

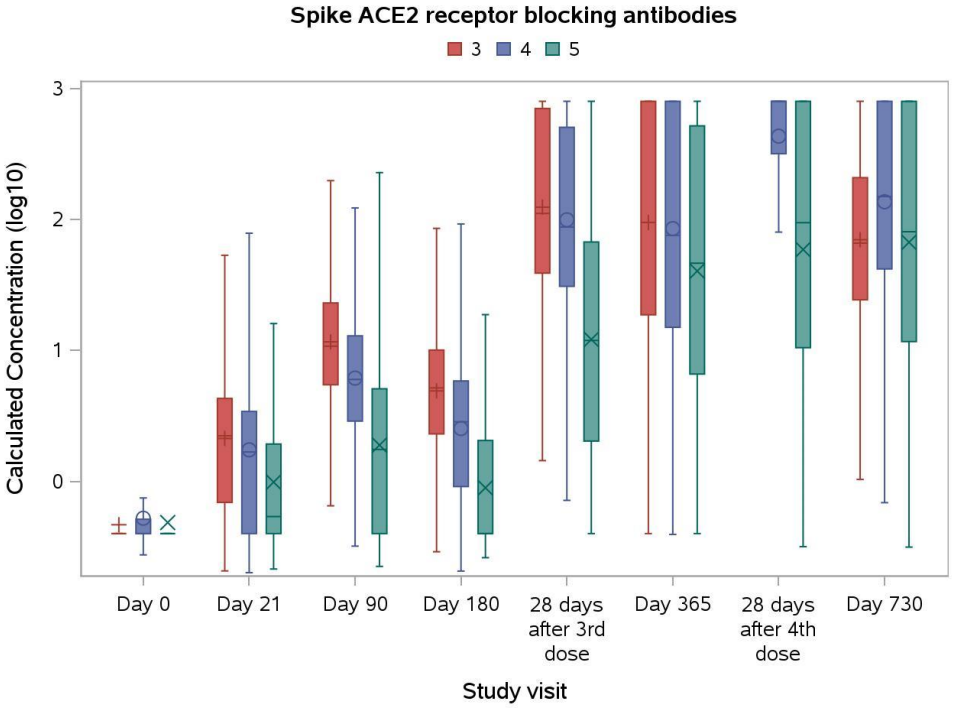
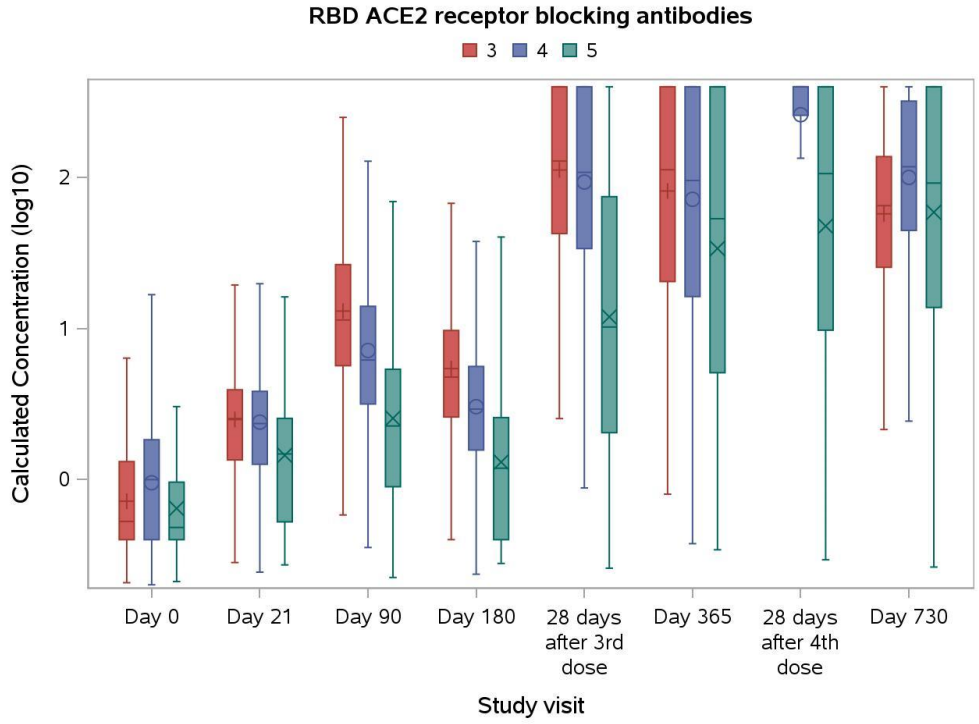


Figure 4 Distribution of RBD ACE2 receptor blocking antibodies at each study visit, by number of doses received prior to the 2 year study visit



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 4. Table 5 shows the number and percentage with nucleocapsid titers >3000 U/mL at each main study visit.

Overall, half of the cohort had tested positive for SARS-CoV-2 at least once in the 2 years since their first vaccination and 70% had nucleocapsid titers >3000 U/mL. A higher proportion of individuals who had received only 3 vaccines by their 2 year study visit had experienced a breakthrough infection either defined by a positive PCR test (63%) or by nucleocapsid titers >3000 U/mL (79%) at their 2 year study visit compared to those who had received 4 (47% and 68%) or 5 vaccine doses (48% and 58%).

Table 4 Number of participants testing positive for SARS-CoV-2, by number of doses received at 2 year visit

		Vaccine status at 2 year visit		
	Total (N=5202)	*3 Doses (N=809)*	*4 Doses (N=4004)*	*5 Doses (N=310)*
Ever tested for SARS-CoV-2 reported via KIDS (N, % of total)	5009 (96.3)	797 (98.5)	3840 (95.9)	294 (94.8)
Number of PCR tests since first vaccine dose (median, IQR)	5 (2, 10)	8 (3, 15)	4 (2, 9)	6 (2, 11)
Number of antigen tests since first vaccine dose (median, IQR)	3 (1, 7)	5 (2, 9)	3 (1, 6)	2 (0, 6)
Number PCR positive for SARS-CoV-2 reported via KIDS (N, % of total)	2584 (49.7)	510 (63.0)	1867 (46.6)	150 (48.4)
Days from first vaccine dose to first SARS-CoV2 positive test (median, IQR)	314 (261, 354)	263 (223, 338)	317 (273, 356)	347 (323, 398)
Age Group (n, % in category)				
<55	854 (65.8)	428 (68.4)	352 (62.0)	41 (64.1)
55-64	694 (50.9)	58 (47.5)	593 (51.4)	26 (40.6)
>=65	1036 (40.8)	24 (39.3)	922 (40.4)	83 (45.6)
Gender (n, % in category)				
Male	1075 (47.5)	152 (55.9)	830 (45.9)	69 (45.1)
Female	1509 (51.4)	358 (66.7)	1037 (47.2)	81 (51.6)

*Note individuals who had received <3 doses (n= 67) and those who had received > 5 doses (n=12) are included in the overall results but due to small numbers their results are not presented separately

Table 5 Number of participants with nucleocapsid titers >3000 U/mL at each study visit

		Vaccine status at 2 year visit		
	Total (N=5202)	*3 Doses (N=809)*	*4 Doses (N=4004)*	*5 Doses (N=310)*
CoV-2 Nucleocapsid (SERO)				
Enrolment (n, %)				
<=3000	4662 (90.3)	730 (90.9)	3578 (90.0)	285 (93.1)
>3000	502 (9.7)	73 (9.1)	398 (10.0)	21 (6.9)
Visit 2 (n, %)				
<=3000	4453 (89.6)	658 (88.8)	3463 (89.5)	276 (92.9)
>3000	518 (10.4)	83 (11.2)	405 (10.5)	21 (7.1)
Visit 3 (n, %)				
<=3000	4252 (87.6)	623 (89.1)	3292 (87.1)	275 (90.8)
>3000	602 (12.4)	76 (10.9)	487 (12.9)	28 (9.2)
Visit 4 (n, %)				
<=3000	4235 (85.5)	617 (84.3)	3337 (85.6)	221 (88.0)
>3000	720 (14.5)	115 (15.7)	563 (14.4)	30 (12.0)
Visit 5 (n, %)				
<=3000	2291 (46.5)	275 (35.3)	1904 (48.5)	92 (60.5)
>3000	2632 (53.5)	505 (64.7)	2019 (51.5)	60 (39.5)
Visit 6 (n, %)				
<=3000	1505 (30.6)	159 (20.9)	1203 (31.7)	125 (42.1)
>3000	3416 (69.4)	601 (79.1)	2590 (68.3)	172 (57.9)

*Note individuals who had received <3 doses (n= 67) and those who had received > 5 doses (n=12) are included in the overall results but due to small numbers their results are not presented separately

Deaths

There were 101 (1.3%) deaths reported in the study during the 2 year period follow receipt of the first vaccine dose. 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 93 deaths recorded in the CPR registry that were outside of the period for reporting SAE (Table 6).

Table 6 Characteristics of participants who died in the two years following their first SARS-CoV-2 vaccine dose

	Total (N=101)
Number of persons (%)	
Age Group	
<55	7 (6.9)
55-64	19 (18.8)
>=65	75 (74.3)
Gender	
Male	57 (56.4)
Female	44 (43.6)
Death reported as an SAE	
Yes	8 (7.9)
No	93 (92.1)
Reasonable probability of relatedness to vaccination	
No	8 (100)
Median (interquartile range, IQR)	
Age at enrolment (years)	74 (64, 80)
Time from first vaccine dose (days)	414 (281, 570)

Study continuation beyond 2 years

Individuals who returned for their 2 year study visit were asked if they were willing to continue participate in ENFORCE beyond the original 2 years. The information in the following section therefore only includes information on individuals who have provided informed consent to continue in the study beyond 2 years. The question around participating in the extended study was included after some participants had already completed their two year study visit, therefore additional participants may be included in future reports if the sites subsequently obtain consents from individuals who were not asked at an earlier study visit.

Participant demographics

A total of 4416 (64%) participants consented to remain in the study beyond the initial 2 years. Table 7 gives an overview of the characteristics of those who consented compared to those who did not consent or had withdrawn or died prior to their 2 year study visit. Of those agreeing to continue in the study 47% were aged ≥65 at initial study enrolment, and 18% were individuals in the increased risk vaccine priority group.

Of 2525 not consenting for extended follow-up, approximately 50% had already withdrawn prior to their 2 years visit, including the 101 participants who had died.

Table 7 Characteristics of participants who have consented to remain in the study beyond the original 2 year period

		Consented to remain in study beyond 2 years	
	Total (N=6941)	*No (N=2525)*	*Yes (N=4416)*
Age at enrolment (median, IQR)	64 (53, 75)	61 (51, 75)	64 (54, 74)
Age Group (N, %)			
<55	1971 (28.4)	861 (34.1)	1110 (25.1)
55-64	1762 (25.4)	544 (21.5)	1218 (27.6)
>=65	3208 (46.2)	1120 (44.4)	2088 (47.3)
Gender (N, %)			
Male	3013 (43.4)	1109 (43.9)	1904 (43.1)
Female	3928 (56.6)	1416 (56.1)	2512 (56.9)
Original Vaccine type (N,%)			
Pfizer-BioNTech	3823 (55.1)	1598 (63.3)	2225 (50.4)
Moderna	2620 (37.7)	677 (26.8)	1943 (44.0)
AstraZeneca/mRNA	498 (7.2)	250 (9.9)	248 (5.6)
Vaccine priority group (N,%)			
1. Individuals at increased risk	1599 (23.0)	791 (31.3)	808 (18.3)
2. Health care workers	589 (8.5)	265 (10.5)	324 (7.3)
3. General population	4753 (68.5)	1469 (58.2)	3284 (74.4)
Enrolment date (median, IQR)	APR21 (MAR21, MAY21)	MAR21 (MAR21, MAY21)	APR21 (MAR21, MAY21)

Autumn vaccination 2023

Demographics

Table 8 gives the characteristics of participants who have a received a booster vaccine dose in October 2023 compared to those who have not. The median age of those who received a vaccine this Autumn was significantly higher than those who did not (72 years vs. 59 years, p<0.0001). Ninety percent of participants vaccinated in October 2023 had previously received 4 doses and were receiving their 5th vaccine dose (n=1329). Almost all participants vaccinated in October 2023 received a bivalent vaccine with Omicron XBB.1.5, the majority from Pfizer-BioNTech (84%).

Table 8 Participant demographics comparing those who received a booster vaccine in October 2023 to those who did not

		Autumn Vaccine		
	Total (N=4416)	*No (N=2933)*	*Yes (N=1483)*	*p-value*
Age at enrolment (median, IQR)	64 (54, 74)	59 (51, 69)	72 (67, 78)	.
Age Group (N, %)				<.0001
<55	1110 (25.1)	1036 (35.3)	74 (5.0)	.
55-64	1218 (27.6)	975 (33.2)	243 (16.4)	.
>=65	2088 (47.3)	922 (31.4)	1166 (78.6)	.
Gender (N, %)				<.0001
Male	1904 (43.1)	1180 (40.2)	724 (48.8)	.
Female	2512 (56.9)	1753 (59.8)	759 (51.2)	.
Original Vaccine type (N,%)				<.0001
Pfizer-BioNTech	2225 (50.4)	1286 (43.8)	939 (63.3)	.
Moderna	1943 (44.0)	1406 (47.9)	537 (36.2)	.
AstraZeneca/mRNA	248 (5.6)	241 (8.2)	7 (0.5)	.
Vaccine priority group (N,%)				<.0001
1. Individuals at increased risk	808 (18.3)	453 (15.4)	355 (23.9)	.
2. Health care workers	324 (7.3)	293 (10.0)	31 (2.1)	.
3. General population	3284 (74.4)	2187 (74.6)	1097 (74.0)	.
Number of doses previously received (N,%)				<.0001
≤3 doses	743 (16.8)	732 (25.0)	11 (0.7)	.
4 doses	3430 (77.7)	2101 (71.6)	1329 (89.6)	.
≥5 doses	243 (5.5)	100 (3.4)	143 (9.6)	.

Study visits

Of the 1483 participants who have received a booster vaccine dose in October 2023, 885 (60%) had a study visit prior to their booster dose and so far 59 (4%) have had a study visit a median of 21 days after their booster dose, 57 (4%) had both a pre and post vaccine visit (Table 9).

Table 9 Number and percentage of participants who received a booster in October with completed study visits

	Total (N=1483)
Received a booster dose October 2023 (N, %)	1483 (100)
Visit X (0-34 days prior to booster dose) (N, %)	885 (59.7)
Days from study visit to booster dose (median, IQR)	6 (2-11)
Visit Xc (28 days after fifth dose) (N, %)	59 (4.0)
Days from booster dose to study visit (median, IQR)	21 (20, 22)

Safety and Monitoring

Local and systemic reactions for 5th vaccine doses received in October 2023

Table 10 outlines the number of participants reporting any local or systemic reactions after receiving their 5th vaccination in October. Data is limited to individuals where the vaccine received in October was their 5th booster dose, due to very small number in the other groups. The total number of participants experiencing any symptoms are reported as well as the number experiencing each individual symptom. To date from the 1329 participants who received a 5th dose in October 2023, 568(43%) completed a symptom form for the first 7 days and 431 (32%) for the following 8-14 days after vaccination.

Table 10 Number and percentage reporting local/systemic reactions within 0-7 days and 8-14 days following a 5th vaccine dose, overall for booster vaccine received in October

	Total	
	First 7 days (N=568)	*8-14 days (N=431)*
Number of persons (%)		
Any clinical symptoms	320 (56.3)	125 (29.0)
Any local symptoms at injection site	429 (75.5)	91 (21.1)
Symptoms reported		
Muscle pain	171 (30.5)	61 (14.3)
Joint pain	102 (18.4)	41 (9.8)
Fatigue	214 (38.4)	91 (21.7)
Fever	60 (10.9)	12 (2.9)
Headache	147 (26.6)	52 (12.5)
Nausea	49 (9.0)	17 (4.1)
Chills	60 (10.9)	17 (4.1)
Local symptoms at injection site		
Redness	87 (16.2)	23 (5.5)
Swelling	136 (25.8)	22 (5.4)
Tenderness	421 (75.4)	88 (21.1)
Median (interquartile range, IQR)		
Number of symptom boxes completed	10 (10, 10)	10 (10, 10)

Adverse and Serious Adverse Events

This section gives an overview of the AEs and SAEs reported following a booster vaccine dose received in October 2023. There have been <5 AE or SAE reported so far from the 1483 participants who received a new booster dose in October 2023

Deaths

There have been eleven deaths among individuals who consented to remain in the study beyond the original 2 year period. All of these deaths occurred prior to October of this year and so none of these individuals had received a booster dose this Autumn.