STUDY PROTOCOL

1. STUDY INFORMATION

Title	**Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries: thromboembolic and thrombocytopenic outcomes, myocarditis and pericarditis**
Protocol version identifier	1.1
Date of the latest version of the protocol	03-10-2022
EU PAS Register number	
Medicinal products	Comirnaty (BNT162b2) Spikevax (mRNA-1273 [Moderna covid-19 vaccine])
Marketing authorization holder(s)	Pfizer/BioNTech Moderna
Research question and objectives	**Primary objectives – vaccine safety objectives:** 1. To evaluate the association between COVID-19 vaccines and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries (addresses objective #1 in the technical specifications). 2. To evaluate the association between COVID-19 vaccines and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries (Objective #2). **Secondary objectives – outcome after infection objectives:** 3. To evaluate the association between COVID-19 infection and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #1). 4. To evaluate the association between COVID-19 infection and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries (Objective #2).
Countries of study	Denmark, Norway, Finland, and Sweden
Authors	Professor Anders Hviid, Kristina Dvoncova

2. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

TABLE OF CONTENTS

3. RESPONSIBLE PARTIES

All main responsible parties including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country/organisation in which the study is to be performed and other relevant study sites are presented in the table below.

Name	**Professional Title**	**Over qualifications and role in the study of the organization**	**Affiliation and address**
Jesper Kjær	Director of Department	Overall management including project management, ensuring clinical and regulatory anchoring and contract management	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, DK-2300 Copenhagen S, Denmark
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Anders Hviid	Professor	Scientific coordination and supervision (principal investigator); overall coordination and oversight of the study; responsible for the submission of deliverables	The University of Copenhagen, Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, Faculty of Health and Medical Sciences, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark
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Øystein Karlstad	Senior researcher	Senior epidemiologist; local scientific coordination, review and approval of deliverables. Conduct the Norwegian analyses. Critical revision of manuscript(s)	Norwegian Institute of Public Health, Department of Chronic diseases, P.O.Box 222-Skøyen, NO-0213 Oslo, Norway
Rickard Ljung	Professor	Senior epidemiologist; local scientific coordination, review and approval of deliverables. Conduct the Swedish analyses. Critical revision of manuscript(s).	Swedish Medical Products Agency, Division of Use and Information, SE3751 03 Uppsala, Sweden

The table below presents all named scientific personnel in the study group together with their respective role in the study.

Name	**Affiliation**	**Role in the study**	**Description of the function**
Anders Hviid	KU (DK)	Principal investigator	Overall coordination and oversight of the study; responsible for the submission of deliverables
Kristyna Faksova	SSI (DK)	Junior Epidemiologist	Literature review, local project management ENCEPP and STROBE compliance. Drafting manuscripts.
Kristina Dvoncova	SSI (DK)	Junior Epidemiologist	Local project management, drafting study protocols and manuscripts.
Emilia Myrup Thiesson	SSI (DK	Statistician	Conduct the Danish analyses and meta-analyses of country-specific results.
Jørgen Vinsløv Hansen	SSI (DK	Statistician	Conduct the Danish analyses and statistical supervision.
Petteri Hovi	THL (FI)	Senior epidemiologist	Local scientific coordination review and approval of deliverables.
Hanna Nohynek	THL (FI)	Senior epidemiologist	Scientific supervision.
Tuomo Nieminen	THL (FI)	Senior epidemiologist	Conduct the Finnish analyses.
Esa Ruokokoski	THL (FI)	Statistician	Finnish data management.
Øystein Karlstad	FHI (NO)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Hanne Løvdal Gulseth	FHI (NO)	Senior epidemiologist	Scientific supervision.
German Tapia	FHI (NO)	Senior epidemiologist	Conduct the Norwegian analyses.
Nina Gunnes	FHI (NO)	Statistician	Conduct the Norwegian analyses.
Inger Johanne Bakken	FHI (NO)	Statistician	Conduct the Norwegian analyses.
Rickard Ljung	SWE MPA (SE)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.

Nicklas Pihlström	SWE MPA (SE)	Statistician	Conduct the Swedish analyses.
Anders Sundström	SWE MPA (SE)	Statistician	Conduct the Swedish analyses.

4. ABBREVIATIONS

AZD1222	Oxford-AstraZeneca adenovirus viral vector vaccine, Vaxzevria
BNT162b2	BioNTech-Pfizer mRNA vaccine, Comirnaty
mRNA-1273	Moderna mRNA vaccine, Spikevax
ICD-10	International classification of diseases revision 10
COVID-19	Coronavirus 2019
RT-PCR	Reverse transcription polymerase chain reaction
SCCS	Self-controlled case series analysis
STROBE	Strengthening the reporting of observational studies in Epidemiology.
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

5. ABSTRACT

Rationale and background: There is a clear need for a comprehensive mapping of the safety of COVID-19 vaccination in children/adolescents focusing on rare adverse events of special interest such as myocarditis, thromboembolism and thrombocytopenia.

Research question and objectives: The overall aim of this project is to take advantage of the Nordic setting (Denmark, Sweden, Norway, and Finland) and conduct nationwide cohort studies of current COVID-19 vaccine safety issues in children/adolescents.

Primary objectives – vaccine safety objectives:

1. To evaluate the association between COVID-19 vaccines and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries (addresses objective #1 in the technical specifications).
2. To evaluate the association between COVID-19 vaccines and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #2).

Secondary objectives – outcome after infection objectives:

3. To evaluate the association between COVID-19 infection and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #1).

4. To evaluate the association between COVID-19 infection and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #2).

Study design: Nationwide register-based cohort studies in Denmark, Finland, Norway and Sweden during the study period 27 December 2020 to date of the latest available data for each country. To take full advantage of the nationwide and longitudinal nature of the Nordic cohorts, we will leverage three complementary survival analysis approaches; 1) observed vs expected analyses providing standardised morbidity ratios and risk differences, 2) contemporary cohort analyses providing adjusted rate ratios and excess risk, and 3) self-controlled case series analyses nested in the cohorts providing rate ratios and excess risk, which are by design un-confounded by time-independent covariates.

Population: The source cohorts will consist of all individuals 5 to 19 years of age during the study period of 27 December 2020 to the date of the latest available data for each country. We will include the 5 to 19-year-old populations of Denmark, Norway, Finland and Sweden (12 to 19; no vaccination in younger children) in our studies. Exclusion criteria will be a positive RT-PCR test before the study period starts, as well as will be a censoring criterion in the primary analyses of vaccine safety. In the secondary analyses of infection risk, vaccination will be a censoring criterion.

Variables: The following study outcomes will be identified in national hospitalisation registers based on ICD-10 codes. The outcomes of interest will be Myocarditis/pericarditis, thromboembolism and thrombocytopenia.

Data sources: Nationwide demography and health registers within each participating country.

Study size: We expect the Nordic countries to contribute with a total population of 4.2 million children/adolescents. Among the European countries that have implemented childhood/adolescent COVID-19 vaccination, the uptake rates in the Nordic countries compare well. The uptake in the Nordic countries is in the upper end of the range of uptakes among children/adolescents in the European region.

Data analysis: We will analyse the follow-up periods and outcome counts using three complementary survival analysis approaches; 1) observed vs expected analyses providing standardized morbidity ratios and risk differences, 2) contemporary cohort analyses providing adjusted rate ratios and excess risk, and 3) self-controlled case series analyses nested in the cohorts providing rate ratios and excess risk, which are by design unconfounded by time-independent covariates. We will include an adjustment age, sex, year and calendar month,

country-specific region, maternal country of birth (Nordic, Western, non-Western), comorbidities and vaccination priority group.

Milestones: Study preparations were initiated on 31 May 2022. The start of the detailed study planning will begin 3 August 2022 and the start of the data analyses will be 1 October 2022 and the study report is expected to be finalized by 3 January 2023.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason

6. MILESTONES

Milestones	Planned dates
Study Plan	September 5, 2022
Study Protocol (posted on EU-PAS register).	October 3, 2022
Registration in the EU-PAS Register	October 3, 2022
Study Report (posted on EU-PAS register).	January 3, 2023
Manuscript(s) draft(s) ready.	February 3, 2023

7. RATIONALE AND BACKGROUND

The initial phase 3 clinical trials demonstrating the efficacy and safety of the mRNA and adenovirus viral vector vaccines were conducted in adults only, as were the later trials of inactivated vaccines.[1–5] Although COVID-19 is milder in children than in adults, the infection also poses risks to children e.g. in the form of a multi-systemic inflammatory syndrome in children (MIS-C). In addition, several societal effects should not be overlooked; children can be a reservoir and play an important role in the continued transmission of the infection in society while lock-down measures and quarantine regulations keeping children at home are likely to be detrimental to their general well-being. Following the adult clinical trials, clinical trials in children and adolescents of decreasing age have been conducted. This includes two phases 3 trials of the BNT162b2 (Pfizer-BioNTech) vaccine in 12 to 15-year-olds and in 5 to 11-year-olds, respectively, and a phase 3 trial of the mRNA-1273 (Moderna) vaccine in 12 to 17-year olds.[6–8] While these trials have demonstrated satisfactory efficacy and safety, the number of participants has been modest (1517, 1131 and 2489 vaccinated in the BNT162b2 trial of 5 to 11-year-olds, the BNT162b2 trial of 12 to 15-year-olds and the mRNA trial of 12 to 17-year-olds, respectively) and the follow-up periods short. Thus, we have little clinical trial evidence with respect to rare adverse events or long-term adverse events following COVID-19 vaccination in children. Reassuringly, no major safety issues have appeared during the autumn/winter vaccinations of children/adolescents in 2021/22. However, there is a clear need for a comprehensive mapping of the safety of COVID-19 vaccination in children/adolescents focusing on rare adverse events of special interest such as myocarditis, thromboembolism and thrombocytopenia.

Myocarditis and pericarditis following COVID-19 vaccination

It is now well established that the risk of myocarditis and pericarditis is increased in the weeks following vaccination with the mRNA vaccines.[9–11] The association appears to be stronger for mRNA-1273 compared to BNT162b2, for the second dose compared to the first, for males compared to females and for younger adults compared to older adults.[11] The evidence on myocarditis following vaccination in children and adolescents is scarce. In both Israel and Hong Kong, increased risks have been reported in adolescents after vaccination with BNT162b2.[12,13] A US case series of fifteen patients 12 to 18 years of age described primarily myocarditis shortly after vaccination in boys and after the second dose[14], and a Danish case series described only one patient among 5 to 11-year-olds based on case ascertainment from all Danish paediatric departments.[15] In our Nordic study of myocarditis, we found an increased risk of myocarditis among 12 to 15-year-old boys after the first dose (rate ratio 4.8) and after the second dose (rate ratio, 13.9) compared to unvaccinated.[11] In our study, the latest date of

data availability was 5 October 2021, and thus in our proposed analyses, we will be able to add more statistical power to the estimation of the association in 12 to 15-year-olds and evaluate the association in the 5 to 11-year-olds (vaccination begun on 25 November 2021 in Denmark, the first country in Europe to recommend vaccination of 5 to 11-year-olds).

Thromboembolism and thrombocytopenia following COVID-19 vaccination

Both adenovirus viral vector vaccines, the AZD1222 (Oxford/AstraZeneca) and the Ad26.COV2.S (Johnson & Johnson), have been linked to the risk of rare but serious thromboembolisms presenting with thrombocytopenia and bleeding (TTS, thromboembolism with thrombocytopenia syndrome).[16–20] The association appears to be strongest in females and younger adults. The evidence is less clear on a possible association with mRNA vaccines,[17,21] and there is a paucity of research on the association in children and adolescents. We will be able to provide much-needed insights into the association between mRNA vaccination and thromboembolism and thrombocytopenia in children and adolescents.

8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this project is to take advantage of the Nordic setting (Denmark, Sweden, Norway, and Finland) and conduct nationwide cohort studies of current COVID-19 vaccine safety issues in children/adolescents and provide guidelines on rapid assessment of associations between COVID-19 vaccination and following outcomes in children/adolescents.

Primary objectives – vaccine safety objectives:

1. To evaluate the association between COVID-19 vaccines and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries (addresses objective #1 in the technical specifications).
2. To evaluate the association between COVID-19 vaccines and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #2).

Secondary objectives – outcome after infection objectives:

3. To evaluate the association between COVID-19 infection and myocarditis/pericarditis in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #1).
4. To evaluate the association between COVID-19 infection and thromboembolic and thrombocytopenic outcomes in children/adolescents aged 5 to 19 years in the Nordic countries. (Objective #2).

In primary objectives #1-#2 we aim to evaluate the association between COVID-19 vaccines and outcomes like myocarditis/pericarditis, thromboembolic and thrombocytopenic in children and adolescents aged 5 to 19 years in the Nordic countries.

For secondary objectives #1 -#2 we will provide comparable estimates of the associations between confirmed COVID-19 infection in children and adolescents aged 5 to 19 years and the outcomes under study in the Nordic countries.

9. RESEARCH METHODS

9.1 Study setting and period

The study objectives will be addressed through nationwide register data available to us, and construct country-specific cohorts of 5 to 19 years old with individual-level information on dates of vaccination and dates of adverse event outcomes together with relevant covariate information. The study period will be from 27 December 2020 to date of latest available data for each country (August 1, 2020 to February 28, 2022, the period of wide-spread PCR testing for SARS-CoV-2, for the associations between infection and study outcomes).

The Nordic countries provide a unique setting for the study of COVID-19 vaccine safety in childhood. Firstly, the ubiquitous nationwide demography and health registers, which include COVID-19 immunization and surveillance registers, allow for study cohorts with a combined size of 4.2 million children/adolescents aged 5 to 19 years. Secondly, the Nordic countries have had high vaccine uptake during the vaccination rollouts compared to many other European countries. Thirdly, the Nordic countries all have universal healthcare free of charge, reducing concern about selection bias, and homogeneous data sources, which are easily combined. Fourthly, the Nordic countries have nationwide hospitalisation registers; most study outcomes will be best ascertained in the specialised hospital setting in contrast to primary care databases. Finally, the Nordic countries already have a proven record of joint accomplishments in conducting rapid vaccine safety evaluations during the pandemic.

9.2 Study design

We will take advantage of the unique nationwide register data available to us, and construct country-specific cohorts of 5 to 19-year-olds with individual-level information on dates of vaccination and dates of adverse event outcomes together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at birth or immigration, enabling unambiguous linkage between registers. These countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, providing near-complete follow-up of all residents over time. The cohort participants will be followed from 27 December

2020 (the start of vaccination rollouts in the Nordic countries) and classified in a time-varying manner according to vaccination (and infection) status using survival analysis. We will evaluate a) myocarditis/pericarditis (objective #1), and b) thromboembolic and thrombocytopenic outcomes (objective #2). We will take potential confounding factors into account and estimate both rate ratios and excess risks by comparing vaccinated and unvaccinated follow-ups.

9.3 Study population

We will include all individuals 5 to 19 years of age during the study period of 27 December 2020 to date of the latest available data for each country. We will include the 5 to 19-year-old populations of Denmark, Norway, Finland and Sweden (12 to 19; no vaccination in younger children) in our studies. The Nordic populations comprise 4.2 million individuals aged 5 to 19 years with COVID-19 vaccine uptake rates that compare well with other countries in the European region. One of the key strengths of our suggested approach is the use of nationwide data on whole-populations reducing concern about selection bias e.g. by socio-economic differences in who is enrolled in a specific health service provided

9.3 Variables

Vaccination

The Nordic countries implemented national vaccination campaigns against COVID-19 from 27 December 2020, providing free vaccinations to all residents. Phased distribution plans were implemented prioritizing vaccination of individuals at highest risk of COVID-19 complications (nursing home residents, healthcare workers, older age). Denmark, Finland and Norway almost exclusively used mRNA vaccines after full or partial discontinuation of AZD1222 in March 2021 due to serious but rare events of thrombosis with thrombocytopenia. Sweden used AZD1222 for a majority of the population older than 64 years and mRNA vaccines in other age groups. Ad26.COV2.S has seen very limited use. The Nordic countries have vaccinated around 6 times more individuals with BNT162b2 than with mRNA-1273.

COVID-19 vaccination in children/adolescents in the Nordic countries.

In Sweden, 12-17-year-olds have been recommended two doses with a 4-7 week interval. Patients at high risk of severe COVID-19 in this age group have been recommended a third dose. Children 5-11 years of age with (severe) immune deficiency or immunosuppressive treatment have also been recommended with vaccination. The 18-19-year-olds have also been recommended a third dose. Since October 6, 2021, Sweden does not recommend the use of mRNA-1273 for males or females under age 30. For that reason, vaccination schedules including this vaccine (mRNA-1273) are relatively uncommon in the targeted population.

In Norway, 5-11-year-olds at high risk of severe COVID-19 are recommended two doses; it has been possible for all other 5-11-year-olds to also get two doses if desired. Among 12-15-year-olds, one dose has been recommended and the second dose is optional; risk groups have been recommended with two doses. Among 16-17-year-olds, two doses with a 12 weeks interval have been recommended; risk groups have been recommended a shorter interval. The 18-19-year-olds have been recommended two doses with a third dose being optional; risk groups (also 5-11-year-olds) have also been recommended three doses.

In Finland, 5-11-year-olds who are at high risk of severe COVID-19 or are in close contact with an immunocompromised person have been recommended two doses; it has been possible for all other 5-11-year-olds to also get two doses if desired. Among 12-17-year-olds, two doses have been recommended; risk groups have been recommended with three doses. The 18-19-year-olds have been recommended three doses.

In Denmark, all 5-17-year-olds have been recommended two doses; 18-19-year-olds have been recommended three doses. Among 5-17-year-olds at high risk of severe COVID-19, a third dose has been recommended.

In all of the Nordic countries, the 5-11-year-olds that have been vaccinated have received either 1/3 of an adult dose or a specific paediatric formulation with a lower dose.

The primary exposures of interest will be the vaccinations that have been used in the Nordic countries for children and adolescents, the two mRNA vaccines (BNT162b2 and mRNA-1273); some older adolescents may have received an adenoviral vector vaccine, but given the rarity of many of the study outcomes, we will not be able to provide reliable information on these vaccines, and we will censor individuals in our studies receiving an adenoviral vector vaccine. Vaccination will be considered a time-varying exposure and individuals can contribute to follow-up both as unvaccinated and vaccinated. Among the vaccinated, we will further stratify by the specific vaccination schedule received taking into account both vaccine types, dose number and sequence. Using the nomenclature of BNTx or MODx for a BNT162b2- or mRNA-1273 vaccine given as dose number x. We will be able to evaluate the safety of the following homologous and heterologous schedules: BNT1, MOD1, BNT1BNT2, MOD1MOD2, BNT1MOD2, MOD1BNT2, BNT1BNT2BNT3, MOD1MOD2MOD3, BNT1BNT2MOD3, MOD1MOD2BNT3, BNT1MOD2MOD3, MOD1BNT2BNT3, BNT1MOD2BNT3, and MOD1BNT2MOD3. The 3-dose schedules are only relevant for adolescents and the heterologous schedules are relatively uncommon in children/adolescents reducing statistical power in these evaluations.

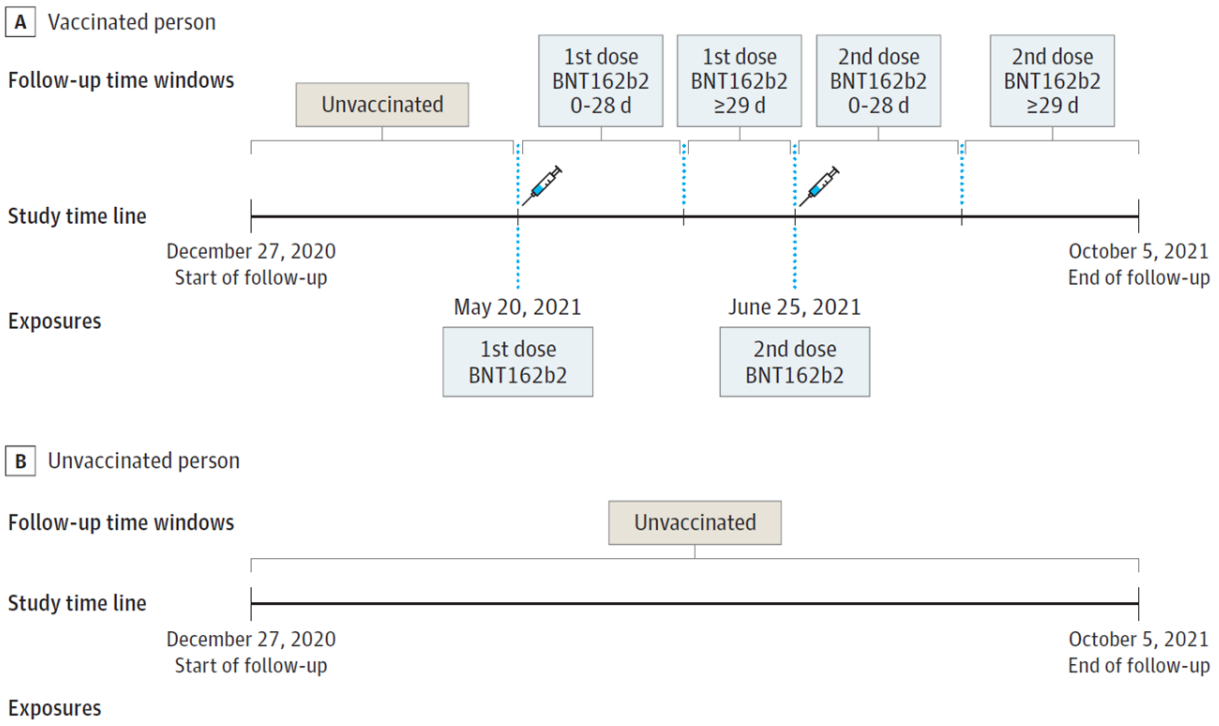
Main risk period of interest

We will define two follow-up periods of interest following vaccination. The acute period of interest will last 28-days following vaccination. The period will start at day 0 (day of vaccination) and will last up to day 27. The post-acute period of interest will start on day 28 following vaccination and will last until another dose (where the person will re-enter the acute period of interest), a censoring event or until the end of the study.

We expect that outcomes such as myocarditis/pericarditis or thromboembolisms will be more likely to occur in the acute risk period following vaccination. The primary comparisons will be between follow-up in the risk period of interest (acute or post-acute) vs unvaccinated follow-up. However, the comparisons between the acute- and the post-acute period will be utilised for sensitivity analyses. COVID-19 infection will be considered a censoring event.

In the figure below (Figure 1), we illustrate how the follow-up in our studies will be classified according to vaccination status. Figure 1A: Example of an individual who was vaccinated with a first dose on May 20, 2021, and followed up in both the acute and post-acute risk periods after the first dose, vaccinated with a second dose on June 25, 2021, and followed up in both the acute and post-acute risk periods until the end of follow-up on October 5, 2021. Figure 1B: Example of an individual who was not vaccinated during the study period and was followed up until the end of follow-up on October 5, 2021. We expect the end of follow-up in the proposed studies to be late 2022, subject to country-specific data availability.

Figure 1. Schematic Illustrations of Follow-up Time Windows in the Cohort Study



Infection

To support risk/benefit evaluations, we will provide comparable estimates of the associations between COVID-19 infection and the outcomes under study. In the secondary objectives on the risk of study outcomes following infection, we will use a positive RT-PCR test as exposure. We will include positive RT-PCR results from August 1, 2020, to February 28, 2022, to cover the period when testing has been accessible to the general population. We will consider infection as a time-varying variable. We will define two periods of interest following infection. The acute period of interest will last 28-days following infection. It will start on day 0 (day of positive RT-PCR test) and will last up to day 27. The post-acute period of interest will start on day 28 following infection and will last until a censoring event or until the end of the study. Vaccination and re-infections will be considered censoring events.

Hospitalisation due to COVID-19

To evaluate the degree to which severity plays a role in an association between infection and the study outcomes we will use COVID-19 hospitalisation as a proxy. The definition of COVID-19 hospitalization will be an event fulfilling the following criteria: a) hospitalisation on the day of or within 14 days of a positive RT-PCR test, b) inpatient contact or at least 12 hours of

contact, c) a COVID-19 relevant diagnosis code (ICD-10: U07.1, B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1). This will allow us to exclude individuals who test positive when hospitalised for non-COVID-19-related conditions. The criteria for hospitalisation due to COVID-19 are subject to country-specific coding practices.

Variants of SARS-CoV-2

In the evaluation of infection risk, variants will be used for stratification. Variants will be defined using periods of predominance specific to each country. The duration of a certain period of predominance of the respective variants was determined based on the current best estimates of each participating country based on when the proportion of sequenced samples exceeded a certain limit. The calendar periods for specific variant dominance are presented in the table below.

	Denmark	**Finland**	**Norway**	**Sweden**
Wuhan	01 February 2020 to 31 December 2020	February 2020 to January 2021	26th February 2020 to 16th February 2021	01 February 2020 to 30 December 2020
Alpha/Beta	15 March 2021 to 30 June 2021	February 2021 to 20 June 2021	17th February 2021 to 18th July 2021	8 March 2021 to 6 June 2021
Delta	15 July 2021 to 15 November 2021	21 June 2021 to 20 December 2021	19th July to 4th January 2022	10 July 2021 to 19 December 2021
Omicron	28 December 2021 till the last available date	21 December 2021 till the last available date	5th January 2021 till the last available date	3 January 2022 till the last day available

Study outcomes

We will identify study outcomes using nationwide hospital registers. Almost all study outcomes are diagnosed in specialist wards in hospitals, especially in children. We will include the following study outcomes identified in the national hospitalisation registers based on ICD-10 codes.

Study outcome	**ICD-10 codes used to identify cases**	
	ICD-10 codes with 3-digits only	ICD-10 codes with 4-digits only
Myocarditis/pericarditis		
1: Myocarditis	I40	I400, I401, I408, I409, I411, I418, I514
2: Pericarditis	I30	I300, I301, I308, I309, I328
Thromboembolism and thrombocytopenia		
3: Thrombosis with thrombocytopenia syndrome		D686G (Danish version; the specific code(s) used may vary between countries, and not all countries have introduced specific TTS codes)
4: Deep vein thrombosis (DVT)	I80	I801-I809, I821, I822, I828, I829
5: Pulmonary embolism (PE)	I26	I260, I269
6: Venous thromboembolism	A composite outcome of DVT or PE	
7: Cerebral venous sinus thrombosis		I636, I676, O225 - Cerebral venous thrombosis in pregnancy, O873 - Cerebral venous thrombosis in the puerperium
8: Splanchnic vein thrombosis	I81	I820, I823,
9: Ischemic stroke	I63	
10: Myocardial infarction	I21	

11: Arterial thromboembolism	A composite outcome of ischemic stroke and myocardial infarction together with I74	

We will utilise washout periods to identify new onset/incident cases. The washout periods will be defined from the first occurrence 'ever' in the register of an outcome. Any recordings of an outcome within the washout period will be considered a new episode. Any recordings after the washout period will be considered a new onset event. For conditions such as myocarditis a washout period of e.g. 3 years is appropriate (since myocarditis can be experienced multiple times).

Many of the diagnoses have been validated in the Nordic registers.[22] As an example, in Denmark, cardiovascular ICD-10 codes were concluded to have high validity, especially in younger adults, and to be well suited for research.[23] In a validation study of Swedish register data, we have estimated a positive predictive value of 92% for a myocarditis diagnosis code (ICD-10) (unpublished).

In the Nordic countries, serious diseases are diagnosed in the specialist care and hospital setting, often in specialised departments, and with very high sensitivity if not entirely captured in the national hospital contact registers used in this study.

Covariates

We will take the following potential confounders into account: age, sex, year and calendar month, country-specific region, maternal country of birth (Nordic, Western, non-Western), comorbidities and vaccination priority group. The vaccination priority group will be used to identify children given priority vaccination due to being at higher risk of severe COVID-19 outcomes. We will use the Nordic hospitalisation register data to define individuals' comorbidities relevant to the outcomes under study.

The table below presents the variables we intend to include and the country-specific data sources, definition details and values.

EXPOSURE VARIABLES				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**

Vaccination schedule	Denmark	*The Danish Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.	Categorical (multiple levels): BNT1, MOD1, BNT1BNT2, MOD1MOD2, BNT1MOD2, MOD1BNT2, BNT1BNT2BNT3, MOD1MOD2MOD3, BNT1BNT2MOD3, MOD1MOD2BNT3, BNT1MOD2MOD3, MOD1BNT2BNT3, MOD1BNT2MOD3, BNT1MOD2BNT3	Yes
	Finland	*The National Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.		
	Norway	*The Norwegian Immunisation Registry (SYSVAK).* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations		
	Sweden	*The National Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.		
Documented SARS-CoV-2 infection	Denmark	*The Danish Microbiology Database.* Defined as the date of a registered positive PCR test for SARS-CoV-2 in the time period from August 1, 2020 to February 28, 2022.	Binary: yes/no	Yes
	Finland	*National Infectious Diseases Register.* Defined as the date of a registered positive PCR test for SARS-CoV-2 in the time period from August 1, 2020 to February 28, 2022.		
	Norway	*Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as the date of a registered positive PCR test or positive serology test for SARS-CoV-2 in the time period from August 1, 2020 to February 28, 2022.		
	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as the date of a registered positive PCR test for SARS-CoV-2 in the time period from August 1, 2020 to February 28, 2022.		
Hospitalization due to COVID-19	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as an event fulfilling the following criteria a) hospitalization on the day of or within 14 days of positive RT- PCR test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a COVID-19 relevant diagnosis code (ICD-10: U07.1, B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)	Binary: yes/no	Yes

	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as an event fulfilling the following criteria a) hospitalization on the day of, within 14 days of or in the two days after a positive PCR test for SARS-CoV-2, b) any of the following main diagnoses codes, J0x, J1x, J20x, J21x, J22x, J46x, J80x, J81x, J82x, J83x, J84x, J851, J86x, U071, U072) c) Speciality code is NOT 98 Allmänmedicin (General practitioner) AND NOT Akutmedicin/allmän medicin (Acute medicine/General practitioner)		
	Norway	*The Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS).* either a) Hospitalized with a COVID code (U071 or U010, depending on date) and codes/symptoms consistent with hospitalization due to COVID, or b) registered as hospitalized due to COVID-19 in the Norwegian intensive and pandemic register (NIPaR)		
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as an event fulfilling criteria a) hospitalization on the day of, within 14 days of or in the two days after a positive PCR test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a COVID-19 relevant diagnosis code (ICD-10: U071, U072, U109, B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)		
Variants of SARS-CoV-2	Denmark	The variant will be defined using the periods of predominance specific to Denmark. Wuhan period – 01 February 2020 – 31 December 2020 Alpha/Beta period – 15 March 2021 – 30 June 2021 Delta period – 15 July 2021 – 15 November 2021 Omicron period – 28 December 2021 – till the last available data	Categorical (3 levels): Alpha/Beta, Delta, Omicron	Yes
	Finland	The variant will be defined using the periods of predominance specific to Finland. Wuhan period –		

		February 2020 - January 2021 Alpha/Beta period – February 2021 - 20 June 2021 Delta period – 21 June 2021 - 20 December 2021 Omicron period – 21 December 2021 - till the last available date		
	Norway	The variant will be defined using the periods of predominance specific to Norway. Wuhan- 26 February 2020 - 16 February 2021 Alpha/Beta period – 17 February 2021 - 18 July 2021 Delta period – 19 July 2021 - 4 January 2022 Omicron period 5 January 2021 - till the last available date		
	Sweden	The variant will be defined using the periods of predominance specific to Sweden. Wuhan – 01 February 2020 - 30 December 2020 Alpha/Beta period – 8 March 2021 – 6 June 2021 Delta period – 10 July 2021 – 19 December 2021 Omicron period – 3 January 2022 - till the last available data		

OUTCOME VARIABLES				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**
Myocarditis	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact	Binary: yes/no ICD-10 codes: I400, I401, I408, I409, I411, I418, I514	Yes
	Finland	*Care register for Health Care* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		

	Norway	*Norwegian Patient Registry and Cause of death registry and Death certificates.* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Pericarditis	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: I300, I301, I308, I309, I328	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Norway	*Norwegian Patient Registry and Cause of death registry and Death certificates.* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Thromboembolism and Thrombocytopenia	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no D686G - Thrombosis with thrombocytopenia syndrome (Danish version, the specific code(s) used may vary between countries, and not all countries have introduced specific TTS codes) ICD-10 codes: I801-I809, I821, I822, I828, I829, I260, I269, I636, I676, I81, I820, I823, K550, I63, I21 A composite outcome of ischemic stroke	Yes
	Finland	*Care register for Health.* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Norway	*Norwegian Patient Registry and Cause of death registry and Death certificates.* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
	Finland	*Care register for Health Care* Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		

	Norway	*Norwegian Patient Registry*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	and myocardial infection together with I74.	
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		

COVARIATES				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**
Age	Denmark	*The Civil Registration System.* Defined as age during follow-up.	Categorical (15 levels): Yearly intervals from 5 to 19 years of age. The following classifications will be used for stratification, a) 5 to 11, 12 to 15, 16 to 19, b) 6 to 11, 12 to 17, and 18 to 19.	Yes
	Finland	*The Finnish Population Information System.* Defined as age during follow-up.		
	Norway	*Norwegian Population Register.* Defined as age during follow-up.		
	Sweden	*The Total Population Register.* Defined as age during follow-up.		
Sex	Denmark	*The Civil Registration System.* Defined as biological sex.	Binary: male/female	No
	Finland	*The Finnish Population Information System.* Defined as biological sex at birth.		
	Norway	*Norwegian Population Register.* Defined as biological sex at birth.		
	Sweden	*The Total Population Register.* Defined as biological sex at birth.		
Calendar month	Denmark	Defined as calendar month during follow-up.	Categorical (multiple levels): Dec 27-31 & Jan 2020 together, and the calendar months until and including the month of the latest available data in each country.	Yes
	Finland	Defined as calendar month during follow-up.		
	Norway	Defined as calendar month during follow-up.		
	Sweden	Defined as calendar month during follow-up.		

Country specific region	Denmark	*The Civil Registration System.* Defined by the place of residence - major administrative regions.	Categorical: (5 levels) Capital, Zealand, Southern Denmark, Central Jutland, Northern Jutland	No
	Finland	*The Finnish Population Information System.* Defined by the place of residence - major administrative regions.	Hospital districts: Helsinki and Uusimaa, Tampere, Turku, Oulu, Other	
	Norway	*Norwegian Population Register.* Defined by the place of residence - major administrative counties (11 categories) or health administrative regions (4 categories)	Counties (11 categories): Troms and Finnmark, Nordland, Trøndelag, Møre and Romsdal, Vestland, Rogaland, Agder, Vestfold and Telemark, Viken, Oslo, Innlandet. Regions (4 categories): Helse Nord. Helse Midt-Norge. Helse Vest. Helse Sør-Øst.	
	Sweden	*The Total Population Register.* Defined by the place of residence - major administrative regions.	Categories are based on city size and urban vs rural.	
Maternal country of birth	Denmark	*The Civil Registration System.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, non-Western	No
	Finland	*The Finnish Population Information System.* Defined as the place of birth of a child´s mother.	NA	
	Norway	*Norwegian Population Register.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, non-Western	
	Sweden	*The Total Population Register.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, non-Western	
Comorbidity 1: Asthma	Denmark	*The National Patient Register.*	Binary: yes/no	Yes

		Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	ICD-10 codes: J45-46	
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
Comorbidity 2: Other chronic respiratory diseases	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute (SII).* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no J41–J44, J47 E84.0 J84	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27, J98	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination. *Swedish Prescribed Drug Register.* Antidiabetic drugs use is defined as ≥2 filled prescriptions during 2020	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27	
	Denmark	*The National Patient Register.*	Binary: yes/no	Yes

Comorbidity 3: Chronic cardiac disease		Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I11.9, I12, I13.1, I13.9, I15 I20-I25 I11.0, I13.0, I13.2, I50	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no We have a more extended CVD risk group:ICD-10 I05,I06,I07,I08,I09,I2,I31,I32,I34,I35,I36,I37,I39,I40,I41,I42,I43,I46,I48,I49,I50 I05,I06,I07,I08,I09,I2,I31,I32,I34,I35,I36,I37,I39,I40,I41,I42,I43,I46,I48,I49,I50; ICPC-2: K74,K75,K76,K77,K78,K82,K83,K87 (	
	Sweden	*National Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	
Comorbidity 4: Renal disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no I12, I13, N00–N05, N07, N08, N11, N14, N18, N19, E10.2, E11.2, E14.2	

	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no (N18.3, N18.4, N18.5)	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	
Comorbidity 5: Diabetes	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: E10-14	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute. Prescription Centre database* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD10-codes: E10, E11, E13, E14 ATC codes: A10A, A10B	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10: E10, E11, E12, E13, E14, ICPC-2: T89, T90	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD10: E10-E14, ATC: A10 last year.	
Comorbidity 6: Autoimmune disease, not including diabetes	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: D510, D590, D591, D690, D693, D86 E035, E039, E050, E055, E059, E063, E065, E271, E272, E310 G04, G131, G35, G36, G61, G700 H20 I00-I02 K50, K51, K732, K743, K900 L10, L12, L130, L40, L63,	Yes

			L80 M05-06, M08, M30, M311, M313, M315-7, M32-34, M350-M353, M358-M359, M45, M60	
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	ICD.10 codes: D86, K50, K51, L40, M02, M05–M07, M13.9, M45, M46.0, M46.1, M46.9, M94.1	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: D510, D590, D591, D690, D693, D86 E035, E039, E050, E055, E059, E063, E065, E271, E272, E310 G04, G131, G35, G36, G61, G700 H20 I00-I02 K50, K51, K732, K743, K900 L10, L12, L130, L40, L63, L80 M05-06, M08, M30, M311, M313, M315-7, M32-34, M350-M353, M358-M359, M45, M60, M60	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: D510, D590, D591, D690, D693, D86 E035, E039, E050, E055, E059, E063, E065, E271, E272, E310 G04, G131, G35, G36, G61, G700 H20 I00-I02 K50, K51, K732, K743, K900 L10, L12, L130, L40, L63,	

			L80 M05-06, M08, M30, M311, M313, M315-7, M32-34, M350-M353, M358-M359, M45, M60	
Comorbidity 7: Epilepsy or convulsions	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
Comorbidity 8: Congenital malformations and chromosomal abnormalities	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
	Sweden	*National Patient Register.*	Binary: yes/no	

		Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
Comorbidity 9: Malignancy or immunodeficiency	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	T86, Z94 C00–C43, C45–C80, C97, D05.1, D39 C81–C85, C88, C90–C96 D70.8, D80–D84, E31.00	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no C0,C1,C2,C3,C4,C5, C6,C7,C80,D32,D33, D35.2,D35.3,D35.4, D42,D43,D44.2,D44 .3,D44.4, C81,C82,C83,C84,C 85,C86,C87,C88, C89,C90,C91,C92,C 93,C94,C95,C96,D4 5,D45,D47, procedures JLE20, RAGG, AAG, WEAOA, WEOB, WEOC, WBOC, WBGM for cancer/malignancy and ICD-10 codes D80,D81,D82,D83,D 84, G35,M05,M08,M06 ,M07,M09,M13,M1 4,K50,K51 for immunodeficiency.	
	Sweden	*National Patient Register and Cancer register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	C00-96, D70-72, D730, D81-84	
Comorbidity 10:	*Denmark*	*The National Patient Register.*	*Binary: yes/no*	*Yes*

Psychiatric disorder		*Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.*	*ICD-10 codes: Any chapter F diagnosis*	
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute. Prescription Centre database,* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: F20–F29 N05AH02 (prescription for clozapine)	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no Any chapter F diagnosis, G30, G31	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Any chapter F diagnosis	
High-risk group	Denmark	The high-risk group will be defined based on the date of the first vaccination and the date of EMA approval of the vaccine for a particular age group for childhood and adolescents, i.e. vaccination before age-specific approval is considered vaccination for the high-risk group. The dates are: 16+ – 21/12/2020, 12-15 yo – 28/05/2021, 5-11 yo – 25/11/2021.	Binary: yes/no	Yes
	Finland	The high-risk group will be defined based on the date of the first vaccination and the date of EMA approval of the vaccine for a particular age group for childhood and adolescents, i.e. vaccination before age-specific approval is considered vaccination for the high-risk group. The dates are: 16+ – 21/12/2020, 12-15 yo – 28/05/2021, 5-11 yo – 25/11/2021.	Binary: yes/no	
	Norway	High- risk group is defined by a list of comorbidities (the comorbidities above, in addition to some	Binary: yes/no	

		comorbidities not listed above (see comments for all codes). In addition, we added nursing home status (everyone in a nursing home is considered high-risk, and there are a few children in them). The dates are the same as in Denmark.		
	Sweden	The high-risk group will be defined based on the date of the first vaccination and the date of EMA approval of the vaccine for a particular age group for childhood and adolescents, i.e. vaccination before age-specific approval is considered vaccination for the high-risk group. The dates are: 16+ – 21/12/2020, 12-15 yo – 28/05/2021, 5-11 yo – 25/11/2021.	Binary: yes/no	

9.4 Data sources

We will use the unique nationwide register data to construct country-specific cohorts with individual-level information on dates of vaccination and dates of outcomes together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at birth or immigration, enabling unambiguous linkage between registers. The data from all the Nordic countries are based on individual-level information and have full availability during the planned study period. The registers are updated daily and there is minimal lag time (except for the vaccination registers and national Swedish and Finnish registers, for which there is a lag of 2 to 4 weeks); we do not expect the lag time of information for these data sources to differentiate between vaccinated and unvaccinated groups). The Nordic countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, providing near-complete follow-up of all residents over time.

In the following table, we present the key data sources (vaccinations, RT-PCR positive tests and hospital contacts) for our proposed study. All data sources are nationwide registers in native format. All study subcontractors have access to their country-specific data and can link data between registers for our study.

Country	**Details of the individual-level data sources**						
Denmark							
Title	**Info**	**Type**	**Setting**	**Availability**	**Update**	**Lag**	**Ref**

The Danish vaccination register	The register holds information on all vaccinations given in Denmark including information on vaccination date, type, dose, and product batch number ever since November 15, 2015 (when reporting to the register became mandatory).	Register	Nationwide	2020 – today	Daily	No lag	[24]
The National patient registry	The register covers all hospital contacts in Denmark with information on the duration of the risk contact, department of admission and other hospital characteristics. Treating physician-assigned diagnoses have been registered according to ICD-10 codes since 1995.	Register	Nationwide	1995 - today	Daily	No lag	[22]
The Danish Microbiology Database	Information on positive results of RT-PCR tests for SARS-CoV-2 will be drawn from The Danish Microbiology Database (MiBa) holds information on all microbiology samples analysed at Danish departments of microbiology, including information on SARS-CoV-2 PCR test results, date of sampling, date of analysis, type of test and interpretation of the test. The SARS-CoV-2 PCR tests have been freely available to all individuals in Denmark regardless of symptom status throughout the COVID-19 pandemic.	Register	Nationwide	2020 – today	Daily	No lag	[25]

Country	**Details of the individual-level data sources**						
Finland							
Title	**Info**	**Type**	**Setting**	**Availability**	**Update**	**Lag**	**Ref**
The National vaccination register	The register, which is based on the Register of Primary Health Care Visits, holds information on all COVID-19 vaccinations administered in Finland. Data include the date of vaccination, vaccine batch number and trade name.	Register	Nationwide	2020 - today	Daily	2-3 weeks	[26]
National Care Register for Health Care	The register comprises information on all in-hospital care (since 1969) and outpatient specialist care (since 1998) in Finland, including admission and discharge dates, whether hospitalization was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department and hospital. The register is held by Finnish Institute for Health and Welfare.	Register	Nationwide	1967 - today	Daily	2-3 weeks	[27]
Finnish National Infectious Diseases Register	The register contains information on notifiable diseases which must be reported by the laboratories and the physician treating the patient, or performing an autopsy, in accordance with the Finnish Communicable Diseases Act. All laboratory-confirmed SARS-CoV-2 infections are	Register	Nationwide	2020 - today	Daily	2-3 weeks	[28]

	recorded in the National Infectious Diseases Register, including the sample. The register is held by the Finnish Institute for Health and Welfare.						

Country	**Details of the individual-level data sources**						
Norway							
Title	**Info**	**Type**	**Setting**	**Availability**	**Update**	**Lag**	**Ref**
The Norwegian immunisation register (SYSVAK)	The register holds information on administered vaccines in Norwegian vaccination programs, including the date of administration and type of vaccine. For the COVID-19 vaccines, reporting to the register has been mandatory.	Register	Nationwide	2020 - today	Daily	No lag	[29]
The Norwegian Patient Registry (NPR)	The register holds information on all contacts with specialist health-care services in Norway, including admission and discharge dates as well as diagnoses (recorded according to ICD-10) during hospitalization or outpatient contact.	Register	Nationwide	2017 - today	Daily	No lag	[30]
Norwegian Surveillance System for Communicable Diseases (MSIS)	The register holds information on selected infectious diseases for which reporting to the register is mandatory. This includes all COVID-19 tests and the date of testing and test results.	Register	Nationwide	2020 - today	Daily	No lag	[31]

Country	**Details of the individual-level data sources**						
Sweden							
Title	**Info**	**Type**	**Setting**	**Availability**	**Update**	**Lag**	**Ref**
Swedish vaccination register	The register contains information on administered COVID-19 vaccines including data on the date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses) since 1 January 2021. The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2020 - today	Daily	No lag	[32]

Swedish national inpatient register	The register comprises information on all in-hospital (since 1987) and out-patient (since 2001) specialist care in Sweden including data on admission and discharge dates, whether hospitalization was planned or acute, codes for discharge diagnoses and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department, and hospital. For the current study period discharge diagnoses were recorded according to the Swedish clinical modification of the ICD-10 (i.e. ICD-10-SE). The register is held by the National Board of Health and Welfare.	Register	Nationwide	2017 - today	Monthly	2–4 week	[33]
Register On Surveillance Of Notifiable Communicable Diseases (Sminet)	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis performing laboratories, the treating physician or the autopsy performing physician, in accordance with the Swedish Communicable Diseases Act. Data include the date of disease occurrence, date of testing, date of positive test and diagnoses. The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2020 - today	Daily	No lag	[34]

9.5 Study size (sample size and power)

We expect the Nordic countries to contribute with a total population of 4.2 million children/adolescents.

Tables with country-specific details on population size and COVID-19 vaccine uptake:

DENMARK (Status as of September 2022)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	209920 (45.2%)	173990 (37.5%)	0 (0.0%)	0 (0.0%)	254504 (54.8%)
12 to 15 yrs	247153 79.4%	241784 77.7%	1245 0.4%	0 (0.0%)	64123 (20.6%)

16 to 19 yrs	251556 (88.8%)	248257 (87.7%)	131209 (46.3%)	172 (0.1%)	31728 (11.2 %)
Total **5 to19 yrs**	708629 (66.9%)	444031 (41.9%)	32454 (3.1%)	172 (0.01%)	350355 (33.1%)

SWEDEN (Status as of August 22)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
12 to 15 yrs	24920 (5.0%)	328492 (66.5%)	1092 (0.2%)	7 (0.0%)	139209 (28.2%)
16 to 19 yrs	18904 (4.1%)	252671 (54.3%)	114084 (24.5%)	525 (0.1%)	79401 (17.1%)
Total **12 to 19 yrs**	43824 (4.6%)	581163 (60.6%)	115176 (12.0%)	532 (0.1%)	218610 (22.8%)

NORWAY (last available)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	6 137 (1.3 %)	1 054 (0.2 %)	7 (0 %)	0	452 024 (98.4 %)
12 to 15 yrs	127 957 (45.2%)	19 694 (6.9%)	167 (0.1%)	6 (0%)	135 297 (47.8%)
16 to 19 yrs	59 682 (21.9%)	132 617 (48.7%)	32 447 (11.9%)	108 (0.04%)	47 401 (17.4%)

Total **5 to 19 yrs**	193 776 (19.1%)	153 365 (15.1%)	32 621 (3.2%)	114 (0.01%)	634 722 (62.6%)

FINLAND (Status as of 27 September 2022)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	104 714 (24.9%)	57 193 (13.6%)	0 (0.0%)	0 (0.0%)	345828 (82.2%)
12 to 17 yrs	283 595 (76.3%)	259 064 (69.7%)	14 495 (3.9%)	0 (0.0%)	88 090 (23.7%)
18 to 24 yrs	360 178 (84.9%)	339 814 (80.1%)	134 059 (31.6%)	1 696 (0.4%)	64 060 (15.1%)
Total **5 to 24 yrs**	748 487 (61.5%)	656 071 (53.9%)	148 554 (12.2%)	1696 (0.14%)	497 978 (40.9%)

Among the European countries that have implemented childhood/adolescent COVID-19 vaccination, the uptake rates in the Nordic countries compare well. The median uptake in the European region among individuals 5 to 17 years of age is 23.3% (range from 2.1 to 44.7%) - https://www.ecdc.europa.eu/sites/default/files/documents/Overview-of-the-implementation-of-COVID-19-vaccination-strategies-and-deployment-plans-in-the-EU-EEA-April-2022.pdf . The uptake in the Nordic countries is in the upper end of the range of uptakes among children/adolescents in the European region.

A unique advantage of our proposal is that as public health institutes we have access to near real-time data. This means that we will be able to 1) take into account all COVID-19 vaccinations administered in the Nordic countries to date, 2) be able to take into account COVID-19 vaccinations among 5 to 19-year-olds in the coming fall and winter of 2022 to the extent that children/adolescents are included in the coming vaccination strategies, 3) be able

to have the longest possible follow-up for adverse events in the post-acute period; we expect to be able to include follow-up through the majority of 2022.

The statistical power of our evaluations will depend on the specific outcomes under study. We recognise that many of the outcomes will be very rare and that we may not be able to evaluate all associations with meaningful precision. Consequently, we will also evaluate the associations between COVID-19 vaccination and overarching categories of outcomes; 1) myocarditis/pericarditis, 2) thromboembolism and thrombocytopenia.

9.6 Data management

Data management will be conducted at the country-specific level and complies with national data security and privacy guidelines. No sensitive data will be shared between countries in this project. Only effect estimates and aggregated data will be shared. Meta-analysis will be used to provide combined Nordic estimates.

9.7 Statistical analysis

We will analyse the follow-up periods and outcome counts using three complementary approaches each with strengths and limitations with respect to the study of vaccine safety. Each outcome will be analysed using all three methods and the results interpreted in the context of each method's strengths and limitations. The following table shows the advantages and disadvantages of the three methods and illustrates well their complementary nature:

	Main advantage	**Main disadvantage**
Observed vs Expected	Can evaluate rare event associations, especially early in vaccination rollout.	No confounder control except age and sex. Compares separate calendar periods (historical comparator).
Contemporary cohort analysis	Nationwide cohort with limited concern about selection and recall bias. Concurrent comparator. Adjustment.	Relies on the availability of confounder information.
Self-controlled case series	No time-invariant confounding by design.	The assumption is that having the outcome has no significant influence on the future probability of exposure.

Observed vs expected analyses

The estimation and comparison of historical rates and post-vaccination rates is a rapid and cost-efficient approach to the surveillance of adverse events of special interest. Such observed vs expected analyses have the potential to investigate early safety concerns and inform vaccination policies, and they can be conducted rapidly – well before a more sophisticated analysis can be planned and carried out.

One highly relevant example of this approach was the thrombosis with thrombocytopenia signal, which prompted the suspension of the use of the Oxford/AstraZeneca COVID-19 vaccine on March 11, 2021, in Denmark and Norway (Supplementary Material 1).[18] Immediately, a collaboration between Denmark and Norway was formed to provide observed vs expected comparisons for a range of thrombotic events based on nationwide register data. The results showed an increased risk of serious thrombotic events primarily in the form of cerebral venous sinus thrombosis following vaccination with the adenoviral vector vaccine, corresponding to 1 case per ~40,000 vaccinations. On March 25, 2021, the vaccine was removed from the Danish program. Norway similarly removed the vaccine from the national program on May 12, 2021. Additional studies have confirmed this vaccine risk.

In each Nordic country, we will calculate historical rates stratified by sex and age (in 1-year age groups) in the period from 2015 (Norway: from 2017) to 2019. Using the historical rates we can calculate the expected number of cases and rates by simple multiplication of the sex and age-stratified follow-up among vaccinated (the acute and post-acute period following vaccination). The expected number of cases and rates can then be compared to the observed number of cases and rates in the post-vaccination periods. Confidence intervals (95%) can be calculated based on the Poisson distribution of the observed counts.

Combined results will be estimated by pooling historical rates by sex and age strata, and post-vaccination case counts and follow-up by sex and age strata, respectively. Observed vs expected measures can then be calculated using the pooled measures.

Contemporary cohort analysis

In each Nordic country, we will estimate adjusted incidence rate ratios and excess risks by comparing post-vaccination (acute and post-acute) follow-up to unvaccinated follow-up from the start of the study on December 27, 2020, until the latest possible date of data availability. As described in Figure 1, individuals who receive another dose, re-enter the acute and post-acute risk periods of interest for this dose. In the analyses of new-onset disease, follow-up is censored when diagnosed. We will use Poisson regression on the outcome counts with the

logarithm of the follow-up time as the offset. We will take potential confounders (above in the text) into account by direct adjustment. Excess risks will be estimated using the incidence rates and the corresponding incidence rate ratios, and 95% confidence intervals will be estimated using the delta method. We have already utilized this approach in the Nordic setting in our recent study of COVID-19 vaccination and myocarditis and pericarditis (Supplementary Material 2).[11] Country-specific estimates will be combined using meta-analyses; the combined incidence rate ratio estimates will be based on random effects models implemented using the mixmeta package in R. We will test the homogeneity of country-specific estimates using Cochran's Q test. Combined excess risks will be estimated using the sum of events and person-years pooled across countries together with the incidence rate ratio; we will use the delta method to calculate 95% confidence intervals assuming independence of the incidence rates and incidence rate ratio estimates.

Self-controlled case series

The self-controlled case series (SCCS) will be nested in our cohorts. The SCCS analyses compare periods of follow-up within vaccinated cases only. Thus, all time-invariant confounders such as comorbidity and lifestyle factors are taken into account by the design. In each Nordic country, we will compare the post-vaccination periods (acute and post-acute after vaccination) to the unvaccinated periods to estimate incidence rate ratios using conditional Poisson regression with direct adjustment for a calendar month. We will use a 14-day pre-risk period of interest before vaccination to take a potential healthy vaccine effect into account. The pre-risk period of interest (which can occur before any dose) will be excluded from the follow-up used in the analyses. As described in Figure 1, individuals who receive another dose, re-enter the acute- and post-acute risk periods of interest for this dose. Being diagnosed is not a censoring criterion in an SCCS analysis, and follow-up is continued to allow for the possibility that an individual is later vaccinated. We will combine country-specific results using the Meta-analyses described above. The main assumption underlying this – study design is having the event under study does not influence the future probability of vaccination – will be tested by 1) increasing the pre-risk period of interest, 2) for acute effects, comparing only the vaccinated period, i.e., acute period vs post-acute period, and 3) visual inspection of bar charts of the number of events in relation to day of vaccination.

We have previously demonstrated our capacity to conduct a Nordic SCCS study on COVID-19 vaccination and thromboembolic and thrombocytopenic outcomes (Supplementary Material 3).[17]

Sensitivity analyses

In addition to taking into account vaccine type, dose number, and sequence, we will conduct sensitivity analyses where we stratify by age (5 to 11, 12 to 15, 16 to 19 years for BNT162b2 evaluations and 6 to 11, 12 to 17, 18-19 years for mRNA-1273 evaluations), sex (male or female), and different risk period of interests of interest (7-days and 8+ days, 14-days and 15+-days post-vaccination, 90 days and 90+ days post-vaccination).

Timelines

If successful, we expect to start the detailed study planning on August 3, 2022 and the statistical analyses on October 1, 2022. We aim to have the final deliverables ready by February 3, 2023.

9.8 Supplementary analyses and quality control

The fact that we are proposing three different approaches (observed vs. expected, contemporary cohort analyses, self-controlled case series) of statistical analyses, so they also constitutes quality control. Considering the strengths and weaknesses of analyses.

9.9 Limitations of the research methods

1. No case validation of recorded ICD-10 diagnoses due to the short time frame of the project; however, for many of the study outcomes, ICD-10 codes have previously been validated as having sufficiently high positive predictive value for observational research.
2. Study outcomes that are not severe, may not be completely captured by hospital records.
3. Many of the outcomes under study are rare, limiting statistical precision, especially in stratified analyses.

10. PROTECTION OF HUMAN PARTICIPANTS

No individual-level data will be shared between parties. Country-specific analyses are conducted on pseudo-anonymised data. All parties adhere to GDPR.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Secondary use of data.

12. ETHICAL ASPECTS

Each country is already working with the data sources in our proposal and has obtained permission for the conduct of vaccination effect studies.

13. OTHER ASPECTS

One of the key advantages of our Nordic setup with participating public health institutes is the availability of near-real-time data. In the context of this proposal, this allows us the opportunity to include follow-up from the coming fall vaccination rollouts if children and adolescents are offered vaccination. The fall recommendations in the Nordic countries will likely include recommendations for all children/adolescents to have received a primary course of two doses.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

We will deliver a protocol detailing our studies of myocarditis/pericarditis and thromboembolic and thrombocytopenic outcomes. The studies of myocarditis/pericarditis and thromboembolic and thrombocytopenic outcomes differ only by study outcome definitions; therefore, we believe that one common protocol describing the data sources and methods will be the best way to fulfil the deliverable #3 requirement.

We expect to deliver two study reports, one on myocarditis/pericarditis (deliverable #4a), and one on thromboembolic- and thrombocytopenic outcomes (deliverable #4b).

We expect to deliver two manuscripts one on myocarditis/pericarditis (deliverable #6aa), and one on thromboembolic- and thrombocytopenic outcomes (deliverable #6ab). The manuscripts will be submitted to peer-reviewed medical journals.

We will adhere to the STROBE and ENCEPP guidelines (including registering the protocols in the EU-PAS register) when reporting results and drafting the manuscript(s).

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