STUDY REPORT

1. TITLE

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

Main authors: Anders Hviid, DMSc

Department of Epidemiology Research

Statens Serum Institut

Copenhagen, Denmark

Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, Faculty of Health and Medical Sciences

University of Copenhagen

Copenhagen, Denmark

Niklas Worm Andersson, MD

Department of Epidemiology Research

Statens Serum Institut

Copenhagen, Denmark

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2. ABSTRACT

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

Keywords: covid-19, comparative vaccine effectiveness, heterologous vaccine schedules, nationwide cohorts, Nordic countries.

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

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

Primary objectives:

1. To provide comparative vaccine effectiveness (VE) estimates for heterologous primary (2-dose) schedules compared to homologous primary (2-dose) schedules as well as heterologous booster (3-dose) schedules compared to homologous booster (3-dose) schedules (i.e. 3-dose and booster dose schedules are used as synonyms throughout the report).
2. To provide comparative VE estimates for both heterologous and homologous booster (3-dose) schedules compared to heterologous and homologous primary (2-dose) schedules.

Secondary objectives:

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

Tertiary objectives:

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

Study design: Nationwide register-based cohort studies. We compared schedules head-to-head for comparative VE estimates using survival analysis to estimate risk differences and risk

ratios from adjusted survival curves. We included adjustment for age, calendar period, sex, region of residence, selected comorbidities, and vaccination priority group.

Setting: Denmark, Finland, Norway, and Sweden during 27 December 2020 to 28 February 2022.

Population: Source cohorts consisted of all individuals five years of age and older at date of first vaccination. Eligibility criteria for study inclusion were having received at least the primary immunization (ie, first and second vaccine dose against covid-19) with either AZD1222, BNT162b2, or the mRNA-1273 vaccines and no positive polymerase chain reaction (PCR) test for SARS-CoV-2 before completing the respective 2- or 3-dose schedule under study (for the purpose of objective #5, being vaccinated was not an eligibility criterion).

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

Variables and data sources: The outcomes of interest were positive PCR test for covid-19 (i.e. documented infection; primary outcome), covid-19 hospitalisation (any and at an intensive care unit [ICU]), and covid-19 mortality. Data sources were nationwide demography- and health registers within each participating country.

Results: Across the four countries and included comparisons, our results largely support that heterologous primary and booster schedules with the AZD, BNT, and/or MOD vaccines provided protection against covid-19 outcomes was not inferior to the effectiveness of homologous schedules (objective 1).

Similarly, our findings largely support that both heterologous and homologous booster dose schedules in the Nordic countries improved the protection against covid-19 outcomes as compared to primary schedules (objective 2). However, while the increased protection against severe covid-19 outcomes of the booster dose schedules was noticeable, the observed effectiveness against documented infection was less distinct for some country-specific comparisons, particularly in Denmark.

Given the high correlation between calendar period and the respective vaccination schedules, and calendar period and the covid-19 variant of predominance, our results within the individual comparisons are primarily variant specific (objective 3). As such, the results from our omicron-specific booster schedules analyses were comparable to the main findings.

Our analyses of waning immunity, where extending the follow-up from 75 days to 180 days for the primary schedules, were not suggestive of an inferior longer-term protection of the heterologous schedules compared with homologous schedules (objective 4).

Our analyses of the vaccine effectiveness of primary schedules among children and adolescents aged 5 to 11 and 12 to 17 years found a high protection against covid-19 endpoints as compared with unvaccinated (objective 5); this includes risk of hospitalisation and MIS-C for those schedules, countries, and age groups where these severe outcomes could be examined.

Discussion: Key points for interpreting the study results and the individual comparisons of each country include the strong correlation between calendar time and the specific vaccine schedules as well as limitations to the outcome definitions. For the former, this means that the observed comparative effectiveness for each schedule was primarily variant specific and related to/affected by the covid-19 scenarios within the country at that specific time such as differences in infection rates and policies. For the latter, the outcome of documented infection was particularly vulnerable to difference sources of ascertainment bias. These include differences in population infection rates and national testing policies and strategies across countries as well as over time, and differences in test- and risk behaviour between compared schedules as well as over time and potentially also between countries. In addition, the outcome of documented infection did not differentiate on symptomatic or asymptomatic covid-19. Furthermore, while the severe covid-19 endpoints were not considered influenced by these types of ascertainment biases, a limitation to these endpoints include the relative rarity of cases (also ascribed to the protection afforded by the covid-19 vaccines). Therefore, the identified number of cases for the respective outcomes was low to none for many comparisons, especially if the number of vaccinated individuals was relatively small. Consequently, not all preplanned comparisons could provide adequate estimates for these severe outcomes in all countries. For the vast majority of the comparisons, the country-specific analyses were too heterogeneous for combined meta-analysis.

Previous studies to assess the effectiveness of heterologous primary and booster schedules are few and most studies compared with unvaccinated individuals to estimate vaccine effectiveness. While the utilised comparative design is a methodological strength to this study, this also precludes the comparison of our results to these other works. The comparative design was a main focus of this study design as comparisons to unvaccinated hold concerns of healthy vaccinee bias and fundamental differences in testing and risk behaviour between vaccinated and unvaccinated groups, in particular when assessing the effectiveness of booster schedules. Also, as the vast majority of the population (at least in the Nordic countries) have received a primary vaccination schedule, those who choose to remain unvaccinated is unlikely to be representative of the general population while these comparisons would provide little evidence

to inform vaccination strategies in the current setting. Moreover, our analyses of booster schedules were mainly conducted during a period of omicron predominance and previous studies that have assessed the effectiveness of booster schedules, including heterologous schedules, for which data are particularly sparse, were carried out when the delta variant was predominant, and limited previous comparative data exist for the risk of severe outcomes during the omicron period.

Lastly, although the primary schedules examined among children aged 5 to 11 years and 12 to 17 years provide increased protection against covid-19 endpoints, the respective results cannot be directly compared across the two age groups as the children aged 5 to 11 years were vaccinated during a period of omicron predominance, and those children aged 12 years or older were primarily vaccinated during a period of delta predominance. Also, the four countries contributed differently to these children and adolescent analyses, and not all countries nor schedules could be used to analyse the risk of severe outcomes. However, for both the younger and older age group of children (omicron and delta variant period, respectively), where analyses were feasible, primary vaccination schedules increased the protection of severe outcomes.

Conclusion: This study compared the effectiveness of 1) heterologous primary- and booster covid-19 vaccination schedules to the corresponding homologous schedules and 2) heterologous or homologous booster schedules to primary schedules in the Nordic countries. Additional sub objectives included examining the (comparative) vaccine effectiveness according to covid-19 variant, waning immunity, and age groups including children and adolescents.

Our results largely support that heterologous primary and booster schedules with the AZD, BNT, and/or MOD vaccines provided protection against covid-19 endpoints that was not inferior to the vaccine effectiveness of homologous schedules with the BNT or MOD vaccine (objective 1). Similarly, our findings largely support that both heterologous and homologous booster doses in the Nordic countries increased the protection against covid-19 outcomes as compared to primary schedules (objective 2). However, while booster doses improved protection against severe covid-19 outcomes, the effectiveness against documented infection was less apparent for some comparisons, particularly in Denmark. These observed differences in the protection against acquiring infection were most likely due to differences in national testing strategies, in background population infection rates, and in testing- and risk behaviour across countries.

Our results within the individual comparisons were primarily variant specific. As such, the administration of booster dose schedules in the Nordic countries were at a time of omicron variant predominance; thus, analyses according the effectiveness against different covid-19 variants (objective 3) were not feasible. When we increased the specificity of the booster

schedule analyses to omicron variant (according to specific calendar period), we found similar results to our main findings.

Our results suggested that the longer-term protection afforded by the heterologous primary schedules was not inferior to the compared homologous primary schedules (objective 4).

Lastly, our analyses of the vaccine effectiveness of primary schedules among children and adolescents showed an increased protection against covid-19 endpoints as compared with unvaccinated (objective 5). Homologous primary schedules increased the protection against severe covid-19 endpoints for both children and adolescent aged 5 to 11 and 12 to 17 years.

Marketing authorization holder: not applicable.

Names and affiliations of principal investigators: Anders Hviid, University of Copenhagen, Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, Faculty of Health and Medical Sciences, Denmark and Statens Serum Institut, Department of Epidemiology Research, Denmark.

3. MARKETING AUTHORIZATION HOLDER(S)

Not applicable.

4. INVESTIGATORS

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 was performed and other relevant study sites are presented in the table below.

Name	**Professional Title**	**Affiliation and address**
Jesper Kjær	Director of department	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, DK-2300 Copenhagen S, Denmark
Niels Henrik Meedom	Project manager and fundraiser	
Anders Hviid	Professor	University of Copenhagen (KU), Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, Faculty of Health and Medical Sciences, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark
Morten Andersen	Professor	
Jesper Hallas	Professor	University of Southern Denmark (SDU), Faculty of Health Sciences, Department of Public Health, J. B. Winsløwsvej 19,2, DK-5230 Odense M, Denmark
Niklas Andersson	MD	Statens Serum Institut (SSI), Department of Epidemiology Research, Artillerivej 5, DK-2300 Copenhagen S, Denmark
Ulrike Baum	PhD	Finnish Institute for Health and Welfare (THL), POBox 30, FI-00271 Helsinki, Finland
Hinta Meijerink	Senior advisor	Norwegian Institute of Public Health (FHI), Department of Infection, Control and Vaccines, P.O.Box 222-Skøyen, NO-0213 Oslo, Norway
Rickard Ljung	Professor	Swedish Medical Products Agency (SWE MPA), Division of Use and Information, SE3751 03 Uppsala, Sweden

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

Name	**Affiliation**	**Role in the study**	**Description of the function**
Anders Hviid	KU (DK)	Principal investigator	Overall coordination and oversight of the study; responsible for the submission of deliverables

Morten Andersen	KU (DK)	Senior pharmacoepidemiologist	Overall supervision and approval of study protocol and final study report
Mia Aakjær	KU (DK)	Pharmacoepidemiologist	Contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.
Jesper Hallas	SDU (DK)	Senior Pharmacoepidemiologist	Scientific review and code review
Lars Christian Lund	SDU (DK)	Pharmacoepidemiologist	Contribute to drafting of study report and manuscript(s), and the manuscript submission process, revisions etc.
Hinta Meijerink	FHI (NO)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Jostein Starrfelt	FHI (NO)	Statistician	Conduct of the Norwegian analyses.
Rickard Ljung	SWE MPA (SW)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Nicklas Pihlström	SWE MPA (SW)	Statistician	Conduct of the Swedish analyses.
Petteri Hovi	THL (FI)	Senior epidemiologist	Review and approval of deliverables.
Tuija Leino	THL (FI)	Senior epidemiologist	Local scientific coordination, review and approval of deliverables.
Eero Poukka	THL (FI)	Medical specialist	Contribute to drafting of study report and manuscript(s), review and approval of deliverables.
Ulrike Baum	THL (FI)	Epidemiologist	Conduct of the Finnish analyses, review and approval of deliverables.
Niklas Andersson	SSI (DK)	Pharmacoepidemiologist	Contribute to drafting of study plan, protocol, study report and manuscript(s), and the manuscript submission process, revisions etc.
Kristyna Faksova	SSI (DK)	Junior epidemiologist	Literature review, local project management, ENCEPP and STROBE compliance.

Emilia Myrup Thiesson	SSI (DK)	Statistician	Conduct of the Danish analyses and responsible for the meta-analyses of all the site-specific results.
Mie Agermose Gram	SSI (DK)	Junior epidemiologist	Review of study report and manuscript(s)
Tjede Funk	SSI (DK)	EPI-ET Fellow	Review of study report and manuscript(s)
Christian Holm Hansen	SSI (DK)	Statistician	Review of study report and manuscript(s)

5. MILESTONES

Milestones	Planned dates
Study Plan	10 March 2022
Study Protocol (posted on EU-PAS register).	31 March 2022
Registration in the EU-PAS Register	31 March 2022
Study Report (final report will be posted on EU-PAS register once approved by the EMA and the contributing parties).	25 July 2022
Manuscript(s) ready for submission.	25 July 2022

6. RATIONALE AND BACKGROUND

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

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

Effectiveness of a heterologous prime-boost schedule

Heterologous AZD1222 / mRNA vaccine prime-boost schedules appear to be just as immunogenic as homologous schedules, and some studies even suggest superior immunogenicity.(6–8) However, the evidence on the effectiveness of prime-boost schedules using heterologous SARS-CoV-2 vaccines are sparse. In Denmark, the effectiveness of a dose of AZD1222 followed by a dose of mRNA vaccine was estimated in a nationwide cohort in the 9 February to 23 June 2021 period.(9) Heterologous vaccination with the combination of AZD1222 and an mRNA vaccine was associated with 88% protection against SARS-CoV-2

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

Effectiveness of 3rd dose boosting schedules

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

A number of observational studies, in particular from Israel, have now provided real-world evidence on the effectiveness of 3. dose schedules.(15–18) In a matched cohort study of a large Israeli health service database including more than 1.4 million individuals, estimated effectiveness against covid-19 hospitalisation, severe covid-19 and fatal covid-19.(17) Compared with receiving only two doses at least 5 months ago, a third dose of BNT162b2 effectively protected against the study outcomes. Follow-up after the 3. dose was limited (median follow-up, 13 days) and thus the study does not provide insights into waning of immunity. In Israel, only the mRNA vaccines are approved for use, and BNT162b2 has been predominantly used. Consequently, the Israeli studies do not inform us on heterologous 3. dose schedules. In a test-negative case-control study using National Health Service data from the UK, a heterologous 3. dose schedule with 2 doses of AZD1222 followed by BNT162b2 was

effective against symptomatic infection, both when compared to unvaccinated and individuals with 2 vaccinations.(19)

Effectiveness against Omicron

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

7. RESEARCH QUESTION AND OBJECTIVES

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

Primary objectives:

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

Secondary objectives:

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

Tertiary objectives:

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

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

For objectives #3-#5, we only evaluated schedules where we had sufficient information, e.g. our evaluation of waning of immunity was limited to 2-dose schedules as only these schedules had sufficient follow-up for this particular objective. Similarly, in variant-specific analyses, we were restricted by the high period-specific correlation between available schedules and dominating variants.

8. AMENDMENTS AND UPDATES TO THE PROTOCOL

Number	Date	Section	Amendment or update	Reason
1.1	22-04-22	Page 13 Pages 21-22 Pages 32-33 Page 39 Page 40 Page 44	- Exclusion criteria for immunocompromised added. - Description of individual autoimmune conditions. - More details on country-specific vaccination strategies. - Example of how to interpret comparative waning. - Adding statistical code review as a QA measure. - Example table for results added.	Incorporating minor comments from EMA assessment of protocol 1.0.
1.2	16-06-22	Page 25 Page 46 Page 48 Page 45	- Included region of residency as covariate. - Included definition details for age and MIS-c outcome for child and adolescent population analysis. Specified analyses for: - Quality control analysis #2 and #3. - Waning immunity – only 2 vs. 2 dose comparisons.	As potential confounder. As not previously specified. As only conducted in DK. As adequate FU is needed.

9. RESEARCH METHODS

9.1 Study setting and period

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

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

9.2 Study design and subjects

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

Eligibility criteria for study inclusion were:

- having received at least the primary immunisation (i.e. 1. and 2. vaccine dose against covid-19) with either AZD1222, BNT162b2 or the mRNA-1273 vaccines (for the purpose of objective #5, being vaccinated was not an eligibility criterion),
- known residency within the specific country,
- and no positive reverse transcription polymerase chain reaction (PCR) test before the study period start and before receiving a 2. or 3. dose in the distinct schedule evaluated.

Moreover, EMA has previously advised that groups of people with severely compromised immune systems should be offered a 3. dose at least 28 days after the 2. dose as part of their primary vaccine series (https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters). Thus, a short inter dose interval (<90-days) between the 2. and 3. dose, was included as an additional exclusion criterion. Consequently, we used the wordings of '3. dose' and 'booster dose' as synonyms throughout the report.

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

9.3 Variables

COVID-19 VACCINATION SCHEDULES

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

	Comparison vaccination schedules (reference)								
	Primary schedules							**Booster schedules**	
	Homologous			**Heterologous**				**Homologous**	
Vaccination schedules (studied schedules)	AZD1 AZD2	BNT1 BNT2	MOD1 MOD2	AZD1 BNT2	AZD1 MOD2	BNT1 MOD2	MOD1 BNT2	BNT1 BNT2 BNT3	MOD1 MOD2 MOD3
Heterologous primary schedules									
AZD1BNT2		**X**							

AZD1MOD2			X						
BNT1MOD2		X							
MOD1BNT2		X							
Heterologous booster schedules									
AZD1AZD2BNT3	X							X	
AZD1AZD2MOD3	X								X
AZD1BNT2BNT3				X				X	
AZD1MOD2MOD3					X				X
BNT1BNT2MOD3		X						X	
MOD1MOD2BNT3			X					X	
BNT1MOD2MOD3						X		X	
MOD1BNT2BNT3							X	X	
BNT1MOD2BNT3						X		X	
MOD1BNT2MOD3							X	X	
Homologous booster schedules									
BNT1BNT2BNT3		X							
MOD1MOD2MOD3			X						

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

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

For objective #1 (VE of heterologous primary and booster vaccination compared to the homologous counterpart [i.e. 2-dose vs. 2-dose and 3-dose vs. 3-dose]), the expected larger-sized homologous mRNA vaccinated group was selected as the comparison schedule. For objective #2 (VE of heterologous and homologous booster vaccination compared to the counterpart primary vaccine schedules [i.e. 3-dose vs. 2-dose]), the equivalent primary vaccine schedules to the two first doses received of the distinct studied booster schedule served as the respective comparison schedule.

OUTCOMES

The endpoints were: 1) a positive PCR test for SARS-CoV-2 (i.e. infection), 2) a covid-19 hospitalisation, 3) covid-19 hospitalisation at an intensive care unit (ICU), and 4) covid-19 related death. In the primary analyses we followed up for the endpoints from start of follow-up defined as day 14 after the index date, and until 75 days had elapsed since the start of follow-

up. These outcome ascertainment periods were chosen to balance: a) that the follow-up among the comparison groups were homogenous in contrast to longer periods of outcome ascertainment where right censoring at study end or another dose may differ substantially between comparison groups, and b) that we needed to have sufficient follow-up for the assessment of hospitalisation and mortality. When evaluating waning of immunity, follow-up for endpoints was continued beyond day 75.

Covid-19 hospitalisation including ICU admission

Covid-19 hospitalisation was defined as an event fulfilling the following criteria: a) hospitalisation with a PCR positive test for SARS-CoV-2 dated in the time period beginning 14 days before admission (day -14; the day of admission was day 0) and up to and including 2 days after admission (day 2), b) inpatient hospital contact or a hospital contact with a duration of at least 12 hours and c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1 or Z038PA1 – subject to country-specific coding practices, see table below - TIME-VARYING VARIABLES). Thus, individuals who were hospitalised for conditions not related to covid-19, but who coincidentally tested positive in the period around admission (14 days before to 2 days after admission) were included as an endpoint 1 (infection) but not an endpoint 2 (hospitalisation). An example of this could be a patient with a fracture who test positive at admission as part of routine testing. This distinction is particularly important to make during periods of high incidence of infection as in the period of omicron. Covid-19 hospitalisation to an ICU (endpoint 3) was assessed among those individuals fulfilling the criteria for covid-19 hospitalisation (endpoint 2).

Covid-19 related mortality

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

In secondary analyses, all outcomes were sub classified according to SARS-CoV-2 variants of concern using "periods of dominance"-approach where for each country we had identified the periods where specific variants dominated – see subsection *Intended additional analyses* below.

Through use of the planned outcomes, we believed our analyses could provide information on the VE in relation to any SARS-CoV-2 infection as well as severe covid-19. The Nordic health

care registers do not hold information to distinguish between symptomatic and asymptomatic documented SARS-CoV-2 infection.

COVARIATES

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

To account for the risk of severe covid-19, we adjusted for vaccine priority groups, 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 as well as whether being health and social care workers. In the remaining countries, vulnerable individuals (such as those receiving nursing care or living in nursing homes) and healthcare personnel were identified. Further, we also included comorbidities that are related to the risk of severe covid-19 as separate covariates in our adjustment model (see table of included variables below). The selected ICD-10 codes defining the comorbidities are country-specific and have been chosen for general surveillance purposes based on inputs from national experts and country-specific registration practices. In the interest of saving time on developing a common set of diagnoses codes, we chose to take advantage of these coding schemes. In addition, country-specific codes may even be better at identifying comorbidity-related risk groups within each country than common codes.

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

BASELINE VARIABLES

VARIABLE	COUNTRY	DATA SOURCE AND DETAILS	VALUES/CODES
Age	Denmark	*The Civil Registration System.* Defined as age at first covid-19 vaccination. For children (5 to 17 years old), age was defined at 15 June 2021.	Categorical: 5-year bins; and 18-40 years, 40-59, 60-74, and 75+ for stratified analyses of age-specific comparisons.
	Finland	*The Finnish Population Information System.* Defined as age at first covid-19 vaccination. For children (5 to 17 years old), age was defined at 15 June 2021.	
	Norway	*Norwegian Population Register.*	

		Defined as age at first covid-19 vaccination. For children (5 to 17 years old), age was defined by birth year.	
	Sweden	*The Total Population Register.* Defined as age at first covid-19 vaccination. For children (5 to 17 years old), age was defined by birth year.	
Sex	Denmark	*The Civil Registration System.* Defined as biological sex.	Binary: male, female
	Finland	*The Finnish Population Information System.* Defined as biological sex.	
	Norway	*Norwegian Population Register.* Defined as biological sex.	
	Sweden	*The Total Population Register.* Defined as biological sex.	
Residency (citizenship)	Denmark	*The Civil Registration System.* Defined as known national resident.	Binary: yes/no
	Finland	Not available.	
	Norway	*Norwegian Population Register.* Defined as known national resident.	
	Sweden	*The Total Population Register.* Defined as known national resident.	
Calendar month	Denmark	*The Danish Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	Categorical (14 levels): calendar month 1 (27 December 2020 to 31 January 2021) to month 14 (February 2022)
	Finland	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	

	Norway	*The Norwegian Immunisation Register (SYSVAK).* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	
	Sweden	*The National Vaccination Register.* Defined by the date where the respective vaccine dose examined was administered (i.e. 2nd or 3rd dose) and grouped into monthly intervals according to months since start of study period.	
Region of residency	Denmark	*The Civil Registration System.* Defined by last known address at first vaccination.	Categorical: DK, 5 levels; FI, 5 levels; NO, 5 levels; SE, 9 levels
	Finland	*The Finnish Population Information System.* Defined by last known address.	
	Norway	*Norwegian Population Register.* Defined by last known address at first vaccination.	
	Sweden	*The Total Population Register.* Defined by last known address at first vaccination.	
Covid-19 vaccine priority groups	Denmark	*The Danish Vaccination Register.* Defined as governmentally assigned covid-19 vaccine priority groups, prioritised according to the risk of severe infection as well as whether being health and social care workers (assigned before first covid-19 vaccination).	Categorical (4 levels): Target risk groups, healthcare personnel, selected relatives of people at high risk, others
	Finland	*Register of Social Assistance.* Vulnerable individuals defined as individuals in 24-hours care (binary status per 27 December 2020).	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others

		Social and Healthcare Professionals Register. Healthcare personnel defined as individuals with the right to act as health care personnel as of 27 December 2020.	
	Norway	*The Norwegian Information System for the Nursing and Care Sector.* Vulnerable individuals defined as nursing home resident (binary status per 27 December 2020). *State register of employers and employees.* Healthcare personnel defined as binary status per 27 December 2020.	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others
	Sweden	*Register on persons in nursing homes.* Vulnerable individuals defined as nursing home resident (binary status as of December 2020) *The Longitudinal integrated database for health insurance and labour market studies.* Healthcare personnel defined as healthcare worker occupation status as of October 2018 (binary).	Categorical (3 levels): Vulnerable individuals, healthcare personnel, others
Comorbidity 1: Chronic pulmonary disease (CPD)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: J40-J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Comorbidity 1: CPD	Finland	*Care register for Health Care and Register of Primary Health Care Visits.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no ICD-10 codes: J41-J44, J47

Comorbidity 1: CPD	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E84, J41-J47, J701, J703, J84, J98
Comorbidity 1: CPD	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E84, J41-J47 J84, J98
Comorbidity 2: Cardiovascular conditions and diabetes (CVD/DM)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E10-E11, I11.0, I13.0, I13.2, I20-I23, I42.0, I42.6-I42.9, I48, I50.0-I50.3, I50.8, I50.9
Comorbidity 2: CVD/DM	Finland	*Care register for Health Care, Register of Primary Health Care Visits, Special Reimbursement Register and Prescription Centre database.* Defined as primary or secondary diagnoses (look-back 6 years) or drug prescriptions (look-back 4 years) before 27 December 2020.	Binary: yes/no ICD-10 codes: E10, E11, E13, E14, I11–I13, I15, I20–I25 ICPC-2 codes: T89, T90 ATC codes: A10A, A10B
Comorbidity 2: CVD/DM	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: E10-E14 I05-I09, I110, I130, I132, I1420, I20-I23, I25-I28, I33-I39, I426-I429, I48, I50
Comorbidity 2: CVD/DM	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient	Binary: yes/no ICD-10 codes: E10-E14, I05-I09, I110, I2,

		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.	I34-I37, I39, I42, I43, I46, I48-I50 ATC code: A10
Comorbidity 3: Autoimmunity related conditions (AIC)[a]	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: D51.0, D59.0, D59.1, D69.0, D69.3, D86, E05.0, E06.3, E27.1, E27.2, G12.2G, G35, G61.0, G70.0, I00, I01, K50, K51, K74.3, K90.0, L12, L40, L52, L80, L93, M05, M06, M08, M30.0, M31.3, M31.5, M31.6, M32, M33, M34, M35, M45
Comorbidity 3: AIC[a]	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 4 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: D70.81, D70.89, D80–D84, E25.0, E27.1, E27.2, E27.4, E31.0, E89.6, D86*, K50*, K51*, L40*, M02*, M05–M07*, M13.9*, M45*, M46.0*, M46.1*, M46.9*, M94.1* ATC-codes**: H02AB02, H02AB04, H02AB06, H02AB07, L01BA01, L01XC02, L04AA06, L04AA10, L04AA13, L04AA18, L04AA24, L04AA26,

			L04AA29, L04AA33, L04AA37, L04AB, L04AC, L04AD01, L04AD02, L04AX01, L04AX03
Comorbidity 3: AIC[a]	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: G35, K50-K51, M05-M09, M13-M14
Comorbidity 3: AIC[a]	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: D86, G35, K50, K51, L40, M05-M09, M13, M14, M45
Comorbidity 4: Cancer	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: C00–C85 (without C44), C88, C90-C96
Comorbidity 4: Cancer	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no ICD-10 codes: C00–C97 (without C44), D051, D39
Comorbidity 4: Cancer	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: C00-C96 (without C44)
Comorbidity 4: Cancer	Sweden	*National Patient Register.*	Binary: yes/no

		Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	ICD-10 codes: C00-C96 (without C44), D45-D47
Comorbidity 5: Moderate to severe renal disease (CKD)	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of type of hospital contact registered before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61
Comorbidity 5: CKD	Finland	*Care register for Health Care and Special Reimbursement Register.* Defined as primary or secondary diagnoses before 27 December 2020 (look-back 6 years).	Binary: yes/no ICD-10 codes: I12, I13, N00–N05, N07, N08, N11, N14, N18, N19, E10.2, E11.2, E14.2
Comorbidity 5: CKD	Norway	*Norwegian Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in hospital or from private-practicing specialists and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12-I13, N00-N05, N07, N11, N14, N17-N19, Q61
Comorbidity 5: CKD	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before first covid-19 vaccination (look-back 3 years).	Binary: yes/no ICD-10 codes: I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
TIME-VARYING VARIABLES			
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES**
Vaccination status	Denmark	*The Danish Vaccination Register.* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	Categorical (multiple levels): AZD1, AZD1AZD2, AZD1MOD2,
	Finland	*The National Vaccination Register.*	

		Defined according to the specific administered covid-19 vaccines and date of vaccinations.	BNT1BNT2, BNT1, BNT2MOD3 etc.
	Norway	*The Norwegian Immunisation Register (SYSVAK).* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	
	Sweden	*The National Vaccination Register.* Defined according to the specific administered covid-19 vaccines and date of vaccinations.	
Documented SARS CoV-2 infection	Denmark	*The Danish Microbiology Database.* Defined as the date of registered positive PCR test for SARS CoV-2.	Binary: yes/no
	Finland	*National Infectious Diseases Register.* Defined as the date of registered positive PCR test for SARS CoV-2.	
	Norway	*Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as the date of registered positive PCR test for SARS CoV-2.	
	Sweden	*Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as the date of registered positive PCR test for SARS CoV-2.	
Hospitalisation for covid-19	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as hospitalisation on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)	Binary: yes/no

	Finland	*National Care Register for Health Care and the National Infectious Diseases Register.* Defined as hospitalisation on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient hospital contact, and c) a covid-19 relevant main diagnosis (ICD-10: J00-J22, J46, J80-J84, J851, J86, U071, U072).	
	Norway	*The Norwegian Patient Registry and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as hospitalisation on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a covid-19 relevant diagnosis code (ICD-10: B342, B342A, B948A, B972, B972A, B972B, B972B1, Z038PA1)	
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as hospitalisation on the day of, within 14 days of or in the two days after a PCR positive test for SARS-CoV-2, b) inpatient contact or at least 12 hours of contact, c) a covid-19 relevant diagnosis code (ICD-10: U071, U072, U109)	
Intensive care unit admission	Denmark	*The National Patient Register and the Danish Microbiology Database.* Defined as admission to an intensive care unit facility during hospitalisation for covid-19.	Binary: yes/no
	Finland	*Finnish Intensive Care Consortium's Quality Register for Intensive Care, National Care Register for Health Care*	

		and the National Infectious Diseases Register. Defined as admission to an intensive care unit facility during hospitalisation for covid-19.	
	Norway	*The Norwegian Patient Registry (NPR) and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as admission to an intensive care unit facility during hospitalisation for covid-19.	
	Sweden	*The Swedish Patient Register and the Register on surveillance of notifiable communicable diseases (SmiNet).* Defined as admission to an intensive care unit facility during hospitalisation for covid-19.	
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.	Binary: yes/no
	Finland	*The Finnish Population Information System and the National Infectious Diseases Register.* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.	
	Norway	*Norwegian Population Register and the Norwegian Surveillance System for Communicable Diseases (MSIS).* Defined as (the date of) death within 30 days after PCR positive test for SARS-CoV-2.	
	Sweden	*The Total Population Register, 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. Possible to asses cause-of-death using ICD-10 coding of U071, U072, U109.	

[a]Autoimmunity related conditions (AIC) includes diagnoses of 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.

9.4 Data sources

We used the unique nationwide register-data available to us, and constructed country-specific cohorts with individual-level information on dates of vaccination and dates of endpoints together with relevant covariate information. All Nordic residents are assigned a unique personal identifier at birth or immigration, enabling unambiguous linkage between registers. Thus, the data from all the Nordic countries were based on individual-level information and we had full data availability during the study period. The registers are updated daily and there is no lag time (except for the Swedish and Finnish registers, for which there is a lag of 2 to 4 weeks. Given the study end is 28 February 2022, all countries had full data availability). All countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, providing near-complete follow-up of all residents over time.

In the following table, we present the data sources that we used for the study. All data sources are nationwide registers in native format. All study subcontractors had access to their country-specific data and could link data between registers for the purpose of our study.

Data source (country)	**Details of the individual-level data sources**
Denmark	
The Civil Registration System (23)	The register provides the mandatory unique personal identifier for all permanent residents of Denmark, which allows linkage between all Danish health care services and civil registrations systems. The register has existed since 2 April 1968. In addition, it holds general demographic information such as birthdate and sex as well as continuously updated information and dates on historical addresses, immigration and emigration status, and death.

The Danish Vaccination Register (24)	The register holds information on all vaccinations given in Denmark including information on vaccination date, type, dose, and product batch number ever since 15 November 2015 (where reporting to the register became mandatory). Specifically related to this study, the Danish Health Agency have provided the governmentally assigned covid-19 vaccine priority groups that were prioritised groups according to the risk of severe infection as well as whether being health and social care workers.
The Danish Microbiology Database (25)	Information on positive PCR tests for SARS-CoV-2 were drawn from The Danish Microbiology Database (MiBa) that holds information on all microbiology samples analysed at Danish departments of microbiology, including information on SARS-CoV-2 PCR test results, date of sampling, date of analysis, type of test, and interpretation of test. The SARS-CoV-2 PCR tests have been freely available to all individuals in Denmark regardless of symptoms status throughout the covid-19 pandemic.
The National Patient Register (26)	The register covers all hospital-contacts in Denmark with information on the duration of the contact, department of admission and other hospital characteristics. Treating physician-assigned diagnoses have been registered according to ICD-10 codes since 1994.
FINLAND	
Finnish Population Information System (27)	The register is an electronic register including personal data of all permanent residents in Finland. It contains demographic information such as the unique personal identifier in Finland, date of birth, mother tongue as proxy for country of birth, place of residence, date of death, and date of immigration and emigration. The register is held by the Digital and Population Data Services Agency.
Register of Social Assistance (28)	The register holds information on individuals in long-term care and/or with need for social assistance including social rehabilitation. This assistance may be given in nursing homes, people's own homes or other institutions. The register is held by the Finnish Institute for Health and Welfare.
Social and Healthcare Professionals Register (29)	The register contains person-level data on rights to act as health care personnel.
National Vaccination Register (30)	The register, which is based on the Register of Primary Health Care Visits, holds information on all Covid-19 vaccinations administered in Finland. Data include the date of vaccination, vaccine batch number and trade name.

National Infectious Diseases Register (31)	The register contains information on notifiable diseases which must be reported by the laboratories and the physician treating the patient, or performing an autopsy, in accordance with the Finnish Communicable Diseases Act. All laboratory-confirmed SARS-CoV-2 infections are recorded in the National Infectious Diseases Register, including the sample. The register is held by the Finnish Institute for Health and Welfare.
National Care Register for Health Care (32)	The register comprises information on all in-hospital care (since 1969) and outpatient specialist care (since 1998) in Finland, including admission and discharge dates, whether hospitalisation was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department and hospital. The register is held by Finnish Institute for Health and Welfare.
Finnish Intensive Care Consortium's Quality Register for Intensive Care	The register records data on all patients treated in an intensive care unit in Finland.
Special Reimbursement Register and Prescription Centre database	These data collections are maintained by the Finnish Social Insurance Institution. The Special Reimbursement Register allows the identification of individuals entitled to special reimbursement for medical expenses. The Prescription Centre database allows the identification of individuals using selected medications of interest.
Register of Primary Health Care Visits(33)	The register covers all outpatient primary health care services delivered in Finland.
NORWAY	
The Emergency Preparedness Register for COVID-19 (34) (consisting of the data sources below)	Data for this study were obtained through the Emergency preparedness register for covid-19 ("Beredt C19"), which is administered by the Norwegian Institute of Public Health, according to the Norwegian Health Preparedness Act §2-4. The register was established in 2020 to provide authorities with up-to-date information on prevalence, causal relationships, and consequences of the covid-19 epidemic in Norway and includes the total population in Norway. The register includes information already collected in the healthcare system and the national health registries (see the following data sources).
Norwegian Population Register	The register holds information on birthdate, immigration and emigration status as well as and death for all residents of Norway.

State register of employers and employees (NAV AA register) (35)	The register holds lists of all employment relationships in Norway, and employers and contractors are obliged to report their employees and freelancers to the register. Employees are classified according to the Norwegian Standard Classification of Occupations) and can thus be used to obtain data on health care personnel status.
The Norwegian Information System for the Nursing and Care Sector (IPLOS) (36)	The register holds information on the health care services that are provided by municipalities in Norway. Report of applicants and recipients of such services to the register is mandatory for all municipalities. The register includes information on home care service and out-of-hospital institutional care, including short- and long-term nursing home stay.
The Norwegian Immunisation Register (SYSVAK) (37)	The register holds information of administered vaccines in Norwegian vaccination programs, including the date of administration and type of vaccine. For the covid-19 vaccines, reporting to the register have been mandatory.
Norwegian Surveillance System for Communicable Diseases (MSIS)	The register holds information on selected infectious diseases for which reporting to the register is mandatory. This includes all covid-19 tests and the date of testing and test results.
The Norwegian Patient Registry (NPR) (38)	The register holds information on all contacts with specialist health-care services in Norway, including admission and discharge dates as well as diagnoses (recorded according to ICD-10) during hospitalisation or outpatient contact.
SWEDEN	
The Total Population Register (39)	The register contains information on the unique personal identifier for all individuals in Sweden as well as general demographic information such as date of birth, sex, country of birth, place of residence, and date of immigration and emigration. The register is held by Statistics Sweden.
The Cause of Death Register (40)	The register contains information place of residence at time of death, date and underlying cause of death and contributing causes of death.
The Longitudinal Integrated Database For Health Insurance And Labour Market Studies (LISA) (41)	The database contains a wide range of socioeconomic information including occupation (such as healthcare worker). The register is held by Statistics Sweden.
Register On Persons In Nursing Homes (42)	The register holds information on nursing care given to elderly and/or persons with physical, psychiatric or intellectual disabilities at either

	nursing homes, own homes or other institutions. The register is held by the National Board of Health and Welfare.
The National Vaccination Register (43)	The register contains information on administered covid-19 vaccines including data on date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses) since 1 January 2021. The register is held by the Public Health Agency of Sweden.
Register On Surveillance Of Notifiable Communicable Diseases (Sminet) (44)	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis performing laboratories, the treating physician or autopsy performing physician, in accordance with the Swedish Communicable Diseases Act. Data include date of disease occurrence, date of testing, date of positive test and diagnoses. The register is held by the Public Health Agency of Sweden.
The Swedish Patient Register (45,46)	The register comprises information on all in-hospital (since 1987) and out-patient (since 2001) specialist care in Sweden including data on admission and discharge dates, whether hospitalisation was planned or acute, codes for discharge diagnoses and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department, and hospital. For the current study period discharge diagnoses were recorded according to the Swedish clinical modification of the ICD-10 (i.e. ICD-10-SE). The register is held by the National Board of Health and Welfare.

9.5 Bias

Although, the comparative design mitigates potential bias in recording of healthcare information between vaccinated and unvaccinated, there were some potential limitations to the chosen methodological approach. First, our ascertainment of the study outcomes was dependent on secondary use of national microbiology test results. Depending on the country and period, we did not have complete registration of all infected in the population; only those tested positive. Second, we did not have information on symptoms for our PCR positive cases; thus, this outcome may contain both asymptomatic and symptomatic cases. Third, as noted in the '*Variables*' subsection, our outcomes for severe covid-19 (hospitalisation, ICU admission and covid-19 related death) may potentially have captured individuals with an outcome not directly related to covid-19 but where covid-19 was a contributing factor or co-occurred. Fourth, while the study design has a high degree of generalisability to similar general populations, some clinical subgroups were not studied, such as individuals who had received an Ad26.CoV2-S (Johnson & Johnson vaccine), as why the results cannot directly help inform

on the comparative VE in these situations. Similarly, our study objectives did not include analysis on high-risk subgroups such as individuals with immunocompromised conditions. Fifth, our utilised methodology (see the 'Statistical Analysis' subsection below): weighting (for the specified design to address objective #1) and matching (for the specified design to address objective #2) both have strengths and limitations. Advantages of weighting (as opposed to matching) is the potential of preserving a large majority of the total study sample and allowing the assessment of several treatment effects (i.e. average treatment effect for the whole population, ATE). A limitation to this approach is that in case of poor overlap of covariate distributions across comparative groups, this will lower statistical power. Matching has the advantages of providing a 1:1 comparison with intuitive estimates of average treatment effect in the treated (ATT), but limitations to this approach is the discarding of unmatched individuals, which reduces the sample size and generally does not allow for multiple comparisons. A final limitation is that many of the included vaccine schedules are strongly correlated with calendar period. Since calendar period is also strongly correlated with variant dominance, the results of many of the schedule comparisons were expected to be variant-specific.

9.6 Study size (sample size and power)

We expected the Nordic countries to contribute with 19.6 million individuals vaccinated with at least two doses - based on a combined population of 23.1 million and a vaccination uptake of approximately 85% among individuals aged 12 years or older. As the vaccination uptake in the 5- to 11-year olds was lower, we expected at least 50% for one dose of vaccine in the countries that have recommended vaccination in this age group. The policy for vaccination 5- to 11-year olds was different in each country: Denmark recommended vaccination of all 5- to 11-year olds, Finland has also offered vaccination, while Norway and Sweden have recommended vaccination of risk groups among the 5- to 11-year olds. In all Nordic countries, the reduced dosage of BNT162b2 in two doses has been used in this age group. The statistical power depended on the prevalence of the respective schedule being studied and the comparator schedule together with the frequency of the outcomes (PCR positive tests are not uncommon, while covid-19 hospitalisation, ICU admission, and deaths were considered to be rarer). As presented in results below, some comparisons for some outcomes were not applicable due to too few individuals and/or the outcome events being very rare.

The Nordic countries have had similar mass vaccination rollouts with prioritised groups being vaccinated first followed by adult age groups; for both the primary series of 2-doses and for the 3rd booster dose. The two mRNA vaccines and the two viral vector vaccines have been in use in the Nordic countries; the BNT162b2 has been the most used type. The use of the AZD1222 viral vector vaccine early in the rollouts did differ between countries, with Denmark and Norway using it for frontline personnel, while Sweden and Finland used it more generally.

After the VITT signal the vaccine was discontinued first in Denmark and later followed by Norway. In Sweden and Finland, the use of the vaccine was initially restricted to individuals 65 years or older after the VITT signal, but later the vaccine was discontinued. The restricted study designs that we used may have reduced statistical power. However, this was a trade-off in the effort of constructing more comparable groups and, thus, better causal inference.

9.7 Data management

Data management were conducted at the country-specific level and complied with the respective national data security and privacy guidelines. All study subcontractors had access to their country-specific data and could link data between their country's registers for the purpose of our study. Due to the short timeline and resources allocated, data management and analyses were accomplished at the national level (i.e. one large combined database containing fully anonymised individual-level data for all 4 countries was not feasible). No sensitive data were shared between partners in this project. Only effect estimates and aggregated data were shared.

9.8 Statistical analysis

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

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

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

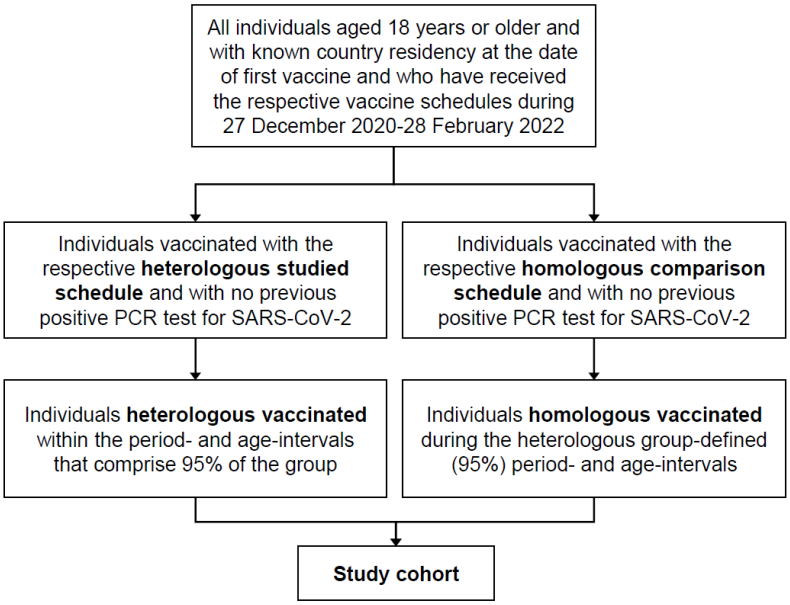
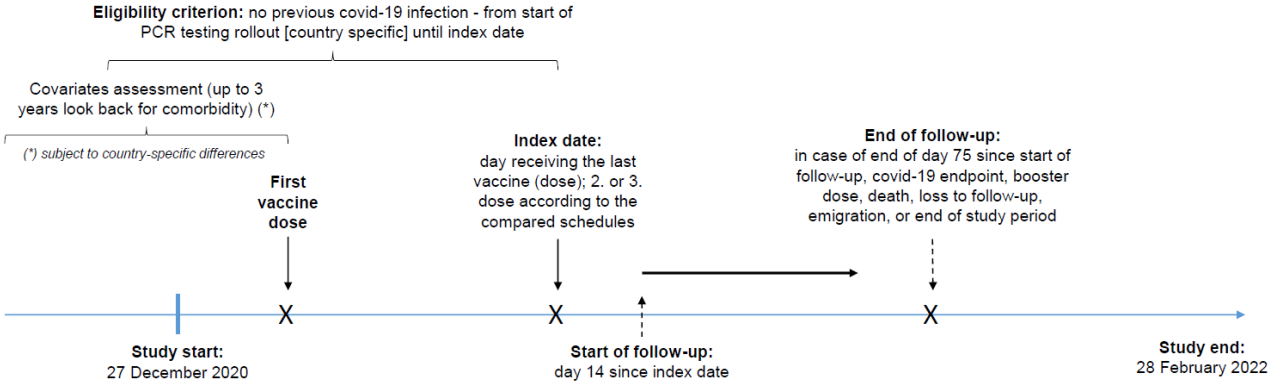


Figure 2. Study design and timeline for the 2- vs 2-dose and 3- vs 3-dose comparisons (study objective #1).



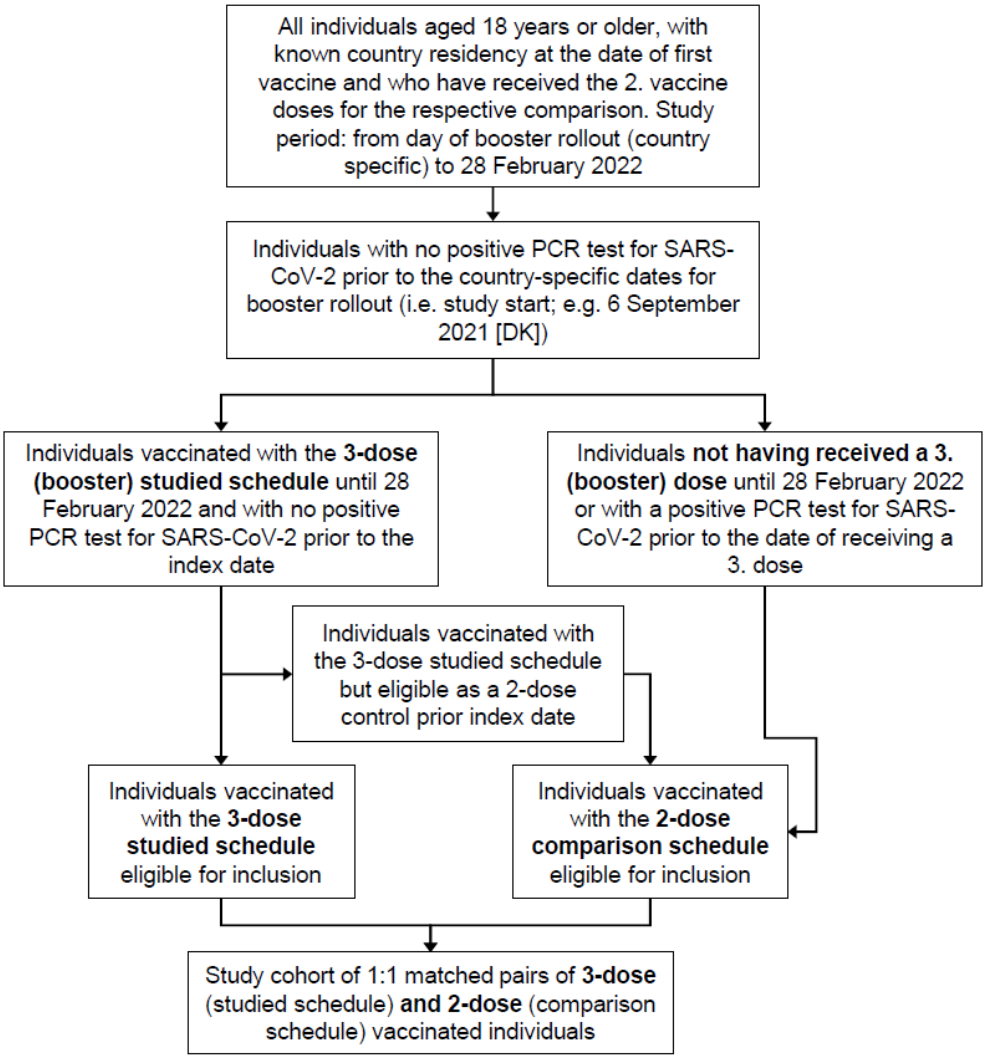
3-dose vs 2-dose comparisons – restriction through matching

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

At the day an individual received a 3. dose (i.e. the index date) of the studied schedule, the individual was matched with an individual having received the respective 2-dose comparison schedule (i.e. controls) but who had not yet received a 3. dose (i.e. at the this date). For each matched pair, the index date of the individual in the 3-dose studied schedule was assigned to the 2-dose comparison schedule control individual. The matched controls were eligible to be included in a 3-dose studied schedule group in case of receiving a future 3. dose to that of the

given matched date. Individuals from the 3-dose studied and the 2-dose comparison schedules were matched on age (5-year bins), calendar month of receiving the 2. dose and a propensity score summarising potential confounders such as sex, region of residency, vaccination priority group, and comorbidity. The time at which an individual was vaccinated with a 2. dose, is highly correlated with risk of severe covid-19 and/or risk behaviour due to the national prioritisation of the rollout of the covid-19 vaccines (e.g. individuals of high risk of severe covid-19 and health care workers were prioritised for earlier vaccination than the general public).

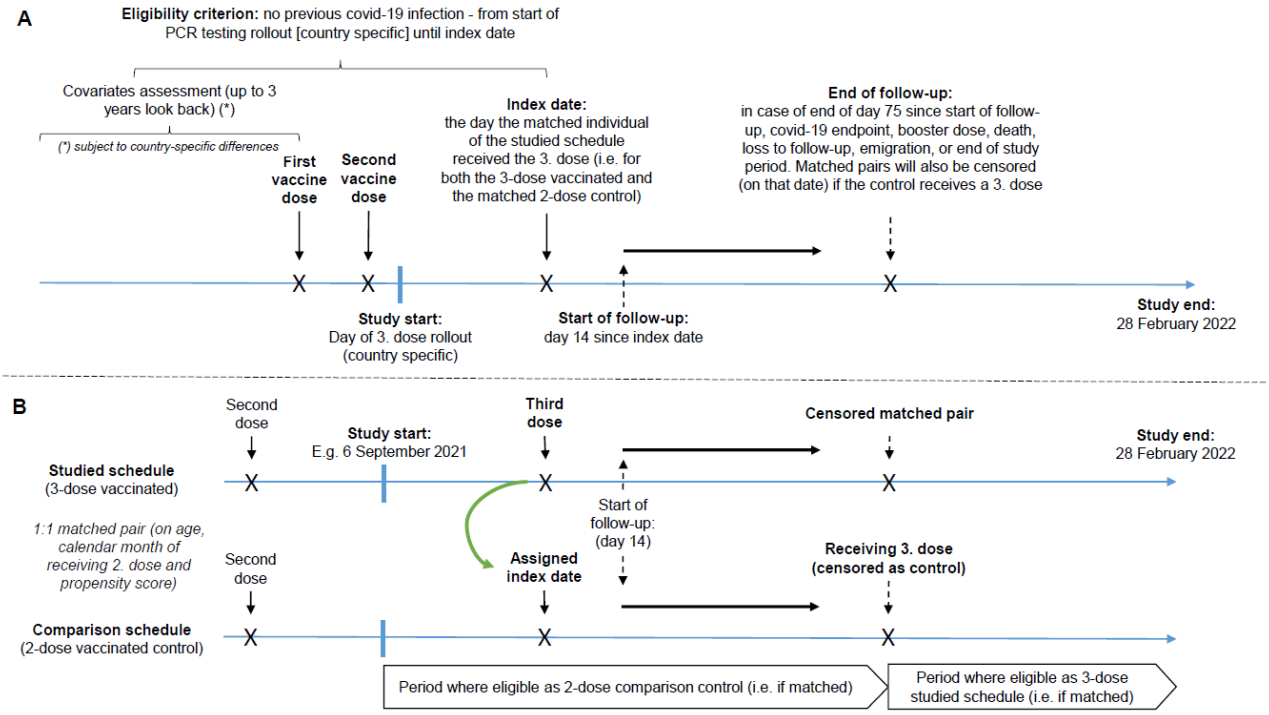
Figure 3. Flow chart of construction of the study cohorts for the 3- vs 2-dose comparisons (study objective #2).



Individuals in the country-specific cohorts were followed from the time they entered one of the vaccination schedules groups and 13 days had passed and until one of the endpoints included in the study, end of endpoint ascertainment period, received a booster dose (a 3. dose for 2-dose schedules and a 4. dose for 3-dose schedules), exit from the cohort due to death, loss to follow-up, emigration, or end of study period, whichever occurred first. I.e. for the 3- vs. 2-dose matched comparisons, follow-up for the matched pairs also ended if the control individual

received a 3. dose (on that date; see example in Figure 4B). Follow-up was conducted separately for each outcome without censoring for the other study outcomes. That is, when evaluating effectiveness against covid-19 hospitalisation to an ICU, having a positive PCR test for SARS-CoV-2 or being covid-19 hospitalised did not right-censor the follow-up for this individual. However, note that when the 14 days and 30 days, respectively, after a positive test had passed, the follow-up was censored in the analyses of hospitalisation and ICU, and mortality, respectively.

Figure 4. Study design and timeline for the 3- vs 2-dose (study objective #2). A: general overview. B: example of a matched pair and censoring.



Adjusted cumulative incidences – heterologous vs homologous comparisons

Risk differences (RDs) and risk ratios (RRs) were estimated using cumulative incidences at day 75 after start of follow-up (i.e. day 14 after index date) for the studied heterologous schedule and the homologous comparison schedule, respectively. Comparative VE was calculated as 1 – RR. The cumulative incidence for the heterologous schedule under investigation was estimated using the Kaplan-Meier estimator, and the cumulative incidence for the homologous comparison schedule was be estimated by an adjusted Kaplan-Meier estimator using inverse probability weights to make the covariate distribution among the individuals with the homologous comparison schedule similar to the individuals of the heterologous schedule under study.(47) The inverse probability weights were calculated as ((1-p0)/(1-pc))/ (p0/pc) with p0 equal to the crude probability of the heterologous schedule examined in the combined population of both schedules, and pc equal to the probability of the heterologous schedule

examined given covariates. The probability of the study heterologous schedule conditional on covariates was estimated in the combined population of both schedules using logistic regression including direct adjustment for year of birth (5 year categories; proxy for age), sex, calendar month (monthly categories), region of residency, comorbidity, and vaccination priority group. Confidence intervals (95% CIs) were calculated using two standard errors of the Kaplan-Meier estimates assuming independence.

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

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

Meta-analyses

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

Intended additional analyses

In secondary analyses, we stratified comparative VE estimates according to calendar periods of Alpha, Delta and Omicron variant dominance (i.e. when it is estimated that the variant of concern accounts for more than 90% of all cases). We also intended to use variant-PCR/WGS results, subject to national availability, in additional variant-specific analysis. However, we only report variant specific estimates based on calendar period stratification due to time constrains of the study report. Likewise, these analyses were only conducted for booster schedules and given that the booster schedules were predominantly rolled out in the Nordic countries during the omicron variant, other variants could not be individually studied. All countries reported omicron-period stratified results for the booster effectiveness analyses (i.e. both weighted and matched analyses). Below the calendar periods for the specific variants of predominance are presented for each country.

Danish variant situation

The calendar periods for specific variant dominance in Denmark are: Alpha/Beta period, 15 March to 30 June 2021; Delta period: 15 July to 15 November 2021; and Omicron period: 28 December 2021 to 28 February 2022. The intermediary transition periods were left out.

Finnish variant situation

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

Norwegian variant situation

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

Swedish variant situation

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

Waning

Differences in waning of immunity were addressed in the head-to-head 2- vs. 2-dose comparisons by estimating comparative VE using cumulative incidences at 30 day-intervals (i.e. day 120, 150, 180). Note that this resulted in estimates of comparative waning, i.e. comparing cumulative incidences at day *X* for the heterologous studied schedule to cumulative incidences at day *X* for the homologous comparison schedule. Example: In the comparison of AZD1BNT2BNT3 vs BNT1BNT2BNT3 we observe a VE at day 75 against infection (testing positive) of 0% (i.e. no difference in cumulative incidences between the two schedules). At day 150, we observe a VE of 20%. Thus, we interpret this as the BNT1BNT2BNT3 waning more than the AZD1BNT1BNT3 schedule. We also evaluated waning of immunity within schedules, to the extent that the available data allows, by comparing cumulative incidences at day *X* to cumulative incidences at day 75.

Based on the data availability we considered further subgrouping in relation to waning immunity such as by age groups.

Please note that only Denmark contributed with results for this analysis due to time constrains for this study report. Additionally, analysis was restricted to 2- vs. 2-dose comparisons due to the relative shorter follow-up for the booster schedules (due to the end of study period), hampering the possibility for assessing longer follow-up.

Subgroup analysis according to age

We conducted stratified analyses according to age groups of 18-39 years, 40-59, 60-74, and 75+, using birth cohort and age at index date – subject to the schedules and comparisons where we had data for this. Please note that only Denmark contributed with results for this analysis due to time constrains for this study report.

Children and adolescents population

As both the utilised vaccine schedules, time of vaccination, and doses differ among children and adolescents to the adult population, the vaccine effectiveness of children and adolescents was examined in a separate cohort. Among adolescents (12- to 17-year olds), we intended to examine similar objectives as outlined for the adult population; however, these analyses were pre-planned to be confined to 2-dose regimens (as the countries have not yet consistently utilised a 3. [booster] dose for this younger population by the time of this study protocol). For children aged 5 to 11 years old, we compared 1 or 2 doses of BNT with unvaccinated children (with a study design similar to that of the 3- vs. 2-dose comparisons in the main cohort), since only BNT162b2 has been used in this age group in the Nordic countries. We evaluated the following endpoints: infection, hospitalisation and diagnosis of multisystem inflammatory syndrome in children (MIS-C). MIS-C was defined and analysed on a country-specific basis where feasible. Overall, MIS-C was captured in two ways: by specific ICD-10 codes (e.g. B972B in Denmark) or less specific related codes (e.g. M303 [Kawasaki] in Denmark) registered within 2 months of a positive test.(48) In Denmark and Finland data on the date of birth were available and defined by the age at 15 June 2022, while only year of birth was available in Norway and Sweden and was defined by the children's turning age in 2021.

9.9 Supplementary analyses and quality control

Quality control was conducted indirectly to evaluate the validity of our main analyses, by 1) making sure that the prevalences of the different schedules and the number of study endpoints matched national surveillance dashboards and reports, 2) conducting comparisons between 2-dose schedules and unvaccinated for all study endpoints, to make sure that we were able to recover VE estimates compatible with the current evidence, and 3) utilising a test-negative study design for selected main comparisons. The two latter were carried out in Denmark only.

We ensured 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).

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

Individuals having received homologous primary (2-dose) vaccine schedules of BNT162b2 and mRNA-1273 (i.e. the two most common schedules) were compared with unvaccinated individuals (controls) with a study design similar to that for objective 2 (i.e. the 3- vs. 2-dose comparison) and as previously done in Denmark.(49) In these sensitivity analyses, we evaluated the infection endpoint (positive PCR test for SARS-CoV-2). Vaccinated individuals were matched 1-to-1 (same matching variables as the main design [except, this analysis did not include calendar month of receiving the 2. dose as not applicable] – age, sex, region of residency comorbidity, and vaccination priority group) with individuals that were unvaccinated at the vaccinee's day of vaccination. Follow-up started on day 14 after the 2. vaccine dose (for both the vaccinated and unvaccinated controls [i.e. unvaccinated controls were assigned the index date of the vaccinated matched individual]) and ended at: the day of testing positive, exit from the cohort due to death, loss to follow-up, emigration, vaccination of the matched unvaccinated control or receipt of a (third) booster dose for vaccinated persons, or end of study period, whichever occurred first. Individuals that were included as unvaccinated controls were also eligible to enter the study as vaccinated. Survival curves for vaccinated and unvaccinated-control groups were estimated using the Kaplan-Meier estimator yielding cumulative incidences at day 75 after start of follow-up. We calculated 95% confidence intervals using the percentile bootstrap method with 1000 repetitions.

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

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

Data on all (positive or negative) test results in Denmark for the period 27 December 2020 to 28 February 2022 were extracted for those aged 18 years or older (as of 27 December 2020). We excluded any negative PCR test results taken within 3 days of a previous negative test result (as these results likely represented the same episode), negative test results taken within 21 days before a positive test result (as these were likely to be false negative), and positive and negative test results within 90 days of a previous positive test result. Since we aimed for evaluating the effectiveness of a 3. dose, only PCR tests taken from the date where the booster doses rollout started (6 September 2021 [week 37, 2021]) were retained for analysis. Participants contributed with only one randomly chosen negative test result in the follow-up period. The 3. (booster) doses were identified after this date and there had to be at least 6 months (from 6 September 2021 to 13 December 2021) or 4.5 months (from 14 December

2021 to 28 February 2022) between the 2. and 3. dose or from 2. dose and onset (i.e. of covid-19 related event). These time periods of "since 2. dose" denotes whether an individual was eligible of receiving a 3. dose as per Danish health authority guidelines on booster vaccination rollout. The effectiveness of a 3. dose from day 14 to day 28 (after the index date) was compared with 2. dose schedules with onsets of events after at least the abovementioned 6 or 4.5 months eligibility criterion as well as to the immediate short period after the booster dose (i.e. the first 2-6 days; day 0 and 1 were not included due to the potential risk of bias related to any testing due to initial reactogenicity).

Comparative VE (1 – the odds of vaccination in cases divided by the odds of vaccination in controls) was estimated using logistic regression (the PCR test result as the dependent variable); cases were those testing positive and controls were those testing negative. The logistic regression models were adjusted for age, sex, calendar week of testing, number of previous tests, vaccine priority group, region of residency, and comorbidity. Please note that only Denmark participated in this sensitivity analysis due to time constrains, and the lack of availability of dates of negative tests in some countries.

10. RESULTS

10.1 Participants and descriptive data

The source cohorts consisted of all individuals in Denmark, Finland, Norway, and Sweden, respectively, aged 18 years or older, who had received at least a primary covid-19 vaccine schedule (2 doses) during the study period, and were eligible for study inclusion (approximately 19.6 million individuals). Table 1 presents the number of included individuals across country and comparisons as well as descriptive data on age, sex, and index date calendar periods for objective 1 (weighted analyses, 2-dose vs. 2-dose and 3- vs. 3-dose) and 2 (matched analyses, 3- vs. 2-dose), respectively.

In general, Sweden had the largest number of heterologous vaccinated individuals followed by Norway, Finland, and Denmark. Across the four countries, a total of 4,530,368 heterologous vaccinated individuals (1,259,575 2-dose and 3,270,809 3-dose vaccinated) were included in the weighted analyses (objective 1) and 2,390,910 heterologous vaccinated individuals were included in the matched analyses (objective 2). The most prevalent heterologous primary (i.e. 2-dose) vaccine schedule in Denmark, Finland, and Sweden was AZD1BNT2 (81,212, 123,251, and 89,177 individuals [in the weighted analysis], respectively), and BNT1MOD2 in Norway (534,531 individuals). The most prevalent heterologous booster (i.e. 3-dose) vaccine schedule was AZD1BNT2BNT3 in Denmark (71,864 individuals [in the weighted analysis]) and

BNT1BNT2MOD3 in Finland, Norway, and Sweden (444,016, 321,250, and 757,011 individuals, respectively).

The sex distribution was close to 50% across most schedules in all countries. However, in Denmark, Norway, and Sweden those who had received AZD1mRNA2(mRNA3) were more likely female (ranging from 65% to 82%), and in Finland individuals who had received MOD1BNT2 were less likely female (30%).

In both Finland and Sweden, those who had received AZD1AZD2 were generally older (a mean age of approximately ≈ 69 years) than the individuals that had received other vaccine schedules. No other major age differences across the various studied vaccine schedules were observed in the four countries; the age means ranged between ≈ 35 to 60 years.

As presented in Table 1, the calendar periods for the index dates of the different comparisons varied broadly across schedules and countries. Figure 5 to 12 shows the density plots by age and index date for each comparison in all four countries.

Table 1. Descriptive results of the individual vaccine schedule comparisons by country.

Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Weighted analyses (2-dose vs 2-dose schedules)								
AZD1BNT2 vs BNT1BNT2								
Denmark	81212	44.1 (12.1)	79.0%	02/05/21 - 25/06/21	198985	57.5 (7.8)	48.2%	02/05/21 - 25/06/21
Finland	123251	58.2 (9.7)	52.3%	10/05/21 - 07/09/21	1563410	52.0 (12.2)	50.7%	10/05/21 - 07/09/21
Norway	122626	43.9 (12.7)	77.6%	10/05/21 - 30/06/21	362166	51.0 (11.5)	51.6%	10/05/21 - 30/06/21
Sweden	89177	46.7 (14.0)	75.4%	04/05/21 - 02/12/21	3521388	48.5 (15.0)	47.7%	04/05/21 - 02/12/21
AZD1MOD2 vs MOD1MOD2								
Denmark	44857	45.9 (11.6)	81.8%	06/05/21 - 30/06/21	40309	57.8 (7.5)	46.6%	06/05/21 - 30/06/21
Finland	27222	57.1 (10.8)	53.7%	07/05/21 - 20/09/21	209659	51.7 (12.9)	49.5%	07/05/21 - 20/09/21
Norway	2882	46.4 (13.5)	65.6%	06/05/21 - 28/10/21	335509	41.5 (12.4)	48.4%	06/05/21 - 28/10/21
Sweden	14883	46.7 (13.8)	75.2%	05/05/21 - 15/12/21	552676	44.5 (14.3)	47.1%	05/05/21 - 15/12/21
BNT1MOD2 vs BNT1BNT2								
Denmark	117	45.9 (22.0)	52.1%	19/03/21 - 06/01/22	2860283	53.8 (16.9)	49.1%	19/03/21 - 06/01/22
Finland	48196	39.0 (14.0)	50.4%	14/07/21 - 27/01/22	1875887	44.1 (13.8)	48.7%	14/07/21 - 27/01/22
Norway	534531	35.1 (10.9)	43.8%	02/08/21 - 29/09/21	906922	39.9 (12.4)	47.3%	02/08/21 - 29/09/21
Sweden	22086	38.5 (14.3)	46.3%	16/07/21 - 08/02/22	2090238	37.4 (11.9)	46.6%	16/07/21 - 08/02/22
MOD1BNT2 vs BNT1BNT2								
Denmark	207	51.0 (22.0)	46.4%	31/03/21 - 12/01/22	2818460	53.6 (16.9)	49.1%	25/03/21 - 12/01/22
Finland	39802	33.8 (14.9)	29.5%	23/06/21 - 21/01/22	2239535	46.7 (15.4)	49.3%	23/06/21 - 21/01/22
Norway	65163	32.4 (10.5)	44.6%	30/07/21 - 13/01/22	1119748	38.2 (13.8)	47.6%	30/07/21 - 13/01/22
Sweden	43363	28.4 (10.6)	44.1%	21/07/21 - 26/01/22	2004279	36.8 (11.4)	46.5%	21/07/21 - 26/01/22
Weighted analyses (3-dose vs 3-dose schedules)								
AZD1AZD2BNT3 vs BNT1BNT2BNT3								
Denmark	946	45.8 (12.5)	63.1%	29/10/21 - 22/01/22	1690791	50.4 (12.7)	48.9%	29/10/21 - 22/01/22

Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Finland	113759	68.4 (2.6)	49.4%	09/11/21 - 25/01/22	343987	72.4 (3.1)	55.3%	09/11/21 - 25/01/22
Norway	743	43.8 (15.6)	44.0%	04/11/21 - 09/02/22	1310498	54.0 (15.4)	51%	04/11/21 - 09/02/22
Sweden	357633	70.5 (7.8)	52.4%	11/11/21 - 17/01/22	1214351	63.6 (10.9)	52.6%	11/11/21 - 17/01/22
AZD1AZD2MOD3 vs MOD1MOD2MOD3								
Denmark	60	50.8 (9.7)	51.7%	09/11/21 - 06/02/22	237523	41.5 (11.5)	46.4%	09/11/21 - 06/02/22
Finland	47069	68.7 (2.9)	49.8%	20/11/21 - 29/01/22	37210	71.9 (3.3)	52.9%	20/11/21 - 29/01/22
Norway	246	50.6 (13.4)	40.7%	14/10/21 - 05/02/22	144256	51.8 (12.4)	48.1%	14/10/21 - 05/02/22
Sweden	121229	69.7 (7.4)	51.2%	11/11/21 - 27/01/22	118248	59.7 (11.9)	49.3%	11/11/21 - 27/01/22
AZD1BNT2BNT3 vs BNT1BNT2BNT3								
Denmark	71864	44.8 (12)	79.4%	08/10/21 - 05/01/22	1259988	48.9 (10.6)	49.9%	08/10/21 - 05/01/22
Finland	101741	58.4 (9.3)	52.5%	15/10/21 - 22/01/22	802276	53.6 (11.8)	53.7%	15/10/21 - 22/01/22
Norway	96911	44.7 (12.6)	78.0%	16/11/21 - 19/01/22	752602	47.9 (12.5)	51.7%	16/11/21 - 19/01/22
Sweden	57480	46.9 (13.3)	77.9%	15/11/21 - 01/02/22	1322373	54.9 (13.7)	51.7%	15/11/21 - 01/02/22
AZD1MOD2MOD3 vs MOD1MOD2MOD3								
Denmark	40838	46.5 (11.4)	82.2%	07/10/21 - 07/01/22	159915	43.8 (12.0)	46.9%	07/10/21 - 07/01/22
Finland	18770	58.1 (9.8)	53.3%	14/10/21 - 25/01/22	104410	55.0 (11.4)	50.8%	14/10/21 - 25/01/22
Norway	1079	51.5 (11.5)	64.8%	17/10/21 - 31/01/22	114959	48.3 (10.5)	47.7%	17/10/21 - 31/01/22
Sweden	4683	50.0 (10.9)	78.1%	15/11/21 - 03/02/22	128883	52.9 (11.6)	48.3%	15/11/21 - 03/02/22
BNT1BNT2MOD3 vs BNT1BNT2BNT3								
Denmark	633	51.0 (15.5)	53.7%	16/09/21 - 01/02/22	2318863	55.4 (15.2)	50.3%	16/09/21 - 01/02/22
Finland	444016	53.5 (13.3)	52.3%	26/11/21 - 04/02/22	1200229	56.9 (15.4)	52.9%	26/11/21 - 04/02/22
Norway	321250	51.8 (11.3)	48.4%	22/10/21 - 01/02/22	1263082	57.8 (13.4)	50.9%	22/10/21 - 01/02/22
Sweden	757011	54.4 (12.9)	47.9%	21/10/21 - 10/02/22	1727033	62.7 (13.5)	52.3%	21/10/21 - 10/02/22
MOD1MOD2BNT3 vs BNT1BNT2BNT3								
Denmark	991	52.4 (21.2)	53.3%	20/09/21 - 31/01/22	2506650	57.7 (16.6)	51.0%	20/09/21 - 31/01/22

Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Finland	61659	54.4 (17.7)	49.5%	17/11/21 - 09/02/22	1371130	58.0 (17.2)	53.5%	17/11/21 - 09/02/22
Norway	120661	47.9 (18.3)	53.9%	19/10/21 - 08/02/22	1499658	57.2 (16.5)	51.4%	19/10/21 - 08/02/22
Sweden	184269	53.6 (20.5)	52.3%	19/10/21 - 10/02/22	1983945	59.2 (17.6)	52.7%	19/10/21 - 10/02/22
BNT1MOD2MOD3 vs BNT1BNT2BNT3								
Denmark	51	57.1 (23.1)	51.0%	25/10/21 - 26/01/22	2325863	57.3 (15.8)	50.5%	25/10/21 - 26/01/22
Finland	10332	43.4 (12.1)	57.3%	19/12/21 - 10/02/22	942735	50.8 (14.6)	51.2%	19/12/21 - 10/02/22
Norway	97079	44.2 (8.4)	44.0%	20/12/21 - 09/02/22	488451	47.0 (9.4)	48.2%	20/12/21 - 09/02/22
Sweden	806	45.6 (11.5)	43.3%	31/10/21 - 12/02/22	1633257	60.8 (13.0)	52.0%	27/10/21 - 12/02/22
MOD1BNT2BNT3 vs BNT1BNT2BNT3								
Denmark	93	62.4 (21.7)	38.7%	22/09/21 - 02/02/22	2524265	57.3 (16.8)	51.0%	22/09/21 - 02/02/22
Finland	4543	50.8 (18.7)	47.9%	24/11/21 - 11/02/22	1328683	56.5 (17.0)	53.1%	24/11/21 - 11/02/22
Norway	12620	32.4 (10.7)	48.8%	20/12/21 - 11/02/22	588157	41.9 (12.5)	48.8%	20/12/21 - 11/02/22
Sweden	2238	37.9 (17.9)	51.8%	20/10/21 - 14/02/22	1984651	58.1 (17.7)	52.5%	20/10/21 - 14/02/22
BNT1MOD2BNT3 vs BNT1BNT2BNT3								
Denmark	24	38.3 (20.1)	50.0%	01/11/21 - 09/02/22	2298307	56.0 (16.0)	50.0%	01/11/21 - 09/02/22
Finland	10236	38.8 (13.1)	46.5%	14/12/21 - 11/02/22	1019991	51.0 (14.7)	51.7%	14/12/21 - 11/02/22
Norway	194343	34.1 (11.2)	45.8%	28/12/21 - 10/02/22	513894	40.0 (12.7)	48.6%	28/12/21 - 10/02/22
Sweden	2884	35.1 (12.6)	49.0%	30/11/21 - 12/02/22	1269768	49.7 (14.9)	50.6%	30/11/21 - 12/02/22
MOD1BNT2MOD3 vs BNT1BNT2BNT3								
Denmark	16	61.3 (22.2)	18.8%	24/09/21 - 26/01/22	2394528	58.2 (15.4)	50.8%	24/09/21 - 26/01/22
Finland	2112	48.1 (14.5)	55.4%	18/12/21 - 10/02/22	975919	51.7 (15.0)	51.4%	18/12/21 - 10/02/22
Norway	7458	42.7 (8.9)	45.9%	21/12/21 - 10/02/22	532352	45.4 (11.0)	48.2%	21/12/21 - 10/02/22
Sweden	433	50.1 (12.5)	49.2%	21/10/21 - 13/02/22	1716478	61.9 (13.5)	52.2%	21/10/21 - 13/02/22
Matched analyses (3-dose vs 2-dose schedules)								
AZD1AZD2BNT3 vs AZD1AZD2								

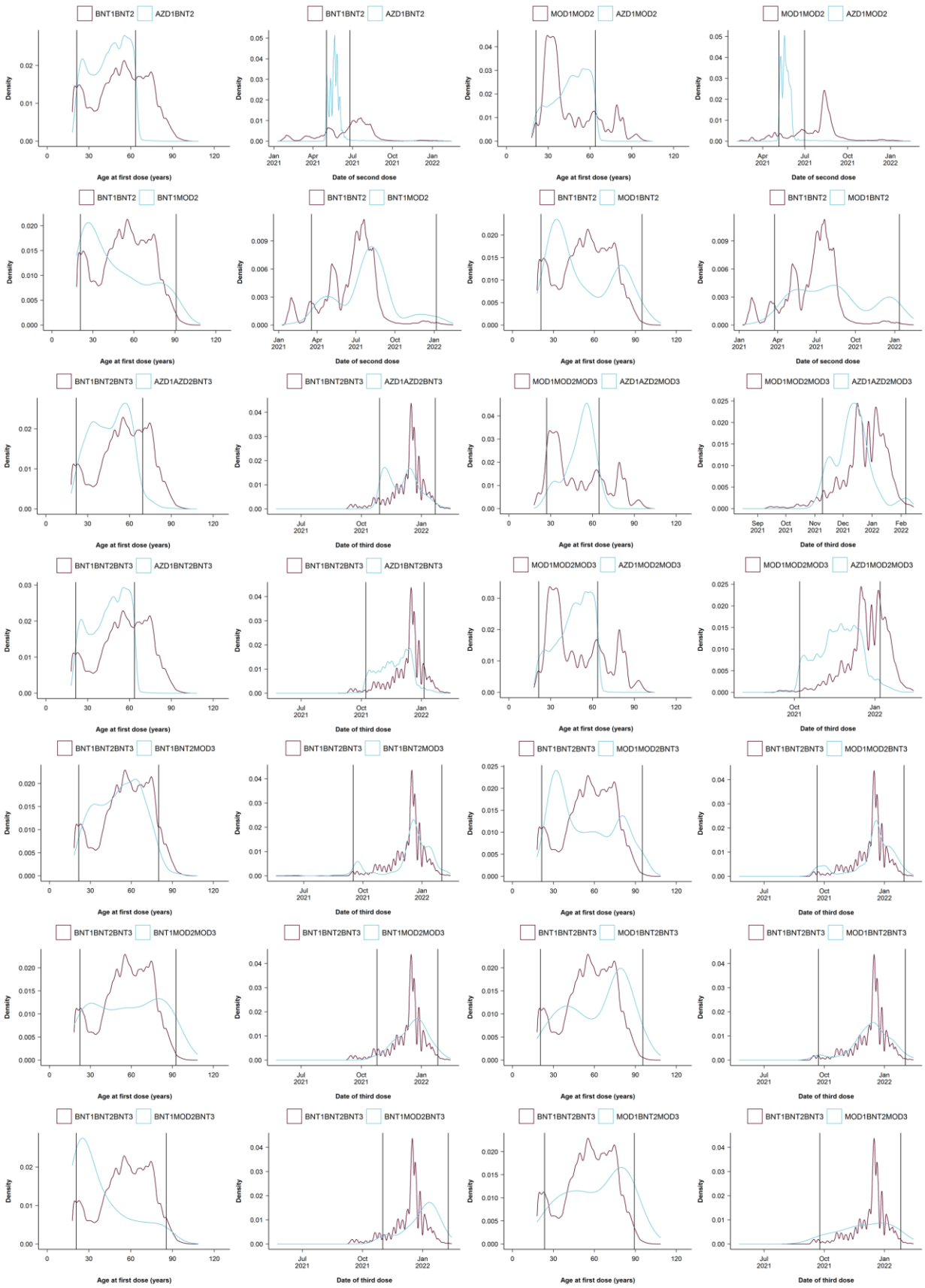
Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Denmark	405	44.8 (13.2)	62.0%	15/10/21 - 28/02/22	405	44.8 (13.2)	60.5%	15/10/21 - 28/02/22
Finland	65346	68.7 (3.6)	48.9%	01/10/21 - 27/02/22	65346	68.7 (3.6)	49.5%	01/10/21 - 27/02/22
Norway	596	43.4 (15.7)	43.5%	14/11/21 - 28/02/22	596	43.4 (15.7)	39.6%	14/11/21 - 28/02/22
Sweden	196464	69 (11.6)	53.5%	14/10/21 - 28/02/22	196464	68.9 (11.6)	51.9%	14/10/21 - 28/02/22
AZD1AZD2MOD3 vs AZD1AZD2								
Denmark	46	51.1 (9.8)	45.7%	18/11/21 - 28/02/22	46	51.3 (9.8)	32.6%	18/11/21 - 28/02/22
Finland	31500	68.9 (3.7)	49.5%	30/09/21 - 27/02/22	31500	69.0 (3.7)	49.2%	30/09/21 - 27/02/22
Norway	218	49.6 (13.9)	40.4%	27/11/21 - 28/02/22	218	49.5 (13.9)	35.8%	27/11/21 - 28/02/22
Sweden	97678	69.3 (9.9)	51.8%	14/10/21 - 28/02/22	97678	69.3 (9.9)	51.1%	14/10/21 - 28/02/22
AZD1BNT2BNT3 vs AZD1BNT2								
Denmark	43554	44.3 (12.8)	79.3%	19/09/21 - 28/02/22	43554	44.3 (12.8)	78.8%	19/09/21 - 28/02/22
Finland	50467	56.9 (11.8)	52.4%	30/09/21 - 27/02/22	50467	56.8 (11.9)	54.2%	30/09/21 - 27/02/22
Norway	44269	42.3 (13.5)	80.3%	14/11/21 - 28/02/22	44269	42.2 (13.5)	76.2%	14/11/21 - 28/02/22
Sweden	37130	45.2 (14.7)	76.5%	14/10/21 - 28/02/22	37130	45.1 (14.7)	74.2%	14/10/21 - 28/02/22
AZD1MOD2MOD3 vs AZD1MOD2								
Denmark	24202	45.5 (12.4)	81.8%	20/09/21 - 28/02/22	24202	45.5 (12.4)	81.9%	20/09/21 - 28/02/22
Finland	10475	56.4 (12.0)	54.9%	30/09/21 - 23/02/22	10475	56.3 (12.0)	54.5%	30/09/21 - 23/02/22
Norway	571	49.1 (13.3)	68.1%	14/11/21 - 28/02/22	571	49 (13.2)	64.6%	14/11/21 - 28/02/22
Sweden	3249	49.1 (12.5)	75.4%	14/10/21 - 28/02/22	3249	48.9 (12.5)	75.4%	14/10/21 - 28/02/22
BNT1BNT2MOD3 vs BNT1BNT2								
Denmark	494	51.9 (16.5)	53.2%	21/09/21 - 28/02/22	494	51.8 (16.5)	52.8%	21/09/21 - 28/02/22
Finland	346020	52.5 (15.3)	54.5%	30/09/21 - 27/02/22	346020	52.5 (15.4)	51.1%	30/09/21 - 27/02/22
Norway	268271	52 (13.2)	49.6%	14/11/21 - 28/02/22	268271	51.9 (13.3)	49.0%	14/11/21 - 28/02/22
Sweden	632846	56.2 (15.1)	49.1%	14/10/21 - 28/02/22	632846	56.1 (15.2)	48.0%	14/10/21 - 28/02/22
MOD1MOD2BNT3 vs MOD1MOD2								

Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Denmark	847	55.5 (22.6)	53.2%	23/09/21 - 28/02/22	847	55.5 (22.7)	52.7%	23/09/21 - 28/02/22
Finland	53322	53.9 (19.3)	49.9%	30/09/21 - 27/02/22	53322	53.9 (19.3)	47.3%	30/09/21 - 27/02/22
Norway	80100	46.0 (18.2)	51.3%	14/11/21 - 28/02/22	80100	45.9 (18.2)	49.8%	14/11/21 - 28/02/22
Sweden	147734	52.3 (21.6)	51.8%	14/10/21 - 28/02/22	147734	52.3 (21.5)	50.5%	14/10/21 - 28/02/22
BNT1MOD2MOD3 vs BNT1MOD2								
Denmark								
Finland	7323	42.0 (14.1)	58.9%	05/10/21 - 27/02/22	7323	42.0 (14.1)	58.9%	05/10/21 - 27/02/22
Norway	72056	43.7 (9.6)	45.3%	17/11/21 - 28/02/22	72056	43.5 (9.7)	42.3%	17/11/21 - 28/02/22
Sweden	651	45.1 (12.3)	43.2%	18/10/21 - 28/02/22	651	45.0 (12.4)	43.0%	18/10/21 - 28/02/22
MOD1BNT2BNT3 vs MOD1BNT2								
Denmark								
Finland	3089	46.3 (19.4)	44.7%	04/10/21 - 27/02/22	3089	46.3 (19.5)	45.0%	04/10/21 - 27/02/22
Norway	8013	32.9 (11.5)	46.3%	16/11/21 - 28/02/22	8013	32.9 (11.5)	44.4%	16/11/21 - 28/02/22
Sweden	1672	35.1 (16.2)	49.6%	19/10/21 - 28/02/22	1672	35.2 (16.1)	42.5%	19/10/21 - 28/02/22
BNT1MOD2BNT3 vs BNT1MOD2								
Denmark	7	31.9 (14.8)	42.9%	24/11/21 - 28/02/22	7	32.3 (15.3)	57.1%	24/11/21 - 28/02/22
Finland	8472	38.1 (14.5)	45.9%	08/10/21 - 27/02/22	8472	38.1 (14.5)	45.2%	08/10/21 - 27/02/22
Norway	145155	34.2 (12.0)	45.4%	15/11/21 - 28/02/22	145155	34.2 (12.0)	42.8%	15/11/21 - 28/02/22
Sweden	2308	34.6 (13.2)	48.1%	20/10/21 - 28/02/22	2308	34.6 (13.1)	45.1%	20/10/21 - 28/02/22
MOD1BNT2MOD3 vs MOD1BNT2								
Denmark								
Finland	1651	46.3 (15.4)	55.5%	19/10/21 - 27/02/22	1651	46.2 (15.5)	56.3%	19/10/21 - 27/02/22
Norway	4345	41.4 (10.5)	47.5%	23/11/21 - 28/02/22	4345	41.2 (10.6)	44.4%	23/11/21 - 28/02/22
Sweden	364	50.8 (13.6)	47.3%	21/10/21 - 28/02/22	364	50.7 (13.7)	43.4%	21/10/21 - 28/02/22
BNT1BNT2BNT3 vs BNT1BNT2								

Studied vs comparison schedule by country	Studied schedule				Comparison schedule			
	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)	Total individuals	Age (mean, SD)	Female sex (%)	Calendar period (min-max)
Denmark	849575	54.9 (20.3)	51.8%	19/09/21 - 28/02/22	849575	54.8 (20.3)	51.2%	19/09/21 - 28/02/22
Finland	839920	55.8 (18.9)	53.7%	30/09/21 - 27/02/22	839920	55.8 (18.9)	53.1%	30/09/21 - 27/02/22
Norway	771189	54.1 (19.4)	52.2%	14/11/21 - 28/02/22	771189	53.9 (19.4)	50.9%	14/11/21 - 28/02/22
Sweden	1303635	57.3 (19.1)	52.5%	14/10/21 - 28/02/22	1303635	57.2 (19.1)	52.1%	14/10/21 - 28/02/22
MOD1MOD2MOD3 vs MOD1MOD2								
Denmark	136397	46.5 (20.5)	48.8%	22/09/21 - 28/02/22	136397	46.4 (20.6)	48.0%	22/09/21 - 28/02/22
Finland	90809	57.2 (17.8)	54.8%	03/10/21 - 27/02/22	90809	57.1 (17.9)	51.5%	03/10/21 - 27/02/22
Norway	78995	50.3 (14.6)	49.2%	14/11/21 - 28/02/22	78995	50.0 (14.6)	48.5%	14/11/21 - 28/02/22
Sweden	136694	58.4 (16.7)	49.8%	14/10/21 - 28/02/22	136694	58.3 (16.8)	49.0%	14/10/21 - 28/02/22

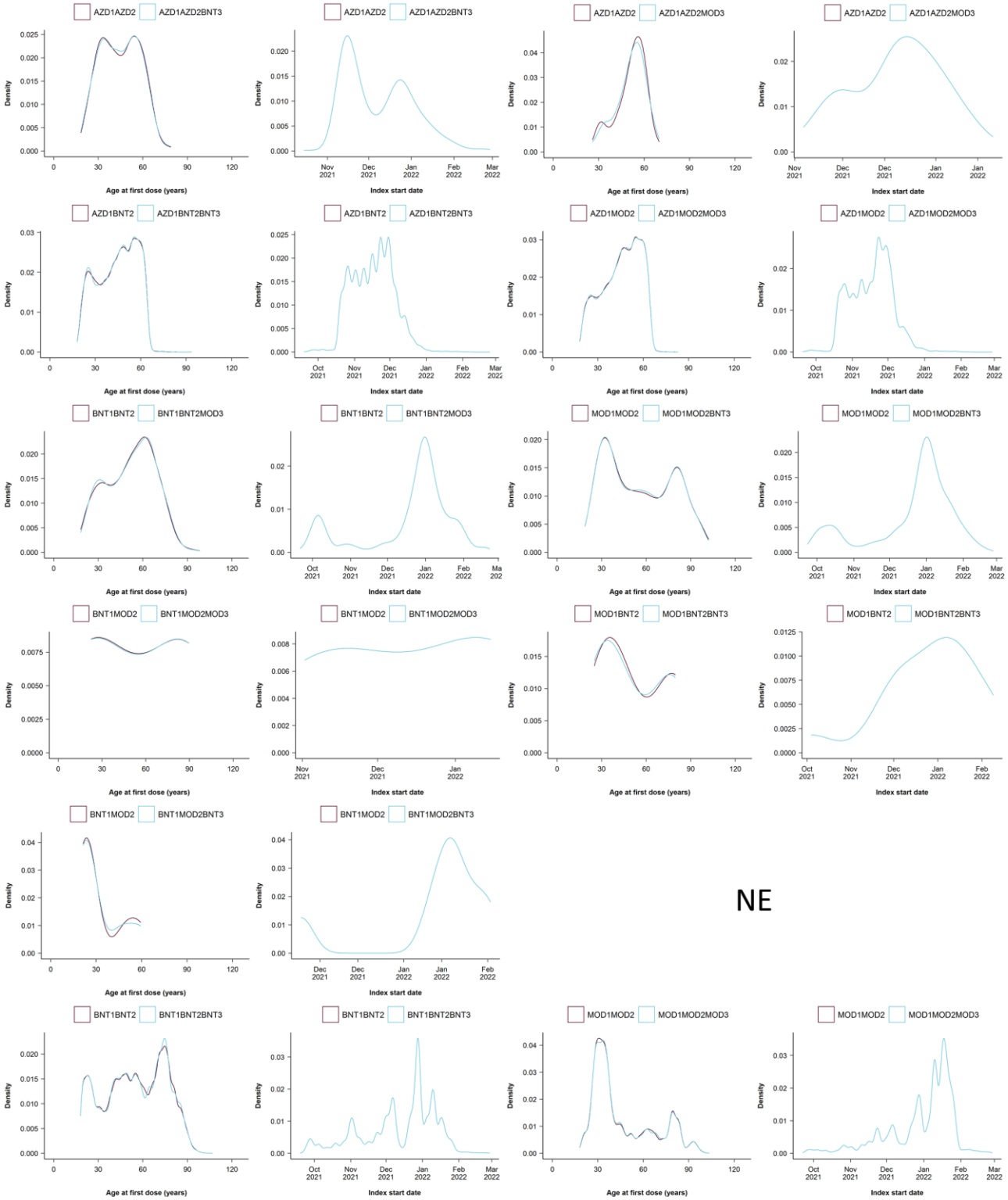
SD denotes standard deviation. Grey shaded cells denotes not estimable.

Figure 5. Density plots for distribution of age and index date for weighted analyses (objective 1) in Denmark.



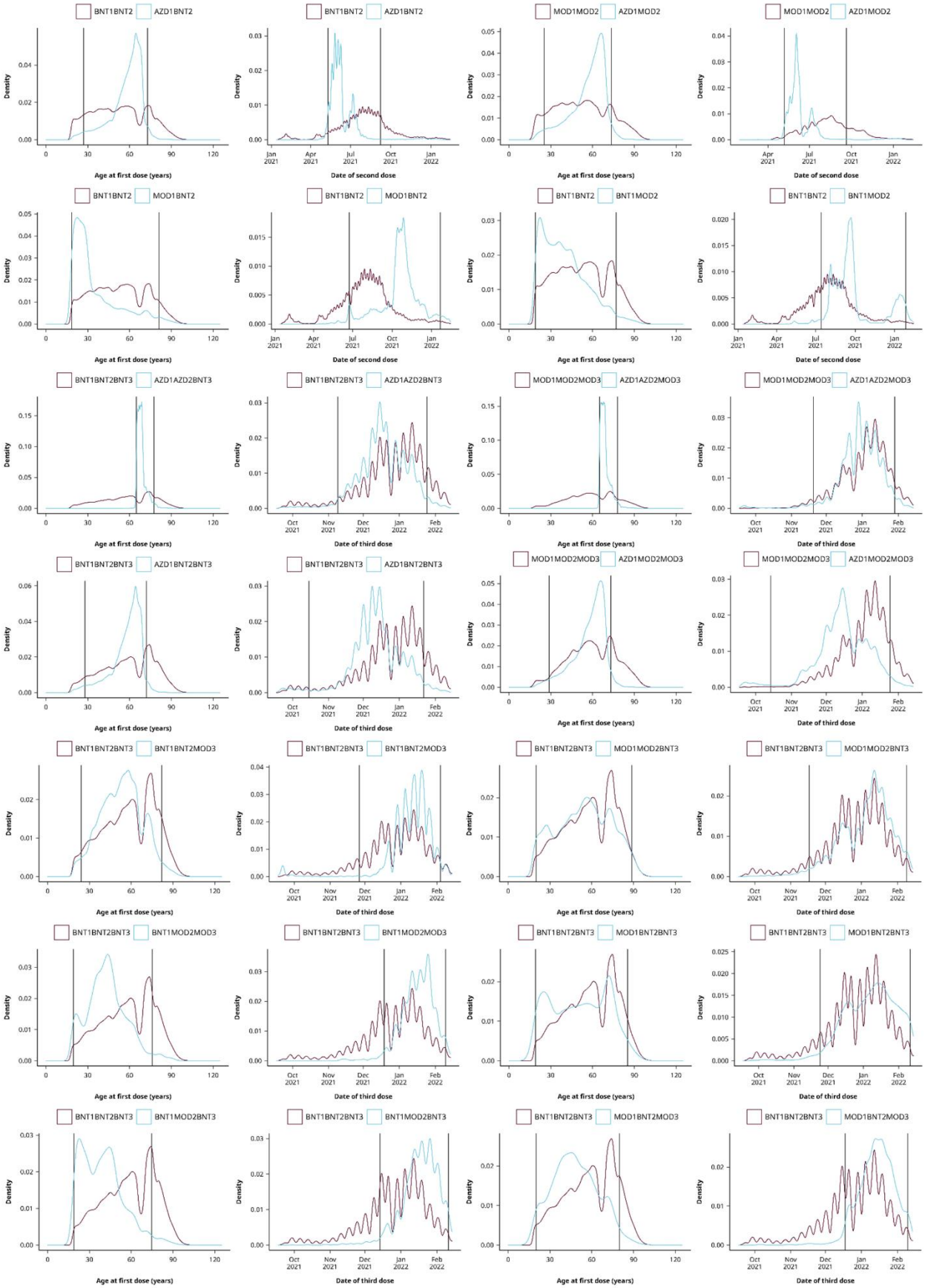
Vertical lines depict the 95% restriction of calendar period for inclusion of vaccine schedules.

Figure 6. Density plots for distribution of age and index date for matched analyses (objective 2) in Denmark.



NE denotes not estimated.

Figure 7. Density plots for distribution of age and index date for weighted analyses (objective 1) in Finland.



Vertical lines depict the 95% restriction of calendar period for inclusion of vaccine schedules.

Figure 8. Density plots for distribution of age and index date for matched analyses (objective 2) in Finland.

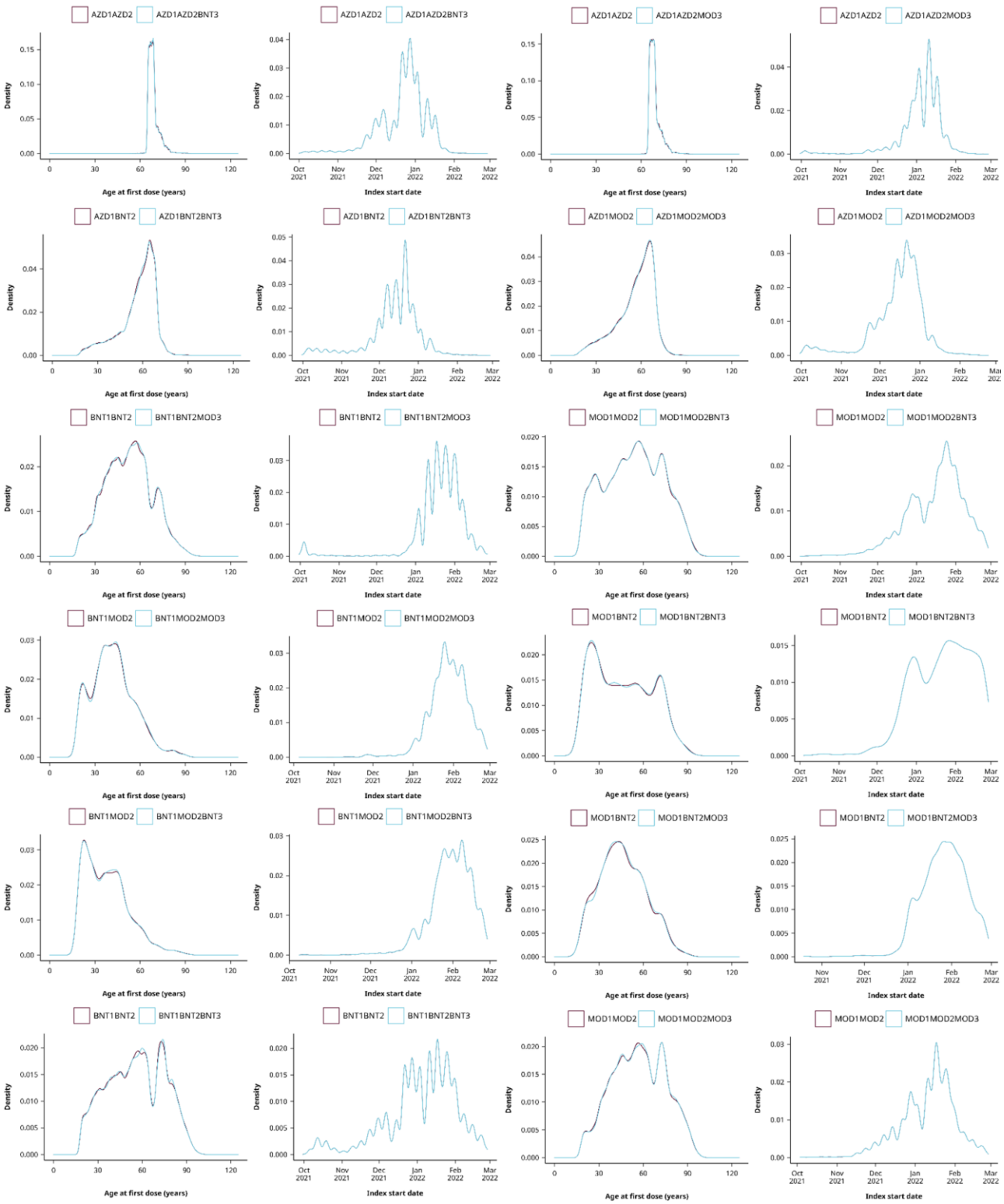
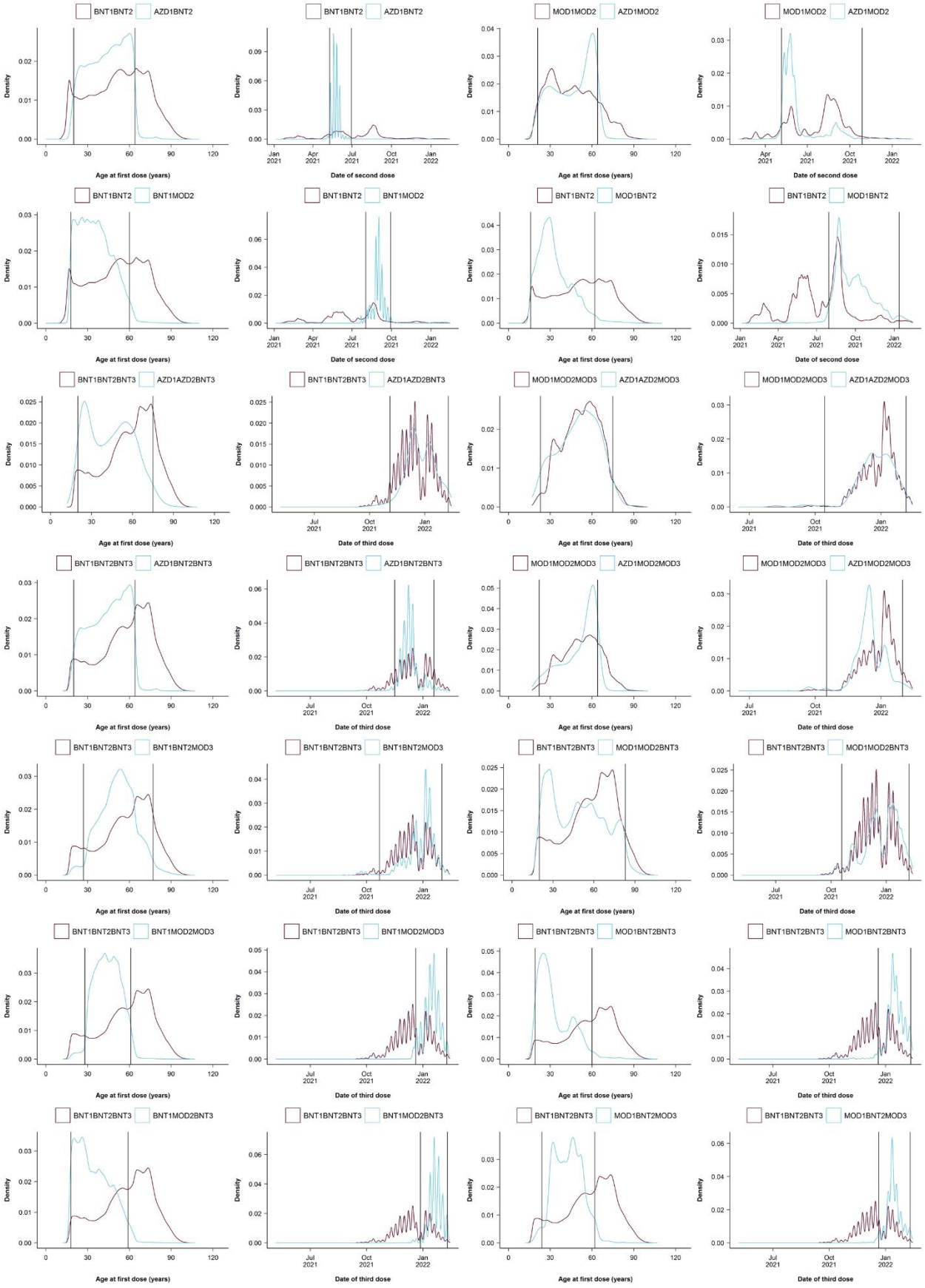


Figure 9. Density plots for distribution of age and index date for weighted analyses (objective 1) in Norway.



Vertical lines depict the 95% restriction of calendar period for inclusion of vaccine schedules.

Figure 10. Density plots for distribution of age and index date for matched analyses (objective 2) in Norway.

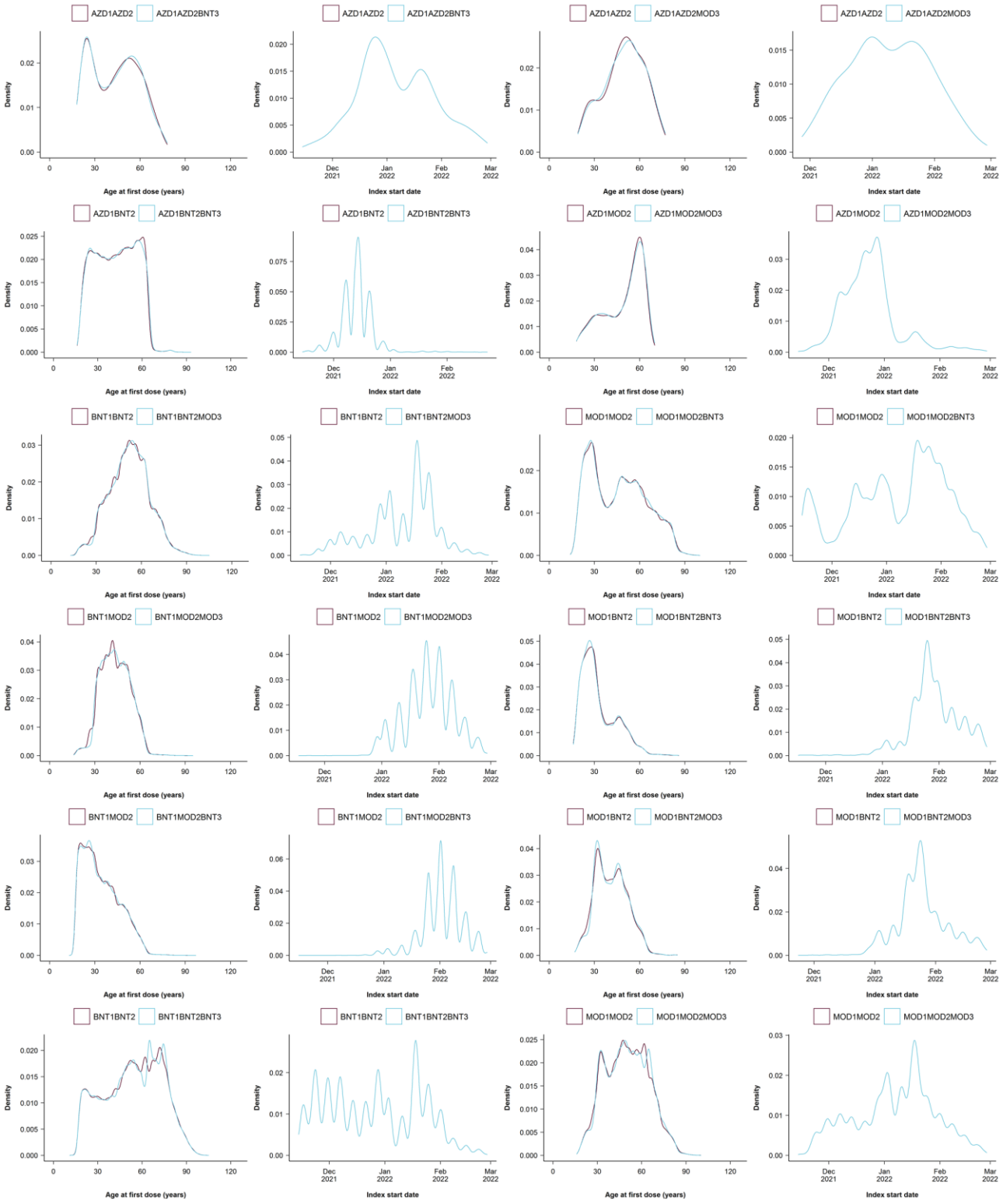
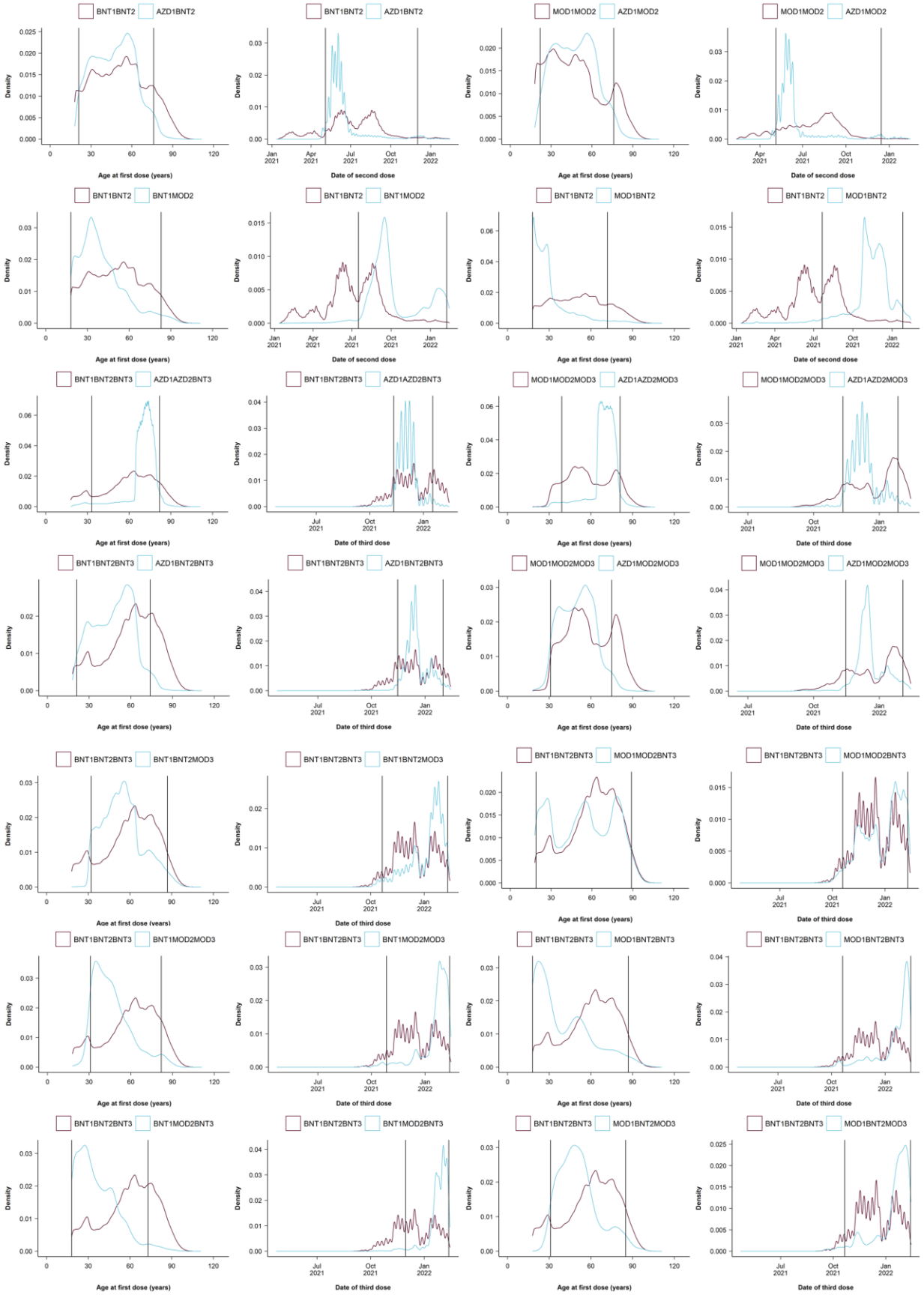
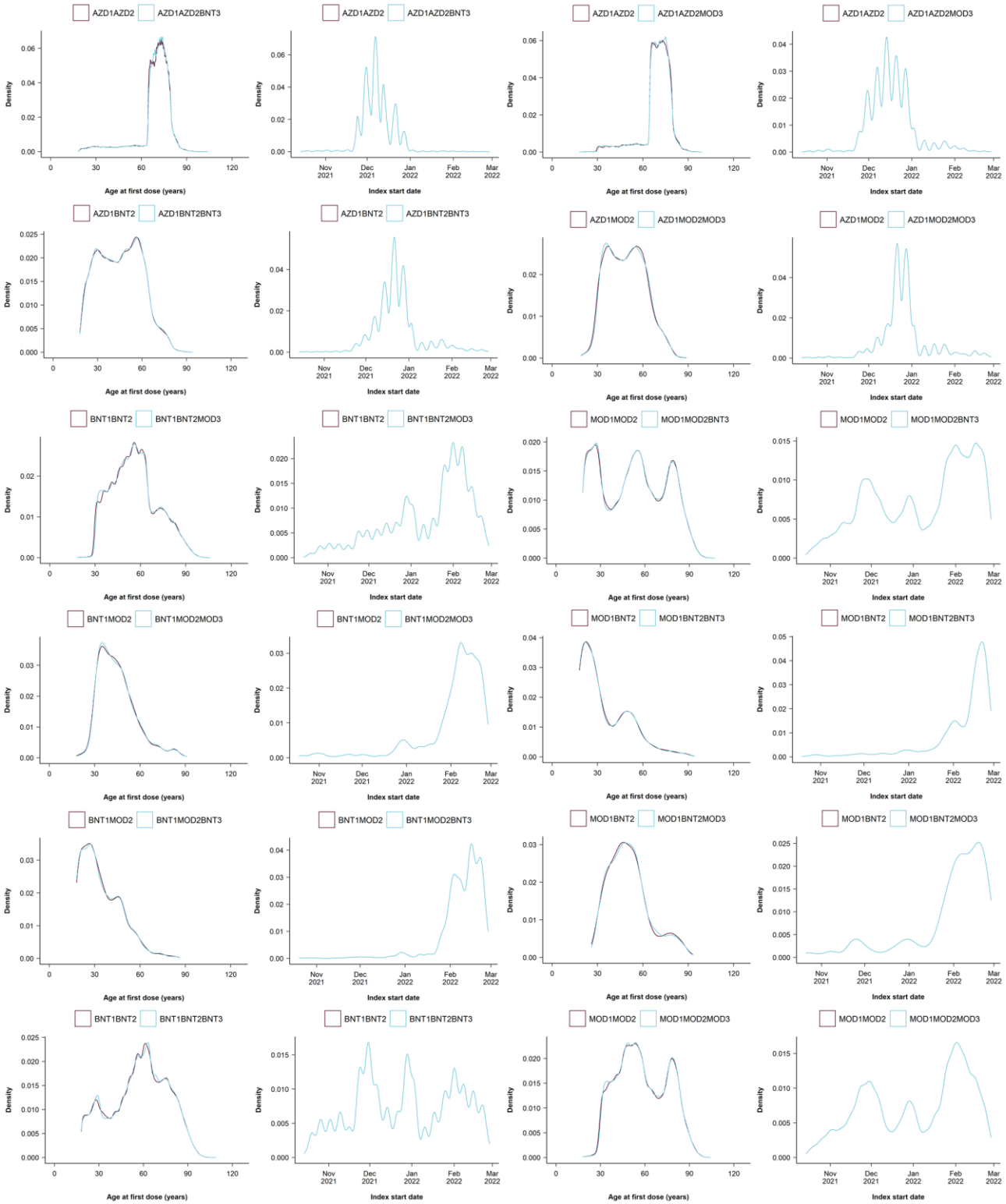


Figure 11. Density plots for distribution of age and index date for weighted analyses (objective 1) in Sweden.



Vertical lines depict the 95% restriction of calendar period for inclusion of vaccine schedules.

Figure 12. Density plots for distribution of age and index date for matched analyses (objective 2) in Sweden.



In Denmark, for the two-dose (primary schedule) comparisons, the calendar periods for inclusion for the studied heterologous schedules with AZD1mRNA2 were less than 2 months (early May 2021 to late June 2021) whereas the calendar periods for inclusion of the mRNA-heterologous primary schedules were around 9 to 10 months (late March 2021 to early January 2022). In Denmark, the calendar periods for inclusion of the booster vaccine schedules started in September 2021 and ended in February 2022 across studied schedules (for both weighted and matched analyses). However, as demonstrated in the density plots of each comparison, December 2021 to January 2022 was the calendar period where most included individuals received their booster dose (in both weighted and matched analyses).

In Finland, the calendar periods for inclusion for the primary vaccine schedule comparisons were between May 2021 and September 2021 for the comparisons that included AZD1, and June 2021 to January 2022 for the mRNA-heterologous primary schedules. For the booster schedules comparisons (both the weighted and matched analyses), the calendar periods for inclusion started in late September/early October 2021 and ended in February 2022. The peak of the roll-out of boosters in Finland was from December 2021 through February 2022 among the included individuals.

In Norway, the calendar periods for inclusion for the primary schedule comparisons started early May 2021 for the comparisons that included AZD1, and mid July 2021 for the comparisons that included mRNA-heterologous schedules. For the booster schedules comparisons (for both the weighted and matched analyses), the calendar periods for inclusion started in late October 2021. However, the majority of booster vaccinations among included individuals in Norway occurred from December 2021 through February 2022.

In Sweden, the calendar periods for inclusion for the primary schedule comparisons started in early May 2021 for the comparisons that included AZD1, and early July 2021 for the comparisons that included mRNA-heterologous schedules. For the booster schedules comparisons (for both the weighted and matched analyses), the calendar periods for inclusion started late October 2021. The majority of booster vaccinations among included individuals in Sweden, however, occurred from December 2021 through February 2022.

Overall, the calendar period for inclusion for primary and booster schedules in the weighted analyses (i.e. 2 vs. 2 dose and 3 vs. 3 dose) started spring and autumn 2021, respectively, in participating countries. Similarly, the calendar period for inclusion for the matched analyses (i.e. 3 vs 2 dose) started autumn 2021. It is worth noting that a high proportion of the weighted booster schedules comparisons (i.e. 3 vs. 3 dose) as well as the matched booster vs. primary schedules comparisons (i.e. 3 vs. 2 dose) was initiated in December 2021 or January/February 2022 – the same period where omicron became the dominant variant in the Nordic countries.

10.2 Outcome data and main results

10.2.1 Comparative vaccine effectiveness of heterologous vs. homologous primary and booster schedules (objective 1; i.e. 2- vs. 2-dose and 3- vs. 3-dose)

Figure 13 to 15 presents the cumulative incidence curves of documented covid-19 infection for the weighted heterologous vs. homologous comparisons (i.e. 2- vs. 2-dose and 3- vs. 3-dose). Few to no events of covid-19 related hospitalisation, ICU admissions, or death occurred across the majority of comparisons in all countries; the country-specific comparisons that yielded a sufficient number of cases for data analysis are presented in Figure 16 and 20, respectively.

Figure 13. Country-specific adjusted cumulative incidence curves of documented covid-19 infection for weighted analyses comparing heterologous and homologous primary vaccine schedules.

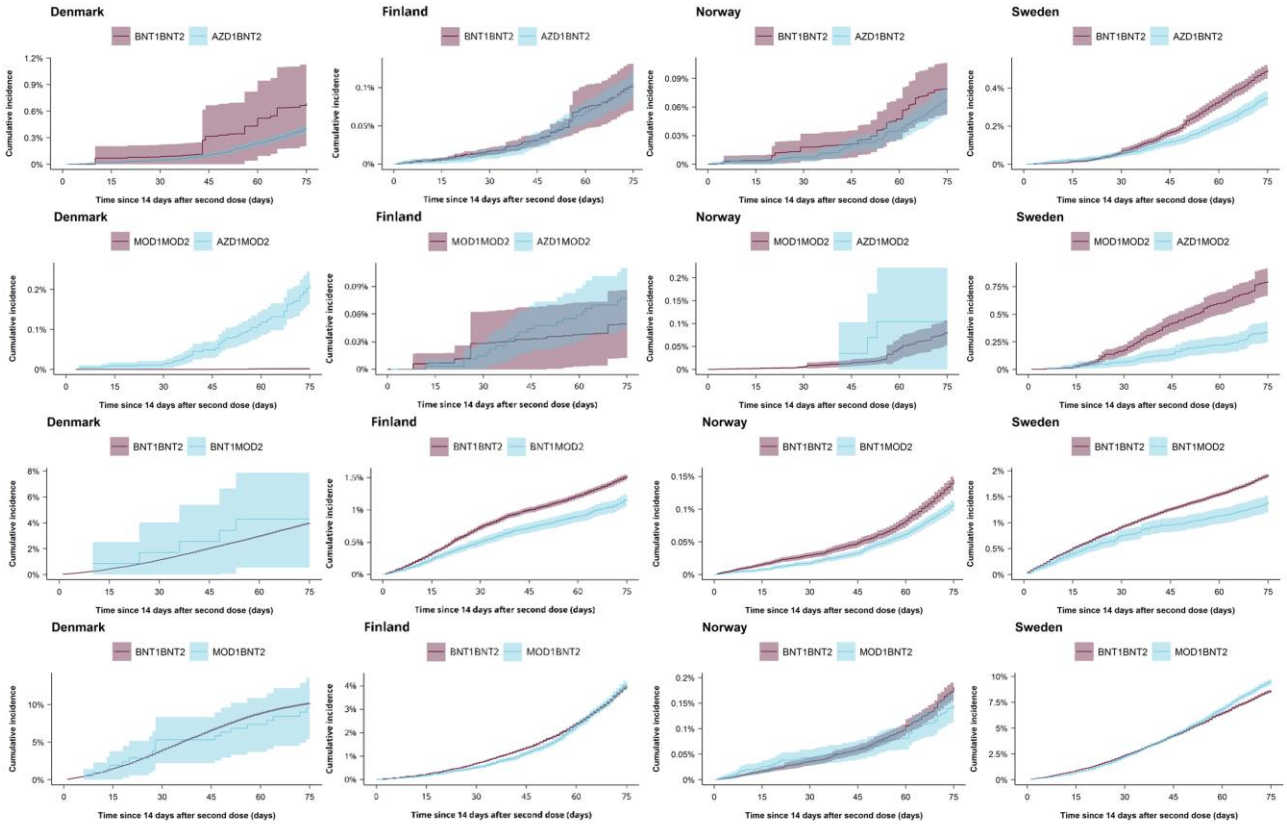


Figure 14. Country-specific adjusted cumulative incidence curves of documented covid-19 infection for weighted analyses comparing heterologous AZD-mRNA booster and homologous mRNA booster vaccine schedules.

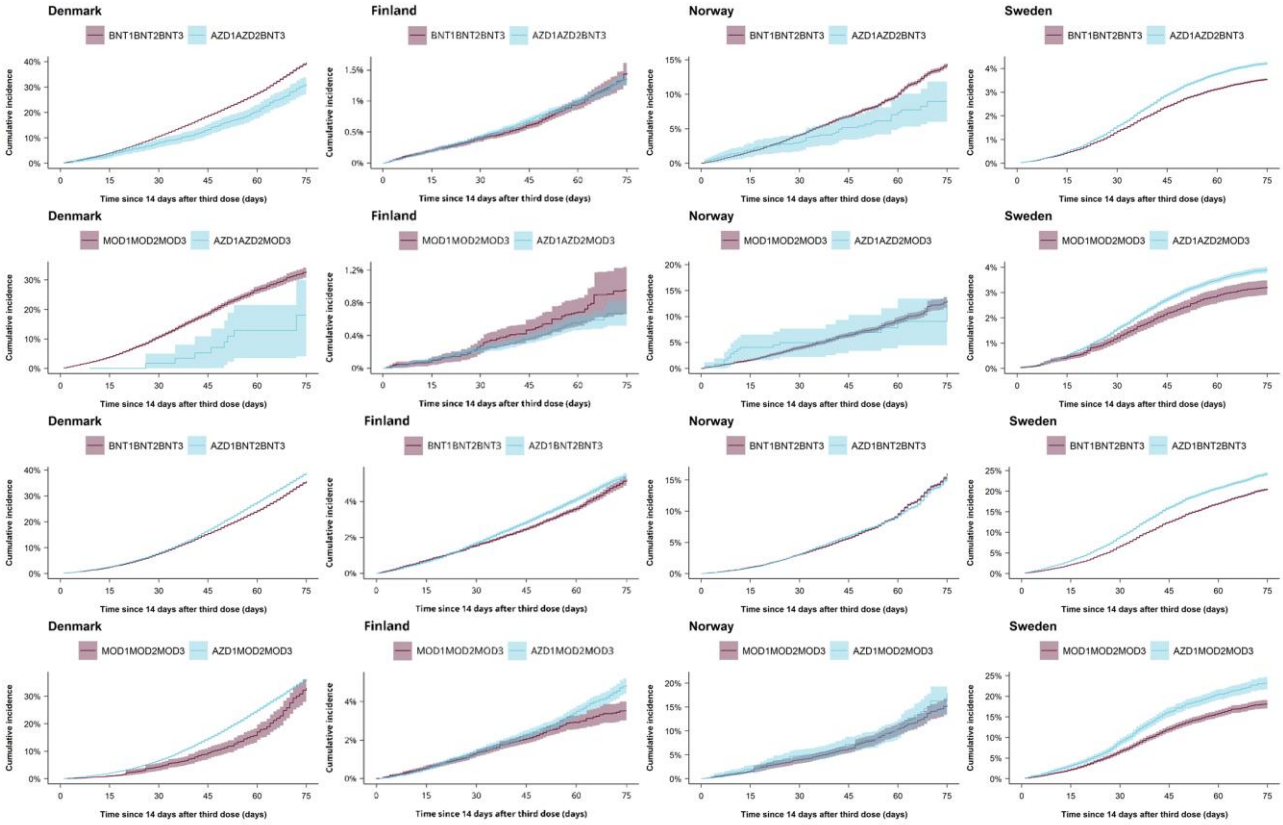


Figure 15. Country-specific adjusted cumulative incidence curves of documented covid-19 infection for weighted analyses comparing heterologous and homologous mRNA booster vaccine schedules.

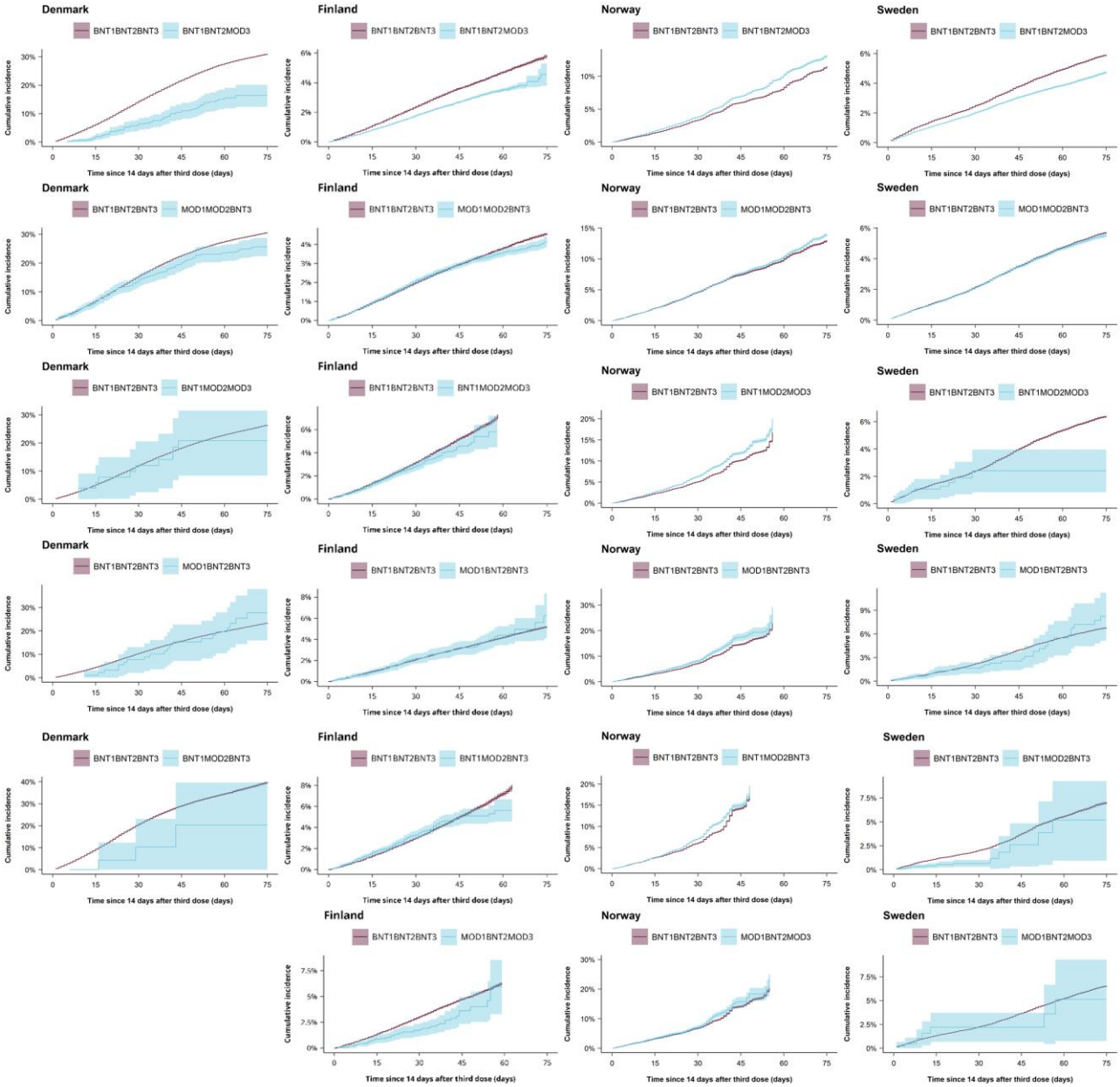
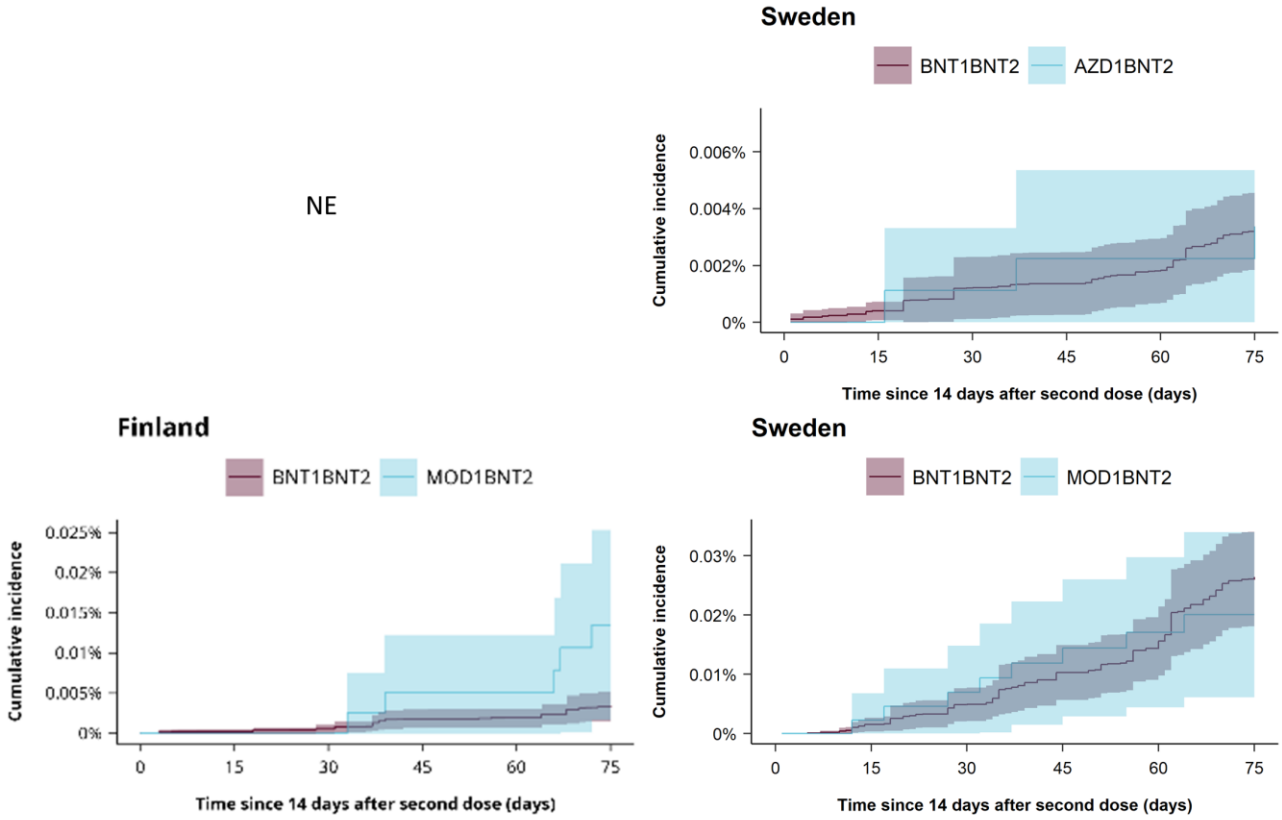
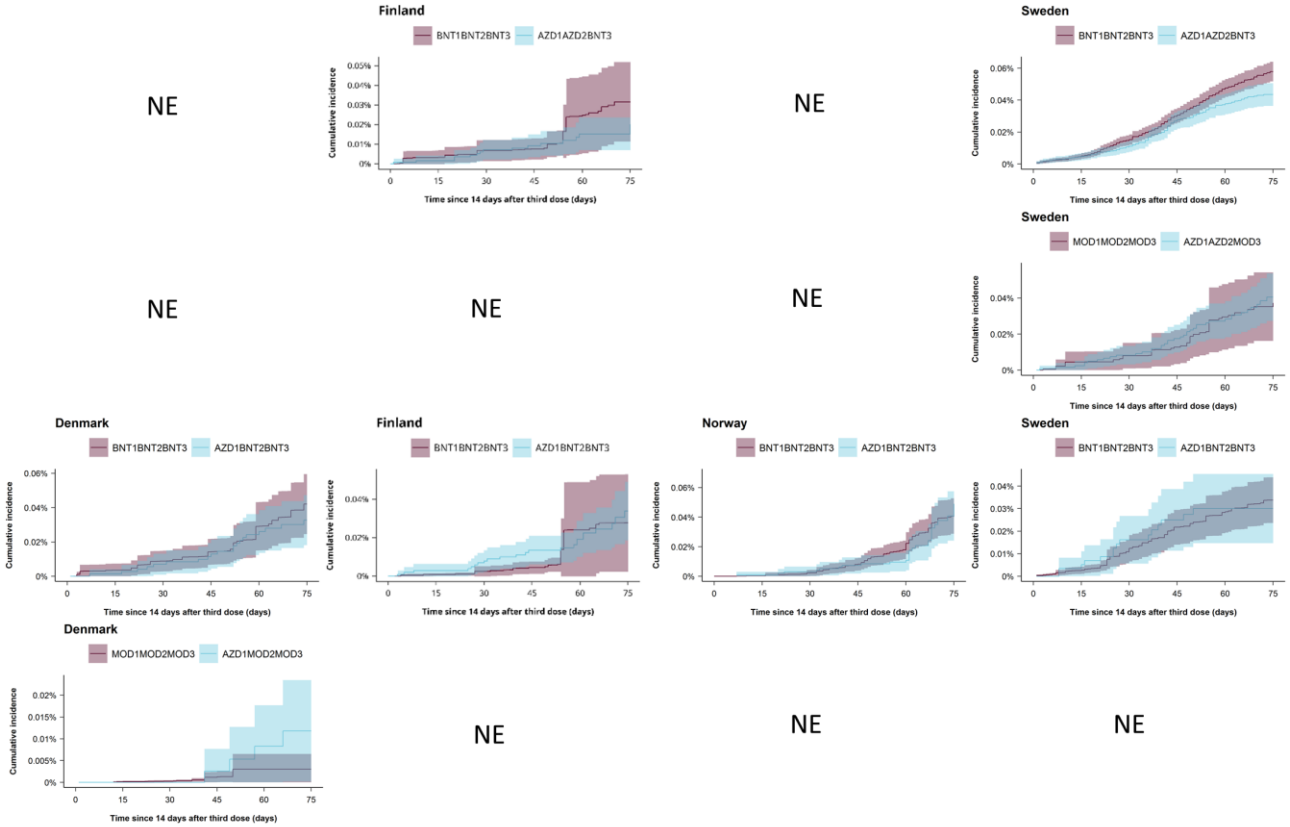


Figure 16. Country-specific adjusted cumulative incidence curves of covid-19 hospitalisation for weighted analyses comparing heterologous and homologous primary vaccine schedules.



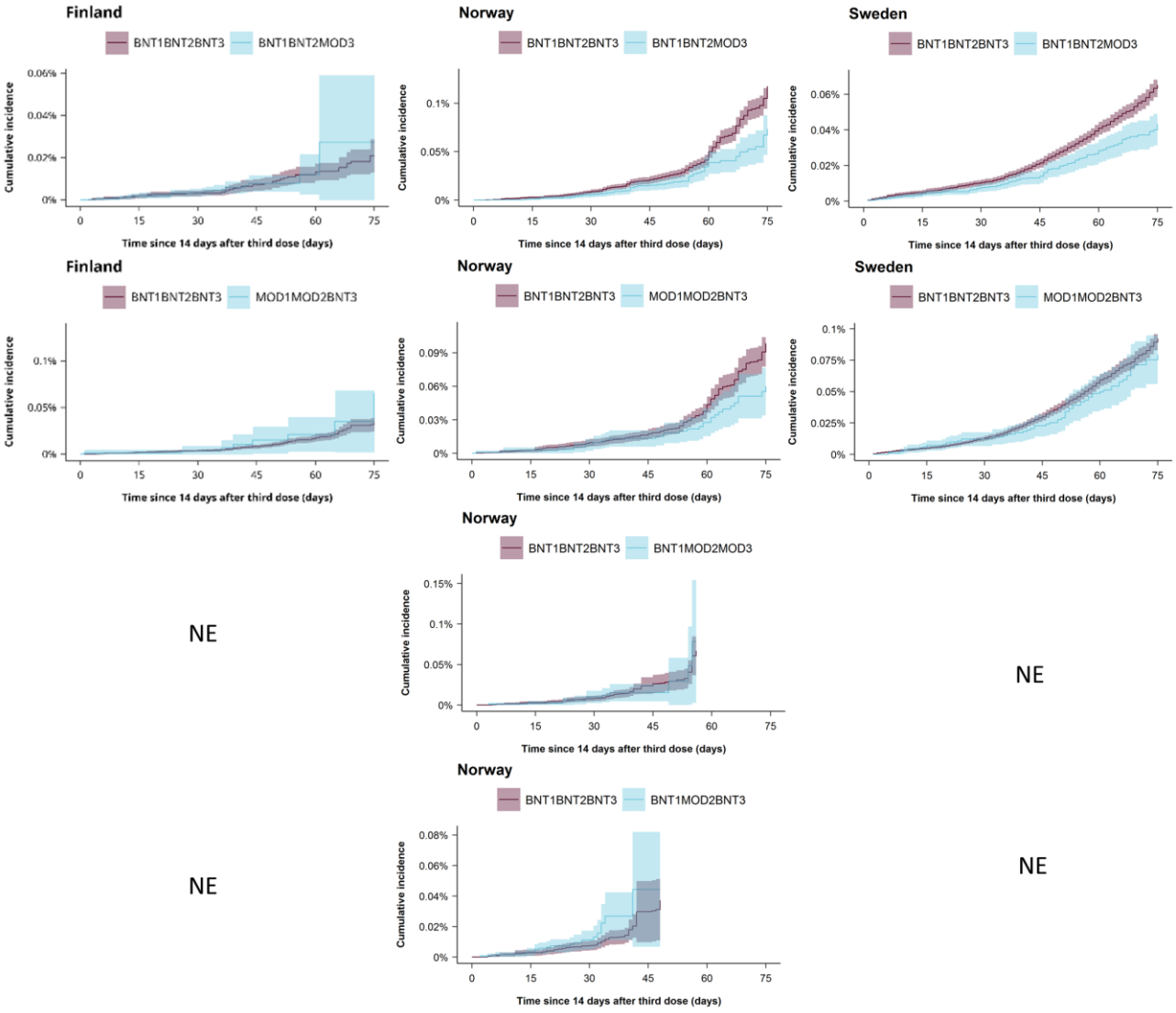
NE denotes not estimated.

Figure 17. Country-specific adjusted cumulative incidence curves of covid-19 hospitalisation for weighted analyses comparing heterologous AZD-mRNA booster and homologous mRNA booster vaccine schedules.



NE denotes not estimated.

Figure 18. Country-specific adjusted cumulative incidence curves of covid-19 hospitalisation for weighted analyses comparing heterologous and homologous mRNA booster vaccine schedules.



NE

NE

NE

NE denotes not estimated.

Figure 19. Country-specific adjusted cumulative incidence curves of covid-19 related intensive care unit admission for weighted analyses comparing heterologous and homologous booster vaccine schedules.

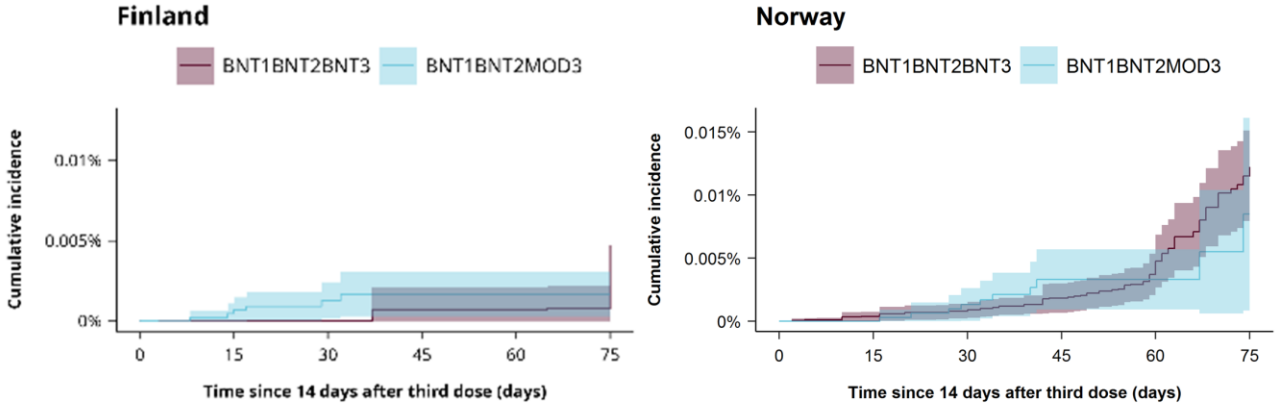
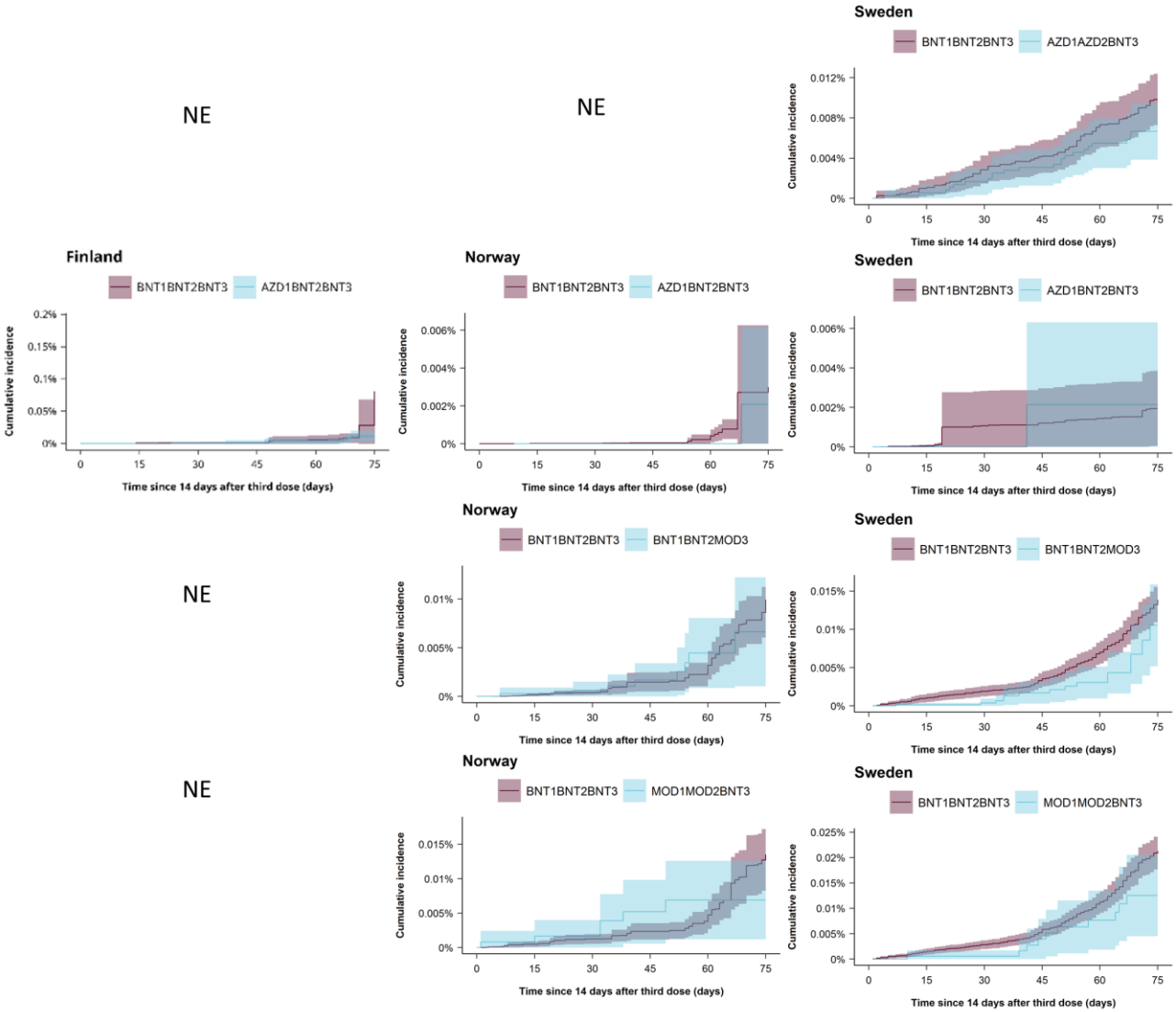


Figure 20. Country-specific adjusted cumulative incidence curves of covid-19 related death for weighted analyses comparing heterologous and homologous booster vaccine schedules.



NE denotes not estimated.

Table 2 and 3 present the number of endpoint events, total person-years, and measures of association for each heterologous vs. homologous comparison across countries. Table 4 presents the results of the meta-analysis, combining the country-specific results for the outcomes of documented infection and hospitalisation.

Table 2. Country-specific associations between covid-19 endpoints and studied heterologous primary vaccine schedules as compared with homologous schedules.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
AZD1BNT2 vs BNT1BNT2				
Documented infection				
Denmark	325 / 16652.1	561 / 40789.5	-0.3% (-0.8% - 0.2%)	41.7% (1.8% - 81.6%)
Finland	130 / 25264.2	3677 / 320470.9	0.0% (0.0% - 0.0%)	-3.8% (-39.8% - 32.2%)
Norway	83 / 25168.6	413 / 74294.8	0.0% (0.0% - 0.0%)	14.9% (-19.5% - 49.2%)
Sweden	314 / 18283.7	18487 / 721734.2	-0.1% (-0.2% - -0.1%)	29.0% (19.5% - 38.5%)
Hospitalisation				
Denmark	0 / 16663.1	3 / 40809.6		
Finland	<5 / 25268.2	11 / 320582.4	0.0% (0.0% - 0.0%)	37.9% (-128.1% - 100%)
Norway	<5 / 25178.6	<5 / 74342.0	0.0% (0.0% - 0.0%)	-24.6% (-356.0% - 100%)
Sweden	3 / 18294.4	127 / 722326.0	0.0% (0.0% - 0.0%)	-3.7% (-128.8% - 100%)
ICU admission				
Denmark	0 / 16663.1	0 / 40809.7		
Finland	0 / 25268.2	<5 / 320582.6		
Norway	0 / 25178.6	0 / 74342.2		
Sweden	0 / 18294.5	0 / 722329.7		
Death				
Denmark	0 / 16672.3	<3 / 40827.1		
Finland	0 / 25270.9	<5 / 320662.2		
Norway	0 / 25178.6	0 / 74342.3		
Sweden				
AZD1MOD2 vs MOD1MOD2				
Documented infection				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Denmark	95 / 9204.3	64 / 8266.3	0.2% (0.2% - 0.3%)	
Finland	21 / 5581.7	337 / 42987.9	0.0% (0.0% - 0.1%)	-56.1% (-190.4% - 78.1%)
Norway	<5 / 591.2	395 / 68742.5	0.0% (-0.1% - 0.1%)	-28.1% (-179.6% - 100%)
Sweden	50 / 3046.3	2817 / 113262.4	-0.5% (-0.6% - -0.3%)	57.8% (44.3% - 71.2%)
Hospitalisation				
Denmark	0 / 9207.9	<3 / 8268.7		
Finland	<5 / 5582.4	0 / 42998.2	0.0% (0.0% - 0.0%)	
Norway	0 / 591.8	0 / 68887.1		
Sweden	0 / 3051.3	18 / 113376.1		
ICU admission				
Denmark	0 / 9207.9	0 / 8268.8		
Finland	<5 / 5582.4	0 / 42998.2	0.0% (0.0% - 0.0%)	
Norway	0 / 591.8	0 / 68887.1		
Sweden	0 / 3051.3	0 / 113376.6		
Death				
Denmark	0 / 9210.8	0 / 8271.1		
Finland	<5 / 5583.0	0 / 43004.9	0.0% (0.0% - 0.0%)	
Norway	0 / 591.8	0 / 68887.1		
Sweden				
BNT1MOD2 vs BNT1BNT2				
Documented infection				
Denmark	5 / 23.4	35543 / 582502.9	0.3% (-3.4% - 3.9%)	-6.5% (-97.9% - 84.9%)
Finland	514 / 8960.7	20331 / 377706.2	-0.4% (-0.5% - -0.3%)	23.8% (16.8% - 30.7%)
Norway	584 / 109557.8	1396 / 185817.9	0.0% (0.0% - 0.0%)	24.4% (16.1% - 32.7%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden	273 / 3863.2	23717 / 418641.9	-0.5% (-0.7% - -0.3%)	26.8% (18.0% - 35.6%)
Hospitalisation				
Denmark	0 / 23.5	123 / 583725.7		
Finland	<5 / 8975.2	33 / 378306.1	0.0% (0.0% - 0.0%)	17.4% (-160.9% - 100%)
Norway	<5 / 109755.0	5 / 186215.5	0.0% (0.0% - 0.0%)	66.3% (-10.5% - 100%)
Sweden	<3 / 3874.9	105 / 419471.9	0.0% (0.0% - 0.0%)	67.2% (1.9% - 100%)
ICU admission				
Denmark	0 / 23.5	10 / 583729.3		
Finland	0 / 8975.2	5 / 378306.8		
Norway	0 / 109755.1	<5 / 186216.4		
Sweden	0 / 3874.9	0 / 419475.3		
Death				
Denmark	0 / 23.6	20 / 584719.5		
Finland	<5 / 8982.8	6 / 378688.6	0.0% (0.0% - 0.0%)	
Norway	0 / 109755.1	0 / 186216.8		
Sweden				
MOD1BNT2 vs BNT1BNT2				
Documented infection				
Denmark	19 / 38.9	36673 / 573402.7	-0.6% (-4.7% - 3.5%)	6.3% (-34.0% - 46.5%)
Finland	1553 / 7835.9	21068 / 453005.0	0.1% (-0.1% - 0.3%)	-2.8% (-8.2% - 2.6%)
Norway	91 / 12993.3	1727 / 225688.5	0.0% (-0.1% - 0.0%)	19.4% (0.9% - 37.9%)
Sweden	3715 / 7914.9	23310 / 403029.7	0.9% (0.6% - 1.2%)	-10.6% (-14.5% - -6.6%)
Hospitalisation				
Denmark	0 / 39.5	128 / 574672.1		
Finland	5 / 7880.7	38 / 453628.0	0.0% (0.0% - 0.0%)	

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	0 / 13155.7	6 / 227565.6		
Sweden	8 / 8052.3	84 / 403919.8	0.0% (0.0% - 0.0%)	24.1% (-33.5% - 81.7%)
ICU admission				
Denmark	0 / 39.5	9 / 574675.9		
Finland	0 / 7880.8	6 / 453628.8		
Norway	0 / 13155.8	<5 / 227567.0		
Sweden	0 / 8052.6	0 / 403922.7		
Death				
Denmark	0 / 40.0	26 / 575702.8		
Finland	0 / 7905.4	7 / 454029.8		
Norway	0 / 13155.8	0 / 227567.4		
Sweden				

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).

Table 3. Country-specific associations between covid-19 endpoints and studied heterologous booster vaccine schedules as compared with homologous booster schedules.

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
AZD1AZD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	241 / 152.3	522034 / 223570.0	-8.5% (-12.0% - -5.1%)	21.5% (12.9% - 30.2%)
Finland	1075 / 17483.8	2604 / 52462.2	-0.1% (-0.3% - 0.1%)	6.1% (-7.5% - 19.8%)
Norway	44 / 98.7	70962 / 184513.7	-5.4% (-8.4% - -2.5%)	37.7% (17.4% - 58.0%)
Sweden	14386 / 66330.0	62873 / 198391.7	0.7% (0.6% - 0.8%)	-19.0% (-21.5% - -16.6%)
Hospitalisation				
Denmark	0 / 160.4	528 / 240491.0		
Finland	15 / 17518.5	56 / 52544.0	0.0% (0.0% - 0.0%)	36.4% (-20.5% - 93.3%)
Norway	<5 / 102.1	595 / 180921.0	0.2% (-0.4% - 0.8%)	
Sweden	145 / 66983.8	509 / 201706.2	0.0% (0.0% - 0.0%)	24.8% (10.1% - 39.5%)
ICU admission				
Denmark	0 / 160.4	41 / 240505.8		
Finland	<5 / 17519.0	<5 / 52545.3	0.0% (0.0% - 0.0%)	-52.0% (-3994121039.1% - 100%)
Norway	0 / 102.1	66 / 180939.4		
Sweden	0 / 66989.2	0 / 201724.1		
Death				
Denmark	0 / 166.4	46 / 254885.0		
Finland	0 / 17546.6	25 / 52610.8		
Norway	0 / 102.1	64 / 180942.9		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden				
AZD1AZD2MOD3 vs MOD1MOD2MOD3				
Documented infection				
Denmark	8 / 9.9	75309 / 24552.4	-14.7% (-27.7% - -1.7%)	44.9% (5.5% - 84.3%)
Finland	182 / 5816.8	195 / 4962.8	-0.3% (-0.6% - 0.0%)	29.5% (3.0% - 56.1%)
Norway	18 / 31.3	11141 / 17372.3	-0.8% (-8.5% - 6.9%)	5.9% (-52.8% - 64.6%)
Sweden	4255 / 21015.2	3903 / 15469.1	0.7% (0.4% - 1.0%)	-21.4% (-33.1% - -9.7%)
Hospitalisation				
Denmark	0 / 10.2	45 / 27450.0		
Finland	<5 / 5822.4	<5 / 4968.6	0.0% (-0.1% - 0.0%)	59.4% (-37.9% - 100%)
Norway	0 / 32.6	40 / 18186.4		
Sweden	39 / 21180.6	32 / 15666.4	0.0% (0.0% - 0.0%)	-8.6% (-75.3% - 58.2%)
ICU admission				
Denmark	0 / 10.2	3 / 27451.4		
Finland	0 / 5822.5	0 / 4968.6	0.0% (0.0% - 0.0%)	
Norway	0 / 32.6	<5 / 18187.5		
Sweden	0 / 21182.0	0 / 15667.5		
Death				
Denmark	0 / 10.4	6 / 29680.7		
Finland	<5 / 5826.8	0 / 4972.7	0.0% (0.0% - 0.0%)	
Norway	0 / 32.6	<5 / 18187.5		
Sweden				
AZD1BNT2BNT3 vs BNT1BNT2BNT3				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Documented infection				
Denmark	26220 / 12183.3	420151 / 173436.5	3.2% (2.7% - 3.7%)	-9.0% (-10.5% - -7.5%)
Finland	4372 / 16756.3	31456 / 95761.7	0.2% (0.0% - 0.5%)	-4.8% (-10.6% - 1.1%)
Norway	11505 / 16567.4	55621 / 96814.9	-0.3% (-0.7% - 0.1%)	2.0% (-0.5% - 4.5%)
Sweden	11190 / 8277.9	66809 / 174424.8	3.7% (3.2% - 4.2%)	-18.0% (-20.6% - -15.5%)
Hospitalisation				
Denmark	20 / 13073.0	389 / 190732.1	0.0% (0.0% - 0.0%)	22.3% (-25.0% - 69.6%)
Finland	23 / 16897.3	44 / 96714.8	0.0% (0.0% - 0.0%)	-22.2% (-147.2% - 100%)
Norway	28 / 17374.2	283 / 100517.2	0.0% (0.0% - 0.0%)	-8.6% (-64.5% - 47.4%)
Sweden	15 / 8706.2	300 / 177466.4	0.0% (0.0% - 0.0%)	11.0% (-41.7% - 63.7%)
ICU admission				
Denmark	0 / 13073.5	26 / 190742.7		
Finland	<5 / 16897.8	<5 / 96715.9	0.0% (0.0% - 0.0%)	
Norway	<5 / 17374.8	28 / 100526.3	0.0% (0.0% - 0.0%)	29.4% (-74.4% - 100%)
Sweden	0 / 8706.8	0 / 177477.6		
Death				
Denmark	0 / 13695.5	26 / 202550.2		
Finland	7 / 17005.8	14 / 97286.3	-0.1% (-0.2% - 0.0%)	86.1% (64.2% - 100%)
Norway	<5 / 17374.9	17 / 100527.6	0.0% (0.0% - 0.0%)	30.2% (-130.3% - 100%)
Sweden				
AZD1MOD2MOD3 vs MOD1MOD2MOD3				
Documented infection				
Denmark	13867 / 7055.4	55094 / 19398.1	3.3% (-0.9% - 7.5%)	-10.0% (-23.9% - 3.9%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Finland	654 / 2969.8	2868 / 11384.6	1.4% (0.7% - 2.0%)	-38.5% (-61.4% - -15.6%)
Norway	123 / 162.3	10156 / 12434.0	2.5% (-1.4% - 6.4%)	-16.4% (-42.5% - 9.7%)
Sweden	873 / 661.3	4315 / 13473.6	5.1% (3.3% - 6.9%)	-28.1% (-39.2% - -17.0%)
Hospitalisation				
Denmark	4 / 7512.5	32 / 22422.5	0.0% (0.0% - 0.0%)	
Finland	0 / 2989.9	<5 / 11466.4		
Norway	0 / 171.7	21 / 13178.5		
Sweden	<3 / 694.5	19 / 13703.0	0.0% (-0.1% - 0.1%)	20.8% (-162.5% - 100%)
ICU admission				
Denmark	0 / 7512.6	3 / 22423.5		
Finland	0 / 2989.9	0 / 11466.5	0.0% (0.0% - 0.0%)	
Norway	0 / 171.7	<5 / 13178.9		
Sweden	0 / 694.5	0 / 13703.8		
Death				
Denmark	0 / 7811.1	3 / 24071.8		
Finland	<5 / 3004.0	0 / 11507.9	0.0% (0.0% - 0.0%)	
Norway	0 / 171.7	<5 / 13178.9		
Sweden				
BNT1BNT2MOD3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	69 / 76.7	591663 / 338099.1	-14.6% (-18.5% - -10.7%)	47.3% (34.7% - 59.8%)
Finland	9070 / 41232.0	35544 / 141235.6	-1.3% (-2.0% - -0.5%)	21.7% (8.6% - 34.8%)
Norway	23135 / 38662.3	64002 / 189502.7	1.7% (1.5% - 1.9%)	-14.8% (-16.9% - -12.7%)

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden	18497 / 75210.5	71837 / 257452.0	-1.2% (-1.3% - -1.1%)	19.7% (18.2% - 21.2%)
Hospitalisation				
Denmark	0 / 79.1	1054 / 359309.9		
Finland	23 / 41483.9	97 / 142294.2	0.0% (0.0% - 0.0%)	-32.2% (-192.2% - 100%)
Norway	70 / 40201.6	672 / 193317.7	0.0% (-0.1% - 0.0%)	37.5% (17.5% - 57.4%)
Sweden	112 / 76258.5	835 / 260554.9	0.0% (0.0% - 0.0%)	33.8% (18.4% - 49.2%)
ICU admission				
Denmark	0 / 79.1	81 / 359339.4		
Finland	6 / 41484.2	<5 / 142296.4	0.0% (0.0% - 0.0%)	64.5% (-1.5% - 100%)
Norway	10 / 40204.5	76 / 193338.5	0.0% (0.0% - 0.0%)	30.6% (-35.2% - 96.4%)
Sweden	0 / 76263.1	0 / 260582.2		
Death				
Denmark	0 / 81.0	151 / 375110.7		
Finland	0 / 41592.4	36 / 142918.0		
Norway	8 / 40204.7	82 / 193343.0	0.0% (0.0% - 0.0%)	33.1% (-26.3% - 92.5%)
Sweden				
MOD1MOD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	215 / 132.3	599081 / 375036.8	-5.0% (-8.2% - -1.8%)	16.4% (6.0% - 26.8%)
Finland	1553 / 6635.2	38441 / 165903.7	-0.4% (-0.7% - -0.1%)	9.2% (2.8% - 15.6%)
Norway	10334 / 15346.5	73584 / 222755.7	1.0% (0.7% - 1.4%)	-8.0% (-10.6% - -5.4%)
Sweden	6059 / 21844.7	80310 / 279610.3	-0.2% (-0.3% - 0.0%)	3.1% (0.5% - 5.8%)
Hospitalisation				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Denmark	0 / 140.3	1390 / 396364.7		
Finland	8 / 6678.1	152 / 167043.1	0.0% (0.0% - 0.1%)	-92.5% (-2049705210.0% - 100%)
Norway	32 / 16082.1	834 / 227663.6	0.0% (-0.1% - 0.0%)	39.4% (14.5% - 64.2%)
Sweden	67 / 22125.8	929 / 283086.2	0.0% (0.0% - 0.0%)	13.9% (-8.9% - 36.6%)
ICU admission				
Denmark	0 / 140.3	99 / 396403.3		
Finland	0 / 6678.1	5 / 167046.6		
Norway	<5 / 16083.2	90 / 227691.0	0.0% (0.0% - 0.0%)	28.8% (-59.7% - 100%)
Sweden	0 / 22128.0	0 / 283116.4		
Death				
Denmark	0 / 146.9	283 / 412300.3		
Finland	<5 / 6697.9	92 / 167720.4	0.0% (0.0% - 0.0%)	-9.3% (-141.0% - 100%)
Norway	6 / 16083.3	130 / 227696.3	0.0% (0.0% - 0.0%)	49.0% (3.4% - 94.5%)
Sweden				
BNT1MOD2MOD3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	10 / 7.3	583124 / 342900.1	-5.7% (-17.2% - 5.9%)	21.4% (-22.2% - 65.0%)
Finland				
Norway	6995 / 7715.1	30755 / 46427.2	3.2% (2.2% - 4.3%)	-19.3% (-25.6% - -13.0%)
Sweden	12 / 51.6	70880 / 235815.4	-4.0% (-5.6% - -2.4%)	62.4% (38.0% - 86.9%)
Hospitalisation				
Denmark	<3 / 7.8	1253 / 367302.4	2.3% (-2.4% - 7.0%)	
Finland				

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Norway	12 / 8165.3	92 / 48402.4	0.0% (-0.1% - 0.1%)	-17.2% (-138.6% - 100%)
Sweden	0 / 52.3	606 / 235284.5		
ICU admission				
Denmark	0 / 7.8	87 / 367337.7		
Finland				
Norway	<5 / 8165.5	5 / 48406.0	0.0% (0.0% - 0.0%)	78.7% (25.3% - 100%)
Sweden	0 / 52.3	0 / 235305.4		
Death				
Denmark	0 / 7.9	247 / 383172.2		
Finland				
Norway	0 / 8165.5	<5 / 48406.2		
Sweden				
MOD1BNT2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	20 / 14.0	607384 / 375742.8	4.3% (-6.7% - 15.2%)	-18.1% (-64.7% - 28.4%)
Finland	122 / 460.7	37753 / 154622.5	1.1% (-1.1% - 3.2%)	-20.4% (-61.3% - 20.5%)
Norway	1064 / 896.4	38236 / 53392.7	6.2% (0.3% - 12.1%)	-27.0% (-52.8% - -1.2%)
Sweden	41 / 137.1	79706 / 273456.5	1.4% (-1.6% - 4.5%)	-21.3% (-66.2% - 23.6%)
Hospitalisation				
Denmark	0 / 14.6	1387 / 397392.7		
Finland	0 / 464.1	119 / 155737.9		
Norway	0 / 972.6	99 / 55893.5		
Sweden	0 / 139.3	861 / 276921.7		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
ICU admission				
Denmark	0 / 14.7	99 / 397431.3		
Finland	0 / 464.1	<5 / 155740.7		
Norway	0 / 972.7	7 / 55897.4		
Sweden	0 / 139.3	0 / 276950.0		
Death				
Denmark	0 / 15.0	279 / 413582.6		
Finland	0 / 466.0	59 / 156395.3		
Norway	0 / 972.7	5 / 55897.6		
Sweden				
BNT1MOD2BNT3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	3 / 2.7	591769 / 330417.4	-19.5% (-41.6% - 2.7%)	48.9% (-6.7% - 100%)
Finland				
Norway	10660 / 11986.6	32303 / 42455.7	1.4% (-0.1% - 2.9%)	-7.8% (-16.0% - 0.4%)
Sweden	19 / 143.9	54414 / 134455.5	-1.8% (-6.0% - 2.3%)	26.1% (-33.2% - 85.3%)
Hospitalisation				
Denmark	0 / 2.8	1130 / 351666.8		
Finland				
Norway	21 / 12655.5	69 / 44598.6	0.0% (0.0% - 0.1%)	-19.2% (-143.2% - 100%)
Sweden	0 / 145.0	170 / 132998.3		
ICU admission				
Denmark	0 / 2.8	78 / 351698.9		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Finland				
Norway	<5 / 12656.0	5 / 44601.2	0.0% (0.0% - 0.0%)	91.1% (68.0% - 100%)
Sweden	0 / 145.0	0 / 133005.3		
Death				
Denmark	0 / 3.1	187 / 367562.2		
Finland				
Norway	<5 / 12656.0	<5 / 44601.4	0.0% (0.0% - 0.0%)	-5.1% (-243.1% - 100%)
Sweden				
MOD1BNT2MOD3 vs BNT1BNT2BNT3				
Documented infection				
Denmark	0 / 2.6	576326 / 360555.3		
Finland				
Norway	649 / 592.1	32573 / 48617.8	2.9% (-2.4% - 8.1%)	-12.9% (-36.6% - 10.7%)
Sweden	10 / 32.1	72227 / 252210.9	-1.4% (-5.7% - 2.8%)	21.8% (-43.1% - 86.8%)
Hospitalisation				
Denmark	0 / 2.6	1305 / 380986.7		
Finland				
Norway	<5 / 647.7	100 / 51714.0	0.0% (-0.1% - 0.0%)	75.6% (25.4% - 100%)
Sweden	0 / 32.6	763 / 255340.6		
ICU admission				
Denmark	0 / 2.6	93 / 381022.9		
Finland				
Norway	0 / 647.7	7 / 51717.7		

Covid-19 outcome	Studied schedule	Comparison schedule	Measures of association at day 75 since start of follow-up[a]	
	Events/PYRS	Events/PYRS	RD (95% CI)	CVE (95% CI)
Sweden	0 / 32.6	0 / 255366.0		
Death				
Denmark	0 / 2.6	235 / 396285.3		
Finland				
Norway	0 / 647.7	6 / 51717.9		
Sweden				

CI denotes confidence interval, CVE comparative vaccine effectiveness, PYRS person-years, and RD risk difference. Grey-colored cells denotes not estimated. [a]Day 75 since start of follow-up equals approximately 3 months since the index date (i.e. start of follow up was 14 days after the index date).

Table 4. Meta-analysis of the country-specific results for the associations between documented covid-19 infection and hospitalisation and studied heterologous vaccine schedules as compared with homologous vaccine schedules.

Studied schedule	Compared schedule	Studied schedule events	Comparative schedule events	RD (95% CI)	CVE (95% CI)	Heterogeneity (p-value)[a]	Contributing countries
Outcome: Documented infection							
AZD1BNT2	BNT1BNT2	852	23138	-0.1% (-0.1%-0.0%)	24.6% (11.3%-37.8%)	<0.0001	DK, FI, SE, NO
AZD1MOD2	MOD1MOD2	<171	3613	0.0% (-0.3%-0.2%)	16.0% (-63.4%-95.5%)	<0.0001	DK, FI, SE, NO
BNT1MOD2	BNT1BNT2	1376	80987	-0.3% (-0.6%-0.0%)	24.7% (20.1%-29.2%)	<0.0001	DK, FI, SE, NO
MOD1BNT2	BNT1BNT2	5378	82778	0.3% (-0.3%-0.8%)	0.0% (-13.4%-13.4%)	<0.0001	DK, FI, SE, NO
AZD1AZD2BNT3	BNT1BNT2BNT3	15746	658473	-3.1% (-7.3%-1.2%)	10.5% (-13.2%-34.2%)	<0.0001	DK, FI, SE, NO
AZD1AZD2MOD3	MOD1MOD2MOD3	4463	90548	0.1% (-0.8%-1.1%)	12.4% (-20.1%-45.0%)	<0.0001	DK, FI, SE, NO
AZD1BNT2BNT3	BNT1BNT2BNT3	53287	574037	1.7% (-0.3%-3.7%)	-7.5% (-15.9%-0.8%)	<0.0001	DK, FI, SE, NO
AZD1MOD2MOD3	MOD1MOD2MOD3	15517	72433	3.0% (0.9%-5.0%)	-22.7% (-34.9%--10.4%)	0.002	DK, FI, SE, NO
BNT1BNT2MOD3	BNT1BNT2BNT3	50771	763046	-3.6% (-10.6%-3.3%)	18.0% (-7.1%-43.1%)	<0.0001	DK, FI, SE, NO
MOD1MOD2BNT3	BNT1BNT2BNT3	18161	791416	-0.7% (-2.7%-1.3%)	4.4% (-5.5%-14.4%)	<0.0001	DK, FI, SE, NO

BNT1MOD2MOD3	BNT1BNT2BNT3	22	654004	-4.0% (-5.6%--2.5%)	46.0% (6.6%-85.5%)	0.7805	DK, SE
MOD1BNT2BNT3	BNT1BNT2BNT3	183	724843	1.3% (-0.5%-3.0%)	-20.0% (-45.4%-5.3%)	0.8449	DK, FI, SE
BNT1MOD2BNT3	BNT1BNT2BNT3	22	646183	-7.2% (-23.0%-8.7%)	38.2% (-2.3%-78.8%)	0.1248	DK, SE
MOD1BNT2MOD3	BNT1BNT2BNT3	10	72227	-1.4% (-9.0%-6.1%)	21.8% (-43.4%-87.0%)	1	SE
Outcome: Hospitalisation							
AZD1BNT2	BNT1BNT2	<13	<143	0.0% (0.0%-0.0%)	8.4% (-87.3%-104.0%)	0.9311	FI, NO, SE
BNT1MOD2	BNT1BNT2	<13	143	0.0% (0.0%-0.0%)	63.3% (15.4%-111.2%)	0.222	FI, NO, SE
MOD1BNT2	BNT1BNT2	13	122	0.0% (0.0%-0.0%)	-0.1% (-115.4%-115.1%)	0.1093	FI, SE
AZD1BNT2BNT3	BNT1BNT2BNT3	86	1016	0.0% (0.0%-0.0%)	8.2% (-20.8%-37.2%)	0.8134	DK, FI, SE, NO
AZD1MOD2MOD3	MOD1MOD2MOD3	<7	51	0.0% (0.0%-0.0%)	-5.8% (-181.1%-169.5%)	0.6257	DK, SE
BNT1MOD2MOD3	BNT1BNT2BNT3	<3	1253	2.3% (-5.5%-10.1%)	-1438.3% (-4430.6%-1554.0%)	1	DK
AZD1AZD2BNT3	BNT1BNT2BNT3	<165	1160	0.0% (0.0%-0.0%)	25.4% (11.2%-39.7%)	0.6937	FI, NO, SE
AZD1AZD2MOD3	MOD1MOD2MOD3	<44	<37	0.0% (0.0%-0.0%)	15.8% (-48.1%-79.7%)	0.5189	FI, SE
BNT1BNT2MOD3	BNT1BNT2BNT3	205	1604	0.0% (0.0%-0.0%)	34.8% (22.6%-46.9%)	0.0521	FI, NO, SE

MOD1MOD2BNT3	BNT1BNT2BNT3	107	1915	0.0% (0.0%-0.0%)	26.1% (1.1%-51.1%)	0.1058	FI, NO, SE

CI denotes confidence interval, CVE comparative vaccine effectiveness, DK Denmark, FI Finland, NO Norway, RD risk difference, and SE Sweden. [a] P-values are calculated by Cochran's Q-test for residual heterogeneity.

2- vs. 2-dose comparisons

For the primary schedule comparisons (2- vs. 2-dose) that included schedules of AZD1mRNA2, the incidence of documented infection was low; the cumulative incidence at day 75 was less than 1% for both the studied and compared schedules and no patterns for differences in the risk were apparent across comparisons and countries. For the primary mRNA vaccine schedules comparisons, the cumulative incidences of documented covid-19 infection varied more (as opposed to the comparisons with the AZD1mRNA2 schedules) across comparisons and countries (with cumulative incidences at day 75 ranging between ≈ 0.1% and 10%).

In Denmark, risk differences of documented infection between heterologous and homologous primary vaccine schedules ranged from -0.6% to 0.3%, with corresponding cVEs ranging between -6.5% and 41.7%.

In Finland, risk differences of documented infection between heterologous and homologous primary vaccine schedules ranged from -0.4% to 0.1%, with corresponding cVEs ranging between -56.1% and 23.8%.

In Norway, risk differences of documented infection between heterologous and homologous primary vaccine schedules ranged from -0.04% to 0.02%, with corresponding cVEs ranging between -28.1% and 24.4%.

In Sweden, risk differences of documented infection between heterologous and homologous primary vaccine schedules ranged from -0.5% to 0.9%, with corresponding cVEs ranging between -10.6% and 57.8%.

Notably, the estimates defining outer range limits were mostly the smaller-sized comparisons, that is, comparisons where estimates were more imprecise in terms of the 95% confidence intervals. For the larger-sized comparisons, differences between compared schedules were generally smaller.

In meta-analyses, combining estimates for documented infection between heterologous and homologous primary vaccine schedules for each country, risk differences ranged from -0.3% to 0.3%, with corresponding cVEs ranging between -0.0% and 24.7%. Tests for heterogeneity showed significant residual heterogeneity in all comparisons.

Few to no events of severe covid-19 endpoints (covid-19 related hospitalisation, ICU admission, and death) was observed within all compared heterologous and homologous primary vaccinated groups and no apparent risk differences were observed. The country-specific results for the outcome of hospitalisation were more homogeneous (p-values did not suggest significant heterogeneity) and combined cVEs ranged from -0.1% to 63.3%, although the risk differences were very low (<0.0%).

3- vs. 3-dose comparisons

For the heterologous vs. homologous booster schedules comparisons (3- vs. 3-dose), the cumulative incidences of documented covid-19 infection at day 75 varied substantially across countries and studied schedules (most likely due to the observed differences in calendar months for the respective studied schedules that were highly correlated to the emergence of the omicron variant and the related-hereto country-specific background infection rates as well as different testing strategies). The cumulative incidences of documented covid-19 infection ranged between ≈ 15% and 40% in Denmark, in Finland ≈ <1% and 7%, in Norway ≈ 8% and 28%, and in Sweden ≈ 2% and 25%. Overall, heterologous and homologous booster vaccinated had close to similar risk of documented covid-19 infections across all comparisons in absolute numbers.

In Denmark, risk differences of documented infection between heterologous and homologous booster vaccine schedules ranged from -19.5% to 4.3%, with corresponding cVEs ranging between -18.1% and 48.9%.

In Finland, risk differences of documented infection between heterologous and homologous booster vaccine schedules ranged from -1.3% to 1.4%, with corresponding cVEs ranging between -38.5% and 29.5%.

In Norway, risk differences of documented infection between heterologous and homologous booster vaccine schedules ranged from -5.4% to 6.2%, with corresponding cVEs ranging between -27.0% and 37.7%.

In Sweden, risk differences of documented infection between heterologous and homologous booster vaccine schedules ranged from -4.0% to 5.1%, with corresponding cVEs ranging between -28.1% and 62.4%.

Notably, the estimates defining outer range limits were mostly the smaller-sized comparisons thus comparisons where estimates were more imprecise in terms of the 95% confidence intervals. For the larger-sized comparisons, differences between compared schedules were generally smaller.

In meta-analyses, combining estimates for documented infection between heterologous and homologous booster vaccine schedules for each country, risk differences ranged from -3.6% to 3.0%, with corresponding cVEs ranging between -23.4% and 20.3%. However, tests for heterogeneity showed that all comparisons but BNT1MOD2MOD3 vs BNT1BNT2BNT3, MOD1BNT2BNT3 vs BNT1BNT2BNT3, and BNT1MOD2BNT3 vs BNT1BNT2BNT3 had significant heterogeneity. The combined number of events of documented infection was few for these three comparisons (22, 183, and 22 events, respectively).

The incidence of severe covid-19 related endpoints (covid-19 related hospitalisation, ICU admission, and death) were low to none for both heterologous and homologous booster vaccinated across all compared schedules and countries. E.g. the cumulative incidences of covid-19 related hospitalisation were less than 0.1% across those schedules that could be included for analyses (and in most comparisons the cumulative incidences were <0.06%). No apparent increased risks of severe covid-19 related outcomes were observed associated with heterologous booster vaccine schedules as compared to homologous booster vaccine schedules. The country-specific results for the outcome of hospitalisation were more homogenous for meta-analysis but not all countries could contribute to all comparisons. The meta-analyses CVEs ranged from -5.8% to 34.8%, although the risk differences were very low (<0.0%).