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Association of AZD1222 and BNT162b2 COVID-19 Vaccination With Thromboembolic and Thrombocytopenic Events in Frontline Personnel

A Retrospective Cohort Study

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Background: In March 2021, several European countries suspended the use of the AZD1222 (Oxford–AstraZeneca) COVID-19 vaccine because of thromboembolic safety concerns. Reports from Norway and Germany subsequently described patients with venous thrombosis and thrombocytopenia within 5 to 16 days of vaccination.

Objective: To evaluate the risk for outcomes related to thrombosis and thrombocytopenia after AZD1222 or BNT162b2 (Pfizer–BioNTech) COVID-19 vaccination.

Design: Nationwide exploratory retrospective cohort study.

Setting: Danish linkable registers on vaccinations, hospitalizations, occupation, and other covariates.

Participants: 355 209 Danish frontline personnel designated for priority COVID-19 vaccination followed from 27 December 2020 (the day of the first COVID-19 vaccination in Denmark) to 13 April 2021.

Measurements: Study outcomes were cerebral venous sinus thrombosis, splanchnic vein thrombosis, pulmonary embolism, deep venous thrombosis, arterial thrombosis, thrombocytopenia, and death. Cumulative incidences of study outcomes within 28 days of vaccination and unvaccinated risk time were compared using adjusted survival curves resulting in risk differences (RDs) at day 28 after vaccination. Adjustment for birth cohort, sex, calendar period, occupation, comorbid conditions, and prescription drug use was included.

Results: Vaccination with AZD1222 versus no vaccination was associated with a significant RD at day 28 for deep venous thrombosis (RD, 8.35 [95% CI, 0.21 to 16.49] per 100 000 vaccinations). The RDs for cerebral venous sinus thrombosis (RD, 1.68 [CI, −0.64 to 4.00] per 100 000 vaccinations) and thrombocytopenia (RD, 2.39 [CI, −1.09 to 5.87] per 100 000 vaccinations) were not significant. No adverse associations were seen for BNT162b2 vaccination.

Limitation: No medical record review; surveillance bias.

Conclusion: In this exploratory retrospective cohort study among frontline personnel in Denmark, receipt of the AZD1222 vaccine was associated with a small excess risk for deep venous thrombosis. Although the corresponding risks for the more rare and severe thrombotic outcomes (such as cerebral venous sinus thrombosis) were not statistically significantly increased, statistical precision was low, and clinically relevant risks could not be excluded with certainty. There was no statistically significant association of BNT162b2 vaccination with thrombotic or thrombocytopenic events.

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In March 2021, several European countries temporarily suspended the use of the AZD1222 (Oxford–AstraZeneca) vaccine because of concerns about its thromboembolic safety (1). These concerns originated from adverse event reports of rare but serious cases of thrombosis. Many of these cases were characterized by multiple thromboses, cerebral venous sinus thrombosis, thrombocytopenia, and bleeding and occurred in healthy women; some were fatal. The European Medicines Agency responded rapidly and on 18 March 2021 issued a statement reaffirming the favorable benefit–risk profile of the vaccine, especially in the current pandemic scenario (2).

Sixteen patients from Norway, Germany, and Austria have been described, presenting with venous thrombosis and thrombocytopenia 5 to 16 days after AZD1222 vaccination (3, 4). Most of these patients had high levels of antibodies against platelet factor 4, and it has been proposed that these cases represent thrombosis with thrombocytopenia syndrome, a novel syndrome with a pathophysiology similar to that of autoimmune heparin-induced thrombocytopenia. A similar clinical picture has also emerged after vaccination with the Ad26.COV2.S (Johnson & Johnson) COVID-19 vaccine in the United States (5).

Although thrombosis with thrombocytopenia syndrome seems to be rare, the risk remains to be more precisely determined, and evidence of the thromboembolic safety of the AZD1222 vaccine is needed. In Denmark, use of the AZD1222 vaccine was suspended on 11 March 2021. The vaccine had been introduced in early February and had primarily been used for persons designated as frontline personnel eligible for priority vaccination by the Danish health authorities. To provide a rapid evaluation of the thromboembolic safety of the AZD1222 vaccine, an exploratory, nationwide, register-based cohort study was done among Danish frontline personnel. The BNT162b2 vaccine (Pfizer–BioNTech) has also been used for frontline personnel in Denmark and was included to evaluate whether thromboembolic safety signals were specific to AZD1222 or applicable to COVID-19 vaccines or vaccinees in general.

METHODS

Study Cohort

A nationwide cohort of all persons born between 1957 and 2005, designated as frontline personnel (health care and social services workers), and eligible for priority vaccination by the Danish authorities was constructed. The unique personal identifier from the Danish Civil Registration System was used to link information from national health care registers to the study cohort (6). Using the identifier, researchers linked information on COVID-19 vaccination status, COVID-19 test status, occupation, comorbid conditions, prescription drug use, region, and hospital contacts for relevant thromboembolic outcomes. The study was approved by the Danish Data Protection Agency (institutional approval reference, 20-1803). Ethical approval is not required for register-based research in Denmark.

Vaccination

Information on dates of COVID-19 vaccination in the study cohort was obtained from the Danish vaccination register (7). In Denmark, as of 13 April 2021, only 3 COVID-19 vaccines have been in use: the 2 messenger RNA vaccines, BNT162b2 and mRNA-1273 (Moderna), and the non-replicating viral vector vaccine AZD1222. In the beginning of the Danish vaccination program, the oldest and most frail persons were vaccinated, followed by groups at risk for severe COVID-19 and frontline personnel. The recommended intervals between the first and second doses are 21 days for the BNT162b2 vaccine, 28 days for the mRNA-1273 vaccine, and 4 to 12 weeks for the AZD1222 vaccine.

Outcomes

Diagnoses of thromboembolic and thrombocytopenic events among study participants were ascertained from the Danish National Patient Register (8). This register comprises individual-level information on hospital contacts with assigned diagnoses coded using the International Classification of Diseases, 10th Revision. Study outcomes were cerebral venous sinus thrombosis, splanchnic vein thrombosis, pulmonary embolism, deep venous thrombosis, arterial thrombosis, and thrombocytopenia (codes are in **Appendix Table 1**, available at Annals.org). Death was also included as a study outcome because it may result from severe thromboembolic events that are not assigned proper codes and thus are not included in the specific outcome categories. All hospital contacts were included, and both primary and secondary diagnoses were considered. Only incident cases were analyzed. For each study outcome, persons who had that outcome between 1 January and 26 December 2020 were not included in the cohort for analysis of that specific outcome. If an individual was a case patient in more than 1 outcome category because of multiple relevant diagnoses, the individual contributed as a case patient in each relevant outcome category.

Potential Confounders

Information on occupation subgrouping (hospital care, other health care, nursing home care, other social services, and frontline personnel without further specification) and comorbid conditions associated with risk for severe COVID-19 (cardiovascular disease, respiratory disease, immune-related disease, and other disease; codes are in **Appendix Table 2**, available at Annals.org) were included because these are likely determinants of the type of vaccine received and the calendar period timing of vaccination. Information on all persons with positive results on a SARS-CoV-2 test (using reverse transcriptase polymerase chain reaction in most cases) from the national COVID-19 surveillance system was obtained. Information on drug use between 1 January and 26 December 2020 was also obtained from the Danish National Prescription Registry (9). The following drug categories were included: oral contraceptives and estrogens, antidiabetic and antiobesity drugs, cardiovascular drugs, and nonsteroidal anti-inflammatory drugs (codes are in **Appendix Table 3**, available at Annals.org). No potential confounders had missing values. Individuals with use of antithrombotic drugs at baseline were excluded.

Statistical Analysis

The study cohort was analyzed using survival analysis with follow-up from 27 December 2020 (the day of the first COVID-19 vaccination in Denmark) to 13 April 2021. Individuals were followed until a study outcome, study end, emigration, or death. Vaccination for COVID-19 (AZD1222, BNT162b2, or unvaccinated) was considered a time-dependent variable, and participants could contribute follow-up to both the unvaccinated and vaccinated groups. Receiving the mRNA-1273 vaccine was considered a censoring event because too few doses were administered to allow for meaningful analyses. Receiving a second dose of a vaccine different from the first dose was another censoring event. Testing positive for SARS-CoV-2 in the period of 26 February 2020 to 13 April 2021 was also considered a censoring event. The risk period of interest was the first 28 days after vaccination (including the day of vaccination).

Risk differences (RDs) at day 28 after vaccination per 100 000 vaccinations were calculated as the difference between the cumulative incidence at 28 days for vaccinated persons and the estimated cumulative incidence at 28 days had the vaccinated persons not been vaccinated. The first was estimated among vaccinated persons by the Kaplan–Meier estimator, and the latter was estimated among unvaccinated persons by an adjusted Kaplan–Meier estimator using inverse probability weights to make the covariate distribution among unvaccinated persons similar to that among vaccinated persons (10). The Kaplan–Meier estimates among vaccinated persons were calculated separately for the 2 vaccine types (AZD1222 and BNT162b2). Observation periods were all 28-day periods in the cohort after any dose of the specific vaccine. Thus, each individual could contribute 2 observations periods if vaccinated 2 times with no event before the second dose. The adjusted Kaplan–Meier estimates among unvaccinated persons were calculated separately for each vaccination group that was compared. Unvaccinated observation periods were obtained by including 28 days of unvaccinated risk time from all individuals starting on 27 December 2020. Those who were still unvaccinated after 28 days then contributed with another 28-day observation period, and so forth until

any vaccination, event, or censoring, whichever came first. The inverse probability weights were calculated as $[(1 - p_0) / (1 - p_c)] / (p_0 / p_c)$, with p_0 equal to the crude probability of the specific vaccination and p_c equal to the probability of the specific vaccination given covariates. The probability of vaccination given covariates was estimated in the population of observation periods among unvaccinated and vaccinated persons of the specific type using logistic regression and including birth cohort (5-year categories), sex, calendar month (December 2020 to January 2021, February 2021, March 2021, or April 2021), occupation, comorbid conditions (yes or no), baseline use of oral contraceptives and estrogens (yes or no), and baseline use of antidiabetic and antiobesity drugs (yes or no). The crude probability was also estimated using logistic regression but without covariates. We calculated 95% CIs using the SEs from the Kaplan–Meier estimates.

We estimated the RDs for the study outcome events at day 28 after a SARS-CoV-2 test with positive results using the same approach; in these analyses, COVID-19 vaccination was an additional censoring event.

Data management and statistical analyses were done using SAS, version 9.4 (SAS Institute). The criterion for statistical significance for the RDs was a 95% CI not including 0. Because of the potential for type I error due to the inclusion of multiple outcomes, findings should be interpreted as exploratory. Because of privacy concerns, we report the number of events as fewer than 3 in cases of 1 or 2 events.

Role of the Funding Source

The study was supported by a grant from the Lundbeck Foundation for vaccine safety research. The funding body had no role in the study design; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit it for publication. All authors are independent from the funding agency.

Results

We identified 383 728 persons born between 1957 and 2005, living in Denmark on 27 December 2020, and designated as frontline personnel by the Danish health authorities. We excluded 10 585 who were using antithrombotic drugs at baseline and 17 934 with a positive result on a SARS-CoV-2 test before study start, yielding a cohort comprising 355 209 participants (**Appendix Figure**, available at Annals.org). The median age at study start was 44 years (interquartile range [IQR], 32 to 54 years), and 82% of participants were female. During the study period, 121 152 participants (34.1%) received a first dose of the AZD1222 vaccine, 101 212 (28.5%) received a first dose of the BNT162b2 vaccine, and 2205 (0.6%) received a first dose of the mRNA-1273 vaccine (**Table 1**). Only 504 (<1% of those vaccinated with AZD1222) received a second dose of AZD1222 vaccine before the end of follow-up because its use was suspended in Denmark on 11 March; in contrast, 96 358 (95%) and 1582 (72%) persons received second doses of BNT162b2 and mRNA-1273, respectively, before the end of follow-up.

The median ages at vaccination with the first dose were 45 years (IQR, 34 to 55 years) for the AZD1222 vaccine, 47 years (IQR, 36 to 56 years) for the BMT162b2 vaccine, and 46 years (IQR, 36 to 56 years) for the mRNA-1273 vaccine. Older groups were more likely to be vaccinated. Other health care and institutional care personnel were more likely to have received the AZD1222 vaccine, whereas hospital and nursing home care personnel were more likely to have received the BNT162b2 vaccine. Vaccine recipients used slightly more prescription drugs than unvaccinated persons (**Table 1**).

During follow-up in the analysis with death as the outcome, 2147 participants received the mRNA-1273 vaccine, 28 were vaccinated with 2 different vaccine types, 127 emigrated, and 9874 tested positive for SARS-CoV-2 —all events resulting in censoring (**Appendix Figure**).

Vaccination with AZD1222 compared with no vaccination was associated with a significant RD at day 28 for deep venous thrombosis (RD, 8.35 [95% CI, 0.21 to 16.49] per 100 000 vaccinations). The RDs for cerebral venous sinus thrombosis (RD, 1.68 [CI, −0.64 to 4.00] per 100 000 vaccinations) and thrombocytopenia (RD, 2.39 [CI, −1.09 to 5.87] per 100 000 vaccinations) were not significant.

The BNT162b2 vaccine was not statistically significantly associated with increased risks for any of the study outcomes (**Table 2**).

Among all thromboembolic outcomes, only 0.77% had a co-occurring thrombocytopenia diagnosis.

A positive test result for SARS-CoV-2 was associated with a nonsignificant RD at day 28 for deep venous thrombosis (RD, 27.84 [CI, −4.17 to 59.85] per 100 000 vaccinations) (**Appendix Table 4**, available at Annals.org).

For the association between AZD1222 vaccination and deep venous thrombosis, ending follow-up on 10 March (RD, 9.64 [CI, −6.35 to 25.63] per 100 000 vaccinations) and including persons with a recent history of deep venous thrombosis (RD, 8.86 [CI, 0.53 to 17.19] per 100 000 vaccinations) had little effect on the point estimate.

Discussion

In this exploratory retrospective cohort study of Danish frontline personnel designated for priority vaccination, receipt of the AZD1222 vaccine was associated with an increased risk for deep venous thrombosis only. Of note, AZD1222 vaccination was also associated with increased risks for cerebral venous sinus thrombosis and thrombocytopenia, but not statistically significantly so. No statistically significant associations were found between BNT162b2 vaccination and any of the study outcomes.

The safety of the AZD1222 vaccine has been evaluated in clinical trials. The first interim analyses of the AZD1222 clinical trials reported 4 thromboembolic events ("[t]hrombotic, thromboembolic, and neurovascular events") among 12 021 persons vaccinated with AZD1222 and 8 among control participants (11). The clinical trials primarily recruited 18- to 55-year-old women from the health care and social services setting with some comorbid conditions at baseline, similar to the Danish population of AZD1222-vaccinated individuals, although participants older than 55 years were included in the current study.

Table 1. Characteristics of 355 209 Danish Frontline Personnel Born Between 1957 and 2005 and Followed From 27 December 2020 to 13 April 2021, According to COVID-19 Vaccination Status on 13 April 2021

Characteristic	COVID-19 Vaccination, *n* (%)			Not Vaccinated During the Study, *n* (%)
	AZD1222	BNT162b2	mRNA-1273	
All	121 152 (100)	101 212 (100)	2205 (100)	130 640 (100)
Sex				
Female	99 004 (81.7)	83 973 (83)	1710 (77.6)	105 963 (81.1)
Male	22 148 (18.3)	17 239 (17)	495 (22.4)	24 677 (18.9)
Age at study start				
14–34 y	32 339 (26.7)	22 951 (22.7)	497 (22.5)	56 558 (43.3)
35–49 y	43 521 (35.9)	37 209 (36.8)	811 (36.8)	40 355 (30.9)
50–63 y	45 292 (37.4)	41 052 (40.6)	897 (40.7)	33 727 (25.8)
Frontline personnel occupation*				
Hospital care	24 895 (20.5)	46 698 (46.1)	774 (35.1)	32 139 (24.6)
Other health care	20 061 (16.6)	9002 (8.9)	276 (12.5)	21 465 (16.4)
Nursing home care	12 317 (10.2)	28 487 (28.1)	305 (13.8)	19 539 (15.0)
Institutional care	46 252 (38.2)	11 764 (11.6)	694 (31.5)	45 258 (34.6)
Not further specified	17 627 (14.5)	5261 (5.2)	156 (7.1)	12 239 (9.4)
Comorbid condition present				
Any comorbid condition†	21 667 (17.9)	19 674 (19.4)	418 (19.0)	24947 (19.1)
Cardiovascular disease	4381 (3.6)	4420 (4.4)	92 (4.2)	3771 (2.9)
Respiratory disease	4015 (3.3)	4009 (4.0)	85 (3.9)	4030 (3.1)
Immune-related disease‡	478 (0.4)	644 (0.6)	15 (0.7)	411 (0.3)
Other disease	15 707 (13.0)	13 707 (13.5)	284 (12.9)	19479 (14.9)
Region§				
North Jutland	14 555 (12.0)	10 767 (10.6)	302 (13.7)	13 107 (10.0)
Mid Jutland	28 499 (23.5)	26 399 (26.1)	340 (15.4)	30 294 (23.2)
Southern Denmark	25 643 (21.2)	20 316 (20.1)	692 (31.4)	31 418 (24.0)
Capital	33 238 (27.4)	30 363 (30.0)	546 (24.8)	35 668 (27.3)
Zealand	19 217 (15.9)	13 367 (13.2)	325 (14.7)	20 153 (15.4)
Drug use				
No drug history	67 297 (55.5)	55 969 (55.3)	1234 (56)	80 167 (61.4)
Any drugs‖	53 855 (44.5)	45 243 (44.7)	971 (44.0)	50 473 (38.6)
Oral contraceptives and estrogens	22 621 (18.7)	17 632 (17.4)	371 (16.8)	23 762 (18.2)
Antidiabetic/antiobesity drugs	3756 (3.1)	3400 (3.4)	62 (2.8)	3128 (2.4)
Cardiovascular drugs	17 359 (14.3)	16 127 (15.9)	325 (14.7)	12 776 (9.8)
NSAIDs and opiates	25 310 (20.9)	21 626 (21.4)	474 (21.5)	22 446 (17.2)

NSAID = nonsteroidal anti-inflammatory drug.
* Groups are mutually exclusive. Other health care is any type of health care that is not administered in a hospital, nursing home, or institutional setting. This group includes specialist practice and dental practice. These are determined via an occupation code listed for all health care personnel.
† Defined as any disease that falls under the categories cardiovascular disease, respiratory disease, immune-related disease, or other disease (**Appendix Table 2**, available at Annals.org).
‡ Includes International Classification of Diseases, 10th Revision, codes B20-B24, Z21, D80-D89, Z923, Z926, and Z94 (excluding Z945 and Z947). These include both acute and chronic conditions.
§ These are administrative and mutually exclusive areas that cover all of Denmark, determined via the individual's registered home address.
‖ Defined as any drugs that fall under the categories oral contraceptives and estrogens, antidiabetic/antiobesity drugs, cardiovascular drugs, or NSAIDs/opiates.

A Danish–Norwegian descriptive study compared current rates of venous thromboembolism in AZD1222 recipients versus historic rates in the 2016-to-2019 period. Compared with our current study, it found a higher RD at 28 days after vaccination for cerebral venous sinus thrombosis (standardized morbidity difference, 2.5 [CI, 0.9 to 5.2] per 100 000 vaccinated) and thrombocytopenia (standardized morbidity difference, 4.2 [CI, 1.6 to 8.0] per 100 000 vaccinated) (12). The 2 study approaches have important differences. In the current analytic study, risks were compared in the same calendar period; a range of individual-level confounders were taken into account, such as comorbid conditions and prescription drug use (most notably oral contraceptive use); SARS-CoV-2 infection was taken into account; comparisons were done within frontline personnel designated for vaccination; and risks were also estimated for BNT162b2 vaccination and SARS-CoV-2 infection for context. The current study is less likely to be biased, and the estimates are less likely to be influenced by unobserved confounding. Despite methodological differences, the results of the 2 studies are compatible, providing greater confidence in the findings of both.

Similar patterns of increased risks for thrombocytopenia and thromboses have also been observed in Scotland and the United Kingdom (13, 14). However,

Table 2. Association Between COVID-19 Vaccines and Selected Outcomes Among 355 209 Danish Frontline Personnel (Health Care and Social Services Workers) Born Between 1957 and 2005 and Followed From 27 December 2020 to 13 April 2021

Outcome*	Within 28 d of COVID-19 Vaccination				Unvaccinated
	AZD1222		BNT162b2		
	Incidence Rate per 100 000 Person-Years (Events/Person-Years)	RD at Day 28 per 100 000 Vaccinations (95% CI)†	Incidence Rate per 100 000 Person-Years (Events/Person-Years)	RD at Day 28 per 100 000 Vaccinations (95% CI)†	Incidence Rate per 100 000 Person-Years (Events/Person-Years)
Cerebral venous sinus thrombosis	<3 events	1.68 (−0.64 to 4.00)	0 (0/13 642)	Not estimable	<3 events
Splanchnic vein thrombosis	<3 events	0.84 (−0.80 to 2.48)	0 (0/13 641)	Not estimable	<3 events
Pulmory embolism	32.8 (3/9156)	0.93 (−2.35 to 4.21)	58.7 (8/13 640)	1.32 (−2.55 to 5.19)	30 (19/63 245)
Deep venous thrombosis	207.6 (19/9151)	8.35 (0.21 to 16.49)	95.3 (13/13 634)	2.05 (−2.49 to 6.59)	66.4 (42/63 214)
Arterial thrombosis	<3 events	Not estimable	<3 events	Not estimable	0 (0/63 252)
Thrombocytopenia	43.7 (4/9154)	2.39 (−1.09 to 5.87)	0 (0/13 638)	Not estimable	19 (12/63 233)
Death	76.4 (7/9158)	−1.61 (−7.22 to 4.00)	22 (3/13 642)	−4.18 (−8.23 to −0.13)	64.8 (41/63 252)

RD = risk difference.
* Categorization is considered inclusive. Diagnoses are determined via specific International Classification of Diseases, 10th Revision, codes (**Appendix Table 1**, available at Annals.org).
† Adjusted for birth cohort, sex, occupation, calendar month, comorbid conditions, use of oral contraceptives, and use of antidiabetic/antiobesity drugs.

there are some differences in the strength of the associations observed, most notably in the U.K. results, perhaps because AZD1222 has been used in the U.K. general population—in contrast to Denmark, where it was used in frontline personnel, who are predominantly younger to middle-aged women.

The induction of autoimmunity against platelet factor 4 (a component of α-granules within platelets) is a plausible mechanism for an association between vaccination and thromboembolic events. This phenomenon has been termed thrombosis with thrombocytopenia syndrome or vaccine-induced immune thrombotic thrombocytopenia (15). Because our study is based only on diagnosis codes, we do not know if the cases occurring after AZD1222 vaccination resemble thrombosis with thrombocytopenia syndrome and vaccine-induced immune thrombotic thrombocytopenia.

The current study has many strengths. A study cohort comprising only frontline personnel avoids concerns about the comparability of frontline personnel with the general population; the AZD1222 vaccine was almost exclusively administered to frontline personnel in Denmark. The inclusion of the BNT162b2 vaccine supports the conclusion that the associations observed for AZD1222 are specific to that vaccine and not to COVID-19 vaccines in general. The restriction to frontline personnel only is critical for the study of adverse events of the BNT162b2 vaccine in such a country as Denmark, where this vaccine was initially also used extensively in those at highest risk for severe COVID-19, who presumably have high baseline risk for thromboembolic and thrombocytopenic events.

The current study has limitations. First, we cannot exclude the possibility that the results are influenced by surveillance bias, whereby less clinically severe forms of such outcomes as deep venous thrombosis and thrombocytopenia are more likely to be diagnosed after AZD1222 vaccination, especially in the period after the Danish safety signal was raised. Second, residual systematic differences between AZD1222 recipients and unvaccinated persons may exist in this observational setting. Although an unobserved confounder might not be able to explain away the point estimate of, for example, the deep venous thrombosis association, it may well render the association statistically nonsignificant. However, an increased risk statistically significantly associated with the BNT162b2 vaccine was not observed, which may limit the likelihood of important unobserved confounding originating from differences between vaccinated and unvaccinated individuals in general. Third, medical record review of cases was not done, and thus the specificity of some of the included diagnostic codes may be lacking. However, this would bias the results toward no association, unless coding of diagnoses differed between exposure groups. In a validation study of venous thromboembolism diagnosis codes in the Danish National Patient Register, the positive predictive value was 88% for a first-time diagnosis (16). Fourth, a time-varying definition of frontline personnel was not used (status was defined on 22 February 2021). More frontline personnel are likely to have been added to this priority group after 22 February. Finally, although concerns about the thromboembolic safety of the AZD1222 vaccine were present before the conduct of the current study, many study outcomes were included, and as such the study should be considered exploratory in nature.

In this exploratory retrospective cohort study among frontline personnel in Denmark, receipt of the AZD1222 vaccine was associated with a small excess risk for deep venous thrombosis. Although the corresponding risks for the more rare and severe thrombotic outcomes (such as cerebral venous sinus thrombosis) were not statistically significantly increased, statistical precision was low, and clinically relevant risks could not be excluded with certainty. No statistically significant association was found between BNT162b2 vaccination and thrombotic or thrombocytopenic events.

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Note: Drs. Hansen and Hviid had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Author contributions are available at Annals.org.

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Appendix Table 1. Overview of ICD-10 Codes Used to Define Primary and Secondary Study Outcomes

Category	ICD-10 Codes
Cerebral venous sinus thrombosis	I636, I676
Splanchnic vein thrombosis	I81, I820, I823
Pulmonary embolism	I26
Deep venous thrombosis	I801-I809, I821, I828, I829
Arterial thrombosis	I74
Thrombocytopenia	D693, D694, D695, D696

ICD-10 = International Classification of Diseases, 10th Revision.

Appendix Table 2. Overview of ICD-10 Codes Used to Define Comorbidity

Category	ICD-10 Codes
Cardiovascular disease	I00-I02, I26-I28, I30-I39, I40-I43, I50-I52, I05-I09, I34-I39, I20-I25, I45-I49, I10-I15
Respiratory disease	J10-J22, J40-J99, J43-J44
Immune-related disease	B20-B24, Z21, D80-D89, Z923, Z926, Z94 (not Z945 or Z947)
Other disease	A15-A19, D50-D64, D709-D77, D65-D69, E10-E14, E65-E68, E15-E90, K70, K71-K77, G10-G14, G20-G23, G35-G37 (not G360), G71-G73, G80-G83, G90-G91 (not G902), G93-G96 G99, M51, N18-N200Y, Z992, Q20-Q34, Z85, Z856-Z857, C81-C96, Z902, Z905

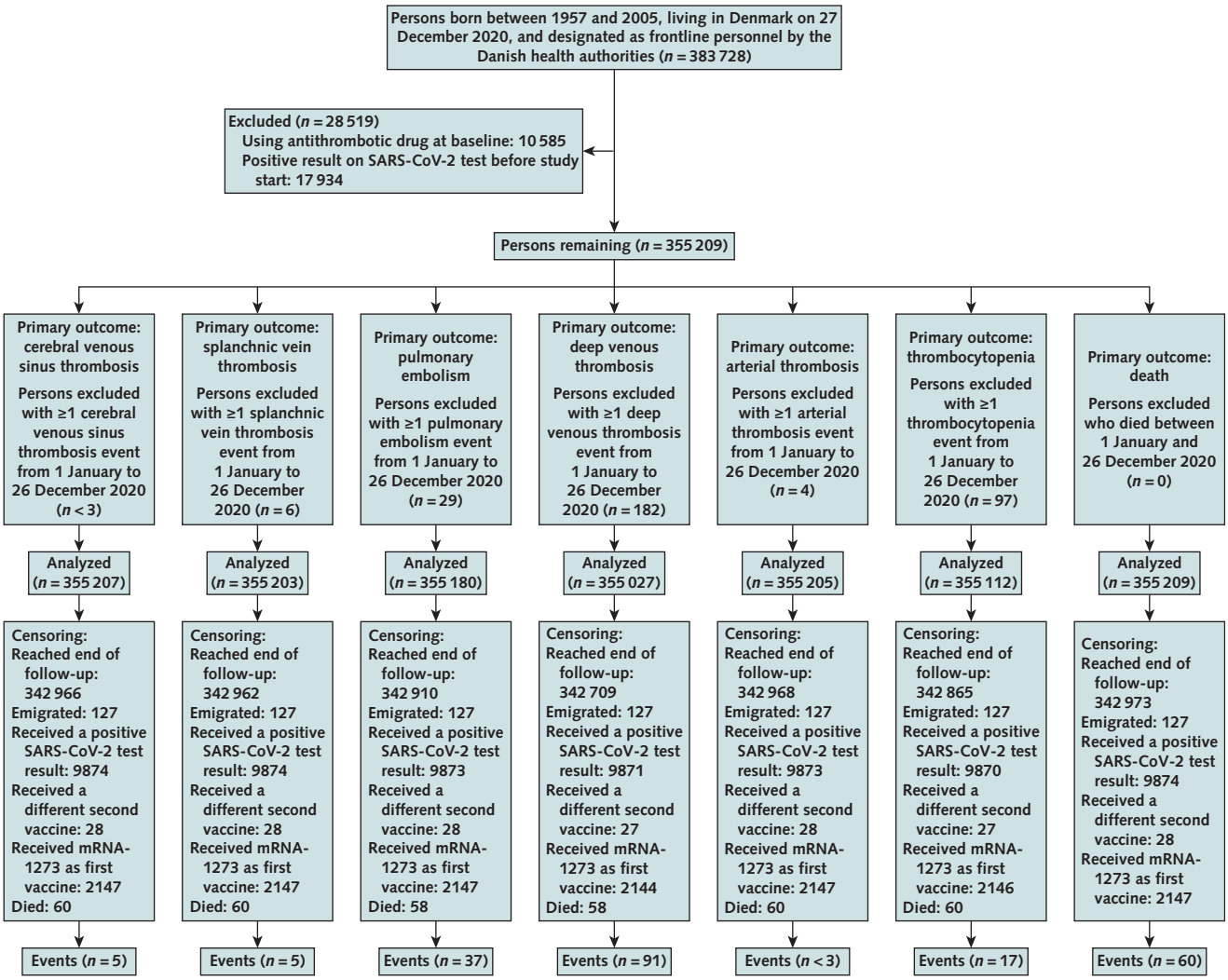
ICD-10 = International Classification of Diseases, 10th Revision.

Appendix Table 3. Overview of ATC Classification Codes Used to Define Prescription Drug Use

Category	ATC Codes
Cardiovascular drugs	C01AA05, C01DA, C03, C07, C08C-D, C09A-D, C10
Antithrombotic drugs	B01
Oral contraceptives and estrogen	G03A, G03C
NSAIDs and opiates	M01A, N02A
Antidiabetic and antiobesity drugs	A08, A10

ATC = Anatomical Therapeutic Chemical; NSAID = nonsteroidal anti-inflammatory drug.

Appendix Figure. Study flow diagram.



Appendix Table 4. Association Between Positive SARS-CoV-2 Test Results and Selected Outcomes Among 373 143 Danish Frontline Personnel (Health Care and Social Services Workers) Born Between 1957 and 2005 and Followed From 27 December 2020 to 13 April 2021

Outcome*	Incidence Rate per 100 000 Person-Years (Events/Person-Years)		RD at Day 28 per 100 000 Vaccinations (95% CI)†
	Period of No Positive Test Result	Within 28 d of a Positive Test Result	
Cerebral venous sinus thrombosis	<3 events	0 (0/901)	Not estimable
Splanchnic vein thrombosis	<3 events	0 (0/901)	Not estimable
Pulmory embolism	29.8 (19/63 831)	<3 events	6.70 (−11.93 to 25.33)
Deep venous thrombosis	67.4 (43/63 800)	444 (4/901)	27.84 (−4.17 to 59.85)
Arterial thrombosis	0 (0/63 838)	<3 events	Not estimable
Thrombocytopenia	18.8 (12/63 820)	0 (0/901)	Not estimable
Death	64.2 (41/63 839)	<3 events	7.67 (−15.15 to 30.49)

RD = risk difference.
* Categorization is considered inclusive. Diagnoses are determined via specific International Classification of Diseases, 10th Revision, codes.
† Adjusted for birth cohort, sex, occupation, calendar month, comorbidity, use of oral contraceptives, and use of antidiabetic/antiobesity drugs.