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Association between ChAdOx1 nCoV-19 vaccination and bleeding episodes: Large population-based cohort study

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ABSTRACT

Objective: To compare prevalence of skin, nose and gingival bleedings after receipt of adeno-vectored or mRNA-vaccines against COVID-19. The hypothesis is that milder symptoms indicating altered thrombocyte function may affect a larger proportion of vaccinated individuals than the recently reported severe cases with thrombosis and thrombocytopenia.

Methods: Using an ongoing large, population-based cohort study, more than 80 000 cohort participants were asked through electronic questionnaires about COVID-19 vaccination and potential side effects during weeks 11–13, 2021. The response rate was 58% (81267/138924). Among the vaccinated, 83% were female, 85% health care workers and 80% were aged 40–55 years.

The prevalence of self-reported episodes of skin, nose and gingival bleedings were compared after mRNA and adenovirus-vectored vaccination. Estimates were adjusted for age, sex, occupation, previous COVID-19 infection and chronic disease.

Results: Four of the 3416 subjects (0.2%) who were vaccinated with a single dose of mRNA vaccine reported skin bleeding as a side effect, as opposed to 163 of 5132 subjects (3.2%) vaccinated with a single dose of the adenovirus-vectored vaccine, OR (odds ratio) = 16.0 (95% confidence interval (CI) 7.5–34.1). Corresponding ORs for nose and gingival bleeding were 8.0 (4.0–15.8) and 9.3 (4.3–20.0), respectively.

Conclusions: These findings could potentially indicate that the adenovirus-vectored vaccine may lead to mild bleeding episodes in a larger proportion of vaccinated individuals, and not only in rare cases with documented thrombosis and thrombocytopenia. Studies are needed to understand the possible mechanisms behind these observations, and to establish or refute whether they share similarities with the severe thromboembolic bleeding complications.

1. Introduction

In Norway, five patients with thrombosis and thrombocytopenia were hospitalized 7 to 10 days after receiving the first dose of a chimpanzee adenovirus-vectored vaccine (expressing the SARS-CoV-2 spike protein) against COVID-19. [1] In all patients, antibodies to platelet factor 4 was detected, suggesting a likely mechanism induced by vaccination. The same findings are reported from 9 patients in Germany. [2] The cases may represent rare events, or they may be the tip of the iceberg, reflecting a more quantitative phenomenon. We hypothesized that if this mechanism were present in a larger proportion of vaccinated subjects, one would expect bleeding episodes. We had the opportunity to test this hypothesis in a large, ongoing, population-based cohort by comparing the prevalence of bleeding episodes in subjects receiving adeno-vectored vaccine with the prevalence in subjects receiving mRNA vaccine.

2. Methods

2.1. Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based cohort including about 280 000 participants based on written informed consent. The main aim is to understand the aetiology of complex diseases. [3] Pregnant women and their

Abbreviations: COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus; MoBa, The Norwegian Mother, Father and Child Cohort Study; EMA, European Medicines Agency; PRAC, Pharmcovigilance Risk Assessment Committee.

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partners were recruited from 1999 through 2008. Parents and children have been followed with questionnaires, registry linkages and a series of sub-studies.[4] Since the end of March 2020, all active adult participants (initially about 149 000 subjects aged 25 to 65 years) have received biweekly mobile-phone questionnaires asking about symptoms related to COVID-19. Since vaccination against SARS-CoV-2 commenced in December 2020, we have included questions on vaccine uptake and side effects.

The vaccination policy in Norway was to start with the elderly population, and then to include critical health care personnel.[5] The Pfizer-BioNTech (BNT162b2) mRNA vaccine was the first to be approved in December 2020 followed by the adeno-vectored vaccine from AstraZeneca (ChAdOx1 nCoV-19), and the Moderna mRNA vaccine in February 2021. The adeno-vectored vaccine was recommended for subjects below 65 years and was mainly distributed to health care personnel.

On March 11, the AstraZeneca vaccine was suspended in Norway following a report in Denmark of a death due to thrombosis after vaccination.[6] On March 13, 2021, the Norwegian Medicines Agency was notified of blood clots and bleeding in younger people and also of severe cases of thrombosis and thrombocytopenia.[7] Consequently, we included questions on bleeding episodes in the questionnaire round issued on March 17.

The response rate to the March 17 questionnaire was 58% (81267/138924). Eleven percent (n = 8699) reported that they had received either an mRNA- or an adeno-vectored vaccine. The dataset was linked to the Norwegian Immunisation Registry (SYSVAK)[8] using each citizen's unique personal identification number. Registration in SYSVAK is mandatory for vaccinations against COVID-19 and was confirmed for 8548 subjects in the dataset. This linked dataset defines the study population. The agreement between reported and registered information on vaccination against COVID-19 was high and a discrepancy was found for only 28 subjects (kappa = 0.99).

2.2. Exposure variables

The exposure variable was vaccination against COVID-19. The vaccine registry holds information on date of vaccination, type of vaccine and vaccine doses for all vaccinations. 5132 subjects had received one dose of the adenovirus-vectored vaccine, while 3416 subjects had received one dose of an mRNA vaccine (3315 had received the Pfizer and 101 the Moderna vaccines). No subjects had received two doses of the adeno-vectored vaccine, and 3135 subjects had received two doses of an mRNA vaccine.

2.3. Outcome variables

The questionnaire issued to MoBa participants initially covered a standard set of side effects derived from the summary of product characteristics (SPC) for the respective COVID-19 vaccines.[9,10] We asked for any perceived side effects of vaccination. If confirmed, we asked how long after vaccination the first side effect occurred. Bruising/skin bleeding, nose bleeding, and gingival bleeding when brushing teeth was included in the questionnaire round 26 issued on March 17, 2021. These are the outcome variables. Participants were asked to check off for the presence for each potential side effect listed. Multiple checks were possible. If the respondents had received two doses of a vaccine, they were asked to report side effects after each dose. For each reported side effect, the duration of the side effect was asked for.

2.4. Other variables

Information on occupation and chronic diseases were linked to the study population from questionnaire data collected from previous rounds during the COVID-19 pandemic. Information on occupation was collected from questionnaire round 3, issued in May 2020. A list of nine choices was included and multiple checks were possible. Due to the vaccination policy, most of the vaccine recipients were health care personnel, and the variable was categorized into "health care personnel", "other occupation" and "missing."

Information on chronic diseases was collected from questionnaire round 2, issued in April 2020. We asked for presence of cancer, asthma, heart disease, diabetes, hypertension or other chronic diseases and multiple checks were possible. The current analyses were performed with each condition separately and combined. Since no association was found for separate conditions, "chronic disease" was categorized and reported as "any chronic disease" defined as "no" and "yes" or "missing."

Information on having had SARS-CoV-2 confirmed in nasal /oral swabs or saliva samples was collected from the March 17, 2021 questionnaire. Participants answered "no," "yes" or "don't know" if they had ever tested positive.

2.5. Statistical method

We calculated the prevalence of bleeding episodes and prevalence odds ratios with 95% confidence intervals, comparing bleeding episodes for the mRNA vaccines and the adenovirus-vectored vaccine. To adjust for potentially confounding variables, we used logistic regression. Analyses were performed using IBM SPSS 26.0.

2.6. Patient and public involvement

MoBa participants were recruited from the general population. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research. However, we have interviewed focus groups consisting of participants for input to the maintenance and strategic development of the cohort.

3. Results

The age and gender distribution of the recipients of the two vaccine types were similar (Table 1). The majority of participants who received the vaccines (>80%) were health care workers, irrespective of vaccine type. Table 1 also demonstrates that the mRNA vaccines were available a few weeks earlier than the adenovirus-vectored vaccine. The prevalences of chronic diseases and prior SARS-CoV-2 test-positivity were also similar between recipients of the two vaccine types.

Skin bleedings were significantly more frequent among recipients of the first dose of the adenovirus-vectored vaccine (3.2%) as compared to the first dose of the mRNA vaccines (0.2%), corresponding to an odds ratio of 16.0 (95% confidence interval (CI) 7.5–34.1). Similar, but somewhat lower associations were found for nose and gingival bleedings (Table 2). Adjusting for other variables did not lead to any major change in the associations (last column Table 2). The only other variable (apart from month of first dose which indirectly indicated the type of vaccine) with a clear association to bleeding episodes, was female gender. Among the recipients of the adenovirus-vectored vaccine, 3.5% (152/4365) of women reported skin bleeding as opposed to 1.4% (11/767) among men, OR 2.5 (95% CI 1.3–4.6). Thirty-seven percent reported prolonged duration of skin bleedings (10% lasting 3–4 weeks). For nose bleedings, 14% reported prolonged duration (3.7% lasting 3–4 weeks), and for gingival bleedings, prolonged duration was reported by 26.5% (10.2% lasting 3–4 weeks).

Table 1
Characteristics of MoBa participants vaccinated against covid-19.

	mRNA vaccine	AstraZeneca
Numbers vaccinated	3416	5132
Age distribution (years), n (%)		
25–34	34 (1.0)	67 (1.3)
35–49	406 (11.9)	576 (11.2)
40–44	1109 (32.5)	1664 (32.4)
45–49	1194 (35.0)	1803 (35.1)
50–54	509 (14.9)	772 (15.0)
55–59	130 (3.8)	219 (4.3)
60–64	18 (0.5)	31 (0.6)
>65	16 (0.5)	0 (0.0)
Sex, n (%)		
Male	596 (17.4)	767 (14.9)
Female	2820 (82.6)	4365 (85.1)
Occupation, n (%)		
Health care workers	2966 (86.8)	4342 (84.6)
Other response	156 (4.6)	357 (7.0)
Missing	294 (8.6)	433 (8.4)
Month of first dose, n (%)		
January	1841 (53.9)	0 (0.0)
February	1341 (39.3)	2423 (47.2)
March	234 (6.8)	2709 (52.8)
Ever tested positive for SARS-CoV-2, n (%)		
Yes	38 (1.1)	51 (1.0)
No/don't know	3378 (98.9)	5081 (99.0)
Any chronic disease, n (%)		
Yes	871 (25.5)	1351 (26.3)
No	2251 (65.9)	3348 (65.2)
Missing	294 (8.6)	433 (8.4)

4. Discussion

In this study, cohort participants vaccinated with the adenovirus-vectored vaccine reported mild bleeding episodes significantly more often compared to recipients of mRNA vaccines. Women were more than twice as likely as men to experience bleeding episodes. This observation is expected if thrombocytopenia is relatively frequent among recipients of the adenovirus-vectored vaccine and could indicate a broader spectrum of associated manifestations. Although this might be possible, it should be clear that this epidemiological study only estimates the exposure-outcome association and does not provide information about mechanisms.

Adjustment for chronic diseases, occupation and prior COVID-19 positivity did not influence the results. The self-reported prevalence of prior test positivity was in accordance with seroprevalence analyses conducted among approximately 10 000 MoBa participants as part of the national COVID-19 monitoring effort.[11]

Most reporting of suspected adverse effects following vaccination is based on spontaneous reporting systems.[12,13] Such data cannot be used to derive side effect rates or compare the safety profile of COVID-19 vaccinations. In contrast, well-established cohorts like MoBa provide ideal frameworks for comparing exposed and unexposed subjects. In the present case, the only difference between the two vaccinated groups is the timing of vaccine delivery, which is not likely to influence the outcome. The strength of MoBa is the large cohort size, the well-established infrastructure and the amount of information on selection issues and confounding variables, thus enabling valid, population-based statistics.[4] A limitation is that the outcomes are self-reported and not observed by physicians. However, the bleeding episodes reported directly from cohort participants in this study would rarely lead to health care attendance. Minor bleeding episodes must be asked for and would be difficult to extract from health care registries.

There is a possibility of awareness bias, i.e. that participants who received the adenovirus-vectored vaccine were more likely to report bleeding episodes, since the occurrence of severe thrombosis and thrombocytopenia as potential adverse effects were publicly known shortly before the questionnaire was sent out. Following a general question on COVID-19 vaccination, the participants were asked to check for a series of listed side effects. Then they answered the question on which vaccine they had received. Given this set-up, we believe systematic over- or underreporting of events according to vaccine-type is less likely. The media focus and public attention in Norway was directed towards the severely ill patients presenting with unusual thromboses and severe thrombocytopenia a few days following administration of the first vaccine dose. The possibility of milder manifestations like skin-, nose- and gingival bleedings was not publicly debated. Although awareness bias may not be completely ruled out, it is unlikely to explain the large differences in reported bleeding episodes observed in the current study.

Since March 11th, the European Medicines Agency (EMA) have issued several statements on the safety of the vaccine, the last on July 14th.[14] After reports of more than 400 suspected cases of thrombosis with thrombocytopenia syndrome (TTS) to Eudra Vigilance, the product information of the vaccine has been updated with information concerning this very rare condition. The vaccine is still in use, and close review by EMA's safety Pharmacovigilance Risk Assessment Committee (PRAC) is continuing. Moreover, PRAC is also reviewing rare cases of blood clots in vaccine recipients in the United States following the use of Janssen's COVID-19 vaccine, which is also an adeno-vectored vaccine. So far, specific risk factors such as age, gender or previous medical history have not been identified.

We found no association with age at vaccination. Increasing age is associated with altered immune responses, also to vaccines.[15] Due to vaccination policies, the current study population was relatively young, thus a full analysis of age effects was not possible. However, we found a higher prevalence of post-vaccination bleeding episodes among women compared to men, in line with the pattern observed among the clinical hospital cases reported from Norway[1] and Germany,[2] indicating that the suggested mechanism is more easily triggered in females. Four of the 5 Norwegian cases[1] were female, and three of them were reported to use hormone medications: one using contraceptive pills, one using contraceptive vaginal ring and one hormone replacement therapy. We had no available information on hormone- or other medications for the current analyses.

Table 2
Reported bleeding episodes after vaccination against covid-19 with either an mRNA vaccine (mainly Pfizer-Biontech) or an adenovirus-vectored vaccine (Oxford-AstraZeneca).

	mRNA vaccine, dose 1	mRNA vaccine, dose 2	AstraZeneca, dose 1	Crude OR* (95% CI)	Adjusted OR** (95 %CI)
Number vaccinated	3416	3135	5132		
Skin bleeding, n (%)	7 (0.2)	13 (0.4)	163 (3.2)	16.0 (7.5–34.1)	13.9 (6.5–29.7)
Nose bleeding, n (%)	9 (0.3)	15 (0.5)	106 (2.1)	8.0 (4.0–15.8)	7.0 (3.5–13.9)
Gingival bleeding, n (%)	7 (0.2)	15 (0.5)	96 (1.9)	9.3 (4.3–20.0)	8.1 (3.7–17.6)

* Odds ratio with 95% confidence interval comparing the bleeding after the first dose of the AstraZeneca vaccine to the bleeding after the first dose of the mRNA vaccine.
** Odds ratio with 95% confidence interval adjusted for age group, sex, chronic disease, ever tested positive for SARS-Cov-2 and occupation, n = 7821 (excluding subjects with missing values for chronic disease and occupation).

There is evidence of higher rates of adverse drug reactions in women as compared to men, and females report more adverse reactions to vaccination than men.[15] Women are known to exhibit elevated humoral and cell-mediated immune responses to both infection and vaccination as compared to men, and both genetic and hormonal factors may play a role [16,17].

5. Conclusions

In the current population-based study we report a higher prevalence of milder bleeding episodes following vaccination with adeno-vectored compared to mRNA vaccines. This observation needs replication, more in-depth clinical descriptions, and further research including relevant measures of immunological factors or other mediators. Identifying predisposing factors and the mechanism(s) behind the observed adverse events is important for the continued safe use of vaccines against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

LT and PM conceptualized and designed the study. LT and PM prepared the study data and performed the statistical analysis. All authors contributed to interpretation of results. LT and PM drafted the first version of the manuscript. AHR and SM contributed to writing and critical revision of the manuscript. All authors approved the final manuscript. LT is the guarantor for the study. The corresponding author confirms that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval

The study was approved by the Regional Ethical Committee South-East, Norway, REC no. 127707, April 2, 2020. The Data Protection Impact Assessment – DPIA was supported by the NIPH data protection manger and recommended by the NIPH June 17, 2020, document no. 18/12211-4.

Data sharing statement

Access to data from MoBa may be granted after application to the MoBa administration, mobaadmin@fhi.no.

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