PASS information

Title	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe
Version identifier of the interim study report	Interim Report 4
Date of last interim study report	30 September 2022
EU PAS register number	EUPAS44273
Active substance	Elasomeran
Medicinal product	Spikevax
Product reference	EMEA/H/C/005791
Procedure number	MEA004.2
Marketing authorisation holder(s)	Moderna Biotech Spain, Calle del Principe De Vergara 132 Plt 12 28002 Madrid, Spain
Joint PASS	No
Research question and objectives	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: • To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: • To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with chronic health conditions, and patients with

	autoimmune or inflammatory disorders
Country(-ies) of study	Denmark, Italy, Norway, Spain, United Kingdom
Authors	[redacted] [redacted] on behalf of the Department of Clinical Epidemiology Aarhus University Hospital Aarhus, Denmark

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Moderna Biotech Spain, S.L. Calle del Principe De Vergara 132 Plt 12 28002 Madrid, Spain
MAH contact person	[redacted] Senior Director, Global Safety Epidemiologist, Pharmacovigilance [redacted] [redacted] Vice President, Clinical Safety and Risk Management [redacted] Moderna Tx 200 Technology Square Cambridge, MA 02139,United States

Table of contents

1. Abstract

Title

Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe

Key words

Observational study; Multi-database study; COVID-19; Spikevax

Rationale and background

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign has been underway in Europe since early 2021. Spikevax (elasomeran), is currently authorised in the European Union and in the United Kingdom for use in persons 6 months of age or older.

This Fourth Interim report was prepared according to the reporting schedule outlined in the Study Protocol Version 1.3, dated 27 September 2022; and according to the SAP Version 2.0, dated 17 June 2022.

Research question and objectives

The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence ofSpikevax?

Primary objective:

- To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

Secondary objective:

- To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with chronic health conditions, and patients with autoimmune or inflammatory disorders.

In accordance with the reporting schedule, this Fourth Interim Report addresses selected study objectives using data available in the most recent data extraction, covering up to 1.5 years after Spikevax availability.

Study design

Per protocol, this study has two phases: signal detection and signal evaluation. For the signal detection phase, a cohort design was applied to obtain age- and sex-standardised morbidity ratios (SMRs) to compare observed vs expected AESI event in the Spikevax recipients. To estimate the expected number of events, country-specific historical general population background rates of the AESI were used. For identified signals, signal evaluation was conducted using an AESI-appropriate study design, choosing between self-controlled designs (self-controlled case series [SCCS] and self-controlled risk interval [SCRI]) and cohort design. The cohort design was also applied in the study of the AESI vaccine-associated enhanced disease (VAED). The cohort design was also used to describe cases of myocarditis and pericarditis according to previous exposure to the COVID-19 vaccination.

Setting

This study is based on electronic, routinely collected data from regional databases or national databases of the participating countries. Per protocol the participating countries (databases) are Denmark (national registries), Italy (Agenzia Regionale di Sanita' della Toscana, ARS), Norway (national registries), Spain (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, SIDIAP), and the United Kingdom (UK, Clinical Practice Research Datalink, CPRD). All participating countries have universal health care for the inhabitants, and their participating databases contain linkable routinely collected data from the primary and/or secondary health sector, including information on births, deaths, vaccines, diagnoses, and prescribed drug use.

Subjects and study size, including dropouts

Owing to lack of data access by the current data custodian, Italy (ARS) did not contribute to this Fourth Interim Report. All individuals in a database-specific data extraction were eligible for inclusion. Spikevax recipients were identified from 11 January 2021 until 31 December 2021 in Norway, until 21 March 2022 in the UK, and until 30 June 2022 in Denmark and Spain. Cohorts of Spikevax recipients were defined separately for first, second, and third Spikevax dose receipt. The expected events in the vaccinated were estimated based on population-based, country-specific historical background rates of the AESIs estimated in each participating database before the COVID-19 pandemic (2017-2019; for Norway 2018-2019). Exclusion criteria were missing data on age and sex, and, for the Spikevax cohorts, receipt of another type of COVID-19 vaccine on the date of a given Spikevax dose receipt. To ensure inclusion of incident AESIs, persons with a given AESI in the 2 years before the follow-up start were excluded from the analysis. Thus, the total data coverage from the lookback period for the historical cohort until the end of the follow-up in the current analysis extended from 01 January 2015 until 30 June 2022.

Variables and data sources

This Fourth Interim Report includes available results from the databases in Denmark, Norway Spain, and the UK. All participating databases have routinely collected data on COVID-19

vaccines, diagnoses recorded in primary and/or secondary care, and outpatient dispensings of prescription medications. The exposure was defined by record of a given dose of Spikevax. The AESIs, subgroups, and other conditions were defined based on routinely recorded primary- or secondary-care diagnoses, and/or medication proxies.

We assessed 38 AESIs, identified as important in studying vaccine safety. Furthermore, we described cases of myocarditis and pericarditis.

In addition to prespecified stratifications on age and sex, subpopulations examined included women of childbearing age, patients with chronic health conditions, patients with autoimmune or inflammatory disorders, patients with indicators of immunocompromised status, and patients previously diagnosed with COVID-19 infection. Covariates included age, sex, and comorbidity burden as measured by the Charlson Comorbidity Index, markers of health care resource utilization, and previous vaccinations. Availability of the covariates were database-specific.

Main statistical methods

Incidence rates were computed and reported per 100,000 person-years. Persons with a prevalent AESI event in previous 2 years were excluded from computation of a given AESI rate. Based on observed vs expected counts, country-specific standardised morbidity ratios (SMRs) were estimated overall and stratified on sex, and age groups. An SMR ≥ 2.0 based on a case count ≥ 5 was defined as signal and are examined further in signal evaluation. The signal evaluation analysis was restricted to the AESIs that were identified as signals in the Third Interim Report and fulfilled the criteria for being evaluated using the SCCS design. In the SCCS the incidence rate ratios (IRRs) were estimated using the standard published methods. For each AESI the main signal evaluation analyses were conducted for specified populations, doses, and risk windows. In a series of sensitivity analyses, robustness of the main analyses was tested against alternating doses, populations, risk windows, and censoring rules. In the cohort design of VAED, logistic regression was used to estimate crude and adjusted odds ratios.

Results

Per the Protocol's reporting schedule, the Fourth Interim Report includes available preliminary results from Denmark, Norway, Spain (SIDIAP), and the UK (CPRD). The following results are included: population description and selection for Denmark, Norway, Spain, and the UK; crude AESI rates in historical and Spikevax cohorts for Denmark, Norway, and Spain; signal detection for Denmark, Norway, and Spain in analyses stratified on age and sex (not analyses stratified on subpopulations); signal evaluation for Denmark, Norway, and Spain; analysis of VAED in Norway; description of cases of myocarditis and pericarditis in Denmark and Norway.

During the study period covered by the current data extraction, the number of eligible Spikevax recipients with at least one dose of Spikevax and no previous record of a COVID-19 vaccine was 564,137 in Denmark, 543,429 in Norway, 621,240 in Spain, and 228,889 in the UK. Rates of the AESI varied widely across the databases. The variation is attributable both to

the database characteristics, to algorithm refinement activities that are in progress within the VAC4EU network, and to data limitations (specifically, in Norway, inflation of some rates was due to lack of specific diagnosis subcodes in the current data extraction, which will be corrected for the final report).

We identified more than 50 strata with SMR ≥2.0 based on ≥5 Spikevax-exposed cases in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalised convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There were a maximum of 11-50 signals in at least one country for the AESIs microangiopathy, coronary artery disease, arrhythmia, cerebrovascular disease, single organ cutaneous vasculitis, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. We did not identify any signals for narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country. Most signals were detected in Spain (SIDIAP).

In the SCCS signal evaluation analyses, incidence rate ratios with point estimates exceeding 1.5 were observed in at least one of the three countries for the AESIs (idiopathic) thrombocytopenia, stress-induced cardiomyopathy, myocarditis, pericarditis, splanchnic vein thrombosis, Acute liver injury, Generalised convulsions, anaphylaxis, and Vaccine-induced immune thrombotic thrombocytopenia. The largest effect sizes were observed for myocarditis and pericarditis.

No indication of VAED was identified in Norway, the only country for which these analyses were performed in this Interim Report. Concerning cohort analyses of myocarditis and pericarditis, the majority of myocarditis and pericarditis cases was male; among the Spikevax exposed the majority had received the second dose of Spikevax before diagnosis of myocarditis in Norway and Denmark or before the diagnosis of pericarditis in Denmark.

Discussion

This Fourth Interim Report includes available preliminary results from Denmark, Norway, Spain (SIDIAP), and UK (CPRD). On the signal detection stage, for each examined AESIs and in each country, SMRs were computed for 840 strata, for all possible combinations of Spikevax doses, time intervals, age, and sex strata. There were more than 50 strata with signals (SMR ≥ 2.0 based on ≥5 Spikevax-exposed cases) in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalised convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause.

Signal evaluation confirmed previous findings of increased rates of myocarditis and pericarditis 0-7 days after the second dose of Spikevax in young males.

Variations in historical rates were observed in the current report owing to differences in setting

(secondary care only or combination of primary or secondary care), limitation in detail level of extracted diagnostic codes in Norway, where only 3-digit ICD-10 codes were available, and because of still ongoing refinement of the AESI-finding algorithms. Main limitations of the analysis include potential misclassification of the study variables, residual confounding unavoidable in observational designs, low precision of some estimates, and potentially high rate of false-positive findings due to multiple comparisons.

The findings of this study based on analysis of secondary routinely collected data with its known strengths and limitations must be interpreted in the context of all available evidence from diverse sources, populations, designs, and disciplines, and based on biological plausibility underlying any putative associations. The results reported here should be considered preliminary and are not interpretable as indicative of any changes to the current benefit-risk profile of Spikevax.

Marketing Authorisation Holder(s)

Moderna Biotech Spain, S.L. Calle del Principe De Vergara 132 Plt 12 28002 Madrid, Spain

Names and affiliations of principal investigators

Name and role	Affiliation
[redacted]	Department of Clinical Epidemiology Aarhus University Hospital Olof Palmes Allé 43-45 8200 Aarhus N, Denmark
[redacted]	Department of Clinical Epidemiology Aarhus University Hospital Olof Palmes Allé 43-45 8200 Aarhus N, Denmark
[redacted]	Department of Clinical Epidemiology Aarhus University Hospital Olof Palmes Allé 43-45 8200 Aarhus N, Denmark

2. List of abbreviations

Abbreviation	Explanation
ACCESS	vACCine COVID-19 monitoring readinESS
ADEM	Acute disseminated encephalomyelitis
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
ARS	Agenzia Regionale di Sanita' della Toscana
ATC	Anatomical Therapeutic Chemical
CHI	Catalan Health Institute
CHMP	Committee for Medicinal Products for Human Use
CDM	Common data model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CVST	Cerebral venous sinus thrombosis
DAP	Database access provider
DIC	Disseminated intravascular coagulation
DRE	Digital Research Environment
DSRU	Drug Safety Research Unit
DVT	Deep vein thrombosis
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETL	Extraction, transformation, and loading
EU	European Union
EU PAS Register	The European Union electronic Register of Post-Authorisation Studies
GBS	Guillain-Barré syndrome
GP	General practitioner
GVP	Guideline on good pharmacovigilance practices
HR	Hazard ratio
ICD-9CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICD-10CM	International Classification of Diseases, 10th Revision, Clinical Modification

ICPC	International Classification of Primary Health Care
IRR	Incidence rate ratio
KUHR	The Norway Control and Payment of Health reimbursement
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
NA	Not available
NHS	National Health Service
OR	Odds ratio
PASS	Postauthorisation safety study
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
RCT	Randomised controlled trial
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCCS	Self-controlled case series
SD	Standard deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SMR	Standardised Morbidity Ratio
SNOMED	Systematised Nomenclature of Medicine
SCRI	Self-controlled risk intervals
SVT	Splanchnic vein thrombosis
UK	United Kingdom
VAC4EU	Vaccine Monitoring Collaboration for Europe
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VITT	Vaccine-induced immune thrombotic thrombocytopenia
WHO	World Health Organisation

3. Investigators

Centre	Role(s)	Address	Main Contact Person
Aarhus University, Denmark	Lead Scientific Centre and Data Access Provider, Denmark	Dept of Clinical Epidemiology Aarhus University Olof Palmes Allé 43-45 8200 Aarhus N, Denmark	[redacted]
University of Oslo, Norway	Data Access Provider, Norway	Pharmacoepidemiology and Drug Safety Research Group University of Oslo PB 1068 Blindern Oslo, Norway	[redacted]
ARS Toscana, Italy	Data Access Provider, Italy	Agenzia Regionale di Sanità della Toscana Osservatorio di Epidemiologia ARS Toscana Via Pietro Dazzi, 1 50141 Florence Italy	[redacted]
IDIAP JGol, Spain	Data Access Provider, Spain	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina Gran Via de les Corts Catalanes, 587, àtic, 08007, Barcelona, Spain	[redacted]
DSRU, UK	Data Access Provider, UK	Drug Safety Research Unit - DSRU Bursledon Hall, Blundell Lane Southampton SO31 1AA United Kingdom	[redacted]

4. Other responsible parties

Centre	Role	Address	Main Contact Person
Julius Clinical Research B.V.	Lead Operating Centre	Julius Clinical Research Broederplein 41-43 3703 CD Zeist The Netherlands	[redacted]
Julius Clinical Research B.V.	Study Analysis Programming	Julius Clinical Research Broederplein 41-43 3703 CD Zeist The Netherlands	[redacted]

5. Milestones

Milestone	Planned date	Actual date*	Comments
Start of data collection	31 December 2021	31 December 2021	
End of data collection	31 March 2023		
Registration in the EU PASregister	Before start of data collection	13 December 2021	
Study interim report 1	30 September 2021	30 September 2021	Contents per protocol: Progress report describing ongoing project development activities
Study interim report 2	31 March 2022	31 March 2022	Preliminary results from selected databases
Study interim report 3	30 September 2022	30 September 2022	Progress report describing ongoing preliminary analyses. Selected preliminary results are provided from four out of five participating databases
Study interim report 4	31 March 2023	31 March 2023	Preliminary results are provided from four out of five participating databases
Final report of study results	31 December 2023		

* Subject to data queues by data custodians

6. Rationale and background

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic (1), and a mass vaccination campaign has been underway in Europe, since 2021 (2, 3). The mRNA-1273 SARS-CoV-2 vaccine, currently known as Spikevax (4), combines mRNA (messenger ribonucleic acid) delivery platform with the stabilised SARS-CoV-2 spike immunogen.

In the pivotal (Coronavirus Efficacy, COVE) phase 3 randomised controlled trial (RCT), Spikevax showed 94.1% efficacy at preventing COVID-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified during the RCT (5). Initial analyses of the ongoing phase 3 COVIAAD RCT (6), assessing safety, reactogenicity, and immunogenicity of Spikevax in patients with rheumatic diseases showed no evidence of an association of the vaccine with severe disease flares (7). There are ongoing trials investigating Spikevax safety and immunogenicity in adults with solid organ transplants (8); and effectiveness and safety among adolescents ages 12-<18 years (9) and among children between ages 6 months and 12 years (10). Spikevax received Conditional Marketing Authorisations by the European Commission on 06 January 2021 (11) and by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) on 08 January 2021 (12). The EMA has subsequently converted the conditional authorisation to standard authorisation (13). Since February 2022, Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older (4). In October 2022, EMA's Committee for Medicinal Products for Human Use (CHMP) recommended including the use in children aged 6 months to 5 years for Spikevax (14). The recommended primary series dosing of Spikevax 0.2 mg/mL is 2 doses 0.5 mL each 28 days apart for individuals 12 years of age and older; 2 doses 0.25 mL each 28 days apart for children 6 through 11 years of age. The recommended dosing for Spikevax 0.1 mg/mL primary series for children 6 years through 11 years of age is 2 doses 28 days apart 0.5 mL each, containing 50 micrograms mRNA each. The recommended dosing for Spikevax 0.1 mg/mL primary series for children 6 months through 5 years of age is 2 doses 28 days apart 0.25 mL each (13).

Table 1 shows the number of Spikevax doses administered in the participating countries.

Table 1. Number of Spikevax doses administered in the participating countries

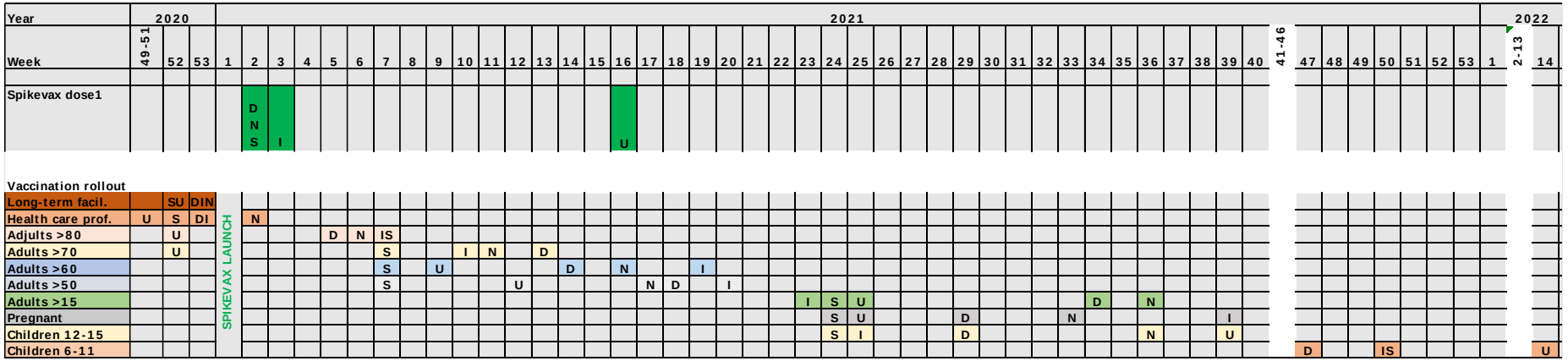
Country	Data updated on	N Spikevax doses* administered
Denmark	19 August 2022	1.7 million
Italy	06 September 2022	34 million
Norway	19 August 2022	2.3 million
Spain	19 August 2022	24 million
United Kingdom (UK)	23 August 2022	3.2 million first and second doses, 9.4 million booster doses

*Includes booster doses unless otherwise specified; as the same person may receive more than one dose, the number of doses is higher than the number of people in the population. (Source for Denmark, Italy, Norway, Spain: https://ourworldindata.org/covid-vaccinations "Which vaccines have been administered in each country?"(2);

Source for the UK: gov.uk (15)).

Figure 1 provides an overview of the rollout of COVID-19 vaccines in the participating countries in relation to Spikevax launch.

Figure 1. Licensing and delivery of the first dose of Spikevax, and starting weeks of the rollout of the primary COVID-19 vaccine series (any vaccine) for selected target groups in the participating countries (week 49/2020 – week 14/2022)



D Denmark, I Italy, N Norway, S Spain, U United Kingdom

Sources: Spikevax, licensed (11, 12); Denmark (16-20); Norway (21-24); Italy (25-30); Spain (31, 32); UK (33-38). Exact boundaries for the age groups may differ slightly by country.

The European Union (EU) Risk Management Plan (RMP) for Spikevax, version 6.3 dated 06 December 2022, lists myocarditis and pericarditis as important identified risks and vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD), as an important potential risks. Missing information includes use in pregnancy (addressed in a separate protocol (39)), and while breastfeeding, long-term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects with unstable health conditions and chronic co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological, disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders (40).

The COVID-19 Vaccine Safety Update for Spikevax dated 11 May 2021, cites reports of cases of myocarditis/pericarditis among mRNA-based vaccinees, warranting further monitoring by the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) (41). On 09 July 2021, PRAC indicated that myocarditis and pericarditis can occur in very rare cases following vaccination with mRNA COVID-19 vaccines, primarily within 14 days after vaccination, more frequently after the second dose. Young age and male sex were the risk factors for the myocarditis/pericarditis occurrence, while among those with myocarditis/pericarditis, older age and comorbidity were risk factors for poor prognosis (42). In an epidemiologic registry-based Danish study of the mRNA COVID-19 vaccines and risk of myocarditis and pericarditis, among 498,814 Spikevax vaccinees, 21 developed myocarditis or myopericarditis within 28 days of vaccination (28-day risk 4.2 per 100,000). The adjusted hazard ratio compared with unvaccinated was 3.92 (95% confidence interval [CI] 2.30 to 6.68); the largest risk among the vaccinated was observed among persons 12-39 years of age and among men, however, the absolute risks were low in all subgroups (43). A subsequent study in four Nordic countries (44) corroborated the Danish findings, as did the study in Italy among mRNA COVID-19 vaccinees ages 12-39 years, reporting the highest risks in males of 12 to 39 years and in males and females 18 to 29 years vaccinated with Spikevax, with risk windows ranging between 7 and 28 days. This study reported increased risk after both primary doses of Spikevax (45). All current evidence points to highest risk in younger age groups, a benign course in most cases, and to the need for additional evidence on risk factors (46). To date, most evidence regarding myocarditis and pericarditis originates from routinely collected data without endpoint validation.

This post authorisation safety study (PASS) is a part of the Spikevax RMP and aims to advance evidence about the safety of Spikevax in routine clinical practice. Safety is being examined using the prespecified adverse events of special interest (AESIs), over a longer-term, and in subgroups of individuals not included or under-represented in the trial populations (47). Among the prespecified AESI, this study uses epidemiologic methods to formally address the important identified risks including myocarditis and pericarditis, and, to the extent possible, VAED and VAERD. This study is being conducted using routinely collected (secondary) data from nationwide or regional databases in five European countries: Denmark, Italy, Norway, Spain, and the UK. The databases were selected based on availability of specific data elements, including information on vaccine brand, frequency of updates, and data recency/lags.

This Fourth Interim Reports addresses selected study objectives using data available in the most recent data extraction, covering up to 1.5 years after Spikevax availability. Annex 2 in Section 16 provides an overview of the analyses available in the current report. Owing to data access issues, this report does not contain results from Italy, details provided in Section 8.

7. Research question and objectives

The overarching causal research question of this study is (48):

Is the occurrence of the AESIs among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in that population in the absence of Spikevax?

The AESIs and the main measure of association for each AESI are listed in Section 9.1, Table 2.

7.1. Primary objective

To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.

7.2. Secondary objective

To assess whether vaccination with Spikevax (for any dose or by dose if feasible) is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with chronic health conditions, and patients with autoimmune or inflammatory disorders.

8. Amendments and updates

The following amendments to the Study Protocol have been noted in the Statistical Analysis Plan (SAP).

Deviation no.	Minor/ major	Description
1	Minor	The AESIs not observable in historical data, VAED and vaccine-induced immune thrombotic thrombocytopenia (VITT), are not included in the signal detection. These AESIs enter into signal evaluation directly.
2	Minor	For the signal evaluation using cohort study with matching on historical controls we now propose to adjust for comorbidities (CCI) instead of matching to enhance efficiency. We still match on age and sex. Adjustment is equivalent to matching and more efficient with respect to computer run time. Note: not included in the Fourth Interim Report. Will be included in the Final Study Report.
3	Minor	For signal evaluation using self-controlled risk intervals (SCRI) design, in the protocol we had written that control windows would have the same length as the risk windows. We now

		propose that the control windows will be longer than the risk windows (maximum 42 days) to gain better precision in the analyses. Note: not included in the Fourth Interim Report. Will be included in the Final Study Report.

In addition, the following deviations occur for this interim report:

Deviation no.	Minor/ major	Description
4	Major	Data from the ARS database is not available for reporting at this time. ARS is an agency of the Tuscany Region of Italy, and acts as a technical and scientific consultant both to the regional government and to the Regional Council. The Tuscany Region transmits a copy of its healthcare administrative data banks to ARS, which is entitled by regional law to process them for its institutional purposes, upon permission of a board representing the Regional Council. In Spring 2022, a communication of the Italian National Authority for Data Protection suggested that this procedure is insufficient when data is used for research purposes. At the same time, invitations to revise data access processes for purposes of research have been shared by the Authority with other research institutions in Italy. Multiple initiatives are ongoing to respond to such invitations. One set of initiatives aims to clarify what procedure would be compatible with the current implementation of the GDPR in the Italian legislation in the specific case of drug safety studies: preliminary legal assessments indicate that this case may fall under special authorization, and allow expedite data access, after communication or agreement with the Italian Regulatory Authority. Another set of initiatives indicate that an update of the legislation would be advisable, to encompass a larger set of data processing activities, and include in a more specific manner the indications of the General Data Protection Regulation. Pending resolution of this legal concern, inclusion of data from ARS in the final study report is considered at risk.

9. Research methods

This report was prepared according to the Study Protocol Version 1.3, dated 27 September

2022 and registered in The European Union electronic Register of Post-Authorisation Studies (EU PAS Register) (49); and according to the SAP Version 2.0, dated 17 June 2022. This Section describes only the research methods applicable per results reported in this Fourth Interim Report. Table 2 gives and overview over the AESI we examined.

Table 2. List of the AESIs and overview of study design

Body system/ Classification	**AESI**
Auto-immune diseases	Guillain-Barré Syndrome (GBS)
	Acute disseminated encephalomyelitis (ADEM)
	Narcolepsy
	Acute aseptic arthritis
	Diabetes type 1
	(Idiopathic) Thrombocytopenia
Cardiovascular system	Microangiopathy
	Heart failure
	Stress-induced cardiomyopathy
	Coronary artery disease
	Arrhythmia
	Myocarditis
	Pericarditis
	Cerebrovascular disease
Circulatory system	Deep vein thrombosis (DVT)
	Pulmonary embolism (PE)
	Single Organ Cutaneous Vasculitis
	Cerebral venous sinus thrombosis (CVST)
	Splanchnic vein thrombosis (SVT)
	Coagulation disorders
	Disseminated intravascular coagulation (DIC)
	Kawasaki disease*
Hepato-gastrointestinal and renal system	Acute liver injury
	Acute kidney injury
Nerves and central nervous system	Generalised convulsions
	Encephalitis/meningoencephalitis
	Transverse myelitis
	Bell's palsy
Respiratory system	Acute respiratory distress syndrome (ARDS)
Skin and mucous membrane, bone and joints system	Erythema multiforme
	Chilblain – like lesions
Other systems	Anosmia, ageusia
	Anaphylaxis
	Multisystem inflammatory syndrome
	Vaccine-associated enhanced COVID-19 disease (VAED) or vaccine associated enhanced respiratory disease (VAERD)
	Vaccine-induced immune thrombotic thrombocytopenia
	Sudden death
	Death of any cause
* More commonly described as an autoimmune disease (50)	

9.1. Study design

For signal detection, the cohort study design was used to estimate Standardised Morbidity Ratios (SMRs) by comparing observed number of AESI with the expected number of AESI based on historical rates (see Section 9.1.1). However, signal detection was not performed for the AESIs VITT and VAED, because historical rates was not available, as they, by definition, can only be observed in COVID-19 vaccinees. VITT was examined in self-controlled designs, while VAED was investigated using a cohort design in a subset of the study population (see Section 9.1.3).

For signal evaluation, we, depending on the nature of an AESI, either applied self-controlled designs or cohort designs, as described in Section 9.1.2.

Finally, outcomes of myocarditis and pericarditis were examined using cohort design in a separate study population, as described in Section 9.1.4.

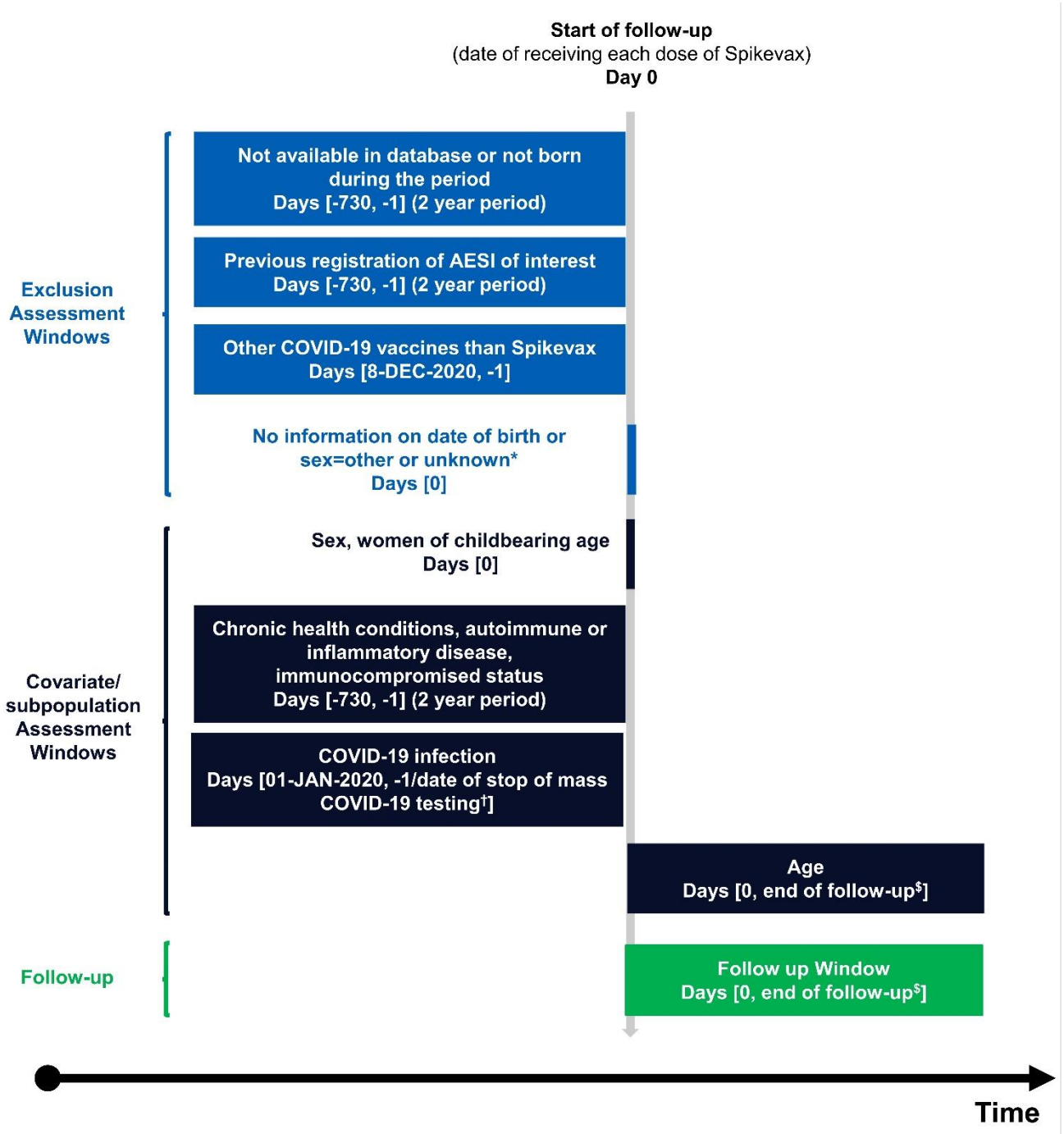
The analyses we provide results for in the Fourth Interim Report is specified in Annex 2 in Section 16 according to country.

9.1.1. *Signal detection*

Signal detection proceeded by comparing the number of observed vs. expected events for each AESI, as previously described in the ADVANCE *Report on appraisal of vaccine safety methods*, referenced by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)'s guidelines on monitoring vaccine safety and effectiveness (51, 52). Indirect standardization according to age and sex was used (53) to estimate the Standardised Morbidity Ratio (SMR), as the number of observed events divided by the number of expected events in Spikevax vaccinees. The expected events in the vaccinated were estimated based on population-based, country-specific historical background rates of the AESIs estimated in each participating database before the COVID-19 pandemic (2017-2019; for Norway 2018-2019 [explained in Section 9.9.5]) (54). The cohort definitions are visualized, using visualisations by Schneeweiss et al.(55), in Figure 2 for the Spikevax cohort and in Figure 3 for the historical cohort.

To ensure capture of potential AESIs both in short - and long-term following a vaccination, the SMRs were estimated in the following time intervals following each dose of Spikevax: 0-2 days, 0-14 days, 0-28 days, 0-42 days, and 0-end of follow-up. The SMRs were stratified by country, age, and sex for the primary objective.

Figure 2. Visualisation of the design for the Spikevax cohorts used to obtain the observed number of AESIs after each dose of Spikevax

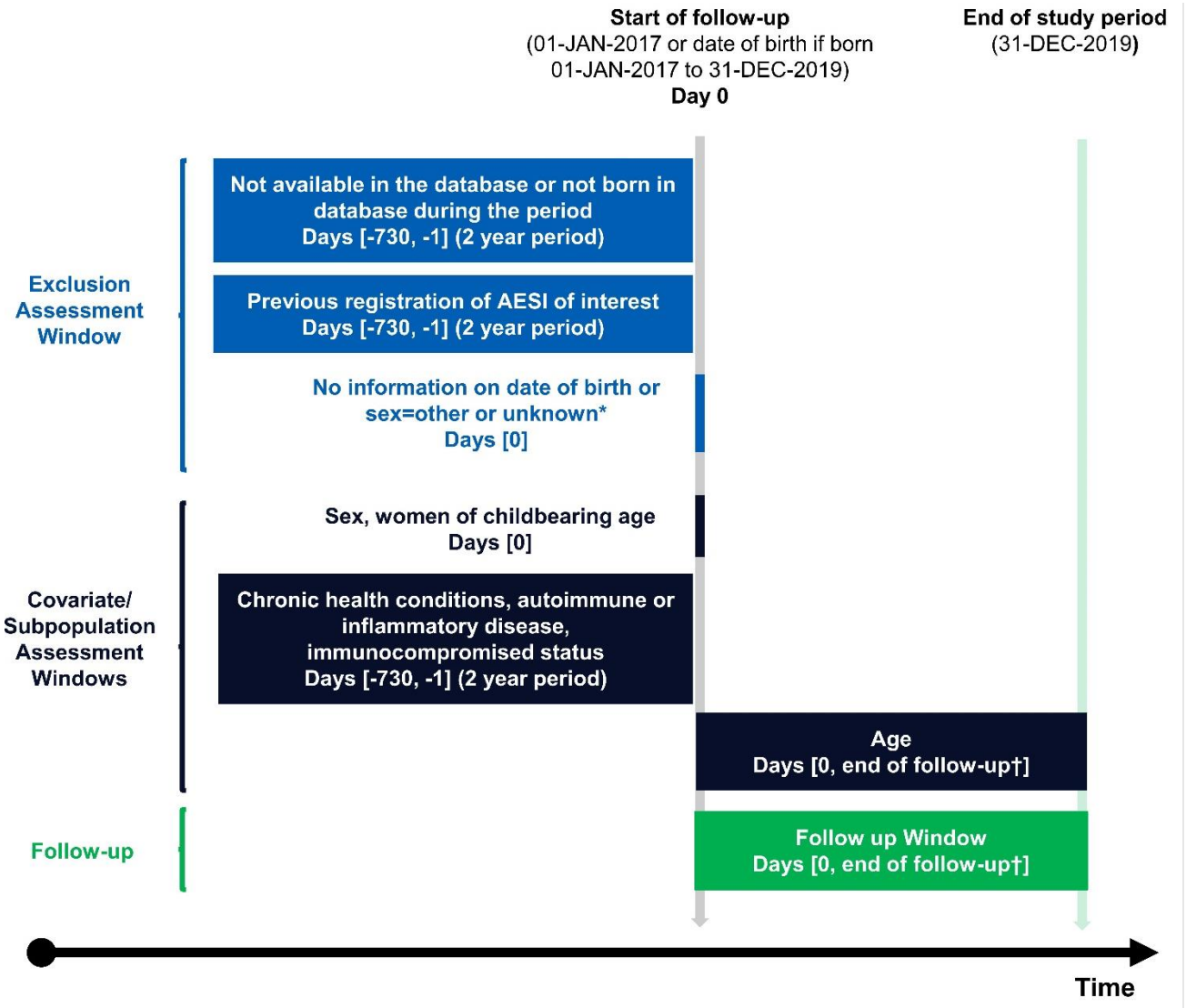


* Exclusions applied as data on age (calculated from date of birth) and sex (female or male) are required for indirect standardization.

† The strategy for testing for COVID-19 disease has varied over the epidemic. In more recent periods, mass testing was stopped, with testing primarily reserved for special situations or specific groups of patients. Therefore, we only included COVID-19 diagnosis occurring before the stop of mass testing/adherence to mass testing in each country (12-FEB-2022 in Norway; 9-MAR-2022 in Denmark, 28-MAR-2022 in Spain, and 31-MAR-2022 in UK) (see Section 9.9.5 for details).

$ Earliest of AESI of interest (only for estimation of observed events), death, database disenrollment, another dose of Spikevax or another COVID-19 vaccine, end of a given risk window (day 2, 14, 28, 42, or last data availability), or last date with available data (31-DEC-2021 in Norway, 21-MAR-2022 in the UK, and 30-JUN-2022 in Denmark and Spain).

Figure 3. Visualisation of the design for the historical cohort used to obtain the estimate of expected rates of AESIs



* Exclusions applied as data on age (calculated from date of birth) and sex (female or male) are required for indirect standardization.

† Earliest of AESI of interest, death, database disenrollment, or 31-DEC-2019.

Note: for the fourth interim report the start of follow-up in Norway was 01-JAN-2018 (see Section 9.9.5 for details).

9.1.2. *Signal evaluation*

In this Fourth Interim Report we aimed to conduct a signal evaluation for VITT and for the signals detected in the Third Interim Report, which included signal detection results for the ARS database covering the Italian Tuscany region until 31 December 2021.

The prespecified signal evaluation criteria were (see also Figure 4):

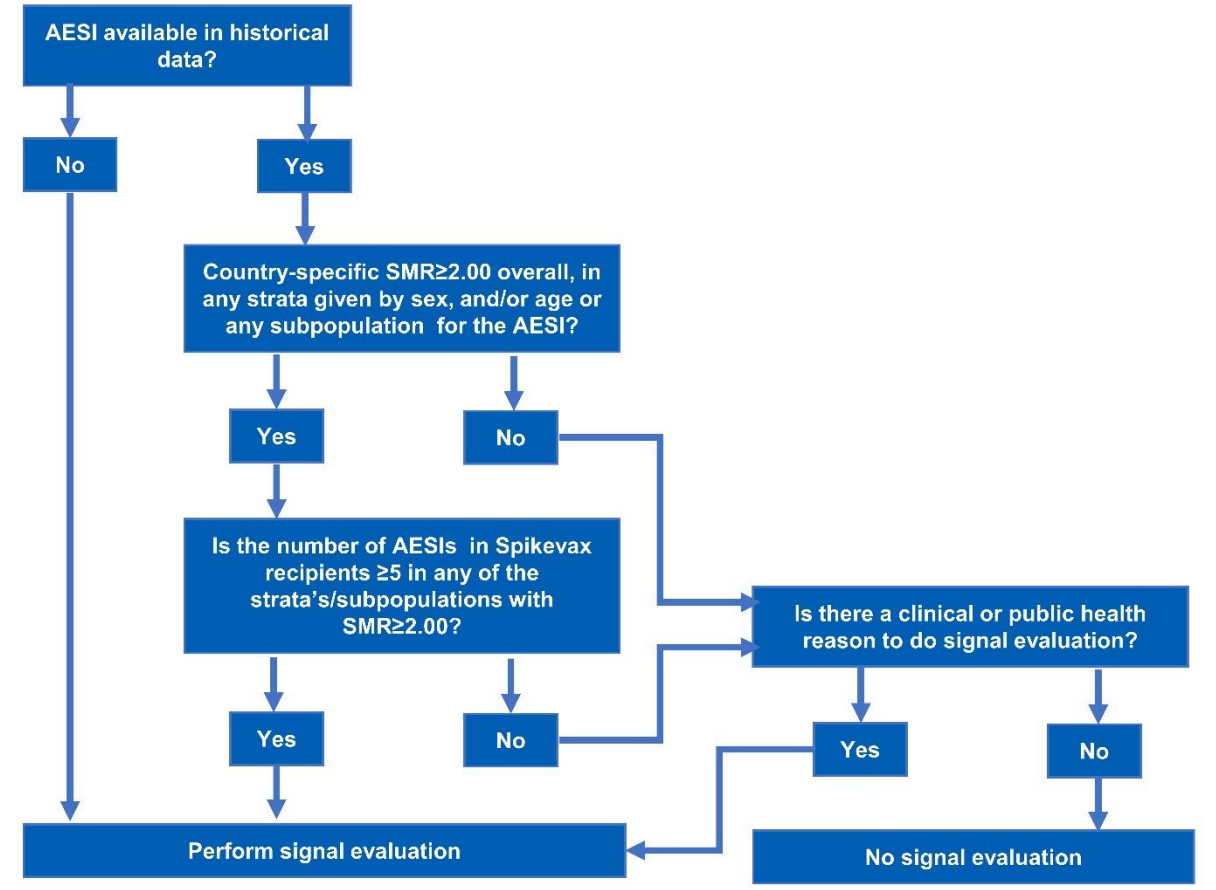
For a given AESI, a signal required the following conditions to be met:

1) An SMR ≥2 in a country-specific overall, age- or sex-specific, or subpopulation-specific analysis AND

2) The number of Spikevax-exposed cases ≥5 in a population/stratum giving rise to that SMR.

The a priori defined criteria were chosen to balance the risks of false positive against false negative signals. In the absence of a consensus about the thresholds, the criteria were based on the regulatory recommendation and ongoing research in using the observed-to-expected analyses in assessment of vaccine safety (56-60). For example, in previous studies, a relative estimate of a minimum of 2 has been described as a threshold for a weak signal (61, 62). In addition, we allowed for a signal evaluation based on a judgement of clinical and/or public health relevance, even if the above criteria were not fulfilled.

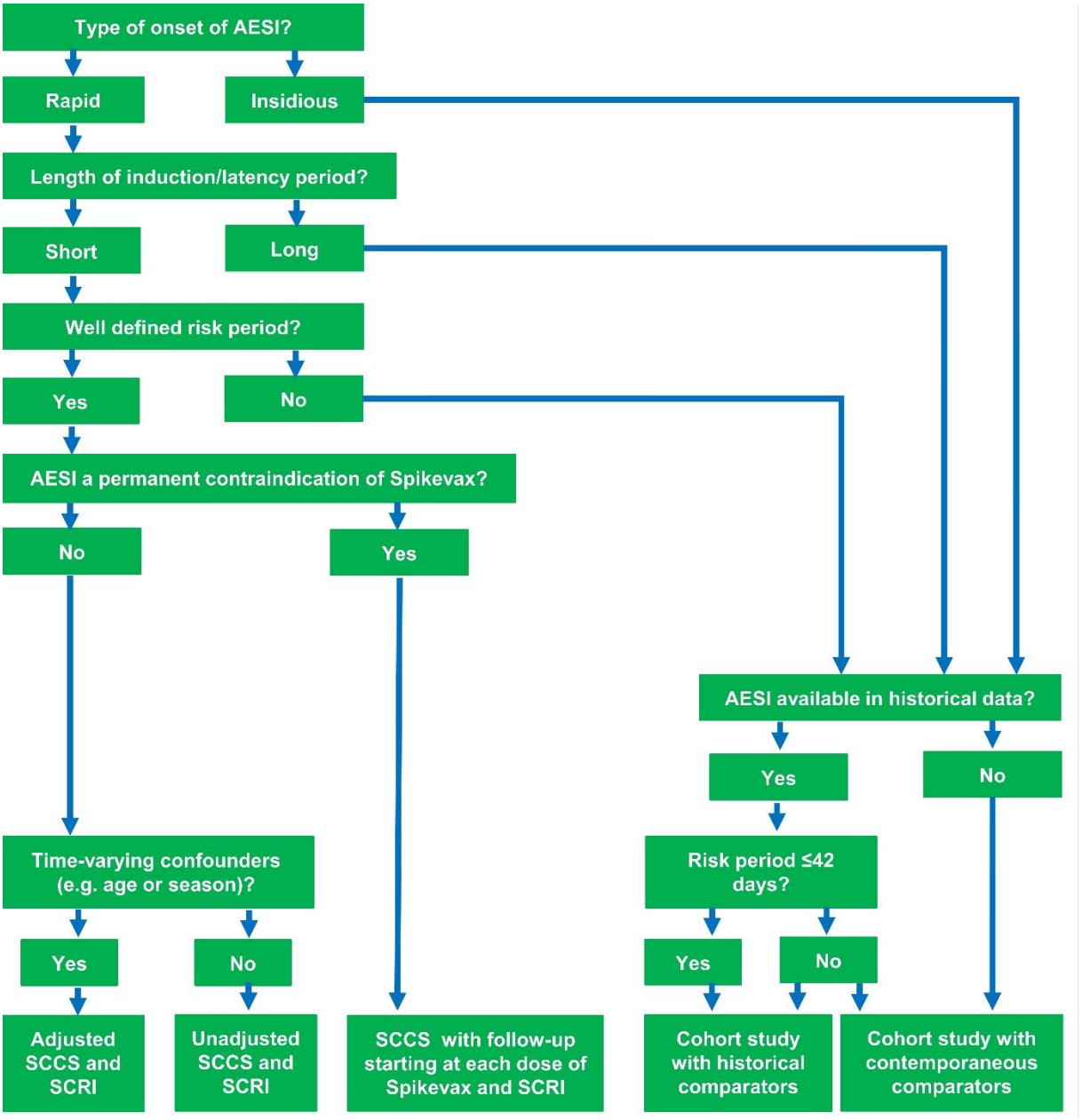
Figure 4. Decision framework for subjecting an AESI to a signal evaluation



Identification of study design for signal evaluation of each AESI

For signal evaluation, we could use self-controlled designs (self-controlled case series [SCCS] and self-controlled risk interval [SCRI]) or cohort designs (matched cohort study with historical comparators or cohort study with contemporaneous comparators). Figure 5 displays the decision flowchart to determine the design to be employed for signal evaluation. The decision depended on characteristics of the AESI, including type of onset (rapid vs insidious), hypothesised length of induction/latency period, ability to define risk periods, the extent to which the AESI affects the likelihood of subsequent vaccination (63, 64). As self-controlled designs inherently adjust for time-invariant confounding (64), they are suitable for AESIs for which it is difficult to identify an unconfounded comparator or to measure confounding, both of which are likely scenarios during a mass vaccination campaign. Therefore, self-controlled designs were the preferred method of signal evaluation, while cohort design was used for signal evaluation of AESIs that could not be accommodated by a self-controlled design (e.g., AESIs with no rapid onset or without a well-defined risk period).

Figure 5. Decision framework for selection study designs in signal evaluation



For each AESI undergoing signal evaluation, decision regarding the study design chosen for signal evaluation was documented in an AESI-specific form, including rationale for the decision. Table 3 presents the framework applied to make decisions regarding the main population, the primary risk window, and the dose of Spikevax to be used as the main analysis of the signal evaluation. If there was only limited evidence to answer the different questions based on the results of signal detection for a specific AESI, then we decided to use the study design prespecified in the SAP for that particular AESI.

Table 3. Selection framework to identify main population, main risk window, and dose of Spikevax for signal evaluation

Characteristics	Questions to consider?	Comments
Age	Are there any age-groups not recommended vaccination during the study period covered by the data (e.g., children)? Is the signal only observed for some age groups (e.g., adults aged 30-45 years; elderly above 75 years)	Evaluation of this was based on: • Age groups recommended Spikevax • Results of signal detection in each country (e.g., SMR close to 1 in some age groups and ≥2 in other age groups would indicate a signal limited to a specific age group) • External information (e.g., reports from other countries, regulatory requests)
Sex	Is the signal detected for both females and males? Is the signal only detected for females? Is the signal only detected for males?	Evaluation of this was based on: • Results of signal detection in each country (e.g., SMR close to 1 in females and ≥2 in males would indicate males) • External information (e.g., reports from other countries, regulatory requests)
Subpopulation	Is the signal only present in subpopulations?	Evaluation of this was based on: • Results of signal detection in each country (SMR close to 1 in general population and ≥2 in patients with autoimmune or inflammatory disorders would indicate patients with autoimmune or inflammatory disorders) • External information (e.g., reports from other countries,

Characteristics	Questions to consider?	Comments
		regulatory requests)
Dose of Spikevax	Is the signal detected for all doses or only specific dose numbers?	Evaluation of this was based on: • Results of signal detection in each country (SMR close to 1 for first dose and ≥2 after second dose would indicate second dose; similar SMR's for all doses would indicate any dose) • External information (e.g., reports from other countries, regulatory requests)
Risk window	In what time period after vaccination does the risk seems to be most increased?	Evaluation of this was based on: • Results of signal detection in each country (SMR close to 1 for 0-7 days after vaccination and ≥2 for 0-42 days would indicate risk window between 8-42 days) • External information (e.g., reports from other countries, regulatory requests; biological plausibility; information from studies on other vaccines)

Spikevax might be given to persons outside the target group. For example, Spikevax might be given to children below 12 years (indication during most of the period covered by the current data extraction) if they have a severe underlying morbidity. We did not include Spikevax vaccinated persons from non-indicated populations in the main analysis to avoid distortion of results by biases related to reasons for off-label use. However, we considered if we had enough data to make a sensitivity analysis including persons who had gotten Spikevax despite being in a non-indicated population. The indications for Spikevax have changed over the study period. Therefore, the indicated population was defined according to the broadest indication that had been used in each country from the first distribution of Spikevax until the date of the data extraction The indicated population for the Fourth interim report was persons ≥12 years and the non-indicated population was persons <12 years.

With a few exceptions (see explanation in Section 9.9.5), we always performed sensitivity analyses for the following populations if not equal to the main population of a given signal evaluation analysis:

- A population including all ages with recommendations for Spikevax and both females and males.
- If one sex was excluded from the main population, analyses were performed for the excluded sex.
- If the age was restricted in the main population (other than due to exclusion of persons with an age range outside Spikevax recommendations) analyses were performed separately in the population with age above the main population and in the population with age below the main population (but only including the age groups above the minimum recommended age for Spikevax vaccination).
- In the main population, we performed sensitivity analyses for the dose definitions not included in the main analysis (if it is possible in that particular design). Overall, we aimed to examine any dose of Spikevax and each dose number of Spikevax separately. Thus, if any dose was included in the main analysis, we performed sensitivity analyses separately for dose one, dose two, and dose three.

Furthermore, sensitivity analysis of risk windows was always performed for the main population when feasible.

Finally, in a sensitivity analysis, SARS-COV-2 infection was an additional censoring criterion, if not included as a censoring criterion in the main analysis.

Overview of selection of study design, primary dose of Spikevax, and main and sensitivity populations

Table 4 gives an overview of AESIs for which signals were detected in the Third Interim Report and the study designs selected for the signal evaluation in the Fourth Interim Report including main measures of association and the reason for selection of the study design.

Table 4. Overview AESIs for which signals were detected in the Third Interim Report, and study design and main outcome measure planned for signal evaluation in the fourth interim report.

Body System/ Classification	AESI	Signal detected	Primary study design	Primary dose of Spikevax	Main measure of association for signal evaluation	Reason for selecting study design
Auto-immune	Guillain-Barré Syndrome	No	NA	NA	NA	NA

Body System/ Classification	AESI	Signal detected	Primary study design	Primary dose of Spikevax	Main measure of association for signal evaluation	Reason for selecting study design
diseases	Acute disseminated encephalomyelitis	No	NA	NA	NA	NA
	Narcolepsy	No	NA	NA	NA	NA
	Acute aseptic arthritis	No	NA	NA	NA	NA
	Diabetes type 1	Yes	Cohort his	Any	HR	No well-defined risk window
	(Idiopathic) Thrombocytopenia	Yes	SCCS	Second	IRR	Fulfil criteria for SCCS
Cardiovascular system	Microangiopathy	Yes	Cohort his	Second	HR	No well-defined risk window
	Heart failure	Yes	Cohort his	Second	HR	No well-defined risk window
	Stress-induced cardiomyopathy	Yes	SCCS	Second	IRR	Fulfil criteria for SCCS
	Coronary artery disease	Yes	Cohort his	Any	HR	No well-defined risk window
	Arrhythmia	Yes	SCCS	Any	IRR	Fulfil criteria for SCCS
	Myocarditis	Yes	SCCS	Second	IRR	Fulfil criteria for SCCS
	Pericarditis	Yes	SCCS	Second	IRR	Fulfil criteria for SCCS
	Cerebrovascular disease	Yes	SCCS	Any	IRR	No clear pattern, use SAP pre-specification[$]
Circulatory system	Deep vein thrombosis (DVT)	Yes	SCCS	Any	IRR	No clear pattern, use SAP pre-specification[$]

Body System/ Classification	AESI	Signal detected	Primary study design	Primary dose of Spikevax	Main measure of association for signal evaluation	Reason for selecting study design
	Pulmonary embolism (PE)	No	NA	NA	NA	NA
	Single Organ Cutaneous Vasculitis	No	NA	NA	NA	NA
	Cerebral venous sinus thrombosis (CVST)	No	NA	NA	NA	NA
	Splanchnic vein thrombosis (SVT)	Yes	SCCS	Second	IRR	No clear pattern, use SAP pre-specification[$]
	Coagulation disorders	Yes	Cohort his	Any	HR	No well-defined risk window
	Disseminated intravascular coagulation (DIC)	No	NA	NA	NA	NA
	Kawasaki disease	No	NA	NA	NA	NA
Hepato-gastrointestinal and renal system	Acute liver injury	Yes	SCCS	Second	IRR	No clear pattern, use SAP pre-specification[$]
	Acute kidney injury	Yes	Cohort his	Any	HR	No well-defined risk window
Nerves and central nervous system	Generalised convulsions	Yes	SCCS	Any	IRR	Fulfil criteria for SCCS
	Encephalitis/meningoencephalitis	No	NA	NA	NA	NA
	Transverse myelitis	No	NA	NA	NA	NA
	Bell's palsy	No	NA	NA	NA	NA
Respiratory system	Acute respiratory distress syndrome (ARDS)	Yes	Cohort contem	Any	HR	No well-defined risk window

Body System/ Classification	AESI	Signal detected	Primary study design	Primary dose of Spikevax	Main measure of association for signal evaluation	Reason for selecting study design
Skin and mucous membrane, bone and joints system	Erythema multiforme	No	NA	NA	NA	NA
	Chilblain – like lesions	No	NA	NA	NA	NA
Other systems	Anosmia, ageusia	No	NA	NA	NA	NA
	Anaphylaxis	Yes	SCCS	First	IRR	Fulfil criteria for SCCS
	Multisystem inflammatory syndrome	No	NA	NA	NA	NA
	Vaccine-associated enhanced COVID-19 disease (VAED) or vaccine associated enhanced respiratory disease (VAERD)	NA*	Cohort†	NA	OR	Can only be indirectly assessed by comparing severity of COVID-19 depending on exposure status (Spikevax vaccination or no COVID-19 vaccination)
	Vaccine-induced immune thrombotic thrombocytopenia	NA*	SCCS	Second	IRR	Fulfil criteria for SCCS
	Sudden death	No	NA	NA	NA	NA
	Death of any cause	Yes	Cohort his	Any	HR	No well-defined risk window

Body System/ Classification	AESI	Signal detected	Primary study design	Primary dose of Spikevax	Main measure of association for signal evaluation	Reason for selecting study design
Abbreviations: Cohort contem=Cohort study with contemporaneous comparators; Cohort his=Cohort study with matched historical comparators; HR=hazard ratio; IRR=Incidence rate ratio; NA=Not available; OR=Odds ratio; SCCS=self-controlled case series* Historical rates cannot be used for these AESIs, as they can by definition only be observed in COVID-19 vaccinees. Therefore, no signal detection results were available. † This cohort study is designed specifically for this outcome and are described in Section 9.1.3 $ When the evidence from signal detection needed to decide on the study design was limited for a specific AESI, then we used the design prespecified in the SAP for that AESI. For instance, that occurred when only few signals were detected for an AESI and other SMRs were close to 1. Note: For the Fourth Interim Report, it was not possible to perform cohort studies with matched historical comparators.						

The implementation of the planned analyses was challenged by the complexities associated with the analysis itself, heterogeneous multi-database, multi-health care setting setup, adaptation of novel tools, and short timelines. Therefore, the Fourth Interim Report contains a selected subset of the final planned analyses from selected databases (See Annex 2 in Section 16 for an overview). Since the Third Interim Report, advances have been made towards all planned analyses and quality assurance. This section described only the methods relevant for the results reported in the Fourth Interim Report.

Table 5 gives an overview of the main population and sensitivity populations selected for each AESI.

Table 5. Overview of age and sex of the main population and the sensitivity populations according to AESI requiring signal evaluation

AESI	Main population	Sensitivity population 1	Sensitivity population 2	Sensitivity population 3
Diabetes type 1	Females and males aged 12 to 44 years	Females aged 12 to 44 years	Males aged 12 to 44 years	Females and males aged 12 years or older
(Idiopathic) Thrombocytopenia	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Microangiopathy	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Heart failure	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Stress-induced cardiomyopathy	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Coronary artery disease	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA

AESI	Main population	Sensitivity population 1	Sensitivity population 2	Sensitivity population 3
Arrhythmia	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Myocarditis	Males aged 12 to 30 years	Females aged 12 to 30 years	Males aged 18 years or older	Females aged 18 years or older
Pericarditis	Males aged 12 to 30 years	Females aged 12 to 30 years	Males aged 18 years or older	Females aged 18 years or older
Cerebrovascular disease	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Deep vein thrombosis (DVT)	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Splanchnic vein thrombosis (SVT)	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	Females and males aged 65 years or older
Coagulation disorders	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Acute liver injury	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Acute kidney injury	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Generalised convulsions	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Acute respiratory distress syndrome (ARDS)	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Anaphylaxis	Females aged 12 years or older	Females and males aged 12 years or older	Males aged 12 years or older	NA
Vaccine-induced immune thrombotic thrombocytopenia	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA
Death of any cause	Females and males aged 12 years or older	Females aged 12 years or older	Males aged 12 years or older	NA

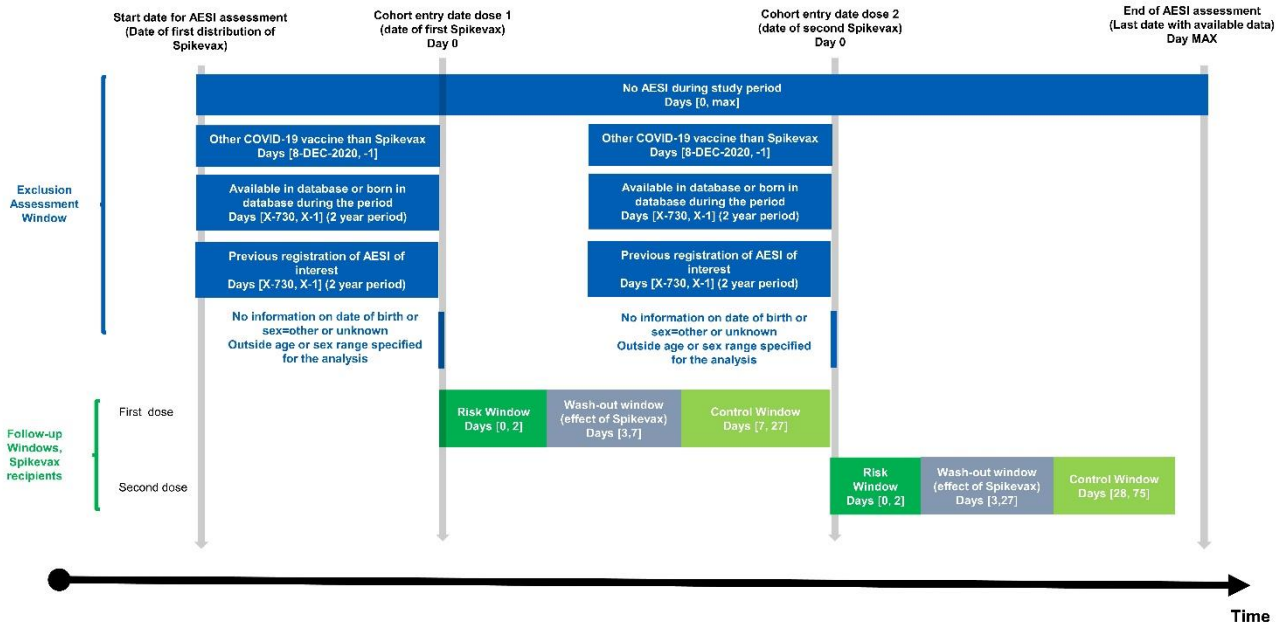
Abbreviations: NA=Not available

Self-controlled case series design

Self-controlled designs are case-only designs, i.e., they are restricted to individuals who experience the specified AESI in a pre-specified time window. The SCCS design uses a pre-specified observation period anchored in calendar time (or age) (65). In the SCCS analysis we included Spikevax recipients who experienced the AESI from the date of the first distribution

of Spikevax in each country and until the last date with available data. To ensure completeness of inclusion of Spikevax vaccinees, we assumed that the date of distribution in each country was the date Spikevax was shipped to that country (11 January 2021 for Denmark, Norway, and Spain, and 1 April 2021 for the UK). The pre-specified observation period is split into a risk period/window with hypothesised increased risk of the AESI, control periods/windows without increased risk, and potentially other windows with hypothesised altered risk. Each person serves as his/her own control, thus removing time-invariant confounding, but the analyses are still susceptible to time-varying confounding from e.g., season (64, 66). It is important to note that methods to adjust for time-varying confounders in the SCCS design are available.(67, 68). In the Fourth Interim Report, we adjusted for month and year using dummy variables in the SCCS design for AESIs where time-varying confounding might be a possibility as further specified in Section 9.9.2. A key assumption of the SCCS design is that an AESI should not appreciably affect subsequent exposures (69). This assumption is likely violated for many of the AESIs included in this study. Therefore, for AESIs that are contraindications to vaccination or are likely to reduce the likelihood of ever getting Spikevax, we did the SCCS analysis separately for each dose of Spikevax and restricted to vaccinated cases with observation starting after each dose of Spikevax (66, 69). That is, we performed SCCS separately for each dose of Spikevax beginning the observation period at the date of vaccination. Figure 6 visualises the SCCS design by dose for the risk window 0 to 2 days. For AESIs that might rather temporarily reduce the likelihood of vaccination, we introduced a healthy vaccinee window/pre-exposure risk window of 14 days before each dose of Spikevax, where we would expect a lower rate of AESIs (66, 69). This window was excluded from the control window. As an example, Figure 7 visualises the design of the standard SCCS with the risk window 0 to 14 days.

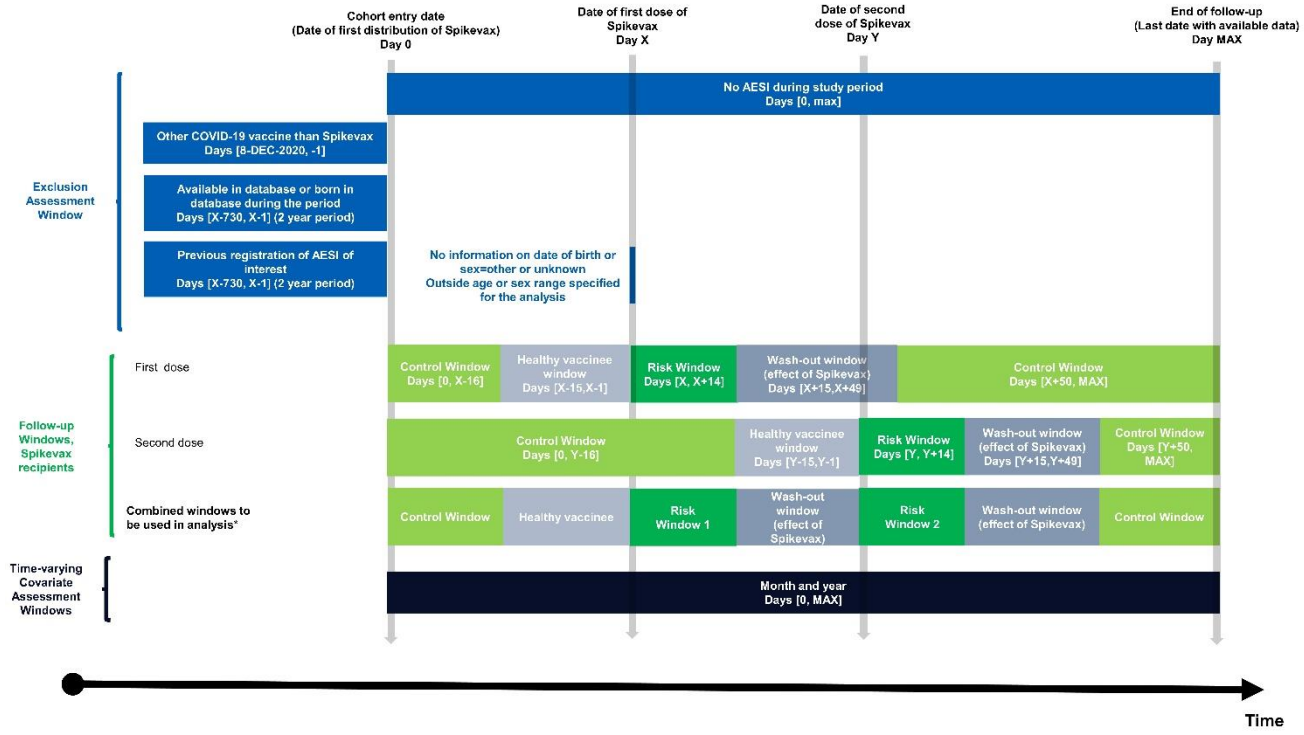
Figure 6. Visualization of SCCS design by dose with the risk window 0 to 2 days



Note: Date of first distribution of Spikevax was 11-JAN-2021 in Denmark, Norway, and Spain and 01-APR-2021 in the UK.

Follow-up was also stopped on the earliest of following events if they occurred inside one of the specified windows: death (only if the AESI do not increase the risk of death), database disenrollment, or last date with available data (31-DEC-2021 in Norway; 21-MAR-2022 in UK; 30-JUN-2022 in Denmark and Spain).

Figure 7. Visualization of standard SCCS design with the risk window 0 to 14 days



Note: Date of first distribution of Spikevax was 11-JAN-2021 in Denmark, Norway, and Spain and 01-APR-2021 in the UK.

Follow-up was also be stopped on the earliest of the following events if they occurred inside one of the specified windows: death (only if the AESI do not increase the risk of death), database disenrollment, get another COVID-19 vaccine, or last date with available data (31-DEC-2021 in Norway; 21-MAR-2022 in UK; 30-JUN-2022 in Denmark and Spain).

* If a time period was a risk window for any Spikevax doses, then it was a risk window in the combined definition. If a time period was an induction/wash-out window and not a risk window for any Spikevax doses, then it was an induction/wash-out window in the combined definition. If a time period was a healthy vaccinee window and not a risk window or induction/wash-out window for any Spikevax doses, then it was a healthy vaccinee window in the combined definition. If a period was a control window and not a risk window, induction/wash-out window, or healthy vaccinee window for any Spikevax doses, then it was a control window in combined definition.

Table 6 summarises design decisions for each AESI which we investigated with SCCS. Decisions about selection of the primary and sensitivity doses followed the principles described above in Table 3. However, for AESIs that could be contraindications to further Spikevax vaccinations we could not include an analysis of any dose, because we could only perform

analyses separately for each dose of Spikevax. Decisions about primary risk windows followed the principles described above in Table 3 and we further considered below rules for identifying different types of windows in the SCCS design:

We only considered risk windows in the interval 0-42 days after each dose of Spikevax.

Days between day 0 and 49 relative to each dose of Spikevax was assumed to be an induction window or washout window if it is not included in a risk window. Thus, these days would not be included in the control window.

Fourteen days to one day before each administration of each Spikevax dose was defined as a healthy vaccinee window/pre-exposure risk window if it was not included in a risk window or a washout/induction window.

For AESIs that were not considered contraindications to Spikevax vaccination we performed the standard SCCS, where control windows included all time between the date of distribution of Spikevax and end of follow-up except windows specified as risk windows, induction/washout windows, or healthy vaccinee windows as illustrated in Figure 7.

For AESIs that were considered contraindications to Spikevax vaccination or thought to reduce the likelihood of ever getting Spikevax, we could only perform SCCS separately for each dose of Spikevax with inclusion at the date of the specified dose. Control windows were selected independently for each dose to ensure that we would not include days in the control window where the patient could have been vaccinated with the next dose of Spikevax according to the official information about time intervals between subsequent doses. We set the start of the control windows earlier than in the standard SCCS to enhance the chance of observing enough days in the control windows and because AESIs that are contraindication to vaccination are likely to be proximal in time to the date of vaccination. This also means that the length of induction/wash-out windows was reduced. For the first dose of Spikevax, we pre-specified that the control window should end no later than day 27, because the minimum recommended interval between dose 1 and 2 of Spikevax was 28 days. For the second and third dose of Spikevax, we pre-specified that the control window should end no later than day 75. The selection of the end of the control window was based on the minimum interval between subsequent doses recommended in any of the settings and with exclusion of the 14-day healthy vaccinee window. In the UK, the minimum recommended interval between the second and third dose was 3 months (≈90 days) (70). In Denmark and the UK, those special groups that have been recommended a fourth dose earlier than the general population had an interval of minimum 3 months between the third and the fourth dose (71, 72).

In all analyses, follow-up ended at database disenrollment (for other reasons than death) or at the last date of available data. Whenever the AESI is assumed not to increase the risk of death, we assumed that the event was independent of the end of follow-up and we stopped follow-up at time of death (68). If the AESI is not a contraindication to COVID-19 vaccination (and thus analysed by what we term standard SCCS), we censored follow-up if a person got a different COVID-19 vaccine (or fourth dose of Spikevax). We assumed that getting another vaccine would impact the risk of getting the AESI. This type of censoring does not violate any

SCCS assumptions, if getting the AESI and changing vaccines are independent events which we assumed they were (68). We did not include receipt of other COVID-19 vaccines a reason to end follow-up in the by dose design performed for AESIs that might be a contraindication to vaccination. Getting another COVID-19 vaccine could be an indication that the AESI had not yet occurred, as the AESI would most likely also be a contraindication to other COVID-19 vaccines. Thus, stopping follow-up at other COVID-19 vaccines would be informative end of follow-up. However, we limited the observation period after each dose of Spikevax to the minimum interval recommended between consecutive doses as described above, to minimize the risk of including time windows with exposure to other COVID-19 vaccines into the control windows.

For the analyses, we defined all AESIs as non-recurrent events (i.e., only included their first occurrence within the study period), because of difficulty in distinguish an ongoing condition from a new onset within the relatively short study periods using the secondary routinely collected data at hand.

Table 6. Overview of SCCS design for each AESI

AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
(Idiopathic) Thrombocytopenia	By dose	Primary dose: Second dose	0-14 (primary); 0-14 and removing any time that are also part of healthy vaccinee windows (sensitivity); 0-42 (sensitivity); 7-14 (sensitivity)	43-75	Leave the database, or last date with available data
		Sensitivity dose 1: First dose	0-14	15-27	
		Sensitivity dose 2: Third dose	0-14	43-75	
		Sensitivity dose 3: NA	NA	NA	

AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
Stress-induced cardiomyopathy	Standard SCCS	Primary dose: Second dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity); 1-28 (sensitivity); 15-42 (sensitivity)	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data
		Sensitivity dose 1: Any dose	1- 42		
		Sensitivity dose 2: First dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Arrhythmia	Standard SCCS	Primary dose: Any dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity); 1-28 (sensitivity); 15-42 (sensitivity)	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another COVID-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data
		Sensitivity dose 1: First dose	1- 42		
		Sensitivity dose 2: Second dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Myocarditis	By dose	Primary dose: Second dose	0-7 (primary); 0-21 (sensitivity	28-75	Leave the database, or last date with available data
		Sensitivity dose 1: First dose	0-7	8-27	

AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
		Sensitivity dose 2: Third dose	0-7	28-75	
		Sensitivity dose 3: NA	NA	NA	
Pericarditis	By dose	Primary dose: Second dose	0-7 (primary); 0-21 (sensitivity	28-75	Leave the database, or last date with available data
		Sensitivity dose 1: First dose	0-7	8-27	
		Sensitivity dose 2: Third dose	0-7	28-75	
		Sensitivity dose 3: NA	NA	NA	
Cerebrovascular disease	Standard SCCS	Primary dose: Any dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity); 1-28 (sensitivity); 15-42 (sensitivity)	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data
		Sensitivity dose 1: First dose	1- 42		
		Sensitivity dose 2: Second dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Deep vein thrombosis	Standard SCCS and adjustment for month and year	Primary dose: Any dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity); 1-28 (sensitivity);	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data

AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
			15-42 (sensitivity)		
		Sensitivity dose 1: First dose	1- 42		
		Sensitivity dose 2: Second dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Splanchnic vein thrombosis	Standard SCCS and adjustment for month and year	Primary dose: Second dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity); 1-28 (sensitivity); 15-42 (sensitivity)	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data
		Sensitivity dose 1: Any dose	1- 42		
		Sensitivity dose 2: First dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Acute liver injury	Standard SCCS	Primary dose: Second dose	1-42 (primary); 1-42 and removing any time that are also part of healthy vaccinee windows (sensitivity);	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data

AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
			1-28 (sensitivity); 15-42 (sensitivity)	induction/wash out windows	
		Sensitivity dose 1: Any dose	1- 42		
		Sensitivity dose 2: First dose	1- 42		
		Sensitivity dose 3: Third dose	1- 42		
Generalised convulsions	Standard SCCS	Primary dose: Any dose	0-14 (primary); 0-14 and removing any time that are also part of healthy vaccinee windows (sensitivity); 0-2 (sensitivity); 0-28 (sensitivity)	First distribution of Spikevax to end of follow-up disregarding time in risk windows, healthy vaccinee window and induction/wash out windows	Receive another covid-19 vaccine or fourth dose of Spikevax, leave the database, or last date with available data
		Sensitivity dose 1: First dose	0-14		
		Sensitivity dose 2: Second dose	0-14		
		Sensitivity dose 3: Third dose	0-14		
Anaphylaxis	By dose	Primary dose: First dose	0-2 (primary); 0-6 (sensitivity)	7-27	Leave the database, or last date with available data
		Sensitivity dose 1: Second dose	0-2	28-75	
		Sensitivity dose 2: Third dose	0-2	28-75	

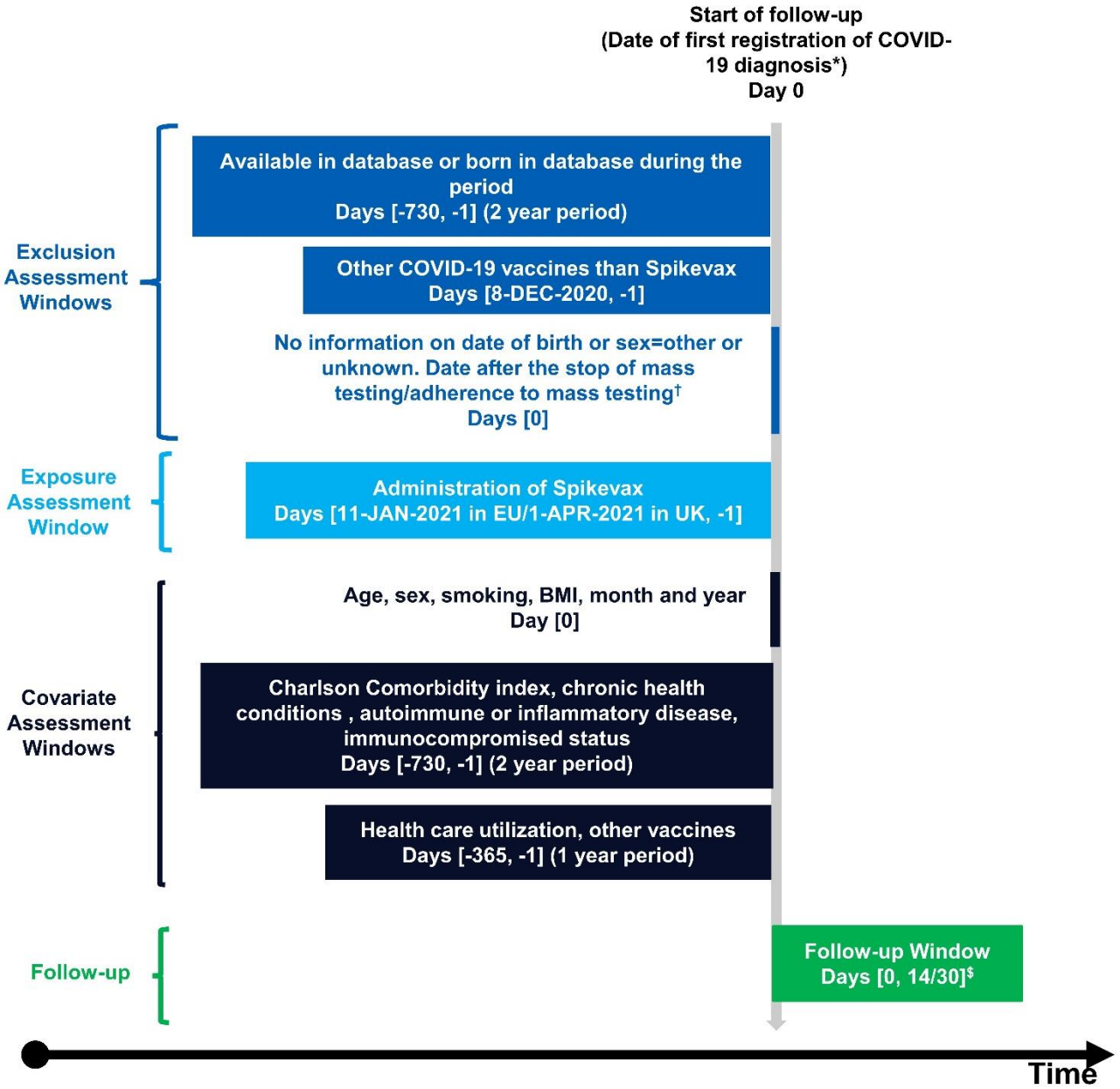
AESI	Analysis*	Doses investigated	Risk windows, days	Control windows, days	End of follow-up†
		Sensitivity dose 3: NA	NA	NA	
Vaccine-induced immune thrombotic thrombocytopenia	By dose	Primary dose: Second dose	0-14 (primary); 0-21 (sensitivity); 7-27 (sensitivity)	28-75	Leave the database, or last date with available data
		Sensitivity dose 1: First dose	0-14	15-27	
		Sensitivity dose 2: Third dose	0-14	28-75	
		Sensitivity dose 3: NA	NA	NA	

Abbreviations: NA=Not available
* For AESIs that were not a contraindication to Spikevax vaccination, we performed standard SCCS using control windows both before and after Spikevax vaccination (if within the defined study period). For AESIs specified as a contraindication for Spikevax or for which medical doctors or patients are likely to perceive them as a contraindication, the analysis was done by dose with population selection decided for each dose and only time after that specific dose was included in the analysis.
† For all AESIs we also included a sensitivity analysis where infection with COVID-19 was included as an additional criterion for end of follow-up.

9.1.3. *Cohort study of VAED*

As the base population for this cohort, we identified those who were alive, members of a given database and diagnosed with COVID-19 (based on positive polymerase chain reaction (PCR) test result or diagnosis code for COVID-19) from the first distribution of Spikevax in each country (11 January 2021 in Denmark, Norway, and Spain and 01 April 2021 in UK) and until 30 days before last date with available data. We excluded persons that had received COVID-19 vaccines other than Spikevax before the COVID-19 disease. Thus, we defined the exposed group as those receiving any Spikevax vaccination before the COVID-19 disease and the unexposed group was those without a record of a COVID-19 vaccination before the COVID-19 disease. We followed the included patients for 14 days for hospitalisations and 30 days for intensive care unit admissions and mortality. The design is illustrated in Figure 8.

Figure 8. Visualization of the design of the cohort study to examine VAED



* We only included COVID-19 diagnosis after the first distribution of Spikevax (11-JAN-2021 in Denmark, Norway, and Spain and after 1.APR-2021 in the UK) and until 30 days before the last date with available data (31-DEC-2021 in Norway; 21-MAR-2022 in UK; 30-JUN-2022 in Denmark and Spain)

† The strategy for testing for COVID-19 disease has varied over the epidemic. In more recent periods, mass testing for all have been stopped and testing have been reserved for special situations/patients. Therefore, we exclude persons recorded with COVID-19 after the stop of mass testing/adherence to mass testing in each country (12-FEB-2022 in Norway; 9-MAR-2022 in Denmark, 28-MAR-2022 in Spain, and 31-MAR-2022 in UK). For further information see Section 9.9.5.

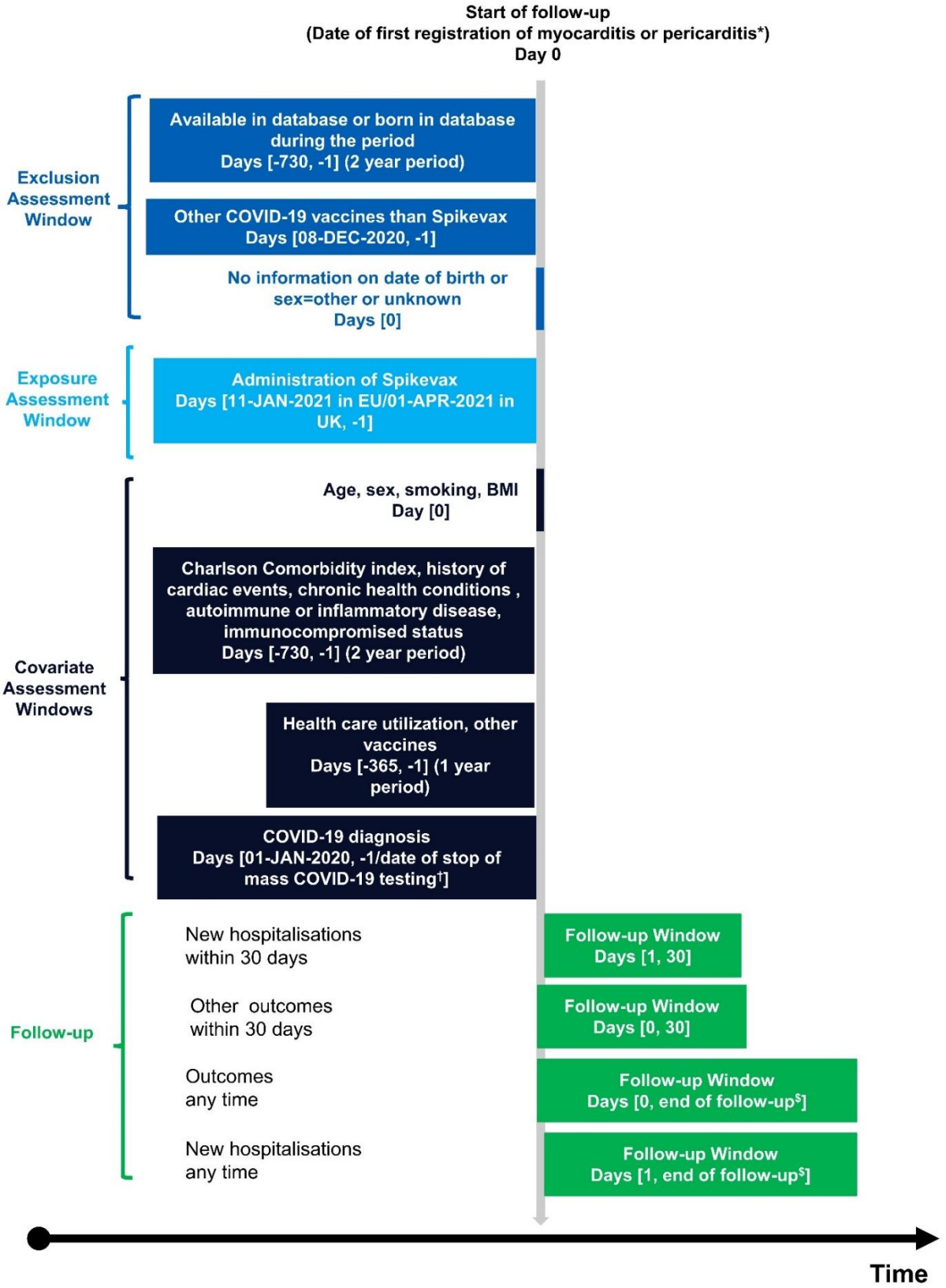
$ The patients were followed for 14 days for recordings of hospital admissions and for 30 days for recordings of admissions to intensive care units and deaths.

9.1.4. *Cohort study of outcomes of myocarditis and pericarditis*

In the cohort study to assess outcomes of myocarditis/pericarditis, we included all cases of myocarditis and pericarditis in Spikevax vaccinated persons and persons not vaccinated with

any COVID-19 vaccines at any time prior to event onset. We followed these patients for hospitalisations and deaths within 30 days and hospitalisations and deaths until end of follow-up. The design is illustrated in Figure 9.

Figure 9. Visualization of the design of the study of outcomes of myocarditis and pericarditis



* We only included patients diagnosed with myocarditis/pericarditis after the first distribution of Spikevax (11-JAN-2021 in Denmark, Norway, and Spain and after 1.APR-2021 in the UK) and until 30 days before the last date with available data (31-DEC-2021 in Norway; 21-MAR-2022 in UK; 30-JUN-2022 in Denmark and Spain)

† The strategy for testing for COVID-19 disease has varied over the epidemic. In more recent periods, mass testing for all have been stopped and testing have been reserved for special situations/patients. Therefore, we only included COVID-19 diagnosis occurring before the stop of mass testing/adherence to mass testing in each country (12-FEB-2022 in Norway; 9-MAR-2022 in Denmark, 28-MAR-2022 in Spain, and 31-MAR-2022 in UK). For further information see Section 9.9.5.

$ earliest of outcome of interest, death, database disenrollment, or last date with available data (31-DEC-2021 in Norway; 21-MAR-2022 in UK; 30-JUN-2022 in Denmark and Spain).

9.2. Setting

This study is based on electronic, routinely collected data from regional or national databases of the participating countries. All participating countries have universal health care for the inhabitants, and their participating databases contain linkable routinely collected data from the primary and/or secondary health sector, including information on births, deaths, diagnoses, and prescribed drug use (Section 9.4 provides additional details).

9.2.1. *Study periods*

For the analyses involving Spikevax recipients, the earliest inclusion date was the date of first distribution of Spikevax: 11 January 2021 in Denmark, Norway, and Spain; and 01 April 2021 in the UK. The follow-up ended on the date recommended for each database based on reliability of the data on the date of the most recent extraction: 31 December 2021 in Norway, 21 March 2022 in the UK, and 30 June 2022 in Denmark and Spain. The purpose of the historical cohort was to define background rates of the AESI, from 01 January 2017 until 31 December 2019. To ensure inclusion of incident AESIs, persons with a given AESI in the 2 years before the follow-up start were excluded from the analysis. Thus, the total data coverage from the lookback period for the historical cohort until the end of the follow-up in the current analysis extended from 01 January 2015 until 30 June 2022.

9.3. Subjects

The overall source population is the population contributing to the participating databases. The inclusion and exclusion criteria for the study populations based on study phase/design are described below.

9.3.1. *Signal detection*

For the signal detection phase, we defined the Spikevax cohort and the historical cohort.

Spikevax cohort

The source population for this cohort were members of a given database who had a record of receiving at least one dose of Spikevax in the period from 11 January 2021 in Denmark, Norway, and Spain; and from 01 April 2021 in the UK and until the last date with available data in each database (see Section 9.2.1). The inclusion and exclusion criteria were reapplied on each date of Spikevax vaccination for each person, thus creating a separate cohort defined by each dose of Spikevax. We applied the following exclusion criteria:

1. Age ≥ 2 years on the date of Spikevax vaccination and were not members of the database in the previous 2 years before administration of Spikevax (no 2-year

lookback)

2. Age < 2 years on date of Spikevax vaccination and not a member of the database since birth
3. Missing date of birth
4. Missing data on sex
5. In each AESI-specific analysis, persons with a prevalent AESI in 2 years before the Spikevax administration
6. Receipt of another COVID-19 vaccine before the date of receiving Spikevax

The follow-up started on the date of receiving each dose of Spikevax. As increased rates for some AESIs might only be expected during a limited time interval after vaccination with Spikevax, analyses were performed with follow-up ending on the following number of days after each dose of Spikevax vaccination (also known as the end-of-risk-window): 2, 14, 28, 42, or until last date with available data (note: the specified days will be included for assessing AESIs and person-years at risk). Thus, in the analyses to identify observed events subjects were followed until the earliest date of the following: AESI of interest, death, database disenrollment, receipt of another dose of Spikevax or another COVID-19 vaccine, end-of-risk-window, or last date with available data. In analyses to identify the person years to be used to estimate expected events, subjects were followed until the earliest date of the following: death, database disenrollment, receipt of another dose of Spikevax or another COVID-19 vaccine, end-of-risk-window, or last date with available data.

Historical cohort

The source population for this cohort were members of a given database who either were alive on 01 January 2017 (01 January 2018 in Norway) or were born between 01 January 2017 (01 January 2018 in Norway) and 31 December 2019 followed through 31 December 2019. We applied the following exclusion criteria:

1. Age ≥ 2 years on 01 January 2017 (01 January 2018 in Norway) and were not a database member between 01 January 2015 (01 January 2016 in Norway) to 31 December 2016 (31 December 2017 in Norway) (no 2-year lookback)
2. Age <2 years on 01 January 2017 (01 January 2018 in Norway) and not a member of the database since birth.
3. Missing date of birth
4. Missing data on sex
5. In each AESI-specific analysis, persons with a prevalent AESI in 2 years before start of follow-up

Persons in this cohort were followed from 01 January 2017 (01 January 2018 in Norway) (or from date of birth if born after 01 January 2017 [01 January 2018 in Norway]) and until the

earliest date of the following: AESI of interest, death, database disenrollment, or 31 December 2019.

9.3.2. *Signal evaluation*

Self-controlled case series design

For SCCS we identified all persons who had a recording of the specified AESI during the study period running from 11 January 2021 (Denmark, Norway, and Spain) or 01 April 2021 (UK) to 31 December 2021 (Norway), 21 March 2022 (UK), or 30 June 2022 (Denmark and Spain).

Among these persons we made the following exclusions:

1. Did not get any Spikevax vaccination during follow-up
2. Age ≥ 2 years on the date of cohort entry and were not members of the database in the previous 2 years before administration of Spikevax (no 2-year lookback)
3. Age <2 years on date of cohort entry and not a member of the database since birth
4. Missing date of birth
5. Missing data on sex
6. In each AESI-specific analysis, persons with a prevalent AESI in 2 years before the cohort entry
7. Receipt of another COVID-19 vaccine before the date of cohort entry

In this population, we further selected the main population and sensitivity populations based on age and sex as specified in Table 5, Section 9.1.2.

For the standard SCCS the date of cohort entry was the start of the study period 11 January 2021 (Denmark, Norway, and Spain) or 01 April 2021 (UK), for the SCCS by dose the date of cohort entry was the date of vaccination with each dose of Spikevax.

9.3.3. *Cohort study of VAED*

The source population for this cohort were members of a given database who had a record of COVID-19 infection in the period from 11 January 2021 in Denmark, Norway, and Spain and from 01 April 2021 in the UK and until 30 days before the last date with available data in each database (31 December 2021 in Norway, 21 March 2022 in the UK, and 30 June 2022 in Denmark and Spain). We applied the following exclusion criteria on the date of the recording of COVID-19 infection:

1. Age ≥ 2 years on the date of COVID-19 infection and were not members of the database in the previous 2 years before COVID-19 infection (no 2-year lookback)
2. Age < 2 years on date of COVID-19 infection and not a member of the database since birth

3. Missing date of birth
4. Missing data on sex
5. Receipt of another COVID-19 vaccine before the date of COVID-19 infection
6. The date of recording COVID-19 infection was after the of stopping mass testing/adherence to mass testing in each country (12-FEB-2022 in Norway; 9-MAR-2022 in Denmark, 28-MAR-2022 in Spain, and 31-MAR-2022 in UK). For further information see Section 9.9.5.

9.3.4. *Cohort study of outcomes of myocarditis and pericarditis*

Identification of myocarditis and pericarditis cases was done as two separate cohorts, but following the same principles as described below.

We identified all persons who had a recording of myocarditis/pericarditis during the study period running from 11 January 2021 in Denmark, Norway, and Spain; from 01 April 2021 in the UK and until 30 days before the last date with available data in each database (31 December 2021 in Norway, 21 March 2022 in the UK, and 30 June 2022 in Denmark and Spain).

We applied the following exclusion criteria on the date of the recording of myocarditis/pericarditis:

1. Age ≥ 2 years on the date of myocarditis/pericarditis diagnosis and were not members of the database in the previous 2 years before myocarditis/pericarditis diagnosis (no 2-year lookback)
2. Age < 2 years on date of myocarditis/pericarditis diagnosis and not a member of the database since birth.
3. Receipt of another COVID-19 vaccine than Spikevax before the date of myocarditis/pericarditis diagnosis.
4. Missing date of birth
5. Missing data on sex

9.4. Variables

9.4.1. *Exposure: Spikevax vaccination*

We used dates of Spikevax vaccination as recorded in the routinely collected data in the participating databases. Whenever the administration date of Spikevax vaccination was recorded, this was used as the date of Spikevax vaccination. If the administration date was not recorded, the date of recording of the Spikevax vaccination was used as the date of Spikevax vaccination. Whenever dates of Spikevax vaccination were 20 or less days apart, the

earliest date of Spikevax vaccination was retained. We chronologically classified doses of Spikevax vaccination dose 1, dose 2, dose 3, or later doses.

9.4.2. *Adverse events of special interest*

For the Fourth Interim Report, we identified the AESIs other than "Death of any cause" based on diagnosis codes recorded during routine health care, using database specific standard vocabularies (ICD-10 [Danish modification] in Denmark, ICD-10CM in Spain, ICD-10 in Norway, and MEDCODEIDs in the UK). Codes were identified by mapping relevant concepts in a clinical definition using the application CodeMapper with a subsequent clinical review, to make a semiautomatic and transparent identification of case definitions using codes from different coding systems (73). As CodeMapper does not include MEDCODEIDs, all codelists in the CPRD were mapped manually using previous evidence and local clinical expertise. Many of the definitions have been used in the ACCESS project, an EMA-commissioned study to estimate background rates of the COVID-19 vaccine AESIs (64, 74). Whenever necessary, the ACCESS definitions were refined and missing definitions added. Whenever relevant, published studies have been consulted for earlier definitions. The process of refinement has been ongoing since the Third Interim Report. The process of technical and clinical review is ongoing and is being currently conducted by the VAC4EU task force dedicated for this task.

For the AESIs anaphylaxis, diabetes type 1, and heart failure, definitions of prevalent events were broader than definitions of incident events. For anaphylaxis and diabetes type 1, prevalent events were identified based on medication proxy in addition to a diagnosis code. For heart failure, definition of prevalent events included chronic conditions. The principle behind this approach is prioritizing sensitivity of an algorithm when excluding persons with prevalent events and prioritizing specificity of an algorithm when identifying endpoints. However, for Norway it was not possible to use medication proxies (see more in Section 9.9.5). An overview of the included codes is given in the standalone document Appendix 1_codelist and algorithms.

The AESI "Death of any cause" was defined for persons with a non-missing date of death using the recorded death date.

In some countries it was not possible to measure some of the AESIs for reasons such as lacking extraction of the needed codes, missing codelists for a specific vocabulary, codes only available for some of the study period, and codes only extracted on "parent" level (e.g., ICD10 codes on the three-digit level). Overall, this resulted in no reporting on acute kidney injury and multisystem inflammatory syndrome in Denmark, no reporting on narcolepsy, sudden death, chilblain–like lesions, anosmia and ageusia, erythema multiforme, anaphylaxis, and multisystem inflammatory syndrome in Norway, and no reporting of narcolepsy and sudden death in Spain (Specific reason for each country and AESI is given in Section 9.9.5). In Norway, due to unavailability of specific ICD-10 codes I01.2 "Acute rheumatic myocarditis", I09.0 "Rheumatic myocarditis", and I51.4" "Myocarditis, unspecified", persons identified with AESI myocarditis may also include persons with all subcodes of the respective parent codes I01 "Rheumatic fever with heart involvement", I09 "Other rheumatic heart diseases", I51 "Complications and ill-defined descriptions of heart disease". The AESI pericarditis in Norway,

in addition to the specific codes "I01.0 Acute rheumatic pericarditis" and "I24.1 Dressler's syndrome", the AESI definition includes all subcodes in the respective codes I01 "Rheumatic fever with heart involvement", and I24 "Other acute ischaemic heart diseases". Because of myocarditis and pericarditis being a known signal and for the sake of transparency, it was decided to proceed with signal detection and evaluation of the AESI myocarditis and AESI pericarditis in all countries with available data. For the sake of simplicity, in this Fourth Interim Report, the terminology "myocarditis" and "pericarditis" has been retained.

9.4.3. *Other outcomes*

Table 7 gives an overview of the outcomes included in the study of VAED. It was not possible to distinguish if the outcome occurred because of COVID-19 or if the outcome occurred in persons having COVID-19, but without the two events being related.

Table 7. Overview of outcomes included in the analysis of VAED

Outcome	**Definitions**
Hospitalisation	A record of a hospitalisation from the date of COVID-19 diagnosis and the subsequent 14 days
Admission to intensive care	A record of an admission to an intensive care unit from the date of COVID-19 diagnosis and the subsequent 30 days
Death	Date of death from the date of COVID-19 diagnosis and the subsequent 30 days

9.4.4. *Subpopulations*

Per protocol, the following five subpopulations were identified for the secondary objectives.

- Women of childbearing age, defined as females who were between 12 and 49 years of age (both ages included) at the start of follow-up
- Patients with chronic health conditions (used in current analysis as a proxy to RMP-specified subgroup "frail subjects with unstable health conditions and chronic co-morbidities")
- Patients with autoimmune or inflammatory disorders
- Patients with indicators of immunocompromised status
- Patients previously diagnosed with COVID-19 infection

Table 8 gives an overview of the conditions included in each subpopulation identified based on diagnosis codes. Table 8 also include information related to the use of medication proxies for some categories (no medication proxies were applied in Norway for the current report).

Table 8. Overview of the definitions of the subpopulations.

Subpopulation	Main disease categories	Sub-disease categories (all identified by diagnosis codes)	Medication proxies
Patients with chronic health conditions	Cardiovascular disease	Infarction myocardial	Yes
		Angina pectoris	
		Arrhythmia	
		Heart failure	
		Myocarditis	
		Pericarditis	
		Heart disease valvular	
		Haemorrhage cerebral stroke	
		Infarction cerebral stroke	
		Capillary leak syndrome	
		Deep vein thrombosis	
		Hypertension	
		Microangiopathy	
		Vascular disease peripheral	
		Arterial thromboembolism	
		Cardiomyopathy	
		Pulmonary embolism	
		Ischemic cerebral attack transient	
		Vasculitis any	
		Thromboembolic venous all	
	Diabetes types 1 and 2		Yes
	Chronic Neurological diseases	Generalised convulsions	No
		Dementia	No
		Demyelination multiple sclerosis	No
		Hemiplegia	No
		Parkinson’s disease	No
		Neuron motor disease	No
		Down's syndrome	No
		Learning disability	No
		Cerebral palsy	No
		Haemorrhage cerebral stroke	No
		Infarction cerebral stroke	No
		Ischemic cerebral attack transient	No
	COPD		Yes
Patients with autoimmune or inflammatory disorders	Arthritis rheumatoid		No
	Autoimmune thyroiditis		No
	Vasculitis any		No
	Gout		No
	Diabetes type 1		Yes
	Demyelination multiple sclerosis		No
	Systemic lupus erythematosus		No
	Psoriatic arthritis		No
	Sjögren's syndrome		No

Subpopulation	Main disease categories	Sub-disease categories (all identified by diagnosis codes)	Medication proxies
	Polymyalgia rheumatica		No
	Psoriasis		No
	Inflammatory bowel disease, (ulcerative colitis, and Cohn's disease)		No
	Arthritis spondylarthritis, any		No
Patients with indicators of immunocompromised status	Autoimmune or inflammatory disorders	Arthritis rheumatoid	No
		Autoimmune thyroiditis	No
		Vasculitis any	No
		Gout	No
		Diabetes type 1	Yes
		Demyelination multiple sclerosis	No
		Systemic lupus erythematosus	No
		Psoriatic arthritis	No
		Sjögren's syndrome	No
		Polymyalgia rheumatica	No
		Psoriasis	No
		Inflammatory bowel disease, (ulcerative colitis, and Cohn's disease)	No
		Arthritis spondylarthritis, any	No
	Immunodeficiencies, any		No
	Specific haematological neoplasms		No
	Organ transplant recipient		No
Patients previously diagnosed with COVID-19 infection	COVID-19	Defined based on diagnosis codes and/or PCR test results	No

An overview of the included codes is given in the standalone document "Appendix 1_codelist and algorithms.xls".

9.4.5. *Co-morbidities*

For each person we estimated the Charlson co-morbidity index based on diagnosis codes recorded within the two years preceding the start of follow-up (75). We grouped the score on the Charlson co-morbidity index into the following groups: 0, 1, or ≥2.

For the analysis of the outcomes of myocarditis and pericarditis, we defined the variable "History of cardiac events" as a record of diagnosis codes for any of the conditions listed below within the two years preceding the start of follow-up:

- Heart failure
- Myocarditis
- Pericarditis

- Heart disease, valvular
- Cardiomyopathy
- Arrhythmia

An overview of the included codes is given in the standalone document Appendix 1_codelist and algorithms.

9.4.6. *Health resource utilization*

We defined several variables that would indicate the use of health care within the year before the start of follow-up:

- *At least one vaccine (other than COVID-19 vaccines): Yes, no*
- *At least one inpatient hospitalisation: Yes, no*
- *At least one outpatient hospital or specialist contact: Yes, no*
- *Primary care contacts: 0-1, ≥2*

9.4.7. *Other variables*

We defined sex as recorded in each database.

We defined age based on the date of birth. We measured age in years and grouped age into the following age groups for reporting of results:

- Children and adolescents (0-17 years)
  - Children (<12 years)
  - Adolescents (12 – 17 years)
- Adults (18 – -64 years)
  - 18 – 24 years
  - 25 – 34 years
  - 35 – 44 years
  - 45 – 54 years
  - 55 – 64 years
- Elderly (≥65 years)
  - 65 – 74 years
  - 75 – 79 years

- ≥80 years

9.5. Data sources and measurement

Below is first an overall description of all participating databases, which is followed by a more detailed description of the data sources used for different variables.

9.5.1. *Data sources*

Denmark: National registries

All Danish registers used in this study have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information (76). Unambiguous person-level linkage across all data sources is possible via a unique identifier used in all Danish public records, originally developed for taxation. Results on this study are based on data from the following registries: the Danish National Prescription Registry (tracks dispensing of prescription medications from 1995, including dispensing date, Anatomical Therapeutic Chemical (ATC) code, product code and amount). The Danish National Health Service Register (records general practitioner (GP) contacts including examinations, procedures, pregnancy-related visits and vaccinations [other than COVID-19], but no diagnosis codes are included); the Danish Civil Registration System (sex, date of birth, migration, vital status); the Danish National Patient Registry (records diagnoses and procedures from all hospitalizations since 1977 and all hospital encounters since 1995); Danish Vaccination Registry (COVID-19 vaccinations). The Danish databases were characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits, and risk assessment and could participate in near real-time monitoring (77). Danish registries are listed as a resource in the EU PAS Register (https://www.encepp.eu/encepp/viewResource.htm?id=42187).

Norway: National registries

All Norwegian registers used in this study have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.4 million inhabitants plus historical information. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. The Norwegian national identity number was introduced in the 1960s. This identifier is assigned to every person at birth or upon immigration; it is 11 digits long and encodes date of birth and sex. The identifier is included in all national registries, allowing accurate linkage among them. The Norwegian data sources included the following national registers: the National Registry and Statistics Norway (data on sex, date of birth, migration, vital status); the Norwegian Immunisation Registry (SYSVAK) (information on COVID-19 vaccinations and other vaccines); the Norwegian Surveillance System for Communicable Diseases (information on results of PCR SARS-Cov-2 tests), and the Norwegian Patient Registry.

Spain: SIDIAP

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' - SIDIAP; www.sidiap.org) was created in 2010 by the Catalan Health Institute (CHI) and the IDIAPJGol Institute (78). It includes information collected since 01 January 2006 during routine visits at 278 primary care centres pertaining to the CHI in Catalonia (North-East Spain) with 3,414 participating GPs. SIDIAP has pseudo-anonymised records for 5.7 million people (80% of the Catalan population) being highly representative of the Catalan population. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs, paediatricians, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals and primary care laboratory test results. It can also be linked to other data sources, such as the hospital discharge database, on a project-specific basis. Health professionals record this information using the clinical modification of International Classification of Diseases, 10th Revision (ICD-10CM) codes, ATC codes and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. In relation to vaccines, SIDIAP includes all routine childhood and adult immunizations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. The SIDIAP database is updated annually at each start of the year. With the COVID-19 pandemic, there is the possibility to have shorter term updates to monitor the evolution of the pandemic. Recent reports have shown the SIDIAP data to be useful for epidemiological research. SIDIAP is an ENCePP centre (https://www.encepp.eu/encepp/viewResource.htm?id=4646). The SIDIAP database was characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment (77).

UK: CPRD

The CPRD from the UK collects the computerised medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also record information stemming from specialist referrals, and hospitalizations. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Most of the data are coded in MEDCODEID, which are unique codes used by CPRD for the medical terms selected by the GPs (Read and SNOMED codes). The dataset is generalizable to the UK population based upon age, sex, socioeconomic class, and national geographic coverage. There are currently approximately 41 million patients (including transferred out and deceased patients acceptable for research purposes) – of which 13 million are active (still alive and registered with the GP practice) – in approximately 1345 practices (https://cprd.com/Data).

CPRD data includes information on demographics, GP/primary care healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, primary care prescriptions, immunisations and preventive treatments, death (date) and referrals to other care settings.

GPs receive information on diagnoses and procedures from hospital discharge and clinic summaries which, although not comprehensively recorded by GPs, can be coded in the GP medical records and translated into MEDCODEID codes within CPRD. Furthermore, information from hospital discharge and clinic summaries recorded by GPs as free text information is not available in CPRD.

CPRD is listed under the ENCePP resources database, and access was provided by the Drug Safety Research Unit (DSRU). The CPRD was not yet characterised in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been used in vaccine studies.

9.5.2. *Measurement*

COVID-19 vaccines

In Denmark, information on COVID-19 vaccination, including the date and the manufacturer, was obtained from the register of COVID-19 vaccines, which is a COVID-19 vaccination related subset of the Danish Vaccination Registry (79, 80). In Norway, information on COVID-19 vaccination, including the date and the manufacturer, was obtained from the Norwegian Immunization Registry (81). In Spain, information on all vaccines administered at primary care centres and at mass vaccination centres are available and include type of vaccine, the date of vaccination, and, for COVID-19 vaccine, the vaccine manufacturer. In the UK, information on COVID-19 vaccination is updated in the GP medical records by the NHS in connection with the administration of vaccines, conducted during consultations or from other NHS immunisation services. Dates of COVID-19 vaccination are recorded as the date associated with the vaccination and are available in the CPRD drug issue table. Information on the manufacturer is available from the product identification number.

Diagnoses and medication use

For this interim report, we defined the AESIs, the subpopulations, and co-morbidities based on diagnosis codes from various sources and in some cases, medication proxies from prescriptions or dispensings.

In Denmark information on diagnoses was obtained from the Danish National Patient Registry, which records diagnoses according to the Danish version of ICD-10 for all contacts with Danish hospitals. Information on medication use from the Danish National Prescription Registry included information on dates of dispensing and ATC-codes.

In Norway, information about hospital contacts was available from the Norwegian Patient Register, which used ICD-10 codes. Medication use was not available in the data extraction available for this report (see Section 9.9.5).

In Spain, the diagnoses originate from two different sources. 1) The registry of primary care

diagnoses includes medical diagnoses registered using ICD-10CM codes in primary care either as a result of a physical visit, telephone consultation or based on information obtained from other health care providers (e.g., hospital physicians). 2) The registry of hospital discharges included diagnoses registered during hospital contacts and are recorded according to ICD-10CM codes. In the current data extraction, only data since 2016 on hospital discharges were available. In SIDAP, information on medication originates from the registry of drug prescriptions redeemed at community pharmacies using ATC codes. Over the counter medication is not included and medication dispensed at hospital pharmacies are not included.

In the UK, information on diagnosis codes, in the form of MEDCODEIDs, were available in the CPRD table for observations, either as a result of a physical visit, telephone consultation or based on information obtained from other health care providers (e.g., hospital physicians). It is compulsory for specialists and hospitals to send a letter to GPs with information on the health service provided to the GP's patients during specialist or hospital contact. The GP or a trained staff member may update GP medical records based on information from specialists and hospitals that then become available in the CPRD observations table. However, free-text information from the patient's GP medical records is not available in CPRD. Information on medication use, in the form of PRODCODEIDs, were available in the CPRD Drug issue file which contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. We identified the PRODCOIDs for the medication proxies used for this report.

Health care resource utilization

Table 9 gives an overview of the availability of information on different variables of health care resource utilization in each database and, if available, the source of the information.

Table 9. Overview of availability and source of information on health resource utilization according to database

	Availability, source			
Variable	**Denmark**	**Norway**	**Spain (SIDIAP)**	**UK (CPRD)**
Vaccinated with other vaccines than COVID-19 vaccines during the previous year	The Danish National Health Service Register	The Norwegian immunization registry	SIDIAP vaccination table	CPRD Observation file and Drug issue file
At least one inpatient	The Danish National	The Norwegian Patient Register	Hospital discharge	Not available for this interim

	Availability, source			
Variable	**Denmark**	**Norway**	**Spain (SIDIAP)**	**UK (CPRD)**
hospitalisation within the previous year	Patient Registry		database	report
At least one outpatient hospital or specialist contact within the previous year	The Danish National Patient Registry	The Norwegian Patient Register	SIDIAP database and hospital discharge database	Not available for this interim report
Primary care contacts within the previous year	The Danish National Health Service Register	Not available for this interim report	SIDIAP database	CPRD Consultation file

Basic demographic characteristics: Deaths, database disenrollment, date of birth, sex

In Denmark, data on demographic characteristics were obtained from the Danish Civil Registration System, which records information on vital status, sex, and migrations (enrolment/disenrollment) of all Danish residents.

In Norway, data on demographic characteristics were obtained from the Norwegian Population Registry and from Statistics Norway, which record information on sex, vital status, and migrations (enrolment/disenrollment) for all Norwegian residents.

In Spain, the basic demographic characteristics are collected in the registry of persons assigned to a primary care physician in the Catalan region. A person keeps the same ID number even if they change primary care physician.

In the UK, the basic demographic characteristics are collected from a table of patients registered in a GP practice, which contribute to the CPRD. For persons above 15 years only year of birth is recorded, therefore we defined the date of birth as 01 July of the specified year of birth. For persons aged 0 to 15 years both month and year of birth is recorded, therefore we defined the date of birth as the 15 of the specified month and year. Persons are included in the CPRD database from the date they enrol in a practice contributing to CPRD, when the patient de-register from that practice the patient will be recorded as disenrolled. If the patient later should register at another practice contributing to CPRD, the patient will get an additional

record with a new id and enrolment date (it is not possible to link such records). If the patient later re-enrols at a practice where they have previously been enrolled, the earliest recordings of enrolment and disenrollment dates will be removed and only the latest enrolment (and potentially disenrollment) date will be retained.

COVID-19 cases

Presence of COVID-19 infection was defined using a combination of diagnosis codes for COVID-19 (identified in the same registries as described in Section 9.5.1) or positive PCR tests for COVID-19. Both primary and secondary diagnosis codes were used in identification, implying inclusion of persons contacting hospitals because of COVID-19 and because of other reasons with COVID-19.

In Denmark, information on positive COVID-19 PCR tests was obtained from the Danish Registry of COVID-19 tests. The Danish Departments of Clinical Microbiology and Statens Serum Institut carried out laboratory analysis, registration, and release of the national SARS-CoV-2 surveillance data for the present study. In Norway, information on positive COVID-19 PCR tests came from the Norwegian Surveillance System for Communicable Diseases. In Spain information on positive COVID-19 PCR tests, including test date, came from the registry of COVID-19 tests.

The strategy for testing for COVID-19 disease has varied over the pandemic. In more recent periods, mass testing for the entire population has been stopped and testing has been reserved for special situations/patients. Therefore, we did not consider recording COVID-19 infection or test after the stop of mass testing/adherence to mass testing in each country. (12-FEB-2022 in Norway; 9-MAR-2022 in Denmark, 28-MAR-2022 in Spain, and 31-MAR-2022 in UK). See Table 10 for reasons for the dates selected at each site and see Section 9.9.5 for further information on this decision.

Table 10. Overview of dates when COVID-19 mass testing was no longer performed in each country and the reason for the selected dates

Country	Date	Reason
Denmark	09-MAR-2022	On 10 March 2022, the Danish National Board of Health announces new regulations regarding testing for COVID-19. Now tests are only recommended for persons at increased risk of severe COVID-19, which include persons ≥65 years of age, pregnant women or persons who for other reasons are at increased risk of severe COVID-19 (82).
Norway	12-FEB-2022*	From the 12 February 2022, the Norwegian government removes the requirement that close contacts to a positive individual must take a PCR test. Hereafter, only adults with symptoms are recommended to test themselves. Children at schools and kindergarten (even in the presence of

Country	Date	Reason
		symptoms) do not have to test themselves anymore (83).
Spain	28-MAR-2022	The indication for doing COVID-19 diagnostic tests was modified on 23 March 2022 to be implemented on 28 March 2022. This new strategy focused on people with risk factors (over 60 years, immunosuppressed and pregnant), vulnerable areas (health and socio-sanitary) and serious cases. Surveillance focused on these groups. The diagnosis of patients with mild symptoms compatible with COVID-19 was made according to their clinical management needs (84).
United Kingdom	31-MAR-2022*	Free testing for the public ended on 01 April 2022 as part of the government's Living with COVID plan, but asymptomatic testing continued to be used in some settings during periods of high case rates (85).
*These dates are after the last date with available data for the present report. Therefore, it will not have an impact on the results.		

9.6. Bias

This study addresses potential bias both on design and the analysis stage. At the signal detection stage, bias related to different distribution of age and sex between the Spikevax cohort and the historical cohort was reduced using indirect standardization according to age and sex. In self-controlled designs, time-invariant confounders are inherently adjusted for, time-varying confounding is reduced by adjustment for month and year where indicated. For analysis of VAED, we adjust analyses for the measured potential confounders.

9.7. Study size

We included all eligible Spikevax recipients participating databases. Precision calculations based on the assumptions about the AESI rates were provided in the Study Protocol and the SAP.

9.8. Data transformation

This study uses the Vaccine monitoring Collaboration for Europe (VAC4EU, https://vac4eu.org/) research environment and the publicly available ConcePTION common data model (CDM) (86, 87). Each data access provider (DAP) extracted, transformed, and loaded (ETL) the data into the ConcePTION CDM, according their ETL design and the ETL instructions provided by the principal investigator. After transforming the original data into the CDM tables, the DAPs ran centrally distributed common scripts to generate study variables, perform analyses, and produce aggregated analysis results. These results were transferred to

the Digital Research Environment (DRE), where the final analyses and report tables where generated.

9.9. Statistical methods

The Final Study Report will be prepared in accordance with the SAP version in force at the time (currently SAP Version 2.0, dated 17 June 2022). This Section describes only the statistical methods relevant to the analyses reported in this report.

9.9.1. *Main summary measures*

In the descriptive analyses, we used frequencies and percentage for categorical variables. We used arithmetic means with standard deviations (SD) and medians with quartiles for continuous variables. We used incidence rates per 100,000 person-years and associated 95% CI to describe occurrence of AESIs and other outcomes.

9.9.2. *Main statistical methods*

Signal detection

We estimated the crude incidence rates per 100,000 person-years in the Spikevax cohort and in the historical cohort by dividing the number of observed incident AESI events by the number of person-years. The 95% CIs for rates were estimated using exact Poisson method. As most AESIs are expected to be rare, indirect standardization was used (53) to estimate SMRs for each AESI as the number of observed events divided by the number of expected events in Spikevax recipients. The number of expected events was estimated by multiplying the rate in historical cohort by the observed person time in strata based on sex and age (1 year age intervals until 95 years). We estimated 95%-CI of the SMRs using Byar's approximation (formula 2.13 p. 69) in Breslow and Day (88). The analyses were done separately by length of end-of-risk-period (2, 14, 28, 42, or until last date with available data) and by dose of Spikevax (1, 2, 3, any).

We reported the results according to sex (both sexes, female, and male) and age groups (<12 years, 12 – 17 years, 18 – 24 years, 25 – 34 years, 35 – 44 years, 45 – 54 years, 55 – 64 years, 65 – 74 years, 75 – 79 years, ≥80 years, children (<18 years), adults (18-64 years), elderly (≥ 65 years), and all ages).

Other designs

In this Section we briefly outline the methods separately for each study design. However, there are some considerations that are relevant for several designs. For other designs than the self-controlled analyses, we will always present an unadjusted estimate and an estimate adjusted for age, sex and potentially other key confounders (exact details are given for each analysis). When deciding which additional covariates to adjust for in the primary analysis, we followed the recommendation to include less parameters than the number of events divided by 10 (89).

Self-controlled case series

The SCCS design provided an estimate of the IRR and was implemented following the

guidelines in Whitaker et al. 2006 (90) and Petersen et al 2016 (69). For AESIs, we regarded as potential contraindications to vaccination we conducted the analyses by dose, with start of follow-up at the date of receiving each dose (91). The specifics of how we partitioned the observed time into risk windows, induction/wash-out windows, healthy vaccinee windows and control windows are described in Section 9.1.2, Table 6, Figure 6, and Figure 7. For AESIs where we judged that time-varying confounding was possible, we adjusted for month and year, by splitting the observation periods according to month and year.

In signal detection, the association measure was the SMR, in signal evaluation, the association measure was IRR, and in the cohort design of VAED, the measure of association was odds ratios (ORs). All measures of association were reported with 95% CIs.

9.9.3. *Missing values*

As this study is based on routinely collected health care data, absence of an AESI-defining diagnosis was assumed to indicate absence of the AESI rather than evidence of missing data on that AESI. In the rare cases of true missing data (e.g., <0.1% records in United Kingdom with missing information on sex), records were excluded from the analyses, and imputation was not attempted.

9.9.4. *Sensitivity analyses*

We performed the following sensitivity analyses for signal evaluation:

1) provided results for the doses that was not specified as the primary dose of interest (see Table 4)

2) Used alternative populations (see Table 5)

3) Used COVID-19 infection as an additional censoring criterion (for ARDS not used COVID-19 infection as a censoring criteria)

4) For self-controlled designs, used alternative risk windows (see Table 6)

9.9.5. *Amendments to the statistical analysis plan*

Amendment number	**Description of Amendment**
1	For diabetes type 1, myocarditis, and pericarditis, we did not completely follow the prespecified criteria for selection of sensitivity populations for signal evaluation. However, we ensured to have broad population selections for the sensitivity populations to ensure a full overview of all populations that could potentially be affected by AESIs. The reasons for this deviation were: - Diabetes type 1 usually occurs in younger persons and risk of misclassification between diabetes type 1 and 2 in older persons.

Amendment number	Description of Amendment
	- The risk groups implicated by other studies for myocarditis and pericarditis indicated potential for age and sex differences, which we wanted to reflect.
3	The strategy for testing for COVID-19 disease has varied over the pandemic. In more recent periods, mass testing for the entire population has been stopped and testing has been reserved for special situations/patients. This could lead to bias in analyses depending on the recording of COVID-19 infections if only patients with increased risk of severe COVID-19 disease would be recorded, as this could be related both to the likelihood of COVID-19 vaccination and AESIs. Therefore, we decided not to consider recordings of COVID-19 infection or test after the stop of mass testing/adherence to mass testing in each country (date are included in Table 10) for the following: - Definition of the subpopulation of patients previously diagnosed with COVID-19 - Definition of the population to be included in the study of VAED
4	Due to delays in data access, the Norwegian data delivery contained less information than planned, which could have some effects on the results: - The extracted population was reduced in two ways: First, the population for the historical cohort only included persons living in Norway on 1 January 2018 and onwards (this resulted in the historical cohort for signal detection covering 2018-2019 instead of 2017-2019 as planned). Second, immigrants to Norway who had not received the standard personal identification number was not included in the population, which overall resulted in a slightly reduced population and thereby precision. However, this should not introduce any systematic error. - The data extraction did not include information about medication and primary care contacts before 2018. We decided not to use diagnoses from primary care and medication proxies from Norway. Therefore, we only used information from hospital contacts to define AESIs and covariates. - The extracted data from hospital contacts did for most diagnoses only include ICD-10 codes at the three-digit level, i.e., "parent" codes only (except for COVID-19 related diagnoses). This means that whenever

Amendment number	Description of Amendment
	code lists only include specific "children subcodes", the occurrence of AESIs would be overestimated when using the "parent" code. This is evident, e.g., for the AESI narcolepsy in which use of the "parent" code (G47) results in inclusion of all types of sleeping disorders, and sudden death, in which case use of the "parent" code (I46) results in inclusion of any cardiac arrest (also those not resulting in sudden death). In addition, ICD-10 chapters L, T and R are not included in the current extraction (except R09, R73, R95, R96, R98, and R99), which meant that we did not capture AESIs chilblain–like lesions, anosmia and ageusia, erythema multiforme, and anaphylaxis. For multisystem inflammatory syndrome, only the code U10.9 ("Multisystem inflammatory syndrome associated with COVID-19") was included in the data extraction, therefore it was only possible to identify multisystem inflammatory syndrome in the Spikevax cohorts. Given the above, for Norway, we decided to not report results for narcolepsy, sudden death, chilblain–like lesions, anosmia and ageusia, erythema multiforme, anaphylaxis, and multisystem inflammatory syndrome. - Full information on emigration and immigration was not available (only the latest emigration status was available). Therefore, we could not exclude persons who had not been in the database the two years before the index date as this data was unknown to us. This resulted in slightly higher analysis populations and that some persons might have had the AESIs in the two years before the index date but had not been correctly excluded.
5	At the time of closing the codelist for the Fourth Interim Report, the codelist did not contain any codes for acute kidney injury from Danish modification of ICD-10. Also, the codelist only contained codes for multisystem inflammatory syndrome related to COVID-19 from Danish modification of ICD-10. Therefore, it was only possible to identify multisystem inflammatory syndrome in the Spikevax cohorts. Thus, we do not report any results on acute kidney injury and multisystem inflammatory syndrome from Denmark.
6	At the time of closing the codelist for the Fourth Interim Report, the codelist did not contain any codes for sudden death for ICD-10CM (used in Spain). Also, the codelist only included one parent code for narcolepsy in ICD-10CM, which was not used in the Spanish data. Therefore, we do not

Amendment number	Description of Amendment
	report results on narcolepsy and sudden death from Spain.

9.10. Quality control

All DAPs implemented local data management plans to ensure the quality of their handling of the local data, subject to standard quality control by the respective data custodians. After converting the original data to the CDM, the data underwent two levels of quality checks: level 1 (completeness) and level 2 (logical consistency). These level checks were reviewed with the DAPs and signed off when sufficient quality was ensured.

Analysis scripts underwent a review by a second programmer and were tested before deployment on an imputed dataset and later on a portion of the ETL data at each DAP. Double programming for some of the analyses are ongoing as an additional quality control. Country specific results were reviewed for plausibility by the principal investigators and the co-investigators in each country.

10. Results

The results are presented in the Appendix Tables listed in Section 15.1. Numbering of the tables encodes the AESI, country, and dose of Spikevax. Table 11 shows the indexing used for AESIs, doses, and countries.

Table 11. Overview of indexing used for table numbering to indicate AESI, dose of Spikevax, and country

Arabic numbers specifying AESI		Roman numbers specifying the dose of Spikevax		Upper case letter specifying Country	
AESI	**Arabic number**	**Dose of Spikevax**	**Roman number**	**Country**	**Upper case letter**
Guillain-Barré Syndrome	1	First	I	Denmark	A
Acute disseminated encephalomyelitis	2	Second	Ii	Italy*	B
Narcolepsy	3	Third	Iii	Norway	C
Acute aseptic arthritis	4	Any	Iv	Spain	D
Diabetes type 1	5			United Kingdom	E
Idiopathic thrombocytopenia	6				
Microangiopathy	7				
Heart failure	8				
Stress-induced cardiomyopathy	9				
Coronary artery disease	10				
Arrhythmia	11				
Myocarditis	12				
Pericarditis	13				
Cerebrovascular disease	14				
Deep vein thrombosis	15				
Pulmonary embolism	16				
Single organ cutaneous vasculitis	17				
Cerebral venous sinus thrombosis	18				
Splanchnic vein thrombosis	19				
Coagulation disorders	20				
Disseminated intravascular coagulation	21				
Kawasaki disease	22				
Acute liver injury	23				
Acute kidney injury	24				
Generalised convulsions	25				
Encephalitis/meningoencephalitis	26				
Transverse myelitis	27				
Bell’s palsy	28				
Acute respiratory distress syndrome	29				
Erythema multiforme	30				
Chilblain – like lesions	31				

Arabic numbers specifying AESI		Roman numbers specifying the dose of Spikevax		Upper case letter specifying Country	
AESI	**Arabic number**	**Dose of Spikevax**	**Roman number**	**Country**	**Upper case letter**
Anosmia/ageusia	32				
Anaphylaxis	33				
Multisystem inflammatory syndrome	34				
Sudden death	35				
Death of any cause	36				
Vaccine-induced immune thrombotic thrombocytopenia	37				
* As specified in Section 8, no data from Italy are included in the Fourth Interim Report. However, the alphabetic indexing of countries remains unchanged to allow the possibility of all planned data being included in in the final report.					

10.1. Participants

10.1.1. *Signal detection*

Denmark

In the nationwide registry-based data in Denmark, there were 668,881 persons with at least one dose of Spikevax in the first-dose base population. After applying the exclusion criteria, the first-dose Spikevax cohort included 564,137 persons (84.3% of the base population). The most prevalent exclusion criterion, 86,525 persons (12.9%), was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (Table 1.A., Appendix_Table_1_2_3). Among those, 531 (0.6%) had previously received the Pfizer vaccine, 52,170 (60.3%) the Astra Zeneca vaccine, and 33,845 (39.1%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 632,106 persons, 557,801 (88.2%) were included (Table 1.A., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort of 437,907 persons, 429,798 persons (98.1%) were included (Table 1.A., Appendix_Table_1_2_3). Persons excluded from the second-dose Spikevax cohort because of a previous record of another type of COVID-19 vaccine are described in Table 2.ii., Appendix_Table_1_2_3. No persons were excluded because of previous COVID-19 vaccines from the third-dose Spikevax cohort (Table 2.iii).

From the base population of 5,910,232 persons for the historical cohort, 5,758,622 (97.4%) were included in the analysis (Table 1.A., Appendix_Table_1_2_3).

Norway

In the nationwide registry-based data in Norway, there were 1,288,649 persons with at least one dose of Spikevax in the first-dose base population. After applying the exclusion criteria, the first-dose Spikevax cohort included 543,429 persons (42.2% of the base population). The most prevalent exclusion criterion was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (745,220 persons [57.8% of base population]; Table 1.C.,

Appendix_Table_1_2_3). Among those, 745,220 persons, 741,449 (99.5%) had previously received the Pfizer vaccine, 13,022 (1.7%) the Astra Zeneca vaccine, and 245 (<0.1%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 448,093 persons, 430,162 persons (96.0%) were included (Table 1.C., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort with of 69,400 persons, 69,367 persons (>99.9%) were included (Table 1.C., Appendix_Table_1_2_3). Persons excluded from the second-dose Spikevax cohort and third-dose Spikevax cohort because of a previous record of another type of COVID-19 vaccine are described in Table 2.ii. and 2.iii (Appendix_Table_1_2_3), respectively.

All 5,567,138 included in the base population for the historical cohort were also included in the analysis (Table 1.C., Appendix_Table_1_2_3).

Spain

In Spain/SIDIAP database, there were 2,706,804 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 621,240 persons (23.0% of the base population). The most prevalent exclusion criterion was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (2,019,774 persons [74.6% of the base population] Table 1.D., Appendix_Table_1_2_3). Among those 2,019,774 persons, 1,359,626 (67.3%) had previously received the Pfizer vaccine, 517,892 (25.6%) the Astra Zeneca vaccine, and 152,654 (7.6%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 554,273 persons, 530,383 persons (95.7%) were included (Table 1.D., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort of 231,692 persons, 228,076 persons (98.4%) were included (Table 1.D., Appendix_Table_1_2_3). Persons excluded from the second-dose Spikevax cohort and third-dose Spikevax cohort because of a previous record of another type of COVID-19 vaccine are described in Table 2.ii. and 2.iii(Appendix_Table_1_2_3), respectively.

United Kingdom

In the UK/CPRD database, there were 1,762,665 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 228,889 persons (13.0% of the base population). The most prevalent exclusion criterion was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (1,206,466 persons [68.4% of the base population] Table 1.E., Appendix_Table_1_2_3). Among those 1,206,466 persons, 827,711 (68.6%) had previously received the Astra Zeneca vaccine, 388,752 (32.2%) the Pfizer vaccine, and <0.1% received the Johnson and Johnson vaccine or another type of COVID-19 vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 276,570 persons, 196,647 persons (71.1%) were included (Table 1.E., Appendix_Table_1_2_3). From the base

population for the third-dose Spikevax cohort of 75,751 persons, 56,649 persons (74.8%)were included (Table 1.E., Appendix_Table_1_2_3). Persons excluded from the second-dose Spikevax cohort and third-dose Spikevax cohort because of a previous record of another type of COVID-19 vaccine are described in Table 2.ii. and 2.iii (Appendix_Table_1_2_3), respectively.

10.1.2. *Signal evaluation*

Self-controlled case series design

We identified the cases meeting the inclusion criteria. The number of cases for each analysis is displayed in the respective table showing the results (Appendix_Table_8) and in Table 14, Section 10.4.2.

10.1.3. *Cohort study of VAED*

In Norway, we identified 212,030 persons registered with COVID-19 between 11 January 2021 and 01 December 2021 (Table 18, Appendix_Table_18_19_20). Of these, we could include 147,515 in the analysis as either Spikevax-exposed at the time of diagnosis of COVID-19 (8554, 5.8%) or unexposed to any type of COVID-19 vaccine at the time of diagnosis of COVID-19 (138,961, 94.2%; Table 19, Appendix_Table_18_19_20).

10.1.4. *Cohort study of outcomes of myocarditis and pericarditis*

In Norway, we included in this analysis 3946 cases of myocarditis or other conditions captured by the respective parent ICD-10 codes as described in Section 9.4.2., Among those, 331 (8.4%) had been exposed to Spikevax before the diagnosis of myocarditis and the remaining 3615 persons (91.6%) had not been exposed to any type of COVID-19 vaccine before the diagnosis of myocarditis (Table 21.12, Appendix_Table_21). In Denmark, we included a total of 274 myocarditis cases of which 65 (23.7%) had been exposed to Spikevax before the diagnosis of myocarditis and the remaining 209 persons (76.3%) had not been exposed to any type of COVID-19 vaccine before the diagnosis of myocarditis (Table 21.12, Appendix_Table_21).

In Norway, we included 1063 cases of pericarditis or other conditions captured by the respective parent ICD-10 codes as described in Section 9.4.2. Among those, 177 (16.7%) had been exposed to Spikevax before the diagnosis of pericarditis and the remaining 886 persons (83.3%) had not been exposed to any type of COVID-19 vaccine before the diagnosis of pericarditis (Table 21.13, Appendix_Table_21). In Denmark, we included a total of 800 pericarditis cases of which 124 (15.5%) had been exposed to Spikevax before the diagnosis of pericarditis and the remaining 676 persons (84.5%) had not been exposed to any type of COVID-19 vaccine before the diagnosis of pericarditis (Table 21.13, Appendix_Table_21).

10.2. Descriptive data

10.2.1. *Signal detection*

Denmark

The cohorts had similar proportions of males and females (Table 3.A.,

Appendix_Table_1_2_3). The first- and the second-dose Spikevax cohorts had a slightly lower median age (36 years, quartile 1 – quartile 3 [Q1-Q3]= 31-59) than both the historical cohort (41 years, Q1-Q3=20-60) and the third-dose Spikevax cohort (40 years, Q1-Q3=32-64; Table 3.A., Appendix_Table_1_2_3). The proportion of women of childbearing age was higher in all dose-specific Spikevax cohorts (29-33%) than in the historical comparison cohort (22.5%) (Table 3.A., Appendix_Table_1_2_3). The first- and the second-dose Spikevax cohorts and the historical cohort had a similar proportion of patients with chronic health conditions (approx. 33%), while in the third-dose Spikevax cohort this proportion was 38.2%. The Spikevax cohorts and the historical cohort had similar proportions of persons with autoimmune or inflammatory disorders (approx. 3%); or indicators of immunocompromised status (approx. 3%) (Table 3.A., Appendix_Table_1_2_3). Proportion of persons with a previous COVID-19 infection (9.9%) was the highest in the third-dose Spikevax cohort (Table 3.A., Appendix_Table_1_2_3).

Norway

The historical cohort had a lower median age (37 years, Q1-Q3=19-56) than both the first-dose Spikevax cohort (42 years, Q1-Q3=30-56) the second-dose Spikevax cohort (45 years, Q1-Q3=32-59) and the third-dose Spikevax cohort (64 years, Q1-Q3=54-70; Table 3.C., Appendix_Table_1_2_3). Accordingly, the proportion of women of childbearing age was considerably lower in the cohort that had received the third dose of Spikevax (10.0%; Table 3.C., Appendix_Table_1_2_3) than in the other cohorts (31.2% in the first-dose Spikevax cohort, 29.0% in the second- dose Spikevax cohort, and 24.5% in the historical cohort). The third-dose of Spikevax cohort had a higher proportion of patients with chronic health conditions (24.7%) than the first-, and the second-dose Spikevax cohorts or the historical cohort (approx. 10-12%; Table 3.C., Appendix_Table_1_2_3). The cohort of persons receiving the third dose of Spikevax also had a higher proportion of patients with autoimmune or inflammatory conditions and immunocompromised patients (Table 3.C., Appendix_Table_1_2_3) than the other cohorts. Among persons who had received the first dose of Spikevax, 4.2% had previously had a recorded COVID-19 infection (Table 3.C., Appendix_Table_1_2_3).

Spain/SIDIAP

The first-dose Spikevax cohort had the lowest median age (37 years, Q1-Q3=25-53) and the third-dose Spikevax cohort had the highest median age (52 years [Q1-Q3=39-58]; Table 3.D., Appendix_Table_1_2_3). The third-dose Spikevax cohort had higher prevalence of chronic health conditions (36.9%) compared with 32.8% in the historical cohort and approx. 24-25% in first- and second-dose Spikevax cohorts (Table 3.D., Appendix_Table_1_2_3). The third-dose Spikevax cohort also had a higher proportion of patients with autoimmune or inflammatory conditions and immunocompromised patients than the other cohorts (Table 3.D., Appendix_Table_1_2_3). Among person who had received the first dose of Spikevax, 16.6% had previously had a recorded COVID-19 infection; the corresponding proportion was 9.6% in the second-dose Spikevax cohort and 8.4% in the third-dose Spikevax cohort (Table 3.D., Appendix_Table_1_2_3).

United Kingdom

The Spikevax cohorts included more females (55-56%) than the historical cohort (50%) and had a lower median age (33-35 years) than the historical cohort (43 years [Q1-Q3=21-61]; Table 3.E., Appendix_Table_1_2_3). The Spikevax cohorts also included less patients with chronic health conditions (e.g., 21.8% in first-dose Spikevax cohort vs. 50.9% in the historical cohort), autoimmune or inflammatory conditions (e.g., 1.6% in first-dose Spikevax cohort vs. 5.4% in the historical cohort), and indicators of immunocompromised status (e.g., 2.3% in first-dose Spikevax cohort vs. 6.7% in the historical cohort) than the historical cohort (Table 3.E., Appendix_Table_1_2_3). Proportion of persons with a previous COVID-19 infection (13.5%) was the highest in the third-dose Spikevax cohort (Table 3.E., Appendix_Table_1_2_3).

10.2.2. *Signal evaluation*

Self-controlled case series design

This design did not include any description of cases.

10.2.3. *Cohort study of VAED*

In Norway, the Spikevax vaccinees had a higher median age of 41 years (Q1-Q3=30-51) than the cohort not exposed to any type of COVID-19 vaccine, with median age of 19 years (Q1-Q3=11-36; Table 19, Appendix_Table-18_19_20). Furthermore, the Spikevax vaccinees had a higher comorbidity burden and a higher level of utilisation of health care before infection with COVID-19 than the cohort not exposed to any type of COVID-19 vaccine. Among the Spikevax vaccinees, 62.4% had been vaccinated with the second dose of Spikevax longer than 14 days before being recorded with COVID-19 infection in Norway (Table 19, Appendix_Table-18_19_20).

10.2.4. *Cohort study of outcomes of myocarditis and pericarditis*

Overall, more males than females experienced myocarditis and pericarditis (e.g., 72.3% males in the Spikevax exposed Danish myocarditis cases, Table 21.12, Appendix_Table_21). Generally, the Spikevax exposed pericarditis cases had less comorbidity and health resource utilization than the persons not exposed to any type of COVID-19 vaccine before the date of pericarditis diagnosis, expect for previous recordings of COVID-19 infection, which was higher in the Spikevax exposed (Table 21.13, Appendix_Table_21). For myocarditis cases the differences on comorbidity and health resource utilization between Spikevax exposed an unexposed was not that clear (Table 21.12, Appendix_Table_21).

Among the Spikevax exposed the majority had received the second dose of Spikevax before diagnosis of myocarditis (76.9% in Denmark and 51.0% in Norway; Table 21.12, Appendix_Table_21) or before the diagnosis of pericarditis in Denmark (74.2%; Table 21.13, Appendix_Table_21). In the Spikevax exposed, the proportion of males ages 18-29 years experiencing myocarditis before 8 days after the second dose of Spikevax was 16.9% in Denmark and 3.2% in Norway; similar proportions for pericarditis were 7.3% in Denmark and 9.3% in Norway (Table 21.12 and Table 21.13, Appendix_Table_21).

10.3. Outcome data

Table 12 summarises the crude country/database-specific historical incidence rates of the AESIs. In Norway, for most AESIs, the historical rates tended to be higher or substantially higher than previously published rates owing to insufficient granularity of diagnostic codes supplied with the current data delivery from the Norwegian registries. Therefore, the Norwegian historical incidence rates are usable in this analysis for technical purposes of comparison and are not interpretable as the rates of the specific events (see Section 9.9.5 for further information). Table 4 in Appendix_table_4 provides an overview of the crude incidence rates further stratified on age and sex for each AESI. For the Spikevax vaccinated, the crude incidence rates are given stratified on dose, age, and sex. For easier navigation of Appendix_Table_4, please refer to Table 11, Section 10 explaining the indexing used for AESIs, doses, and countries.

Table 12. Overview of the crude incidence rate in the historical cohort for both sexes and all ages combined

		Overall crude incidence rate per 100,000 person years (95%-CI) in the historical cohort		
Body system/ Classification	**AESI**	**Denmark**	**Norway**	**Spain**
Auto-immune diseases	Guillain-Barré Syndrome (GBS)	2.3 (2.1-2.6)	8.8 (8.3-9.4)	3.8 (3.5-4.1)
	Acute disseminated encephalomyelitis (ADEM)	0.55 (0.45-0.68)	9.5 (8.9-10.1)	0.44 (0.35-0.56)
	Narcolepsy	3.3 (3.1-3.6)	ND	ND
	Acute aseptic arthritis	3.1 (2.9-3.4)	108 (106-110)	0.69 (0.57-0.83)
	Diabetes type 1	34.0 (33.1-34.9)	122 (122-124)	16.5 (15.9-17.2)
	(Idiopathic) Thrombocytopenia-	16.1 (15.5-16.8)	88.2 (86.4-90.0)	142 (140-144)
Cardiovascular system	Microangiopathy	3.9 (3.7-4.3)	28.0 (27.0-29.0)	5.3 (4.9-5.7)
	Heart failure	230 (227-232)	537 (532-541)	446 (443-449)
	Stress-induced cardiomyopathy	4.4 (4.1-4.7)	25.4 (24.5-26.4)	3.8 (3.5-4.1)
	Coronary artery disease	315 (312-318)	580 (576-585)	211 (209-213)
	Arrhythmia	759 (755-764)	1404 (1397-1412)	1325 (1320-1331)
	Myocarditis	4.4 (4.1-4.7)	104 (103-106)	3.4 (3.2-3.7)

		Overall crude incidence rate per 100,000 person years (95%-CI) in the historical cohort		
Body system/ Classification	**AESI**	**Denmark**	**Norway**	**Spain**
	Pericarditis	14.6 (14.0-15.2)	32.2 (31.1-33.2)	25.4 (24.6-26.2)
	Cerebrovascular disease	343 (340-346)	441 (437-445)	287 (285-290)
Circulatory system	Deep vein thrombosis (DVT)	140 (138-142)	173 (170-175)	1.7 (1.6-2.0)
	Pulmonary embolism (PE)	97.7 (96.2-99.3)	124 (122-126)	57.4 (56.2-58.5)
	Single Organ Cutaneous Vasculitis	16.4 (15.8-17.0)	113 (111-115)	8.6 (8.1-9.0)
	Cerebral venous sinus thrombosis (CVST)	1.9 (1.7-2.1)	292 (289-295)	1.1 (0.96-1.3)
	Splanchnic vein thrombosis (SVT)	6.2 (5.9-6.6)	93.5 (91.6-95.3)	18.7 (18.0-19.3)
	Coagulation disorders	257 (254-259)	712 (707-717)	367 (364-370)
	Disseminated intravascular coagulation (DIC)	1.0 (0.86-1.2)	2.9 (2.6-3.2)	4.0 (3.7-4.3)
	Kawasaki disease*	0.96 (0.82-1.1)	3.4 (3.0-3.7)	0.70 (0.58-0.84)
Hepato-gastrointestinal and renal system	Acute liver injury	46.0 (45.0-47.0)	146 (143-148)	61.5 (60.3-62.7)
	Acute kidney injury	ND	232 (229-235)	426 (423-429)
Nerves and central nervous system	Generalised convulsions	87.9 (86.5-89.3)	149 (147-152)	48.4 (47.3-49.4)
	Encephalitis/meningo encephalitis	5.3 (4.9-5.6)	9.5 (8.9-10.1)	5.9 (5.5-6.2)
	Transverse myelitis	0.52 (0.41-0.64)	10.3 (9.7-10.9)	0.80 (0.67-0.95)
	Bell's palsy	20.6 (20.0-21.4)	49.3 (48.0-50.6)	73.1 (71.8-74.4)
Respiratory system	Acute respiratory distress syndrome (ARDS)	179 (177-181)	282 (279-285)	7.4 (6.9-7.8)
Skin and mucous membrane, bone and joints system	Erythema multiforme	4.1 (3.8-4.4)	ND	8.0 (7.6-8.4)
	Chilblain – like lesions	0.58 (0.47-0.71)	ND	0.036 (0.013-0.079)
Other systems	Anosmia, ageusia	9.3 (8.8-9.7)	ND	27.4 (26.6-28.2)

		Overall crude incidence rate per 100,000 person years (95%-CI) in the historical cohort		
Body system/ Classification	**AESI**	**Denmark**	**Norway**	**Spain**
	Anaphylaxis	15.0 (14.4-15.6)	ND	13.3 (12.7-13.8)
	Multisystem inflammatory syndrome	ND	ND	3.8 (3.6-4.2)
	Sudden death	2.0 (1.8-2.3)	ND	ND
	Death of any cause	969 (964-974)	746 (741-751)	896 (891-900)
Abbreviations: CI=confidence interval; ND=No data * More commonly described as an autoimmune disease (50)				

In Denmark, acute kidney injury and MIS were not assessed in this report (for further information see Section 9.9.5). For all other potential AESIs, based on the current event definitions, at least one event was detected in the Spikevax cohort in Denmark (any dose, all ages, both sexes) through the end of the follow- except for Kawasaki disease.

In Norway, narcolepsy, sudden death, chilblain–like lesions, anosmia/ageusia, erythema multiforme, anaphylaxis, and MIS were not assessed in this report (for further information see Section 9.9.5). For all other potential AESIs, based on the current event definitions, at least one event was detected in the Spikevax cohort (any dose, all ages, both sexes) through the end of the follow-up in Norway.

In Spain, narcolepsy and sudden death were not assessed in this report (for further information see Section 9.9.5). For all other potential AESIs, based on the current event definitions, at least one event was detected in the Spikevax cohort (any dose, all ages, both sexes) through the end of the follow-up in Spain.

The above results do not represent signals. The preliminary results on potential signals are described in Section 10.4.

10.4. Main results

10.4.1. *Signal detection*

The SMRs for the entire population and stratified according to sex and age groups are provided for first, second, third, or any dose of Spikevax in different risk periods after Spikevax vaccination.

Appendix_Table_5 displays the estimated SMRs for each AESI. Cells containing SMRs of ≥2 based on ≥5 Spikevax-exposed cases are shown in yellow colour to indicate that the definition of a signal is fulfilled. In total SMRs, are estimated for 840 strata for each AESI in each country, covering dose 1, 2, and 3 and any dose (combining data from dose 1, 2, and 3), five

different time intervals after Spikevax vaccination (0-2 days, 0-14 days, 0-28 days, 0-42 days, and 0-end of follow-up), three divisions on sex (both, female, male), and 14 age groups (all ages, children and adolescents [0-17 years], <12 years, 12 – 17 years, adults [18 – -64 years], 18 – 24 years, 25 – 34 years, 35 – 44 years, 45 – 54 years, 55 – 64 years, Elderly [≥65 years], 65 – 74 years, 75 – 79 years, ≥80 years).

Table 13, below, provides an overview of number of strata with SMR ≥ 2.0 based on ≥5 Spikevax-exposed cases according to AESI and country including reference to the appropriate output tables displaying the signals. Spain detected the majority of signals. We identified more than 50 strata with SMR ≥ 2.0 based on ≥5 Spikevax-exposed cases in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalised convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There were a maximum of 11-50 signals in at least one country for the AESIs microangiopathy, coronary artery disease, arrhythmia, cerebrovascular disease, single organ cutaneous vasculitis, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. We did not identify any signals for narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country.

Table 13. Overview of age- and sex-SMRs ≥ 2.0 where ≥5 observed Spikevax-exposed cases of the specified AESI with references to the relevant output tables

Body system/ Classification	AESI	Number of strata with SMR≥2 and ≥5 Spikevax-exposed cases*			Appendix tables with details of results
		Denmark	Norway	Spain	
Auto-immune diseases	Guillain-Barré Syndrome (GBS)	0	0	8	5.1.iii.D.; 5.1.iv.D.
	Acute disseminated encephalomyelitis (ADEM)	0	3	0	5.2.ii.C.
	Narcolepsy	0	NA	NA	
	Acute aseptic arthritis	9	3	2	5.4.ii.A.; 5.4.iii.A.; 5.4.iv.A.; 5.4.i.C.; 5.4.ii.C.; 5.4.ii.D.; 5.4.iv.D.
	Diabetes type 1	1	3	54	5.5.ii.A.; 5.5.i.C.; 5.5.iv.C.; 5.5.i.D.; 5.5.ii.D.; 5.5.iii.D.; 5.5.iv.D.
	(Idiopathic) Thrombocytopenia	5	0	117	5.6.i.A.; 5.6.iv.A.; 5.6.i.D.; 5.6.ii.D.; 5.6.iii.D.; 5.6.iv.D.
Cardiovascular system	Microangiopathy	1	0	45	5.7.iii.A.; 5.7.i.D.; 5.7.ii.D.; 5.7.iv.D.
	Heart failure	5	0	139	5.8.i.A.; 5.8.ii.A.; 5.8.i.D.; 5.8.ii.D.; 5.8.iii.D.; 5.8.iv.D.

Body system/ Classification	AESI	Number of strata with SMR≥2 and ≥5 Spikevax-exposed cases*			Appendix tables with details of results
		Denmark	Norway	Spain	
	Stress-induced cardiomyopathy	0	0	1	5.9.iv.D.
	Coronary artery disease	2	0	49	5.10.i.A.; 5.10.i.D.; 5.10.ii.D.; 5.10.iii.D.; 5.10.iv.D.
	Arrhythmia	0	0	25	5.11.i.D.; 5.11.ii.D.; 5.11.iii.D.; 5.11.iv.D.
	Myocarditis	70	22	49	5.12.i.A.; 5.12.ii.A.; 5.12.iii.A.; 5.12.iv.A.; 5.12.ii.C.; 5.12.iv.C.; 5.12.ii.D.; 5.12.iii.D.; 5.12.iv.D.
	Pericarditis	56	67	38	5.13.i.A.; 5.13.ii.A.; 5.13.iv.A.; 5.13.i.C.; 5.13.ii.C.; 5.13.iv.C..; 5.13.i.D.; 5.13.ii.D.; 5.13.iii.D.; 5.13.iv.D.
	Cerebrovascular disease	3	0	22	5.14.ii.A.; 5.14.i.D.; 5.14.ii.D.; 5.14.iii.D.; 5.14.iv.D.
Circulatory system	Deep vein thrombosis (DVT)	1	0	3	5.15.ii.A.; 5.15.iv.D.
	Pulmonary embolism (PE)	6	4	300	5.16.i.A.; 5.16.ii.A.; 5.16.iv.A.; 5.16.i.C.; 5.16.iv.C.; 5.16.i.D.; 5.16.ii.D.; 5.16.iii.D.; 5.16.iv.D.
	Single Organ Cutaneous Vasculitis	4	0	35	5.17.ii.A.; 5.17.ii.D.; 5.17.iii.D.; 5.17.iv.D.
	Cerebral venous sinus thrombosis (CVST)	0	0	0	
	Splanchnic vein thrombosis (SVT)	4	1	132	5.19.ii.A.; 5.19.iv.A.; 5.19.i.C.; 5.19.i.D.; 5.19.ii.D.; 5.19.iii.D.; 5.19.iv.D.
	Coagulation disorders	0	0	218	5.20.i.D.; 5.20.ii.D.; 5.20.iii.D.; 5.20.iv.D.
	Disseminated intravascular coagulation (DIC)	0	0	2	5.21.iv.D.
	Kawasaki disease	0	0	0	

Body system/ Classification	AESI	Number of strata with SMR≥2 and ≥5 Spikevax-exposed cases*			Appendix tables with details of results
		Denmark	Norway	Spain	
Hepato-gastrointestinal and renal system	Acute liver injury	2	2	172	5.23.ii.A.; 5.23.iv.A.; 5.23.i.C.; 5.23.i.D.; 5.23.ii.D.; 5.23.iii.D.; 5.23.iv.D.
	Acute kidney injury	NA	0	248	5.24.i.D.; 5.24.ii.D.; 5.24.iii.D.; 5.24.iv.D.
Nerves and central nervous system	Generalised convulsions	3	0	116	5.25.iii.A.; 5.25.iv.A.; 5.25.i.D.; 5.25.ii.D.; 5.25.iii.D.; 5.25.iv.D.
	Encephalitis/meningoencephalitis	0	3	23	5.26.ii.C.; 5.26.ii.D.; 5.26.iii.D.; 5.26.iv.D.
	Transverse myelitis	0	0	0	
	Bell's palsy	0	0	22	5.28.i.D.; 5.28.ii.D.; 5.28.iii.D.; 5.28.iv.D.
Respiratory system	Acute respiratory distress syndrome (ARDS)	0	3	146	5.29.iii.C.; 5.29.i.D.; 5.29.ii.D.; 5.29.iii.D.; 5.29.iv.D.
Skin and mucous membrane, bone and joints system	Erythema multiforme	6	NA	42	5.30.ii.A.; 5.30.iv.A.; 5.30.i.D.; 5.30.iii.D.; 5.30.iv.D.
	Chilblain – like lesions	7	NA	0	5.31.ii.A.; 5.31.iii.A.; 5.31.iv.A.
Other systems	Anosmia, ageusia	66	NA	122	5.32.i.A.; 5.32.ii.A.; 5.32.iii.A.; 5.32.iv.A.;5.32.i.D.; 5.32.ii.D.; 5.32.iii.D.; 5.32.iv.D.
	Anaphylaxis	0	NA	36	5.33.i.D.; 5.33.ii.D.; 5.33.iv.D.
	Multisystem inflammatory syndrome	NA	NA	51	5.34.i.D.; 5.34.ii.D.; 5.34.iii.D.; 5.34.iv.D.
	Sudden death	0	NA	NA	
	Death of any cause	0	0	126	5.36.i.D.; 5.36.ii.D.; 5.36.iii.D.; 5.36.iv.D.

Body system/ Classification	AESI	Number of strata with SMR≥2 and ≥5 Spikevax-exposed cases*			Appendix tables with details of results
		Denmark	Norway	Spain	
Abbreviations: SMR=Standardised Morbidity Ratio; NA=not available * In total, SMRs were estimated for 840 strata for each AESI in each country, covering dose 1, 2, and 3 and any dose (combining data from dose 1, 2, and 3), five different time intervals after Spikevax vaccination (0-2 days, 0-14 days, 0-28 days, 0-42 days, and 0-end of follow-up), three divisions on sex (both, female, male), and 14 age groups (all ages, children and adolescents [0-17 years], <12 years,12 – 17 years, adults [18 – -64 years], 18 – 24 years, 25 – 34 years, 35 – 44 years, 45 – 54 years, 55 – 64 years, Elderly [≥65 years], 65 – 74 years, 75 – 79 years, ≥80 years).					

Below we describe the distribution of signals for AESIs with at least one stratum with SMR ≥ 2.0 based on ≥5 Spikevax-exposed cases.

Guillain-Barré Syndrome

No signal was identified in Denmark, Norway or Spanish males. For adult Spanish females in the time interval 0 days to end of follow-up after any dose of Spikevax a signal was detected with an SMR of 2.33 (95% CI=1.24-3.99; Table 5.1.iv.D, Appendix_Table_5).

Acute disseminated encephalomyelitis

No signal was identified in Denmark and Spain. In Norway, acute disseminated encephalomyelitis had signals for males e.g., in the time interval 0 to 42 days after the second dose of Spikevax in adult males there was a signal with an SMR of 2.73 (95% CI=0.88-6.37; Table 5.2.ii.C, Appendix_Table_5).

Acute aseptic arthritis

Most signals for acute aseptic arthritis were identified in Denmark, where the SMRs were generally highest in periods before 42 days after Spikevax vaccination (Table 5.4.ii.A, Table 5.4.iii.A and Table 5.4.iv.A, Appendix_Table_5). As an example, for adult males there was a signal in the period 0 to 28 days after any dose of Spikevax with an SMR of 2.03 (95% CI=0.65-4.73; Table 5.4.iv.A, Appendix_Table_5)

Diabetes type 1

In Spain signal was detected across age and sex groups, doses of Spikevax and different time periods after vaccination. For instance, a signal was detected for all males in the period 0-28 days after Spikevax vaccination with an SMR of 2.08 (95% CI=1.29-3.19; Table 5.5.iv.D, Appendix_Table_5)

(Idiopathic) Thrombocytopenia

No signals were detected in Norway and only 3 signals in Denmark. However, in Spain many signals were detected in the eldest part of the population after all doses of Spikevax and with the highest SMRs in the time periods closest to vaccination (Table 5.6.i.D, Table 5.6.ii.D, Table 5.6.iii.D, and Table 5.6.iv.D, Appendix_Table_5). For instance, a signal was found for elderly of both sexes in the period 0-2 days after vaccination with the any dose of Spikevax with an SMR of 3.64 (95% CI=1.88-6.36; Table 5.6.iv.D, Appendix_Table_5)

Microangiopathy

No signals were detected in Norway and only 1 signal in Denmark. In Spain, signals were scattered around age and sex groups and seems to involve all time periods after vaccination. As an example, the SMR for both sexes of all ages during the entire follow-up period after any dose of Spikevax was 2.09 (95% CI=1.55-2.76; Table 5.7.iv.D, Appendix_Table_5)

Heart Failure

No signals were detected in Norway. There was no clear pattern for the signals identified in Denmark and Spain as they were scattered around sex, age groups, doses of Spikevax, and time periods after vaccination. For instance, a signal was identified for Spanish females 0-2 days after any dose of Spikevax with an SMR of 2.32 (95% CI=1.32-3.76; Table 5.8.iv.D, Appendix_Table_5).

Stress-induced cardiomyopathy

No signal was identified in Denmark and Norway. Only one signal was detected Spain, specifically in adult Spanish males during the entire follow-up period after any dose of Spikevax with an SMR of 2.41 (95% CI=0.78-5.62; Table 5.9.iv.D, Appendix_Table_5).

Coronary artery disease

No signals were detected in Norway and only 2 signals in Denmark. In Spain signals occurred after all doses of Spikevax, but the number of signals was highest after the second dose and mainly affected the elderly. For instance, there was a signal for elderly of both sexes in the time period 0-2 days after the second dose of Spikevax with an SMR of 4.36 (95% CI=1.99-8.27; Table 5.10.ii.D, Appendix_Table_5)

Arrhythmia

No signal was identified in Denmark and Norway. There was no clear pattern for the signals identified in Spain as they were scattered around sex, age groups, doses of Spikevax, and time periods after vaccination. For instance, there was a signal for elderly of both sexes in the time period 0-2 days after the second dose of Spikevax with an SMR of 2.25 (95% CI= 1.48-3.27; Table 5.11.ii.D, Appendix_Table_5)

Myocarditis

In Denmark, Norway and Spain, most signals were identified after the second dose of Spikevax and in the combined analysis of all doses of Spikevax, particularly among males aged 18-24 years, 25-34 years, and 35-44 years. The SMRs were generally highest in the time period close to the date of vaccination compared with the entire follow-up period after vaccination. For instance, the SMR was 23.2 (95%-CI=11.1-42.7) in Danish males aged 25-34 years in the period 0-14 days after the second dose of Spikevax, while it was 2.48 (95%-CI=1.36-4.16) during the entire follow-up period after the second dose of Spikevax (Table 5.12.ii.A, Appendix_Table_5).

Pericarditis

In Spain most signals were identified after the first dose of Spikevax. In both Denmark and

Norway, most signals were identified after the second dose of Spikevax and in the combined analysis of all doses of Spikevax, but there were also some signals after the first dose of Spikevax. Many signals were seen in younger males, but there were also some signals in younger females. The SMRs were generally highest in the time period close to the date of vaccination compared with the entire follow-up period after vaccination. For instance, the SMR was 32.0 (95%-CI=10.3-74.8) in Norwegians of both sexes aged 18-24 years in the period 0-2 days after any dose of Spikevax, while it was 3.25 (95%-CI=1.82-5.36) during the entire follow-up period after any dose of Spikevax (Table 5.13.iv.C, Appendix_Table_5).

Cerebrovascular disease

No signals were detected in Norway. There was no clear pattern for the signals identified in Denmark and Spain as they were scattered around sex, age groups, doses of Spikevax, and time periods after vaccination. For instance, a signal was identified in Spain for person aged 55-64 years old of both sexes in the period 0-14 days after the first dose of Spikevax with an SMR of 2.40 (95% CI=1.45-3.76; Table 5.14.i.D, Appendix_Table_5).

Deep vein thrombosis

No signals were detected in Norway. Only one signal was detected in Denmark after the second dose of Spikevax and three signals were detected in Spain after any dose of Spikevax.

Pulmonary embolism

The majority of signals was detected in Spain covering all doses of Spikevax and all time periods after Spikevax vaccination. The SMR during the entire follow-up period after any dose Spikevax for all age and sex groups combined was 3.17 (95% CI=2.93-3.43; Table 5.16.iv.D, Appendix_Table_5).

Single Organ Cutaneous Vasculitis

No signals were detected in Norway and only 4 signals in Denmark. In Spain all signals occurred in the time period covering the entire follow-up period and only after the second, third and any dose of Spikevax. For instance, a signal was identified for all age and sex groups combined for the entire follow-up period after any dose Spikevax with an SMR of 2.38 (95% CI=1.81-3.07; Table 5.17.iv.D, Appendix_Table_5)

Splanchnic vein thrombosis

The majority of signals were detected Spain. No signals were detected in the time period 0-2 days after vaccination. Otherwise, the signals were spread over time periods after vaccination, doses of Spikevax, age and sex. As an example, there was a signal for all age and sex groups combined for the entire follow-up period after any dose Spikevax with an SMR of 2.33 (95% CI=1.99-2.71; Table 5.19.iv.D, Appendix_Table_5)

Coagulation disorders

No signals were detected in Denmark and Norway. In Spain, signals were found for all doses of Spikevax and all time periods after Spikevax cover a range of age groups for both sexes. However, for any dose of Spikevax most signals were confined to the elderly. For instance,

there was a signal for the elderly of both sexes during the entire follow-up period after any dose of Spikevax with an SMR of 2.35 (95%-CI=2.20-2.50; Table 5.20.iv.D, Appendix_Table_5)

Disseminated intravascular coagulation

No signal was detected in Denmark and Norway and only two signals were detected in Spain.

Acute liver injury

The majority of signals were detected in Spain. No signals were detected in the period 0-2 days after vaccination. Otherwise, the signals were spread over time periods after vaccination, doses of Spikevax, age and sex. As an example, there was a signal for all age and sex groups combined for the entire follow-up period after any dose Spikevax with an SMR of 2.13 (95% CI=1.96-2.31; Table 5.23.iv.D, Appendix_Table_5)

Acute kidney injury

Signals were only detected in Spain scattered over doses of Spikevax, periods after vaccination, age and sex. As an example, there was a signal for all age and sex groups combined 0-42 days after any dose Spikevax with an SMR of 2.03 (95% CI=1.87-2.19; Table 5.24.iv.D, Appendix_Table_5)

Generalised convulsions

No signals were detected in Norway and only 3 signals in Denmark. In Spain no signals were detected in the period 0-2 days after vaccination. Otherwise, the signals were spread over time periods after vaccination, doses of Spikevax, age and sex. As an example, there was a signal for all age and sex groups combined 0-42 days after any dose Spikevax with an SMR of 2.21 (95% CI=1.74-2.77; Table 5.25.iv.D, Appendix_Table_5)

Encephalitis/meningoencephalitis

No signals were detected in Denmark and only 3 signals in Norway. In Spain no signals occurred after the first dose of Spikevax and no signals were detected in the period 0-14 days after Spikevax vaccination. As an example, there was a signal during the entire follow-up period after the second dose of Spikevax for all age and sex groups combined with an SMR of 2.09 (95%-CI=1.40-3.00; Table 5.26.ii.D, Appendix_Table_5).

Bell's palsy

No signal was detected in Denmark and Norway. There was no clear pattern for the signals identified in Spain as they were scattered around sex, age groups, doses of Spikevax, and time periods after vaccination. For instance, there was a signal for elderly males in the time period 0-28 days after any dose of Spikevax with an SMR of 2.19 (95% CI=1.23-3.62; Table 5.28.iv.D, Appendix_Table_5)

Acute respiratory distress syndrome

No signals were detected in Denmark and only 3 signals were detected in Norway. In Spain, the signals were spread over time periods after vaccination, doses of Spikevax, age and sex. As an example, there was a signal for all age and sex groups combined for the entire follow-up

period after any dose Spikevax with an SMR of 5.41 (95% CI=4.53-6.40; Table 5.29.iv.D, Appendix_Table_5)

Erythema multiforme

A few signals were detected after the second and any dose of Spikevax in Denmark. For instance, a signal was detected for both sexes of all ages in the period 0-42 days after vaccination with any dose of Spikevax with an SMR of 2.34 (95%-CI=0.94-4.82; Table 5.30.iv.A, Appendix_Table_5). In Spain most signals seemed to be related to occurrence of signals after the first dose of Spikevax. For instance, there was a signal for all age and sex groups combined for the time period 0-14 days after the first dose of Spikevax with an SMR of 6.43 (95%-CI=2.77-12.7, Table 5.30.i.D, Appendix_Table_5). This AESI was not assessed in Norway.

Chilblain–like lesions

No signal was identified in Spain and this AESI was not assessed in Norway. In Denmark, a few signals were detected after the second, the third, and any dose of Spikevax during the entire follow-up period. For instance, a signal was detected for both sexes of all ages during the entire follow-up period after vaccination with any dose of Spikevax with an SMR of 2.91 (95%-CI=1.45-5.2; Table 5.31.iv.A, Appendix_Table_5).

Anosmia, ageusia

Signals occurred after all doses of Spikevax and for both females and males and different durations of follow-up since vaccination in Denmark and Spain. For instance, in Denmark a signal was detected for both sexes of all ages during the period 0-28 days after vaccination with any dose of Spikevax with an SMR of 2.37 (95%-CI=1.53-3.5; Table 5.32.iv.A, Appendix_Table_5). This AESI was not assessed in Norway.

Anaphylaxis

No signal was identified in Denmark and this AESI was not assessed in Norway. In Spain signals was detected after the first, second and any dose of Spikevax. The SMRs where high in the time period 0-2 days after vaccination in some of the age and sex strata, but as there where < 5 Spikevax exposed cases no signals were recoded. As an example of a signal, the SMR was 3.04 (95%-CI=1.39-5.78) in the period 0-14 days after vaccination with the first dose of Spikevax for all age and sex groups combined (Table 5.33.i.D, Appendix_Table_5).

Multisystem inflammatory syndrome

This AESI was not assessed in Denmark and Norway. In Spain, the signals were spread over time periods after vaccination, doses of Spikevax, age and sex. As an example, there was a signal for all age and sex groups combined for the entire follow-up period after any dose Spikevax with an SMR of 3.47 (95% CI=2.53-4.65; Table 5.34.iv.D, Appendix_Table_5)

Death of any cause

No signal was detected in Denmark and Norway. In Spain there was no signals in the period 0-14 days after Spikevax vaccination, but otherwise occurred after all doses of Spikevax. For

any dose of Spikevax a signal was detected during the entire follow-up period for all age and sex groups combined with an SMR of 2.90 (95%-CI=2.82-2.98; Table 5.36.iv.D, Appendix_Table_5)

10.4.2. *Signal evaluation*

Self-controlled case series design

Table 14 gives an overview of the results for the primary SCCS design for each AESI investigated by SCCS. There were few cases of myocarditis and pericarditis, but still the analysis showed considerably increased rates 0 to 7 days after the second dose of Spikevax compared with 28-75 days after the second dose of Spikevax in males aged 12-30 years; the lowest IRR was 4.50 (95%-CI=1.01-20.1) for pericarditis in Spain and the highest IRR was 42.0 (95%-CI=5.17-341) for myocarditis in Spain. For myocarditis, the rate was also increased in the risk window 0-21 days (e.g., IRR=15.3 [95%-CI=1.88-124] in Spain) and for males aged 18 years of older (e.g., IRR=16.0 [95%-CI=4.24-60.3] in Spain) in all countries (Table 9.12, Appendix_Table_8). No cases of myocarditis were observed after the third dose (Table 8.12, Appendix_Table_9). For pericarditis, the rate was also increased in the risk window 0-21 days (e.g., 13.1 [95%-CI=1.58-109] in Denmark) and for males 18 years or older in Denmark and Norway (e.g., 5.54 [95%-CI=2.53-12.1] in Denmark), and for females aged 18 years or older in Norway (4.80 [95%-CI=1.29-17.9]; Table 9.13, Appendix_Table_9). In addition, the rate of pericarditis was also increased in the risk window 0-7 days after the first dose of Spikevax in Norway and Spain (e.g., IRR=5.83 [95%-CI=1.51-22.6] in Spain; Table 8.13, Appendix_Table_8)

Although the second dose of Spikevax was defined as the primary exposure for idiopathic thrombocytopenia and vaccine-induced immune thrombotic thrombocytopenia, more cases occurred after the first dose of Spikevax with an IRR of 1.74 (95%-CI=1.03-2.94) in Norway for both AESIs (Table 8.6 and table 8.37, Appendix_Table_8), noting that absence of ICD-10 codes more granular than the 3-digit level for Norway in this report limits the interpretability of these analyses. Similarly, for stress induced cardiomyopathy more cases occurred after the first dose compared with the second dose in Norway and the IRR after the first dose was 2.17 (95%-CI=1.08-4.36; Table 8.9, Appendix_Table_8).

The IRR for generalised convulsions 0-14 days after any dose of Spikevax in females and male aged 12 years or older was 1.74 (95%-CI=1.10-2.76) in Spain. For the risk window 0-28 days, we found a similar IRR in Spain (1.65 [95%-CI=1.21-2.25]; Table 9.25, Appendix_table_9). When using only the risk window 0-14 days after the third dose of Spikevax the IRR was 2.34 (95%-CI=1.14-4.81) in Denmark and 2.51 (95%-CI=1.22-5.17) in Spain (Table 8.25, Appendix_Table_8).

The primary analysis for anaphylaxis examined the risk window 0-2 days after the first dose of Spikevax in females aged 12 years or older and identified an IRR of 1.67 (95%-CI=0.19-14.9) in Denmark and 1.67 (95%-CI=0.63-4.44) in Spain. When conducting the same analysis in a population consisting of both females and males aged 12 years or older the IRR was 6.67 (95%-CI=0.42-107) in Denmark and 2.42 (95%-CI=0.77-7.61) in Spain (Table 9.33,

Appendix_table_9). When examining the risk window 0-2 days after the second dose of Spikevax the IRR was 4.57 (95%-CI=0.95-22.0) in Denmark and 3.43 (95%-CI=0.99-11.9) in Spain (Table 8.33, Appendix_table_8).

Table 14. Overview of the results of main SCCS analysis for each AESI investigated by SCCS

	Primary analysis				Results			
AESI	**Analysis***	**Population**	**Dose**	**Risk window, days**	**Country**	**N events in risk window**	**N events in control window**	**Incidence rate ratio (95% CI)**
(Idiopathic) Thrombocytopenia	By dose	F&M ≥12 years	Second dose	0-14	Denmark	7	10	1.54 (0.59-4.05)
					Norway	14	15	1.86 (0.88-3.91)
					Spain	45	91	1.09 (0.76-1.55)
Stress-induced cardiomyopathy	Standard SCCS	F&M ≥12 years	Second dose	1-42	Denmark	< 5	26	0.65 (0.088-4.80)
					Norway	< 5	32	0.93 (0.28-3.10)
					Spain	< 5	23	2.04 (0.47-8.85)
Arrhythmia	Standard SCCS	F&M ≥12 years	Any dose	1-42	Denmark	1229	4473	1.02 (0.96-1.09)
					Norway	1000	2864	1.09 (1.01-1.17)
					Spain	1335	6168	1.03 (0.97-1.09)
Myocarditis	By dose	M 12-30 years	Second dose	0-7	Denmark	8	< 5	16.0 (4.24-60.3)
					Norway	11	< 5	33.0 (7.31-149)
					Spain	7	< 5	42.0 (5.17-341)

	Primary analysis				Results			
AESI	**Analysis***	**Population**	**Dose**	**Risk window, days**	**Country**	**N events in risk window**	**N events in control window**	**Incidence rate ratio (95% CI)**
Pericarditis	By dose	M 12-30 years	Second dose	0-7	Denmark	5	< 5	30.0 (3.50-257)
					Norway	9	6	9.00 (3.20-25.3)
					Spain	< 5	< 5	4.50 (1.01-20.1)
Cerebrovascular disease	Standard SCCS	F&M ≥12 years	Any dose	1-42	Denmark	530	1906	1.04 (0.95-1.15)
					Norway	239	723	1.04 (0.90-1.21)
					Spain	269	1417	0.87 (0.76-0.99)
Deep vein thrombosis	Standard SCCS and adjustment for month and year	F&M ≥12 years	Any dose	1-42	Denmark	156	614	0.96 (0.79-1.17)
					Norway	151	433	1.07 (0.87-1.31)
					Spain	< 5	15	0.24 (0.027-2.17)
Splanchnic vein thrombosis	Standard SCCS and adjustment for month and year	F&M ≥12 years	Second dose	1-42	Denmark	< 5	38	0.84 (0.19-3.72)
					Norway	41	243	1.32 (0.91-1.91)
					Spain	11	191	0.90 (0.46-1.74)
Acute liver injury	Standard SCCS	F&M ≥12 years	Second dose	1-42	Denmark	14	177	1.28 (0.74-2.21)

	Primary analysis				Results			
AESI	**Analysis***	**Population**	**Dose**	**Risk window, days**	**Country**	**N events in risk window**	**N events in control window**	**Incidence rate ratio (95% CI)**
					Norway	46	387	0.95 (0.70-1.29)
					Spain	35	585	1.12 (0.79-1.57)
Generalised convulsions	Standard SCCS	F&M ≥12 years	Any dose	0-14	Denmark	<15	136	1.31 (0.73-2.37)
					Norway	24	260	0.90 (0.59-1.36)
					Spain	20	216	1.74 (1.10-2.76)
Anaphylaxis	By dose	F ≥12 years	First dose	0-2	Denmark	< 5	< 5	1.67 (0.19-14.9)
					Norway	ND	ND	ND
					Spain	5	20	1.67 (0.63-4.44)
Vaccine-induced immune thrombotic thrombocytopenia	By dose	F&M ≥12 years	Second dose	0-14	Denmark	0	< 5	NR
					Norway	14	25	1.67 (0.86-3.26)
					Spain	16	39	1.31 (0.73-2.35)

Abbreviations: CI=confidence interval; F=Female; M=Male; ND=No data; NR=not reportable (due to zero events in at least one exposure group)
* For AESIs that were not a contraindication to Spikevax vaccination, we performed standard SCCS using control windows both before and after Spikevax vaccination (if within the defined study period). For AESIs specified as a contraindication for Spikevax or for which medical doctors or patients are likely to perceive them as a contraindication, the analysis was done by dose with population selection decided for each dose and only time after that specific dose was included in the analysis.

10.4.3. *Cohort study of VAED*

In Norway, being Spikevax-exposed was associated with a lower risk of hospitalisation within 14 days (OR=0.20; 95%-CI=0.17-0.24), intensive care admission within 30 days (OR= 0.091; 95%-CI=0.038-0.18), and death within 30 days (OR=0.13; 95%-CI=0.071-0.22) compared with persons not vaccinated with any type of COVID-19 vaccine at the time of COVID-19 infection in analyses adjusted for age, sex, Charlson comorbidity index, and month and year of COVID-19 diagnosis (Table 20.a, Appendix_Table_18_19_20). Similar results were found when stratified on age groups (Table 20.b-d, Appendix_Table_18_19_20).

10.5. Other analyses

None.

10.6. Adverse events/adverse reactions

In this study, based on secondary use of routinely collected data from electronic health care records, adverse events/adverse reactions are not analysed beyond those potential events that are already addressed in the protocol. The reporting of suspected adverse reactions in the form of individual case safety reports in studies based on secondary data is not required (92, 93).

11. Discussion

11.1. Key results

This Fourth Interim Report includes selected preliminary results from Denmark, Norway, Spain (SIDIAP), and UK (CPRD), i.e., from all four countries in the current data extraction.

During the study period covered by the current data extraction, the number of eligible Spikevax recipients with at least one dose of Spikevax was 564,137 in Denmark, 543,429 in Norway, 621,240 in Spain, and 228,889 in UK. Approximately half of the Spikevax vaccinees were men except in the UK with 56% men. The vaccinees' median age in the participating databases ranged from 33 to 42 years at the time of their first Spikevax dose. In Norway, Spain, and UK, more than half of the persons getting at least one dose of Spikevax, were ineligible and excluded from the present study because they had received another type of COVID-19 vaccine before the first dose of Spikevax.

The signal detection stage was performed for Denmark, Norway, and Spain in the Fourth Interim Report. For each examined AESI and in each country, SMRs were computed for 840 strata, for all possible combinations of Spikevax doses, time intervals, age, and sex strata. There were more than 50 strata with signals (SMR ≥ 2.0 based on ≥5 Spikevax-exposed cases) in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalised convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There were a maximum of 11-50 signals in at least one country for the

AESIs microangiopathy, coronary artery disease, arrhythmia, cerebrovascular disease, single organ cutaneous vasculitis, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. There were no signals for the AESIs narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country. Because of limitations of the current case definitions, the AESI acute kidney injury and multisystem inflammatory syndrome was not assessed in Denmark, narcolepsy and sudden death were not evaluated in Spain, and the AESIs narcolepsy, erythema multiforme, Chilblain-like lesions, anosmia/ageusia, anaphylaxis, multisystem inflammatory syndrome, and sudden death were not evaluated in Norway.

In the Fourth Interim Report, we performed signal evaluation of the signals identified in the Third Interim Report based on data from the Tuscany region, Italy. The signal evaluation proceeded for the AESIs deemed fit for the SCCS design. In addition, vaccine-induced immune thrombotic thrombocytopenia entered directly into signal evaluation as it can only be detected assessed in vaccinated subjects. The AESIs examined with SCCS were idiopathic Thrombocytopenia, stress-induced cardiomyopathy, arrhythmia, myocarditis, pericarditis, cerebrovascular disease, deep vein thrombosis, splanchnic vein thrombosis, acute liver injury, generalised convulsions, anaphylaxis, and vaccine-induced immune thrombotic thrombocytopenia. In all countries contributing data to signal evaluation (Denmark, Norway, and Spain), there were considerably increased rates of myocarditis and pericarditis 0 to 7 days after the second dose of Spikevax compared with 28-75 days after the second dose of Spikevax in males aged 12-30 years with IRRs ranging between 4 and 42. This is in line with previous reports in many international studies (43, 94-103). Only few cases of anaphylaxis were detected, and Spikevax could not clearly be linked to anaphylaxis in the biologically plausible risk window 0-2 days after vaccination although the IRRs were increased. Most cases of idiopathic thrombocytopenia, vaccine-induced immune thrombotic thrombocytopenia, and stress-induced cardiomyopathy occurred after the first dose of Spikevax. In Norway, the first dose was associated with increased rate of these AESIs. Spikevax vaccination was associated with increased rate of generalised convulsions 0-14 days after vaccination, particularly after the third dose. No clear indication of increased rates for the other examined AESIs was indicated.

Based on the analysis of VAED in Norway, there was no indication that Spikevax vaccination any time before COVID-19 infection was associated with an increased risk of hospitalisation within 14 days after recording COVID-19 infection, or of an intensive care unit admission or death within 30 days after recording COVID-19 infection.

11.1.1. *Historical rates*

Country-specific rates of AESI are dependent on the contributing health sector (provenance), granularity of the available vocabularies, and completeness of recording, underscoring the importance of within-country comparisons (105, 106). Overall, there was a large variation in the magnitude of historical incidence rates of the AESI in the participating databases. Case definitions and limitations of data delivered is one reason for the observed variation. However,

a recent examination of 12 data sources specifically aimed at COVID-19 vaccine AESI (including SIDIAP and CPRD, used in this study) reported a wide variation of background rates not explainable by age and database effects previously observed, as rates could vary by up to 1,000-fold even after adjusting for age and sex. Other factors influencing rates were the choice of anchoring date for the time-at-risk start, with shorter times-at-risk being more susceptible to the choice of anchoring date. Choice of database or provenance (106) produced up to 100-fold variation in incidence rates, while secular or seasonal trends were found to be less important (107). These findings underscore importance of the interpretation of the results in the context of design and analytic decisions (107). Variations in historical rates were observed in the current report owing to the reasons outlined above and because of still ongoing refinement of the AESI-finding algorithms.

Denmark

Population rates of multiple AESIs have been assessed in previous studies, including rates in the populations used in the present study (106, 108-112). Definitions of AESIs may differ across published studies and can be based on routinely recorded diagnoses, laboratory data, or primary data collection/clinical examinations. These differences in definitions may or may not translate into differences in observed rates, depending on the data flow and patterns underlying a given data source.

In Denmark, the overall (all ages, both sexes) historical population rates were broadly consistent with those previously reported for the AESIs: Guillain-Barré Syndrome (106, 108, 112, 113); acute disseminated encephalomyelitis (114-116), with the exception of the rates reported in the ACCESS project, which were, however, based on the broad definition of the event (106); narcolepsy (108, 111, 112, 117); acute aseptic arthritis (though no good evidence on population rates could be identified, the closest was evaluated for a clinical diagnosis juvenile and rheumatoid arthritis in patients under age 18 years) (112); diabetes type 1 (though misclassification in these and other data with diabetes type 2 is likely since no age restriction was imposed (118)) (112, 118, 119); idiopathic thrombocytopenia (108, 109, 112); microangiopathy (120); heart failure (121); stress-induced cardiomyopathy (122, 123); coronary artery disease (109); myocarditis (43, 46, 98); pericarditis (43, 46); deep vein thrombosis (106, 109); pulmonary embolism (106, 109); single organ cutaneous vasculitis (124); cerebral venous sinus thrombosis (109); splanchnic vein thrombosis (109); disseminated intravascular coagulation (106, 109); Kawasaki disease (106, 108, 109, 125, 126); generalised convulsions (127); encephalitis/meningoencephalitis (106); transverse myelitis (106, 108, 112); Bell's palsy (108, 112, 128); acute respiratory distress syndrome (129); erythema multiforme (130); Chilblain – like lesions (106); anaphylaxis (106, 112, 131); multisystem inflammatory syndrome (132); and death of any cause (106, 133).

The overall historical population rates in Denmark were meaningfully higher in the current study than previously reported highest estimates, per 100,000 person-years, for arrhythmia 759 vs. 583 (134), cerebrovascular disease 343 vs. 162 (109); coagulation disorders 257 vs. 45 (109); acute liver injury 46 vs. 30 (135, 136); and anosmia/ageusia 9.3 vs 1.1 (106). In most cases, this was due to broader definitions used in the current study. For example,

published rates for arrhythmia are based on atrial fibrillation, while AESI cerebrovascular disease and coagulation disorders are broad and are open to variation in clinical interpretation. The reason for higher rates of anosmia/ageusia in the historical data are unclear, but could plausibly be attributed to random error because the event is rare. Acute liver injury is difficult to capture with sufficient specificity with diagnosis codes.

Overall historical rate of sudden death in Denmark in this study was considerably lower than previously reported (43, 112), however, the previously reported estimates are not directly comparable as the only available estimates were for broader conditions of death of unknown cause or cardiac arrest (with or without resuscitation).

For some AESI (primarily without well-defined diagnosis codes), single organ cutaneous vasculitis, acute aseptic arthritis, microangiopathy acute aseptic arthritis, ARDS, or erythema multiforme no good-quality independent evidence for Denmark could be identified, in which case we used rates cited in physicians' handbooks (not necessarily estimated using Danish data) or similar conditions. Rates for acute kidney injury were not estimated because of the missing reliable definition, and rates of MIS were not observed. In the published evidence rates for acute kidney injury depend strongly on the definition used, with laboratory-based definitions producing incidence rates that are higher than diagnosis-code rates (136-138).

Norway

In the current data extraction in Norway, the diagnosis ICD-10 codes are available only at a high chapter "parent" level. No granular "child" subcodes have been delivered except for COVID-19 diagnoses. Lack of the subcodes has different effect on the estimated AESI rates, from none (when entire chapters define events) to considerable (when only small and less prevalent subset of subcodes defines events). The interpretability of the results is affected correspondingly. Furthermore, the current extraction in Norway does not contain diagnosis codes for estimating rates of the AESI erythema multiforme, Chilblain – like lesions, anosmia/ageusia, or anaphylaxis.

In Norway, the overall (both sexes, all ages) population historical incidence rates of the AESIs were broadly consistent with published evidence for the AESIs acute disseminated encephalomyelitis (106); acute aseptic arthritis (106); diabetes type 1 (139), heart failure (140); stress-induced cardiomyopathy (141); coronary artery disease (based on IR for acute myocardial infarction is 260-280 for acute myocardial infarction, which is only a component of the AESI) (140); cerebrovascular disease based on published rates of stroke, which is a component of the AESI (140); deep vein thrombosis (106) (142); pulmonary embolism (142); disseminated intravascular coagulation (106); Kawasaki disease (108), acute kidney injury (106), encephalitis/meningoencephalitis (106); splanchnic vein thrombosis (109); and death of any cause (143).

The overall historical rates in Norway were higher for the following AESIs, some of which could be attributable to the unavailability of specific diagnosis codes: GBS (144); idiopathic thrombocytopenia (106); microangiopathy (106); arrhythmia (145); myocarditis (98, 106), pericarditis (98) cerebral venous sinus thrombosis (106); acute liver injury (106); transverse

myelitis (106); coagulation disorders (109); Bell's palsy and acute respiratory distress syndrome (106).

The overall historical rates in Norway were lower than previously reported in the ACCESS project for the AESI generalised convulsions (106). No external evidence for comparison could be identified for the AESI single organ cutaneous vasculitis.

Spain

Majority of the historical rates reported from SIDIAP were broadly consistent with those reported previously from similar data (146, 147) including published but not peer-reviewed evidence (146). However, for some AESI, including chilblain-like lesions, the historical incidence rates were not consistent with those previously reported in the ACCESS study based on data similar to that used here (106). For example, historical rates of chilblain-like lesions were considerably lower while historical rates of all-cause mortality were considerably higher than those reported previously (106), which is subject to ongoing inquiry. Despite the expectation of the COVID-19 pandemic with a reduction in use of health services during 2020, decrease is observed. On the other hand, there was an increase in private coverage, particularly among the less affluent population, and probably an increase in the registration of other diseases (148).Due to shortcomings of the healthcare systems, the COVID-19 pandemic may have also resulted in increased deaths from other causes (149).

11.2. Limitations

Results presented in this report must be interpreted in the context of several important limitations related to limitations of operational definitions of the underlying clinical concepts; limitations of data available in the current extraction; inherent limitations of the routinely collected data; limitations related to general ability of the underlying data source to measure a given health concept of exposure, outcomes, and covariates; and inherent limitations of the statistical analyses.

Most importantly, the current results are still preliminary, given the ongoing adaptation and refinement of the ConcePTION CDM environment to the study of vaccine safety (86). The algorithms to define some AESIs were used previously in the ACCESS project (74), while others were defined de-novo within the VAC4EU Consortium. All definitions of incident AESIs used in the current report are based on database-specific diagnosis codes. Compared with the Third Interim Report, the AESI case-finding algorithms underwent further review and refinement by a bespoke VAC4EU task force. This work is still in progress, and the current AESI definitions will be finalized in time for use in the Final Study Report. For the current report, the review of the AESI definitions was prioritized over the definitions of the covariates.

All AESIs are subject to a certain degree of misclassification, including potentially inflated SMRs due to differential misclassification, which cannot be ruled out for selected AESIs, such as myocarditis and pericarditis, anosmia/ageusia, or anaphylaxis, potentially due to differential detection and recording among Spikevax vaccinees compared with the historical cohort. However, for other AESIs the use of narrow AESI definitions (prioritising specificity), and assuming that any misclassification is nondifferential with respect to the Spikevax exposure

status (for example, a known and likely "contamination" of diabetes type 1 by diabetes type 2 exacerbated by age), the relative measures of association are expected to be unbiased even if sensitivity of identification is low (150). However, other external factors not related to Spikevax vaccination might result in differences between historical comparators and Spikevax vaccinees like changes in coding practices, organization of health care, or differences in other risk factors for the AESIs over time, particularly COVID-19 infection might be a risk factor for some of the AESIs.

This study aimed to examine a standard set of potential vaccine-related AESIs as well as specific events identified by previous evidence. A biological mechanism has not been defined for all AESI. Operational definitions of the AESIs originating from routinely collected health data are subject to inherent information bias, or measurement error. The sources of measurement errors include diagnostic mistakes, recording errors, and misclassification of true events by case-defining algorithms (151). The direction and the magnitude of errors is not always possible to estimate. Case-defining algorithms based on standard vocabularies are imperfect measures of the underlying clinical events, whose validity and completeness depends on referral patterns and on the condition itself. Completeness and validity of case-defining algorithms are expected to be database-dependent. Some data sources, such as Nordic population registries, can be expected to capture well "hard" endpoints that typically lead to hospital encounters such as acute myocardial infarction. At the same time, they are expected to have lower completeness than e.g., GP-based databases such as SIDIAP or CPRD in capturing conditions and events based on symptoms or treated preferentially in primary care. In this analysis, information bias related to AESI misclassification is counteracted to some extent by applying narrow, and therefore relatively more specific, definitions (106).

The level of evidence available for benchmarking of observed AESI rates differs by AESI. Certain prior publications were from the same group and used similar algorithms and therefore cannot be considered fully independent from the algorithms used here. This applies to e.g., the rates reported in the ACCESS or ADVANCE projects (106, 108), some of which may have undergone refinement for the present study. For some AESIs that are symptom based, rare or may not uniformly lead to contact to health care, the level of available prior evidence is low and may not originate from any of the participating countries. Events that are potentially not equally well measured in all participating databases given the data flow and the available codes for definitions include acute aseptic arthritis, microangiopathy, single-organ vasculitis, erythema multiforme.

With respect to defining the RMP-specified subgroups, the available routinely collected data has inherent limitations. For example, the RMP-defined subgroup "frail subjects with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)" was represented by persons in the study population with any history of a qualifying condition recorded during the 2-year lookback period, regardless of age or frailty, as frailty is a difficult concept to define in routinely collected data. Thus, this subgroup in the current study cannot be restricted to subjects who are frail; instead, it represents subjects with a history of any specific chronic condition regardless of frailty or whether or not the condition is stable.

Some of the SMR estimates and IRR estimates had low precision, as many AESIs are, by definition, rare events and were examined in limited subgroups based on age and sex. Another limitation can be the typical age range of the AESI, for instance Kawasaki disease have the highest incidence in children below five years (50), where Spikevax vaccination was very limited.

Finally, the per-protocol quality controls have been implemented to a broader extent than in the previous interim report. Specifically, two programmers implemented the analyses supervised by investigators examining the output for internal consistency, plausibility of the observed AESI historical rates have undergone plausibility benchmarking against published evidence.

A "signal" in this study was defined as contrast-specific SMR≥2 & N≥5, which is unavoidably arbitrary to an extent. The criteria were chosen to balance the risks of false positive against false negative signals. Because magnitude and precision are the main characteristics of estimates of association, the criteria for triggering signal evaluation were chosen to identify signals with clinically important magnitude of the risk increase observable in routinely collected data, combined with precision afforded by the set minimum number of exposed cases. Given that we evaluated the criteria for 840 strata for each AESI in each country (in total, 90,720 strata), the large number of comparisons carried out will produce false-positive findings by chance. This, by design (in addition to uncontrolled confounding), is one rationale for not interpreting signal detection results as evidence of causal relation, but as a screening tool for further signal evaluation. Specific for the SIDIAP in the current report, a large number of signals were detected for AESIs idiopathic thrombocytopenia, splanchnic vein thrombosis and acute liver injury, while the SCCS signal evaluation analysis could not confirm the signal (56). Unavoidably, the chosen criteria for signals, are partially arbitrary. As missing of an important signal is of a major concern, the protocol provides for examining signals that do not satisfy the prespecified criteria but are identified by e.g., external evidence.

One potential limitation is at least partial circularity of the evidence by using partially overlapping data to evaluate the signals as the data that were used in signal detection. At the same time, signal detected in one database are evaluated in all databases, which is a strength of the current approach, along with the typically recommended refinement of exploration of biases in sensitivity analyses as applied in this study (152).

The signals entering the signal evaluation phase we used a decision framework to decide which type of analysis should be used in the signal evaluation (self-controlled designs or cohort studies). The decision was based on features of each design, the AESI, and the results from signal detection in the Third Interim report. However, the choice might not always be clear as items like rapid onset and short latency can be difficult to evaluate. We mainly assessed if there appeared to be a clear risk window in signal detection with high SMRs/many signals within 0-42 days after Spikevax vaccination. If this was the case, we found the AESI eligible for the SCCS analysis.

The validity of the SCCS analysis depend on fulfilment of the assumption of the method or

making adequate adaptions to accommodate that the assumptions are not fulfilled (69). We provided a series of sensitivity analyses altering risk periods, population included and how to define follow-up. The sensitivity analyses did not to any great extent alter the conclusion from the primary analysis, but could give some additional important information for other doses, risk windows and populations.

11.3. Interpretation

Given the limitations outlined in Section 11.2, results provided in this Fourth Interim Report should be treated as preliminary with the main purpose to demonstrate further progress in (1) obtaining the pertinent multinational data; (2) applying the ConcePTION framework (CDM and quality and analysis pipeline), originally designed to study medication safety in pregnancy (86) to the study of the vaccine safety in the general population; and (3) of conducting the federated analyses on DRE.

This Fourth Interim Report provides an overview of the number and characteristics of the Spikevax vaccinees who received Spikevax as their first primary COVID-19 vaccination in Denmark, Norway, Spain, and the UK. With respect to signal detection, the signals detected for the AESIs myocarditis, pericarditis, and anaphylaxis was expected, while large number of signals detected in Spain for other AESIs are subject to further investigation and refinement. The signals confirmed at the signal evaluation stage broadly fall into two categories: 1) expected previously reported signals (myocarditis, pericarditis, anaphylaxis); 2) new signals subject to refinement of the underlying algorithms or correctly applying existing ones by using granular diagnosis codes (generalized convulsions in Denmark and Spain, idiopathic thrombocytopenia in Norway, VITT in Norway, and stress induced cardiomyopathy in Norway). Identification of expected signals and lack of confirmation of most other signals at the signal evaluation stage is reassuring, pending final refinement of the AESI-defining algorithms in the Final Study Report. The results of the signal detection analysis should not be interpreted as indicative of the risk-benefit balance of Spikevax and given potential non-causal explanations of the signal detection results. Elevated all-cause mortality has not been reported for Spikevax in either randomised trials (5) or in observational data, such as a Center for Disease Control (CDC) study of seven Integrated Health Care Organizations, in December 2020–July 31, 2021. The latter analysis showed a 60-80% reduction in the non–COVID-19 mortality with Spikevax vaccination (153). The signal for acute respiratory distress syndrome may be explained by COVID-19 infection prevalent in the Spikevax source population in general and absent in the historical cohort. Censoring by infection was not applied owing to potentially informative time-dependent selective reporting of COVID-19 cases after the end of mass testing. Other reasons could include low historical rates and changes in diagnostic process. Detection of signals for myocarditis and pericarditis were in line with those AESIs being important identified risks. The risk was further substantiated by the signal evaluation showing increased risk 0 to 7 days after the second dose of Spikevax for young males.

Per protocol, AESIs with SMRs ≥ 2.0 and ≥5 Spikevax-exposed cases are those to be subjected to a formal signal evaluation. These necessarily arbitrary criteria were selected based on the judged minimally important magnitude of potential association with a precision

achievable by at least 5 exposed cases. Furthermore, the observed-to-expected approach to signal detection has primarily been described for spontaneous reporting, while methodology for inferences from routinely collected data is still being developed. The chosen criteria were explicitly on clinical importance and precision rather than statistical significance (154). The interpretation of vaccine safety data is inherently complicated by the problem of multiplicity, with the tension between reducing both type I error rate (detecting associations that are spurious) positive rate and the type II error rate (failing to detect true associations) (155). In this study, the multiplicity is amplified by the large number of AESIs, exposure categories, strata, and subgroups. At the same time, the unprecedented environment created by the COVID-19 pandemic for vaccine surveillance exacerbates the well-known masking effect, in which signals one vaccine may be both hidden (or amplified) by the presence of other reported vaccines, and inherently confounding issue epidemiologically (59)

Furthermore, none of the AESI underwent adjudication, clinical, pharmacological and epidemiological review of identified temporal associations is important. This study, by design, can only provide epidemiological signal evaluation. As shown in the IMI PROTECT project, as much as three out of four temporal associations identified in the initial screen could be dismissed from further evaluation as false-positives, following review (156).

The findings of this study based on analysis of secondary routinely collected data with its known strengths and limitations must be interpreted in the context of all available evidence from diverse sources, populations, designs, and disciplines, and based on biological plausibility underlying any putative associations.

11.4. Generalisability

Results presented in this report are based on the data collected in up to 1.5 years following the launch of Spikevax and cover four out of five participating countries. Results of the signal detection cover three out of four countries contributing data to this Fourth Interim Report. Given the preliminary nature of the analysis due evolving variable definitions, potential channelling bias, or secular trends, the results presented here should not be generalized to other countries or periods of vaccination.

12. Other information

None.

13. Conclusion

The results reported here should be considered preliminary and are not interpretable as indicative of any changes to the current benefit-risk profile of Spikevax. Results inclusive of all participating countries and all study objectives are planned for presentation in the Final Study Report pending confirmation of the ARS database as detailed in Section 8.

14. References

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157-60.

2. Statistics and Research. Coronavirus (COVID-19) Vaccinations 2022 [cited 2022 07 September]. Available from: https://ourworldindata.org/covid-vaccinations?country=~DNK#which-vaccines-have-been-administered-in-each-country.

3. Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, et al. A global database of COVID-19 vaccinations. Nat Hum Behav. 2021.

4. EMA. Spikevax (previously COVID-19 Vaccine Moderna) 2022 [cited 2022 07 September]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax.

5. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.

6. ClinicalTrials.gov. COVID-19 Vaccine in Immunosuppressed Adults With Autoimmune Diseases (COVIAAD) [cited 2022 07 September]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04806113.

7. Colmegna I, Useche M, Rampakakis E, Amiable N, Rollet-Labelle E, Bessette L, et al. COVID-19 Vaccine in Immunosuppressed Adults with Autoimmune Diseases [abstract]. https://acrabstracts.org/abstract/covid-19-vaccine-in-immunosuppressed-adults-with-autoimmune-diseases/. Accessed 11 February 2022. Arthritis Rheumatol2021.

8. A Study to Evaluate Safety and Immunogenicity of mRNA-1273 Vaccine to Prevent COVID-19 in Adult Organ Transplant Recipients and in Healthy Adult Participants [cited 2022 02 March]. Available from: https://clinicaltrials.gov/ct2/show/NCT04860297.

9. A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove). Available from: https://clinicaltrials.gov/ct2/show/NCT04649151.

10. A Study to Evaluate Safety and Effectiveness of mRNA-1273 COVID-19 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age [cited 2022 02 March]. Available from: https://clinicaltrials.gov/ct2/show/NCT04796896.

11. EMA. EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU 2021 [cited 2021 02 June]. Available from: https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu.

12. MHRA. Regulatory approval of COVID-19 Vaccine Moderna 2021 [cited 2021 2 June]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna#history.

13. EMA. Spikevax (previously COVID-19 Vaccine Moderna), Authorisation details 2022 [cited 2023 16 February]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax#authorisation-details-section.

14. EMA. EMA recommends approval of Comirnaty and Spikevax COVID-19 vaccines for children from 6 months of age 2022 [cited 2023 16 March]. Available from: https://www.ema.europa.eu/en/news/ema-recommends-approval-comirnaty-spikevax-covid-19-vaccines-children-6-months-age.

15. GOV.UK. Coronavirus vaccine - weekly summary of Yellow Card reporting (Section 2 for doses

administered by manufacturer) 2022 [cited 2022 07 September]. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.

16. Statens-Serum-Institut. Første sending vaccine fra Moderna 2021 [cited 2022 12/8/2022]. Available from: https://www.ssi.dk/aktuelt/nyheder/2021/forste-sending-vacciner-fra-moderna.

17. Syddanmark R. Region Syddanmark modtager 5.000 Moderna-vacciner 2021 [cited 2022 12/8/2022]. Available from: https://regionsyddanmark.dk/om-region-syddanmark/presse-og-nyheder/nyhedsarkiv/2021/januar/region-syddanmark-modtager-5-000-moderna-vacciner.

18. Sundhedsstyrelsen. Så er vi i gang - i dag bliver de første vaccineret mod COVID-19 2020 [cited 2022 12/8/2022]. Available from: https://www.sst.dk/da/nyheder/2020/saa-er-vi-i-gang---i-dag-bliver-de-foerste-vaccineret-mod-covid-19.

19. Sundhedsstyrelsen. Nu kan alle gravide og ammende blive vaccineret mod COVID-19 2021 [cited 2021 30 July]. Available from: https://www.sst.dk/da/Nyheder/2021/Nu-kan-alle-gravide-og-ammende-blive-vaccineret-mod-COVID-19.

20. Sundhedsstyrelsen. Vaccinationskalender, 1. juli 2021 2021 [cited 2022 12/8/2022]. Available from: https://www.sst.dk/-/media/Udgivelser/2021/Corona/Vaccination/Kalender/Specificeret-vaccinationskalender-01072021.ashx.

21. Folkehelseinstituttet. Antall vaksinasjoner etter sykdom fordelt på dag, 01.01.2021 - 31.01.2021 2022 [cited 2022 1/9/2022]. Available from: https://statistikk.fhi.no/sysvak/antall-vaksinerte?etter=diagnose&diagnose=COVID_19&fordeltPaa=dag&fraDato=2021-01-01&tilDato=2021-01-31&preparat=MOD03_001.

22. Folkehelseinstituttet. Antall vaksinasjoner etter sykdom fordelt på dag, 21.12.2020 - 31.01.2021 2022 [cited 2022 1/9/2022]. Available from: https://statistikk.fhi.no/sysvak/antall-vaksinerte?etter=diagnose&diagnose=COVID_19&fordeltPaa=dag&fraDato=2020-12-21&tilDato=2021-01-31&preparat=MOD03_001,ASZ03_001,BNT03_001.

23. Folkehelseinstituttet. Vaksineringsscenario 2021 [cited 2022 1/9/2022]. Available from: https://www.fhi.no/contentassets/71e97765e43c41ee8f059efbd4016ca8/vedlegg/2021.01.29_vaksineringsscenario.pdf.

24. Folkehelseinstituttet. Coronavirus vaccine for adolescents 12-15 years 2021 [updated 26/1/2022; cited 2022 1/9/2022]. Available from: https://www.fhi.no/en/publ/information-letters/coronavirus-vaccine-for-adolescents-12-15-years/.

25. ToscanaNotizie. Vaccini Moderna, da lunedì 18 gennaio le prime somministrazioni 2021 [cited 2022 5/9/2022]. Available from: https://www.toscana-notizie.it/-/vaccini-moderna-da-luned%C3%AC-18-gennaio-le-prime-somministrazioni.

26. Toscana R. CoViD19 - MONITORAGGIO VACCINAZIONI 2022 [cited 2022 5/9/2022]. Available from: https://governo.it/it/cscovid19/report-vaccini/.

27. Report Vaccini Anti COVID-19 2022 [cited 2022 5/9/2022]. Available from: https://www.governo.it/it/cscovid19/report-vaccini/.

28. Salute Md. OGGETTO: Raccomandazioni per l'organizzazione della campagna vaccinale contro SARS-CoV-2/COVID-19 e procedure di vaccinazione. 2022.

29. Vaccinazione anti-SARS-CoV-2/COVID-19. 2021.

30. Salute Md. Indicazioni ad interim su "Vaccinazione contro il COVID-19 in gravidanza e allattamento". 2021.

31. Catalunya Gd. Dades COVID 2022 [updated 24/7/2022; cited 2022 5/9/2022]. Available from: https://dadescovid.cat/.

32. Estrategia de vacunación COVID-19 [updated 2/9/2022; cited 2022 5/9/2022]. Available from: https://www.vacunacovid.gob.es/.

33. England N. Moderna jabs mark new milestone in NHS vaccination programme 2021 [cited 2022 5/9/2022]. Available from: https://www.england.nhs.uk/2021/04/moderna-jabs-mark-new-milestone-in-nhs-vaccination-programme/.

34. Sasse T, Hodgkin R. Coronavirus vaccine rollout [updated 30/3/2022; cited 2022 5/9/2022]. Available from: https://www.instituteforgovernment.org.uk/explainers/coronavirus-vaccine-rollout.

35. England N. NHS invites people aged 60-plus to get life-saving COVID vaccination 2021 [updated 21/2/2021; cited 2022 5/9/2022]. Available from: https://www.england.nhs.uk/2021/02/nhs-invites-people-aged-60-plus-to-get-life-saving-covid-vaccination/.

36. England N. NHS England invites everyone aged 50 and over to be jabbed as NHS vaccination programme marks 100th day 2021 [updated 17/3/2021; cited 2022 5/9/2022]. Available from: https://www.england.nhs.uk/2021/03/nhs-england-invites-everyone-aged-50-and-over-to-be-jabbed-as-nhs-vaccination-programme-marks-100th-day/.

37. COVID-19 Vaccination Statistics. NHS England, 2022 1/9/2022. Report No.

38. Gynaecologists RCoOa. COVID-19 vaccines, pregnancy and breastfeeding FAQs [cited 2022 5/9/2022]. Available from: https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-womens-health/vaccination/covid-19-vaccines-pregnancy-and-breastfeeding-faqs/.

39. EU PAS Register. EUPAS44450. Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries (COVID-19). 2021.

40. EMA. COVID-19 Vaccine Moderna Risk Management Plan 2022 [cited 2022 08 September]. Available from: https://www.ema.europa.eu/documents/rmp-summary/spikevax-previously-covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf.

41. EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-6 May 2021 2021 [cited 2021 02 June]. Available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-3-6-may-2021.

42. EMA. Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis, 09 July 2021 2021 [cited 2021 28 July]. Available from: https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis.

43. Husby A, Hansen JV, Fosbol E, Thiesson EM, Madsen M, Thomsen RW, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ. 2021;375:e068665.

44. Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, et al. SARS-CoV-2 Vaccination

and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiol. 2022;7(6):600-12.

45. Massari M, Spila Alegiani S, Morciano C, Spuri M, Marchione P, Felicetti P, et al. Postmarketing active surveillance of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in persons aged 12 to 39 years in Italy: A multi-database, self-controlled case series study. PLoS Med. 2022;19(7):e1004056.

46. Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, et al. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review. BMJ. 2022;378:e069445.

47. EMA. COVID-19 vaccines: development, evaluation, approval and monitoring 2021 [cited 2021 28 July]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring#monitoring-vaccine-safety-and-use-in-real-life-section.

48. Hernan MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health. 2004;58(4):265-71.

49. EU PAS Register. EUPAS44273. Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe (COVID-19) 2021. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=45470.

50. Ramphul K, Mejias SG. Kawasaki disease: a comprehensive review. Arch Med Sci Atheroscler Dis. 2018;3:e41-e5.

51. ENCePP. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. 14.2. Vaccine safety and effectiveness [cited 2021 29 July]. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide14_2.shtml.

52. VAC4EU. ADVANCE. Report on appraisal of vaccine safety methods 2014 [cited 2021 29 July]. Available from: https://vac4eu.org/wp-content/uploads/2019/03/ADVANCE_D4-2_appraisal-safety-methods_final_PU.pdf.

53. Schoenbach V. Understanding the Fundamentals of Epidemiology: An Evolving Text 2010 [cited 2021 30 July]. Available from: http://www.epidemiolog.net/evolving.

54. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines 2021 [cited 2021 03 June]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=37274.

55. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019;170(6):398-406.

56. EMA. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases 2013 [cited 2023 16 March]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf.

57. EMA. Guideline on good pharmacovigilance practices (GVP). Module IX – Signal management (Rev 1) 2017 [cited 2023 15 March]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf.

58. ENCePP. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Chapter 10: Signal

detection methodology and application 2023 [cited 2023 15 March]. Available from: https://www.encepp.eu/standards_and_guidances/methodologicalGuide10.shtml.

59. Harpaz R, DuMouchel W, Van Manen R, Nip A, Bright S, Szarfman A, et al. Signaling COVID-19 Vaccine Adverse Events. Drug Saf. 2022;45(7):765-80.

60. Mahaux O, Bauchau V, Van Holle L. Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf. 2016;25(2):215-22.

61. Coloma PM, Trifiro G, Schuemie MJ, Gini R, Herings R, Hippisley-Cox J, et al. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? Pharmacoepidemiol Drug Saf. 2012;21(6):611-21.

62. de Bie S, Coloma PM, Ferrajolo C, Verhamme KM, Trifiro G, Schuemie MJ, et al. The role of electronic healthcare record databases in paediatric drug safety surveillance: a retrospective cohort study. Br J Clin Pharmacol. 2015;80(2):304-14.

63. Li R, Stewart B, Weintraub E. Evaluating efficiency and statistical power of self-controlled case series and self-controlled risk interval designs in vaccine safety. J Biopharm Stat. 2016;26(4):686-93.

64. Dodd C, Williame C. Safety evaluation of COVID-19 vaccines in electronic healthcare databases: a protocol template from the ACCESS project 2020 [cited 2021 14 June].

65. Whitaker H. The self controlled case series method. BMJ. 2008;337:a1069.

66. Baker MA, Lieu TA, Li L, Hua W, Qiang Y, Kawai AT, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. Am J Epidemiol. 2015;181(8):608-18.

67. Farrington CP, Whitaker HJ. Semiparametric Analysis of Case Series Data. Journal of the Royal Statistical Society Series C (Applied Statistics). 2006;55(5):553-94.

68. Whitaker HJ, Ghebremichael-Weldeselassie Y, Douglas IJ, Smeeth L, Farrington CP. Investigating the assumptions of the self-controlled case series method. Stat Med. 2018;37(4):643-58.

69. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.

70. Agency UHS. Guidance: COVID-19 vaccination: a guide to booster vaccination for individuals aged 18 years and over and those aged 16 years and over who are at risk 2022 [updated 2/2/2022; cited 2022 18/8/2022]. Available from: https://www.gov.uk/government/publications/covid-19-vaccination-booster-dose-resources/covid-19-vaccination-a-guide-to-booster-vaccination-for-individuals-aged-18-years-and-over.

71. Agency UHS. Guidance: A guide to the spring booster for those aged 75 years and older and older residents in care homes 2022 [updated 24/3/2022; cited 2022 18/8/2022]. Available from: https://www.gov.uk/government/publications/covid-19-vaccination-spring-booster-resources/a-guide-to-the-spring-booster-for-those-aged-75-years-and-older-residents-in-care-homes.

72. Anbefalinger vedr. 4. stik covid-19 vaccine til personer med svært nedsat immunforsvar [press release]. 2022.

73. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom M, et al. CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiol Drug Saf. 2017.

74. ACCESS Dashboard [cited 2022 14 September]. Available from: http://www.encepp.eu/phact_links.shtml.

75. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

76. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clinical Epidemiology. 2019;11:563-91.

77. Sturkenboom M, Braeye T, van der Aa L, Danieli G, Dodd C, Duarte-Salles T, et al. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. Vaccine. 2020;38 Suppl 2:B8-B21.

78. Recalde M, Rodriguez C, Burn E, Far M, Garcia D, Carrere-Molina J, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022;51(6):e324-e36.

79. Grove Krause T, Jakobsen S, Haarh M, Molbak K. The Danish vaccination register. Euro Surveill. 2012;17(17).

80. Statens-Serum-Institut. Registration of vaccines in the Danish Vaccination Register (DDV) 2023 [cited 2023 17 March]. Available from: https://covid19.ssi.dk/vaccination/registrering-af-vacciner-i-ddv.

81. Norwegian Institute of Public Health. Norwegian Immunisation Registry SYSVAK [cited 2023 27 March]. Available from: Norwegian Immunisation Registry SYSVAK.

82. Sundhedsstyrelsen. Fremover skal kun syge testes for covid-19 2022 [10/2/2023]. Available from: https://www.sst.dk/da/Nyheder/2022/Fremover-skal-kun-syge-testes-for-covid-19.

83. omsorgsdepartementet H-o. Bare de med symptomer skal teste seg 2022. Available from: https://www.regjeringen.no/no/aktuelt/bare-de-med-symptomer-skal-teste-seg/id2900883/.

84. Sanidad Md. Estrategia de Vigilancia y Control frente a la COVID-19 tras la fase aguda de la pandemia. Actualización 23 de marzo 2022. . 2022.

85. Iacobucci G. Covid-19: Who will be eligible for free testing from 1 April? BMJ. 2022;376:o807.

86. Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther. 2022;111(1):321-31.

87. ConcepTION [cited 2022 14 September]. Available from: https://www.imi-conception.eu/wp-content/uploads/2020/10/ConcePTION-D7.5-Report-on-existing-common-data-models-and-proposals-for-ConcePTION.pdf.

88. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ. 1987(82):1-406.

89. Harrell FE, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, and Measuring and Reducing Errors. Statistics in Medicine. 1996;15(4):361-87.

90. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med. 2006;25(10):1768-97.

91. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354.

92. EMA. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1) 2014 [cited 2022 10 February]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf.

93. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies 2017 [cited 2022 10 February]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices.

94. Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021;385(23):2140-9.

95. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021;6(10):1202-6.

96. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021;385(23):2132-9.

97. Husby A, Kober L. COVID-19 mRNA vaccination and myocarditis or pericarditis. Lancet. 2022;399(10342):2168-9.

98. Karlstad O, Hovi P, Husby A, Harkanen T, Selmer RM, Pihlstrom N, et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiol. 2022;7(6):600-12.

99. Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022;10(7):679-88.

100. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. 2022;327(4):331-40.

101. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022;28(2):410-22.

102. Schauer J, Buddhe S, Gulhane A, Sagiv E, Studer M, Colyer J, et al. Persistent Cardiac Magnetic Resonance Imaging Findings in a Cohort of Adolescents with Post-Coronavirus Disease 2019 mRNA Vaccine Myopericarditis. J Pediatr. 2022;245:233-7.

103. Wong HL, Hu M, Zhou CK, Lloyd PC, Amend KL, Beachler DC, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet. 2022;399(10342):2191-9.

104. Carrillo-Larco RM, Altez-Fernandez C. Anosmia and dysgeusia in COVID-19: A systematic review. Wellcome Open Res. 2020;5:94.

105. Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, et al. Quantifying outcome misclassification in multi-database studies: The case study of pertussis in the ADVANCE project. Vaccine. 2020;38 Suppl 2:B56-B64.

106. Willame C, Dodd C, Duran CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023;41(1):251-62.

107. Ostropolets A, Li X, Makadia R, Rao G, Rijnbeek PR, Duarte-Salles T, et al. Factors Influencing Background Incidence Rate Calculation: Systematic Empirical Evaluation Across an International Network of Observational Databases. Front Pharmacol. 2022;13:814198.

108. Willame C, Dodd C, van der Aa L, Picelli G, Emborg HD, Kahlert J, et al. Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. Drug Saf. 2021;44(3):383-95.

109. Dag Berild J, Bergstad Larsen V, Myrup Thiesson E, Lehtonen T, Grosland M, Helgeland J, et al. Analysis of Thromboembolic and Thrombocytopenic Events After the AZD1222, BNT162b2, and MRNA-1273 COVID-19 Vaccines in 3 Nordic Countries. JAMA Netw Open. 2022;5(6):e2217375.

110. Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ. 2021;373:n1435.

111. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine. 2013;31(8):1246-54.

112. Rasmussen TA, Jorgensen MR, Bjerrum S, Jensen-Fangel S, Stovring H, Ostergaard L, et al. Use of population based background rates of disease to assess vaccine safety in childhood and mass immunisation in Denmark: nationwide population based cohort study. BMJ. 2012;345:e5823.

113. Levison LS, Thomsen RW, Christensen DH, Mellemkjaer T, Sindrup SH, Andersen H. Guillain-Barre syndrome in Denmark: validation of diagnostic codes and a population-based nationwide study of the incidence in a 30-year period. Clin Epidemiol. 2019;11:275-83.

114. Otallah S. Acute disseminated encephalomyelitis in children and adults: A focused review emphasizing new developments. Multiple Sclerosis Journal. 2021;27(8):1153-60.

115. Lægehåndbogen. sundhed.dk. Acute disseminated encephalomyelitis 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/neurologi/tilstande-og-sygdomme/inflammatoriske-sygdomme/akut-dissemineret-encephalomyelit/.

116. Boesen MS, Blinkenberg M, Koch-Henriksen N, Thygesen LC, Uldall PV, Magyari M, et al. Implications of the International Paediatric Multiple Sclerosis Study Group consensus criteria for paediatric acute disseminated encephalomyelitis: a nationwide validation study. Developmental Medicine & Child Neurology. 2018;60(11):1123-31.

117. Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet Neurol. 2014;13(6):600-13.

118. Carstensen B, Ronn PF, Jorgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. BMJ Open Diabetes Res Care. 2020;8(1):e001071.

119. Svensson J, Carstensen B, Molbak A, Christau B, Mortensen HB, Nerup J, et al. Increased risk of childhood type 1 diabetes in children born after 1985. Diabetes Care. 2002;25(12):2197-201.

120. Lægehåndbogen. sundhed.dk. Systemic vasculitis 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/reumatologi/tilstande-og-sygdomme/systemiske-inflammationer/vaskulitter-systemiske/.

121. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, et al. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. Circulation. 2017;135(13):1214-23.

122. Butt JH, Bang LE, Rorth R, Schou M, Kristensen SL, Yafasova A, et al. Long-term Risk of Death and Hospitalization in Patients With Heart Failure and Takotsubo Syndrome: Insights From a Nationwide Cohort. J Card Fail. 2022;28(10):1534-44.

123. Lægehåndbogen. sundhed.dk. Stress cariomyopathy 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hjerte-kar/tilstande-og-sygdomme/hjertesvigt/stress-kardiomyopati/.

124. Lægehåndbogen. sundhed.dk. Microscopic polyangiitis 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/reumatologi/tilstande-og-sygdomme/systemiske-inflammationer/mikroskopisk-polyangiitis/.

125. Fischer TK, Holman RC, Yorita KL, Belay ED, Melbye M, Koch A. Kawasaki syndrome in Denmark. Pediatr Infect Dis J. 2007;26(5):411-5.

126. Piram M. Epidemiology of Kawasaki Disease in Europe. Front Pediatr. 2021;9:673554.

127. Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res. 2007;76(1):60-5.

128. Lægehåndbogen. sundhed.dk. Facial palsy 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/neurologi/tilstande-og-sygdomme/nervelaesioner/facialisparese/.

129. Lægehåndbogen. sundhed.dk. ARDS 2022 [cited 2023 02 March]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/lunger/tilstande-og-sygdomme/oevrige-sygdomme/ards/.

130. Lægehåndbogen. sundhed.dk. Erythema multiforme 2022 [cited 2023 02 March]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hud/tilstande-og-sygdomme/erytemer/erythema-multiforme/.

131. Jeppesen AN, Christiansen CF, Froslev T, Sorensen HT. Hospitalization rates and prognosis of patients with anaphylactic shock in Denmark from 1995 through 2012. Journal of Allergy and Clinical Immunology. 2016;137(4):1143-7.

132. Nygaard U, Holm M, Hartling UB, Glenthoj J, Schmidt LS, Nordly SB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. Lancet Child Adolesc Health.

2022;6(7):459-65.

133. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021;373:n1114.

134. Hegelund ER, Kjerpeseth LJ, Mortensen LH, Igland J, Berge T, Anjum M, et al. Prevalence and Incidence Rates of Atrial Fibrillation in Denmark 2004-2018. Clin Epidemiol. 2022;14:1193-204.

135. Lægehåndbogen. sundhed.dk. Medically induced liver injury 2022 [cited 2023 02 February]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/mave-tarm/tilstande-og-sygdomme/lever/leverskader-medikamentinduceret/.

136. EUPAS. EUPAS13413 unpublished 2022 [cited 2023 02 February]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=50541.

137. Carlson N, Hommel K, Olesen JB, Soja AM, Vilsboll T, Kamper AL, et al. Dialysis-Requiring Acute Kidney Injury in Denmark 2000-2012: Time Trends of Incidence and Prevalence of Risk Factors-A Nationwide Study. PLoS One. 2016;11(2):e0148809.

138. Sawhney S, Bell S, Black C, Christiansen CF, Heide-Jorgensen U, Jensen SK, et al. Harmonization of epidemiology of acute kidney injury and acute kidney disease produces comparable findings across four geographic populations. Kidney Int. 2022;101(6):1271-81.

139. Tidsskriftet. Hvor mange har diabetes i Norge i 2020? 2020 [cited 2023 03 March]. Available from: https://tidsskriftet.no/2020/11/kronikk/hvor-mange-har-diabetes-i-norge-i-2020.

140. statistikbank.fhi.no. Hjerte- og karregisteret [cited 2023 03 March]. Available from: https://statistikkbank.fhi.no/hkr/.

141. Tidsskriftet. Takotsubo syndrome in Sørlandet Hospital Arendal 2010–16 2019 [cited 2023 03 March]. Available from: https://tidsskriftet.no/en/2019/01/originalartikkel/takotsubo-syndrome-sorlandet-hospital-arendal-2010-16.

142. Ghanima W, Brodin E, Schultze A, Shepherd L, Lambrelli D, Ulvestad M, et al. Incidence and prevalence of venous thromboembolism in Norway 2010-2017. Thromb Res. 2020;195:165-8.

143. Folkehelseinstituttet. The Cause of Death Registry of Norway 2023 [cited 2023 17 March]. Available from: https://statistikkbank.fhi.no/dar/.

144. Farbu E, Rudolph T, Stefansdottir S. Guillain Barre syndrome--Incidence and clinical course in Southern Rogaland, Norway. Clin Neurol Neurosurg. 2016;141:33-7.

145. Kjerpeseth LJ, Igland J, Selmer R, Ellekjaer H, Tveit A, Berge T, et al. Prevalence and incidence rates of atrial fibrillation in Norway 2004-2014. Heart. 2021;107(3):201-7.

146. Miriam Sturkenboom DM, Olga Paoletti, Airam de Burgos-Gonzalez, Patricia García-Poza, Consuelo Huerta, Ana Llorente- García, Mar Martin-Perez, Maria Martinez, Ivonne Martin, Jetty Overbeek, Marc Padros-Goossens, Patrick Souverein, Karin Swart, Olaf Klungel, Rosa Gini. Cohort monitoring of 29 Adverse Events of Special Interest prior to and after COVID-19 vaccination in four large European electronic healthcare data sources (not peer reviewed). 2022.

147. Li X, Raventos B, Roel E, Pistillo A, Martinez-Hernandez E, Delmestri A, et al. Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis. BMJ. 2022;376:e068373.

148. Bartoll-Roca X, Pérez K, Artazcoz L. Agència de Salut Pública de Barcelona. Informe de resultats de l'Enquesta de Salut de Barcelona del 2021 2022 [cited 2023 27 March]. Available from: https://www.aspb.cat/wp-content/uploads/2022/11/ASPB_Enquesta-Salut-Barcelona-2021.pdf.

149. Institut d'Estadística de Catalunya. Defuncions i taxa bruta de mortalitat 2023 [cited 2023 27 March]. Available from: https://www.idescat.cat/indicadors/?id=anuals&n=10344&lang=en.

150. Jurek AM, Greenland S, Maldonado G, Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int J Epidemiol. 2005;34(3):680-7.

151. Maclure M, Schneeweiss S. Causation of bias: the episcope. Epidemiology. 2001;12(1):114-22.

152. Wang SV, Kulldorff M, Glynn RJ, Gagne JJ, Pottegard A, Rothman KJ, et al. Reuse of data sources to evaluate drug safety signals: When is it appropriate? Pharmacoepidemiol Drug Saf. 2018;27(6):567-9.

153. CDC. Morbidity and Mortality Weekly Report (MMWR). COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021 2021 [cited 2022 26 March]. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7043e2.htm.

154. Poole C. Low P-values or narrow confidence intervals: which are more durable? Epidemiology. 2001;12(3):291-4.

155. Nauta J. Vaccine Safety. In: Nauta J, editor. Statistics in Clinical and Observational Vaccine Studies. Cham: Springer International Publishing; 2020. p. 177-88.

156. Wisniewski AF, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, et al. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf. 2016;39(6):469-90.

15. Annex 1: List of stand-alone documents

15.1. Output tables with study results

Appendix_Tables_1_2_3.xlsx
Appendix_Table_4.xlsx
Appendix_Table_5.xlsx
Appendix_Table_8.xlsx
Appendix_Table_9.xlsx
Appendix_Table_18_19_20.xlsx
Appendix_Table_21.xlsx

15.2. Diagnosis and medication codes used to define study variables

Appendix 1_codelist and algorithms.xlsx

16. Annex 2: Analyses included in the Fourth Interim Report

	Preliminary results included in Fourth Interim Report								
	Signal detection			Signal evaluation					
Country	Population description and selection	Crude incidence rates and SMRs stratified on age and sex	Crude incidence rates and SMRs in subpopulations	SCCS	SCRI	Cohort study with matched historical comparators	Cohort study with contemporaneous comparators	Cohort study of VAED	Prognosis post myocarditis/ pericarditis
Denmark	Yes	Yes	No	Yes	No	No	No	No	Descriptive
Italy	No	No	No	No	No	No	No	No	No
Norway	Yes	Yes	No	Yes	No	No	No	Yes	Descriptive
Spain	Yes	Yes	No	Yes	No	No	No	No	No
United Kingdom*	Yes	No	No	No	No	No	No	No	No

* Analyses are limited to the population description and selection in the CPRD, which is primarily related to the CPRD data quality issue communicated by the CPRD to the users (e-mail communication on file). This issue has impacted all downstream activities and deliverables across the VAC4EU studies that involve the current data extraction.

Signature Page for VV-CLIN-010242 v1.0

Approval	[redacted]ce 28-Mar-2023 18:12:48 GMT+0000

Approval	[redacted]ilance 29-Mar-2023 15:26:55 GMT+0000

Signature Page for VV-CLIN-010242 v1.0