PASS information

Title	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe
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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
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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 coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign is currently underway in Europe. The Moderna mRNA-1273 vaccine, known as Spikevax, combines Moderna's messenger ribonucleic acid (mRNA) delivery platform with the stabilised SARS-CoV-2 spike immunogen. Spikevax has been conditionally authorised in the European Union and in the United Kingdom since January 2021. 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.

This Third Interim report was prepared according to the reporting schedule outlined in the Study Protocol Version 1.2, dated 27 September 2021; 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

Study design

Per protocol, this study has two phases: signal detection and signal evaluation. Only signal detection analysis was conducted for this report. For the signal detection, a cohort design was applied to obtain age-and sex-standardised morbidity ratios (SMRs) to compare observed vs expected AESI events in the Spikevax recipients. To estimate the expected number of events, population-based, country-specific historical general population background rates of the AESI were used.

Setting

This study is based on electronic, routinely collected data from regional databases 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.

Subjects and study size, including dropouts

All individuals in a database-specific data instance were eligible for inclusion. Spikevax recipients in Denmark, Italy, Norway, and Spain were identified from 11 January 2021 and until 31 December 2021. Cohorts of Spikevax recipients were defined separately for first, second, and third Spikevax dose receipt. The purpose of the historical cohort was to define background rates of the AESI in a given population, from 01 January 2017 to 31 December 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 31 December 2021.

Variables and data sources

This Third Interim Report includes selected results from the databases in Denmark (national registries), Italy (Agenzia Regionale di Sanita' della Toscana, ARS), Norway (national registries), and Spain (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, SIDIAP). Results from the UK (Clinical Practice Research Datalink, CPRD) were unavailable for inclusion in this report. 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 and subgroups were defined based on routinely recorded primary- or secondary-care diagnoses, and/or medication proxies.

Based on observed vs expected counts, country-specific standardised morbidity ratios (SMRs) were estimated overall and stratified on sex, and age groups. Persons with a prevalent AESI event in previous 2 years were excluded from computation of a given AESI rate. An SMR ≥ 2.0 based on a case count ≥ 5 was defined as signal and are examined further in signal evaluation. This Third Interim Report contains results of signal detection only. Signal

evaluation results will be conducted in subsequent reports.

Results

Per the Protocol's reporting schedule, this Third Interim Report contains description of the progress made since the Second Interim Report , the challenges encountered, and proposed mitigation strategies. In addition, the Third Interim Report includes selected preliminary results from Denmark, Italy (ARS), Norway, and Spain (SIDIAP). The following results are included: population description and selection for Denmark, Italy (Spikevax and historical cohorts), Norway and Spain (Spikevax cohorts); crude AESI rates in Spikevax (ARS, Norway) and historical (ARS) cohorts; and signal detection results (SMRs) in Italy. Subgroups and subpopulations are reported descriptively in terms of number and prevalence in a given population.

During the study period covered by the current data instance, the number of eligible Spikevax recipients with at least one dose of Spikevax was 563,998 in Denmark, 428,779 in Italy, 532,797 in Norway, and 587,436 in Spain.

Rates of several AESIs were lower than expected in Italy, subject to further investigation and quality control.

Results of the signal detection, available from the Italy/ARS database, identified the following AESIs as fulfilling prespecified criteria for additional signal evaluation based on at least one analysis performed: Diabetes type 1, (Idiopathic) Thrombocytopenia , Microangiopathy, Heart failure, Stress-induced cardiomyopathy, Coronary artery disease, Arrhythmia, Myocarditis, Pericarditis, Cerebrovascular disease, Deep vein thrombosis, Splanchnic vein thrombosis, Coagulation disorders, Acute liver injury, Acute kidney injury, Generalised convulsions, Acute respiratory distress syndrome, Anaphylaxis, and Death of any cause. No signal evaluation was undertaken, and signal detection was not conducted in other databases.

Discussion

This Third Interim Report contains preliminary study results from the selected participating countries/databases. Compared with the Second Interim Report, the main progress in the data implementation consists of the addition of selected results from Denmark and Norway; extending the observation period by 4 months; use of further refined operational definitions of AESI and subgroups, and identification of points of challenge and strategies to mitigate them. Crude incidence rates of the AESIs in the Spikevax and the historical cohorts, reported in Italy and in Norway were broadly plausible, except for selected AESIs in Italy, subject to checking in subsequent reports.

Results of the signal detection, available from a single participating country should not be interpreted in the light of lack of the result of a formal signal evaluation and are subject to biases.

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. Further

implementation of the quality control measures will occur in the subsequent reports. Results inclusive of all participating countries and all study objectives will be presented and interpreted in the Final Study Report.

Marketing Authorisation Holder(s)

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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
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-Barre syndrome
GP	General practitioner
GVP	Guideline on good pharmacovigilance practices
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
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
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
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

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4. Other responsible parties

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

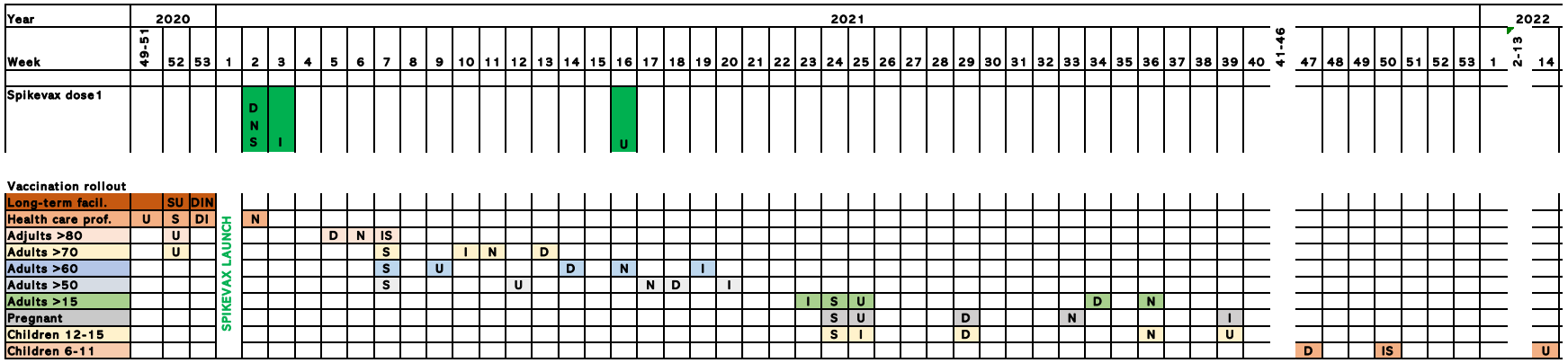
Table 1. Number of Spikevax doses administered in the participating countries

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; 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 (Denmark, Italy, Norway, Spain): https://ourworldindata.org/covid-vaccinations "Which vaccines have been administered in each country?"(2); Source (UK): gov.uk (13)).

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



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

Sources: Spikevax, licensed (11, 12); Denmark (14-18); Norway (19-22); Italy (23-28); Spain (29, 30); UK (31-36). Exact boundaries for the age groups may differ slightly by country.

The European Union (EU) Risk Management Plan (RMP) for Spikevax, version 4.2 dated 26 August 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 risk. Missing information includes use in pregnancy (addressed in a separate protocol (37)), 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 (38).

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) (39). 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 occurrence, while among those with myocarditis/pericarditis, older age and comorbidity were risk factors for poor prognosis (40). In an epidemiologic registry-based Danish study of mRNA COVID 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 risk increase was driven by persons 12-39 years of age and by women, however, the absolute risks were low in all subgroups(41). A subsequent study in four Nordic countries (42) corroborated the Danish findings, as did the study among mRNA COVID-19 vaccinees aged 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 (43). 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 (44).

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 will be 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 trial populations (45). Among the prespecified AESI, this study will 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 in five European countries: Denmark, Italy, Norway, Spain, and the UK. The countries were selected based on availability of specific data elements, including information on vaccine brand, frequency of updates, and data recency/lags. According to the study Protocol, this Third Interim Report is expected to include a status update, providing an overview of any progress made from the Second Interim Report.

Section 16 describes in detail 1) the project progress made by the research team since the Second Interim Report; 2) the challenges identified; and 3) the mitigation strategies to address the challenges in preparing the Fourth Interim Report and the Final Study Report. In addition to the contents specified in the protocol, the Third Interim Report includes available results from Denmark, Italy, Norway, and Spain as further specified in Table 6.

7. Research question and objectives

The overarching causal research question of this study is (46):

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. Note: No results for VAED and VITT are included in this interim report.
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: This amendment does not affect results reported in the present

		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: No SCRI analyses are included in this interim report.
4	Minor	Renamed the subgroup "frail subjects with unstable health conditions and chronic co-morbidities" to "patients with chronic health conditions" to acknowledge that frailty and unstable conditions are not well measured in the available data sources

9. Research methods

This report was prepared according the research methods described in the Study Protocol Version 1.2, dated 27 September 2021 and registered in The European Union electronic Register of Post-Authorisation Studies (EU PAS Register) (47); and according to the SAP Version 2.0, dated 17 June 2022. This section described only the research methods applicable per results reported in this Third Interim Report (Table 6).

9.1. Study design

For the signal detection, the cohort study design was used.

This interim report contains preliminary results of the signal detection phase (see Section 9.1.1). Historical rates cannot be used for the AESIs VITT and VAED, as they, by definition, can only be observed in COVID-19 vaccinees. Therefore, these AESIs are not included in the signal detection. Instead VITT enters directly into signal evaluation and VAED is investigated in a separate cohort design. No results for VAED and VITT are included in the present report, but they will be included in future reports (see Table 6 for an overview of included results).

Table 2. List of AESIs and overview of study design and main measure of association for signal detection

Body system/ Classification	AESI	Study design for signal detection	Main measure of association
Auto-immune diseases	Guillain-Barré Syndrome (GBS)	Observed vs expected	SMR
	Acute disseminated encephalomyelitis (ADEM)	Observed vs expected	SMR
	Narcolepsy	Observed vs expected	SMR
	Acute aseptic arthritis	Observed vs expected	SMR
	Diabetes type 1	Observed vs expected	SMR
	(Idiopathic) Thrombocytopenia	Observed vs expected	SMR
Cardiovascular system	Microangiopathy	Observed vs expected	SMR
	Heart failure	Observed vs expected	SMR
	Stress-induced cardiomyopathy	Observed vs expected	SMR
	Coronary artery disease	Observed vs expected	SMR
	Arrhythmia	Observed vs expected	SMR
	Myocarditis	Observed vs expected	SMR
	Pericarditis	Observed vs expected	SMR
	Cerebrovascular disease	Observed vs expected	SMR

Circulatory system	Deep vein thrombosis (DVT)	Observed vs expected	SMR
	Pulmonary embolism (PE)	Observed vs expected	SMR
	Single Organ Cutaneous Vasculitis	Observed vs expected	SMR
	Cerebral venous sinus thrombosis (CVST)	Observed vs expected	SMR
	Splanchnic vein thrombosis (SVT)	Observed vs expected	SMR
	Coagulation disorders	Observed vs expected	SMR
	Disseminated intravascular coagulation (DIC)	Observed vs expected	SMR
	Kawasaki disease	Observed vs expected	SMR
Hepato-gastrointestinal and renal system	Acute liver injury	Observed vs expected	SMR
	Acute kidney injury	Observed vs expected	SMR
Nerves and central nervous system	Generalised convulsions	Observed vs expected	SMR
	Encephalitis/meningoencephalitis	Observed vs expected	SMR
	Transverse myelitis	Observed vs expected	SMR
	Bell's palsy	Observed vs expected	SMR
Respiratory system	Acute respiratory distress syndrome (ARDS)	Observed vs expected	SMR
Skin and mucous membrane, bone and joints system	Erythema multiforme	Observed vs expected	SMR
	Chilblain – like lesions	Observed vs expected	SMR
Other systems	Anosmia, ageusia	Observed vs expected	SMR
	Anaphylaxis	Observed vs expected	SMR
	Multisystem inflammatory syndrome	Observed vs expected	SMR
	Vaccine-associated enhanced COVID-19 disease (VAED) or vaccine associated enhanced respiratory disease (VAERD)*	NA†	NA†
	Vaccine-induced immune thrombotic thrombocytopenia*	NA†	NA†
	Sudden death	Observed vs expected	SMR
	Death of any cause	Observed vs expected	SMR
Abbreviations: NA=not available; SMR=Standardised Morbidity Ratio *Historical rates cannot be used for these AESIs, as they can, by definition, be observed only in COVID-19 vaccinees. Therefore, these AESIs are not included in the signal detection. Instead VITT enters directly into signal evaluation and VAED is investigated in a separate cohort design. †Not included in this interim report, but planned for future interim reports.			

9.1.1. Signal detection

Signal detection proceeded by comparing the number of observed vs. expected events for each AESI, as previously recommended 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 (48, 49). Indirect standardization according to age and sex was used (50) to estimate Standardised Morbidity Ratio (SMR), as the number of observed events divided by the number

of expected events in Spikevax recipients. Population-based, country-specific historical background rates of the AESI estimated in each participating database before the COVID-19 pandemic (2017-2019) served as estimates of the expected rates in the unvaccinated (51). The cohort definitions are shown in Figure 2 for the Spikevax cohort and in Figure 3 for the historical cohort (All visualisations of study designs in this report were inspired by Schneeweiss et al.(52)).

To ensure capture of risk increases both in short - and long-term following a vaccination, the SMRs were estimated in the following time intervals after the date of 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 and by country. To contextualise the SMRs, we also provide number of events and crude incidence rates within the same intervals and strata for both the historical cohort and the Spikevax cohort.

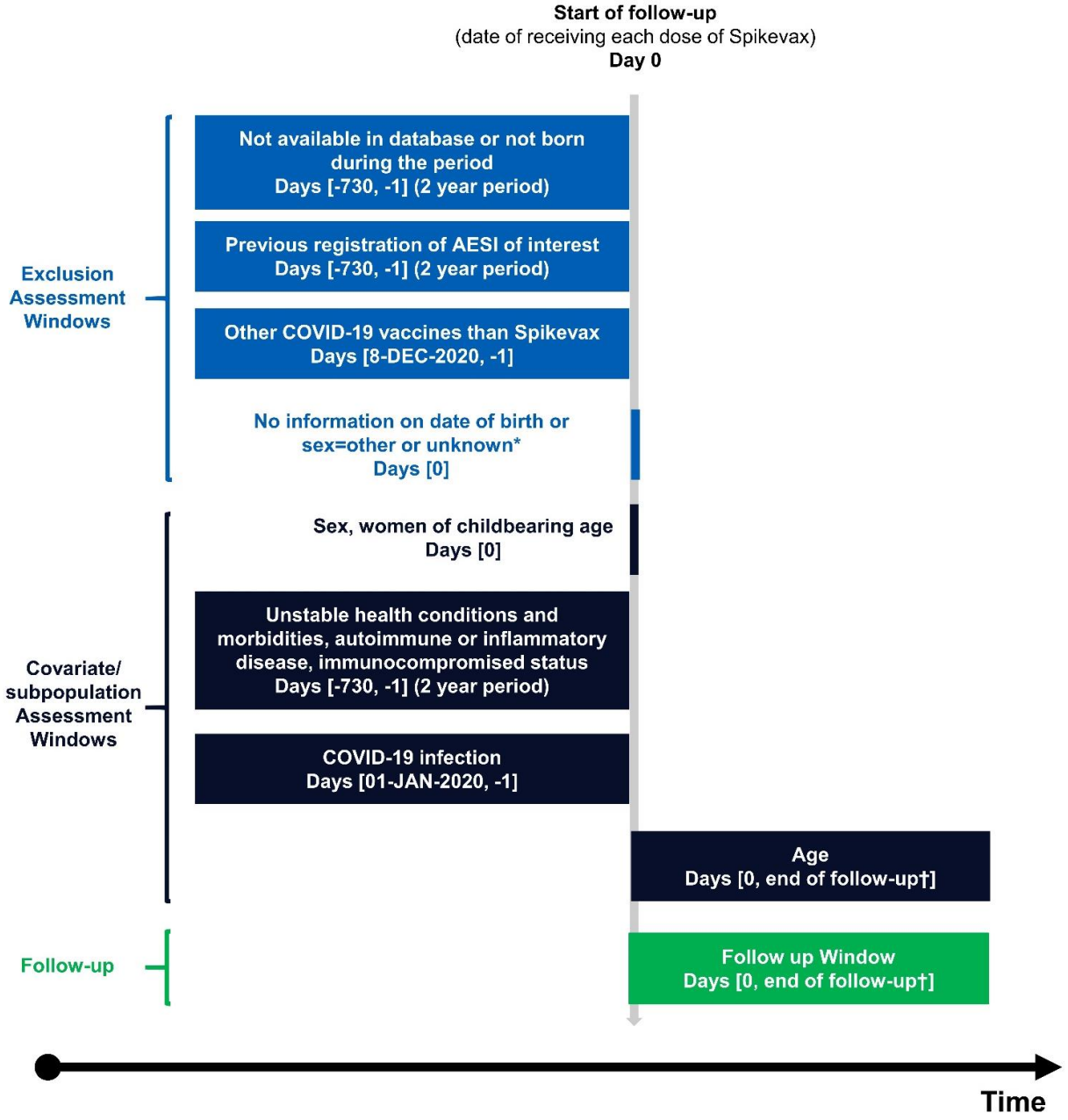
The Third Interim Report contains a subset of the planned results from the signal detection analysis according to availability for the following participating countries/databases: Denmark, Italy, Norway, and Spain. Table 6 gives the exact details of the currently available results and Section 16.2 gives an overview of the actions taken and planned to be able to include full signal detection analysis for the Fourth Interim Report.

For a given AESI, a signal is defined if both of the following conditions are met:

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

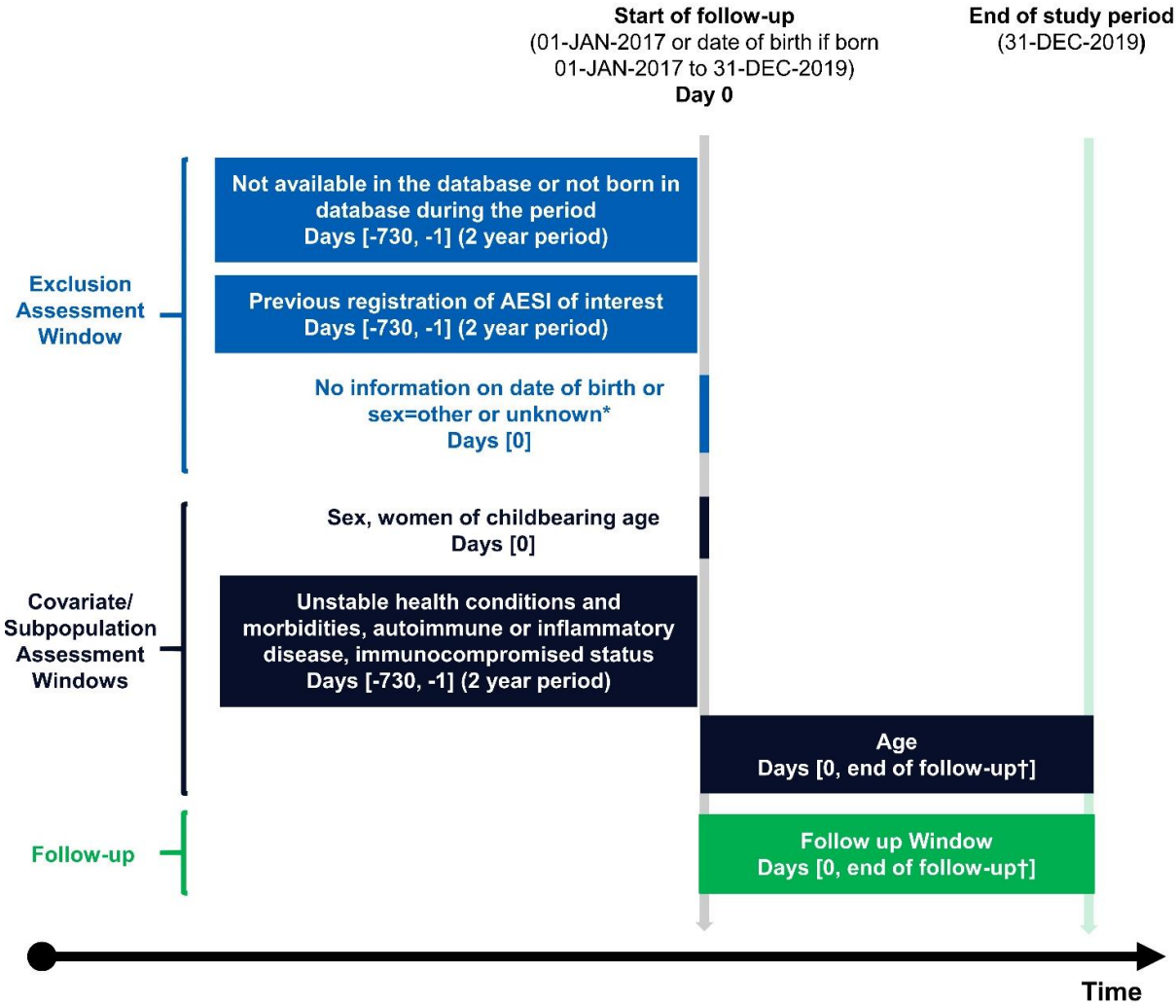
2) The number of Spikevax-exposed cases is ≥5 or higher within that analysis.

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



* Exclusions made as data on age (calculated from date of birth) and sex (female or male) are required for indirect standardization.
† 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 Denmark, Italy, Norway, and Spain).

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



* Exclusions made 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.

9.2. Setting

This study is based on electronic, routinely collected data from regional databases 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, Italy, Norway, and Spain. 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 Denmark, Italy, Norway, 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 31 December 2021.

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 after 11 January 2021 and 31 December 2021, followed until 31 December 2021 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 in 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 exit, 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 exit, 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 or were born between 01 January 2017 and 31 December 2019 followed through 31 December 2019. We applied the following exclusion criteria:

1. Age ≥ 2 years on 01 January 2017 and were not a database member between 01 January 2015 to 31 December 2016 (no 2-year lookback)
2. Age <2 years on 01 January 2017 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 follow-up start

Persons in this cohort were followed from 01 January 2017 (or from date of birth if born after 01 January 2017) and until the earliest date of the following: AESI of interest, death, database disenrollment, or 31 December 2019.

9.4. Variables

9.4.1. Exposure: Spikevax vaccination

We defined dates of Spikevax vaccination based on the routinely collected Spikevax vaccination dates as recorded in the participating databases. If the administration date of Spikevax vaccination was recorded this was used as the date of Spikevax vaccination, however, if the administration date was not reported, then the date of recording of the Spikevax vaccination was used. In cases of records of Spikevax vaccination occurring within 20 days of a previous recording of Spikevax, only the first date of Spikevax vaccination was

retained. We chronologically classified doses of Spikevax vaccination dose 1, dose 2 or later doses.

9.4.2. Adverse events of special interest

For the Third Interim Report, we identified the AESIs other than "Death of any cause" (Table 2) based on diagnosis codes recorded during routine health care, using database specific vocabularies. 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 (53). Many of the definitions have been used in the vACCine COVID-19 monitoring readinESS (ACCESS) project, an EMA-commissioned study to estimate background rates of the COVID-19 vaccine AESIs (54, 55). Whenever necessary, the ACCESS definitions were refined and missing definitions added. The process of refinement of case-finding algorithms is ongoing (Section 16.2 provides an elaboration).

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 Denmark it was not possible to apply the different definitions for prevalent AESI events, affecting, in this report, only descriptive data (Section 16.2 describes relevant strategies for refinement of variable definitions).

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

9.4.3. Subpopulations

Per-protocol, the following five subpopulations were identified 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 3 gives an overview of the conditions included in each subpopulation identified based on diagnosis codes. Table 3 also include information related to the use of medication proxies for some categories (No medication proxies were applied in Denmark for the current analysis).

In the current report, prevalence of the different subpopulations is reported descriptively only. No rates or SMRs are presented in these subgroups.

Table 3. 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		No
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
	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

Section 15.2 provides list of all diagnosis and drug codes used to define the study variables.

9.4.4. Other variables

We defined sex based on registration in the included databases.

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 regardless of inclusion of their results in the Third Interim Report, 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 (56). 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: Danish National Prescription Registry (tracks dispensings or prescription medications from 1995 and, including dispensing date, Anatomical Therapeutic Chemical (ATC) code, product code and amount). Danish National Health Service Register (records referrals to primary care services, including general practitioner (GP) contacts, examinations, procedures, pregnancy-related visits, vaccinations (other than COVID-19); psychologist or psychiatrist and other primary care provider visits; etc); the Danish Civil Registration System (sex, date of birth, migration, vital status); 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 (57). Danish registries are listed as a resource in the EU PAS Register (https://www.encepp.eu/encepp/viewResource.htm?id=42187).

Italy: the ARS database

The Agenzia Regionale di Sanita' della Toscana (ARS) is a research institute of the Tuscany Region, whose population amounts to around 3.6 million inhabitants. The ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care

prescriptions of drugs that are intended for outpatient or community setting, which are linkable at the individual level with hospital admissions, admissions to emergency care, records of exemptions from co-payment, diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. Mother-child linkage is possible through the birth registry. Vaccine data is available since 2016 for children and since 2019 for adults. The ARS database is considered fit for purpose for vaccine coverage, benefits and risk assessment when using the new vaccine registry (from 2019) (57). The ARS Toscana database is an ENCePP centre (https://www.encepp.eu/encepp/viewResource.htm?id=8133).

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 Norway Control and Payment of Health Reimbursement (KUHR) (data on diagnoses and procedures following contact with specialist outpatient clinics and the primary care system/GPs); the Norwegian Immunisation Registry (SYSVAK) (information on COVID-19 vaccinations); the Norwegian Surveillance System for Communicable Diseases (information on results of PCR SARS-Cov-2 tests), Norwegian Patient Registry and the Norwegian Prescription Database (NorPD, https://www.encepp.eu/encepp/viewResource.htm?id=25552). Data from the latter two resources were unavailable for this Third Interim Report, but will be available for the subsequent reports (Section 16.2).

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. 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 International Classification of Diseases, 10th Revision (ICD-10) 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 (57).

9.5.2. Measurement

COVID-19 vaccines

In Denmark, information on COVID-19 vaccines including date and manufacturer was obtain from a register of COVID-19 vaccines, which was based on the Danish Vaccination Registry. In Italy, the vaccination registry includes information on vaccines given by paediatricians or by the local health units, but do not include vaccines administrated by GPs. The registry includes information on date of vaccination, type of vaccine and the vaccine manufacturer. In Norway, information on COVID-19 vaccines including date and manufacturer was obtained from the Norwegian Immunization Registry. In Spain, information on all vaccines administered at primary care centres and mass vaccination centres are available, and include type of vaccine, date of vaccination and for COVID-19 vaccine the manufacturer.

Diagnoses and medication use

For this interim report, we defined AESIs, subpopulations, and comorbidities 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 record diagnosis according to the Danish version of ICD-10 for all contacts with Danish hospitals. For the present report it was not possible to include information on medication use from the Danish National Prescription registry, but will be included in next report.

In the Italian data from the Tuscan region, diagnosis codes originate from four different register sources: 1) The Tuscan discharge records include persons discharged from a Tuscan hospital and persons who are legal residents in Tuscany and have been discharged from any Italian hospital. Diagnoses are registered according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes. 2) The emergency admission registry contains records from every admission to an emergency room in the Tuscan region and

reports diagnoses by ICD-9CM codes. 3) The register of mental health services includes patients admitted to treatment pathways in a Tuscan regional Mental Health service and reports diagnoses both according to ICD-9CM and ICD-10 codes. 4) The exemption registry records diagnoses of persons who have been exempt from co-payment. Usually, Tuscan citizens are required to cover part of the cost of health care by paying a share of the value of certain services. Exemption from this duty is available either due to low income, certain diseases or age (general exemption for citizens under the age of six or over sixty-five years of age, unless they are in a favourable income situation). Diagnoses are recorded using ICD-9CM codes. In Italy, information on medication use originated from two registries, which both use ATC codes in the recording: 1) Registry of medication dispensed at community pharmacies. 2) Registry of medications dispensed at hospital pharmacies for outpatient use.

In Norway, information on diagnoses was obtained from the Norway Control and Payment of Health reimbursement (KUHR), which contain information on (I) primary care encounters coded, according to International Classification of Primary Health Care (ICPC); (II) specialist outpatient encounters coded according to the ICD-10 classification. The KUHR is an administrative database based on electronically submitted reimbursement claims from physicians to the Norwegian Health Economics Administration. There was no information on inpatient diagnosis (i.e., diagnosis given at hospital admission and during the hospital stay) or use of medication available from Norway for this report due to delays from data providers (see Section 16.2 for details).

In the Spanish data from the Catalan region, the diagnoses originate from two different sources. 1)The registry of primary care diagnoses includes medical diagnoses registered by International Classification of Diseases, 10th Revision, Clinical Modification (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 data extraction only data since 2016 on hospital discharges was available. In SIDAP data, information on medication originates from a 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.

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 Italy, the basic demographic characteristics are collected from a registry collecting information on all persons assigned to a primary care physician in Tuscany. If a primary care physician retires the patients will be lost from the registry and reappear in the database (with same ID number) when they register with a new primary care physician. Therefore, we have continued to follow-up for persons who get a new primary care physician <1 year (=365 days) after the last registration with the previous primary care physician. The observation period of

newborns was set to start at the date of birth if they were registered with a primary care physician <60 days after the date of birth. The registration of the population was supplemented with information from the hospital discharge registry of newborns not recorded in the registry of primary care physicians (potentially because they died shortly after birth).

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.

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.

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 Italy, information on positive COVID-19 PCR test was obtained from the COVID-19 registry of the Italian National Institute of Health. This registry contains information on the first-time registrations of positive PCR tests including the date of testing. However, in the most recent period this registry also started to include antigen tests and the different test types are not distinguishable from the database records. 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 registry of COVID-19 tests.

9.6. Bias

This study addresses potential bias both on design and the analysis stage. At the signal detection stage (analysis provided here), 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. Future signal evaluation analyses will include confounding control.

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) (58, 59). 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, 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.

For Denmark, due to server capacity issue (Section 16.2), it was not possible to run the centrally distributed scripts, but the provided analyses were produced using locally generated SAS scripts translated from the centrally distributed R scripts.

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 means with standard deviations (SD) and medians with quartiles for continuous variables.

9.9.2. Main statistical methods

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 (50) to estimate Standardized Morbidity Ratio (SMR) 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 (60). 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).

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 records were excluded from the analyses, and imputation was not attempted.

9.9.4. Sensitivity analyses

Not performed for the Third Interim Report.

9.9.5. Amendments to the statistical analysis plan

None.

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. For Denmark it was not possible to perform the level checks due to server capacity issues (see Section 16.2).

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'ed data at each DAP. Double programming of portions of the analysis per SAP is being prepared and will be conducted in subsequent reports (Section 16.2). Country specific-results were reviewed for plausibility by the principal investigators and the co-investigators in each country.

10. Results

10.1. Participants

Denmark

In the nationwide registry-based data in Denmark, there were 669,538 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 563,998 persons (84.2% of the base population). The most prevalent exclusion criterion, 87,139 persons (13.0%) 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, 1,094 (1.3%) had previously received the Pfizer vaccine, 52,195 (59.9%) the Astra Zeneca vaccine, and 33,877 (38.9%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 632,664 persons, 557,833 persons (88.2%) were included (Table 1.A., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort with of 439,010 persons 430,912 persons (98.2%) (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 5,910,875 persons for the historical cohort, 5,759,099 (97.4%) were included in the analysis (Table 1.A., Appendix_Table_1_2_3).

Italy

In Italy/ARS database, there were 956,060 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 428,779 persons (44.8% of the base population). The most prevalent exclusion criterion (490,372, 51.3% of the base population) was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (Table 1.B., Appendix_Table_1_2_3). Among those, 311,457 (63.5%) had previously received the Pfizer vaccine, 152,605 (31.1%) the Astra Zeneca COVID-19 vaccine, and 30,123 (6.1%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 399,564 persons, 376,633 (94.3%) were included (Table 1.B., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort of 74,787 persons, 73,607 (98.4%) were included (Table 1.B., 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. Due to a small count of persons (11) excluded from the third-dose Spikevax cohort, only their count can be reported.

From the base population of 3,611,578 for the historical cohort, 3,440,645 (95.3%) were included in the analysis (Table 1.B., Appendix_Table_1_2_3).

Norway

In the nationwide registry-based data in Norway, there were 1,293,026 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 532,797 persons (41.2% of the base population). The most prevalent exclusion criterion was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (743,160 persons [57.5% of base population]; Table 1.C., Appendix_Table_1_2_3). Among those 743,160 persons, 739,198 (99.5%) had previously received the Pfizer vaccine, 13,209 (1.8%) the Astra Zeneca vaccine, and 306 (<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 455,076 persons, 430,767 persons (94.7%) were included (Table 1.C., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort with of 71,432 persons, 71,276 persons (99.8%) were included (Table 1.C., 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. Due to small number of persons (35), excluded from the third-dose Spikevax cohort, only their count can be reported.

The historical cohort data were unavailable for Norway in this report and will be included in the subsequent reports (see Section 16.2 for details).

Spain

In Spain/SIDIAP database, there were 1,748,457 persons with at least one dose of Spikevax. After applying the exclusion criteria, the first-dose Spikevax cohort included 587,436 persons (33.6% of the base population). The most prevalent exclusion criterion was receipt of other types of COVID-19 vaccines before the first dose of Spikevax (1,126,622 persons [64.4% of the base population] Table 1.D., Appendix_Table_1_2_3). Among those 1,126,622 persons, 586,734 (52.1%) had previously received the Pfizer vaccine, 433,275 (38.5%) the Astra Zeneca vaccine, and 110,494 (9.8%) the Johnson and Johnson vaccine (Table 2.i., Appendix_Table_1_2_3).

From the base population for the second-dose of Spikevax of 475,163 persons, 459,399 persons (96.7%) were included (Table 1.D., Appendix_Table_1_2_3). From the base population for the third-dose Spikevax cohort with of 96,229 persons, 95,653 persons (99.4%) were included (Table 1.D., 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. Due to small number of persons (30), excluded from the third-dose Spikevax cohort, only their count can be reported.

10.2. Descriptive data

Denmark

The Spikevax 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 Spikevax cohorts (29-33%) than in the historical comparison cohort (22.5%) (Table 3.A., Appendix_Table_1_2_3). The Spikevax cohort and the historical cohort had a similar proportion of patients with chronic health conditions (6-7%); autoimmune or inflammatory disorders (1.4-2%); or indicators of immunocompromised status (1.5-2%) (Table 3.A., Appendix_Table_1_2_3). Proportion of persons with a previous COVID-19 infection (10.1%) was the highest in the third-dose Spikevax cohort (Table 3.A., Appendix_Table_1_2_3).

Italy/ARS

The Spikevax cohorts consisted of more males (e.g., 51.9% for the first dose of Spikevax) compared with the historical cohort (47.9%; Table 3.B., Appendix_Table_1_2_3). The first-dose Spikevax cohort had a lower median age (43 years, quartile 1 – quartile 3 [Q1-Q3]=29-58) than both the historical cohort (49 years, Q1-Q3=28-66) and the third-dose Spikevax cohort(59 years, Q1-Q3=49-66; Table 3.B., Appendix_Table_1_2_3). In the cohorts receiving the first and second dose of Spikevax, the proportion of women of childbearing age (≈31%) was higher than in the historical comparison cohort (20.4%) and the cohort that had received the third dose of Spikevax (12.7%; Table 3.B., Appendix_Table_1_2_3). The cohort of persons receiving the third dose of Spikevax had a higher proportion of patients with chronic health conditions (61.1%) compared with the historical comparison cohort (47.8%) and the cohorts

receiving a first or second dose of Spikevax (≈38%; Table 3.B., 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.B., Appendix_Table_1_2_3). Among person who had received the first dose of Spikevax, 8.0% had previously had a recorded COVID-19 infection (Table 3.B., Appendix_Table_1_2_3).

Norway

The first-dose Spikevax cohort had a lower median age (42 years, quartile 1 – quartile 3 [Q1-Q3]=30-57) than both the second-dose Spikevax cohort (46 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). Consequently, the proportion of women of childbearing age was considerably lower in the cohort that had received the third dose of Spikevax (10.2%; Table 3.C., Appendix_Table_1_2_3) than in the other cohorts (30.9% in the first-dose Spikevax cohort and 28.9% in the cohort for the second dose of Spikevax). The cohort of persons receiving the third dose of Spikevax had a higher proportion of patients with chronic health conditions (38.9%) compared with the cohorts receiving the first (18.5%) or second dose of Spikevax 20.7%; Table 3.B., 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). Among person who had received the first dose of Spikevax, 4.3% had previously had a recorded COVID-19 infection (Table 3.C., Appendix_Table_1_2_3).

Spain/SIDIAP

The first-dose and second-dose Spikevax cohorts had similar characteristics, but differed considerably from the third dose cohort, which had more females (53.2% compared with 48.5% in the first-dose cohort), a higher median age (56 years [Q1-Q3=48-68] compared with 37 years [Q1-Q3=26-53] in the first-dose cohort), and more patients with chronic health conditions (63.0% compared with 35.2% in the first-dose cohort; Table 3.D., 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.D., Appendix_Table_1_2_3). Among person who had received the first dose of Spikevax, 15.9% had previously had a recorded COVID-19 infection; the corresponding proportion was 6.8% in the second dose cohort and 9.6% in the third dose cohort (Table 3.D., Appendix_Table_1_2_3).

10.3. Outcome data

Table 4s in Apendix_Table_4_part1 and Apendix_Table_4_part2 show country-specific crude incidence rates of the AESIs in the historical cohort from Italy and in the dose-specific Spikevax cohorts from Italy and Norway, according to post-dose observation period, overall and stratified on sex and age.

In Italy/ARS database, at least one event was detected in the Spikevax cohort based on the current event definitions, after vaccination and until the end of the follow-up: ADEM (Table 4.2.iv.B), type 1 diabetes (Table 4.5.iv.B), ITP (Table 4.6.iv.B), microangiopathy (Table

4.7.iv.B), heart failure (Table 4.8.iv.B), stress-induced cardiomyopathy (Table 4.9.iv.B), coronary artery disease (Table 4.10.iv.B), arrhythmia (Table 4.11.iv.B), myocarditis (Table 4.12.iv.B), pericarditis (Table 4.13.iv.B), cerebrovascular disease (Table 4.14.iv.B), DVT (Table 4.15.iv.B), single-organ cutaneous vasculitis (Table 4.17.iv.B), CVST (Table 4.18.iv.B), splanchnic vein thrombosis (Table 4.19.iv.B), coagulation disorders (Table 4.20.iv.B), DIC (Table 4.21.iv.B), acute liver injury (Table 4.23.iv.B), acute kidney injury (Table 4.24.iv.B), generalised convulsions (Table 4.25.iv.B), encephalitis/meningoencephalitis (Table 4.26.iv.B), ARDS (Table 4.29.iv.B), erythema multiforme (Table 4.30.iv.B), anaphylaxis (Table 4.33.iv.B), and death of any cause (Table 4.36.iv.B).

In the registry-based data from Norway, at least one event was detected in the Spikevax cohort based on the current event definitions, after vaccination and until the end of the follow-up: GBS (Table 4.1.iv.C), narcolepsy (Table 4.3.iv.C), type 1 diabetes (Table 4.5.iv.C), ITP (Table 4.6.iv.C), microangiopathy (Table 4.7.iv.C), heart failure (Table 4.8.iv.C), coronary artery disease (Table 4.10.iv.C), arrhythmia (Table 4.11.iv.C), myocarditis (Table 4.12.iv.C), cerebrovascular disease (Table 4.14.iv.C), DVT (Table 4.15.iv.C), pulmonary embolism (Table 4.16.iv.C), single-organ cutaneous vasculitis (Table 4.17.iv.C), CVST (Table 4.18.iv.C), splanchnic vein thrombosis (Table 4.19.iv.C), coagulation disorders (Table 4.20.iv.C), Kawasaki disease (Table 4.22.iv.C), acute liver injury (Table 4.23.iv.C), acute kidney injury (Table 4.24.iv.C), generalised convulsions (Table 4.25.iv.C), encephalitis/meningoencephalitis (Table 4.26.iv.C), ARDS (Table 4.29.iv.C), erythema multiforme (Table 4.30.iv.C), anosmia/ageusia (Table 4.32.iv.C), anaphylaxis (Table 4.33.iv.C), sudden death (Table 4.35.iv.C), and death of any cause (Table 4.36.iv.C).

The above results do not represent signals. The preliminary results on potential signals (outcomes meeting prespecified criteria for further analysis in future reports) are described in Section 10.4.

10.4. Main results

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 data from Italy in Table 5s, Appendix_Table_5_part1 and Appendix_Table_5_part2. Cells containing SMRs of ≥2 based on ≥5 Spikevax-exposed cases are shown in yellow colour.

Table 4, below, provides an overview of age- and sex-SMRs ≥ 2.0 where ≥5 observed Spikevax-exposed cases of the specified AESI were identified in Italy/ARS, with references to the appropriate output tables.

Table 4. Overview of age- and sex-SMRs ≥ 2.0 where ≥5 observed Spikevax-exposed cases of the specified AESI for Italy/ARS, with references to the relevant output tables

Body system/ Classification	AESI	SMR≥2 and ≥5 Spikevax-exposed cases in some	Appendix tables with details of results

		database-specific analyses	
Auto-immune diseases	Guillain-Barré Syndrome (GBS)	No	
	Acute disseminated encephalomyelitis (ADEM)	No	
	Narcolepsy	No	
	Acute aseptic arthritis	No	
	Diabetes type 1	Yes	Table 5.5.iv.B
	(Idiopathic) Thrombocytopenia	Yes	Table 5.6.ii.B, Table 5.6.iv.B
Cardiovascular system	Microangiopathy	Yes	Table 5.7.ii.B
	Heart failure	Yes	Table 5.8.i.B, Table 5.8.ii.B, Table 5.8.iii.B, Table 5.8.iv.B
	Stress-induced cardiomyopathy	Yes	Table 5.9.ii.B, Table 5.9.iv.B
	Coronary artery disease	Yes	Table 5.10.ii.B, Table 5.10.iii.B, Table 5.10.iv.B
	Arrhythmia	Yes	Table 5.11.i.B, Table 5.11.ii.B, Table 5.11.iii.B, Table 5.11.iv.B
	Myocarditis	Yes	Table 5.12.ii.B, Table 5.12.iv.B
	Pericarditis	Yes	Table 5.13.ii.B, Table 5.13.iv.B
	Cerebrovascular disease	Yes	Table 5.14.i.B, Table 5.14.iii.B, Table 5.14.iv.B
Circulatory system	Deep vein thrombosis (DVT)	Yes	Table 5.15.i.B, Table 5.15.ii.B, Table 5.15.iii.B, Table 5.15.iv.B
	Pulmonary embolism (PE)	No	
	Single Organ Cutaneous Vasculitis	No	
	Cerebral venous sinus thrombosis (CVST)	No	
	Splanchnic vein thrombosis (SVT)	Yes	Table 5.19.ii.B, Table 5.19.iv.B
	Coagulation disorders	Yes	Table 5.20.i.B, Table 5.20.ii.B, Table 5.20.iii.B, Table 5.20.iv.B
	Disseminated intravascular coagulation (DIC)	No	
	Kawasaki disease	No	
Hepato-gastrointestinal and renal system	Acute liver injury	Yes	Table 5.23.i.B, Table 5.23.ii.B, Table 5.23.iv.B
	Acute kidney injury	Yes	Table 5.24.i.B, Table 5.24.ii.B, Table 5.24.iii.B, Table 5.24.iv.B

Nerves and central nervous system	Generalised convulsions	Yes	Table 5.25.i.B, Table 5.25.ii.B, Table 5.25.iv.B
	Encephalitis/meningoencephalitis	No	
	Transverse myelitis	No	
	Bell's palsy	No	
Respiratory system	Acute respiratory distress syndrome (ARDS)	Yes	Table 5.29.i.B, Table 5.29.ii.B, Table 5.29.iii.B, Table 5.29.iv.B
Skin and mucous membrane, bone and joints system	Erythema multiforme	No	
	Chilblain – like lesions	No	
Other systems	Anosmia, ageusia	No	
	Anaphylaxis	Yes	Table 5.33.ii.B, Table 5.33.iv.B
	Multisystem inflammatory syndrome	No	
	Sudden death	No	
	Death of any cause	Yes	Table 5.36.i.B, Table 5.36.ii.B, Table 5.36.iii.B, Table 5.36.iv.B
Abbreviations: SMR=Standardised Morbidity Ratio			

The following AESI had at least one estimated SMR of ≥2 where ≥5 Spikevax-exposed cases contributed to the assessment:

Diabetes type 1

In Italy, a signal was found in only one stratum covering males aged 45-54 years in the time interval 0 days to end of follow-up after any dose of Spikevax with an SMR of 2.63 (95% CI=0.85-6.15; Table 5.5.iv.B, Appendix_Table_5_part1). In most other strata's the SMR's was below 2 (Table 5.5.i.B, Table 5.5.ii.B, Table 5.5.iii.B, and Table 5.5.iv.B, Appendix_Table_5_part1).

(Idiopathic) Thrombocytopenia

In Italy, signals were detected after the second and any dose of Spikevax in males and for both sexes combined in the interval 0 days after Spikevax vaccination until end-of follow-up (Table 5.6.ii.B and Table 5.6.iv.B, Appendix_Table_5_part1). For instance, the SMR was 2.08 (95% CI=1.04-3.73) for any dose of Spikevax in the interval 0 days to end-of follow-up for both sexes (Table 5.6.iv.B, Appendix_Table_5_part1).

Microangiopathy

In Italy, a signal was found in the stratum covering both sexes of any age in the time interval 0 days to end of follow-up after second dose of Spikevax with an SMR of 2.03 (95% CI=0.66-4.75; Table 5.7.ii.B, Appendix_Table_5_part1). Overall, there was no cases in the interval 0 to 42 days after any dose of Spikevax, therefore SMR's was only estimable in the interval 0 days after Spikevax vaccination to end of follow-up (Table 5.7.i.B, Table 5.5.ii.B, Table 5.7.iii.B, and Table 5.7.iv.B, Appendix_Table_5_part1).

Heart Failure

In Italy, signals were detected both after the first, second, third and any dose of Spikevax among both females and males, but appeared to be mainly confined the oldest age group and within all time periods after Spikevax vaccination (Table 5.8.i.B, Table 5.8.ii.B, Table 5.8.iii.B and Table 5.8.iv.B, Appendix_Table_5_part1). Most signals were detected after the second dose of Spikevax; for both sexes of all ages the SMR was 2.02 (95% CI=1.45-2.74) in the interval 0 days after second dose of Spikevax until end of follow-up (Table 5.8.ii.B, Appendix_Table_5_part1).

Stress-induced cardiomyopathy

In Italy, no cases occurred in males after Spikevax vaccination. Therefore, all detected signals were related to females (Table 5.9.i.B, Table 5.9.ii.B, Table 5.9.iii.B and Table 5.9.iv.B, Appendix_Table_5_part1). Signals was detected for the second and any dose of Spikevax mainly in the interval 0 days after Spikevax vaccination until end of follow-up. For females of all ages the SMR was 2.07 (95% CI=1.16-3.41) in the interval 0 days after any dose of Spikevax vaccination until end of follow-up (Table 5.9.iv.B, Appendix_Table_5_part1).

Coronary artery disease

In Italy, signals were detected after the second, third, and any dose of Spikevax (Table 5.10.ii.B, Table 5.10.iii.B and Table 5.10.iv.B, Appendix_Table_5_part1). Only a few strata had signals and it was mainly confined to females or the combined analysis of both sexes covering different interval after Spikevax vaccination.

Arrhythmia

In Italy, signals were detected both after the first, second, third, and any dose of Spikevax for both females and males (Table 5.11.i.B, Table 5.11.ii.B, Table 5.11.iii.B and Table 5.11.iv.B, Appendix_Table_5_part1). Only a few strata had signals mainly covering intervals between 0 to 42 days after Spikevax vaccination, except for the third dose of Spikevax where signal was also detected in the interval 0 days after Spikevax vaccination until end of follow-up. For any dose of Spikevax, only one signal was detected for males aged 35-44 years in the interval 0 to 14 days after Spikevax vaccination with an SMR of 2.19 (95% CI=1.05-4.02; Table 5.11.iv.B, Appendix_Table_5_part1).

Myocarditis

In Italy, signals were detected after the second, third, and any dose of Spikevax (Table 5.12.ii.B, Table 5.12.iii.B and Table 5.12.iv.B, Appendix_Table_5_part1). Only a few strata had signals and it was confined to females or the combined analysis of both sexes. Often, the SMR was highest in the interval 0 to 2 days after Spikevax vaccination, but no signal was detected in this interval because there was < 5 Spikevax-exposed cases in that interval. Generally, signals were only detected in the interval 0 days after Spikevax vaccination until end of follow-up, as an example for females aged 75-79 years the SMR was 2.69 (95% CI=1.29-4.94) in that interval after any dose of Spikevax (Table 5.12.iv.B, Appendix_Table_5_part1).

Pericarditis

In Italy, signals were detected in a few strata for males after the second dose and after any dose of Spikevax (Table 5.13.ii.B and Table 5.13.iv.B, Appendix_Table_5_part1). For males of any ages after the second dose, a signal was detected in the interval 0 days after Spikevax vaccination until end of follow-up with and SMR=2.11 (95% CI=0.84-4.34; Table 5.13.ii.B, Appendix_Table_5_part1). However, the SMR was higher in the interval 0-14 days after the second dose of Spikevax (SMR=6.23 [95% CI=0.7-22.5]), but it did not qualify as a signal because there was < 5 Spikevax-exposed cases in that interval (Table 5.13.ii.B, Appendix_Table_5_part1).

Cerebrovascular disease

Signals was only detected in four strata in Italy; covering both females, males, and the combined analysis of both sex and for the first, third and any dose of Spikevax (Table 5.14.i.B., Table 5.14.ii.B., and Table 5.14.iv.B., Appendix_Table_4_part1). For example, the SMR was 2.37 (95% CI=0.76-5.54) for males aged 25-34 years during the interval 0 days after vaccination until end of follow-up for any dose of Spikevax (Table 5.14.iv.B., Appendix_Table_4_part1).

Deep vein thrombosis

In Italy, signals were detected after all doses of Spikevax, but mainly for females and the analysis combining the two sexes for persons above 54 years of age (Table 5.15.i.B , Table 5.15.ii.B. Table 5.15.iii.B, and Table 5.15.iv.B, Appendix_Table_5_part2). Signals was found in most intervals after Spikevax vaccination. For instance, for females aged 75-79 years a signal with an SMR of 2.94 (95% CI=1.08-6.41) was detected in the interval 0 to 42 days after any dose of Spikevax and a signal was also detected in the interval 0 days after any dose of Spikevax until end of follow with an SMR of 2.31 (95% CI=1.23-3.95; Table 5.15.iv.B, Appendix_Table_5_part2).

Splanchnic vein thrombosis

In Italy, signals were detected after the second and any dose of Spikevax (Table 5.19.ii.B and Table 5.19.iv.B, Appendix_Table_5_part2). Only a few strata had signals and it was confined to males or the combined analysis of both sexes, mainly for the elderly and covering most intervals after Spikevax vaccination. As an example of a signal, the SMR was 2.27 (95% CI=0.98-4.47) in the interval 0 to 28 days after vaccination with any dose of Spikevax in Elderly of both sexes (Table 5.19.iv.B, Appendix_Table_5_part2).

Coagulation disorders

In Italy, signals were detected after all doses of Spikevax (Table 5.20.i.B , Table 5.20.ii.B, Table 5.20.iii.B, and Table 5.20.iv.B, Appendix_Table_5_part2). Signals was detected for both females and males, several age groups, and for all intervals after Spikevax vaccination. For instance, signals were detected for persons of both sexes aged 75-79 years in the interval 0 to 28 days after vaccination with the second dose of Spikevax with an SMR of 3.58 (95% CI=1.72-6.59) and in the interval 0 days after second dose of Spikevax until end of follow-up

with an SMR of 2.24 (95% CI=1.61-3.04; Table 5.20.ii.B, Appendix_Table_5_part2).

Acute liver injury

In Italy, signals were detected after the first, second, and any dose of Spikevax in elderly females or in the analysis combining both sexes (Table 5.23.i.B, Table 5.23.ii.B, and Table 5.24.iv.B, Appendix_Table_5_part2). As an example, for elderly females after any dose of Spikevax, signals were detected in the interval 0 to 28 days after vaccination (SMR=3.08 [95% CI=1.12-6.7]) and in the interval 0 days after vaccination until end of follow-up (SMR=2.28 [95% CI=1.18-3.98]; Table 5.24.iv.B, Appendix_Table_5_part2)

Acute kidney injury

In Italy, signals were detected after all doses of Spikevax in many strata's covering both males and females and most age groups (Table 5.24.i.B, Table 5.24.ii.B, Table 5.24.iii.B, and Table 5.24.iv.B, Appendix_Table_5_part2). The SMR's was high in all time periods after Spikevax vaccination. As an example, after any dose of Spikevax for both sexes of all ages, signals were detected in the interval 0 to 14 days after vaccination (SMR=2.07 [95% CI=1.62-2.60]) and in the interval from date of vaccination until end of follow-up (SMR=2.20 [95% CI=2.01-2.40]; Table 5.24.iv.B, Appendix_Table_5_part2).

Generalised convulsions

In Italy, signals were detected after the first, second, and any dose of Spikevax in both females and males (Table 5.25.i.B, Table 5.25.ii.B, and Table 5.25.iv.B, Appendix_Table_5_part2). The SMRs were generally highest in the interval 0 to 2 days after vaccination for the first dose and any dose of Spikevax, but no signal was detected in this interval due to <5 Spikevax-exposed cases in that interval (Table 5.25.i.B and Table 5.25.iv.B, Appendix_Table_5_part2). In the analysis of any dose of Spikevax for persons of all ages and both sexes, there was a signal detected for the interval 0 to 14 days after Spikevax vaccination with an SMR of 2.97 (95% CI=1.19-6.11; Table 5.25.iv.B, Appendix_Table_5_part2).

Acute respiratory distress syndrome

In Italy, signals were detected after all doses of Spikevax for persons of both sexes ≥55 years and in most intervals after vaccination except 0 to 2 days after vaccination (Table 5.29.i.B, Table 5.29.ii.B, Table 5.29.iii.B, and Table 5.29.iv.B, Appendix_Table_5_part2). The signals detected in persons aged ≥55 years, was strong enough to also make signals detectable in the analysis combining all age groups. As an example, in the analysis of all age groups combined after any dose of Spikevax, a signal with an SMR of 2.48 (95% CI=1.94-3.13) was detected in the interval 0 days after vaccination to end of follow-up and a signal with a similar SMR (2.61 [95% CI=1.35-4.56]) was detected in the interval 0 to 14 days after any dose of Spikevax (Table 5.29.iv.B, Appendix_Table_5_part2).

Anaphylaxis

In Italy, signals were detected after the second and any dose of Spikevax in males or in the combined analysis of both sexes (Table 5.33.ii.B and Table 5.33.iv.B,

Appendix_Table_5_part2). There were no anaphylaxis cases detected in the interval 0-14 days after any dose of Spikevax (Table 4.33.iv.B, Appendix_Table_4_part2). Consequently, we only detected signals in the interval from date of vaccination until end of follow-up, for example the SMR was 4.76 (95% CI=2.28-8.75) in this interval for both sexes after any dose of Spikevax (Table 5.33.iv.B, Appendix_Table_5_part2).

Death of any cause

In Italy, signals were detected after all doses of Spikevax in many strata's covering both males and females and most age groups (Table 5.36.i.B, Table 5.36.ii.B, Table 5.36.iii.B, and Table 5.36.iv.B, Appendix_Table_5_part2). Generally, the SMR's was below 1 in the first 2 days after Spikevax vaccination, but increased when including more follow-up time after Spikevax vaccination. For both sexes after any dose of Spikevax, the SMR was 2.29 (95% CI=2.19-2.40) in the interval from date of Spikevax vaccination until end of follow-up (Table 5.36.iv.B, Appendix_Table_5_part2).

10.5. Other analyses

No other analyses reported.

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 (61, 62).

11. Discussion

11.1. Key results

Per Protocol's reporting schedule, this Third Interim Report contains description of the progress made since the Second Interim Report including description of progress, identified challenges and mitigation strategies. In addition, the Third Interim Report includes selected preliminary results from Denmark, Italy (ARS), Norway, and Spain (SIDIAP).

During the study period covered by the current data instance, the number of eligible Spikevax recipients with at least one dose of Spikevax was 563,998 in Denmark, 428,779 in Italy, 532,797 in Norway, and 587,436 in Spain. Approximately half of the Spikevax vaccinees were men, and the vaccinees' median age in the participating databases ranged from 36 to 56 years. In Italy, Norway, and Spain, more than half of the persons getting at least one dose of Spikevax, were excluded from the present study because they had received another type of COVID-19 vaccine before the first dose of Spikevax. Crude incidence rates of the AESIs were reported in Italy (Spikevax and the historical cohorts) and in Norway (Spikevax cohorts). Rates of the following AESI in Italy were lower than expected: acute aseptic arthritis,

idiopathic thrombocytopenia, microangiopathy, and heart failure. These and other underlying algorithms are subject to further quality control.

Results of the signal detection, available from Italy/ARS database, identified the following AESIs as fulfilling the current definition of a signal: Diabetes type 1, (Idiopathic) Thrombocytopenia , Microangiopathy, Heart failure, Stress-induced cardiomyopathy, Coronary artery disease, Arrhythmia, Myocarditis, Pericarditis, Cerebrovascular disease, Deep vein thrombosis, Splanchnic vein thrombosis, Coagulation disorders, Acute liver injury, Acute kidney injury, Generalised convulsions, Acute respiratory distress syndrome, Anaphylaxis, Death of any cause. No signal evaluation was undertaken to confirm any of the signals.

11.2. Limitations

Results presented in this report are subject to several important limitations.

Most importantly, the current results should be interpreted as preliminary, given the ongoing adaptation and refinement of the ConcePTION CDM environment to the study of vaccine safety (58). The algorithms to define some AESIs were used previously in the ACCESS project (55), 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 and medication proxies. Compared with the Second Interim Report, all algorithms underwent review and further refinement however, this work is still ongoing (Section 16.2). One reason for any differences among country-specific rates are differences in health sectors generating the records in the underlying databases and granularity of the underlying vocabularies, affecting the ability to capture the sought conditions. Specifically in the current report in Norway, rates of AESI defined by hospital encounters or medication proxies are likely to be underestimates, as hospitalization and medication dispensing data were not delivered in the current data extraction in Norway. Apparent underestimation of several AESI rates in Italy is subject to further checking and quality control. The AESI event counts are being used in the current analysis solely for obtaining a relative estimate of association (SMRs) for the purposes of signal detection. Given the use of narrow AESI definitions (prioritising specificity), and assuming that any misclassification of some AESI is nondifferential with respect to the Spikevax exposure status, the relative measures of association are expected to be unbiased even if sensitivity of identification is low (63). Furthermore, for diabetes type 1, misclassification by type 2 diabetes and cannot be ruled out. For death of all causes, results may be manifestation of a sick vaccinee effect. In December 2020, the European Centre for Disease Prevention and Control (ECDC) identified the older age groups, healthcare workers, and persons with underlying chronic conditions as the priority groups for vaccination (65). In summary, all AESI are subject to a certain degree of misclassification.

At the same time, inflated SMRs due to differential misclassification cannot be ruled out for selected AESIs, such as myocarditis, anosmia/ageusia, or anaphylaxis, potentially due to differential detection and recording among Spikevax vaccinees compared with the historical cohort. The unexpected potential signal for myocarditis seen in females but not in males in the current analysis is contrary to most existing evidence for this AESI, which may be a

manifestation of a differential misclassification and should be investigated further. 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)" is 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 analysis is not 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. The variable definitions subjected to further refinement and benchmarking will be used in the subsequent reports.

Second, 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.

Third, many of the SMR estimates had low precision. Precision is expected to improve as more databases, observations, and time periods are included in the subsequent reports. At the same time, many AESIs are inherently rare events.

Fourth, given the timelines for report submission relative to the actual dates of data extractions, it was not feasible to implement all per-protocol quality controls in this Third Interim Report. Specifically, while two programmers implemented the analyses supervised by investigators examining the output for internal consistency, no double programming was undertaken, nor were the plausibility of the observed AESI historical rates systematically checked against the literature. Double-programming of selected analysis steps in selected database will be implemented for the next interim report (elaboration in Section 16.2). Furthermore, The ConcePTION pipeline includes level 3 checks (semantic harmonisation), which were not performed for the current interim report due to time constraints. The level 3 checks focus on rates of AESIs and distribution of vaccines, which are already partly include in the results present for the current interim report. Level 3 checks will be implemented before conducting the final analyses.

Fifth, the criteria for a "signal" were defined as contrast-specific SMR≥2 & N≥5. As any criteria, the criteria for signal detection are somewhat arbitrary. The criteria are meant to balance the risks false positive vs false negative signals. Because magnitude and precision are the main characteristics of estimates of association, the criteria were chosen to afford a minimum magnitude and minimum precision that would trigger further evaluation. A similar approach/threshold has been used previously (64). Differences in database specific SMRs are partially driven by the type of routinely collected data they have (i.e., diagnoses from primary vs secondary care).

The current study can only address safety concerns for the period with available data, currently at the maximum 11 months after vaccination. Future updates will allow formal

assessment of potential longer-term safety concerns as more observation time accumulate. As the last per-protocol data extraction is scheduled for March 2023, or approximately 2 years after the first distribution of Spikevax, this study will assess effects occurring 2 years after vaccination.

11.3. Interpretation

Given the limitations outlined in Section 11.2 and in Section 16.2, results provided in this Third 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 (58) to the study of the vaccine safety in the general population; and (3) of conducting the federated analyses on DRE.

This Third 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, Italy, Norway, and Spain. The results of the signal detection analysis should not be interpreted as indicative of the risk-benefit balance of Spikevax in the absence of the results of AESI-specific signal evaluation and given potential non-causal explanations of the signal detection results. In Italy, vaccination started in January 2021 with healthcare workers and socio-healthcare workers, residents and staff of long-term facilities for the elderly; elderly older than ages 75 - 79 years (66). 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 (67). Cause-of-death data are not available for this analysis. 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. Detection of signals for myocarditis and pericarditis were in line with those AESIs being important identified risks, however, the subgroups for myocarditis were not consistent with most evidence pointing to the highest risk in younger men. At the same time, myocarditis primarily affects young men in the general population. Some observed signals were not plausible, e.g., for anaphylaxis, the risk window is not consistent with the hypothesised risk period shortly after vaccination. The AESI coagulation disorders is a composite of several other AESI examined separately (see Section 15.2). Chance cannot be ruled out as the cause of some of the findings.

Per protocol, AESIs with SMRs ≥ 2.0 and ≥5 Spikevax-exposed cases are those to be subjected to a formal signal evaluation. Thus, SMRs are not designed for causal inference regarding an association between Spikevax receipt and occurrence of a given AESI. Per-protocol formal signal evaluation will be undertaken in subsequent reports using the per-protocol defined AESI-appropriate study designs and control of confounding.

11.4. Generalisability

Results presented in this report are based on the data collected in the first year following the

launch of Spikevax and cover four out of five participating countries. Results of signal detection cover only one participating country. Given the changing vaccination schedules, and the preliminary nature of the analysis due to lack of formal epidemiologic evaluation to control confounding, 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 will be presented and interpreted in the Final Study Report.

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. 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.

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

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

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

22. 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/.

23. 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.

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

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

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

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

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

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

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

31. 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/.

32. 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.

33. 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/.

34. 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/.

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

36. 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-women-s-health/vaccination/covid-19-vaccines-pregnancy-and-breastfeeding-faqs/.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

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

47. 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.

48. 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.

49. 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.

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

51. 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.

52. 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.

53. 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.

54. 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].

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

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the Vaccine Adverse Event Reporting System (VAERS): a case study of febrile seizures after a 2010-2011 seasonal influenza virus vaccine. Drug Saf. 2013;36(7):547-56.

65. ECDC. TECHNICAL REPORT Overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK, 02 December 2020 2020 [cited 2022 27 March]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Overview-of-EU_EEA-UK-vaccination-deployment-plans.pdf.

66. ECDC. TECHNICAL REPORT Overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK, 29 March 2021 2021 [cited 2022 27 March]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Overview-implementation-COVID-19-vaccination-strategies-vaccine-deployment-plans.pdf.

67. 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.

15. Annex 1. List of stand-alone documents

15.1. Output tables with study results

Appendix_Tables_1_2_3.xlsx
Appendix_Table_4_part1.xlsx
Appendix_Table_4_part2.xlsx
Appendix_Table_5_part1.xlsx
Appendix_Table_5_part2.xlsx

The table numbering can include information about what AESI, country or dose of Spikevax the table relates. Table 5 shows the indexing used for AESIs, doses, and countries.

Table 5. 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				
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				
Anosmia/ageusia	32				
Anaphylaxis	33				
Multisystem inflammatory syndrome	34				
Sudden death	35				
Death of any cause	36				

15.2. Diagnosis and medication codes used to define study variables

Spikevax Interim 3 Code list 2022_09_20.xlsx

16. Annex 2. Additional information: Progress report and mitigation strategies

This Annex contains 1) an overview of the progress since the Second Interim Report against the planned contents (Section 16.1); 2) a list of challenges proactively identified during preparation of the Third Interim Report, reasons for each challenge, and proposed strategies to mitigate those going forward to ensure continued delivery of the planned report contents (Section 16.2).

16.1. Progress from the Second Interim Report (Submitted in March 2022) to the Third Interim Report (Due on 30 September 2022)

Per Study Protocol (Section 12, Table7, version 1.2 dated 27 Sep 2021), the planned contents of the Third Interim Report consist of a status update, providing an overview of any updates to the project during the applicable calendar quarter. Given the public-health importance of this study, in addition to the status and progress updates planned per-protocol, the Third Interim Report also contains selected preliminary results from the most recent data extraction in a subset of the participating countries (Table 6). These preliminary results are subject to several limitations and challenges, as discussed Section 11.2 of the Third Interim Report.

16.1.1. Overview of the progress since the Second Interim Report against the planned contents

Area	Progress
Participating countries	The Third Interim Report includes selected results from two new participating data source are included, specifically, results from Denmark and Norway, in addition to selected results from Italy/ARS, and Spain/SIDIAP.
Follow-up of subjects over time	End of follow-up for AESI has been extended by approximately 4 months.
AESIs, subpopulations, and co-variates	As part of a VAC4EU-wide effort, all code lists to identify the AESIs, the subpopulations and the covariates have undergone another round of review. In addition, medication proxies have been added to selected AESI definitions. This work is ongoing within VAC4EU.
Transparency of reporting source data for AESI rates	The Third Interim Report presents information about the number of the events and crude incidence rates in the historical cohort and the Spikevax cohort stratified by age and sex and within subpopulations for special interest. The previous report contained rates for the historical cohort only without providing the event counts. This reporting practice improves transparency.
Improved adjustment for age in signal detection	In the Third Interim Report, the SAP-specified analysis of age as time-varying variable is implemented in estimating the SMRs. In the Second Interim Report, SMRs were computed based on age at start of the follow-up.

Table 6. Overview of database-specific preliminary results included in the Third Interim Report

Country	Preliminary results included in Third Interim Report

	Signal detection					Signal evaluation	Cohort study of VAED	Prognosis post myocarditis/pericarditis
	Population description and selection	Crude incidence rates	Subpopulation incidence rates	SMRs stratified on age and sex	SMRs in subpopulations			
Denmark	Spikevax and historical cohorts	No	No	No	No	No	No	No
Italy	Spikevax and historical cohorts	Spikevax and historical cohorts	No	Yes	No	No	No	No
Norway	Spikevax cohorts	Spikevax cohorts	No	No	No	No	No	No
Spain	Spikevax cohorts	No	No	No	No	No	No	No
United Kingdom	No	No	No	No	No	No	No	No

16.2. Challenges identified during preparation of the Third Interim Report, reasons for each specific challenge, and proposed mitigation strategies

Conduct of a multinational safety study of COVID-19 vaccine in a setting of multiple newly launched vaccines, mass vaccination campaign, and changing (country-specific) recommendations in the light of rapidly accumulating evidence has brought about several unforeseen logistic and administrative challenges in implementing the current study protocol. To ensure delivery of quality per-Protocol planned evidence in future study reports (most importantly, in the Final Study Report), the identified challenges among specific processes are listed in the order of the overall study implementation, together with their identified causes and proposed mitigation strategies.

Process	Challenge	Identified cause(s)	Mitigation strategy
Data access: Norway	The following data elements were not available for Norway - The historical cohort - Data on hospital diagnoses - Data on outpatient dispensings	1. The unusually long waiting times for data delivery on inpatient hospital diagnosis (Patient Registry of Norway) and community-pharmacy dispensings (Norwegian Prescription Database). 2. Because of an oversight in the data application, the data received covered only Spikevax vaccinees, and not the historical cohort, requiring an update.	An ethical approval for the study to include the historical cohort has been applied for and obtained on 29 September 2022. Accordingly, an updated data application is being prepared for submission to the data custodians in October 2022. All study-specific data on all study populations are expected to be available for the subsequent planned data extractions. The wait time from the current Norway data delivery will be factored into future report planning timelines. Confirmation on the expected data availability and delivery will occur in advance of the date that allows for an adequate time buffer to address unexpected issues.
Data access: Italy/ARS Toscana	Uncertainty about availability of data from this database beyond the Third Interim Report	Local authorities require renewal of data access approvals	Pending decisions of the local data custodians/data access authorities. Additional updates/decisions are expected by the end of 2022-
Data extraction: UK/CPRD	DSRU experienced slow times in data extraction at the CPRD	Larger-than-previous dataset needed for the upcoming reports	The DSRU team has escalated the issue with the CPRD on 27 July 2022, resulting in some limited additional support from CPRD and in improved extraction times starting 24 August 2022. To ensure timely extractions going forward, the strategy of earlier data extraction and scripts testing on portions of the data will be applied to accelerate the process.
Data management and cleaning: Time and computational resources	Larger-than-expected time and computational resources required for completion of the ETL and the level-checks.	The expected resource expenditures were underestimated based on the experience with the ACCESS project, which was a pilot project with less data involved.	Given the importance of having sufficient time for ETL and level checks and creation of the study population, earlier data extractions will be conducted, as a necessary trade-off between quality and quantity of the data in favour of quality. Therefore, data extraction for inclusion in the Fourth Interim Report is planned for October 2022 instead of December 2022.

Process	Challenge	Identified cause(s)	Mitigation strategy
Operational definitions of the study variables	Large variability of some observed AESI rates and comorbidities prevalences across the participating databases	Need for further refinement of operational definitions of the study variables	A centralized effort to harmonize the process around code definitions and study variables has been set up within VAC4EU. Use of medication proxies will be phased in in all countries.
Server capacity and waiting times: Denmark	Due to the large size of the analysis dataset (a total-population historical cohort) of data, the level-check and the analytic R scripts could not be run on the allocated server space. Uploading of external analytic scripts are subject to waiting times	In Denmark, researchers access individual-level registry data only via logging in at servers hosted by the Danish Health Data Authority. The Authority's server space is therefore shared by all researchers involved in the analysis of the data. The currently allocated server space to this project was not sufficient for running the analytic scripts. Additionally, all external analytic scripts to be run on the Danish data require a review by the staff of the Authority before being uploaded.	The following mitigation strategies are being implemented: 1. Requesting increased server space from the Danish Health Data Authority 2. Reducing the size of the extracted data 3. Fragmentation of the datasets during running of the scripts 4. Strategies of smaller, modular scripts and advanced testing before implementing on larger datasets, as described below
Server capacity issues: Spain/SIDIAP	SIDAP experienced a server crash, which limited the server time available for the current analysis.	Despite the replacement of the server in Dec 2022, SIDIAP experienced again capacity issues at the new server	The SIDIAP team has addressed the issue and server is functioning again. Going forward, the SIDIAP has implemented procedures and made expertise available for handling potential future server crashes. Furthermore, this issue may also be alleviated by increased efficiency of the statistical scripts.

Process	Challenge	Identified cause(s)	Mitigation strategy
Creating and testing analytic scripts		Increasing script efficiency in programming and testing.	Several strategies are being implemented to optimize and harmonize analytic scripts 1. Testing and debugging of the new level-check and analytic scripts on earlier data instances 2. Testing and debugging of the new level-check and analytic scripts on one data source ahead of implementing the final scripts in all data sources 3. Adopting, whenever possible, a modular approach to programming, to enable rapid identification and correction of any issues and improved control of the computer resources 4. A VAC4EU-wide programming working group is being considered

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