STUDY PROTOCOL

1. STUDY INFORMATION

Title	**Effectiveness of bivalent Covid-19 booster vaccines in the Nordic countries**
Protocol version identifier	1
Date of latest version of protocol	3 October 2023
EU PAS Register number	[N/A]
Medicinal products	Comirnaty Original/Omicron BA.1 (BNT162b2) Comirnaty Original/Omicron BA.4-5 (BNT162b2) Comirnaty Original monovalent (BNT162b2) Spikevax Original/Omicron BA.1 (mRNA-1273 [/Moderna covid-19 vaccine]) Spikevax Original/Omicron BA.4-5 (mRNA-1273 [/Moderna covid-19 vaccine]) Spikevax Original monovalent (mRNA-1273 [/Moderna covid-19 vaccine]) Vaxzevria (ChAdOx1-S [/AZD1222])
Marketing authorization holder(s)	Pfizer/BioNTech Moderna AstraZeneca
Research question and objectives	The aim of this project is to evaluate the comparative effectiveness of the bivalent boosters in preventing severe Covid-19 outcomes and all-cause mortality among individuals aged 50 years or older with 1 year of follow-up.
Country(-ies) of study	Denmark, Norway, Finland, and Sweden
Authors	Anders Hviid; Niklas Andersson

2. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

TABLE OF CONTENTS

3. RESPONSIBLE PARTIES

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

Name	Professional Title	Over qualifications and role in the study of the organization	Affiliation and address
Jesper Kjær	Director of department	Project management, QA, involvement in scientific tasks, ensuring regulatory anchoring. Overall and contract management	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, 2300 Copenhagen S, Denmark
Niels Henrik Meedom	Project manager and fundraiser		
Anders Hviid	Professor	Study principal investigator; overall coordination and oversight of the study, responsible for the submission of deliverables	Statens Serum Institut, Department of Epidemiology Research, Artillerivej 5, 2300 Copenhagen S, Denmark
Niklas Andersson	Researcher	Pharmacoepidemiologist; Danish principal investigator, scientific coordination and conduct of Danish analyses, responsible for the meta-analyses of all the site-specific results, literature review, ENCEPP, STROBE compliance, drafting study protocols, reports and manuscripts, submission process, revisions etc.	
Eero Poukka	Researcher	Epidemiologist; Finnish principal investigator, local scientific coordination and analyses conduct, review and approval of deliverables, and critical revision of manuscripts.	Finnish Institute for Health and Welfare, Mannerheimintie 166, 00271 Helsinki, Finland
Hinta Meijerink	Senior advisor	Senior epidemiologist; Norwegian principal investigator, local scientific coordination and analyses conduct, review and approval of deliverables, and critical revision of manuscripts.	Norwegian Institute of Public Health, Department of Infection, Control and Vaccines, PO Box 222-Skøyen, 0213 Oslo, Norway
Rickard Ljung	Professor	Senior epidemiologist; Swedish principal investigator, local scientific coordination and analyses conduct, review and approval of deliverables, and critical revision of manuscripts	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.

Organisation	**Name**	**Function in the study**	**Description of the function**
SSI (DK)	Anders Hviid	Principal investigator	Overall coordination and oversight of the study; responsible for the submission of deliverables
SSI (DK)	Niklas Worm Andersson	Danish principal investigator	Scientific coordination of Danish analyses, drafting study protocols, reports and manuscripts.
SSI (DK)	Emilia Myrup Thiesson	Statistician	Conduct of Danish analyses, meta- analyses of country-specific results.
SSI (DK)	Mie Agermose Gram	Junior epidemiologist	Local project management, literature review, drafting study protocols, reports and manuscripts.
DKMA (DK)	Elvira Bräuner	Senior epidemiologist	Project management including contribution to discussions about impact of results on regulatory decision-making
THL (FI)	Tuija Leino	Senior epidemiologist	Local administrative coordination, scientific supervision.
THL (FI)	Eero Poukka	Finnish principal investigator	Scientific coordination of Danish analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
THL (FI)	Jori Tapio Mikael Perälä	Statistician	Conduct of Finnish analyses
SWE MPA (SE)	Rickard Ljung	Swedish principal investigator	Scientific coordination of Swedish analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
SWE MPA (SE)	Nicklas Pihlström	Statistician	Conduct of the Swedish analyses.
FHI (NO)	Hinta Meijerink	Norwegian principal investigator	Scientific coordination of Norwegian analyses, drafting study protocols, reports and manuscripts. Approval of deliverables.
FHI (NO)	Hanna Løvdal Gulseth	Senior epidemiologist	Local administrative coordination, scientific supervision.
FHI (NO)	Anja Brathen Kristoffersen	Statistician	Conduct of the Norwegian analyses.
FHI (NO)	Marissa Erin LeBlanc	Statistician	Conduct of the Norwegian analyses.
FHI (NO)	Jørgen Midtbø	Statistician	Conduct of the Norwegian analyses.

4. ABSTRACT

Rationale and background: The larger Nordic countries of Denmark, Finland, Norway, and Sweden, provide a unique setting for the study of Covid-19 vaccination effectiveness. The ubiquitous nationwide demography- and health registers, which includes SARS-CoV-2 immunization and surveillance registers, allows for very large study cohorts with near real-time data availability. Available evidence suggests that bivalent booster vaccinations during autumn 2022 provided additional protection against Covid-19 hospitalisations while protection against any SARS-CoV-2 infection is more modest. The bivalent booster vaccines were offered to the general public as a fourth dose during autumn 2022 as well as an additional booster for immunocompromised individuals. However, current studies only provide insight on effectiveness in follow-up periods that do not extend beyond 2-6 months and on the Omicron subvariants prevailing during the study period.

Research question and objectives: The aim of this project is to evaluate the comparative effectiveness of the bivalent boosters in preventing severe Covid-19 outcomes and all-cause mortality among individuals aged 50 years or older with up to 1 year of follow-up.

Primary objectives:

1. To provide estimates of VE against severe Covid-19 outcomes at day 365 after immunisation with a BA.1 or BA.4-5 bivalent booster as a fourth dose, comparing a) the BA.1 and BA.4-5 bivalent booster against not having received a fourth dose and b) between the BA.1 and BA.4-5 bivalent and the original monovalent booster.
2. To provide estimates of waning of VE against severe Covid-19 outcomes as the three-monthly relative reduction in vaccine effectiveness until day 365 after immunisation with a BA.1 or BA.4-5 bivalent booster as a fourth dose, comparing a) the BA.1 and BA.4-5 bivalent booster against not having received a fourth dose and b) between the BA.1 and BA.4-5 bivalent and the original monovalent booster.
3. To provide estimates of VE against all-cause mortality at 3, 6, and 9 months post discharge for COVID-19 hospitalisation, comparing a) individuals who received BA.1 and BA.4-5 bivalent boosters as fourth dose against individuals not having received a fourth dose and b) individuals who received the BA.1, BA.4-5 bivalent or original monovalent boosters.

Secondary objectives:

4. To provide VE estimates at day 90/180/365 (pending data distribution) after immunisation with a bivalent booster among immunocompromised individuals.

5. To provide VE estimates at day 365 after immunisation with a bivalent booster among females and males, and 50-69-year-olds and 70+-year-olds.
6. To provide VE estimates at day 365 after immunisation with a bivalent booster according to time since a previous infection.
7. To provide VE estimates at day 365 after immunisation with a bivalent booster according to time between-dose intervals (for both the primary course and the booster doses).
8. To provide VE estimates at day 365 after immunisation with a bivalent booster according to the vaccine brand received as fourth dose.

Study design: Nationwide register-based cohort analyses in Denmark, Finland, Norway, and Sweden during the study period from 27 December 2020 until latest available date in 2023 at time of analyses (e.g., 30 September 2023).

Population: Source cohorts will consist of all individuals who are known residents in the four Nordic countries and have received at least three vaccine doses (i.e., a primary two-dose vaccination course and one booster) with the AZD1222 (Vaxzevria, Oxford-AstraZeneca; as part of the primary vaccination only), BNT162b2, and/or mRNA-1273 vaccines between 27 December 2020 and latest available date in 2023. The main study cohort will consist of individuals who are at least 50 years of age in Denmark, 60 in Finland, 65 in Norway, and 50 in Sweden and eligible fourth dose recipients will include those receiving a fourth dose after (including on this day) 1 September 2022 in Denmark, 18 July 2022 in Finland, and 1 July 2022 in Norway and Sweden. Secondary study cohorts will consist of 1) main study cohort individuals hospitalized for Covid-19 and 2) immunocompromised individuals aged ≥18 years.

Variables: The outcomes of interest will be Covid-19 hospitalisation, Covid-19 mortality and all-cause mortality for the third primary objective. Covariates will be variables of demography, comorbidity, and previous Covid-19 infection and vaccination.

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

Study size: We expect to include at least 3.37 million individuals who have received 4 doses of Covid-19 vaccines (representing a primary course followed by two booster doses) across the 4 Nordic countries. The statistical power of our proposed study is reflected in the VE results from our recent Nordic study on the VE of the bivalent boosters (based on data up until April 2023).(1)

Data analysis: Using target trial emulation, we will compare bivalent booster dose recipients head-to-head and with unboosted individuals as well as between booster recipients in matched survival

analysis that provides comparative effectiveness estimates while taking into account a range of covariates.

Milestones: Study start: 1 August 2023; study planning meeting: 16 August 2023; final first version of study protocol: 5 September 2023; study report: 1 December 2023; manuscript draft: 1 April 2024.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason

6. MILESTONES

Milestones	Planned dates
Study start	1 August 2023
Study planning meeting	16 August 2023
Study Protocol submission (posted on EU-PAS register when approved by EMA).	5 September 2023
Registration in the EU-PAS Register	5 September 2023
Study Report submission (posted on EU-PAS register when approved by EMA).	1 December 2023
Manuscript(s) ready for submission.	1 April 2024

7. RATIONALE AND BACKGROUND

The emergence of the SARS-CoV-2 Omicron variant in late 2021 quickly raised concerns about the effectiveness of the original monovalent Covid-19 vaccines. Bivalent booster vaccinations, which incorporated components from both the ancestral strain and the Omicron variant, were developed to improve protection against the new predominant variant. Subsequently, bivalent boosters were introduced in many countries, including the Nordic countries during autumn 2022 as a 4th dose to the general adult population (and as any additional booster for immunocompromised indiviudals) and results from a number of studies evaluating the effectiveness of bivalent booster vaccinations in different populations and settings are now available.

The protection afforded by the bivalent boosters against SARS-CoV-2 infection appears to be modest.(2–4) In the United States, Link-Gelles and colleagues investigated the comparative effectiveness of bivalent mRNA booster doses against symptomatic SARS-CoV-2 infection in individuals who had previously received monovalent vaccines only.(2) The study found that a bivalent mRNA booster dose provided additional protection against symptomatic XBB/XBB.1.5 infection for at least the first three months after vaccination in individuals who had previously received 2-4 monovalent vaccine doses. Vaccine effectiveness was 52% against symptomatic BA.5 infection and 48% against symptomatic XBB/XBB.1.5 infection in persons aged 18-49 years. A cohort study conducted in the Netherlands by Huiberts and colleagues, assessed the comparative effectiveness of bivalent BA.1 vaccination against self-reported Omicron SARS-CoV-2 infection.(3) The study involved 32,542 participants who had previously received primary and one or two monovalent booster Covid-19 vaccinations. The results showed 31% effectiveness in 18-59-year-olds and 14% effectiveness in 60-85-year-olds, indicating that a bivalent booster provided little additional benefit in preventing SARS-CoV-2 infection. A study in Qatar evaluated the comparative effectiveness of the bivalent mRNA-1273.214 vaccine against SARS-CoV-2 infection in individuals aged 12 and older.(4) The study reported a modest protection of 24.7% against infection with the bivalent vaccine in a period dominated by the Omicron XBB subvariants. The protection was 16.4% among persons with no prior infection and 35.3% among persons with prior infection.

In contrast to infection, the bivalent boosters appear to protect well against severe Covid-19 outcomes such as hospitalisation and death.(5–11) In an early US study, a bivalent booster dose offered significant additional protection against Covid-19-associated hospitalisations among adults aged 65 and older.(6) When compared to unvaccinated individuals, the vaccine effectiveness was 84%, and when compared to individuals who had received two or more doses of monovalent mRNA vaccines it was 73%. In Israel, the comparative effectiveness of a bivalent booster dose in reducing

hospitalisations and deaths due to Covid-19 in individuals aged 65 years or older was evaluated in a study cohort comprising 569,519 participants, including 134,215 (24%) who were given a bivalent booster.(9) The results showed that those who received the bivalent mRNA booster had a lower rate of Covid-19 related hospitalisations compared to those who did not receive the booster corresponding to an effectiveness of 72%. These findings emphasise the importance of bivalent mRNA booster vaccinations in populations at high risk of severe Covid-19. In a larger cohort of individuals aged 12 years or older from North Carolina, a bivalent booster (1.07 million vaccine recipients) was more effective than a monovalent booster (292,659 individuals), with a vaccine effectiveness of 61.8% against severe infection resulting in hospitalisation or death, compared to 24.9% for the monovalent booster.(7,8) Evidence of waning was observed after a peak at 4 weeks, although less pronounced for the bivalent booster. The Moderna and Pfizer-BioNTech bivalent boosters showed similar effectiveness. In our recent Nordic study, we examined the comparative vaccine effectiveness of the bivalent mRNA-booster vaccines in 3.37 million individuals aged 50 or older.(1) The study found that receipt of a bivalent BA.4-5 booster as a fourth dose was associated with a country-combined VE against Covid-19 hospitalisation of 67.8%, while the corresponding VE for bivalent BA.1 boosters was 65.8%. In addition, we observed no significant difference between BA.4-5 and BA.1 boosters when directly compared.

In summary, the available evidence suggest that bivalent booster vaccinations can provide additional protection against severe Covid-19 events and, to a lesser extent, infections. However, current studies only provide insight on effectiveness in follow-up periods that do not extend beyond 2-6 months and on the Omicron subvariants prevailing during the study period.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this project is to evaluate the comparative effectiveness of the bivalent boosters in preventing severe Covid-19 outcomes and all-cause mortality among individuals aged 50 years or older with 1-year of follow-up.

Primary objectives:

1. To provide estimates of VE against severe Covid-19 outcomes at day 365 after immunisation with a BA.1 or BA.4-5 bivalent booster as a fourth dose, comparing a) the BA.1 and BA.4-5 bivalent booster against not having received a fourth dose and b) between the BA.1 and BA.4-5 bivalent and the original monovalent booster.

2. To provide estimates of waning of VE against severe Covid-19 outcomes as the three-monthly relative reduction in vaccine effectiveness until day 365 after immunisation with a BA.1 or BA.4-5 bivalent booster as a fourth dose, comparing a) the BA.1 and BA.4-5 bivalent booster against not having received a fourth dose and b) between the BA.1 and BA.4-5 bivalent and the original monovalent booster.
3. To provide estimates of VE against all-cause mortality at 3, 6, and 9 months post discharge for COVID-19 hospitalisation, comparing a) individuals who received BA.1 and BA.4-5 bivalent boosters as fourth dose against individuals not having received a fourth dose and b) individuals who received the BA.1, BA.4-5 bivalent, or original monovalent boosters.

Secondary objectives:

4. To provide VE estimates at day 90/180/365 (pending data distribution) after immunisation with a bivalent booster among immunocompromised individuals.
5. To provide VE estimates at day 365 after immunisation with a bivalent booster among females and males, and 50-69-year-olds and 70+-year-olds.
6. To provide VE estimates at day 365 after immunisation with a bivalent booster according to time since a previous infection.
7. To provide VE estimates at day 365 after immunisation with a bivalent booster according to time between-dose intervals (for both the primary course and the booster doses).
8. To provide VE estimates at day 365 after immunisation with a bivalent booster according to the vaccine brand received as fourth dose.

Objective #1-2 and #5-8 will be examined within our main study cohort. Objective #3 will be examined within a subpopulation of the main study cohort consisting of those hospitalized for Covid-19. Objective #4 will be examined within a secondary cohort consisting of individuals with presumed immunocompromised conditions aged ≥18 years.

9. RESEARCH METHODS

9.1 Study design

We will take advantage of the unique nationwide register-data available to us, and construct country cohorts with individual-level information on dates of vaccination and dates of effectiveness end-points together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at time of birth or immigration, enabling linkage between registers. The four 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. The cohort participants will be classified according to Covid-19 vaccinations received and followed up using survival analysis. We will utilize comparative designs avoiding comparisons with unvaccinated individuals. This will reduce concern about selection bias due to inherent differences in who chooses to remain unvaccinated.

The study period will start on 1 September 2022 in Denmark, 18 July 2022 in Finland, and 1 July 2022 in Norway and Sweden. These country-specific start dates correspond to when fourth dose vaccination was offered to the general public within the respective country. The study period will end on last date of data availability at time of analyses during autumn 2023 (tentative date: 30 September 2023).

The overall research design builds on target trial emulation methodologies to infer causal relative and absolute effect estimates according to average treatment effect among treated. Key components of the specification and emulation of the pragmatic target trials of the effectiveness of the bivalent Covid-19 booster vaccines against severe Covid-19 using Nordic nationwide registry data are including in table below.

Protocol	**Target Trials Specification**	**Target Trials Emulation**
Eligibility criteria	For the general population target trials (objective #1-#2, #5-#8) • Aged ≥50 years in Denmark and Sweden, ≥60 in Finland, and ≥65 in Norway (country-specific age cut-off for booster recommendations) • Have a known residency within the specific country • Have received three doses of AZD1222, BNT162b2, or mRNA-1273 vaccines only (AZD1222 as part of the primary vaccination course only) • Did not receive a booster (i.e., the third or fourth vaccine dose) within 90 days after the last received vaccine dose • Did not receive the fourth dose before the country-specific start dates • No history of Covid-19 hospitalization prior to the country-specific start dates For the immunocompromised population target trials (objective #4) • Aged ≥18 years in Denmark, Finland, Norway, and Sweden • Have a known residency within the specific country • Have received three doses of AZD1222, BNT162b2, or mRNA-1273 vaccines only (AZD1222 as part of the primary vaccination course only) • No history of Covid-19 hospitalization prior to the country-specific start dates	Same as for the target trials.

	• Have an immunocompromised condition (ascertained by registered diagnosis of solid malignancy, hematologic malignancy, rheumatologic or inflammatory disorder, other intrinsic immune condition or immunodeficiency, organ or stem cell transplant, or received a Covid-19 vaccine dose equivalent of booster dose for immunocompromised)	
Treatment strategies	For the target trial comparing booster vs unboosted: 1) Receive a BA.1 or BA.4-5 bivalent booster 2) Do not BA.1 or BA.4-5 bivalent booster and continue being unboosed during follow-up For the target trial comparing between boosters: 1) Receive a BA.1 bivalent booster 2) Receive a BA.4-5 bivalent booster 3) Receive an original monovalent The bivalent (or original monovalent) booster is received as a 4th dose within the general population (objective #1-#2, #5-#8) and as any booster (≥4th) dose for the immunocompromised population (objective #4)	Same as for the target trials. We define the date of booster vaccination (that is, the index date) according to the registered date of administration.
Treatment assignment	Individuals are randomly assigned to a strategy at baseline in a 1:1 ratio (for immunocompromised population, conditional on number of previous doses received). Individuals will be aware of the assigned treatment strategy.	Individuals are assigned to the strategy compatible with their type of booster received; randomization is assumed conditional on matching (in a 1:1 ratio) on baseline covariates; unboosted are assigned the index date of the matched booster recipient.
Outcomes	Covid-19 hospitalization (ascertained by positive SARS-CoV-2 PCR test in relation to Covid-19 registered inpatient hospitalization) and Covid-19 death (ascertained by positive SARS-CoV-2 PCR test in relation to any (or Covid-19 cause-specific [in Norway]) death.	Same as for the target trials.
Follow-up	Follow-up for each individual will start at day 8 from treatment assignment (to ensure full immunisation among booster recipients) and end on day of outcome event, death, loss to follow-up, receipt of additional booster, 365 days (and 180 days for immunocompromised population) after baseline, or end of data collection, whichever occurs first.	Same as for the target trials.
Causal contrast of interest	Per-protocol	Observational analog to per-protocol effect.
Statistical analysis	Kaplan-Meier estimator to obtain cumulative incidence for each treatment strategy during follow-up. Compare cumulative incidence across treatment strategies by risk ratios (to obtain VE) and risk differences. Person-time since baseline will be stratified consecutive in three-months periods with the Kaplan-Meier estimator to estimate third-monthly changes in VEs; these VEs will contribute to meta-regression estimating comparative waning.	Same as for the target trial except observational analogs of per-protocol.

	Subgroup analyses by sex (female/male), age (</≥70 years), time between vaccine dose (between primary course and 3rd dose and 3rd and 4th dose; for general population target trial), and vaccine brand (Pfizer-BioNTech/Moderna).	

9.2 Setting

The overall source cohort will consist of all individuals aged 18 years or older as of the country-specific start dates.

The main cohort (i.e., the general population cohort) for objective #1-3 and #5-8 will consist of individuals who:

1) Are aged ≥50 years in Denmark and Sweden, ≥60 in Finland, and ≥65 in Norway (country-specific age cut-off for booster recommendations)
2) Have a known residency within the specific country
3) Have received AZD1222, BNT162b2, or mRNA-1273 vaccines only (AZD1222 as part of the primary vaccination course only)
4) Did not receive a booster (i.e., the third or fourth vaccine dose) within 90 days after the last received vaccine dose
5) Did not receive the fourth dose before the country-specific start dates (as this would indicate individuals who were particularly vulnerable to severe disease or individuals with immunocompromising conditions and thus would not be representative of the target general population)
6) No history of Covid-19 hospitalization prior to the country-specific start dates

Objective #3 will be evaluated in secondary cohorts consisting of individuals hospitalized for Covid-19 from the main cohort.

Objective #4 will be evaluated in secondary cohorts consisting of presumed immunocompromised individuals aged ≥18 years. Immunocompromised will be defined as fulfilling at least 1 of the conditions in the table below:

Immunocompromised condition	**Definition**
Solid malignancy (1)	ICD-10 codes: C00–C80 (except C44) registered within 3 years prior to the index date

Hematologic malignancy (2)	ICD-10 codes: C81–C86, C88, C90–C96, D46, D47, D61.0, D70.0, D61.2, D61.9, D71 registered within 3 years prior to the index date
Rheumatologic or inflammatory disorder (3)	ICD-10 codes: D86, E85 [except E85.0], G35, J67.9, L40.1, L40.5, L93, L94, M05–M08, M30, M31.3, M31.5, M32–M35, M46 registered within 3 years prior to the index date
Other intrinsic immune condition or immunodeficiency[a] (4)	ICD-10 codes: B20, B21, B22, B231, B232, B24, B9735, D27.9, D61, D72.8, D80, D81 [except D81.3], D82–D84, D89 [except D89.2], K70.3, K70.4, K72, K74.3–K74.6 [except K74.60 and K74.69], N04, O987, R18, Z21, Z992 registered within 3 years prior to the index date
Organ or stem cell transplant (5)	ICD-10 codes: T86 [except T86.82–T86.84, T86.89, and T86.9], Z94, and Z98.85 registered within 3 years prior to the index date
Received a Covid-19 vaccine dose equivalent of booster dose for immunocompromised (6)	Either 1) any booster dose (≥3rd dose) within 90 days of the last dose[b], 2) receipt of fourth dose before the roll-out of the 4th dose boosters[c], or 3) receipt of fifth or more vaccine dose doses prior to start of study period

Definitions of immunocompromised condition 1 to 5 are adapted and modified from Embi et al.(12) and Hughes et al.(13) [a]We will examine data to determine whether a diagnosis of HIV (ICD-10 codes B20, B21, B22, B231, B232, B24, 0987, Z21) should be included. We do not have access to data on CD4-cell count; if HIV is very rarely occurring (which we assume), we will most likely not include these diagnosis codes in the immunocompromised definition. [b]Covid-19 vaccination courses in the Nordic countries for the general population has generally had time intervals of 6 months or more between boosters. [c]Of note, the start date for the roll-out of the fourth dose was earlier than start of the study period in Finland, Norway, and Sweden, as vulnerable and the elderly living in nursing homes were initially prioritized during Spring 2022, before the fourth dose was rolled out to the general population. The exact start date of the roll-out is to be specified in Finland, Norway, and Sweden (approximately February/March 2022), while it coincides with the start of the study period in Denmark (being 1 September 2022).

9.3 Variables

Exposures

The Nordic countries implemented national vaccination campaigns against SARS-CoV-2 from December 27, 2020, providing free vaccinations to all residents. Phased distribution plans were implemented prioritising vaccination of individuals at highest risk of Covid-19 complications (nursing home residents, healthcare workers, and individuals of older age). Denmark 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. The AZD1222 was similarly halted in Finland and Sweden for the younger population but continued as part of the utilized primary course schedules for the population older than 64 years. The mRNA vaccines have been predominantly used in all countries for booster vaccinations. Ad26.COV2.S has seen very limited use. The Nordic countries have vaccinated around 6 times more individuals with BNT162b2 than with mRNA-1273. Prioritized fourth dose vaccination rollouts to the vulnerable elderly and those living in nursing home

facilitieswere initiated in spring 2022 in Finland, Norway and Sweden, and has been offered more broadly to the general population since summer 2022. Fourth dose vaccination in Denmark was initiated in September 2022, coinciding with the time of the authorization of use of the bivalent boosters. Similar to previously received vaccination doses, the fourth vaccine dose has been classified according to vaccine brand and also according to whether it was a bivalent BA.1, bivalent BA.4-5, or monovalent (original) mRNA-booster vaccine.

For objective #3, we will for the 4 vs 3 dose comparison combine BA.1 and BA.4-5 bivalent boosters to increase statistical power. Depending on data availability, we will stratify this analysis by bivalent booster type.

Outcomes

Covid-19 hospitalisation will be defined as first inpatient hospitalisation with a registered Covid-19-related diagnosis and a positive PCR test for SARS-CoV-2 (within 14 days before to 2 days after the day of admission). We will define Covid-19 death as death within 30 days of a positive PCR test for SARS-CoV-2 in Denmark, Finland, Sweden, while we in Norway it will be defined as death with Covid-19-specific diagnosis registered as the main or contributary cause of death (owing to data availability). In the table below, we provide further details.

Outcome variable	**Country**	**Data source and details**
Covid-19 hospitalisation	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as a hospitalisation with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) a Covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as a hospitalisation with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient hospital contact, and c) a Covid-19 relevant main diagnosis (ICD-10: J00-J22, J46, J80-J84, J851, J86, U071, U072).
	Norway	*The Norwegian Intensive Care and Pandemic Registry (NIPaR).* Defined as an individual with a positive PCR test for SARS-CoV-2 who were inpatient hospitalised and where Covid-19 was registered as the main cause of hospitalisation.
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as a hospitalisation with a PCR positive test for SARS-CoV-2 within 14 days before to 2 days after the admission date, b) inpatient contact or at least 12 hours of contact, and c) a Covid-19 relevant diagnosis code (ICD-10: U071, U072, U109)
Covid-19 death	Denmark	*The Civil Registration System and the Danish Microbiology Database.* 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 with a registered ICD-10 code of U071, U072, U109, or U099 as the main or contributing cause of death.
	Sweden	*The Total Population Register, the Cause of Death 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.

All-cause mortality will be defined as a recording of death in the respective administrative demographic register (vital status is prospectively updated in these registers and also include information on the date of death).

Covariates

For our main cohort analysis objective #1-2 and #5-8, we will take the following potential confounders into account: age (using birth cohort), sex, region of residency, calendar time of last mutual vaccine dose (i.e., either third or fourth dose depending on boosted vs unboosted- [i.e., 4 vs 3-] or between boosters- [i.e., 4 vs 4-] analyses), vaccination priority group (nursing home residents, healthcare personnel, at risk of severe Covid-19 due to comorbidities), previous SARS-CoV-2 infection and selected comorbidities. For the Covid-19 hospitalised cohort analysis (objective #3), we will also include length of hospitalisation as a covariate (as a proxy for severity of event) but not use previous SARS-CoV-2 infection history (as per eligibility criteria, all included are SARS-CoV-2 infected [as hospitalised due to this infection] and any previous SARS-CoV-2 infection is most likely not a strong confounder within the comparison). For the immunocompromised cohort analysis (objective #4), we will also include subtype of immunocompromised condition (as categorized in the 6 levels in the table above). In addition, we will assess the data distribution to help find the optimal categorization of the variables 'Time since SARS-CoV-2 infection', 'Time between primary course and first booster', and 'Time between first and second booster'. Further details of covariate definitions are provided in table below.

Variable	**Country**	**Data source and details**	**Values/codes**
Age	Denmark	*The Civil Registration System.* Recorded birth year. Age defined as the country-specific start date minus birth year.	Categorical (for adjustment, using birth year): 5-year bins Binary (for stratification): </≥ 70 years
	Finland	*The Finnish Population Information System.* Recorded birth year. Age defined as the country-specific start date minus birth year.	

Variable	Country	Data source and details	Values/codes
	Norway	*Norwegian Population Register.* Recorded birth year. Age defined as the country-specific start date minus birth year.	
	Sweden	*The Total Population Register.* Recorded birth year. Age defined as the country-specific start date minus birth year.	
Sex	Denmark	*The Civil Registration System.* Defined as registered sex.	Binary: male, female
	Finland	*The Finnish Population Information System.* Defined as registered sex.	
	Norway	*Norwegian Population Register.* Defined as registered sex.	
	Sweden	*The Total Population Register.* Defined as registered sex.	
Calendar time period of last mutual vaccine dose[a]	Denmark	*The Danish Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e., third or fourth dose).	Categorical (monthly [up to 33 levels]): 1 (27 December 2020-31 January 2021) to month 33 (September 2023)
	Finland	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e., third or fourth dose).	
	Norway	*The Norwegian Immunisation Register (SYSVAK).* Defined by the date where the respective vaccine dose examined was administered (i.e., third or fourth dose).	
	Sweden	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered i.e., third or fourth dose).	
Region of residency	Denmark	*The Civil Registration System.* Defined by last known address at the country-specific start date for the rollout of the fourth vaccine dose.	Categorical: Denmark, 5 levels; Finland, 5 levels; Norway, 5 levels; Sweden, 9 levels
	Finland	*The Finnish Population Information System.* Defined by last known municipality of residence.	
	Norway	*Norwegian Population Register.* Defined by last known address at the country-specific start date for the rollout of the fourth vaccine dose.	
	Sweden	*The Total Population Register.* Defined by last known address at the country-specific start date for the rollout of the fourth vaccine dose.	
Covid-19 vaccine priority groups[b]	Denmark	*The Danish Vaccination Register.* Defined as governmentally assigned Covid-19 vaccine priority groups, prioritised according to the risk of severe Covid-19 as well as whether being health and social care workers (last update 24 May 2021).	Categorical (3 levels): Severe Covid-19 risk group, healthcare personnel, others

Variable	Country	Data source and details	Values/codes
	Finland	*Register of Social Assistance.* Severe Covid-19 risk group was defined as vulnerable individuals in 24-hours care (binary status per 27 December 2021). *Social and Healthcare Professionals Register.* Healthcare personnel defined as individuals with the right to act as health care personnel as of 27 December 2021.	
	Norway	*The Norwegian Information System for the Nursing and Care Sector.* Severe Covid-19 risk group was defined as vulnerable individuals being residents at nursing homes (binary status per 27 December 2020). *State register of employers and employees.* Healthcare personnel defined as binary status per 27 December 2020.	
	Sweden	*Register on persons in nursing homes.* Severe Covid-19 risk group was defined as vulnerable individuals being residents at nursing homes (binary status as of 31 December 2020) *The Longitudinal integrated database for health insurance and labour market studies.* Healthcare personnel defined as healthcare worker occupation status as of 31 October 2018 (binary).	
Comorbidity 1: Chronic pulmonary disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: J40-J47, J60–J67, J684, J701, J703, J841, J920, J961, J982, J983)
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no (ICD-10 codes: J41-J44, J47)
	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)
	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	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: E10-E11, I110, I130, I132, I20-I23, I420, I426-I429, I48, I500-I503, I508, I509)
	Finland	*Care register for Health Care, Register of Primary Health Care Visits, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses (look-back 6 years) or drug	Binary: yes/no (ICD-10 codes: E10, E11, E13-E14, I11–I13, I15, I20–I25; ICPC-2 codes: T89, T90; ATC codes: A10A, A10B)

Variable	Country	Data source and details	Values/codes
		prescriptions (look-back 3 years) before 27 December 2020.	
	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)
	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, I20-I28, I34-I37, I39, I42, I43, I46, I48-I50; ATC code: A10)
Comorbidity 3: Autoimmunity-related conditions[c]	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: D510, D590, D591, D690, D693, D86, E050, E063, E271, E272, G122G, G35, G610, G700, I00, I01, K50, K51, K743, K900, L12, L40, L52, L80, L93, M05, M06, M08, M300, M313, M315, M316, M32, M33, M34, M35, M45)
	Finland	*Care register for Health Care, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses (look-back 6 years) or drug prescriptions (look-back 3 years) before 27 December 2020. **Only if patient also used one of the listed drugs (marked with **)* ***Only if patient also had one of the diagnoses (marked with *)*	Binary: yes/no (ICD-10 codes: D7081, D7089, D80–D84, E250, E271, E272, E274, E310, E896, D86*, K50*, K51*, L40*, M02*, M05–M07*, M139*, M45*, M460*, M461*, M469*, M941*; ATC-codes**: H02AB02, H02AB04, H02AB06, H02AB07, L01BA01, L01XC02, L04AA06, L04AA10, L04AA13, L04AA18, L04AA24, L04AA26, L04AA29, L04AA33, L04AA37, L04AB, L04AC, L04AD01, L04AD02, L04AX01, L04AX03)
	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)
	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 the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: C00–C85 (without C44), C88, C90-C96)

Variable	Country	Data source and details	Values/codes
	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no (ICD-10 codes: C00–C97 (without C44), D051, D39)
	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))
	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	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before the start date for the country-specific rollout of the fourth vaccine dose (look-back 3 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61)
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no (ICD-10 codes: I12, I13, N00–N05, N07, N08, N11, N14, N18, N19, E102, E112, E142)
	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)
	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 since SARS-CoV-2 infection	Denmark	*The Danish Microbiology Database.* Defined as the date of any (last) registered positive PCR test for SARS-CoV-2 prior to the start date for the country-specific rollout of the fourth vaccine dose.	Categorical (for both adjustment and stratification; 3 levels): <6months, 6-12 months, >12 months
	Finland	*National Infectious Diseases Register.* Defined as the date of any (last) registered positive PCR test for SARS-CoV-2 prior to the start date for the country-specific rollout of the fourth vaccine dose.	
	Norway	*Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as the date of any (last) registered positive PCR test for SARS CoV-2 prior to the start date for the country-specific rollout of the fourth vaccine dose.	
	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as the date of any (last) registered positive PCR test for SARS-CoV-2 prior the start date for the country-specific rollout of the fourth vaccine dose.	
	Denmark	*The Danish Vaccination Register.*	

Variable	Country	Data source and details	Values/codes
Time between primary course and first booster		Defined according to the specific administered Covid-19 vaccines and date of vaccinations.	Binary (for stratification only): </≥ 12 months
	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.	
Time between first and second booster	Denmark	*The Danish Vaccination Register.* Defined according to the specific administered Covid-19 vaccines and date of vaccinations.	Binary (for stratification only): </≥ 12 months
	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.	
Length of Covid-19 hospitalisation	Denmark	*The National Patient Register and the Danish Microbiology Database.* Time between admission and final discharge date.	Categorical (adjustment variable for objective #3 only; 4 levels)[e]: ≤2 days, 3-5 days, 6-14 days, >14 days
	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Time between admission and final discharge date.	
	Norway	*The Norwegian Intensive Care and Pandemic Registry (NIPaR).* Time between admission and final discharge date.	
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Time between admission and final discharge date.	

[a] Due to data availability in Sweden, the country-specific end of study period might be some weeks earlier. For the bivalent 4 dose vs monovalent 4 dose comparisons, we will consider whether alternative time period bins should be used for these analyses to optimize the balance between covariate control and matched cohort size. [b] To account for the risk of severe Covid-19, we will adjust for targeted Covid-19 high-risk groups of severe Covid-19, specifically established for each country. In Denmark, the Covid-19 vaccine priority groups were governmentally assigned and individuals were prioritised according to the risk of severe infection (identified by the treating physicians) as well as whether being health or social care workers. In the remaining countries, the variable was constructed based on the identification of vulnerable individuals (as defined by those receiving nursing care or living in nursing homes) and whether being health or social care workers. [c] Autoimmunity-related conditions includes a range disorders such as inflammatory bowel diseases, diseases involving the blood, immune mechanism or endocrine systems, inflammatory rheumatic diseases, psoriasis, lupus erythematosus, multiple sclerosis; subject to country-specific definitions. The selected diagnosis codes to define comorbidities were country-specific, based on inputs from national experts and country-specific registration practices as part of the general national surveillance purposes. This was done as we anticipated that

country-specific definitions were likely better at identifying comorbidity-related risk groups within each country than a common set of code definitions. [d] The date defines the first day where omicron (sublineages BA.1 and BA.2) accounted for ≥90% of all registered SARS-CoV-2 infection cases within the country as per national surveillance data of SARS-CoV-2 variants. [e] Upon examination of the data distribution, we will consider whether this variable should be included as a spline instead of categorical.

9.4 Data sources

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. Given the no-to-very-little lag time of the data source, our analyses will be reflecting real-time information. We will have full data availability for all variables (with no missing data; all the exposures, outcomes, or covariates are either present or not) during the study period and as reporting to national registers is mandatory/structurally implemented, this provides a near-complete follow-up of all residents over time.

Country/data source	**Details**
Denmark	
The Civil Registration System (14)	The register provides the unique personal identifier for all permanent residents of Denmark that allows linkage between all Danish health care registers and civil registrations systems. 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 (15)	The register holds information on all vaccinations administered in Denmark including vaccination date, type/trade name, dose, and product batch number ever since Nov 15, 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 prioritised groups according to the risk of severe infection as well as whether being health and social care workers.
The Danish Microbiology Database (16)	Information on positive PCR tests for SARS-CoV-2 are obtainable via The Danish Microbiology Database (MiBa) that has data on all microbiology samples analysed at Danish microbiology departments as well as test results, date of sampling, date of analysis, type of test, and interpretation of test. The SARS-CoV-2 PCR tests are freely available to all individuals in Denmark regardless of symptoms status.
The National Patient Register (17)	The register holds information on all hospital contacts in Denmark including the duration of the contact, and diagnoses, which are assigned by the treating physician and registered according to ICD-10 classification system (since 1994).
Finland	
Finnish Population Information System (18)	The register is held by the Digital and Population Data Services Agency and contains personal data on all permanent residents in Finland such as the unique personal identifier, date of birth, place of residence, date of death, and date of immigration, and emigration.
Register of Social Assistance (19)	The register is held by the Finnish Institute for Health and Welfare and contains information on individuals receiving long-term care and/or social assistance (in e.g., nursing homes, people's own homes or other institutions) including social rehabilitation.

Country/data source	Details
Social and Healthcare Professionals Register (20)	The register holds data on individuals right to act as health care personnel.
National Vaccination Register (21)	The register is based on the Register of Primary Health Care Visits and contains information on all Covid-19 vaccinations administered in Finland including date of vaccination, batch number, and trade name.
National Infectious Diseases Register (22)	The register is held by the Finnish Institute for Health and Welfare and contains information on notifiable diseases in accordance with the Finnish Communicable Diseases Act that must be reported by the laboratories and the treating-physicians, or the physician performing an autopsy and hold information on sample dates of all laboratory-confirmed SARS-CoV-2 infections in Finland
National Care Register for Health Care (23)	The register is held by the Finnish Institute for Health and Welfare and comprises information on all inpatient and outpatient hospital contacts in Finland, including admission and discharge dates, whether hospitalisation was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, and whether discharged as deceased, to own private residence or other health care facilities.
Special Reimbursement Register and Prescription Centre database	These databases are maintained by the Finnish Social Insurance Institution. The Special Reimbursement Register holds information on individuals entitled to special reimbursement for medical expenses. The Prescription Centre database holds information on individuals using selected medications of interest.
Register of Primary Health Care Visits (24)	The register is held by Finnish Institute for Health and Welfare and holds data on all primary health care services delivered in Finland.
Norway	
The Emergency Preparedness Register for Covid-19 (25) (consisting of the data sources below)	Data for the Norwegian analyses were collected 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 captures the entire population. The register includes information from the healthcare system and the national health registers presented below.
Norwegian Population Register	The register holds information on birthdate, immigration, emigration status, and death for all residents of Norway.
State register of employers and employees (NAV AA register) (26)	The register holds lists of all employment relationships in Norway for which employers and contractors are obliged to report to. Employees are classified according to the Norwegian Standard Classification of Occupations which we then used to identify whether individuals were health care personnel.
The Norwegian Information System for the Nursing and Care Sector (IPLOS) (27)	The register contains information on the health care services provided by municipalities and reporting of applicants and recipients of such services is mandatory in Norway. Available data includes information on home care services and out-of-hospital institutional care, including nursing home stays.
The Norwegian Immunisation Register (SYSVAK) (28)	The register holds information on administered vaccines in through the Norwegian vaccination programme, including date of administration and type of vaccine/trade name. For the Covid-19 vaccines, reporting to the register is mandatory.

Country/data source	Details
Norwegian Surveillance System for Communicable Diseases (MSIS)	The register holds information on selected infectious diseases for which reporting to the register is mandatory, including all Covid-19 tests and testing date and results.
The Norwegian Patient Registry (NPR) (29)	The register holds data on all contacts with specialist health-care services in Norway, including admission and discharge dates diagnoses recorded according to ICD-10 during hospitalisation or outpatient contact.
The Norwegian Intensive Care and Pandemic Registry (NIPaR) (30)	This is a national clinical registry that was expanded to include Covid-19 patients in conjunction with the Covid-19 pandemic. The register holds information on all patients who have tested positive for SARS-CoV-2 and were admitted to hospital including intensive care unit admissions. It is mandatory for all Norwegian hospitals to report to this register.
Sweden	
The Total Population Register (31)	The register is held by Statistics Sweden and contains data on the unique personal identifier assigned to all individuals in Sweden plus general demographic information such as date of birth, sex, country of birth, place of residence, and date of immigration and emigration.
The Cause of Death Register (32)	The register holds information on date of death and underlying as well as contributing causes of death.
The Longitudinal Integrated Database For Health Insurance And Labour Market Studies (LISA) (33)	The database is held by Statistics Sweden and holds many socioeconomic variables such as data on occupation which we used to identify whether individuals were health care personnel.
Register On Persons In Nursing Homes (34)	The register is held by the National Board of Health and Welfare and holds data on nursing care given in either nursing homes, own homes or other institutions to elderly and/or persons with physical, psychiatric or intellectual disabilities.
The National Vaccination Register (35)	The register is held by the Public Health Agency of Sweden and contains information on administered Covid-19 vaccines in Sweden including data on date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses).
Register On Surveillance Of Notifiable Communicable Diseases (Sminet) (36)	The register is held by the Public Health Agency of Sweden and 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 included are e.g., date of disease occurrence, date of testing, date of positive test, and diagnoses.
The Swedish Patient Register (37,38)	The register is held by the National Board of Health and Welfare and comprises data on all in- and outpatient hospital specialist care in Sweden including data on dates of admission and discharge, whether hospitalisation was planned or acute, codes for discharge diagnoses (recorded according to ICD-10-SE) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, and type of department.

9.5 Study size (sample size and power)

Based on data from our previous work, we expect to be able to include at least 3.4 million individuals who have received a bivalent or monovalent booster as a fourth Covid-19 vaccine dose across the 4

Nordic countries (1.6 million BA.4-5 booster; 1.0 million BA.1 booster; and 0.9 million ancestral-strain monovalent booster vaccinated).(1) The statistical power of our proposed study is reflected in the VE results from our recent Nordic study on the VE of the bivalent boosters (based on data up until April 2023).(1) Based on these data (with follow-up to day 90 from the fourth dose vaccination date), we expect to be able to include at least 2,250 Covid-19 hospitalised individuals across the four countries who at time of hospitalisation had previously received four vaccine doses. The statistical power, however, will most likely be reduced for some subgroup analysis, also owing to the restricted target trial emulation study design. However, this is a trade-off in the effort of constructing more comparable groups and, thus, better causal inference.

9.6 Data management

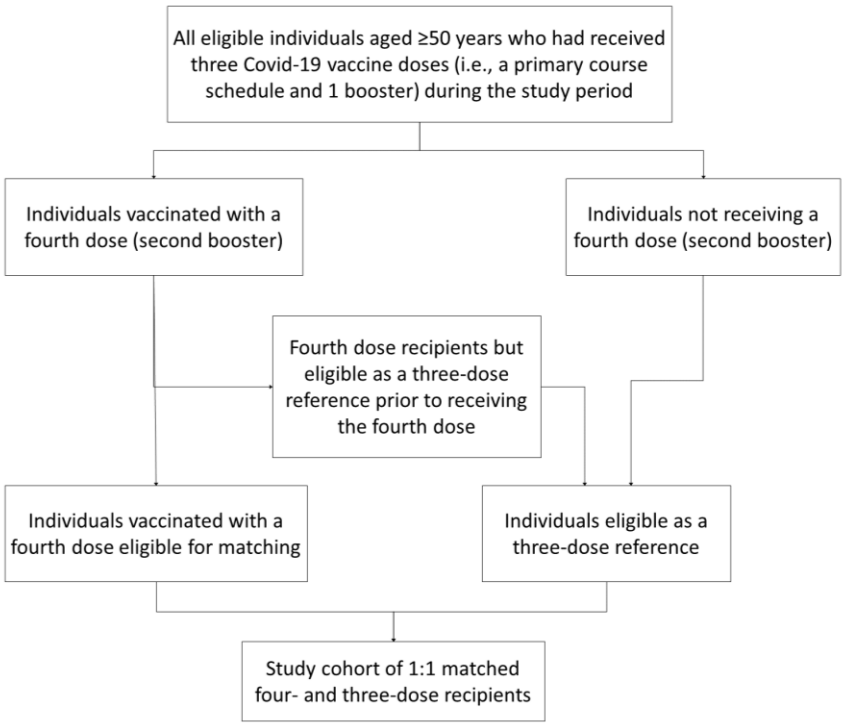
No individual-level data can or will be shared between countries or with EMA. Each country is the sole data owner and controller of their own data. Only country-specific results will be shared and combined results will be generated using meta-analysis. Data management and statistical analyses will be conducted using a Common Data Model (CDM). The analytical group in Denmark will code the statistical analyses using R-scripts (R version 4.2.2.). The R-scripts will be made available on GitHub (also during the programming phase to facilitate input and comments). The analysts in each of the participating countries will then run the R-scripts and return the output to Denmark. The country-specific results will be combined using meta-analysis in Denmark.

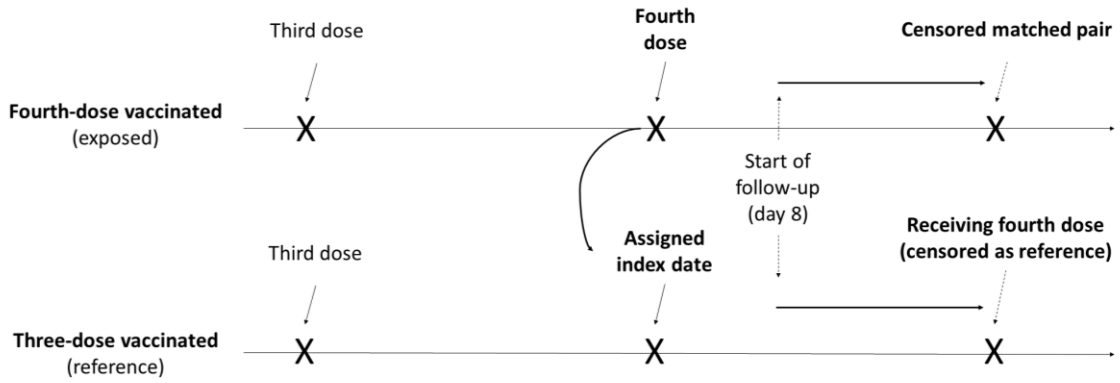
9.7 Data analysis

Procedures

We will use a matched study design to evaluate the effectiveness of a bivalent BA.1 or BA.4-5 (or monovalent [original]) mRNA-booster vaccine (as the fourth dose) in comparison with having received three monovalent vaccine doses only (i.e., nonboosted with a fourth dose) as well as between fourth dose recipients. For the boosted vs nonboosted (i.e., 4 vs 3 dose) comparisons, individuals who have received a fourth dose will be matched on the day of vaccination with individuals who have not yet received a fourth dose. Individuals will be matched on age (5-year bins), calendar time according to when the third dose was received (monthly bins), and a propensity score including sex, region of residence, vaccination priority groups (i.e., individuals at high-risk of severe Covid-19 or healthcare workers), selected comorbidities (chronic pulmonary disease, cardiovascular conditions or diabetes, autoimmunity-related conditions, cancer, and moderate to severe renal disease), and previous history of SARS-CoV-2 infection characteristics. The day the fourth dose was administered within each matched pair will serve as the index date for both individuals. If individuals who were included as a

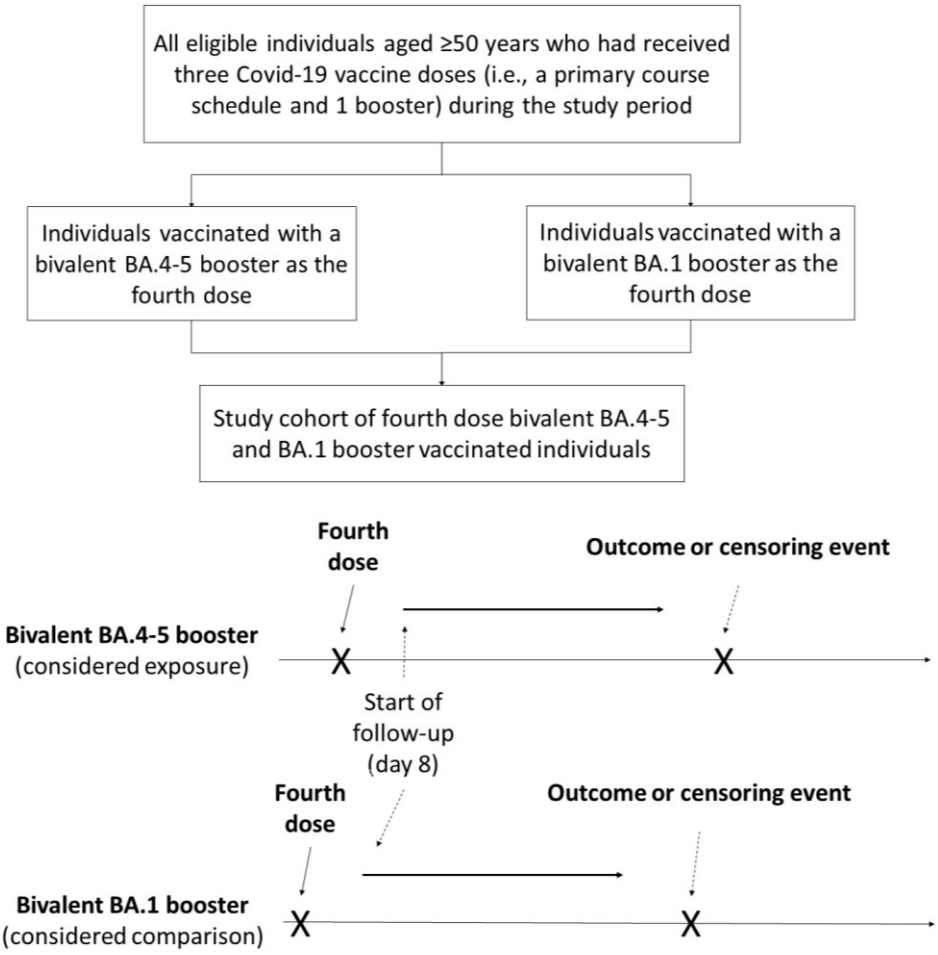
matched nonboosted (previously three-dose vaccinated) individual (i.e., a reference individual) received a fourth dose later than the assigned index date, they will be allowed to potentially re-enter as a fourth-dose recipient in a new matched pair on that given date. The figure below illustrates the study cohort construction.





For the between booster (i.e., 4 vs 4 dose) comparison, BA.4-5 booster and BA.1 booster recipients (as a fourth dose) will be matched on age (5-year bins), calendar time according to when the fourth dose was received (monthly bins), and a propensity score including sex, region of residence, vaccination priority groups (i.e., individuals at high-risk of severe Covid-19 or healthcare workers), selected comorbidities (chronic pulmonary disease, cardiovascular conditions or diabetes, autoimmunity-related conditions, cancer, and moderate to severe renal disease), and previous history of SARS-CoV-2

infection. The day the fourth dose was administered will serve as the index date for each respective individual. The figure below illustrates the study cohort construction.



We will follow individuals from day 8 after the index date (to ensure full immunisation among booster recipients) up until the day of an outcome event, 365 days has passed since the index date (i.e., allowing up to 357 days of follow-up since day 8), receipt of additional booster, death, emigration, or end of the study period, whichever occurs first.

Statistical analysis

We will use logistic regression to estimate the propensity score of receiving a specific booster dose given covariates as predictors. We will match (without replacements) on age, calendar time of last mutual vaccine dose (i.e., third or fourth dose), and the propensity score (with a calliper width of 0.01).

Cumulative incidences will be estimated by the Kaplan-Meier estimator, and from these we will calculate the comparative VE as 1 – risk ratio at day 365. The corresponding 95% CI will be calculated using the delta method. Country-specific estimates will be combined by random-effects meta-analyses implemented using the *mixmeta* package in R.

Comparative waning will be estimated using meta-regression.(39) First, we will estimate the VEs (in the specific comparison being evaluated) in each consecutive three-months period (day 8-90, day 91-180, 181-270, and 271-365) by stratification on time since booster vaccination. Second, the resulting estimates will be analysed using meta-regression to provide a ratio of VEs per three-month intervals as a measure of waning.

Subgroup analyses will be conducted according to sex, age groups (</≥70 years), time since last SARS-CoV-2 infection (<6, 6-12, >12 months), time between primary course and first booster (</≥ 12 months), time between first and second booster (</≥ 12 months), and bivalent booster brand (Pfizer-BioNTech and Moderna).

All-cause mortality (objective #3)

We will examine risk of all-cause mortality at 3, 6, and 9 months since recovery from first Covid-19 hospitalisation. The source population for this cohort will be the same as the main cohort for the main comparative analyses (i.e., individuals aged ≥50 years who have received at least 3 doses of vaccine and no previous Covid-19 hospitalisation prior to study start). Recovery will be defined as discharge from an inpatient hospital stay for Covid-19 (i.e., similar to the outcome definition used in the main analyses). We will start follow-up on day 8* since discharge, to ensure that there are no rapid re-hospitalisations (if this occurs, the individual, can re-enter the cohort on day 8* after discharge from the re-hospitalisation) and end follow-up on outcome event of all-cause mortality; emigration; Covid-19 vaccination; day 90, 180, or 270; or end of study period. Since this is likely to be a cohort of limited size, we will utilize a complete cohort analysis using multivariate Cox regression model with covariate adjustment (same covariates as main analyses, except not previous SARS-CoV-2 infection, and including length of hospitalization). The exposure (Covid-19 vaccination status [4 vs 3 doses]) will be evaluated at time of Covid-19 hospitalisation (admission date). Dependent on data availability we will consider further categorization of the associations according to subgroups similar to those of the main cohort analyses.

**Day 8 is a prespecified arbitrary best guess. The final grace period will be determined by examining the distribution of days after discharge for any rehospitalisations in the Danish data. Depending on the data distribution, we will decide if it is necessary to perform additional sensitivity analysis in this regard.*

Immunocompromised (objective #4)

In secondary cohorts of individuals aged ≥18 years with presumed immunocompromised conditions, we will evaluate the effectiveness of the bivalent boosters received as the ≥4th dose. We will utilize the same analytical matched approach as in the main analysis described above. Dependent on the data distribution, time of VE assessment may be day 180 or day 365 since booster vaccination. Similarly, dependent on data availability, we will further subgroup bivalent booster recipients according to booster received as fourth, fifth, or ≥sixth dose, and we will endeavour to assess similar subgroups as in the main cohort subgroup analyses including waning VE analysis. The VE estimates will be indirectly compared with the VE estimates from the main cohort analysis while stressing the limitations of such indirect comparisons.

9.8 Supplementary analyses and quality control

Quality control will be conducted indirectly to evaluate the validity of our main analyses, by 1) making sure that the prevalence of the different schedules and the number of study endpoints match national surveillance dashboards and reports, 2) descriptive and analytical results cohere to our previous findings, and 3) using a Common Data Model (CDM), by which national register data are standardised to a common structure, format and terminology in order to allow the same statistical programming scripts to be used in each country. The use of a CDM with common statistical programming scripts will facilitate efficient use of resources and reproducibility of the statistical analyses. We will ensure the scientific quality of the work, by division of review tasks (including statistical code review) and responsibilities in a timely fashion and by adhering to the ENCePP Code of Conduct (see attachment). We will perform matching quality diagnostics to assess the control of matched parameters. For the 4 vs 3 dose comparisons, we will include a sensitivity analysis where starting follow after day 21/28 after the index date for the main comparison to further reduce the potential of transient healthy vaccinee effect around the time of vaccination as well as *spill-over effect* (that is, prior to the index date) given that some severe Covid-19 events may take longer time to develop. Lastly, in case data do not allow for 365-day effectiveness estimation (e.g., owing to heavy censoring of matched pairs), we will, similarly to the comparison analyses among immunocompromised, use an alternative shorter length of follow-up (e.g., day 180/270).

9.9 Limitations of the research methods

The study has a number of limitations. First, the observational nature of the study hampers the possibility to fully exclude residual unmeasured confounding. A major concern would be presence of such unmeasured confounding factors that were unevenly distributed between compared matched

groups (i.e., not indirectly adjusted for by the set of included covariates, that is, proxies). We will include a range of pre-specified confounders and study a population representative of the general audience targeted for bivalent booster vaccinations. The precision of our exposure, Covid-19 vaccination, will rely on the registered vaccination within the registers and recorded time of administration. To the best of our knowledge, the assignment of the type of booster as the fourth dose was unselective during the study period (except for the initial prioritisation of older and vulnerable individuals during the first two weeks of study period in Denmark) and our study period should reflect a time of which fourth dose vaccination was offered to the general public.

For the outcomes of Covid-19 hospitalisation and death, our outcome definition will most likely also capture a small proportion of cases where the infection with SARS-CoV-2 only partly contributed to or coincided with the timing of hospitalisation, that is, hospitalisations or deaths where SARS-CoV-2 infection were not the sole cause. In addition, those acquiring SARS-CoV-2 infection (and who were hospitalised or died) without PCR test results we will not capture; we have no information on at-home antigen testing for SARS-CoV-2 infection. PCR testing has been advised as confirmatory to antigen testing and recommended for individuals at risk of severe Covid-19. Any of such outcome misclassification would most likely tend to bring the estimates toward a null effect.

These abovementioned potential limitations are mitigated by our utilization of an active comparative design as opposed to comparisons with unvaccinated. In the 4 vs 3 comparisons (i.e., fourth dose boosted vs nonboosted), the follow-up among those who have not received a fourth dose is contributed from individuals who have yet to receive a fourth dose and individuals who will never receive a fourth dose. In the more immediate time-periods following the index date, the comparison is dominated by the former group while closer to day 365 of follow-up the comparison is dominated by the latter group. Individuals who never receive a fourth dose are more likely to be different from those who elect to get booster vaccination and this can introduce e.g., healthy vaccinee bias if these differences are not accounted for by the included covariates.

Our statistical precision will rely on the overlap of covariate distributions between comparisons (affecting the final matched cohort sizes). As a consequence, the possibilities for direct head-to-head comparison between bivalent and monovalent boosters as a fourth dose will most likely be limited due to the less overlap of calendar periods of use and the need for stringent control hereof (due to otherwise potential confounding by e.g., differences in waning of third dose, background population infection rates, and circulating variants).

Both vaccination status and SARS-CoV-2 variants of predominance are strongly correlated with calendar time. This limits possibilities for directly comparing effectiveness estimates obtained during different variants predominance periods (background transmission rates and population characteristics most likely differ) as well as evaluating longer-term follow-up effectiveness in relation to only one SARS-CoV-2 variant. As such, the analyses will instead reflect evaluations of the initiated Covid-19 vaccination strategies at that given time.

We aim to perform a panel of different subgroup and secondary analyses to extend current knowledge of the impact of timing of vaccination in relation to both previous SARS-CoV-2 infection and vaccination schedules received. However, we do not aim to address hybrid immunity of vaccination followed by a subsequent infection on future Covid-19 risk, given that such analysis with use of observational data would be hampered by collider bias.(40)

As we take confounders into account by matching to emulate a target trial that provides causal inference of the effectiveness of bivalent booster vaccination, our estimands represent the average treatment effect among treated, and, thus, results from the individual matched comparisons should primarily be interpreted separately. Consequently, an indirect comparison of for example VE among immunocompromised with VE in the general (immunocompetent) population is not ideal. Research questions such as "*is the special vaccination schedule for immunocompromised, with shorter interval between doses and more vaccinations necessary?*" and "*does the special vaccination schedule for immunocompromised have the desired effect on VE?*" are not straightforward and cannot be directly answered by use of our observational data. This would necessitate a comparison group of immunocompromised following the vaccination schedules of the general population and no overlap of such treatment strategies (i.e., vaccination programmes) exists within our real-world data due to the distinct vaccination recommendations set out for individuals with immunocompromised conditions by the national health authorities. However, if the size of the data allows, we will be able provide VE as well as waning effectiveness estimates among immunocompromised which can assist the evaluation of such study questions to some extent.

Given the broad inclusion within each Nordic country, our results will likely have a high degree of generalisability to other similar populations. However, our assessment of the comparative effectiveness of bivalent mRNA-booster vaccines given as a fourth dose against severe Covid-19 outcomes may only indirectly support any evaluation of the effectiveness of these vaccines within other Covid-19 vaccination schedule scenarios. Our findings may similarly not directly generalize to certain subpopulations not individually studied or to populations with a demographically different

composition. Such subpopulations include for example the general population younger than 50 years old or other specific clinical subgroups that were not studied.

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:

- Tables of baseline characteristics before and after matching
- Figures of matching quality diagnostics
- Figures of cumulative incidences of severe Covid-19 outcomes until day 365 since day of fourth dose vaccination
- Tables of effectiveness estimates for all and by subgroups of the main study cohort
- Figures of waning VE for main study cohort (and immunocompromised study cohort if possible)
- Tables of association estimates for all and by subgroups of the all-cause mortality cohort
- Tables of effectiveness estimates for all and by subgroups of the immunocompromised study cohort

We anticipate multiple manuscripts, and findings will be reported to the general public by institutional press releases upon acceptance in academic peer-review journals or upon uploading to pre-print server (if decided relevant to do so).

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

Example of tables of main results:

	Country-combined measures of association (95% CI) at day 365 of follow-up			
	COVID-19 hospitalization		COVID-19 death	
	RD	CVE	RD	CVE
4- vs 3-dose schedule analysis				
Fourth dose bivalent BA.1 boosted vs nonboosted				
All	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)
Strata				
Male	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)
Female	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)	XX (XX to XX)
<70 years				
≥70 years				
<6 months since last SARS-CoV-2 infection				
6-12 months since last SARS-CoV-2 infection				
>12 months since last SARS-CoV-2 infection				
<1 year between primary course and booster				
≥1 year between primary course and booster				
<1 year between first and second booster				
≥1 year between first and second booster				
BNT162b2 as fourth dose				
mRNA-1273 as fourth dose				
Fourth dose bivalent BA.4-5 boosted vs nonboosted				
All				
Strata				
Etc.				
Fourth dose monovalent (original) boosted vs nonboosted (additional comparison)				
All				
Strata				
Etc.				
4- vs 4-dose schedule analysis				
Bivalent BA.4-5 vs bivalent BA.1 boosted				
All				
Strata				
Etc.				
Bivalent BA.4-5 vs monovalent (OG) boosted (additional comparison)				
All				
Strata				
Etc.				
Bivalent BA.1 vs monovalent (OG) boosted (additional comparison)				
All				
Strata				
Etc.				

13. REFERENCES

1. Andersson NW, Thiesson EM, Baum U, Pihlström N, Starrfelt J, Faksová K, et al. Comparative effectiveness of bivalent BA.4-5 and BA.1 mRNA booster vaccines among adults aged ≥50 years in Nordic countries: nationwide cohort study. BMJ. 2023 Jul 25;382:e075286.

2. Link-Gelles R. Early Estimates of Bivalent mRNA Booster Dose Vaccine Effectiveness in Preventing Symptomatic SARS-CoV-2 Infection Attributable to Omicron BA.5– and XBB/XBB.1.5–Related Sublineages Among Immunocompetent Adults — Increasing Community Access to Testing Program, United States, December 2022–January 2023. MMWR Morb Mortal Wkly Rep [Internet]. 2023 [cited 2023 Jan 31];72. Available from: https://www.cdc.gov/mmwr/volumes/72/wr/mm7205e1.htm

3. Huiberts AJ, Gier B de, Hoeve CE, Melker HE de, Hahné SJ, Hartog G den, et al. Effectiveness of bivalent mRNA booster vaccination against SARS-CoV-2 Omicron infection, the Netherlands, September to December 2022. Eurosurveillance. 2023 Feb 16;28(7):2300087.

4. Hiam Chemaitelly, Houssein H. Ayoub, Sawsan AlMukdad, Jeremy Samuel Faust, Patrick Tang, Peter Coyle, et al. Bivalent mRNA-1273.214 vaccine effectiveness in Qatar. medRxiv. 2023 Jan 1;2023.04.15.23288612.

5. Tenforde MW. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults — VISION Network, Nine States, September–November 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2023 [cited 2023 Apr 25];71. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7153a1.htm

6. Surie D. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years — IVY Network, 18 States, September 8–November 30, 2022. MMWR Morb Mortal Wkly Rep [Internet]. 2022 [cited 2022 Dec 22];71. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e2.htm

7. Lin DY, Xu Y, Gu Y, Zeng D, Wheeler B, Young H, et al. Effectiveness of Bivalent Boosters against Severe Omicron Infection. New England Journal of Medicine. 2023 Jan 25;0(0):null.

8. Lin DY, Xu Y, Gu Y, Zeng D, Sunny SK, Moore Z. Durability of Bivalent Boosters against Omicron Subvariants. New England Journal of Medicine. 2023 Apr 12;0(0):null.

9. Arbel R, Peretz A, Sergienko R, Friger M, Beckenstein T, Duskin-Bitan H, et al. Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study. The Lancet Infectious Diseases [Internet]. 2023 Apr 13 [cited 2023 Apr 20];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00122-6/fulltext

10. Grewal R, Buchan SA, Nguyen L, Nasreen S, Austin PC, Brown KA, et al. Effectiveness of mRNA COVID-19 monovalent and bivalent vaccine booster doses against Omicron severe outcomes among adults aged ≥50 years in Ontario, Canada [Internet]. medRxiv: medRxiv; 2023 [cited 2023 Apr 18]. p. 2023.04.11.23288403. Available from: https://www.medrxiv.org/content/10.1101/2023.04.11.23288403v1

11. Kirsebom FCM, Andrews N, Stowe J, Ramsay M, Bernal JL. Long-term duration of protection of ancestral-strain monovalent vaccines and effectiveness of the bivalent BA.1 boosters against COVID-19 hospitalisation during a period of BA.5, BQ.1, CH.1.1. and XBB.1.5 circulation in England [Internet]. medRxiv; 2023 [cited 2023 Apr 18]. p. 2023.03.31.23288018. Available from: https://www.medrxiv.org/content/10.1101/2023.03.31.23288018v1

12. Embi PJ. Effectiveness of 2-Dose Vaccination with mRNA COVID-19 Vaccines Against COVID-19–Associated Hospitalizations Among Immunocompromised Adults — Nine States, January–September 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021 [cited 2022 Jan 10];70. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e3.htm

13. Hughes K, Middleton DB, Nowalk MP, Balasubramani GK, Martin ET, Gaglani M, et al. Effectiveness of Influenza Vaccine for Preventing Laboratory-Confirmed Influenza Hospitalizations in Immunocompromised Adults. Clin Infect Dis. 2021 Dec 6;73(11):e4353–60.

14. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014 Aug;29(8):541–9.

15. Krause TG, Jakobsen S, Haarh M, Mølbak K. The Danish vaccination register. Euro Surveill. 2012 Apr 26;17(17):20155.

16. Voldstedlund M, Haarh M, Mølbak K, MiBa Board of Representatives. The Danish Microbiology Database (MiBa) 2010 to 2013. Euro Surveill. 2014 Jan 9;19(1):20667.

17. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clinical Epidemiology. 2015 Nov;449.

18. Digi- ja väestötietovirasto [Internet]. [cited 2022 Mar 20]. Population Information System | Digital and population data services agency. Available from: https://dvv.fi/en/population-information-system

19. Finnish Institute for Health and Welfare (THL), Finland [Internet]. [cited 2022 Mar 20]. Register of Social assistance - THL. Available from: https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/social-assistance

20. Terhikki Register [Internet]. [cited 2022 Mar 20]. Terhikki Register - valvira englanti. Available from: http://www.valvira.fi/web/en/healthcare/professional_practice_rights/terhikki_register

21. Baum U, Sundman J, Jääskeläinen S, Nohynek H, Puumalainen T, Jokinen J. Establishing and maintaining the National Vaccination Register in Finland. Euro Surveill. 2017 Apr 27;22(17):30520.

22. Finnish Institute for Health and Welfare (THL), Finland [Internet]. [cited 2022 Mar 20]. Finnish National Infectious Diseases Register - THL. Available from: https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-diseases-register

23. Finnish Institute for Health and Welfare (THL), Finland [Internet]. [cited 2022 Mar 20]. Care Register for Health Care - THL. Available from: https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care

24. Finnish Institute for Health and Welfare (THL), Finland [Internet]. [cited 2022 Mar 29]. Register of Primary Health Care visits - THL. Available from: https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/register-of-primary-health-care-visits

25. Lindman AES. Norwegian Institute of Public Health. [cited 2022 Mar 20]. Emergency preparedness register for COVID-19 (Beredt C19). Available from: https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/

26. nav.no [Internet]. [cited 2022 Mar 20]. State Register of Employers and Employees (Aa-registeret). Available from: https://www.nav.no/en/home/employers/nav-state-register-of-employers-and-employees

27. Helsedirektoratet [Internet]. [cited 2022 Mar 20]. Iplos-registeret. Available from: https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/iplos-registeret

28. Trogstad L, Ung G, Hagerup-Jenssen M, Cappelen I, Haugen IL, Feiring B. The Norwegian immunisation register--SYSVAK. Euro Surveill. 2012 Apr 19;17(16):20147.

29. Bakken IJ, Ariansen AMS, Knudsen GP, Johansen KI, Vollset SE. The Norwegian Patient Registry and the Norwegian Registry for Primary Health Care: Research potential of two nationwide health-care registries. Scand J Public Health. 2020 Feb;48(1):49–55.

30. Helse Bergen [Internet]. [cited 2022 Oct 16]. Registrering i Norsk pandemiregister – informasjon til ansatte. Available from: https://helse-bergen.no/norsk-pandemiregister/registrering-i-norsk-pandemiregister-informasjon-til-ansatte

31. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016 Feb;31(2):125–36.

32. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017 Sep;32(9):765–73.

33. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019 Apr;34(4):423–37.

34. Socialstyrelsen [Internet]. [cited 2022 Mar 20]. Registret över insatser till äldre och personer med funktionsnedsättning. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/aldre-och-personer-med-funktionsnedsattning/

35. Chrapkowska C, Galanis I, Kark M, Lepp T, Lindstrand A, Roth A, et al. Validation of the new Swedish vaccination register - Accuracy and completeness of register data. Vaccine. 2020 May 22;38(25):4104–10.

36. Rolfhamre P, Jansson A, Arneborn M, Ekdahl K. SmiNet-2: Description of an internet-based surveillance system for communicable diseases in Sweden. Euro Surveill. 2006;11(5):103–7.

37. Socialstyrelsen [Internet]. [cited 2022 Mar 20]. National Patient Register. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/

38. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011 Jun 9;11:450.

39. Horne EMF, Hulme WJ, Keogh RH, Palmer TM, Williamson EJ, Parker EPK, et al. Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose: OpenSAFELY cohort study using linked electronic health records. BMJ. 2022 Jul 20;378.

40. Monge S, Pastor-Barriuso R, Hernán MA. The imprinting effect of covid-19 vaccines: an expected selection bias in observational studies. BMJ. 2023 Jun 7;381:e074404.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

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: Effectiveness of bivalent Covid-19 booster vaccines 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: 05/September/2023

Signature: