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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Date of last version of protocol	19 August 2021
EU PAS register number	Protocol will be registered before start of the data collection
Active substance	COVID-19 mRNA-1273 vaccine (nucleoside modified)
Medicinal product	COVID-19 Vaccine Moderna/Spikevax
Product reference	EMEA/H/C/005791
Procedure number	MEA004.2
Marketing authorisation holder(s)	Moderna Biotech Spain, S.L. Calle Monte Esquinza 30 28010 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 unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders
Country(-ies) of study	Denmark, Italy, Norway, Spain, United Kingdom
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1. Table of contents

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
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
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
ECMO	Extracorporeal membrane oxygenation
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
EEA	European Economic Area
GBS	Guillain-Barré syndrome
GDPR	General Data Protection Regulation
GVP	Guideline on good pharmacovigilance practices
ICD-9CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Health Care
ICU	Intensive care unit
IRR	Incidence rate ratio
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder

Abbreviation	Explanation
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
NIAID	National Institute of Allergy and Infectious Diseases
PASS	Postauthorisation safety study
PE	Pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMR	Standardised Morbidity Ratio
SNOMED	Systematised Nomenclature of Medicine
SPEAC	Safety Platform for Emergency vACcines
SCCS	Self-controlled case-series
SCRI	Self-controlled risk intervals
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVT	Splanchnic vein thrombosis
TBD	To be determined
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VTE	Venous thromboembolism
VITT	Vaccine-induced immune thrombotic thrombocytopenia
WHO	World Health Organisation

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4. Abstract

Title

Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the COVID-19 mRNA-1273 Vaccine in Europe

mRNA-1273-P904, Protocol Version 1.2, 27 September 2021

Coordinating investigator: Professor Vera Ehrenstein, Aarhus University, Denmark

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. A mass vaccination campaign is currently underway in Europe. The mRNA-1273 vaccine, currently known as Spikevax,[1] combines Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilised SARS-CoV-2 spike immunogen.

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 unstable health conditions and morbidities, and patients with autoimmune or inflammatory disorders

Study design

This study will proceed in two phases: signal detection and signal evaluation.

For the signal detection stage, population-based, country-specific historical general population background rates of the AESI estimated in the participating databases/countries from 2017-

2019 will be used as estimates of the expected rates in the unvaccinated. Rates in Spikevax recipients will be compared with the historical pre-pandemic rates. All comparisons will be conducted stratified by country, and within each country further stratified on sex, and age groups.

For the signal evaluation stage, conducted as needed based on findings from signal detection, analytic approaches will be selected based on the best methodologic fit for a given AESI. It is anticipated that a combination of self-controlled designs and cohort designs using either historical or concurrent unexposed comparators will be utilised.

Population

Recipients of Spikevax will be identified between 6 January 2021 (date of the earliest approval of Spikevax in Europe) and 31 December 2022 and members of the database source population selected for each study design, including persons providing historical rates from 2017-2019, will be eligible for inclusion in the study and will constitute the overall cohort. Subgroups of interest will include adolescents, adults, elderly individuals, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and morbidities, and patients with autoimmune or inflammatory disorders (defined below). Individuals receiving more than one type of COVID-19 vaccine will be excluded.

Variables

Cohort members will be described with respect to available demographic characteristics, medical history, medication use, and receipt of other vaccines.

Outcomes of interest will include AESI primarily based on the list defined by the Safety Platform for Emergency vACcines (SPEAC) and endorsed for COVID-19 vaccine safety assessment by the WHO Global Advisory Committee for Vaccine Safety, by the EMA and by the US CDC. Other AESI may be considered if relevant signals appear during the study conduct or additional outcomes are added to the ACCESS protocol.

Data sources

This study is planned as analysis of routinely collected health data in secondary automated electronic data sources in Denmark, Italy, Norway, Spain, and the UK, selected based on availability of the required routinely collected data, including information on vaccine brand and frequency of data updates.

Study size

As of 1 June 2021, it is estimated that the participating databases together will be able to identify at least 431,216 recipients of Spikevax.

Data analysis

For signal detection, incidence rates among Spikevax vaccinees will be computed and compared using relative or absolute measures of association against appropriate (e.g., age- sex- country-specific) general population background AESI rates.

For signal evaluation using self-controlled designs, the ratio between the incidence rate estimate in the risk period and the incidence rate estimate in the control period (incidence rate ratio) will be computed using conditional Poisson regression. For parallel cohort designs, appropriate contrasts will be estimated in exposed vs. unexposed cohorts, while controlling for measured confounding. Whenever appropriate incidence rate ratios (IRRs) will be estimated with appropriate 95% confidence intervals (CIs).

Milestones

Data collection will continue through 31 March 2023 with a final study report planned by December 2023.

5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
2	Date	Text	Text	Text
…	Date	Text	Text	Text

6. Milestones

Milestone	Planned date*
Start of data collection	31 December 2021
End of data collection	31 March 2023
Study progress report 1	30 September 2021
Study progress report 2	31 March 2022
Study progress report 3	30 September 2022
Study progress report 4	31 March 2023
Registration in the EU PAS register	Upon approval by regulatory authorities
Final report of study results	31 December 2023

* Subject to data queues by data custodians; refer to Section 12 “Plans for disseminating and communicating study results” for planned contents of the progress reports

7. 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. A mass vaccination campaign is currently underway in Europe.[2] [3]

The mRNA-1273 vaccine was co-developed by the Cambridge, Massachusetts-based biotechnology company Moderna, Inc., and the United States (US) National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The vaccine, currently known as Spikevax,[1] combines Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilised SARS-CoV-2 spike immunogen, developed by NIAID.

Spikevax has been administered in Phase 1,[4] [5] Phase 2,[6] and Phase 3[7] [8] clinical trials. The pivotal Phase 3 efficacy trial was conducted at 99 centres across the US among persons at high risk for SARS-CoV-2 infection or its complications. Volunteers (N=30,420) were randomly assigned in a 1:1 ratio to receive two injections of Spikevax or placebo 28 days apart, and more than 96% of the participants received both injections. The primary endpoint was prevention of COVID-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2. The vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified.[7] This trial, titled "A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19" (clinicaltrials.org identifier NCT04470427), has entered an open-label phase, which aims to assess the vaccine's long-term efficacy, safety, and immunogenicity. Another ongoing Phase 3 trial of Spikevax titled "Vaccine in Immunosuppressed Adults With Autoimmune Diseases (COVIAAD)" (clinicaltrials.org identifier NCT04806113) aims to assess safety, reactogenicity, and immunogenicity in patients with rheumatic diseases., Spikevax was authorised across the European Union (EU), following conditional marketing authorisation by the European Commission on 06 January 2021[9] and was approved on 08 January 2021 by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).[10] Currently, Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.[1] Figure 1 shows vaccine doses distributed by the manufacturers to EU/EEA (European Economic Area) countries by product as of 23 May 2021.

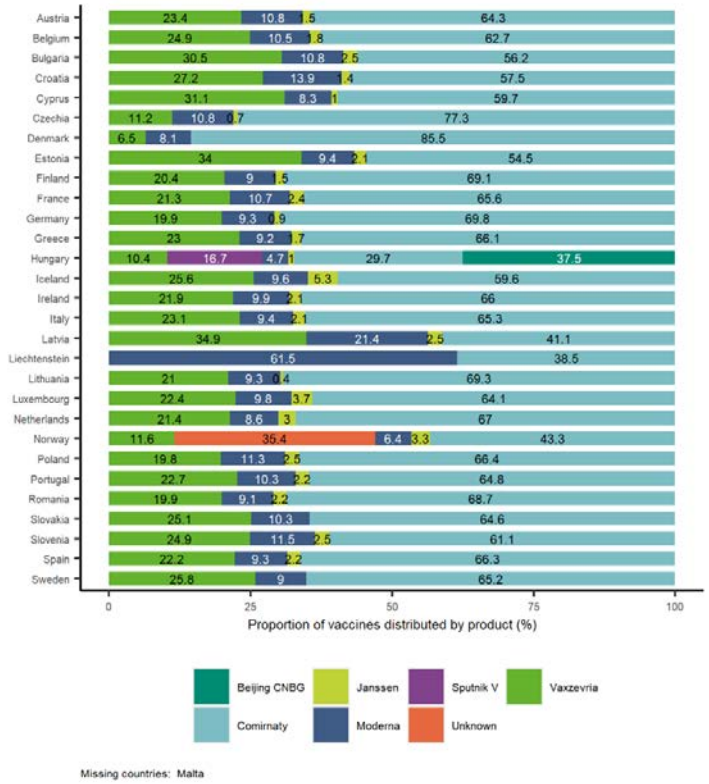

Figure 1 Vaccine doses distributed by the manufacturers to EU/EEA countries by product as of 23 May 2021 (Source: https://covid19-vaccine-report.ecdc.europa.eu/). UK data: UK has secured early access to 517 million doses of eight of the most promising vaccine candidates. This includes agreements with: Pfizer/BioNTech for 100 million doses; Oxford/AstraZeneca for 100 million doses; Moderna for 17 million doses; Janssen for 30 million doses; Novara for 60 million doses; Valneva for 100 million doses; CureVac for 50 million doses; GlaxoSmithKline and Sanofi Pasteur for 60 million doses (Source: https://www.gov.uk/government/news/more-than-20-million-uk-adults-receive-both-doses-of-covid-19-vaccine). In the UK vaccination with Moderna started 7 April 2021 (https://coronavirus.data.gov.uk/details/about-data).

Other vaccines against COVID-19 that have been to date authorised for use in the EU are: BioNTech-Pfizer (conditional marketing authorization on 21 December 2020); AstraZeneca (conditional marketing authorization on 29 January 2021), Johnson & Johnson (conditional marketing authorization on 11 March 2021). Vaccines still in development include Sanofi-GSK and CureVac.

The EU Risk Management Plan (RMP) for Spikevax lists anaphylaxis and myocarditis/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 and while breastfeeding (to be addressed in a separate protocol), 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.[11] The COVID-19 Vaccine Safety Update for Spikevax, dated 11 May

2021, mentions reports of cases of myocarditis/pericarditis (reported in other mRNA-based vaccines) for further monitoring by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).[12]

On 09 July 2021, PRAC concluded that myocarditis and pericarditis can occur in very rare cases following vaccination with the two current mRNA COVID-19 vaccines. This conclusion was reached after an in-depth review of 145 cases of myocarditis in the European Economic Area (EEA) among people who received Comirnaty and 19 cases among people who received Spikevax. PRAC also reviewed reports of 138 cases of pericarditis following the use of Comirnaty and 19 cases following the use of Spikevax. The PRAC concluded that the cases primarily occurred within 14 days after vaccination, more frequently after the second dose, with young age, and male sex identified as potential risk factor for occurrence. Among those with myocarditis/pericarditis, advanced age and concomitant diseases were risk factors for subsequent mortality. As PRAC qualified this adverse event of special interest (AESI) as 'very rare', an updated product information will list myocarditis and pericarditis as side effects with unknown frequency and health care professionals are advised that the cases may need specialist care.[13] To summarise, although vaccine trials are usually large, they may not detect rare adverse events. In addition, there is a high safety standard applied to a preventive agent administered to individuals in their usual state of health. This study will fill gaps in knowledge about the safety of the COVID-19 Vaccine Moderna in routine clinical practice, over a longer-term, and in subgroups of individuals not included or under-represented in trial populations.[14] In this study, such groups include children and adolescents and persons with selected chronic morbidities, as described above. Furthermore, this study will formally address the important identified potential safety concerns including myocarditis/pericarditis, anaphylaxis, and, to the extent possible if observed, VAED and VAERD.

The European Medicines Agency (EMA)'s Consideration on core requirements for RMPs of COVID-19 vaccines in the Guide on Good Pharmacovigilance Practices (GVP) state that it is essential that each decision to classify a (potential) risk of a vaccine is evidence-based and adequately presented and justified.[15] [16] In addition, the Brighton Collaboration has developed and is maintaining and updating a Priority List of Adverse Events of Special Interest (AESI) for COVID-19 vaccines, endorsed by the World Health Organisation (WHO) Advisory Committee on Vaccine Safety.[17] The EMA-commissioned "Vaccine COVID-19 monitoring readiness" (ACCESS) study has estimated background rates of these AESI in multiple European data sources.[18]

This post authorisation safety study (PASS) aims to carry out signal detection followed, if necessary, by safety evaluation of identified possible signals of Spikevax in routine clinical practice in five European countries during the ongoing mass vaccination campaign. This study is planned as analysis of routinely collected health data in secondary automated electronic data sources covering all or portions of the populations in Denmark, Italy, Norway, Spain, and the UK, selected based on availability of the required routinely collected data, including information on vaccine brand and frequency of data updates. This study is a Category 3 Required Pharmacovigilance Activity in the RMP, and will address areas of missing information including safety of use in patients who are immunocompromised, patients previously diagnosed with

COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders. The objectives related to the COVID-19 Vaccine Moderna in pregnancy are addressed in a separate protocol (internal reference mRNA-1273-P905).

8. Research question and objectives

The overarching research question of this study is as follows, formulated in terms of causal inference/counterfactual outcomes[19]:

Is the occurrence of each AESI 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?

Because there is no single perfect measure of the expected (counterfactual) occurrence of the AESI, the latter will be estimated using different comparators.

Different study designs will be employed to address the study objectives. Signal detection will be achieved using a cohort design with historical comparators from the ACCESS project (Section 9.1.1). Signal evaluation will be achieved using self-controlled designs or parallel cohort designs (Section 9.1.2). These approaches have been described as applicable to vaccine safety monitoring using routinely collected health data.[20]

8.1. Primary objective

To assess whether vaccination with Spikevax (by dose number as 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.

Because all available sources of expected rates have limitations, the different sources of expected rates that will be used in comparative analysis will include: (refined) historical rates using the ACCESS project methodology, within-individual expected rates afforded by self-controlled designs, and contemporaneous rates in persons not vaccinated with any COVID-19 vaccines, or rates in historically matched controls in parallel cohort design.

8.2. 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 unstable health conditions and morbidities, and patients with autoimmune or inflammatory disorders.

9. Research methods

This protocol is prepared based on the methodology developed as part of the EMA-commissioned and other scientific efforts of COVID-19 vaccine safety assessment preparedness, specifically, design options introduced in the published templates for assessment of COVID-19 vaccine safety (EUPAS39361).[21] Detailed description of the research methods, including the final definitions of the study variables, will be provided in the Statistical Analysis Plan (SAP), which will be a standalone technical document kept on file, and developed with clinical and statistical input from the participating database experts.

9.1. Study design

This study will proceed in two phases: signal detection and signal evaluation. The signal detection phase can be viewed as a screening phase, aimed at identifying AESI's that warrant a closer evaluation in elaborate designs. Thus, the signal detection phase serves to focus the evaluation on only those AESI, which could plausibly, be adverse events. The ADVANCE *Report on appraisal of vaccine safety methods*, referenced by the ENCePP's guidelines on monitoring vaccine safety and effectiveness[22] explains that observed vs. expected analyses may be used to detect and initially assess new signals in a timely manner without generating large numbers of false positives.[23]

9.1.1 Signal detection: cohort study with historical rates

Because this study will take place during a mass vaccination campaign, rates of the AESI among the unvaccinated persons are not likely to be representative of the appropriate background/expected rates (1) due to healthy vaccinee/sick vaccinee effect and (2) because the ongoing pandemic is expected to have distorted health care utilisation, at least for a portion of the study period. Therefore, for the signal detection stage, it is proposed to use population-based, historical background rates of the AESI estimated in the participating databases/countries before the COVID-19 pandemic (2017-2019) as estimates of the expected rates in the unvaccinated.[24] Indirect standardization according to age and sex will be used because for many of the AESI's, few events are expected.[25] Specifically, the Standardised Morbidity Ratio (SMR) will be estimated as the number of observed events divided by the number of expected events in Spikevax recipients (see Section 9.7.2 for computational details). As increased rates for some AESI might only be expected in a limited time interval after vaccination with Spikevax, the SMRs will be estimated in the following time intervals relative to the date of each dose of the COVID-19 Moderna vaccine: 0-2 days, 0-14 days, 0-28 days, 0-42 days and 0-end of follow-up. Due to variations of population and background rates in the participating databases and health care systems in each country, SMR will be reported by country. The SMRs for all Spikevax recipients will also be stratified by age and sex. No standardisation variables other than country, age, and sex will be applied.

A signal will be defined as present if a country-specific overall or age and/or sex-specific SMR for an AESI is 2 or higher where the number of database-specific exposed cases is 5 or higher. Signals may also be investigated if these conditions are not met, but there is a clinical or public health reason for further investigations (eg., very rare conditions).

9.1.2 Signal evaluation

Signals detected during the signal detection stage will undergo signal evaluation. For signal evaluation, two main types of study design are proposed: self-controlled designs and cohort designs. The specific study design will depend on characteristics of a given AESI, including type of onset (rapid vs insidious), hypothesised length of induction/latency period, ability to define risk periods, the extent to which the AESI affect the likelihood of vaccination, the ability to identify a suitable comparator, and the ability to measure AESI-specific confounders.[26 27] As self-controlled designs inherently adjust for time-invariant confounding, they are suitable for AESI's for which it is difficult to identify a suitable comparator or to measure confounding, both of which are likely scenarios during a mass vaccination campaign. Furthermore, self-controlled designs are primarily suitable for events with acute onset, short induction/latency, and a well-defined risk period. For AESI where these conditions are not fulfilled and appropriate adaptations of the self-controlled design are not feasible, the cohort design will be used. As selection of study design will partly depend on information that will become available during the conduct of the study, the final selection of study design is not possible beforehand. However, based on the characteristics of the AESI, ability to define comparator, and potential confounding, both described above and in the following sections, we have made a list of the most likely study designs for each AESI presented in **Error! Reference source not found.**.

Table 1. Overview of proposed study design for the included AESI (Please note that the final decision about study design, might partly depend on information that will become available during the conduct of the study, e.g. clear identification of risk intervals)

Body system/ Classification	AESI	Most likely study design
Auto-immune diseases	Guillain-Barré Syndrome (GBS)	Self-controlled designs
	Acute disseminated encephalomyelitis (ADEM)	Self-controlled designs
	Narcolepsy	Cohort
	Acute aseptic arthritis	Self-controlled designs
	Diabetes type 1	Cohort
	(Idiopathic) Thrombocytopenia	Self-controlled designs
Cardiovascular system	Microangiopathy	Self-controlled designs
	Heart failure	Self-controlled designs
	Stress-induced cardiomyopathy	Self-controlled designs
	Coronary artery disease	Self-controlled designs
	Arrhythmia	Self-controlled designs
	Myocarditis	Self-controlled designs
	Pericarditis	Self-controlled designs
	Cerebrovascular disease	Self-controlled designs
Circulatory system	Deep vein thrombosis (DVT)	Self-controlled designs
	Pulmonary embolism (PE)	Self-controlled designs
	Single Organ Cutaneous Vasculitis	Self-controlled designs
	Cerebral venous sinus thrombosis (CVST)	Self-controlled designs
	Splanchnic vein thrombosis (SVT)	Self-controlled designs
	Coagulation disorders	Self-controlled designs

	Disseminated intravascular coagulation (DIC)	Self-controlled designs
	Kawasaki disease	Self-controlled designs
Hepato-gastrointestinal and renal system	Acute liver injury	Self-controlled designs
	Acute kidney injury	Self-controlled designs
Nerves and central nervous system	Generalised convulsions	Self-controlled designs
	Encephalitis/meningoencephalitis	Self-controlled designs
	Transverse myelitis	Self-controlled designs
	Bell's palsy	Self-controlled designs
Respiratory system	Acute respiratory distress syndrome (ARDS)	Self-controlled designs
Skin and mucous membrane, bone and joints system	Erythema multiforme	Self-controlled designs
	Chilblain – like lesions	Self-controlled designs
Other systems	Anosmia, ageusia	Self-controlled designs
	Anaphylaxis	Cohort or SCRI with only post-vaccination control periods (anaphylaxis permanent contraindication to vaccination)
	Multisystem inflammatory syndrome (MIS)	Self-controlled designs
	Vaccine-associated enhanced COVID-19 disease (VAED) or vaccine associated enhanced respiratory disease (VAERD)	Cohort study with contemporaneous unvaccinated controls
	Vaccine-induced immune thrombotic thrombocytopenia	Self-controlled designs
	Sudden death	Cohort
	Death of any cause	Cohort

Note: Choice of study design mainly guided by "Rapid assessment of COVID-19 vaccines safety concerns through electronic health records: a protocol template from the ACCESS project".[28]

9.1.2.1 Self-controlled designs

Self-controlled designs are case-only designs, i.e., they are restricted to individuals who experience the specified AESI in a pre-specified time window. The pre-specified time-window is split into a risk period/window with hypothesised increased risk of the AESI and control periods/windows without increased risk. Each person serves as his/her own control, thus controlling for time-invariant potential confounders.[27] Depending on AESI, two types of self-controlled designs may be applied: the self-controlled case-Series (SCCS) design and the self-controlled risk interval (SCRI) design; the latter is essentially a simplified version of the SCCS design. A distinguishing feature between the SCCS and SCRI designs is the selection of the observation period used to identify relevant cases of the specific AESI. The SCCS uses a prespecified observation period anchored in calendar time (or age).[29] The observation period for each subject is split into risk windows and control windows (as illustrated in Figure 2).[30]

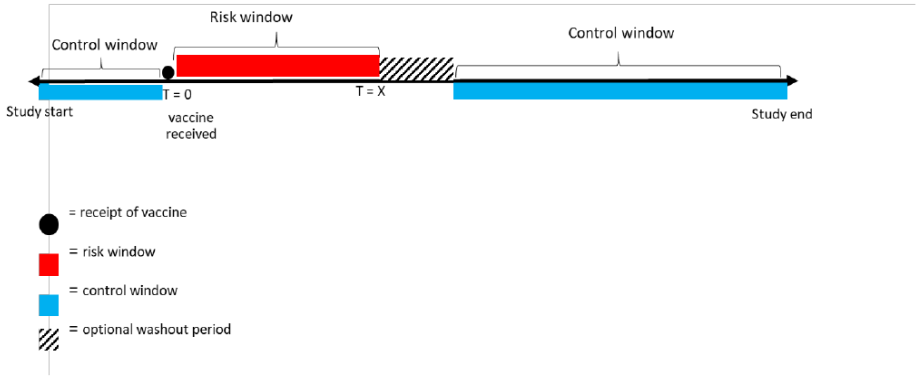

Figure 2 Self-Controlled Case Series design (risk windows are AESI-specific and are based on hypothesized plausible vaccine-AESI induction period).[27]

The SCRI design uses the date of vaccination as the index date for the observation period. Thus, for the SCRI design include cases of the AESI occurring in risk periods and control periods defined relative to the date of receiving Spikevax. The risk and the control period are of the same length. Figure 3 illustrates an example for risk and control periods 42 days long.

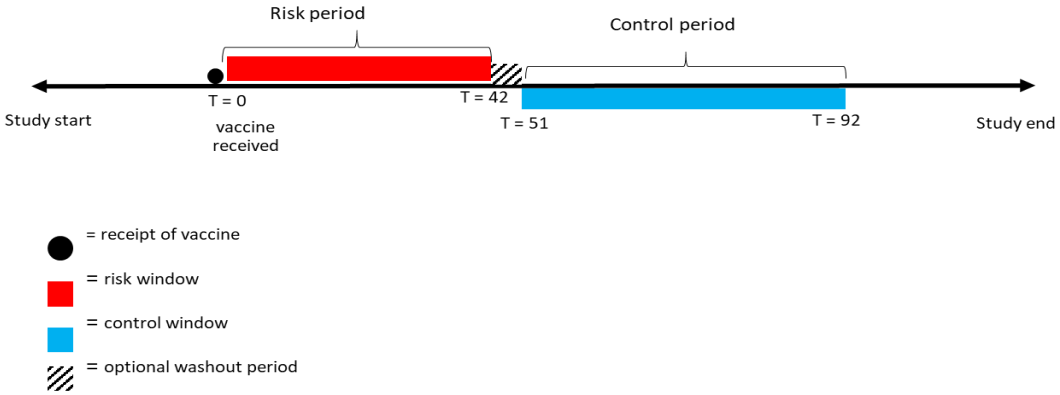

Figure 3 Self-Controlled Risk Interval design (illustration only for a hypothetical risk/control period of 42 days, risk intervals are AESI-specific and are based on hypothesised plausible vaccine-AESI induction period)[27]

The self-controlled methods, by definition, control time-invariant confounding, but are still susceptible to time-varying confounding from age and season. As the SCRI design often uses relatively short risk and control periods and the periods are close in time, this could minimise time-varying confounding.[30] However, this comes with a cost of lower power due to shorter control periods in the SCRI design than in the SCCS design.[26] It is important to note that methods to adjust for time-varying confounders in the SCCS design are available.[31 32] To adjust for time-varying confounders it might be an advantage also to include unvaccinated cases.[31]

Selection between the SCCS design and the SCRI design will depend on the observed rate of the specific AESI (low rates would favour the SCCS design), and on presence of time-varying

confounders (would favour the SCRI design if it appears that it would not be possible to properly adjust for time-varying confounders in the SCCS design). In addition, for an AESI that is a contraindication to vaccination, the SCRI design with post-vaccination control period can be used.[30]

Under the SCCS design, the analysis will include Spikevax recipients who experience the AESI during the observation period from the date of the first distribution of Spikevax in each site and until the last date with available data. Inclusion of the AESI among persons not receiving any COVID-19 vaccine during the observation period may also be considered.

If using the SCRI design, the analysis will include AESI cases occurring during the risk or control interval specified for each AESI and indexed on the date of receiving Spikevax (only including cases who have received Spikevax).

In both the SCCS and SCRI design, risk periods/windows are AESI-specific and will be defined for each vaccine dose.

9.1.2.2 Parallel cohort designs

Self-controlled designs are the preferred method of evaluation of vaccine safety and will be applied whenever possible. However, not all AESI are amenable to examination with self-controlled designs. Signals of AESI with properties not amenable to evaluation by self-controlled designs will undergo evaluation using one or more of the versions of the parallel cohort design with different bias structures following the triangulation approach.[33]

1) Cohort study with contemporaneous comparators, consisting of persons unvaccinated against COVID-19. In each country, the observation will start on the date of country-specific availability of Spikevax and will include all persons in the population on that date. Thus, all members of the study population will start as unexposed to Spikevax. On the date of the person's first dose of Spikevax, the person's exposure status will change to exposed to Spikevax (time-varying exposure). Follow-up will be censored at receipt of other COVID-19 vaccines, death, emigration, or end of observation. This design will enable comparison with contemporaneous COVID-19 unvaccinated cohort. Thereby, limiting the possibility for confounding due to time-varying factors like change in referral practices and changes in health seeking behaviour related to the COVID-19 pandemic. However, there is a great risk of bias due to confounding by indication and healthy vaccinee bias.[34]

2) Matched cohort study with historical comparators will include all recipients of Spikevax from the date of vaccination with the first dose (exposed subject). For each exposed subject we will identify a comparator subject matched on age, sex, chronic morbidity and contribution to the same database as the exposed subject 4 years before the exposed subject received Spikevax (potentially +/- 7 days, excepting individuals <4 years of age in the event that vaccination is observed in young children). This design will to some extent reduce healthy vaccinee bias/confounding by indication. However, bias might be related to other factors affecting the rate of AESI over time.

For each cohort study we will follow the subjects until the earliest of the specified AESI, death, emigration, or end of follow-up (administrative censoring). For AESI with a clearly specified risk period we will only follow subject until end of the specified risk period. Furthermore, follow-up will be censored on the date of receipt of another COVID-19 vaccine.

We will adjust the analyses by traditional confounder adjustment as it has been shown to perform well as relative to different propensity scores methods, particularly considering that we have a limited number of measured confounders and for some AESI relatively rare events where trimming may present a challenge.[35] Adjustment strategies may be revisited to include alternative approaches (e.g., propensity score methods) in the event that a specific outcome of interest requires adjustment for more confounders than was anticipated.

9.2. Setting

This study will be multi-database, utilizing routinely collected health data of various types in five European countries: Denmark, Italy, Norway, Spain, and the United Kingdom. The source population in each country will be the population that contributes to each of the databases. The study databases are representatives of their source population (see Appendix 1 for details). Briefly, in Denmark and Norway, the registries have full population coverage with respect to the available routinely collected data. The regional databases in Italy (ARS) and Spain (SIDIAP) are representative with respect to background rates and demographic distributions of the underlying regional populations (Tuscany and Catalonia, respectively). The CPRD is broadly representative of the UK population.

9.2.1 Study period

Recipients of Spikevax will be identified between 06 January 2021 (date of the earliest approval of Spikevax in Europe) and 31 December 2022. The final data extraction is planned for 31 March 2023. The background rates of the AESI will be estimated in the period between 2017 and 2019.

9.2.2 Inclusion criteria

All persons with a record of at least one dose of Spikevax in each database between 06 January 2021 and 31 December 2022 and members of the database source population selected for each study design (Section 9.1), including persons providing historical rates, will be eligible for inclusion in the study and will constitute the overall cohort.

9.2.3 Exclusion criteria

Moderna vaccinees with a record of another COVID-19 vaccine before their first dose of Spikevax will be enumerated, and their demographic characteristics will be described. These individuals will be excluded from all other analyses; Moderna vaccinees receiving another

COVID-19 vaccine after Spikevax will be censored on the date of receipt of the other vaccine (as specified in Section 9.1).

9.3. Variables

Availability and definition of specific variables varies by data source. All data-source specific variable definitions and country-specific data availability will be specified in the SAP.

9.3.1 Exposure

The exposure will be defined by a record of receipt of at least one dose of Spikevax (including any variants or boosters once authorised) between 06 January 2021 and 31 December 2022. For both Spikevax and other COVID-19 vaccines, it is possible to ascertain the vaccine brand and/or applicable vaccine characteristics from the available data. Exposure to each dose in the order received (e.g., first dose, second dose) or any dose of Spikevax will be assessed.

9.3.2 Outcome

This study draws the list of the AESI definitions from the ACCESS project or other published sources (Table 2).[24] The list includes broadly defined conditions, primarily based on those defined by the Safety Platform for Emergency vACcines (SPEAC) and endorsed for COVID-19 vaccine safety assessment by the WHO Global Advisory Committee for Vaccine Safety, by the EMA, and by the US CDC. For most of the AESI, the Brighton Collaboration case definitions are available.[17] Definitions, codes and proposed algorithms for the AESI have been published[36] and the definitions have been used for estimation of pre-pandemic population background rates.[18 24] These definitions will be reviewed and refined prior to the analysis based on expert input in each participating country. The refinements may include specifications regarding the code types (procedure/diagnosis/drug), setting (inpatient/outpatient/emergency), and/or sector (primary/secondary). For the self-controlled analysis, definition of an AESI will include the length of the 'clean window' and lengths of the risk interval, as well as the lengths of the pre-vaccination and post-vaccination control intervals. Lengths of the risk intervals will be guided by previous literature on the specific AESI, biological plausibility, and the evidence from the signal detection phase of the time-periods after vaccination with the highest SMRs. For instance, for events of anaphylaxis, which are expected to have rapid onset after vaccination, we will likely propose the risk interval 0-2 days. The approach described in the in the published US PASS[37] will be used as the starting point and subsequently adapted to the EU setting. However, there is an inherent uncertainty about the true length of most risk intervals, which will be addressed by applying sensitivity analyses.

The initial diagnosis codes defining the study variables are provided in Annex 1. The final (refined) operational definitions for each AESI and other study variables will be included in the SAP. Other AESI may be considered if relevant signals appear during the study conduct or if additional AESI become added to the ACCESS protocol or SPEAC.

Table 2. AESI (pregnancy-related AESI will be addressed in a separate protocol, internal reference mRNA-1273-P905)

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

9.3.3 Covariates

The key covariates will include country of residence, calendar time, age, sex, selected morbidities, Charlson Comorbidity Index (CCI), history of COVID-19 infection, other COVID-19 vaccinations, other vaccinations (eg, influenza, hepatitis B), health care utilisation as measured by the frequency of inpatient, outpatient, and primary-care encounters. For Spikevax, characteristics of utilization will be described, including doses received, formulation (if additional options become available during the study period), and proportion of women with identifiable pregnancy, including trimester of administration, whenever available. Furthermore, in databases with available information (e.g., SIDIAP, CPRD), covariates will include smoking and body mass index.

Annex 1 provides a summary of availability of different data types from in the participating databases.

9.3.4 Subgroups

The following subgroups will be specified (given sufficient subgroup size) to identify subgroups of interest and additional subgroups may be added if identified during the study conduct:

- Country
- Sex
- Age groups (may be revised base on size)
    - Children and adolescents (0-17years)
        - 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
- Seasonality (if relevant)
- Calendar period (if relevant)
- Dose (if sufficient group size)

In addition, in addressing the secondary objectives, the following subpopulations will be defined:

- Women of childbearing age (12-49 years)
- Patients with a history of COVID-19 infection
- Patients with unstable health conditions and co-morbidities, including:
  - Chronic obstructive pulmonary disease (COPD)
  - Diabetes, chronic neurological disease,
  - Cardiovascular disorders
- Patients with autoimmune or inflammatory disorders
- Indicators of immunocompromised status (subject to data availability/sufficient group size)

9.4. Data sources

This study will be based on electronic, routinely collected data in five European countries (listed alphabetically): Denmark, Italy, Norway, Spain, and the UK. The participating databases cover the underlying countries' population fully or partially. Table 3 provides overview of the data sources in each country. Additional description of the participating data sources is provided in Annex 3. Most databases and data access providers (DAPs) have contributed to the ACCESS protocol and are considered fit for purpose through that contribution or other previous experience in vaccine studies. The data access providers have committed to cooperate on addressing the study objectives .

Table 3 Summary of the data sources by country

Country	Denmark	Italy	Norway	Spain	UK
Data access provider	Aarhus University	ARS	University of Oslo	IDIAP	DSRU

Type of data	Record linkage	Record linkage	Record linkage	Record linkage & GP	GP medical record
Data source name	Danish registries	ARS	Norwegian registries	SIDIAP	CPRD
Size of data in 2019	5.7 M	3.5 M	5.4 M	5.8 M	16 M
Type of data					
Diagnosis coding	ICD-10	ICD-9CM/SNOMED	ICD-10CM/ICPC	ICD-10CM	ICD-10/READ/SNOMED
Hosp. discharge diagnoses	yes	Yes	yes	yes	yes
Intensive care unit (ICU) admission	yes	Yes	yes	no	yes
Extracorporeal membrane oxygenation (ECMO) use	no	No	yes	no	yes
Date of death	yes	Yes	yes	yes	yes
Emergency unit visit diagnoses	yes	Yes	yes	yes	yes
Outpatient specialist visit diagnoses	Yes	No	yes	No./Yes referrals to specialists	yes
Primary care diagnoses	no	No	yes	yes	yes
COVID-testing	Yes	Yes (only positive results)	yes	yes	yes
Medicines dispensing outp.(pharmacy)	yes	Yes	yes	yes	no
Medicines inpatient	Some	Some	yes	no	no
Medicines prescribing	no	No	no	yes	yes
COVID-19 Vaccine brand	yes	Yes	yes	yes	yes

9.5. Study size

Table 4 shows the total number of doses administered in each participating country as of 01 June 2021. In observational studies based on routinely collected data, where investigators do not control the study size, it is of interest to estimate the magnitude of an effect that can be ruled out with the available data and its precision.[38] As proposed by Rothman and Greenland, study precision is expressed "by designing a study that gives an upper limit for the confidence interval that has a specified probability of being below a chosen value. The multiplier Z [in the calculations] is derived from the desired confidence level: Z is the value of the standard normal distribution such that the area under the curve from −Z to +Z equals the confidence level. Z is

1.96 for 95% confidence." (Rothman and Greenland, 2018, p. 600).[38] Specifically, of interest is the magnitude of the upper 95% confidence limit that can be ruled out for an AESI, given a background AESI rate, total group size, and the relative size of the exposed and the comparator cohorts (allocation ratio). Here, it is (conservatively) assumed that in each country the number of persons in the Spikevax exposed cohort equals to ½ of the total doses administered. For databases with partial population coverage (Italy, Spain, UK), this is multiplied by the proportion of the country population covered by the database. All computations are based on country-specific background rates as reported in the ACCESS project (Table 5).[18]

Table 4 Total doses of Spikevax administered the participating countries as of 01 June 2021

Country	Moderna doses administered as of June 2021
Denmark	292,599
Italy	3,084,998
Norway	165,876
Spain	2,257,066
UK	400,000
TOTAL:	**6,200,539**

(Source: ECDC https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab and Moderna)

Table 5 presents ranges of the rare AESI from the ACCESS project.

Table 5 Range of 2019 background rates per 100,000 person-years of rare AESI in the participating countries

AESI	Range **observed in 2019 in participating databases** (rounded)
Anaphylaxis	8 to 19
CVST without TP	0.1 to 2
Myocarditis	2 to 11
VTE with TP	0.1 to 1

Source: ACCESS project (https://vac4eu.org/covid-19-tool/)[18]

The precision computations (Table 6) are provided for AESI with low estimated country-specific background rates, as those require largest study size and allow for ruling out larger upper 95% confidence limits. For AESI with higher rates, lower upper 95% confidence limits can be ruled out with smaller cohort sizes.

Table 6 Upper limits of 95% confidence interval for rate ratios that can be ruled out with 80% probability and with 90% probability in parallel cohort designs (assumed allocation ratio 5:1)

Country	Moderna COVID-19 Vaccinees as of 1 June 2021 covered by the database*	AESI rate in comparator, per 1000 person-years	AESI rate in exposed, per 1000 person-years	Maximum upper limit of 95% CI that can be ruled out	
				with 80% probability	with 90% probability

Denmark	146,300	1	1	1.29	1.34
		0.1	0.1	2.23	2.53
		0.01	0.01	12.65	18.84
Italy	77,125	1	1	1.42	1.50
		0.1	0.1	3.02	3.59
		0.01	0.01	32.94	57.02
Norway	82,938	1	1	1.40	1.48
		0.1	0.1	2.90	3.43
		0.01	0.01	29.08	49.36
Spain	112,853	1	1	1.34	1.40
		0.1	0.1	2.49	2.88
		0.01	0.01	17.97	28.29
UK	12,000	1	1	2.43	2.79
		0.1	0.1	16.47	25.57
		0.01	0.01	7040.52	28301.81
TOTAL	431,216	1	1	1.16	1.19
		0.1	0.1	1.60	1.72
		0.01	0.01	4.38	5.53

*Estimated conservatively as 1/2 of the total of number of administered doses multiplied by the proportion of the country population covered by the database (Denmark 100%; Italy 5%, Norway 100%; Spain 10%; UK 6%).
Assumptions: True IRR=1; follow-up length = 1 year; allocation ration comparator:exposed = 5:1

9.6. Data management

This study, which will be conducted based on this common protocol, will use the Vaccine monitoring Collaboration for Europe (VAC4EU, https://vac4eu.org/) research environment based on a common protocol, common SAP, and a common data model (CDM).[39] The work will be conducted using a distributed network of the participating data access providers (DAPs), all of whom have experience with and have contributed to the ACCESS project. The work will proceed according to Model C (Figure 3): each DAP will extract the data required for the study and transform their local patient level data into a CDM. It is proposed to use the ConcePTION CDM, which is publicly available.[39] Extraction, transformation, and loading (ETL) design and instructions are available, as well as tools to check the quality of the data for the AESI estimated and utilised for the ACCESS background rate protocol. A common program to run quality checks, data transformation, and analysis will be prepared, verified and distributed to all DAPs. Aggregate results and summary estimates resulting from the programs will be returned to the coordinating centre for pooled meta-analysis and reporting. The full approach will be developed and described in the SAP.

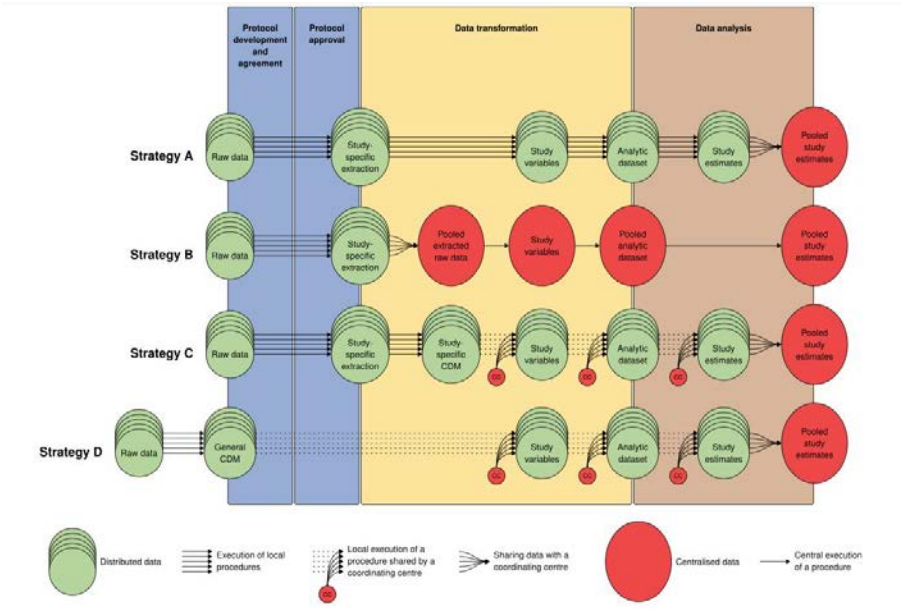

Figure 4. Options for multi-database studies in Europe

9.7. Data analysis

The details of the data analysis, including planned tables, figures, and listings for inclusion in the final study report will be provided in the SAP.

9.7.1 Descriptive analyses

Attrition diagrams demonstrating the loss of subjects applying inclusion and exclusion criteria will be provided. For each implemented study design, demographic characteristics of the study population (e.g., age at study entry, sex) and baseline characteristics (e.g. chronic morbidities) will be summarised for the study population from each data source, using descriptive statistics where available. Counts and percentages/proportions will be presented for categorical variables (age at study entry in categories, sex). Means, standard errors, medians and interquartile ranges will be presented for continuous variables (eg., age at study entry). The proportion of missing data will be described when appropriate.

9.7.2 Measures of occurrence and measures of association

For signal detection, the underlying analytic principle is the observed - expected (O-E) analysis, which aims to compare AESI rates in vaccinees, with the rates expected for a non-vaccinated population as similar as possible in its demographic and other relevant characteristics to the vaccinated population. Such analyses are typically crude and control for a limited number of confounders.[23] For this study, we will, by country, estimate the indirectly age- and sex-standardised SMR for Spikevax recipients, largely following the approach in a recently published study on the association between COVID-19 vaccine Oxford-AstraZeneca and VITT in Nordic data[40]

Briefly, the observed number of incident events in the vaccinees is obtained by following the vaccinees starting on the date of first vaccination and until the earliest of end of relevant risk period (using these different definitions 2, 14, 28 or 42 days or end of data), date of death, emigration, the event of interest, or administrative censoring (end of data). The expected number of events in the vaccinees is estimated based on the incidence rates of a given AESI in the prespecified comparators. The members of the comparator cohorts are followed for AESI occurrence from an appropriate index date until the earliest of emigration, death, or occurrence of a given AESI. From these incidence rates, the expected number of AESI events in the vaccinees is estimated using indirect standardisation. Specifically, age-, sex-, and country-specific incidence rates will be multiplied by the age-, sex-, and country-specific follow-up time accumulated in the vaccinated cohorts during a relevant risk period. For each age-, sex-, and country-specific stratum of the vaccinees, this will yield a count for the number of expected events, subsequently summed across strata.[40] (Please see also Section 9.1.1). [23]

For signal evaluation using self-controlled designs, the ratio between the incidence rate estimate in the risk period and the incidence rate estimate in the control period (incidence rate ratio) will be computed using conditional Poisson regression. For parallel cohort designs, appropriate contrasts will be estimated in exposed vs. unexposed cohorts, while controlling for measured confounding. All incidence rate ratios (IRRs) will be estimated with appropriate 95% confidence intervals (CIs).

An incidence rate is the ratio of the number of AESI cases observed during the follow-up time among study participants divided by the sum person-time contributed by all participants.

9.7.3 Subgroup analyses

All relevant analyses will be stratified by country, age, sex, calendar time, and seasonality if applicable. The analyses of the secondary objectives will be repeated in subpopulations (i.e., subsets of the population of special interest) defined in section 9.3.4.

9.7.4 Sensitivity analyses

Sensitivity analysis will focus on the robustness of results regarding assumptions of the study design, outcome definitions, assumed period of risk, and availability of key data elements and should be conducted for the rapid assessment studies and may include the following:

- For comparisons against background AESI rates, alternative AESI definitions may be considered, for example broad/vs narrow definitions based on selection of diagnosis codes, use of treatment proxies, or selection of a health care setting (primary/hospital) in defining event algorithms. For AESI leading to hospitalizations, definitions based on primary discharge diagnoses may be considered if relevant.
- For self-controlled designs, if the risk window is not well known, analyses with alternative risk intervals will be conducted.
- Recomputing selected estimates with SARS-COV-2 infection as an additional censoring criterion

- To characterise measured risk factors and sequelae of cases of myocarditis and pericarditis, in an exploratory sensitivity analysis, exposed and unexposed myocarditis and pericarditis cases will be described with respect to demographic characteristics (age, sex). Furthermore, investigative clinical markers, relevant healthcare utilization, and cardiac outcomes will be explored over the available follow-up time after observed myocarditis and pericarditis events. This analysis will be performed to the extent possible under each country's data protection regulations and existing restrictions on reporting low cell counts.
- Pending adequate sample size, sensitivity analyses that separately consider individuals with a third dose may be conducted, noting that this subgroup may require further refinement in the SAP as heterologous vaccine use may be common and is excluded from the main analyses.

9.7.5 Data integration

Results will be presented separately for each database/country and pooled across countries. Meta-analysis will be conducted using standard methods: heterogeneity will be assessed and visualizations such as forest plots be provided. Because of the expected variation in effect estimates of data-sources, we recommend random effect models.[41]

9.8 Quality control

The source, electronic routinely collected data, proposed for use in this study will undergo standard curation and quality-check procedures and curation by the data custodians. Standard operating procedures or internal process guidance at each research centre will be adhered to for the conduct of the study. These procedures will include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, and standards for writing analysis plans. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each partner should maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents.

This study will be conducted in accordance with the GVP, including the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct.[16]

9.9 Limitations of the research methods

Among the vaccinees, rates of AESI among healthcare workers (healthy vaccinees) may be diluted resulting in a downward bias of estimates of association. On the other hand, rates of AESI among the elderly may be overestimated (sicker vaccinees), resulting in an upward bias of estimates of association. Therefore, at the signal detection phase, it is important that the background AESI rates are representative of the counterfactual rates among the appropriate subgroups of vaccinees, by age, sex, calendar period, season, chronic morbidity level, and other relevant subgroups.

Limitations of the methods suggested for the signal evaluation phase include uncertainty around appropriate risk intervals (potentially diluted associations due to outcome misclassification), potential upward bias from an AESI being a contraindication for vaccination in SCCS design, and challenges in defining an unbiased unvaccinated unexposed cohort, as contemporaneous unvaccinated persons during mass vaccination campaign may systematically differ from vaccinees (unknown direction of bias). Thus, upward or downward bias from unmeasured confounding cannot be ruled out by any one method, a limitation that may be remedied somewhat by the suggested triangulation approach. Limitations of using historical comparators in estimating expected AESI rates include potential time-dependent nature of the rates, seasonality, and secular trends in AESI diagnostic, coding, reporting, or treatment practices.[20] Furthermore, the length of a risk period for some AESI is not known and will be based on biologically plausible assumptions.

Given the multiplicity and the heterogeneity of the AESI, the selected data sources will differ with respect to their availability of specific data types (eg., primary care vs. secondary care diagnoses/dispensings vs. prescriptions), and thus will differ with respect to the availability/completeness of data on all AESI-specific confounders, which is a limitation of this study. Furthermore, despite the large size of the underlying populations, the size of the Moderna COVID-19 exposed cohort may be relatively small, thus precluding identification of relevant signals, especially for rare AESI.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

The proposed studies are non-interventional studies, re-using routinely collected health and administrative data. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data access provider should apply for an independent ethics committee or other review according to local regulations. Data protection and privacy regulations (GDPR) will be observed in collecting, forwarding, processing, and storing data from study participants. Whenever required by data protection regulations, implicit or explicit cell counts that potentially allow for identification of individuals (e.g., counts of 1-4 in most countries), appropriate masking methods will be applied. All participating investigators/data access providers will obtain all required governance approval for conducting this study. Only aggregate results will be shared. Security processes should be in place to ensure the safety of all systems and data. Every effort should be made to ensure that data are kept secure so that they cannot be accessed by anyone except the study

team. Appropriate data storage and archiving procedures will be followed by each DAP and the coordinating centre, with periodic backups.

11 Management and reporting of adverse events/adverse reactions

Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable.[16 42] According to the GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products "All adverse events/reactions collected as part of [non-interventional post-authorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report." Module VIII – Post-Authorization Safety Studies, echoes this approach. The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.[12 15]

12 Plans for disseminating and communicating study results

Per GVP Module VIII: "For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication."[42]

The protocol and the final study report will be subject to mandatory publication in the EU PAS register and will comply with ENCePP or Code of Conduct, according to which study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[43]

RECORD, and RECORD-PE[44 45] checklist will be followed, and recommendations on reproducible reporting of electronic health care data base studies should be followed.[46]

Table 7 specifies dates of planned data extraction by each DAP and summarises planned contents of the progress and final reports, based on the planned data extractions.

Table 7. Planned data extractions and contents of study reports.

Milestone	Date	Data extraction planned				
		Denmark (national registries)	Norway (national registries)	Italy (ARS Toscana)	Spain (SIDIAP)	UK (CPRD)
DATA EXTRACTION 1 (SELECTED DAPS) = START OF DATA COLLECTION*	30-Sep-21	No	No	Yes	Yes	Yes
Study progress report 1 Planned content: status update providing an overview of progress towards finalization of the study design, application for data, initial steps towards execution of planned analyses	30-Sep-21					
Study progress report 2 Planned content: Preliminary descriptive and comparative analyses, limited to data access partners with shortest approval timelines (DATA FROM 31 DEC 21 EXTRACTION)	31-Mar-22					
DATA EXTRACTION 2 (SELECTED DAPS)*	30-Jun-22	Yes	Yes	Yes	Yes	Yes
Study progress report 3 Planned content: status update providing an overview of any updates to the project during the applicable calendar quarter	30-Sep-22					
DATA EXTRACTION 3 (SELECTED DAPS)*	31-Dec-22	Yes	No	Yes	Yes	Yes
Study progress report 4 Planned content: Preliminary descriptive and comparative analyses, all data access partners. Site-specific analyses only. (DATA FROM 30 JUN 22 EXTRACTION)	31-Mar-22					
DATA EXTRACTION 4 (ALL DAPS) - END OF DATA COLLECTION*	31-Mar-23	Yes	Yes	Yes	Yes	Yes
Final report of study results Planned content: Final descriptive and comparative analyses, all data access partners. Site specific and meta-analyses. (DATA FROM 31 MAR 23 EXTRACTION)	31-Dec-23					

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1		18 Aug 2021	Preliminary algorithms20210818.xlsx
2		18 Aug 2021	Main PASS Summary of data availability20210818.xlsx
…	Number	Date	text

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Comments:

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

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7,8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☒	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.5
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5

Comments:

Target population: NA because results are expected to inform safety for all vaccinees Hypotheses are not stated, but explicitly the null hypothesis is that of no association between Spikevax and any AESI.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	

Comments:

No sampling is done per se, but some databases cover partial population of their respective countries.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1, 9.4
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.4

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.4

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.7.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.3.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.3.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.4
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.7.5
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

ENCePP publication of the study protocol and the study results is taken as independent review of study results.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Prof. Vera Ehrenstein, MPH, DSc

Date: 25/06/2021

Signature: _____

Annex 3. Additional information

Appendix 1: Description of the participating data sources

Denmark: Danish population registries

Denmark has a tax-funded health care system ensuring universal access to health care, and with this system health contacts are recorded in administrative and health registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish resident, originally for taxation purposes. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers. All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. The Danish National Prescription Registry includes data on all outpatient dispensing of medications and vaccines at Danish pharmacies from 1995 and onwards, including dispensing date, ATC code, product code and amount. The Danish National Health Service Register includes data on primary care services, including general practitioner contacts, examinations, procedures, pregnancy-related visits, vaccinations (other than COVID-19); psychologist or psychiatrist and other primary care provider visits; etc. From the Danish Civil Registration System, data on demographics (sex, date of birth) and censoring (migration, vital status). The Danish National Patient Registry contains diagnoses and procedures from all hospitalizations since 1977 and contacts to hospital outpatient clinics since 1995. 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. Use of the Danish Vaccination Registry will be involved to ascertain vaccinations outside GP offices and to ascertain vaccine brand. Danish health care and the flow of data into the registries have been described in a recent publication (https://www.ncbi.nlm.nih.gov/pubmed/31372058).

Italy: ARS database

The Italian National Healthcare System is organised at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia Regionale di Sanita' della Toscana (ARS) is a research institute of the Tuscany Region. 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 with each other at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry,

induced terminations registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic SNOMED codes. 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 was characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment when using the new vaccine registry (from 2019).

Norway: Norwegian population registries

The core data that University of Oslo (UIO) has access to is the health care administrative databases of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist health care services. 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 most commonly used registries are administrated by The Norwegian Institute of Public Health, The Norwegian Directorate of Health and Statistics Norway. 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 code is included in all national registries, allowing accurate linkage among them. Information about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/

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, pediatricians 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 by project basis. Health professionals gather this information using 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 in order to monitor the evolution of the pandemic. Recent reports have shown the SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database www.encepp.eu/encepp/resourcesDatabase.jsp). The SIDIAP database was characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment.

United Kingdom: CPRD & HES

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerised medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available. The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage when GOLD & Aurum versions are used. There are currently approximately 42 million patients (acceptable for research purposes) – of which 13 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (https://cprd.com/Data). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read and SNOMED codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a proportion of the CPRD panel practices (>80%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data. CPRD is listed under the ENCePP resources database, access will be provided by the DSRU. The CPRD was not yet characterised in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been largely used in vaccine studies. The HES database contains details of all admissions to National Health System (NHS) hospitals in England; approximately 60% of GP practices in the CPRD are linked to the HES database. Not all patients in the CPRD have linked data (e.g. if they live outside England or if their GP has not agreed that their data should be used in this way). As with standard CPRD patients, HES data are limited to research-standard patients. CPRD records are linked to the HES using a combination of the patient's NHS number, gender and date of birth. The Drug Safety Research Unit (DSRU) is the leading UK centre for pharmacovigilance and pharmacoepidemiology which has led and coordinated many large studies across the UK. The Unit has ample experience

of monitoring the post-authorisation safety of vaccines, notably active surveillance on the H1N1 swine flu vaccine and an active surveillance study and six enhanced passive surveillance studies on the children's seasonal influenza vaccine. The DSRU works with the UK's National Institute for Health Research (NIHR) Clinical Research Network, which facilitates research in the National Health Service (NHS) and provides access to a large network of research-ready health care professionals, including GPs. The DSRU also has experience of study designs based on patient reported outcomes.