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: immune-mediated diseases**
Protocol version identifier	1.2
Date of the latest version of the protocol	13-12-2022
EU PAS Register number	EUPAS48979
Medicinal products	Comirnaty (BNT162b2 [BioNTech-Pfizer COVID-19 vaccine]) Spikevax (mRNA-1273 [Moderna COVID-19 vaccine])
Marketing authorization holder(s)	Pfizer/BioNTech Moderna
Research question and objectives	**Primary objectives – vaccine safety objectives:** • To conduct a feasibility study on the association between COVID-19 vaccination and 47 different immune-mediated diseases (both new onset and flares) including autoimmune hepatitis and type 1 diabetes in children/adolescents aged 5 to 19 years in the Nordic countries. **Secondary objectives – outcome after infection objectives:** • To evaluate the association between COVID-19 infection and 47 different immune-mediated diseases in children/adolescents aged 5 to 19 years in the Nordic countries.
Countries of study	Denmark, Norway, Finland, and Sweden
Authors	Professor Anders Hviid, Kristina Dvoncova

2. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

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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
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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. Local scientific coordination Denmark.	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
Petteri Hovi	Docent	Senior epidemiologist; local scientific coordination Finland, review and approval of deliverables. Critical revision of manuscript(s).	Finnish Institute for Health and Welfare, Mannerheimintie 166, Helsinki, Finland, P.O.Box 30, FI-00271
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Rickard Ljung	Professor	Senior epidemiologist; local scientific coordination Sweden, review and approval of deliverables. 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. Local scientific coordination Denmark.
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	Conducts the Danish analyses and meta-analyses of country-specific results.
Jørgen Vinsløv Hansen	SSI (DK	Statistician	Conducts the Danish analyses and statistical supervision.
Petteri Hovi	THL (FI)	Senior epidemiologist	Local scientific coordination Finland, review and approval of deliverables.
Hanna Nohynek	THL (FI)	Senior epidemiologist	Scientific supervision.
Tuomo Nieminen	THL (FI)	Statistician	Conducts the Finnish analyses.
Esa Ruokokoski	THL (FI)	Statistician	Finnish data management.
Øystein Karlstad	FHI (NO)	Senior epidemiologist	Local scientific coordination Norway, review and approval of deliverables.
Hanna Løvdal Gulseth	FHI (NO)	Senior epidemiologist	Scientific supervision.
German Tapia	FHI (NO)	Senior epidemiologist	Conducts the Norwegian analyses.
Nina Gunnes	FHI (NO)	Statistician	Conducts the Norwegian analyses.
Inger Johanne Bakken	FHI (NO)	Statistician	Conducts the Norwegian analyses.

Rickard Ljung	SWE MPA (SW)	Senior epidemiologist	Local scientific coordination Sweden, review and approval of deliverables.
Nicklas Pihlström	SWE MPA (SW)	Statistician	Conducts the Swedish analyses.
Anders Sundström	SWE MPA (SW)	Statistician	Conducts 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 disease 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 rare adverse events that debut in children and adolescents and may have a more insidious onset such as immune-mediated diseases.

Research question and objectives: The overall aim of this project is to conduct a feasibility study of the possible associations between COVID-19 vaccination in children/adolescents and a wide range of immune-mediated conditions, and to provide general considerations on the rapid assessment of associations between COVID-19 vaccination and immune-mediated diseases in children/adolescents. The secondary aim of the project is also to evaluate the association between COVID-19 infection and immune-mediated diseases in children/ adolescents.

Primary objectives – vaccine safety objectives:

1. To conduct a feasibility study on the association between COVID-19 vaccination and 47 different immune-mediated diseases (both new onset and flares) including autoimmune hepatitis and type 1 diabetes in children/adolescents aged 5 to 19 years in the Nordic countries.

Secondary objectives – outcome after infection objectives

2. To evaluate the association between COVID-19 infection and 47 different immune-mediated diseases in children/adolescents aged 5 to 19 years in the Nordic countries.

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 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 not 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. A positive RT-PCR test will be an exclusion criterion before the study period starts, as well as a censoring criterion during follow-up in the primary analyses of vaccine safety. In the secondary analyses of associations with infection, vaccination will be a censoring criterion.

Variables: The study outcomes will be identified in national hospitalisation registers based on ICD-10 codes. The outcomes of interest will be 47-immune mediated diseases in children/adolescents aged 5 – 19 years.

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. The uptake in the Nordic countries is at the upper end of the range of uptakes among children/adolescents in the European region.

Data analysis: We will analyse the follow-up periods of new-onset and flares of immune-mediated diseases in main risk periods and post-acute risk periods following exposure together with outcome counts using three different survival analysis approaches. In the observed vs expected analyses, we will use indirect standardisation by age and sex. In the contemporary cohort analyses, we will use Poisson regression with adjustment for age, sex, year and calendar month, country-specific region, maternal country of birth, comorbidities and vaccination priority group. In self-controlled case series analyses, we will use conditional logistic regression with adjustment for calendar month. Country-specific estimates will be combined using meta-analyses.

Milestones: The start of detailed study planning began on 3 August 2022 and the start of the data analyses on 1 October 2022 the study report is expected to be finalized by 3 February 2023.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
1.2.	17-11-2022	Page 1 Page 5-6 Page 8 Page 10 Page 11-14 Page 42-45 Page 48-49 All pages	- Exclusion of general considerations and timely assessment from study objectives. - Research question and objectives modified in the abstract. - Milestones of the project were modified according to the EU PASS requirements. - Expansion of the rationale for selection of the immune-mediated disease outcomes. - Description of study design updated. Risk periods of interest was elaborated. - Description of statistical analyses updated, including statistical power. - A new section on the "general considerations for timely assessment of vaccine safety" added. - Typos correction and redundant text removal.	Incorporating the major and minor comments from EMA assessment of study protocol version 1.1.

6. MILESTONES

Milestones	**Planned dates**
Start of data collection	3 August 2022
End of data collection	1 October 2022
Study Protocol (posted on EU-PAS register).	16 December 2022
Registration in the EU-PAS Register	16 December 2022
Final report of study results (posted on EU-PAS register).	3 February 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] Following the adult clinical trials, clinical trials in children and adolescents of decreasing age have been conducted. This includes two phase 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 were 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 rare adverse events that debut in children and adolescents and may have a more insidious onset such as immune-mediated diseases.

Immune-mediated diseases following COVID-19 vaccination

Immune-mediated diseases are often linked to childhood vaccinations due to temporal association purely by chance since many of these conditions have onset in childhood or early adulthood. However, there are a number of associations that are likely to be causal such as the 1976 swine flu vaccine and Guillain-Barré syndrome, and H1N1 influenza vaccination and narcolepsy.[9] This necessitates careful surveillance of immune-mediated adverse events following vaccination. Case reports and spontaneous reports have already linked several autoimmune conditions, such as Bell's palsy, Guillain-Barré syndrome and transverse myelitis, to COVID-19 vaccination, but few analytical observational studies have been conducted. In an observational study of primary care records from the United Kingdom and Spain, no safety signals were observed between COVID-19 vaccines and the immune-mediated neurological events of Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis.[10] However, this study only considered adults and the use of primary care records is not ideal for the identification of conditions best ascertained in specialist care. In a Hong Kong study of 3.9 million individuals 16 years of age or older, an association between the first dose of BNT162b2 and narcolepsy and related disorders was reported.[11] In another Hong Kong study of 396,800 adolescents (12 to 18 years of age), the risk of a range of adverse events of special interest

(including several autoimmune diseases) was compared among vaccinated individuals within 28-days of vaccination and unvaccinated individuals.[12] No associations were detected, but there were very few outcomes precluding strong conclusions. An important limitation of currently available observational studies is the lack of sufficient follow-up outside of the immediate weeks following vaccination; the new onset of immune-mediated disease may be insidious and long-term follow-up is needed to fully evaluate the safety of vaccines with respect to immune-mediated conditions. In this study, we expect to be able to provide follow-up for immune-mediated conditions at least 6 to 12 months after vaccination.

Selection of study outcomes

In our study, we will include 47 immune-mediated diseases divided into seven categories according to affected organ system: Thyroid, Gastrointestinal, Musculoskeletal/Systemic, Hematologic, Dermatologic, Neurologic, and Miscellaneous. These have been selected based on our previous work on the risk of immune-mediated diseases following quadrivalent human papillomavirus vaccination in the Nordic setting. In our study of human papillomavirus vaccination we evaluated 53 safety outcomes, most of them immune-mediated, in a Danish-Swedish cohort of adolescent 10-to-17-year-old girls.[13] The key motivation for the selection of the original 53 outcomes were, a) previous hypothesized links with childhood vaccination, b) well-defined outcomes in the context of ICD-10 coding, and c) broadly representative of most immune-mediated outcomes occurring in this age-group. In the current study, we use the same registers and ICD-10 codes and the age-groups are largely overlapping (10 to 17 vs 5 to 19 years of age) supporting the use of the existing immune-mediated outcomes list in the current study also. We will also include immune-mediated outcomes such as Guillain-Barré syndrome, transverse myelitis, autoimmune hepatitis and type 1 diabetes which have already been linked to COVID-19 vaccination.[14-16]

8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this project is to conduct a feasibility study of the possible associations between COVID-19 vaccination in children/adolescents and a wide range of immune-mediated conditions, and to provide general considerations on the rapid assessment of associations between COVID-19 vaccination and immune-mediated diseases in children/adolescents. The secondary aim of the project is also to evaluate the association between COVID-19 infection and immune-mediated diseases in children/ adolescents.

Primary objectives – vaccine safety objectives:

1. To conduct a feasibility study on the association between COVID-19 vaccination and 47 different immune-mediated diseases (both new onset and flares) including autoimmune hepatitis and type 1 diabetes in children.

Secondary objectives – risk/benefit evaluation objectives:

2. To evaluate the association between COVID-19 infection and 47 different immune-mediated diseases in children/adolescents aged 5 to 19 years in the Nordic countries.

9. RESEARCH METHODS

9.1 Study setting and period

The study objectives will be addressed through nationwide register-data. We will 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 the date of the latest available data for each country. For the associations between infection and study outcomes, the study period will be restricted to 1 August 2020 to 28 February 2022, the period of widespread PCR testing for SARS-CoV-2.

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 vaccination 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 organisations representing the Nordic countries in this proposal have access to near-real-time data, which is a key advantage in the study of rare immune-mediated adverse events that do not necessarily only occur in an acute period following vaccination. Finally, the Nordic countries have nationwide hospitalisation registers; most of the study outcomes will be best ascertained in the specialised hospital setting in contrast to primary care databases.

9.2 Study design

We will conduct nationwide register-based cohort studies in the four larger Nordic countries (Denmark, Sweden, Norway, and Finland). We will use survival analysis methods. The cohort participants will be followed from 27 December 2020 (the start of vaccination rollouts in Nordic countries) and classified in a time-varying manner according to vaccination (and infection)

status. Rates of study outcomes will be assessed in pre-defined risk periods of interest following vaccination and compared to unvaccinated follow-up periods.

Main risk periods of interest

We will define separate risk periods of interest for new onset of disease (both short-term and long-term onset) and for disease flares - see table below. The distinction between new onsets of short- and long-term immune-mediated disease takes into account that these outcomes can have both a relatively acute onset, such as for Guillain-Barré syndrome, and a more insidious onset, such as type 1 diabetes. By definition, flares are acute worsening of already present disease following vaccination, hence the use of a 4-week acute risk period.

	Main risk period of interest	**Post-acute risk period**
I. Short-term new onset	Day 0 - 41	Day 42 till the end of the study
II. Long-term new onset	Day 0 - 179	Day 180 till the end of the study
III. Flares of pre-existing conditions	Day 0 - 27	Day 28 till the end of the study

Most available studies of COVID-19 vaccine safety have focused on an acute risk period following vaccination such as 28- or 42-days.[17-18] This has allowed for the identification of adverse events such as thromboembolism with thrombocytopenia syndrome and myocarditis.[19-20] These durations are also consistent with previous vaccine safety work on e.g. Guillain-Barré syndrome. In a previous population-based cohort study in the United Kingdom and Spain (with 8,330,497 participants), a 21-day risk period after vaccination was used for assessment of the association between COVID-19 vaccination, SARS-CoV-2 infection and risk of immune-mediated neurological events.[21] Another study from Israel evaluating both new onset disease and flares for 27 study outcomes after COVID-19 vaccination used a 28-day risk period after vaccination.[22]

For outcomes with a more insidious onset or significant lag between onset of symptoms and diagnosis, a longer risk period is appropriate. In our study, the choice of a 180-day risk period takes into account the scale of the typical duration of follow-up that we can expect in our study (9 to 12 months) while still providing reasonable time for either an insidious onset or diagnostic lag. We will also include post-acute periods for new-onset of both short- and long-

term immune-mediated disease. These periods will primarily be used as reference period alternatives to unvaccinated follow-up in sensitivity analyses.

The acute risk periods will start on day 0 (the day of vaccination) and will last up to and including day 27, 41 or 179 corresponding to risk period lengths of 28-days, 42-days and 180-days (see table above). The post-acute period of interest will start on day 29, 43 or 181 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. Infection will be a censoring event for the evaluations of vaccination as an exposure and vaccination will be a censoring event for the evaluations of infection as an exposure.

In the figure below (Figure 1) we illustrate different follow-up scenarios according to the main risk period of interest.

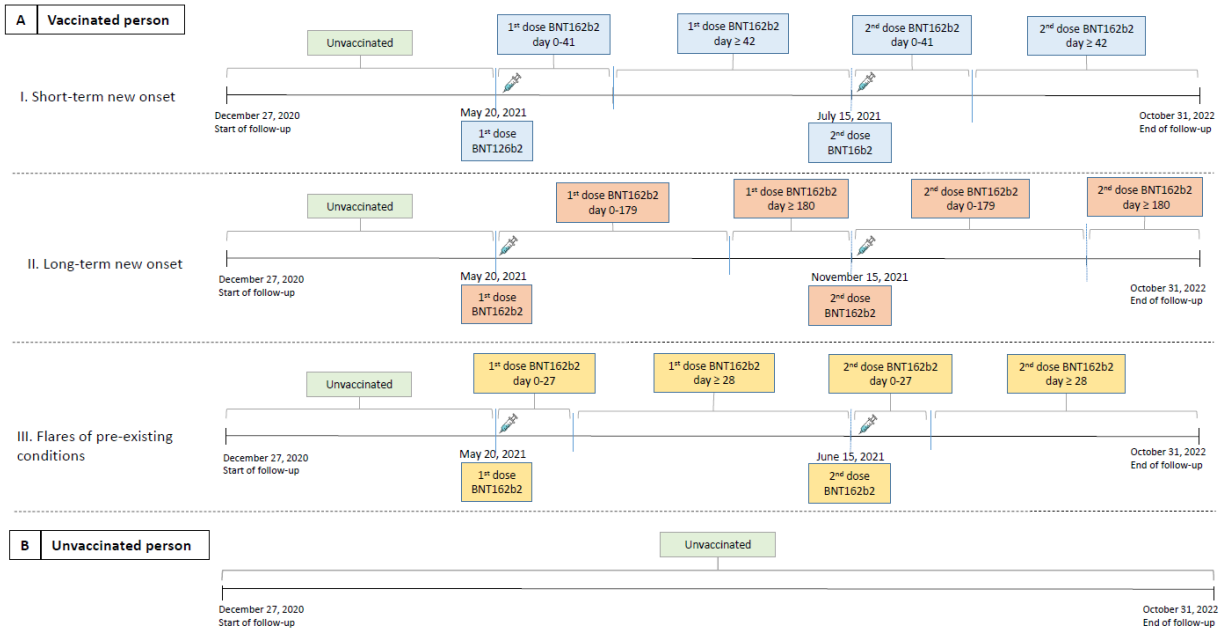
Figure 1A (I. Short-term new onset): Example of an individual who was vaccinated with a first dose on 20 May 2021, and followed up 42 days from the first dose, vaccinated with a second dose on 15 July 2021, and followed up 42 days after a second dose.

Figure 1A (II. Long-term new onset): Example of an individual who was vaccinated with a first dose on 20 May 2021, and followed up 180 days from the first dose, vaccinated with a second dose on 15 November 2021, and followed up 180 days after a second dose.

Figure 1A (III. Flares of pre-existing conditions): Example of an individual who was vaccinated with a first dose on 20 May 2021, and followed up 28 days from the first dose, vaccinated with a second dose on 15 June 2021, and followed up 28 days after a second dose.

Figure 1B (reference cohort): Example of an individual who was not vaccinated and was followed up until the end of follow-up on 31 October 2022. 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



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.

9.4 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 the highest risk of COVID-19 complications (nursing home residents, healthcare workers, and 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 vaccination. The 18-19-year-olds have been recommended a booster 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 children/adolescent 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 two doses. Among 16-17-year-olds, two doses with a 12 week interval have been recommended; risk groups have been recommended a shorter inter-dose interval.

The 18-19-year-olds have been recommended two doses with a booster dose being optional; risk groups (also 5-11-year-olds) have also been recommended booster 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 a booster dose. The 18-19-year-olds have been recommended booster doses.

In Denmark, all 5-17-year-olds have been recommended two doses; 18-19-year-olds have been recommended a booster dose. Among 5-17-year-olds at high risk of severe COVID-19, a booster 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. 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 (subject to statistical power) be able to evaluate the safety of the following homologous and heterologous schedules: BNT1, MOD1, BNT1BNT2, MOD1MOD2, BNT1MOD2, MOD1BNT2, BNT1BNT2MOD3, MOD1MOD2BNT3, BNT1MOD2MOD3, MOD1BNT2BNT3, BNT1MOD2BNT3, and MOD1BNT2MOD3. The booster-dose schedules are only relevant for adolescents and the heterologous schedules are relatively uncommon in children/adolescents reducing statistical power in these evaluations.

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 outcome following infection, we will use a positive RT-PCR test as exposure. We will include positive RT-PCR results from 1 August 1 2020 to 28 February 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 (the day of the 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 of COVID-19 infection 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, within 14 days of a positive RT-PCR test or 2 days before a positive 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 the 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**
Index	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 to 28 February 2022	21 December 2021 to 28 February 2022	5 January 2021 to 28 February 2022	3 January 2022 to 28 February 2022

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/adolescents. 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
Immune-mediated diseases - Thyroid		
1: Graves´ disease		E050
2: Hashimoto's thyroiditis		E063
3: Other hyperthyroidism		E051, E052, E053, E054, E055, E058, E059
4: Hypothyroidism	E03	E032, E033, E034, E035, E038, E039
Immune-mediated diseases – Gastrointestinal		
5: Celiac disease		K900
6: Crohn´s disease	K50	K500, K501, K508, K509
7: Ulcerative colitis	K51	K510, K511, K512, K513, K514, K515, K518, K519
8: Pancreatitis	K85	K850, K851, K853, K858, K859, K861, K861F (DK only)
9: Primary biliary cirrhosis		K743

10: Autoimmune hepatitis		K754
Immune-mediated diseases – Musculoskeletal/systemic		
11: Ankylosing spondylitis and axial spondylarthritis	M45	M081, M460, M461
12: Behcet's syndrome		M352
13: Henoch-Schönlein's purpura		D690, D690B (DK only)
14: Juvenile arthritis	M08	M080, M082, M083, M084, -M088, M089
15: Kawasaki disease		M303
16: Myositis	M60	M600, M601, M602, M608, M609, G724
17: Polyarteritis nodosa		M300, M302
18: Polymyositis/dermatomyositis	M33	M330, M331, M332, M339
19: Reiter's syndrome		M023
20: Rheumatoid arthritis	M05	M050, M051, M052, M053, M058, M059, M060, M061, M064, M068
21: Psoriatic arthropathies	M07	L405, M090, M070, M071, M072, M073, M074, M075, M076
22: Sjögren's syndrome		M350
23: Systemic lupus erythematosus	M32	M320, M321, M328, M329
24: Systemic sclerosis (scleroderma)	M34	M340, M341, M342, M348, M349

25: Vasculitis, unspecified		M301, M302, M308, M310, M311, M314, M315, M316, M317, M318, M319, I776, I731
26: Wegener's granulomatosis		M313
Immune-mediated diseases - Hematologic		
27: Autoimmune hemolytic anaemia		D590, D591
28: Idiopathic thrombocytopenic purpura		D693
29: Pernicious anaemia		D510, D510A (DK only)
Immune-mediated diseases - Dermatologic		
30: Erythema nodosum	L52	L529
31: Localised lupus erythematosus	L93	L930, L931, L932
32: Localised scleroderma		L940, L941, L943
33: Pemphigoid	L12	L120, L121, L122, L123, L128, L129
34: Pemphigus foliaceus		L102
35: Pemphigus vulgaris		L100
36: Psoriasis	L40	L400, L401, L402, L403, L404, L405, L408, L409
37: Vitiligo	L80	L809
38: Dermatologic vasculitis	L95	L950, L951, L958, L959
Immune-mediated diseases - Neurologic		
39: Guillain-Barré syndrome		G610

40: Multiple sclerosis	G35	G359
41: Other demyelinating disorders		G361, G368, G369, G371, G372, G374, G375, G378, G379
42: Narcolepsy		G474
Immune-mediated diseases - Miscellaneous		
43: Acute rheumatic fever	I00, I01	I009, I010, I011, I012, I018, I019
44: Addison's disease		E271, E272
45: Raynaud's disease		I730
46: Sarcoidosis	D86	D860, D861, D862, D863, D868, D869
47: Type 1 diabetes	E10	E100, E101, E102, E103, E104, E105, E106, E107, E108, E109

Identification of new-onset and flares of immune-mediated diseases

We will utilise look-back periods to identify new onset/incident cases (defined as the first occurrence of a diagnosis without preceding occurrences in a longer look-back period) or new episodes (defined as the first occurrence of a diagnosis without preceding occurrences in a shorter look-back period). For conditions such as rheumatoid arthritis or type 1 diabetes, an indefinite look-back period will be appropriate (since the condition is chronic). We will categorise hospital contacts as either 1) inpatient care, or 2) outpatient contacts. In the evaluations of flares, in contrast to new onset, we will utilise a look-back period of shorter duration, e.g. 30 days. Thus, three recordings of a hospital contact in 90 days with 30 days between them will count as one case in the new onset analyses and three episodes in the flares analyses. It is notable, that for most of the diseases, 'flares' as defined above do not necessarily represent separate waves of disease activity, but may together be markers of disease-activity waves lasting for weeks or months. We will also consider using the number of hospital visits/contacts without a short duration look-back period. This will depend on the observed distribution of "flares" using the different approaches.

Many of the diagnoses have been validated in the Nordic registers.[23] As an example, in Denmark, the National patient registry showed high validity and reliability in identifying ulcerative colitis and Crohn´s disease.[24] Similarly, in a validation study of ICD-10 codes conducted in the Swedish National Patient Register, a positive predictive value of 97% for Crohn´s disease and 98% for ulcerative colitis was estimated.[25]

In the Nordic countries, serious disease will be diagnosed in the specialist care and hospital setting, often in specialised departments, and captured in our hospital contact registers used in our study if it is diagnosed.

Many of the included immune-mediated conditions will be rare; some particularly so in children/adolescents. These are included to provide as complete a picture as possible of immune-mediated conditions, and also to inform on the incidence in children/adolescents even if very low.

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,	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	BNT1BNT2MOD3, MOD1MOD2BNT3, BNT1MOD2MOD3, MOD1BNT2BNT3, MOD1BNT2MOD3, BNT1MOD2BNT3	
	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 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 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 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 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 a 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 the 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 – 28 February 2022	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 – 28 February 2022		

	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 – 28 February 2022		
	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 – 28 February 2022		

OUTCOME VARIABLES – composite outcomes in addition to the 47 study outcomes specified above				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**
Immune-mediated diseases - Thyroid	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10codes: E050, E051, E052, E053, E054, E055, E058, E059, E063, E03, E032, E033, E034, E035, E038, E039	Yes
	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.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Immune-mediated diseases - Gastrointestinal	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: K900, K50, K500, K501, K508, K509, K51, K510, K511,	Yes
	Finland	*Care register for Health Care* Defined as primary or secondary		

		diagnosis of the inpatient or outpatient contact.	K512, K513, K514, K515, K518, K519, K85, K850, K851, K853, K858, K859, K861, K861F (DK only) K743, K754	
	Norway	*Norwegian Patient Registry*. 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.		
Immune-mediated diseases – Musculoskeletal/ systematic	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: M081, M45, M460, M461, M352, D690, D690B (DK only), M08, M080, M082, M083, M084, M088, M089, M303, M60,M600, M601, M602, M608, M609, G724, M300, M302, M33, M330, M331, M332, M339, M023, M05, M050, M051, M052, M053, M058, M059, M060, M061, M064, M068, L405, M07, M070, M071, M072, M073, M074, M075, M076, M090, M350, M32, M320, M321, M328, M329, M34, M340, M341, M342, M348, M349, M301, M302, M308, M309, M310, M311, M314, M315, M316, M317, M318, M319, 1776, I731	Yes
	Finland	*Care register for Health is* Defined as the 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.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Immune-mediated diseases - Hematologic	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: D590, D591, D693, D510, D510A (DK only)	Yes
	Finland	*Care register for Health is* Defined as the 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.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Immune-mediated diseases – Dermatologic	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: L52, L529, L93, L930, L931, L932, L940, L941, L943, L12, L120, L121, L122, L123, L128, L129, L102, L100, L40, L400, L401, L402, L403, L404, L405, L408, L409, L80, L809, L95, L950, L951, L958, L959	Yes
	Finland	*Care register for Health is* Defined as the 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.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Immune-mediated diseases - Neurologic	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: G610, G35, G359, G361, G368, G369, G371, G372, G374, G375, G378, G379, G474	Yes
	Finland	*Care register for Health Care is* Defined as the 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.		
	Sweden	*National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.		
Immune-mediated diseases – Miscellaneous	Denmark	*The National Patient Register*. Defined as primary or secondary diagnosis of the inpatient or outpatient contact.	Binary: yes/no ICD-10 codes: I00, I01, I009, I010, I011, I012,	Yes
	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.	I018, I019, E271, E272, I730, D86, D860, D861, D862, D863, D868, D869, E10, E100, E101, E102, E103, E104, E105, E106, E107, E108, E109	
	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, and 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 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, and 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, and non-Western	
	Sweden	*The Total Population Register.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, and non-Western	
Comorbidity 1:	Denmark	*The National Patient Register.*	Binary: yes/no	Yes

Asthma		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 ICD-10 codes: 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 ICD-10 codes: 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 ICD-10 codes: 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 ICD-10 codes: (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 codes: 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 ICD-10 codes: 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, L80 M05-06, M08, M30, M311, M313, M315-7, M32-34, M350-M353, M358-M359, M45, M60	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: 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	Binary: yes / no ICD-10 codes:	Yes

		contact registered before the first COVID-19 vaccination.	G40, R56	
	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.	Binary: yes/no 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.* 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: 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.	Binary: yes/no ICD-10 codes: 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 ICD-10 codes: 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,C85,C86,C87,C88,C89,C90,C91,C92,C93,C94,C95,C96,D45,D45,D47, procedures JLE20, RAGG, AAG, WEAOA, WEOB, WEOC, WBOC, WBGM for cancer/malignancy and ICD-10 codes D80,D81,D82,D83,D84, G35,M05,M08,M06,M07,M09,M13,M14,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.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	
Comorbidity 10: Psychiatric disorder	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: Any chapter F diagnosis	Yes
	Finland	*Care register for Health Care and Statistics on reimbursements for medical expenses, Social Insurance Institute. Prescription Centre database,*	Binary: yes/no ICD-10 codes: F20–F29	

		Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	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 ICD-10 codes: 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 of 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 of 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 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). In one study we have used vaccination before recommendation as a risk group indication, so we could use that as well? The dates are the same as in Denmark.	Binary: yes/no	

	Sweden	High- risk group is defined by a list of comorbidities (the comorbidities above, in addition to some 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). In one study we have used vaccination before recommendation as a risk group indication, so we could use that as well? The dates are the same as in Denmark.	Binary: yes/no	

9.5 Data sources

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 15 November 2015 (when reporting to the register became mandatory).	Register	Nationwide	2020 – today	Daily	No lag	[27]
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	[26]

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), which 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	[28]

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	[29]
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	[30]
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 recorded in the National Infectious Diseases Register, including the sample. The register is held by the Finnish Institute for Health and Welfare.	Register	Nationwide	2020 - today	Daily	2-3 weeks	[31]

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	32
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	33
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	34

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	35
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	36
Register On Surveillance Of Notifiable	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the	Register	Nationwide	2020 - today	Daily	No lag	37

Communicable Diseases (Sminet)	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.						

9.6 Study size (sample size and power)

We expect the Nordic countries to contribute with a total population of 4.2 million children/adolescents. The below tables show 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 (Status as of 23 September 2022)	**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 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 at the upper end of the range of uptakes among children/adolescents in the European region.

9.7 Data management

Data management will be conducted at the country-specific level and complies with national data security and privacy guidelines. All study subcontractors have access to their country-specific data and can link data between their country's registers for our study. No sensitive data will be shared between partners in this project. Only effect estimates and aggregated data will be shared.

9.8 Statistical analyses

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 illustrates the complementary nature of the selected methods together with their advantages and disadvantages:

	Main advantage	**Main disadvantage**
Observed vs Expected	Can evaluate rare event associations especially early in vaccination roll-out.	No confounder control except age and sex, and compares separate calendar periods (historical comparator).
Contemporary cohort analysis	Nationwide cohort with limited concern about selection- and recall	Relies on the availability of

	bias. Concurrent comparator. Adjustment.	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 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 11 March 2021, in Denmark and Norway.[20] 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 25 March 2021, the vaccine was removed from the Danish program. Norway similarly removed the vaccine from the national program on 12 May 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 2017) to 2019. Using these 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

comparing post-vaccination (acute and post-acute) follow-up to unvaccinated follow-up from the study starting 27 December 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 for this dose. In the analyses of new-onset disease, follow-up is censored when diagnosed. When evaluating flares in contrast to new onset, we will not censor at the first event. We will use log-linear Poisson regression on the outcome counts with the logarithm of the follow-up time as the offset. We will take potential confounders (as specified in 9.3 Variables - covariates) into account by direct adjustment. Excess risks will be estimated using the incidence rates and the corresponding incidence rate ratios; 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.[11] Country-specific estimates will be combined using meta-analyses; the combined rate ratio estimates will be based on random effects models implemented using the mixmeta package of R. We will test the homogeneity of country-specific estimates using the Cochran Q test. Combined excess risks will be estimated using the sum of events and person-years pooled across countries together with the rate ratio; we will use the delta method to calculate 95% confidence intervals assuming independence of the incidence rates and 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 design. In each Nordic country, we will compare the post-vaccination periods (acute and post-acute after vaccination) to the unvaccinated periods to estimate rate ratios using conditional Poisson regression with direct adjustment for the calendar month. We will use a 14-day pre-risk period before vaccination to take a potential healthy vaccinée effect into account. The pre-risk period (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 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. For the evaluation of new-onset disease, we will only use the first registered event since the study outcomes are rare. For the evaluation of flares, we will use all registrations of events (fulfilling the short washout period criteria). We will combine country-specific results using the inverse variance weighting method. The main assumption underlying this method, that having the event under study does not influence the future probability of vaccination will be tested by 1) increasing the pre-risk period, 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.

The SCCS approach is best suited for outcomes where a main risk period can be well-defined.

Statistical power

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) immune-mediated disease – thyroid, 2) immune-mediated disease – gastrointestinal, 3) immune-mediated disease – musculoskeletal/systemic, 4) immune-mediated disease - hematologic, 5) immune-mediated disease - dermatologic, 6) immune-mediated disease – neurologic, and 7) immune-mediated disease – miscellaneous.

A previously conducted nationwide population-based cohort study in Denmark has provided background incidence rates for selected immune-mediated outcomes in a paediatric population; 2 300 227 live-born infants born 1 January 1980 till 31 December 2009. This includes incidence rates for rare outcomes such as autoimmune thrombocytopenia (0.32 per 100 000 person years), acute transverse myelitis (0.36 per 100 000 person years), narcolepsy (0.48 per 100 000 person years), optic polyneuritis (0.60 per 100 000 person years), and Guillain-Barré syndrome (0.67 per 100 000 person years). Higher incidence rates were observed for juvenile and rheumatoid arthritis (16.73 per 100 000 person years) and type 1 diabetes mellitus (17.71).[38] These incidence rates of immune-mediated diseases are comparable with the results of a study conducted in European Healthcare Databases over the period 2003 to 2014.[39]

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), sex (male or female), and different alternative risk periods of interest (14-days and 15+ days post-vaccination and 90 days and 91+ days post-vaccination).

9.9 Supplementary analyses and quality control

The use of three different statistical analyses approaches (observed vs. expected analyses, contemporary cohort analyses, and self-controlled case series analyses) constitutes our primary quality control. The strength and limitations of these approaches complement each other well. If the three methods yield similar results, this supports that validity of the results.

We will utilise a common data model for the Nordic register data together with standardised analysis scripts which will support the quality of the statistical analyses. The scientific quality of our work will be ensured by adhering to the ENCePP Code of Conduct.

9.10 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. The occurrence of outcomes is defined using dates of hospital contacts. For some outcomes, especially immune-mediated outcomes, there will be some delay between symptom onset and diagnosis. There is no information on symptom onset in the register data.
3. Study outcomes that are not severe, may not be completely captured by hospital records.
4. Many of the outcomes under study are rare, limiting statistical precision, especially in stratified analyses.
5. We will have to use proxies (number of hospital contacts) for the identification of flares. Information on increased disease activity is not available from the registers.

9.11 Strengths of the research methods

The main strength of the study is that as public health institutes we have access to near real-time data. This means that we will be able:

1. To take into account all COVID-19 vaccinations administered in the Nordic countries to date.
2. To take into account COVID-19 vaccinations among 5 to 19-year-olds in the coming fall and winter of 2022-23 to the extent that children/adolescents are included in the coming vaccination strategies.
3. 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.

10. GENERAL CONSIDERATIONS FOR THE TIMELY ASSESMENT OF VACCINE SAFETY ISSUES RELATED TO IMMUNE-MEDIATED DISEASES IN CHILDREN AND ADOLESCENTS

The assessment of vaccine safety related to immune-mediated diseases is an important part of post-authorisation safety studies in particular among children and adolescents. The characteristics specific to the study of these vaccine safety issues are presented in the table below.

Characteristics of vaccine safety issues in children and adolescents related to immune-mediated diseases
• Rare events (very low frequency of occurrence) • Specific sex and age-related patterns of onset • Either acute onset of diagnosis, or lag between onset of general symptoms and assignment of diagnosis • Lack of comprehensive understanding of the aetiology • General population concern that could result in vaccination hesitancy

Therefore conducting an assessment of vaccine safety issues related to immune-mediated diseases requires specific methodological considerations. Some methodological challenges of studying this class of safety outcomes have been described previously.[40] Well-designed post-licensure safety evaluations should be based on data sources and methods fulfilling a number of requirements:

Requirements of well-designed studies
• Long follow-up periods after vaccination should be possible to identify insidious onset disease • Long historical look-back periods should be possible to ensure that incidents cases during follow-up are not prevalent cases • Large population sizes needed to identify rare event associations • Access to timely updated databases/registers to ensure rapid assessment of signals and hypotheses • Representative data sources used for the study - e.g. nationwide register data. • Study population with sufficient vaccine uptake. • Ability to control confounding by design (e.g. using SCCS method) or by inclusion of information on potential confounders

- Low risk of bias due to exposure misclassification – access to valid individual level vaccination information
- Low risk of bias due to outcome misclassification – medically validated chart outcomes or outcomes with high-validity using diagnostic classification schemes

11. 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.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable. Secondary use of data.

13. ETHICAL ASPECTS

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

14. 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 study, 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.

15. PLANS FOR DISSEMINATION AND COMMUNICATION

We expect to deliver one study report on the feasibility study of 47 immune-mediated outcomes which will also include a comprehensive discussion of the timely assessment of vaccine safety issues related to immune-mediated diseases in children and adolescents.

We will also deliver one manuscript on the feasibility study of 47 immune-mediated outcomes. The manuscript will be submitted to a peer-reviewed medical journal.

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

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