STUDY PROTOCOL

1. STUDY INFORMATION

Title	Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination schedules in the Nordic countries
Protocol version identifier	1.0
Date of latest version of protocol	31 March 2022
EU PAS Register number	Study not yet registered.
Medicinal products	Comirnaty (BNT162b2) Vaxzevria (ChAdOx1-S [/AZD1222]) Spikevax (mRNA-1273 [/Moderna covid-19 vaccine])
Marketing authorization holder(s)	Pfizer/BioNTech AstraZeneca Moderna
Research question and objectives	The overall aim of this project is to provide combined and country-specific (Denmark, Norway, Finland, Sweden) estimates of SARS-CoV-2 vaccination schedule effectiveness using comparative study designs.
Country(-ies) of study	Denmark, Norway, Finland, and Sweden
Authors	Anders Hviid; Niklas Andersson

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
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
Niels Henrik Meedom	Project manager and fundraiser		
Anders Hviid	Professor	Scientific coordination and supervision (principal investigator); overall coordination and oversight of the study; responsible for the submission of deliverables	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
Morten Andersen	Professor	Senior pharmacoepidemiologist; overall supervision contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.	
Jesper Hallas	Professor	Senior pharmacoepidemiologist; conducting scientific review and code review, contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.	University of Southern Denmark, Faculty of Health Sciences, Department of Public Health, J. B. Winsløwsvej 19,2, DK-5230 Odense M, Denmark
Niklas Andersson	MD	Pharmacoepidemiologist; contribute to drafting the study protocol, conduct of the Danish analyses and responsible for the meta-analyses of all the site-specific results, Literature review, ENCEPP, STROBE compliance, the study report and final manuscript(s) submission process, revisions etc.	Statens Serum Institut, Department of Epidemiology Research, Artillerivej 5, DK-2300 Copenhagen S, Denmark
Ulrike Baum	PhD	Epidemiologist; local scientific coordination, review and approval of deliverables. Conduct of the Finnish	Finnish Institute for Health and Welfare, POBox 30, FI-00271 Helsinki, Finland

		analyses. Critical revision of manuscript(s).	
Hinta Meijerink	Senior advisor	Senior epidemiologist; local scientific coordination, review and approval of deliverables. Conduct of the Norwegian analyses. Critical revision of manuscript(s)	Norwegian Institute of Public Health, Department of Infection, Control and Vaccines, P.O.Box 222-Skøyen, NO-0213 Oslo, Norway
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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
Morten Andersen	KU (DK)	Senior pharmacoepidemiologist	Overall supervision and approval of study protocol and final study report
Mia Aakjær	KU (DK)	Pharmacoepidemiologist	Contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.
Jesper Hallas	SDU (DK)	Senior Pharmacoepidemiologist	Scientific review and code review
Lars Christian Lund	SDU (DK)	Pharmacoepidemiologist	Contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.
Hinta Meijerink	FHI (NO)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.

Jostein Starrfelt	FHI (NO)	Statistician	Conduct of the Norwegian analyses.
Rickard Ljung	SWE MPA (SW)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Nicklas Pihlström	SWE MPA (SW)	Statistician	Conduct of the Swedish analyses.
Petteri Hovi	THL (FI)	Senior epidemiologist	Review and approval of deliverables.
Tuija Leino	THL (FI)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Eero Poukka	THL (FI)	Medical specialist	Contribute to drafting of study report and manuscript(s), review and approval of deliverables.
Ulrike Baum	THL (FI)	Epidemiologist	Conduct of the Finnish analyses, review and approval of deliverables.
Niklas Andersson	SSI (DK)	Pharmacoepidemiologist	Contribute to drafting of study plan, protocol, study report and manuscript(s), and the manuscript submission process, revisions etc.
Kristyna Faksova	SSI (DK)	Junior epidemiologist	Literature review, local project management, ENCEPP and STROBE compliance.
Emilia Myrup Thiesson	SSI (DK)	Statistician	Conduct of the Danish analyses and responsible for the meta-analyses of all the site-specific results.
Mia Agermose	SSI (DK)	Junior epidemiologist	Review of study report and manuscript(s)
Tjede Funk	SSI (DK)	Junior epidemiologist	Review of study report and manuscript(s)
Christian Holm Hansen	SSI (DK)	Statistician	Review of study report and manuscript(s)

4. ABSTRACT

Rationale and background: Both heterologous and booster vaccination schedules with covid-19 vaccines are considered instrumental in controlling covid-19. However, data to help inform on the effectiveness of these vaccination regimens in real world settings are limited.

Research question and objectives: The overall aim of this project is to provide combined and country-specific (Denmark, Finland, Norway and Sweden) estimates of covid-19 vaccination schedule effectiveness using comparative study designs.

Primary objectives:

- To provide comparative vaccination effectiveness (VE) estimates for heterologous primary (2-dose) schedules compared to homologous primary (2-dose) schedules as well as heterologous booster (3-dose) schedules compared to homologous booster (3-dose) schedules.
- To provide comparative VE estimates for both heterologous and homologous booster (3-dose) schedules compared to heterologous and homologous primary (2-dose) schedules.

Secondary objectives:

- To provide comparative VE estimates for selected schedules in the periods of Alpha, Delta and Omicron dominance (with variant specific endpoint information to the extent this is possible).
- To explore a) waning of immunity comparing time-since vaccination periods within selected schedules and b) comparative waning comparing time-since vaccination across selected schedules.

Tertiary objectives:

- To provide VE estimates comparing vaccinated to unvaccinated in a child-adolescent population of individuals aged 5 to 17 years.

Study design: Nationwide register-based cohort studies in Denmark, Finland, Norway and Sweden during the study period 27 December 2020 to 28 February 2022.

Population: Source cohorts will consist of all individuals five years of age and older at date of first vaccination. Eligibility criteria for study inclusion will be having received at least the primary immunization (ie, first and second vaccine dose against covid-19) with either AZD1222, BNT162b2, or the mRNA-1273 vaccine and no positive polymerase chain reaction

(PCR) test for SARS-CoV-2 before completing the respective 2- or 3-dose schedule under study.

Variables: The outcomes of interest will be positive PCR test for covid-19 (primary outcome), covid-19 hospitalization (any and at an intensive care unit [ICU]) and covid-19 mortality.

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

Study size: We expect the Nordic countries to contribute with 19.6 million individuals vaccinated with at least two doses - based on a combined population of 23.1 million and a vaccination uptake of 85% among individuals aged 12 years or older. We expect the uptake of 2 doses among 5- to 11-year olds to be 50% in the countries where vaccination has been recommended for this age group. The exact sample size within each comparison will depend on the prevalence of the schedules being studied.

Data analysis: We will compare schedules head-to-head and provide comparative VE estimates using survival analysis to estimate risk differences and risk ratios from adjusted survival curves. We will include adjustment for age, calendar period, sex, comorbidities and vaccination priority group.

Milestones: Study preparations were initiated 25 February 2022. Start of study and data analysis will be 1 April 2022 and the study report is expected to be finalized by 30 June 2022.

5. AMENDMENTS AND UPDATES

None to date.

Number	Date	Section	Amendment or update	Reason

6. MILESTONES

Milestones	Planned dates
Study Plan	10 March 2022
Study Protocol (posted on EU-PAS register).	31 March 2022
Registration in the EU-PAS Register	31 March 2022
Study Report (posted on EU-PAS register).	30 June 2022
Manuscript(s) ready for submission.	25 July 2022

7. RATIONALE AND BACKGROUND

At the end of 2020, mass vaccination programs against the SARS-CoV-2 virus were launched on an unprecedented global scale. The early clinical trials of the two mRNA vaccines, BNT162b2 (BioNTech-Pfizer) and mRNA-1273 (Moderna), had demonstrated surprisingly high vaccine efficacy in preventing symptomatic infection against the original strain.(1,2) This was followed by the two adenoviral vector vaccines, AZD1222 (Oxford-AstraZeneca) and Ad26.COV2.S (Johnson & Johnson-Janssen), also demonstrating their potential in combating the SARS-CoV-2 virus.(3,4) However, how clinical efficacy translates into vaccination effectiveness in the real world setting is complex. Firstly, a number of outcomes are either not included in the clinical trials or cannot be assessed due to lack of statistical power, but are still of great public health importance. This includes effectiveness against transmission, severe covid-19 and fatal covid-19. Secondly, the trial participants do not always match the target populations of mass vaccination programs well with respect to age and covid-19 risk factors. Finally, effectiveness in the observational setting is dynamic and is influenced by a number of factors, a) pathogen-level factors such as predominant variants of concern, b) individual-level factors such as waning of immunity and c) community-level factors such as the degree of herd immunity and testing patterns.

Today, it is clear, that while real world evidence does support the effectiveness of the SARS-CoV-2 vaccines, especially against severe disease, waning of immunity and the emergence of variants of concern with the potential to evade immune responses has resulted in a situation where control of the virus through immunization is a continually moving target.(5) In the current setting, key components to a successful national vaccination strategy involves a) extending the protection of individuals at risk of severe covid-19 by booster doses, and b) reducing transmission to individuals at risk of severe covid-19 by population-level boosting of immunity. To achieve these goals in practice, the use of heterologous schedules are unavoidable due to supply- and logistical issues. Thus, there is an urgent need for observational studies evaluating the effectiveness of heterologous schedules, in particular schedules involving boosting with 3rd doses.

Effectiveness of a heterologous prime-boost schedule

Heterologous AZD1222 / mRNA vaccine prime-boost schedules appear to be just as immunogenic as homologous schedules, and some studies even suggest superior immunogenicity.(6–8) However, the evidence on the effectiveness of prime-boost schedules using heterologous SARS-CoV-2 vaccines are sparse. In Denmark, the effectiveness of a dose of AZD1222 followed by a dose of mRNA vaccine was estimated in a nationwide cohort in the 9

February to 23 June 2021 period.(9) Heterologous vaccination with the combination of AZD1222 and an mRNA vaccine was associated with 88% protection against SARS-CoV-2 infection when compared to being unvaccinated. However, notable limitations include limited duration of follow-up after the 2nd dose and the use of unvaccinated as a comparison group, which may introduce bias e.g. through differences in testing patterns. In Sweden, the effectiveness of a AZD1222 / mRNA prime-boost schedule was estimated in a nationwide cohort with follow-up ending on August 23, 2021.(10) Compared to unvaccinated individuals, the prime-boost schedule provided an effectiveness of 68% against symptomatic infection in contrast to 50% for the homologous AZD1222 schedule ($p<0.001$). Also in this study, the duration of follow-up after the 2. dose was limited (mean duration, 76 days), precluding further exploration of waning of immunity. In Finland, effectiveness against covid-19 hospitalization was also high, >95% for heterologous AZD / mRNA schedules (compared to unvaccinated) among healthcare professionals.(11)

Effectiveness of 3rd dose boosting schedules

It is now clear that the protection against infection afforded by the currently available SARS-CoV-2 vaccines dissipates quickly in contrast to protection against severe covid-19.(12) This fact, together with the emergence of the Omicron variant of concern has highlighted the need for further boosting of immunity in the general population. Immunogenicity and reactogenicity data from phase 2 trials supports that 3rd dose schedules are associated with 1) many fold increases in neutralization antibody levels shortly after vaccination compared to shortly after 2nd dose schedules, and 2) comparable reactogenicity to 2nd dose schedules.(13) In the COV-BOOST study, both homologous and heterologous 3rd dose schedules were evaluated for seven SARS-CoV-2 vaccines.(14) The mRNA vaccines as 3rd doses demonstrated the highest increases in neutralizing antibody levels in both homologous and heterologous schedules. Reactogenicity and safety was broadly similar, except for increased reactogenicity in schedules with mRNA-1273 as a third dose.

A number of observational studies, in particular from Israel, have now provided real-world evidence on the effectiveness of 3. dose schedules.(15–18) In a matched cohort study of a large Israeli health service database including more than 1.4 million individuals, estimated effectiveness against covid-19 hospitalization, severe covid-19 and fatal covid-19.(17) Compared with receiving only two doses at least 5 months ago, a third dose of BNT162b2 effectively protected against the study outcomes. Follow-up after the 3. dose was limited (median follow-up, 13 days) and thus the study does not provide insights into waning of immunity. In Israel, only the mRNA vaccines are approved for use, and BNT162b2 has been predominantly used. Consequently, the Israeli studies do not inform us on heterologous 3. dose

schedules. In a test-negative case-control study using National Health Service data from the UK, a heterologous 3. dose schedule with 2 doses of AZD1222 followed by BNT162b2 was effective against symptomatic infection, both when compared to unvaccinated and individuals with 2 vaccinations.(19)

Effectiveness against Omicron

The emergence of the Omicron variant of concern at the end of 2021 poses a significant challenge to the current vaccination programs. Immunogenicity studies have revealed that two doses provide many fold lower levels of neutralizing antibodies against Omicron than against the original Wuhan strain, and that three doses are needed to provide neutralizing antibody levels comparable to levels observed against the Wuhan strain following two doses.(20) The majority of the real-world evidence on vaccination schedules have been generated during a period where the Alpha and Delta variants have dominated. Studies of effectiveness against Omicron are currently rare. In the UK, a two-dose schedule provided little to no protection against symptomatic infection with the Omicron variant, while a third dose of BNT162b2, both in a homologous- and a heterologous schedule, provided protection of 75.5% and 71.4%, respectively.(21) In Denmark, effectiveness against infection with Omicron was moderate (55.2%) in the first month after two doses and declined rapidly. A third dose re-established the moderate protection against infection (54.6%).(22)

8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this project is to provide combined and country-specific (Denmark, Finland, Norway and Sweden) estimates of SARS-CoV-2 vaccination schedule effectiveness using comparative study designs.

Primary objectives:

- To provide comparative vaccination effectiveness (VE) estimates for heterologous primary (2-dose) schedules compared to homologous primary (2-dose) schedules as well as heterologous booster (3-dose) schedules compared to homologous booster (3-dose) schedules.
- To provide comparative VE estimates for both heterologous and homologous booster (3-dose) schedules compared to heterologous and homologous primary (2-dose) schedules.

Secondary objectives:

- To provide comparative VE estimates for selected schedules in the periods of Alpha, Delta and Omicron dominance (with variant specific endpoint information to the extent this is possible).
- To explore a) waning of immunity comparing time-since vaccination periods within selected schedules and b) comparative waning comparing time-since vaccination across selected schedules.

Tertiary objectives:

- To provide VE estimates comparing vaccinated to unvaccinated in a child-adolescent population of individuals aged 5 to 17 years.

In objective #1, our aim is to answer the question *are heterologous schedules non-inferior compared to homologous schedules*? In objective #2, our aim is to answer the question *what additional benefits will a third dose provide*?

For objectives #3-#5, we will only evaluate schedules where we have sufficient information, e.g. our evaluation of waning of immunity in 2-dose schedules will be limited to the dose interval between the 2. and 3. dose and in 3-dose schedules by the end of study period. Similarly, in variant-specific analyses, we are restricted by the close period-specific correlation between available schedules and dominating variants.

9. RESEARCH METHODS

9.1 Study setting and period

The comparative effectiveness objectives will be addressed through nationwide register-based cohort studies in Denmark, Finland, Norway and Sweden during the study period 27 December 2020 to 28 February 2022. The study period end of 28 February 2022 has been chosen to reflect the significant change in testing strategy in several Nordic countries in the beginning of March 2022.

The Nordic countries provide a unique setting for the study of SARS-CoV-2 vaccination effectiveness. Firstly, the ubiquitous nationwide demography- and health registers, which includes SARS-CoV-2 immunization and surveillance registers, allow for study cohorts with a combined size of 20 million vaccinated individuals. Secondly, both pandemic control, testing and vaccination strategies have varied significantly between countries, allowing for the exploration of heterogeneity in effectiveness accordingly. Finally, the Nordic countries already

have a proven record of accomplishment in conducting rapid vaccination effect evaluations during the pandemic.

9.2 Study design

The source cohort will consist of all individuals aged five years and older as ascertained by the date of first vaccination. The main cohort will consist of individuals aged 18 years or older. We will examine an additional cohort of individuals aged 5 to 17 years old in tertiary analyses – note that not all countries can contribute information in the 5- to 11-year olds. The cohort participants will be classified according to SARS-CoV-2 vaccinations received and followed from the 2. or 3. dose using survival analysis. For 5- to 11-year olds, only the BNT162b2 in a reduced dose has been approved for use (since 25 November 2021). We will apply different study designs according to the objective in question; see subsection *Statistical Analysis* below.

Eligibility criteria for study inclusion will be:

- having received at least the primary immunization (i.e. 1. and 2. vaccine dose against covid-19) with either AZD1222, BNT162b2 or the mRNA-1273 vaccines,
- known residency within the specific country,
- and no positive reverse transcription polymerase chain reaction (PCR) test before the study period start and before receiving a 2. or 3. dose in the distinct schedule evaluated.

We will use comparative designs to evaluate the majority of the objectives; thus, we will avoid comparisons with unvaccinated individuals. This will reduce concerns about bias due to inherent differences in who chooses to remain unvaccinated during the pandemic as well as concerns about healthy vaccinee bias whereby individuals recently vaccinated may be healthier than unvaccinated individuals, since current illness can delay vaccination appointments. This will also reduce concerns about ascertainment bias due to differences in testing behavior between vaccinated and unvaccinated groups. Finally, the research questions at hand are inherently comparative in the real-world setting of a completed mass vaccination rollout. Therefore, it is not a matter of vaccine vs no vaccine, but whether a heterologous schedule is non-inferior to a homologous schedule with respect to comparative VE and whether a third dose increases VE compared to two doses. Individuals who remain unvaccinated at this point in time, are unlikely to be swayed by further real-world evaluations of effectiveness.

9.3 Variables

COVID-19 VACCINATION SCHEDULES

The nationwide registers provide full information on vaccination status including data on specific vaccine brand and date of administration. We will compare the specific heterologous and homologous (2-dose) primary- and (3-dose) booster vaccination schedules according to the study objectives. The date of the respective 2. or 3. vaccine dose examined will serve as the index date. The table below presents the intended vaccine schedules to be studied and comparison schedules.

	Comparison vaccination schedules (reference)								
	Primary schedules							**Booster schedules**	
	Homologous			**Heterologous**				**Homologous**	
Vaccination schedules (studied schedules)	AZD1 AZD2	BNT1 BNT2	MOD1 MOD2	AZD1 BNT2	AZD1 MOD2	BNT1 MOD2	MOD1 BNT2	BNT1 BNT2 BNT3	MOD1 MOD2 MOD3
Heterologous primary schedules									
AZD1BNT2		X							
AZD1MOD2			X						
BNT1MOD2		X							
MOD1BNT2		X							
Heterologous booster schedules									
AZD1AZD2BNT3	X							X	
AZD1AZD2MOD3	X								X
AZD1BNT2BNT3				X				X	
AZD1MOD2MOD3					X				X
BNT1BNT2MOD3		X						X	
MOD1MOD2BNT3			X					X	
BNT1MOD2MOD3						X		X	
MOD1BNT2BNT3							X	X	
BNT1MOD2BNT3						X		X	
MOD1BNT2MOD3							X	X	
Homologous booster schedules									
BNT1BNT2BNT3		X							
MOD1MOD2MOD3			X						

AZD, AZD1222; BNT, BNT162b2; MOD, mRNA-1273. Vaccine abbreviations numbered 1 to 3 reflect the respective vaccines received as 1st, 2nd and 3rd dose. Red: Delta, green: Omicron.

Colors indicate the variant that the specific studied vaccination schedule will primarily have provided protection against in the general population (i.e. not subpopulations targeted for priority vaccination such as frontline personnel, the elderly and individuals at risk of severe covid-19).

For objective #1 (VE of heterologous primary and booster vaccination compared to the homologous counterpart [i.e. 2-dose vs. 2-dose and 3-dose vs. 3-dose]), the expected larger-sized homologous mRNA vaccinated group will be the comparison schedule. For objective #2 (VE of heterologous and homologous booster vaccination compared to the counterpart primary vaccine schedules [i.e. 3-dose vs. 2-dose]), the comparison schedule will be the equivalent primary vaccine schedules to the two first doses received of the distinct studied booster schedule. By the intended comparisons presented above, the study will provide a comprehensive overview of the comparative VE of the majority of schedules used in the Nordic countries.

OUTCOMES

The endpoints will be: 1) a positive PCR test for SARS-CoV-2 (i.e. infection), 2) a covid-19 hospitalization, 3) covid-19 hospitalization at an intensive care unit (ICU) and 4) covid-19 related death. In the primary analyses we will follow up for the endpoints from start of follow-up defined as day 14 after the index date, and until 75 days have elapsed since the start of follow-up. These outcome ascertainment periods have been chosen to balance: a) that the follow-up among the comparison groups will be homogenous in contrast to longer periods of outcome ascertainment where right censoring at study end or another dose may differ substantially between comparison groups, and b) that we need to have sufficient follow-up for the assessment of hospitalization and mortality. When evaluating waning of immunity, follow-up for endpoints will continue beyond day 75.

Covid-19 hospitalization

Covid-19 hospitalization will be defined as an event fulfilling the following criteria: a) hospitalization with a PCR positive test for SARS-CoV-2 dated in the time period beginning 14 days before admission (day -14; the day of admission is day 0) and up to and including 2 days after admission (day 2), b) inpatient hospital contact or a hospital contact with a duration of at least 12 hours and c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1 or Z038PA1 – subject to country-specific coding practices, see table below - TIME-VARYING VARIABLES). Thus, individuals who are hospitalized for conditions not related to covid-19, but who accidentally test positive in the period around admission (14 days before to 2 days after admission) will be included as an endpoint 1 (infection) but not an

endpoint 2 (hospitalization). An example of this could be a patient with a fracture who test positive at admission as part of routine testing. This distinction is particularly important to make during periods of high incidence of infection as in the period of omicron. Covid-19 hospitalization to an ICU (endpoint 3) will be assessed among those individuals fulfilling the criteria for covid-19 hospitalization (endpoint 2).

Covid-19 related mortality

Covid-19 related death will be defined as death within 30 days after PCR positive test for SARS-CoV-2. While this definition will allow us to assess the outcome contemporarily (i.e. no lag time) and is an epidemiological standard measure of infection-related mortality, a limitation to this approach is that it does not include covid-19 related death later than 30 days and may include deaths not specifically related to severe covid-19. Potential bias from these limitations, however, are mitigated by use of the comparative design (in which, we would not expect the risk of potential misclassification to be different between comparative groups). Some countries may be able to supplement with information from cause-of-death registers, but the inclusion of this information will be subject to availability.

In secondary analyses, all outcomes will be sub classified according to SARS-CoV-2 variants of concern using either a "periods of dominance"-approach where for each country we have identified the periods where specific variants dominated or, subject to data availability, variant-PCR and WGS results – see subsection *Intended additional analyses* below.

Through use of the planned outcomes, we will be able to provide information on the VE in relation to any SARS-CoV-2 infection as well as severe covid-19. In addition, variant-specific secondary analyses will provide information on VE according to specific variants of concern. The Nordic health care registers do not hold information to distinguish between symptomatic and asymptomatic documented SARS-CoV-2 infection.

COVARIATES

We will take the following potential confounders into account: age (using year of birth), sex, calendar month and vaccination priority group (nursing home residents, healthcare personnel and individuals at risk of severe covid-19 due to comorbidities).

To account for the risk of severe covid-19, we will adjust for vaccine priority groups; specifically established for each country. In Denmark, the covid-19 vaccine priority groups were governmentally assigned and individuals were prioritized according to the risk of severe infection as well as whether being health and social care workers. In the remaining countries, vulnerable individuals (such as those receiving nursing care or living in nursing homes) and healthcare personnel will be identified. Further, we will also include comorbidities that are

related to the risk of severe covid-19 as separate covariates in our adjustment model (see table of included variables below). The selected ICD-10 codes defining the comorbidities are country-specific and have been chosen for general surveillance purposes based on inputs from national experts and country-specific registration practices. In the interest of saving time on developing a common set of diagnoses codes, we have chosen to take advantage of these coding schemes. In addition, country-specific codes may even be better at identifying comorbidity-related risk groups within each country than common codes.

The intended included variables and the country-specific data sources, definition details and values are presented in the table below.

BASELINE VARIABLES			
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**
Age	Denmark	*The Civil Registration System.* Defined as age at first covid-19 vaccination	Categorical: 5-year bins; and 18-40 years, 40-59, 60-74, and 75+ for stratified analyses of age-specific comparisons.
	Finland	*The Finnish Population Information System.* Defined as age at first covid-19 vaccination.	
	Norway	*Norwegian Population Register.* Defined as age at first covid-19 vaccination.	
	Sweden	*The Total Population Register.* Defined as age at first covid-19 vaccination.	
Sex	Denmark	*The Civil Registration System.* Defined as biological sex.	Binary: male, female
	Finland	*The Finnish Population Information System.* Defined as biological sex.	
	Norway	*Norwegian Population Register.* Defined as biological sex.	
	Sweden	*The Total Population Register.*	

		Defined as biological sex.	
Residency (citizenship)	Denmark	*The Civil Registration System.* Defined as known national resident.	Binary: yes/no
	Finland	Not available.	
	Norway	*Norwegian Population Register.* Defined as known national resident.	
	Sweden	*The Total Population Register.* Defined as known national resident.	
Calendar month	Denmark	*The Danish Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	Categorical (14 levels): calendar month 1 (27 December 2020 to 31 January 2021) to month 14 (February 2022)
	Finland	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	
	Norway	*The Norwegian Immunisation Register (SYSVAK).* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	
	Sweden	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	
	Denmark	*The Danish Vaccination Register.*	Categorical (4 levels): Target risk groups,

Covid-19 vaccine priority groups		Defined as governmentally assigned covid-19 vaccine priority groups, prioritized according to the risk of severe infection as well as whether being health and social care workers (assigned before first covid-19 vaccination).	healthcare personnel, selected relatives of people at high risk, others
	Finland	*Register of Social Assistance.* Vulnerable individuals defined as individuals in 24-hours care (binary status per 27 December 2020). *Social and Healthcare Professionals Register.* Healthcare personnel defined as individuals with the right to act as health care personnel.	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others
	Norway	*The Norwegian Information System for the Nursing and Care Sector.* Vulnerable individuals defined as nursing home resident (binary status per 27 December 2020). *State register of employers and employees.* Healthcare personnel defined as binary status per 27 December 2020.	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others
	Sweden	*Register on persons in nursing homes.* Vulnerable individuals defined as nursing home resident (binary status as of December 2020) *The Longitudinal integrated database for health insurance and labour market studies.* Healthcare personnel defined as healthcare worker occupation status as of October 2018 (binary).	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others

Comorbidity 1: Chronic pulmonary disease (CPD)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: J40-J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Comorbidity 1: CPD	Finland	*Care register for Health Care and Register of Primary Health Care Visits.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 3 years).	Binary: yes/no ICD-10 codes: J41-J47 ICPC-2: R96
Comorbidity 1: CPD	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E84, J41-J47, J701, J703, J84, J98
Comorbidity 1: CPD	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E84, J41-J47 J84, J98
Comorbidity 2: Cardiovascular conditions and diabetes (CVD/DM)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E10-E11, I11.0, I13.0, I13.2, I20-I23, I42.0, I42.6-I42.9, I48, I50.0-I50.3, I50.8, I50.9
Comorbidity 2: CVD/DM	Finland	*Care register for Health Care, Register of Primary Health Care Visits, Special Reimbursement Register and Prescription Centre database.*	Binary: yes/no ICD-10 codes: E10, E11, E13, E14, I11–I13, I15, I20–I25, I50

		Defined as primary or secondary diagnoses or drug prescriptions before 27 December 2020 (look-back 3 years).	ICPC-2 codes: T90, T89 ATC codes:A10A, A10B
Comorbidity 2: CVD/DM	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E10-E14 I05-I09, I110, I130, I132, I1420, I20-I23, I25-I28, I33-I39, I426-I429, I48, I50
Comorbidity 2: CVD/DM	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years). *Swedish Prescribed Drug Register.* Antidiabetic drugs use defined as ≥2 filled prescriptions during 2020.	Binary: yes/no ICD-10 codes: E10-E14, I05-I09, I110, I2, I34-I37, I39, I42, I43, I46, I48-I50 ATC code: A10
Comorbidity 3: Autoimmunity related conditions (AIC)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: D51.0, D59.0, D59.1, D69.0, D69.3, D86, E05.0, E06.3, E27.1, E27.2, G12.2G, G35, G61.0, G70.0, I00, I01, K50, K51, K74.3, K90.0, L12, L40, L52, L80, L93, M05, M06, M08, M30.0, M31.3, M31.5, M31.6, M32, M33, M34, M35, M45
Comorbidity 3: AIC	Finland	*Care register for Health Care, Special Reimbursement Register and Prescription Centre database.*	Binary: yes/no ICD-10 codes: D70.81, D70.89, D80–D84,

		Defined as primary or secondary diagnoses or drug prescriptions before 27 December 2020 (look-back 3 years).	E31.00, E25.0, E27.1, E27.2, E27.4, E31.00, E31.01, E31.08, E89.6, D86, K50, K51, L40, M02, M05–M07, M13.9, M45, M46.0, M46.1, M46.9, M94.1 ATC-codes: H02AB02, H02AB04, H02AB06, H02AB07, L01BA01, L01XC02, L04AA06, L04AA10, L04AA13, L04AA18, L04AA24, L04AA26, L04AA29, L04AA33, L04AA37, L04AB, L04AC, L04AD01, L04AD02, L04AX01, L04AX03
Comorbidity 3: AIC	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: G35, K50-K51, M05-M09, M13-M14
Comorbidity 3: AIC	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: D86, G35, K50, K51, L40, M05-M09, M13, M14, M45
Comorbidity 4: Cancer	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: C00–C85 (without C44), C88, C90-C96

Comorbidity 4: Cancer	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 3 years).	Binary: yes/no ICD-10 codes: C00–C97 (without C44), D051, D39
Comorbidity 4: Cancer	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: C00-C96 (without C44)
Comorbidity 4: Cancer	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: C00-C96 (without C44), D45-D47
Comorbidity 5: Moderate to severe renal disease (CKD)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61
Comorbidity 5: CKD	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 3 years).	Binary: yes/no ICD-10 codes: I12, I13, N00–N05, N07, N08, N11, N14, N18, N19, E10.2, E11.2, E14.2
Comorbidity 5: CKD	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12-I13, N00-N05, N07, N11, N14, N17-N19, Q61

Comorbidity 5: CKD	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
TIME-VARYING VARIABLES			
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES**
Vaccination status	Denmark	*The Danish Vaccination Register.* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	Categorical (multiple levels): AZD1, AZD1AZD2, AZD1MOD2, BNT1BNT2, BNT1, BNT2MOD3 etc.
	Finland	*The National Vaccination Register.* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	
	Norway	*The Norwegian Immunisation Register (SYSVAK).* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	
	Sweden	*The National Vaccination Register.* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	
Documented SARS CoV-2 infection	Denmark	*The Danish Microbiology Database.* Defined as the date of registered positive PCR test for SARS CoV-2.	Binary: yes/no
	Finland	*National Infectious Diseases Register.* Defined as the date of registered positive PCR test for SARS CoV-2.	
	Norway	*Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as the date of registered positive PCR test for SARS CoV-2.	

	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as the date of registered positive PCR test for SARS CoV-2.	
Hospitalization for covid-19	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as hospitalization on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)	Binary: yes/no
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as hospitalization on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient hospital contact, and c) main diagnosis starting with one of the following J0, J1, J20, J21, J22, J46, J80, J81, J82, J83, J84, J851, J86, U071, U072).	
	Norway	*The Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as hospitalization on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)	

	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as hospitalization on the day of, within 14 days of or in the two days after a PCR positive 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)	
Intensive care unit admission	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as admission to an intensive care unit facility during hospitalization for covid-19.	Binary: yes/no
	Finland	*Finnish Intensive Care Consortium's Quality Register for Intensive Care, National Care Register for Health Care and the National Infectious Diseases Register.* Defined as admission to an intensive care unit facility during hospitalization for covid-19.	
	Norway	*The Norwegian Patient Registry (NPR) and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as admission to an intensive care unit facility during hospitalization for covid-19.	
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as admission to an intensive care unit facility during hospitalization for covid-19.	
Covid-19 death	Denmark	*The Civil Registration System and the Danish Microbiology Database.*	Binary: yes/no

		Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.	
	Finland	*The Finnish Population Information System and the National Infectious Diseases Register.* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.	
	Norway	*Norwegian Population Register and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.	
	Sweden	*The Total Population Register and the Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2. Possible to asses cause-of-death using ICD-10 coding of U071, U072, U109.	

9.4 Data sources

We will use the unique nationwide register-data available to us, and construct country-specific cohorts with individual-level information on dates of vaccination and dates of endpoints together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at birth or immigration, enabling unambiguous linkage between registers. Thus, 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 no lag time (except for the 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 the comparative vaccinated groups. Furthermore, given the study end is 28 February 2022, all countries are expected to have full data availability). All 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 data sources that will be used for the 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 the purpose of our study.

Data source (country)	**Details of the individual-level data sources**
Denmark	
The Civil Registration System (23)	The register provides the mandatory unique personal identifier for all permanent residents of Denmark, which allows linkage between all Danish health care services and civil registrations systems. The register has existed since 2 April 1968. In addition, it holds general demographic information such as birthdate and sex as well as continuously updated information and dates on historical addresses, immigration and emigration status, and death.
The Danish Vaccination Register (24)	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 (where reporting to the register became mandatory). Specifically related to this study, the Danish Health Agency have provided the governmentally assigned covid-19 vaccine priority groups that were prioritized groups according to the risk of severe infection as well as whether being health and social care workers.
The Danish Microbiology Database (25)	Information on positive PCR tests for SARS-CoV-2 will be drawn from The Danish Microbiology Database (MiBa) that 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 test. The SARS-CoV-2 PCR tests have been freely available to all individuals in Denmark regardless of symptoms status throughout the covid-19 pandemic.
The National Patient Register (26)	The register covers all hospital-contacts in Denmark with information on the duration of the contact, department of admission and other hospital characteristics. Treating physician-assigned diagnoses have been registered according to ICD-10 codes since 1994.
FINLAND	

The Finnish Population Information System (27)	The register is an electronic register including personal data of all permanent residents in Finland. It contains demographic information such as the unique personal identifier in Finland, date of birth, mother tongue as proxy for country of birth, place of residence, date of death, and date of immigration and emigration. The register is held by the Digital and Population Data Services Agency.
Register of Social Assistance (28)	The register holds information on individuals in long-term care and/or with need for social assistance including social rehabilitation. This assistance may be given in nursing homes, people's own homes or other institutions. The register is held by the Finnish Institute for Health and Welfare.
Social and Healthcare Professionals Register (29)	The register contains person-level data on rights to act as health care personnel.
The National Vaccination Register (30)	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.
National Infectious Diseases Register (31)	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.
National Care Register for Health Care (32)	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.
Finnish Intensive Care Consortium's Quality Register for Intensive Care	The register records data on all patients treated in an intensive care unit in Finland.

Special Reimbursement Register and Prescription Centre database	These data collections are maintained by the Finnish Social Insurance Institution. The Special Reimbursement Register allows the identification of individuals entitled to special reimbursement for medical expenses. The Prescription Centre database allows the identification of individuals using selected medications of interest.
Register of Primary Health Care Visits(33)	The register covers all outpatient primary health care services delivered in Finland.
NORWAY	
The Emergency Preparedness Register for COVID-19 (34) (consisting of the data sources below)	Data for this study will be obtained through the Emergency preparedness register for covid-19 ("Beredt C19"), which is administered by the Norwegian Institute of Public Health, according to the Norwegian Health Preparedness Act §2-4. The register was established in 2020 to provide authorities with up-to-date information on prevalence, causal relationships, and consequences of the covid-19 epidemic in Norway and includes the total population in Norway. The register includes information already collected in the healthcare system and the national health registries (see the following data sources).
Norwegian Population Register	The register holds information on birthdate, immigration and emigration status as well as and death for all residents of Norway.
State register of employers and employees (NAV AA register) (35)	The register holds lists of all employment relationships in Norway, and employers and contractors are obliged to report their employees and freelancers to the register. Employees are classified according to the Norwegian Standard Classification of Occupations) and can thus be used to obtain data on health care personnel status.
The Norwegian Information System for the Nursing and Care Sector (IPLOS) (36)	The register holds information on the health care services that are provided by municipalities in Norway. Report of applicants and recipients of such services to the register is mandatory for all municipalities. The register includes information on home care service and out-of-hospital institutional care, including short- and long-term nursing home stay.
The Norwegian Immunisation Register (SYSVAK) (37)	The register holds information of administered vaccines in Norwegian vaccination programs, including the date of administration and type of vaccine. For the covid-19 vaccines, reporting to the register have been mandatory.

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.
The Norwegian Patient Registry (NPR) (38)	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.
SWEDEN	
The Total Population Register (39)	The register contains information on the unique personal identifier for all individuals in Sweden as well as general demographic information such as date of birth, sex, country of birth, place of residence, date of immigration and emigration and date of death. The register is held by Statistics Sweden.
The Longitudinal Integrated Database For Health Insurance And Labour Market Studies (LISA) (40)	The database contains a wide range of socioeconomic information including occupation (such as healthcare worker). The register is held by Statistics Sweden.
Register On Persons In Nursing Homes (41)	The register holds information on nursing care given to elderly and/or persons with physical, psychiatric or intellectual disabilities at either nursing homes, own homes or other institutions. The register is held by the National Board of Health and Welfare.
The National Vaccination Register (42)	The register contains information on administered covid-19 vaccines including data on 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 On Surveillance Of Notifiable Communicable Diseases (Sminet) (43)	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis performing laboratories, the treating physician or autopsy performing physician, in accordance with the Swedish Communicable Diseases Act. Data include date of disease occurrence, date of testing, date of positive test and diagnoses. The register is held by the Public Health Agency of Sweden.

The Swedish Patient Register (44,45)	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.

9.5 Study size (sample size and power)

We expect the Nordic countries to contribute with 19.6 million individuals vaccinated with at least two doses - based on a combined population of 23.1 million and a vaccination uptake of approximately 85% among individuals aged 12 years or older. The vaccination uptake in the 5-to-11 year olds will be lower: we expect at least 50% for one dose of vaccine in the countries that have recommended vaccination in this age group. The statistical power will depend on the prevalence of the respective schedule being studied and the comparator schedule together with the frequency of the outcomes (PCR positive tests are not uncommon in individuals, while covid-19 hospitalization, ICU admission and deaths will be rarer). The restricted study designs that we will use may also reduce statistical power. However, this is a trade-off in the effort of constructing more comparable groups and, thus, better causal inference. The multi-country nature of our study will increase statistical power, especially for comparisons and outcomes where differences will be difficult to identify for single countries.

9.6 Data management

Data management will be conducted at the country-specific level complying with the respective 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 the purpose of our study. Due to the short timeline and resources allocated, data management and analyses will be accomplished at the national level (i.e. one large combined database containing fully anonymized individual-level data for all 4 countries is not feasible). No sensitive data will be shared between partners in this project. Only effect estimates and aggregated data will be shared.

9.7 Statistical analysis

Heterologous vs homologous comparisons – restriction to period- and age overlapping between groups

For the 2- vs 2- and 3- vs 3-dose comparisons (objective #1, heterologous vs homologous), the day the last vaccine was administered in the respective schedules will serve as the index date (see Figure 1 and 2). One main challenge is that vaccination schedules are correlated with age and calendar period. To certify that the vaccination periods (calendar periods where the specific schedule was used) and age intervals are similar between the comparative groups, we will identify the earliest and latest dates and youngest and oldest ages that comprises 95% of the vaccinated individuals in the heterologous schedule under study (i.e. studied schedule). These period- and age-intervals will serve as an eligibility criteria for the homologous comparison schedule vaccinated individuals. That is, to be included in the respective homologous vaccinated comparison schedule cohort, an individual will have to have received their index vaccine dose within the same period- and age-intervals as the heterologous vaccinated group under study. Individuals, both heterologous and homologous vaccinated, that have received their index vaccine dose outside of the distinctly defined period- and age-95%-intervals will be excluded from the cohort analysis. Adjustment will be accomplished through use of inverse probability weights – see subsection *Adjusted cumulative incidences* below. We will take the following potential confounders into account, age (5-year bins), calendar month of receiving the 2. or 3. dose (according to the compared schedules), sex, vaccination priority group and comorbidities.

Figure 1. Flow chart of construction of the study cohorts for the 2- vs 2-dose and 3- vs 3-dose comparisons (study objective #1).

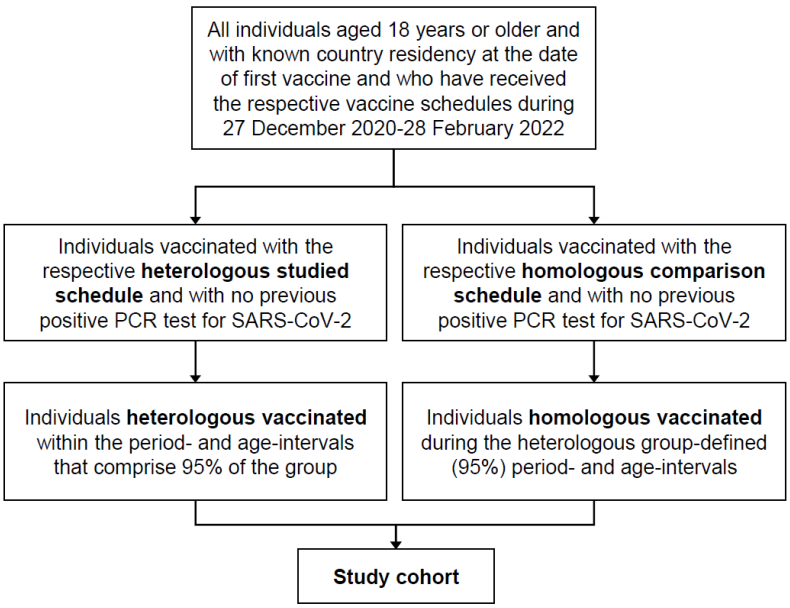
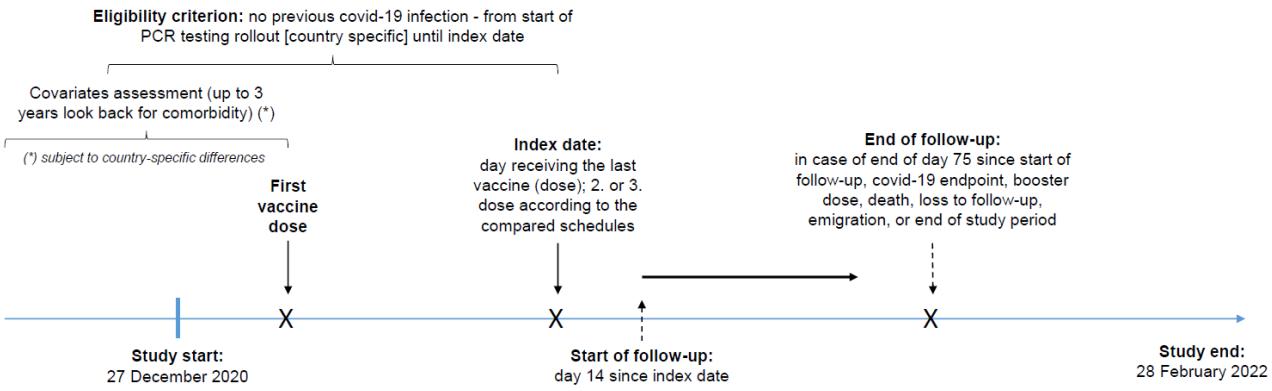


Figure 2. Study design and timeline for the 2- vs 2-dose and 3- vs 3-dose comparisons (study objective #1).

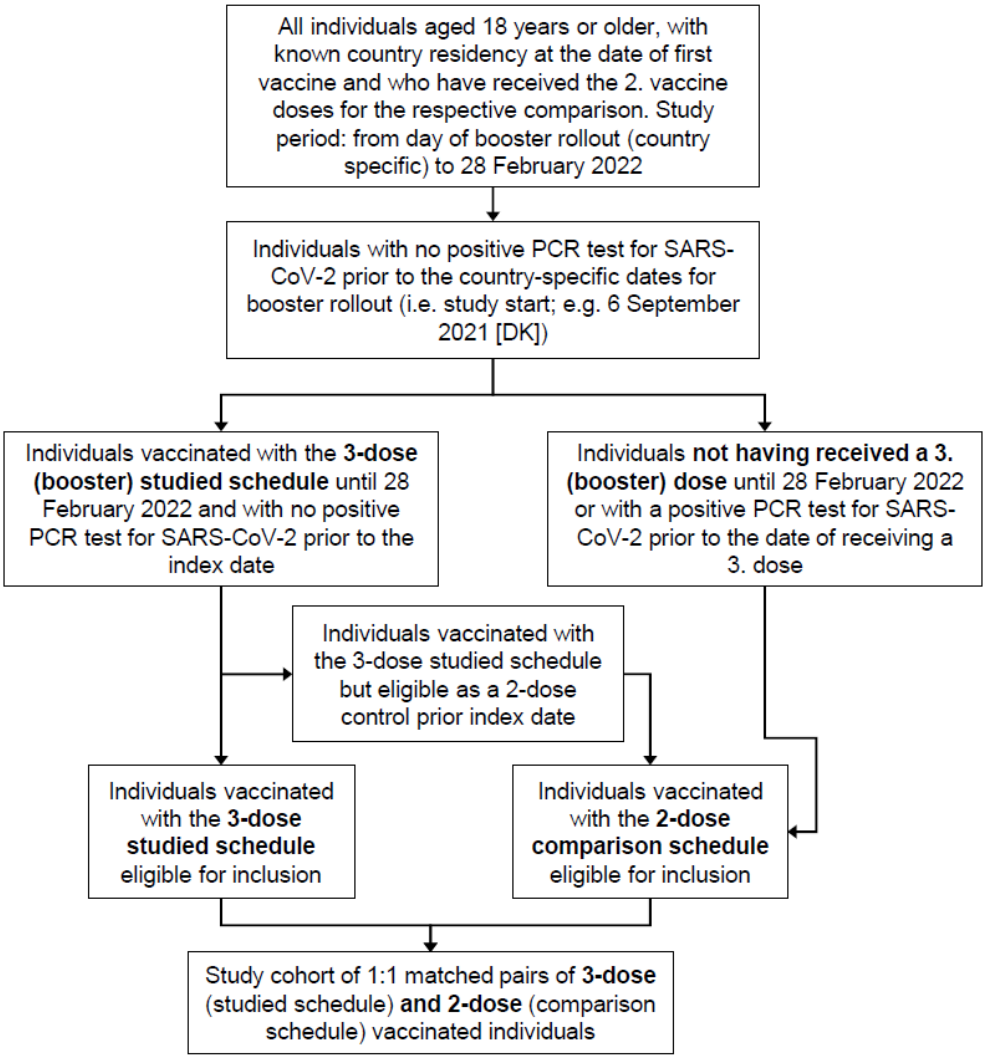


3-dose vs 2-dose comparisons – restriction through matching

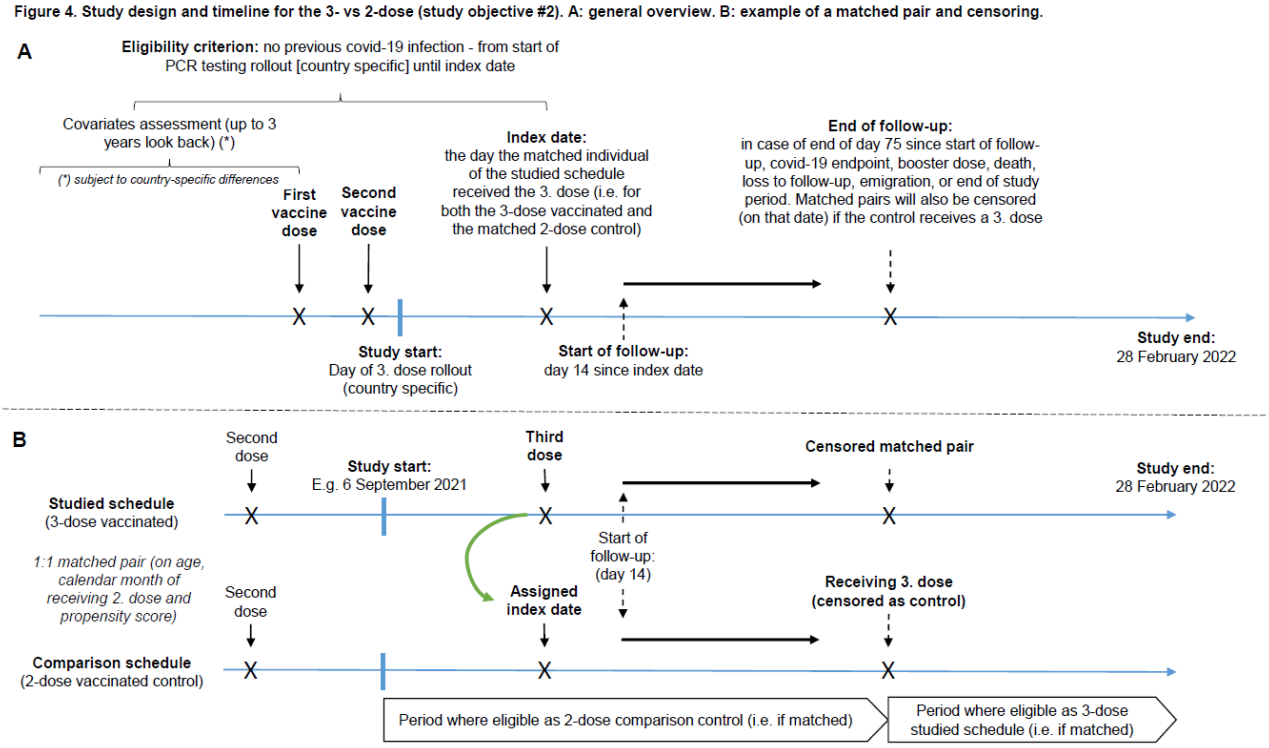
For the 3-dose vs 2-dose comparison (objective #2), we will use a 1-to-1 matched design, similar to previous work (See Figure 3 and 4).(17) The study period will be from the date when rollout of booster doses were initiated, specific for each country (e.g. 6 September 2021 for Denmark and 17 September 2021 for Finland), and until 28 February 2022 (end of study period).

At the day an individual receives a 3. dose (i.e. the index date) of the studied schedule, the individuals will be matched with an individual having received the respective 2-dose comparison schedule (i.e. controls) but have not yet received a 3. dose (i.e. at the this date). For each matched pair, the index date of the individual in the 3-dose studied schedule will be assigned to the 2-dose comparison schedule control individual. The matched controls will be eligible to be included in a 3-dose studied schedule group in case of receiving a future 3. dose to that of the given matched date. Individuals from the 3-dose studied and the 2-dose comparison schedules will be matched on age (5-year bins), calendar month of receiving the 2. dose and a propensity score summarizing potential confounders such as sex, vaccination priority group and comorbidity. The time at which an individual was vaccinated with a 2. dose, is highly correlated with risk of severe covid-19 and/or risk behavior due to the national prioritization of the rollout of the covid-19 vaccines (e.g. individuals of high risk of severe covid-19 and health care workers were prioritized for earlier vaccination than the general public).

Figure 3. Flow chart of construction of the study cohorts for the 3- vs 2-dose comparisons (study objective #2).



Individuals in the country-specific cohorts will be followed from the time they enter one of the vaccination schedules groups and 13 days have passed until one of the endpoints included in the study, end of endpoint ascertainment period, received a booster dose (a 3. dose for 2-dose schedules and a 4. dose for 3-dose schedules), exit from the cohort due to death, loss to follow-up, emigration, or end of study period, whichever occurs first. I.e. for the 3- vs. 2-dose matched comparisons, follow-up for the matched pairs will also end if the control individual receives a 3. dose (on that date; see example in Figure 4B). Follow-up will be conducted separately for each outcome without censoring for the other study outcomes. That is, when evaluating effectiveness against covid-19 hospitalization to an ICU, having a positive PCR test for SARS-CoV-2 or being covid-19 hospitalized does not right-censor the follow-up for this individual. However, note that when the 14 days and 30 days, respectively, after a positive test has passed, the follow-up will be censored in the analyses of hospitalization and ICU, and mortality, respectively.



Adjusted cumulative incidences – heterologous vs homologous comparisons

Risk differences (RDs) and risk ratios (RRs) will be estimated using cumulative incidences at day 75 after start of follow-up (i.e. day 14 after index date) for the heterologous schedule being studied and the homologous comparison schedule, respectively. Comparative VE will be calculated as 1 – RR (for RR < 1.00). The cumulative incidence for the heterologous schedule under investigation will be estimated using the Kaplan-Meier estimator, and the cumulative incidence for the homologous comparison schedule will be estimated by an adjusted Kaplan-Meier estimator using inverse probability weights to make the covariate distribution among the individuals with the homologous comparison schedule similar to the individuals of the heterologous schedule under study.(46) The inverse probability weights will be calculated as ((1-p0)/(1-pc))/ (p0/pc) with p0 equal to the crude probability of the heterologous schedule examined in the combined population of both schedules, and pc equal to the probability of the heterologous schedule examined given covariates. The probability of the study heterologous schedule conditional on covariates will be estimated in the combined population of both schedules using logistic regression including direct adjustment for year of birth (5 year categories; proxy for age), sex, calendar month (monthly categories), comorbidity and vaccination priority group. Confidence intervals (95% CIs) will be calculated using two standard errors of the Kaplan-Meier estimates assuming independence.

Adjusted cumulative incidences - 3-dose vs 2-dose comparisons

Risk differences (RDs) and risk ratios (RRs) will be estimated using cumulative incidences at day 75 after start of follow-up (i.e. day 14 after index date) for the 3. dose schedule being studied and the 2. dose comparator schedule, respectively in the matched populations. Comparative VE will be calculated as 1 – RR (for RR < 1.00). The propensity score for matching will be estimated as the probability of the 3. dose studied schedule conditional on covariates in the combined population of both schedules using logistic regression including direct adjustment for year of birth (5 year categories; proxy for age), sex, calendar month (monthly categories), comorbidity and vaccination priority group. We will calculate 95% CIs using the nonparametric bootstrap method with 1000 repetitions.

Meta-analyses

Where feasible, country-specific effect estimates will be combined using meta-analysis based on random-effects models implemented using *mixmeta* package of R. We will test for homogeneity of effects across countries using the Cochran Q test and will use the delta method to construct 95% CIs assuming independence. For those comparisons where meta-analysis are not feasible, we will present the country-specific results individually.

Intended additional analyses

In secondary analyses, we will stratify comparative VE estimates according to calendar periods of Alpha, Delta and Omicron variant dominance (i.e. when it is estimated that the variant of concern accounts for more than 90% of all cases) or using variant-PCR/WGS results, subject to national availability. These periods will be defined on a country-specific basis, based on the nationally surveillance data on variants of dominance.

Danish variant situation

The calendar periods for specific variant dominance in Denmark are: Alpha/Beta period, 15 March to 30 June 2021; Delta period: 15 July to 15 November 2021; and Omicron period: 28 December 2021 to 28 February 2022. The intermediary transition periods will be left out. As data availability permits, we will in addition assign each endpoint a variant using variant-specific test results or results from whole-genome sequencing (WGS). As an example, in Denmark we utilize both WGS and variant-PCR in covid-19 surveillance.

Finnish variant situation

Alpha/Beta period, 15 March to 9 May 2021; Delta period, 21 June to 27 November 2021; and Omicron period (BA.1), 1 January to 28 February 2022. The intermediary transition periods will be left out.

Norwegian variant situation

Alpha/Beta period, 8 March to 20 June, 2021; Delta period, 19 July to 19 December 2021; and Omicron period, 1 January to 28 February 2022. The intermediary transition periods will be left out.

Swedish variant situation

Alpha/Beta period, 8 March to 6 June 2021; Delta period, 10 July to 19 December 2021; and Omicron period, 3 January to 28 February 2022. The intermediary transition periods will be left out.

Waning

Differences in waning of immunity will be addressed in the head-to-head 2- vs. 2-dose and 3-dose vs. 3-dose comparisons by estimating comparative VE using cumulative incidences at 30 day-intervals (i.e. day 120, 150, 180, 210, 240, 270, 300, 330, and 360 – to the extent that available data allows). Note that this will result in estimates of comparative waning, i.e. comparing cumulative incidences at day *X* for the heterologous studied schedule to cumulative incidences at day *X* for the homologous comparison schedule. Waning of immunity will also be evaluated within schedules, to the extent that the available data allows, by comparing cumulative incidences at day *X* to cumulative incidences at day 75.

Subgroup analysis according to age

We will conduct stratified analyses according to age groups of 18-40 years, 40-59, 60-74 and 75+, using birth cohort and age at index date – subject to the schedules and comparisons where we have data for this.

Children and adolescents population

As both the utilized vaccine schedules, time of vaccination, and doses differ among children and adolescents to the adult population, the vaccine effectiveness of children and adolescents will be examined in a separate cohort. Among adolescents (12- to 17-year olds), we intend to examine similar objectives as outlined for the adult population; however, these analyses will be confined to 2-dose regimens (as the countries have not yet consistently utilized a 3. [booster] dose for this younger population by the time of this study protocol). For children (5- to 11-year olds), we will compare 1 or 2 doses to unvaccinated children (with a study design

similar to that of the 3- vs. 2-dose comparisons in the main cohort), since only BNT162b2 has been used in this age group in the Nordic countries, precluding comparative measures. We will evaluate the following endpoints: infection, hospitalization and diagnosis of multisystem inflammatory syndrome in children (MIS-C).

9.8 Supplementary analyses and quality control

Quality control will be conducted indirectly to evaluate the validity of our main analyses, by making sure that 1) the prevalences of the different schedules and the number of study endpoints match national surveillance dashboards and reports, 2) conduct comparisons between 2-dose schedules and unvaccinated for all study endpoints, to make sure that we are able to recover VE estimates compatible with the current evidence, and 3) utilize a test-negative study design for selected main comparisons.

We will ensure the scientific quality of the work, by division of review tasks and responsibilities in a timely fashion and by adhering to the ENCePP Code of Conduct (see attachment).

Quality control analysis: 2-dose vaccine schedules vs. unvaccinated

Individuals having received homologous primary (2-dose) vaccine schedules of BNT162b2 and mRNA-1273 (i.e. the two most common schedules) will be compared with unvaccinated individuals (controls) with a study design similar to that for objective 2 (i.e. the 3- vs. 2-dose comparison) and as previously done.(47) In these sensitivity analyses, we will evaluate the infection endpoint (positive PCR test for SARS-CoV-2). Vaccinated individuals will be matched 1-to-1 (same matching variables as the main design [except, this analysis will not include calendar month of receiving the 2. dose as not applicable] – age, sex, comorbidity and vaccination priority group) with individuals that were unvaccinated at the vaccinee's day of vaccination. Follow-up will start on day 14 after the 2. vaccine dose (for both the vaccinated and unvaccinated controls [i.e. unvaccinated controls will be assigned the index date of the vaccinated matched individual]) and end at: the day of testing positive, exit from the cohort due to death, loss to follow-up, emigration, vaccination of the matched unvaccinated control or receipt of a (third) booster dose for vaccinated persons, or end of study period, whichever occurs first. Individuals that will be included as unvaccinated controls will also be eligible to enter the study as vaccinated. Survival curves for vaccinated and unvaccinated-control groups will be estimated using the Kaplan-Meier estimator yielding cumulative incidences at day 75 after start of follow-up. We will calculate 95% confidence intervals using the percentile bootstrap method with 1000 repetitions.

Quality control analysis: 3- vs. 2-dose schedule comparisons using a test-negative case-control study design

As an additional quality control, we will apply a test-negative case-control study design as previously done(19,21) to estimate VE against infection (positive PCR test SARS-CoV-2) in 3- vs 2-dose schedule comparisons. The results of these analyses will be compared to the corresponding comparison results from our main analysis. This will inform us on the possible impact of selection bias arising from differences in who is being tested.

Data on all (positive or negative) test results for the period 27 December 2020 to 28 February 2022 will be extracted for those aged 18 years or older (as of 27 December 2020). We will exclude any negative PCR test results taken within 3 days of a previous negative test result (as these results likely represent the same episode), negative test results taken within 21 days before a positive test result (as these are likely to be false negative), and positive and negative test results within 90 days of a previous positive test result. Since we will be evaluating the effectiveness of a 3. dose, only PCR tests taken from the date where the booster doses rollout started, specific for each country (i.e. in Denmark: 6 September 2021 [week 37, 2021]), will be retained for analysis. Participants will contribute with only one randomly chosen negative test result in the follow-up period. The 3. (booster) doses will be identified after this date and there must be at least 6 months (from 6 September 2021 to 13 December 2021 – subject for country-specific variation) or 4.5 months (from 14 December 2021 to 28 February 2022) between the 2. and 3. dose or from 2. dose and onset (i.e. of covid-19 related event). These time periods of "since 2. dose" denotes whether an individuals is eligible of receiving a 3. dose as per national-specific health authority guidelines on booster vaccination rollout. The effectiveness of a 3. dose from day 14 to day 28 (after the index date) will be compared with 2. dose schedules with onsets of events after at least the abovementioned 6 or 4.5 months eligibility criterion as well as to the immediate short period after the booster dose (i.e. the first 2-6 days; day 0 and 1 will not be included due to the potential risk of bias related to any testing due to initial reactogenicity).

VE (1 – the odds of vaccination in cases divided by the odds of vaccination in controls) will be estimated using logistic regression (the PCR test result as the dependent variable); cases will be those testing positive and controls will be those testing negative. The logistic regression models will be adjusted for age, sex, calendar month, vaccine priority group and comorbidity similar to the main analysis.

Please note that country participation for this sensitivity analysis will likewise be subject to the usability of each national booster vaccination rollout strategies to implement this design as well as the availability of dates of negative tests.

9.9 Limitations of the research methods

Although, the planned comparative design mitigates potential bias in recording of healthcare information between vaccinated and unvaccinated, there are some potential limitations to the chosen methodological approach. First, our ascertainment of the study outcomes is dependent on secondary use of national microbiology test results. Depending on the country and period, we will not have complete registration of all infected in the population; only those tested positive. Second, we do not have information on symptoms for our PCR positive cases; thus, this outcome may contain both asymptomatic and symptomatic cases. Third, as noted in the '*Variables*' subsection, our outcomes for severe covid-19 (hospitalization, ICU admission and covid-19 related death) may potentially capture individuals with an outcome not directly related to covid-19 but where covid-19 was a contributing factor or co-occurred. Fourth, while the study design has a high degree of generalizability to similar general populations, some clinical subgroups will not be studied, including: individuals who have received an Ad26.CoV2-S (Johnson & Johnson vaccine), as why the results will not directly help inform on the comparative VE for these situations. Similarly, the proposed study objectives do not include analysis on high-risk subgroups such as individuals with immunocompromised conditions. Fifth, our planned methodology, weighting (for the specified design to address objective #1) and matching (for the specified design to address objective #2) both have strengths and limitations. Advantages of weighting (as opposed to matching) is the potential of preserving a large majority of the total study sample and allowing the assessment of several treatment effects (i.e. average treatment effect for the whole population, ATE). A limitation to this approach is that in case of poor overlap of covariates distribution across comparative groups, this will lower statistical power. Matching has the advantages of providing a 1:1 comparison with intuitive estimates of average treatment effect in the treated (ATT), but limitations to this approach is the discarding of unmatched individuals, which reduces the sample size and generally does not allow for multiple comparisons. A final limitation is that many schedules are strongly correlated with calendar period. Since calendar period is also strongly correlated with variant dominance, the results of many of the schedule comparisons will be variant-specific.

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. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Main results expected in the final study report:

Table 1 will comprise the number of individuals (N[%]) in each country (columns) contributing follow-up in each vaccination schedule under study (rows).

Figure 1 will be a panel of forest plots – one for each schedule comparison. In each single schedule comparison forest plot, the combined VE estimates for each of the four study outcomes will be presented.

Table 2A will present combined VE estimates for the study outcome of PCR positive test for selected schedules according to a) waning of immunity, b) variants, c) age strata and d) vaccination priority group.

Table 2B will present combined VE estimates for the study outcome of covid-19 hospitalization for selected schedules according to a) waning of immunity, b) variants, c) age strata and d) vaccination priority group.

Table 2C will present combined VE estimates for the study outcome of all-cause mortality for selected schedules according to a) waning of immunity, b) variants, c) age strata and d) vaccination priority group.

The country-specific results underlying the combined effect estimates in Figure 1 and Tables 1-2C will be presented in table form in a supplementary appendix.

We anticipate multiple manuscripts.

We will adhere to the STROBE and ENCEPP guidelines when reporting results and drafting the manuscript(s).

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination schedules in the Nordic countries

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7-8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
	2.1.2 The objective(s) of the study?	☒	☐	☐	
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9
4.2	Is the planned study population defined in terms of:				9
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.5 Duration of follow-up	☒	☐	☐	9
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				9
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				9
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				9
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9
10.3 Are descriptive analyses included?	☒	☐	☐	9
10.4 Are stratified analyses included?	☒	☐	☐	9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Anders Hviid

Date: 29/March/2022

Signature: