ENFORCE

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

Monthly Report

Report number: 13

Date Report: 29th February 2024

Date of data extract: 16th January 2024

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Approved by: ENFORCE Scientific Steering Committee

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Finansieret af
Den Europæiske Union
NextGenerationEU

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Contents

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Summary of key changes from previous report

This report focuses on participants in ENFORCE who agreed to remain in the study beyond the initial 2-year follow-up period and received a new vaccine dose in the Autumn 2023 and prior to 31st December 2023.

The report provides an overview of the number of participants who received a new SARS-CoV-2 vaccine dose in Autumn 2023 and how many had a visit immediately before, and 28 days after the new vaccine dose. Additionally, an overview of all AEs and SAEs reported for the vaccines received in Autumn 2023 is included in this report.

Over 90% of those receiving a new vaccine in Autumn 2023 were receiving their 5th SARS-CoV-2 vaccine dose. Thus, only local or systemic reactions reported following a 5th dose in Autumn 2023 are reported. Similarly, the serology results of the study visits occurring in Autumn 2023 are presented only for individuals who received their 5th vaccine dose, due to small numbers in the other groups.

The data included in this report include results collected up to the end of study (31st December 2023).

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.

Study continuation beyond 2 years

Individuals who returned for their 2-year study visit were asked if they were willing to continue to participate in ENFORCE beyond the original 2-year period. The information in this final report therefore only includes results from individuals who have provided informed consent to continue in the study beyond 2 years and includes data up to 31st December 2023.

Participant demographics

A total of 4473 (64%) participants consented to remain in the study beyond the initial 2 years. Table 1 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 48% were aged ≥65 at initial study enrolment, and 19% were individuals in the increased risk vaccine priority group.

Of 2468 not consenting for extended follow-up, approximately 50% had already withdrawn prior to their 2-year visit, including 101 participants who had died.

Table 1 Characteristics of participants who have consented to remain in the study beyond the original 2-year period

		Consent	
	Total (N=6941)	*Not consented (N=2468)*	*Consented (N=4473)*
Age Group (N, %)			
<55	1971 (28.4)	856 (34.7)	1115 (24.9)
55-64	1762 (25.4)	536 (21.7)	1226 (27.4)
>=65	3208 (46.2)	1076 (43.6)	2132 (47.7)
Gender (N, %)			
Male	3013 (43.4)	1076 (43.6)	1937 (43.3)
Female	3928 (56.6)	1392 (56.4)	2536 (56.7)
Original Vaccine type (N, %)			
Pfizer-BioNTech	3823 (55.1)	1548 (62.7)	2275 (50.9)
Moderna	2620 (37.7)	671 (27.2)	1949 (43.6)
Adenoviral Vector/mRNA	498 (7.2)	249 (10.1)	249 (5.6)
Vaccine priority group (N, %)			
1. Individuals at increased risk	1599 (23.0)	751 (30.4)	848 (19.0)
2. Health care workers	589 (8.5)	263 (10.7)	326 (7.3)
3. General population	4753 (68.5)	1454 (58.9)	3299 (73.8)
Enrolment date (median, IQR)	APR21 (MAR21, MAY21)	MAR21 (MAR21, MAY21)	APR21 (MAR21, MAY21)

Breakthrough infections

The number of participants experiencing a positive PCR test following their first vaccination is reported in *Table 2* for the 4473 participants remaining in the study.

Overall, half of the cohort had tested positive for SARS-CoV-2 at least once since their first vaccination and prior to the end of the study (31st December 2023). A higher proportion of younger individuals (< 55 years) had experienced a breakthrough infection defined by a positive PCR test compared to those aged ≥65 years.

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

	Total (N=4473)
Ever tested for SARS-CoV-2 reported via KIDS (N, % of total)	4317 (96.5)
Number of PCR tests since first vaccine dose (median, IQR)	5 (2, 10)
Number of antigen tests since first vaccine dose (median, IQR)	3 (1, 7)
Number PCR positive for SARS-CoV-2 reported via KIDS (N, % of total)	2255 (50.4)
Days from first vaccine dose to first SARS-CoV2 positive test (median, IQR)	311 (259, 354)
Age Group (n, % in category)	
<55	732 (65.7)
55-64	637 (52.0)
>=65	886 (41.6)
Gender (n, % in category)	
Male	932 (48.1)
Female	1323 (52.2)

Autumn vaccination 2023

Demographics

Table 3 gives the characteristics of participants who received a booster vaccine dose in Autumn 2023 compared to those who did not. The median age of those who received a vaccine was significantly higher than those who did not (71 years vs. 54 years, p<0.0001). Ninety percent of participants vaccinated in Autumn 2023 had previously received 4 doses and were receiving their 5th vaccine dose (n=2370). Almost all participants vaccinated in Autumn 2023 received a bivalent vaccine with Omicron XBB.1.5, the majority from Pfizer-BioNTech (90%).

Table 3 Participant demographics comparing those who received a booster vaccine in Autumn 2023 to those who did not

		Autumn Vaccine		
	Total (N=4473)	*No (N=1840)*	*Yes (N=2633)*	*p-value*
Age at enrolment (median, IQR)	64 (55, 74)	54 (46, 59)	71 (64, 78)	.
Age Group (N, %)				<.0001
<55	1115 (24.9)	949 (51.6)	166 (6.3)	.
55-64	1226 (27.4)	733 (39.8)	493 (18.7)	.
>=65	2132 (47.7)	158 (8.6)	1974 (75.0)	.
Gender (N, %)				<.0001
Male	1937 (43.3)	672 (36.5)	1265 (48.0)	.
Female	2536 (56.7)	1168 (63.5)	1368 (52.0)	.
Original Vaccine type (N, %)				<.0001
Pfizer-BioNTech	2275 (50.9)	645 (35.1)	1630 (61.9)	.
Moderna	1949 (43.6)	970 (52.7)	979 (37.2)	.
AstraZeneca/mRNA	249 (5.6)	225 (12.2)	24 (0.9)	.
Vaccine priority group (N, %)				<.0001
1. Individuals at increased risk	848 (19.0)	202 (11.0)	646 (24.5)	.
2. Health care workers	326 (7.3)	260 (14.1)	66 (2.5)	.
3. General population	3299 (73.8)	1378 (74.9)	1921 (73.0)	.
Number of doses previously received (N, %)				<.0001
<=3 doses	742 (16.6)	707 (38.4)	35 (1.3)	.
4 doses	3479 (77.8)	1109 (60.3)	2370 (90.0)	.
>=5 doses	252 (5.6)	24 (1.3)	228 (8.7)	.

Study visits

Of the 2633 participants who have received a booster vaccine dose in Autumn 2023, 1137 (42%) had a study visit prior to their booster dose and 1352 (51%) had a study visit 28 days after their booster dose, 976 (37%) had both a pre and post vaccine visit (Table 4).

Table 4 Number and percentage of participants who received a booster in Autumn 2023 with completed study visits

	Total (N=2633)
Received a booster dose Autumn 2023 (N, %)	2633(100)
Visit X (0-14 days prior to booster dose) (N, %)	1137 (43.2)
Days from study visit to booster dose (median, IQR)	5 (2-9)
Visit Xc (28 days after fifth dose) (N, %)	1352 (51.4)
Days from booster dose to study visit (median, IQR)	28 (25, 31)

Outcomes

Primary Outcome (only in those receiving 5th vaccine dose in Autumn 2023)

As the majority of individuals (90%) were receiving a 5th vaccine in Autumn 2023 the following section is limited to the response in individuals who received a 5th dose in Autumn 2023.

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 ACE2 after the 5th vaccine dose are reported in Table 5.

*Table 5 Presence of antibodies before and after the **5th dose**, Receptor-Binding Domain (RBD) and Total Spike antibody*

	Total (N=2370)
N, with data (% of total)	
Antibody data 0-14 days before 5th dose	1022 (43.1)
Antibody data 28 days after 5th dose	807 (34.1)
ACE2 data 0-14 days before 5th dose	1015 (100)
ACE2 data 28 days after 5th dose	683 (100)
CoV-2 Receptor-Binding Domain (GM, 95%CI)	
0-14 days before 5th dose	358739 (337922, 380837)
28 days after 5th dose	534273 (518721, 550291)
CoV-2 Spike antibody (GM, 95%CI)	
0-14 days before 5th dose	413438 (397159, 430384)
28 days after 5th dose	546050 (537333, 554908)
ACE2 CoV-2 Receptor-Binding Domain (GM, 95%CI)	
0-14 days before 5th dose	72 (66, 79)
28 days after 5th dose	248 (231, 265)
ACE2 CoV-2 Spike antibody (GM, 95%CI)	
0-14 days before 5th dose	72 (65, 79)
28 days after 5th dose	339 (309, 373)

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Safety and Monitoring

Local and systemic reactions (only in those receiving 5th vaccine dose in Autumn 2023)

Table 6 outlines the number of participants reporting any local or systemic reactions after receiving their 5th vaccination in Autumn 2023. Data is limited to individuals where the vaccine received in Autumn 2023 was their 5th booster dose, due to very small numbers in the other groups. The total number of participants experiencing any symptoms are reported as well as the number experiencing each individual symptom. From the 2370 participants who received a 5th dose in Autumn 2023, 1349 (57%) completed a symptom form for the first 7 days and 1385 (59%) for the following 8-14 days after vaccination.

Table 6 Number and percentage reporting local/systemic reactions within 0-7 days and 8-14 days following a 5th vaccine dose in Autumn 2023, overall

	Total	
	First 7 days (N=1349)	*8-14 days (N=1385)*
Number of persons (%)		
Any clinical symptoms	634 (47.0)	329 (23.8)
Any local symptoms at injection site	945 (70.1)	250 (18.1)
Symptoms reported		
Muscle pain	315 (23.7)	149 (10.8)
Joint pain	183 (13.9)	106 (7.8)
Fatigue	427 (32.1)	248 (18.1)
Fever	109 (8.3)	31 (2.3)
Headache	273 (20.7)	140 (10.3)
Nausea	91 (6.9)	51 (3.8)
Chills	123 (9.4)	44 (3.2)
Local symptoms at injection site		
Redness	172 (13.2)	52 (3.8)
Swelling	264 (20.6)	64 (4.7)
Tenderness	927 (69.6)	243 (17.8)
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 vaccine dose received in Autumn 2023. AEs were reported in 39 (1.5%) out of the 2633 participants who received a new booster dose in Autumn 2023 (Table 7). Additionally, 12 SAEs have also been reported following vaccination in Autumn 2023. Details are provided in Table 8.

Table 7 Overview of AEs reported (grade 3 and grade 4) following vaccination in Autumn 2023

	Total (N=2633)
Number of persons (%)	
At least one Adverse Event reported	39 (1.5)
Age Group (n, % in category)	
<55	5 (3.0)
55-64	11 (2.2)
>=65	23 (1.2)
Gender (n, % in category)	
Male	13 (1.0)
Female	26 (1.9)

Table 8 Overview and current status of SAEs reported following vaccination in Autumn 2023

	Total (N=2633)
Total number of participants reporting any SAE (N, %)	12 (0.5)
Age Group (n, % reporting SAE)	
<55	<5*
55-64	<5*
>=65	8 (66,7)
Gender (n, % reporting SAE)	
Male	7 (58.3)
Female	5 (41.7)
Reasonable probability of relatedness to vaccination	
Yes	<5*

*Exact numbers not shown due to small numbers

Deaths

From the 4473 individuals who consented to remain in the study beyond the original 2-year period, 20 participants have died (4.2%). None of these deaths were reported as part of the SAE reporting for the Autumn 2023 booster doses.