EU PE & PV Research Network under a Framework contract following procurement procedure EMA/2017/09/PE (Lot 4)

Final report

Feasibility analysis of an EU infrastructure for COVID-19 vaccine monitoring

This report has been accepted by EMA as a deliverable of the framework contract No EMA/2018/28/PE. This report expresses the expertise of the authors and the ACCESS consortium. It may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties."

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1.Executive summary

1.1 What is ACCESS

The ACCESS (vACCine covid-19 monitoring readinESS) project had the goal to prepare a European infrastructure for the monitoring of the COVID-19 vaccines and for conducting specific studies in a collaborative manner across EU countries. ACCESS is a project that was funded by the European Medicines Agency May 27 2020[1], through a framework agreement with the European Pharmacoepidemiology & Pharmacovigilance Network, which is led by Utrecht University. Partners were 20 organizations. The ACCESS project was coordinated by University Medical Center Utrecht as a partner in the EU PE&PV network.

1.2 Historic context

The 2009 pandemic taught that collaboration between different stakeholders is necessary to monitor vaccine coverage, benefits and risks in Europe, it also recognized the need for infrastructures and a sustainable ecosystem, which was subsequently designed tested in the IMI funded ADVANCE project (2013-2019). ADVANCE created best practice, methods, plus infrastructures and resulted in the creation of the Vaccine monitoring Collaboration for Europe (VAC4EU), a non-for-profit international association (AISBL), ADVANCE products can be found on the VAC4EU website (https://vac4eu.org).
VAC4EU was established as a legal entity in January 2020 and provides a sustainable ecosystem to allow for robust and transparent European collaboration on vaccine coverage, benefits and risk monitoring. ACCESS could capitalize on the solutions and tools from ADVANCE and VAC4EU to rapidly provide scientific support plus governance solution for execution of the studies on COVID-19 vaccines in Europe. VAC4EU facilitates access to tools, members and a large network that collectively can conduct studies together for public and private study requesters. Since January 2020, VAC4EU has welcomed 21 organizations as member.

1.3 Deliverables from the ACCESS project

ACCESS was requested to conduct six main activities:

1. **Provide definitions, codes** (ICD9-CM, ICD10-CM, READ, ICPC and MedDRA) and algorithms to identify 37 pre-specific adverse events of special interest (AESI)
2. Write a **protocol for calculation of background rates AESI** in 7 countries
3. Implement the protocol and **deliver background rates of AESI in 7 countries** based on electronic health records of 130 million persons
4. Write **template protocols for post-introduction monitoring of coverage, effectiveness and safety of COVID-19 vaccines**
   Eight different template protocols (a-g) were written using three different types of data collection, with the idea that each EU country should be able to participate. All protocols will be available from the VAC4EU website once endorsed by EMA.
   - ***Hospital-based studies (primary data collection)***
     a. COVID-19 *vaccine effectiveness* using a test negative design
     b. Case-based safety studies (Self-controlled) to *evaluate safety signals*
   - ***Patient-reported data collection***
     c. Cohort event monitoring of COVID-19 safety directly from vaccinated persons
   - ***Secondary use of electronic health record/registry data***
     d. Retrospective monitoring of COVID-19 vaccine effectiveness

[1] https://www.ema.europa.eu/en/news/ema-commissions-independent-research-prepare-real-world-monitoring-covid-19-vaccines

   e. Rapid assessment of the safety of COVID-19 vaccines
   f. Signal evaluation of the safety of COVID-19 vaccines
   g. Coverage monitoring of COVID-19 vaccines
5. Create a plan for **integration of benefit and risk data** for near real time monitoring
6. **Capacity assessment of EU countries** to participate in any of the 8 studies

Throughout the project life time, draft protocols have been discussed with an advisory committee that was installed by EMA, which had members from the PRAC, CHMP, EMA & ECDC. Comments were received and incorporated. Subsequently protocols went for stakeholder consultation and protocols went through a second update, to incorporate comments from stakeholders. This was conducted for all protocols, except for the cohort event monitoring and coverage protocols.
VAC4EU organized monthly scientific webinars to discuss different aspects of the ACCESS work which were open to the public. All webinars are publicly available from the VAC4EU website.

1.4 Where to find the products from ACCESS?

This deliverable describes the overview of the work and the link to each of the products from activities 1, 2 and 4-6, as well as rebuttal documents on EMA and stakeholder consultations around protocols. All protocols and documents will be available from the VAC4EU website https://vac4eu.org/covid-19-vaccine-monitoring/ and the EU PAS register once accepted by EMA.

The list of AESI plus definitions and codes (activity 1) and the background rate protocol (activity) have already been delivered and approved in August 2020 and are publicly available since September 2020

- List of AESI & definitions & codes (AESI lock point August 2020)

The following protocols were delivered for this final report, rebuttal documents have been submitted to EMA.

Background rates

- Protocol background rates of AESI Background rates of AESI protocol (EUPAS 37273)

Hospital based data collection on safety or effectiveness

- Safety Protocol for Hospital Case–Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project
- Protocol for COVID-19 vaccine effectiveness studies (test-negative design studies): a protocol from the ACCESS project

Patient reported data collection on safety

- Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project

Electronic health care data for coverage, safety and effectiveness

- Rapid assessment of COVID-19 vaccines safety concerns through electronic health records: a protocol template from the ACCESS project
- Safety evaluation of COVID-19 vaccines through electronic health records: a protocol template from the ACCESS project
- Assessment of effectiveness of COVID-19 vaccines through electronic health record: a protocol template from the ACCESS project
- Estimation of COVID-19 vaccine coverage using registers and EHR: a protocol template from the ACCESS project
- Proposal to integrate benefit /risk

1.5 Who will implement the ACCESS protocols?

The ACCESS project is creating preparedness funding is not covering the implementation of the ACCESS protocols through the specific contract. Protocols and products from ACCESS may be used by vaccine manufacturers or public entities (e.g. ECDC, EMA, EC).

1.6 Implementation of COVID-19 vaccine monitoring studies

Every study requester may approach VAC4EU for study implementation, against an open or fixed budget. Implementation of any of the studies can be facilitated through VAC4EU organizational and study governance (for all public and private requests) in 5 steps

1. Study requesters (public or vaccine manufacturers) can contact the VAC4EU secretariat secretariat@vac4eu.org with a request for proposal (RFP)
2. VAC4EU secretariat will share the RFP with the member organizations and inquire about interest to participate, roles, capacities, desired responsibilities. A coordinating center will be agreed by the members. Choice are made based on interest, excellence, experience, price and fairness.
3. The VAC4EU secretariat will respond to the study requester and facilitate negotiations.
4. Once the coordinating center is mutually agreed and the participating organizations, the coordinating center will contract with the study requester and subcontract participating organizations.
5. VAC4EU secretariat will provide the study team access to infrastructure (tools, templates, IT for collaboration).

1.7 Are you interested to become part of VAC4EU and participate in studies?

European public health and research organizations can become a member organization of VAC4EU by writing to secretariat@vac4eu.org and complying to membership rules. This will entitle organization to use VAC4EU services and participation in studies.

Persons can join the scientific community (please sign up on vac4eu website)

2. Background and organization

The novel coronavirus SARS-CoV-2, the cause of COVID-19, has led to a global pandemic since the first notification about pneumonia of unknown origin from Wuhan, China on December 31, 2019.
During 2020 the world has gone through an unprecedented pandemic. The central Chinese city of Wuhan in Hubei province became the focus of the world after a cluster of mysterious pneumonia cases at the end of December 2019 and the virus was identified as a new coronavirus on 8 January, 2020. Efforts to contain the virus to the city of 11 million people failed and, by the end of January, the disease had spread to every province in mainland China and was declared a "public health emergency of international concern" by the WHO. On 30 January 2020, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern. On 11 March 2020, WHO characterised COVID-19 as a pandemic[2].
Almost 1 year later, December 13, 2020, a total of 71,866,583 cases of COVID-19 have been notified worldwide, with 1,607,798 deaths (2.3%). Incidence is highest in Europe and North America and relatively low in Asia, Oceania and Africa, this may be partially due to testing capacity. The largest number of COVID-19 cases have been notified in USA followed by India, Brazil, Russia and France.

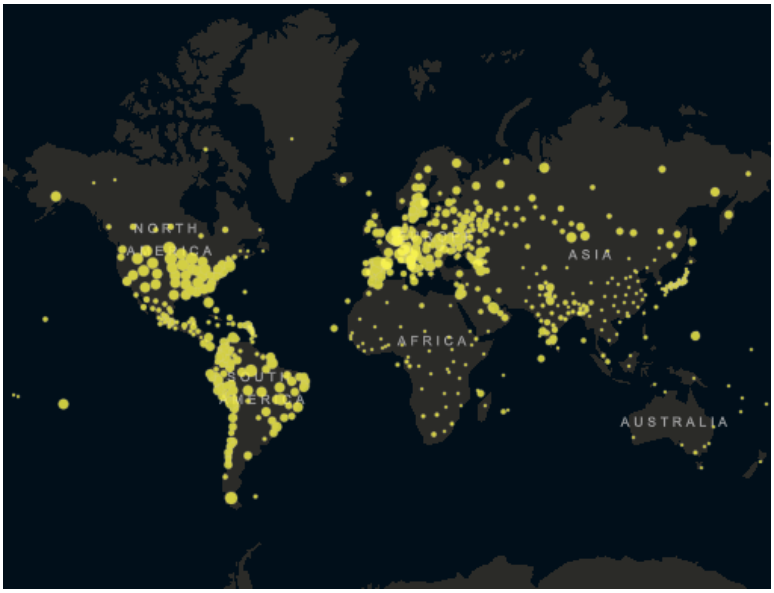

Figure 1: Incidence rates of COVID-19 cases from Johns Hopkins COVID-19 Dashboard (dec 13, 2020)

COVID-19 is the fifth pandemic after the 2018 Spanish flu and has killed more people than any of the non-Spanish flu pandemics. According to the OECD the COVID-19 pandemic has triggered the deepest economic recession in nearly a century, threatening health, disrupting economic activity, and hurting well-being and jobs.[3]

[2] https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
[3] https://www.oecd.org/coronavirus/en/themes/global-economy#data (accessed Dec 12, 2020)

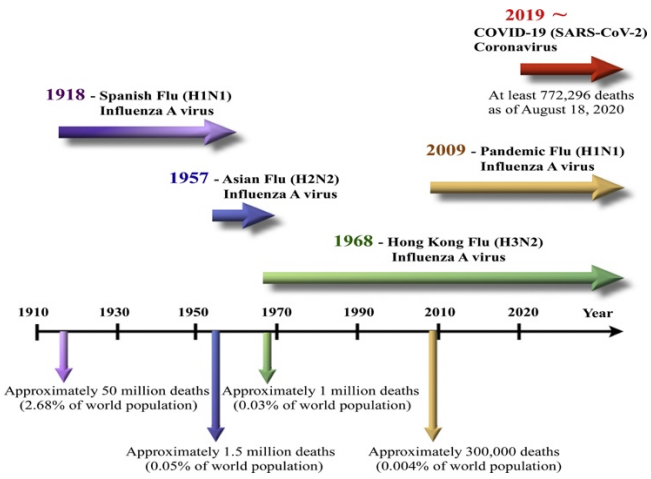

Figure 2: A timeline of five pandemics since 1918 and the globally circulating viruses afterward. Copied without permission from open access publication by Liu YC et al. Biomedical Journal 2020[4]

2.1 Vaccine development

With the early availability of the full sequence of the SARS-CoV-2 genome, developing a vaccine that could help countries to bring citizens' lives back to normal is the highest priority for the global community. It is critical that vaccines are both effective and safe and can be manufactured in sufficient quantities to ensure that they are available globally.

As of 11 December 2020, 273 candidate vaccines are in different stages of development: 215 in preclinical studies; 43 in phase I/II clinical studies; and 14 in phase III studies. Information on candidate COVID-19 vaccines under development is well tracked by the London School of Hygiene and Tropical Medicine.

A striking feature of the vaccine development landscape for COVID-19 is the range of technology platforms being evaluated, including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches[5] Many of these platforms are not currently the basis for licensed vaccines, but experience in fields such as oncology is encouraging developers to exploit the opportunities that next-generation approaches offer for increased speed of development and manufacture.

COVID-19 vaccines may be licensed by the European Medicines Agency (EMA) following an accelerated investigational and licensing procedure. Because the pre-licensure period is short, monitoring of the safety of vaccines in the post-introduction phase will be needed in an efficient manner, with the objective of identifying, assessing and evaluating as rapidly as possible any unintended side effects of vaccination.

[4] https://www.sciencedirect.com/science/article/pii/S2319417020300445
[5] T. Thanh LE, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID -19 vaccine development landscape. Nat Rev Drug Discov. 2020 May;19(5):305-306. doi: 10.1038/d41573-020-00073-5.

Based on recent European Commission communication to the European Parliament[6] there were three contracts in place in October 2020 that allowed the EC purchase of a COVID-19 vaccine once it has proven safe and effective, namely with Astra Zeneca, Sanofi-GSK and Johnson & Johnson. As of November 2020, the Commission continued discussing similar agreements with other vaccine manufacturers (CureVac, Moderna & Pfizer). On Nov 11th, 2020, the commission also secured a contract with Pfizer, on Nov 17th with Curevac and on Nov 25th with Moderna[7]

The Commission has thus far (December 12, 2020) secured access to the following doses of COVID-19 vaccines for Europe:

- Pfizer: 200 million doses & optional 100 million doses
- Moderna: 80 million doses and optional extra 80 million.
- AstraZeneca: 300 million doses.
- Sanofi-GSK: a purchase option for 300 million doses.
- Johnson & Johnson: 200 million doses.
- Curevac: 225 million doses plus an option to request up to a further 180 million doses

It is unknown whether all vaccines will successfully complete the development and authorisation process and thus meet efficacy and safety criteria to be placed on the EU market, but based on recent interim analyses of pivotal phase III trials that show high efficacy, Pfizer may be given emergency use rights in December 2020 in Europe followed by Moderna in January. Pfizer/BioNtech vaccine was approved for emergency use early December by the MHRA and on December 11, 2020 by FDA. Since its license for emergency use, 2 cases of anaphylaxis have occurred.

2.2 Access to vaccines

An allocation methodology agreed between the Commission and Member States[8], ensures that all Member States will have equal access to the available doses based on their population size. Once available and authorised at EU level, all Member States will have access to COVID- 19 vaccines at the same time. The overall number of vaccine doses will be limited during the initial stages of deployment and before production can be ramped up. Moreover, logistics are not easy around the Pfizer vaccine, which needs to be stored at -70 degrees Celsius, and needs to be diluted after which it can only be contained for some hours.

2.3 Highlights of EMA post-introduction safety monitoring approach

The EMA recently published its Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines[9]. Responsibilities are divided between marketing authorization holders, external stakeholders, ICMRA, EMA and NCA. Communication schemes with NCA, MAH and ICMRA are well established, no official communication exists with external stakeholders. EMA is requesting to post on EU PAS register.

The main objectives include

- Active collection of data on rare potential risks

[6] Communication from the Commission to the European Parliament and the Council. Preparedness for COVID-19 vaccination strategies and vaccine deployment. 15 Oct 2020. Available at: https://ec.europa.eu/health/sites/health/files/vaccination/docs/2020_strategies_deployment_en.pdf

[7] Agreed by the Commission and Member States in the Agreement on the joint EU approach to COVID-19 vaccines procurement adopted by the Commission on 17 June and endorsed by all Member States.

[8] WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination. 13 Sep 2020. Available at: https://www.nitag-resource.org/sites/default/files/2020-09/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf

[9] https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf (accessed December 12, 2020)

For COVID-19 vaccines, MAHs will be expected to submit to the Agency monthly summary safety reports in addition to regular PSURs. These will include, among others, information on reported suspected adverse reactions, including adverse events of special interest (AESIs), and sales data. The minimum elements to be addressed in these reports are listed in the coreRMP19.

- Rapid detection, prioritisation and assessment of emerging safety information derived from spontaneous reporting systems, observational studies and other data sources;
- Prompt evaluation of the impact of detected safety issues on the benefit-risk balance of the vaccines, considering exposure and effectiveness data;
- Active surveillance of vulnerable populations, such as pregnant women and older vaccinees;
- Engagement and collaboration with stakeholders including vaccinees and healthcare professionals, marketing authorisation holders (MAHs) and international partners;
- Prompt and effective communication of new information arising from the above activities.

2.4 Exposure information

According to the EMA document, member states will be gathering data on exposure in various manners, for instance by implementing national health data registers to collect information on individual vaccinations. EMA will collect and compile this data from Member States.

2.5 Signal detection by EMA & MAH

COVID-19 vaccines will be subject to additional monitoring, which aims at enhancing the reporting of suspected adverse reactions. The submission of ICSRs with AESIs, or fatal or life-threatening reactions in a shorter timeframe than 15 days should be considered when feasible.
EAM will conduct signal detection based It is anticipated that a high volume of ICSRs related to COVID-19 vaccines will be sent to spontaneous reporting systems, including EudraVigilance, with a relatively short lag after the vaccination campaigns start. Routine signal detection methods may be insufficient to screen such a volume of data efficiently and effectively. EMA and NCAs, within PRAC's signal management review technical working group (SMART WG), are testing several methodologies to address these challenges.
The 30-day timeframe for the confirmation of a validated signal may need to be shortened to allow for discussion of the signal at the forthcoming PRAC meeting. Similarly, shorter than usual timetables for assessment by PRAC (e.g. 30 days) may be warranted for some signals.

2.6 Observational research by MAH, EMA and external parties

For COVID-19 vaccines, the need for observational PASS studies will be carefully considered as routine activities and ongoing or planned clinical trials may not be sufficient to provide adequate data to further characterise identified and potential risks and investigate missing information. At the same time the EMA requests all studies that will be conducted, also not regulatory required studies to be registered in EU PAS.

EMA, ECDC and many national governments are working to secure public funding for vaccine safety monitoring studies from the European Commission[9].

2.7 Transparency of data on products

The EMA has put in place exceptional transparency measures in relation to COVID-19 vaccines. These include the publication of the full RMPs for these products. The Agency will publish regular pharmacovigilance updates on the approved COVID-19 vaccines, with the latest information[9].

3. List of AESI, definitions and codes

ACCESS delivered the following list of AESI that will be used to create background rates which will support EMA and vaccine manufacturers in the assessment of observed/expected calculations on August 15, 2020. Most of the events were obtained from the May 2020 AESI list defined by SPEAC and endorsed by the WHO Global Advisory committee for Vaccine Safety. For most of the AESI, Brighton Collaboration case definitions are available or will come available as well as data collection tools (see www.brightoncollaboration.us for toolbox). The US CDC also used the SPEAC list as basis but included sometimes additional events (especially auto-immune disorders) for their signal detection algorithms.

Table 1. List of AESI plus link to documents and motivation for inclusion, comparison with CDC AESI list and availability of BC case definition and minimal recommended follow-up

Body system / Classification	AESI, event definition and ICD-9/10, READ, ICPC and MedDRA codes (through hyperlinks)	Origin of event on AESI list (green those with BC case definition)	Minimal recommended Follow-up *
Auto-immune diseases	Guillain-Barré Syndrome (1)	SPEAC recommended (associated with other vaccines)	2 months
	Acute disseminated encephalomyelitis (2)	SPEAC recommended	2 months
	Narcolepsy (3)	AS03 in some vaccines	2-3 years
	Acute aseptic arthritis (4)	SPEAC recommended	1 year
	Diabetes (type 1 and broader) (5)	EMA-recommended	1 year
	(Idiopathic)Thrombocytopenia (6)	SPEAC recommended	2 months
	Transverse myelitis	EMA requested	2 months
Cardiovascular system	Acute cardiovascular injury comprising		1 year
	Microangiopathy (7)	SPEAC recommended (COVID_related)	1 year
	Heart failure (8)	SPEAC recommended (COVID_related)	1 year
	Stress cardiomyopathy (9)	SPEAC recommended (COVID_related)	1 year
	Coronary artery disease (10)	SPEAC recommended (COVID_related)	1 year
	Arrhythmia (11)	SPEAC recommended (COVID_related)	1 year
	Myocarditis/pericarditis (12)	SPEAC recommended (COVID_related)	1 year
Circulatory system	Coagulation disorders including Deep vein thrombosis (DVT) , Pulmonary embolus, Cerebrovascular stroke Limb ischemia Haemorrhagic disease (13)	SPEAC advised (COVID_related)	1 year
	Single Organ Cutaneous Vasculitis (14)	SPEAC recommended	2 months
Hepato-gastrointestinal and renal system	Acute liver injury (15)	SPEAC recommended (COVID_related)	1 year
	Acute kidney injury (16)	SPEAC recommended (COVID_related)	1 year
Nerves and central nervous system	Generalized convulsion (17)	SPEAC recommended (associated vacc.)	2 months
	Meningoencephalitis (18)	SPEAC recommended (associated vacc.)	2 months
Respiratory system	Acute respiratory distress syndrome (19)	SPEAC recommended (COVID_related)	1 year
Skin and mucous membrane, bone and joints system	Erythema multiforme (20)	SPEAC recommended	2 months
	Chilblain – like lesions (21)	SPEAC recommended (COVID_related)	1 year
Other system	Anosmia, ageusia (22)	SPEAC recommended (COVID_related)	2 months

	Anaphylaxis (23)	SPEAC recommended (associated with other vaccines)	2 months
	Multisystem inflammatory syndrome (in children) (24)	SPEAC recommended (COVID_related)	1 year
	Death (any causes)	EMA requested	2 months
	Enhanced COVID-19 disease (proxied by level of severity) (26)	SPEAC recommended (COVID_related)	3 years
	Sudden death (27)	EMA requested	2 months
Pregnancy outcome - Maternal	Gestational Diabetes (28)	GAIA, COVAX & CONSIGN interest	1 year
	Preeclampsia (29)	GAIA, COVAX & CONSIGN interest	1 year
	Maternal death (30)	GAIA, COVAX & CONSIGN interest	1 year
Pregnancy outcome - Neonates	Fetal growth restriction (31)	GAIA, COVAX & CONSIGN interest	1 year
	Spontaneous abortions (32)	GAIA, COVAX & CONSIGN interest	1 year
	Stillbirth (32)	GAIA, COVAX & CONSIGN interest	1 year
	Preterm birth (33)	GAIA, COVAX & CONSIGN interest	1 year
	Major congenital anomalies (34)	GAIA, COVAX & CONSIGN interest	1 year
	Microcephaly (35)	GAIA, COVAX & CONSIGN interest	1 year
	Neonatal death (36)	GAIA, COVAX & CONSIGN interest	1 year
	Termination Of Pregnancy for Fetal Anomaly (37)	GAIA, COVAX & CONSIGN interest	1 year

*based on current knowledge although risk windows following COVID-19 vaccines are not known
& If link does not work connect to entire google drive with numbers for AESI

4. Template protocols

4.1 Background

Nine protocols have been written by ACCESS partners to be ready to monitor COVID-19 vaccine coverage, effectiveness and safety. Only the background rate protocol is implemented and conducted as part of the ACCESS project. The other 8 protocols are *template* protocols, which will allow users to rapidly complete a dedicated protocol, based on the setting, type of data availability and request. The safety protocols provide different choices and designs, plus a decision framework to choose, as it is not yet known, which type of adverse event/signal may require further investigation.
ACCESS developed template protocols that were related to the **type of data collection, primary data collection or secondary use of health data** to allow all countries to participate in safety and effectiveness monitoring.

4.4.1 Background rates of AESI study

The ACCESS protocol to calculate background rates of AESI in electronic health data was delivered to EMA August 15 2020, and is listed on the EU-PAS register. It was submitted for external stakeholder advise and adapted based on comments

Abstract of the background rates protocol

Research question and objectives:

Co-primary:

- To estimate the incidence rates of adverse events of special interest (AESI) in the general population by calendar year and data source over the period 2017 to 2020.
- To estimate the incidence of pregnancy outcomes among pregnant women aged between 12 to 55 years old by calendar year and data source over the period 2017 to 2020.

- To estimate the weekly and monthly incidence rates of COVID-19 (overall and by severity level) in 2020 by data source.
- To estimate the monthly incidence rates of multisystem inflammatory syndrome in children (MIS-C) aged between 0 to 19 years old in 2020 by data source.

Secondary:

- To estimate the incidence rates of AESI in the general population by calendar year, sex, age group, and data source over the period 2017 to 2020.
- To estimate the incidence rates of AESI in the general population by month, sex, age group, and data source over the period 2017 to 2020.
- To estimate the incidence rates of multisystem inflammatory syndrome (MIS-C) in children in 2020 by month, sex, age group, and data source.
- To estimate the prevalence of high-risk medical conditions for developing severe COVID-19 by year and data source over the period 2017 to 2020.
- To estimate the incidence rates of AESI in the at-risk population for developing severe COVID-19 by calendar year, sex, age group, and data source over the period 2017 to 2020.

Study design: A retrospective multi-database dynamic cohort study, conducted during the years 2017 to 2020, including the period of SARS-CoV-2 circulation in Europe until the date of last data availability for each data source.

Population: The study population will include all individuals observed in one of the participating data sources for at least one day during the study period (01 January 2017 - last data availability) and who has at least 1 year of data availability before cohort entry, except for individuals with data available since birth.

Variables:

Variables of interest will be

- Person-time: birth and death dates as well as periods of observation.
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify AESI, pregnancy outcomes and at-risk medical conditions.

AESI (see table 1):

Data sources: The study will include data from 10 data sources in 7 European countries (Denmark, Germany, France, Italy, Netherlands, Spain, United Kingdom). Data sources contain health insurance data (BIPS, SNDS), hospitalisation record linkage data (PHARMO, Danish registries, FISABIO, SIDIAP, ARS) or data from general practitioners (CPRD, PEDIANET, BIFAP).

Study size: The study population will comprise approximately 130.6 million individuals.

Data analysis: Incidence rates (and 95%CI) of AESI and pregnancy outcomes by calendar year will be calculated by dividing the number of incident (new) cases by the total person-time (for AESIs) or pregnancies (for pregnancy outcomes) at risk.

Prevalence rates (and 95%CI) of at-risk medical conditions for developing severe COVID-19 by calendar year will be calculated by dividing the number of existing cases in a year by the average of the total number of persons recorded monthly. Incidence rates (and 95%CI) of AESI among at-risk populations will also be computed.

Sensitivity analyses will be conducted according to the time prior to SARS-CoV2 circulation and during SARS-CoV2 circulation period to investigate the impact of circulating virus on incidence rates. Additionally, a sensitivity analysis will be conducting according to the time prior to, during, and after (dependent upon data availability) lock down measures limiting face-to-face healthcare encounters to assess the impact of changes in health care behaviours on the incidence rates. In addition, incidence rates of colonic diverticulitis and hypertension, a serious and non-serious control event, respectively, will be computed.

Review & rebuttal of protocol
The protocol was reviewed by the EMA and stakeholders.

4.4.2 Hospital based data collection for COVID-19 vaccine safety and effectiveness evaluation

ACCESS developed two template protocols that rely on **hospital-based data collections**. One for COVID-19 vaccine safety evaluation and one for effectiveness measurement.
In this design, site investigators would include patients that fit the inclusion criteria and would use the availability of other health records and/or patient data to collect information on covariates and vaccine exposure. Consent would need to be obtained.
Key requirements would be the ability to identify patients, validate the diagnosis and obtain information on vaccination, and covariates from patient, records and other health care providers. Sites capable of participating may be eligible for any type of other event. Most efficient would be case-based designs.
Both protocols based on hospital-based data collection have been reviewed by EMA, the advisory group and the external stakeholders. Rebuttal documents of stakeholder comments are included as follow-up documents.
Relevant template protocols are:

4.4.2.1 Safety Protocol for Hospital Case–Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project

The protocol describes different case-based designs that can be conducted in sentinel hospitals. Table 2 below that is taken from the protocol and provides the decision framework for different designs based on characteristics of the outcome, when using this data collection approach. We provide a summary of the protocol:

Research question and objectives:

Primary objective: To determine whether there is an increased risk of prespecified adverse events << (list the AEs) >> following vaccination with <<specific COVID-19 vaccine product>>

Secondary objectives:

- To determine whether there is an increased risk of prespecified adverse events << (list the AEs) >> in specific vaccine groups defined by platform and/or components (e.g., adjuvant)
- To determine whether risk of <<adverse events>> after COVID-19 vaccination differs by age at vaccination, race, <<comorbidities>>, <<infections>>, <<concomitant vaccinations>>, and <<concomitant medications>>

Study design:

Self-controlled risk interval (SCRI)
A retrospective (multi)-database case-only study that includes only subjects who were vaccinated with <<COVID-19 vaccine>> and experienced <<event>>. The risk and control windows should be prespecified. The study period will begin in each hospital when the vaccine becomes available in the catchment area for the hospital and will end on the last date on which data on vaccinations and hospital discharges is available.

Case-crossover (CCO)

A retrospective (multi)-database case-only study that includes subjects who experienced <<event>>.It considers the occurrence of <<event>> as fixed event and the <<COVID-19 vaccine>> exposure random. The study period should comprise a period during which data on both exposures and outcomes are available.

Case-coverage

The case-coverage design builds upon the framework of the CCO but uses information on vaccination rates in the reference population to adjust for potential temporal trends in exposure.

Population:
The source population for the study will comprise individuals eligible to receive COVID-19 vaccination, considering the product-specific indications and availability of the vaccine, and residing in the catchment areas of participating hospitals. If the COVID-19 vaccine is indicated for a given population, but because of a vaccine shortage is only administered in a more restricted population, the source population will be limited accordingly.

Variables:
<<Adverse event>> should be identified in each participating hospital's discharge database using diagnosis codes, or a combination of diagnosis with procedure or treatment codes. Additionally, electronic laboratory data could be used to identify events, if applicable to the outcome. Exposure status will be identified in confirmed cases. For this study, an indicator for each dose of <<COVID-19 vaccine product>> and date of vaccination will need to be identified for all cases. In the SCRI design, if multiple doses of vaccine are given during the study period, each individual dose will be evaluated separately.

Covariates will include sex, age, country, calendar month of vaccination, other vaccines (Influenza, childhood) and respiratory infections.

Table 2. Decision Framework for Determining Suitability of the SCRI, CCO, or Vaccinated Case-Coverage Design for hospital vase based safety evaluations.

Criteria	Suitability of the SCRI (Postvaccination Control Window)	Suitability of the CCO	Suitability of the Vaccinated Case-Coverage Design
Outcome is treated in the hospital			
Yes	✓	✓	✓
No	X	X	X
Outcome latency			
Short latency	✓	✓	✓
Long latency	X	X	X
Outcome onset			
Acute onset	✓	✓	✓
Gradual onset	X	X	X
Ability to define risk period for outcome following exposure			
Can be clearly defined	✓	✓	✓
Cannot be clearly defined	X	X	X
Effect of outcome on likelihood of vaccination			
Outcome does not affect likelihood of vaccination	✓	✓	✓
Outcome temporarily decreases or increases likelihood of vaccination and the vaccine is a single dose	✓	O	O

Criteria	Suitability of the SCRI (Postvaccination Control Window)	Suitability of the CCO	Suitability of the Vaccinated Case-Coverage Design
Outcome temporarily decreases or increases likelihood of vaccination and the vaccine is multidose	O	O	O
Outcome is a (permanent) contraindication to vaccination and the vaccine is single dose	✓	O	O
Outcome is a (permanent) contraindication to vaccination and the vaccine is multidose	O	O	O
Outcome censors the period of observation for exposure (e.g., the outcome is death)	O	✓	✓
Recurrence of outcome			
Outcome is independently recurrent	✓	✓	✓
Outcome is non-recurrent but rare	✓	✓	✓
Outcome is recurrent, and recurrent events are not independent (e.g., stroke)	✓	✓	✓
Temporal trends in vaccination			
Temporal trends in vaccination are not present during the study period	✓	✓	✓
Temporal trends in vaccination are present during the study period	✓	X	✓

CCO = case-crossover; SCRI = self-controlled risk interval.

Key: Checkmark (✓) indicates design is suitable; X indicates not suitable; O indicates that the study design is possible under certain circumstances.

Review & rebuttal of protocol

The protocol was reviewed by the EMA and stakeholders.

4.4.2.2 Hospital Case– Core protocol for COVID-19 vaccine effectiveness studies (test-negative design studies) A Protocol Template from the ACCESS project

In line with the protocols developed by DRIVE IMI project (https://www.drive-eu.org/) to monitor brand-specific influenza vaccine effectiveness at European level, ACCESS generated a protocol to assess brand/type-specific CVE following a test-negative design. The test-negative design is considered as the most efficient approach currently available for routine assessment of influenza VE.

The test-negative design is a variation of the classical case-control study. Patients fulfilling a previously established case definition are enrolled at hospitals (or Primary Care) and tested for the virus of interest. The VE is estimated comparing the odds of vaccination among patients testing positive (cases) vs. those testing and negative (controls), after adjusting for potential confounders. This design can avoid or minimize biases such as selection bias by healthcare-seeking behaviour, as it is assumed that healthcare-seeking behaviour is similar between the cases and controls. Biases related to exposure misclassification can be also limited by ascertaining vaccination by consulting medical records, vaccination cards or other health registries and avoiding self-reporting.

As with any observational study, vaccine effectiveness estimates following a test-negative design can be biased due to misclassification of disease status. Although, part of this misclassification can be reduced by restricting the analysis to those patients attending hospital a short time after onset of symptoms as we propose in this protocol template, using diagnostic assays with imperfect sensitivity and specificity (RT-PCR for SARS-CoV-2 has proven to significantly vary in its sensitivity), appears to be particularly important with respect to COVID-19.

Review & rebuttal of protocol

The protocol was reviewed by the EMA and stakeholders.

4.4.3 Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project

To support signal detection and estimation of rates of adverse events near real time, ACCESS partners developed a protocol for cohort event monitoring with data collected from patients.

This design includes vaccinated persons and provides periodic follow-up to collected solicited and non-solicited events. This design can be viewed as active surveillance, aimed at both estimating frequencies as well as picking up signals. Requirements are the ability to include vaccines through an online method, periodic follow-up and ability to code and assess reported AEFI. Vaccinees should be able to provide information on vaccine brand and batch.

A summary of the protocol:

Research question and objectives:

Primary aim:

- To generate incidence rates and to describe patterns (e.g. course and impact) of patient-reported AEFIs by COVID-19 vaccine brand on both the national and European level in near real time.

Secondary aims:

- to describe differences in AEFI patterns between different vaccine batches used across the participating countries,
- to identify possible risk factors for AEFIs.

The following questions should be answered:

- What are the reported AEFIs, for each vaccine, in each country?
- What are the frequencies of reported AEFIs for each vaccine, in each country?
- What is the course of reported AEFIs (latency time, outcome, recovery time)?
- What is the impact (medical assistance, hospitalisation, treatment, severity) of reported AEFIs?
- Are there possible risk factors for AEFIs and adverse events of special interest (AESIs)?

Study design: Prospective cohort study. In different countries, on the national level, data should be prospectively collected in near real time, directly from a cohort of vaccine recipients. The common core data from different countries will be pooled and analysed at the European level. Vaccine recipients should be asked to fill in questionnaires at baseline, 1, 3, 6 and 8 weeks and 3 and 6 months after vaccination (from the first dose). The exact timing of the sending of the second questionnaire will depend on the vaccination interval between two doses.

Population: Recipients of COVID-19 vaccines in participating countries consenting to participate and with a baseline questionnaire as well as one questionnaire filled out after vaccination. Participants will be recruited before or at the moment of vaccination, which may differ per country and target group.

Variables:
Vaccines, AEFIs, age, sex, height and weight, geographical area, medical history

Events: Adverse events that are reported after each dose of COVID-19 vaccination, by the patient. Incoming serious adverse events (SAEs) and AESIs or other events that need medical clarification will be assessed by a qualified assessor also with respect to contributing factors on intrinsic and extrinsic causality. If necessary, follow up will be requested by e-mail for verification and upgrading of the clinical documentation grade.

Data sources: Safety data can be directly reported by vaccine recipients in their local language using the Lareb Intensive Monitoring (LIM) web app, which has been built specifically for patient-reported outcomes. Reported data from European countries using this LIM app can be stored in a dedicated central database. Data can also be collected nationally with non-LIM intensive monitoring tools/apps and countries can store and code data locally and share at regular intervals.

Study size: We would recommend to include at least 30,000 vaccine recipients in several countries per brand in total, which should allow for the detection of AEFIs with a frequency ≥1:10,000 on the European level based on the rule of three.

Data analysis: AEFI frequencies within the vaccinated cohort should be reported cumulatively every month, overall and for the different vaccine brands, doses and batches where available. The course of reported AEFIs (latency time, outcome, recovery time) and impact (medical assistance, hospitalisation, treatment, severity) should be assessed. Risk factor analyses should be performed for expected AEFIs and AESIs.

Review & rebuttal of protocol
The protocol was reviewed by the EMA.

4.4.4 Secondary use of health data/registry data for rapid assessment and evaluation of COVID-19 vaccine safety

ACCESS partners have developed 2 different protocols for safety evaluation based on large linked electronic databases. The first one is for a rapid assessment of a safety signal, that will not validate diagnoses nor conduct detailed assessment and adjustment for covariates, but will allow for a quick assessment of the impact. The second protocol is a signal evaluation study. Both template protocols provide different options for designs which will have to be chosen based on the event of interest. Decision frameworks are provided in the protocols and included below.

4.4.4.1 Rapid assessment of COVID-19 vaccines safety concerns through electronic health records: a protocol template from the ACCESS project

As part of the preparedness activities for safety surveillance of COVID-19 vaccines, the rapid assessment template protocol provides a template for quickly developing a full study protocol to perform vaccine safety assessment studies to quantify potential risks through the secondary use of electronic healthcare databases.

The potential designs for rapid safety assessment of vaccines studies include ecological designs, including interrupted time series (ITS) and the unadjusted self-controlled risk interval (SCRI) design.

Electronic health care data source requirements for the application of each study design are described in Table 3.

Table 3. Decision Framework for Determining Suitability of Ecological designs and Unadjusted SCRI for Rapid Assessment of safety signals, based on type of events and vaccination trends

Event criteria	Ecological Designs	Unadjusted SCRI
Event onset		
Acute onset	✓	✓
Gradual onset	O[a]	X
Ability to define risk period for event following exposure		
Can be clearly defined	✓	✓
Cannot be clearly defined	✓	X
Effect of event on likelihood of vaccination		
Event does not affect likelihood of vaccination	✓	✓
Event temporarily decreases or increases likelihood of vaccination	✓	O[b]
Event is a (permanent) contraindication to vaccination	✓	X
Event censors the period of observation for exposure (e.g., death or an outcome that increases the probability of death)	✓	✓
Event is independently recurrent	✓	✓
Event is non-recurrent but rare	✓	✓
Event is recurrent, and recurrent events are not independent (e.g., stroke)	✓	O[b]
Temporal trends in vaccination		
Temporal trends in vaccination are not present during the study period	O[c]	✓
Temporal trends in vaccination are present during the study period	O[c]	✓

Checkmark indicates design is suitable; X indicates not suitable; O indicates that the study design is possible under certain circumstances.

[a] Requires sufficient accrual of post-intervention time for observation of events.

[b] May be used if a healthy vaccinee period to exclude from the pre-vaccination period can be defined.

[c] Requires that the start of the intervention be identifiable for the population under consideration. If timing of vaccination varies within the population under consideration, ecological designs may not be applicable, and the investigator may consider limiting the study population to those for whom the intervention period is identifiable.

Review & rebuttal of protocol

The protocol was reviewed both by the EMA and stakeholders.

4.4.4.2 Safety evaluation of COVID-19 vaccines through electronic health records: a protocol template from the ACCESS project

As part of the preparedness activities for safety surveillance of COVID-19 vaccines, this template protocol provides a template for quickly developing a full study protocol to perform vaccine safety evaluation studies to quantify potential risks through the secondary use of electronic healthcare databases.

The template safety protocol is for the evaluation of safety of COVID-19 vaccine(s) using population based electronic health record databases in Europe. In order to use this specific protocol, electronic health care data on population, events and COVID-19 vaccine administration are required.

The potential designs for safety evaluation of vaccines studies include the cohort, case-control, self-controlled case series (SCCS), self-controlled risk interval (SCRI), and case-crossover (CCO). Table 5 provides a decision framework for the choice of the design based on the characteristics of the event. Details about the designs can be found in the protocol.

Table 5: Decision Framework for Determining Suitability of cohort, case-control, SCCS, SCRI, CCO for signal evaluation

Event criteria	Cohort	Case-control	SCCS	SCRI	CCO
Event latency					
Long latency	✓	✓	O[a]	X	X
Short latency	✓	✓	✓	✓	✓
Outcome onset					
Acute onset	✓	✓	✓	✓	✓
Gradual onset	✓	✓	O[a]	X	X
Ability to define risk period for outcome following exposure					
Can be clearly defined	✓	✓	✓	✓	✓
Cannot be clearly defined	✓	✓	O	X	X
Effect of event on likelihood of vaccination					
Event does not affect likelihood of vaccination	✓	✓	✓	✓	✓
Event temporarily decreases or increases likelihood of vaccination	✓	✓	✓	✓	✓
Event is a (permanent) contraindication to vaccination	O[b]	O[b]	O[b]	O[b]	✓
Event censors the period of observation for exposure (e.g., death or an outcome that increases the probability of death such as myocardial infarction)	✓	✓	X	X	✓
Event is independently recurrent	✓	✓	✓	✓	✓
Event is non-recurrent but rare	✓	✓	✓	✓	✓
Event is recurrent, and recurrent events are not independent (e.g., stroke)	✓	✓	O[c]	X	O
Temporal trends in vaccination					
Temporal trends in vaccination are not present during the study period	✓	✓	✓	✓	✓
Temporal trends in vaccination are present during the study period	✓	✓	✓	✓	O

Checkmark indicates design is suitable; X indicates not suitable; O indicates that the study design is possible under certain circumstances.

[a] Suitable if prodromal symptoms before diagnosis of the outcome do not cause or prevent vaccination, either temporarily or permanently. To address this potential source of bias, every effort should be made to identify the onset of symptoms from the available data such as medical records, rather than relying on the date of diagnosis.

[b] Suitable if the vaccine is given in a single dose. If the vaccine is given in multiple doses, the design is not suitable unless special analytic techniques are applied to handle censored, perturbed, or curtailed post-event exposures.

[c] Suitable if appropriate adaptations to the self-controlled case series are applied (Farrington, 2010)

Review & rebuttal of protocol

The protocol was reviewed by the EMA and stakeholders.

4.4.5 Assessment of effectiveness of COVID-19 vaccines through electronic health record: a protocol template from the ACCESS project

This protocol template describes a general approach for a retrospective cohort study based in existing health data sources to assess effectiveness that may be modified or adapted to specific settings and research questions by future investigators.

Research question and objectives: To evaluate the effectiveness of <<COVID-19 vaccine product>> in reducing the burden of COVID-19, this protocol template addresses the following primary objective:
To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:

- Hospitalisation for COVID-19
- Mortality due to COVID-19

Secondary objectives of this protocol template are the following:

- To evaluate the effectiveness of <<COVID-19 vaccine product>> in preventing the following outcomes:
- Intensive care unit (ICU) admissions for COVID-19
- Medically attended diagnosis of COVID-19 in any setting
- All-cause mortality
- Hospitalisations for respiratory infections
- To evaluate if the effectiveness of <<COVID-19 vaccine product>> varies over clinically meaningful subgroups

Study design: This protocol template describes an observational cohort study of those vaccinated with <<COVID-19 vaccine product>> and those unexposed. The definition of the unexposed group may vary based on the actual use of <<COVID-19 vaccine product>> in the target population and the scientific question of interest.
This protocol template also describes a study feasibility stage, where the availability and validity of information needed to conduct the study will be evaluated, and the study design and analytic approach will be evaluated with a negative control outcome analysis.
Population: This study should be conducted in populations where <<COVID-19 vaccine product>> is approved and recommended for use. Due to rapidly changing COVID-19 incidence and testing/diagnosis capability and processes, exposed and unexposed groups should be drawn from the same time period. The study setting may include multiple existing health care data systems that contain information about vaccination status, hospitalisation records, mortality records, and comorbidity information.
The target population of interest should be consistent with the vaccine's approved indications, recommended use, and actual distribution. Recommendations and priority populations for vaccination may vary over time, and the study eligibility criteria should match.
Variables: <<COVID-19 vaccine product>> exposure status will be identified from vaccination records, as available in each data source. Eligibility criteria will be defined from enrolment, demographic, and clinical information in each data source. Outcomes will be defined in hospitalisation records, mortality records, and other records of diagnoses, as available in each data source. Covariates will consist of demographic and clinical variables necessary to describe differences between exposure groups and control confounding. Covariates will include demographic information, comorbidities, comedication use, health care utilisation, markers of current disease status at time zero, and markers of frailty.
Data sources[10]: [To be determined by the study investigators]
Study size: [To be determined by the study investigators]
Data analysis: Characteristics of the exposed and unexposed groups will be described. Incidence rates of COVID-19 outcomes will be calculated in the exposed and unexposed groups.

[10] Database custodians and research partners will be contacted to explore interest in and availability to participate in the study. [To be included or modified as needed by the study investigators]

Incidence rates of COVID-19 outcomes will be compared between the exposed and unexposed groups, and vaccine effectiveness measures will be estimated. Additional absolute effect measures (e.g., risk difference) and time period–specific effect estimates (e.g., at 3, 6, or 12 months after vaccination) may also be estimated.
Subgroup analyses will separately estimate vaccine effectiveness in clinically meaningful subgroups. Sensitivity analyses will evaluate the robustness of the study approach across multiple variations of the study design.

Review & rebuttal of protocol

The protocol was reviewed by the EMA and stakeholders.

4.4.6 Secondary use of health data/registry data for evaluation of COVID-19 vaccine coverage

As part of the preparedness activities for surveillance of COVID-19 vaccines, this template protocol provides a template for quickly developing a full study protocol to perform vaccine coverage studies through the secondary use of electronic healthcare databases and/or immunization registers.

This protocol template describes a general approach for a study based in existing health data sources that may be modified or adapted to specific settings and research questions by future investigators. The protocol uses a retrospective cohort study and would require data on immunization from registers or electronic data sources that can be linked to the underlying population, preferably stratifiable to the target groups.

Review & rebuttal of protocol

The protocol has been reviewed by the EMA.

4.5 Integration of coverage, safety and effectiveness

Assurance about the performance of the vaccine monitoring system can strengthen the confidence in the regulatory system's ability to measure effectiveness and detect, assess and minimize risks to vaccinated individuals, and ensure that the benefits of vaccination outweigh its risks. In previous work (IMI-ADVANCE), timely monitoring of vaccine benefit-risk measures has been performed through an online dashboard that reported separate and integrated measures of vaccine coverage, benefits and risks using electronic healthcare data[11]. In ACCESS, data sources consist of electronic healthcare databases, prospective studies, and safety data retrieved through health apps.

Monitoring should be understood as a periodic assessment of several key parameters including, coverage, incidence of adverse events, and incidence of the vaccine-preventable disease. When there is an indication that the benefit-risk profile in the population is different from what was expected, a reconsideration of the benefit-risk profile can take place. An online dashboard can help provide stakeholders with insights on how key variables develop over time. The visualizations within the dashboard function as a trigger to indicate when more formal assessments may be warranted. Monitoring should, in principle, start as soon as a new vaccine is introduced in a given country and continue throughout the vaccine's lifecycle.

[11] https://vac4eu.org/benefits-and-risk/

The overall objective of the protocol (appendix 15) is to outline the feasibility of the visualization of information on COVID-19 vaccine coverage, benefits and risks in an online dashboard.

The protocol addresses the following issues:

1. Data flow and processing from decentralized databases to the online dashboard
2. Content of the online dashboard visualisations regarding:
    a. Coverage
    b. Safety (risks)
    c. Effectiveness (benefits)
    d. Integration of benefits and risks
3. Requirements for the assessment of monitoring delays

Review & rebuttal of protocol

The protocol has been reviewed by the EMA.

5. Feasibility analysis for timely monitoring of COVID-19 vaccines

5.1 Introduction

The pre-licensure period of COVID-19 vaccines is short and the number of tested subjects is limited, therefore continuous monitoring of benefits and risks of the vaccines is required when the vaccines are used in a broader population (1).
The ACCESS project has the aim to prepare a European infrastructure for the monitoring of the COVID-19 vaccines and for conducting specific studies in a collaborative manner across EU countries (2). For this purpose, the Vaccine Monitoring Collaboration for Europe (VAC4EU) performed a capacity assessment of organizations in Europe to participate in COVID-19 vaccine monitoring studies.

5.2 Method

As part of the capacity assessment in Europe, VAC4EU has taken the following two step strategy
In September 2020, an initial survey (see annex 1) was launched online by VAC4EU to all EU countries through the following routes.

1) Invitation to the ACCESS consortium
2) Invitation by EMA to the ENCePP network
3) Invitation by EMA through the PRAC
4) Invitation of all public health institutes listed on the ECDC Advisory forum

In the survey we asked for additional contacts and these persons were contacted to ask to complete the survey.

In November 2020, the organizations that had responded to the initial survey that they were willing and able to participate were followed-up with a dedicated survey to inquire more in depth about specific capacity and the national vaccination strategy in their country. Three surveys were designed, for three different types of data collection (electronic health record (EHR)-based data collection, hospital-based data collection and app-based cohort event monitoring). Annex 2-4 provide the questions.

In December 2020, organizations that had not responded to the follow-up survey after several reminders were invited to an online interview to complete the questionnaire.

5.3 Analysis

All data were collected in Surveymonkey, and analysed in a descriptive manner

5.4 Results

5.4.1 Initial responses

The initial survey was completed by 82 respondents in 74 organizations (Table 7), located in 17 different European countries (Figure 3).

Figure 3: Location of organizations that completed the initial survey in October 2020

Majority of responses came from Portugal and Czech Republic, followed by Spain and Italy. Most organizations were public research/health units, 12 respondents were commercial research organizations (CRO).

Table 7: Sites that responded to the initial survey

Country	No.	public RO	Hospital or care facility	Pharmacovigilance center	CRO	Public health institute	Regulatory agency	SME	private non-profit	international association
Belgium	3					1	1			1
Czech Republic	14	1	6		5	1	1			
Croatia	1					1				
Denmark	1	1								
Finland	3	1				2				
France	3	1			2					
Germany	2	2								
Ireland	3		1			1	1			
Italy	6	1			2	2				
Latvia	1						1			
Netherlands	2	1				1				
Norway	1	1								
Portugal	20	1	12	5	1	1				
Romania	1	1								
Slovakia	1	1								
Spain	7	2	1			1	1	1	1	
Sweden	3	1			1		1			
UK	2				1	1				
Total	**74**	**15**	**20**	**5**	**12**	**12**	**6**	**1**	**1**	**1**

Table 8: Overview of responses of countries to participate in certain studies with initial survey

	BE	CZ	CR	DK	FI	FR	DE	IR	IT	LA	NL	NO	PO	RO	SL	ES	SE	UK	N
can you work with industry (only no restrictions)	1	7		1	2	2	2		1				9	1	1	5	1		33
organization already involved in monitoring of COVID-19 vaccines:	1	5	1		2	1	1	2			2		3			6	1	2	27
interest to participate in safety studies on EHR data	2	1		1	2	3	1	1	4		2		7			4	1	1	30
interest to participate in safety studies in hospital data	1	7			1	2		1	3		1		11	1	1	1		1	31
interest to participate in safety studies with apps	1	5			2	2	1		2				11	1		1		1	27
interest to participate in effectiveness studies on EHR data	2	1		1	2	3	1	1	4		2	1	5			5	1	1	30
interest to participate in effectiveness studies on hospital data	1	6		1		2			2		2		8		1	4		1	28
interest to participate in coverage studies on immunization registry data	2	1		1	2	2		3	3		2		8		1	4	1		30
Responses per country	3	14	1	1	3	3	2	3	6	1	2	1	20	1	1	7	3	2	74

Table 8 shows that many organizations can work with industry without restrictions (n=33), 27 organizations are already involved in monitoring of COVID-19 vaccines, most interest is in participation in safety studies both with EHR as well as in hospital.

Table 9 shows the potential participation per country and organization.

Table 9. Organizations that completed the initial survey in October 2020

	Safety based on hospital-based data collection	Safety based on electronic health data	Safety based on app-based prospective data collection	Effectiveness (test negative design)	Effectiveness based on electronic health data
Belgium (+32)[1]	1. Sciensano (institut de santé publique)	1. Sciensano (institut de santé publique) 2. VAC4EU	1. Federal Agency of Medicines and Health Products (FAMHP)	1. Sciensano (institut de santé publique)	1. Sciensano (institut de santé publique) 2. VAC4EU
Czech Republic (+420)[2]	1. Motol University Hospital (Immunology + Infectious Disease) 2. Pharmnet s.r.o. 3. St. Anne´s University Hospital Brno 4. TWMA clinical research and pharmacovigilance 5. University of Defence		1. Pharmnet s.r.o. 2. St. Anne´s University Hospital Brno 3. University of Defence 4. Vaccination and Travel Medicine Centre	1. Motol University Hospital (Immunology + Infectous Disease) 2. Pharmnet s.r.o. 3. Scope International Praha, s.r.o. 4. St. Anne´s University Hospital Brno 5. TWMA clinical research and pharmacovigilance	
Denmark (+45)		1. Aarhus University		1. Aarhus University	1. Aarhus University
Finland (+358)[3]	1. Finnish Institute for Health and Welfare department Health Security	1. Finnish Institute for Health and Welfare department Health Security 2. Finnish Institute for Health and Welfare (THL) department of Public Health Solutions	1. Finnish Institute for Health and Welfare department Health Security 2. Vaccine Research Center*		1. Finnish Institute for Health and Welfare department Health Security 2. Finnish Institute for Health and Welfare (THL) department of Public Health Solutions
France (+33)	1. PRA Health Sciences 2. Université de Bordeaux	1. PELyon 2. PRA Health Sciences 3. Université de Bordeaux	1. PRA Health Sciences 2. Université de Bordeaux	1. PRA Health Sciences 2. Université de Bordeaux	1. PELyon 2. PRA Health Sciences 3. Université de Bordeaux
Germany (+49)		1. Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS	1. SLCMSR e.V. - The Human Motion Institute		1. Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS
Ireland (+353)	1. Rotunda Hospital	1. Rotunda Hospital			1. Rotunda Hospital
Italy (+39)	1. GISED Study Center 2. Lazio Regional Health Service 3. University of Insubria	1. Agenzia regionale di sanità della Toscana 2. Ats Della Val Padana 3. Lazio Regional Health Service 4. Societa' Servizi Telematici – Pedianet	1. Ats Della Val Padana 2. GISED Study Center 3. Societa' Servizi Telematici – Pedianet	1. University of Insubria	1. Agenzia regionale di sanità della Toscana 2. Ats Della Val Padana 3. Lazio Regional Health Service 4. Societa' Servizi Telematici – Pedianet
Latvia (+371)[4]					

Netherlands (+31)[5]	1. University Medical Center Utrecht	1. University Medical Center Utrecht 2. RIVM		1. University Medical Center Utrecht 2. RIVM	1. University Medical Center Utrecht 2. RIVM
Norway (+47)[6]		1. University of Oslo			1. University of Oslo
Portugal (+351)[7]	1. Centro Hospitalar de Lisboa Ocidental 2. Centro Hospitalar de Trás-os-Montes e Alto Douro – CHTMAD 3. Centro Hospitalar Universitário de São João, EPE 4. Centro Hospitalar Universitario Lisboa Central-Hospital Santa Marta 5. Centro Hospitalar Universitário Lisboa Norte (CHULN) 6. COEFVAC - Coimbra Effectiveness of Vaccine 7. Faculty of Medicine, University of Porto 8. Lisbon, Setubal and Santarem Pharmacovigilance Centre 9. Portuguese Institute of Oncology of Coimbra 10. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) 11. Unidade Local de Saude do Litoral Alentejano	1. ARS Norte 2. Centro Hospitalar Universitario Lisboa Central-Hospital Santa Marta 3. Centro Hospitalar Universitário Lisboa Norte (CHULN) 4. IASAUDE, IP-RAM 5. Matosinhos Local Health Unit 6. Portuguese Institute of Oncology of Coimbra 7. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS)	1. ARS Norte 2. Centro Hospitalar de Lisboa Ocidental 3. Centro Hospitalar Tondela-Viseu 4. Centro Hospitalar Universitário Lisboa Norte (CHULN) 5. COEFVAC - Coimbra Effectiveness of Vaccine 6. IASAUDE, IP-RAM 7. Lisbon, Setubal and Santarem Pharmacovigilance Centre 8. Pharmacovigilance Unit of Beira Interior 9. Portuguese Institute of Oncology of Lisbon 10. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) 11. Unidade Local de Saude do Litoral Alentejano	1. Centro Hospitalar de Trás-os-Montes e Alto Douro – CHTMAD 2. Centro Hospitalar Universitario Lisboa Central-Hospital Santa Marta 3. Centro Hospitalar Universitário Lisboa Norte (CHULN) 4. COEFVAC - Coimbra Effectiveness of Vaccine 5. Lisbon, Setubal and Santarem Pharmacovigilance Centre 6. Matosinhos Local Health Unit 7. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) 8. Unidade Local de Saude do Litoral Alentejano	1. Centro Hospitalar Universitário de São João, EPE 2. Centro Hospitalar Universitario Lisboa Central-Hospital Santa Marta 3. Centro Hospitalar Universitário Lisboa Norte (CHULN) 4. Matosinhos Local Health Unit 5. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS)
Romania (+40)	1. University of Medicine and Pharmacy Iuliu Hatieganu		1. University of Medicine and Pharmacy Iuliu Hatieganu		
Slovakia (+421)	1. Pavol Jozef Šafárik University in Košice			1. Pavol Jozef Šafárik University in Košice	
Spain (+34)[8]	1. FISABIO	1. Andalusian Public Health System 2. FISABIO 3. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)	1. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)	1. Andalusian Public Health System 2. Epiconcept 3. FISABIO	1. Andalusian Public Health System 2. FISABIO 3. Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)
Spain (+34)[8]		4. Spanish Agency of Medicines and Medical Devices-AEMPS			4. Spanish Agency of Medicines and Medical Devices-AEMPS

Sweden (+46)[9]		1. Quantify Research			1. Quantify Research
UK (+44)[10]	1. IQVIA	1. IQVIA	1. IQVIA	1. IQVIA	1. IQVIA

Organizations that responded to the follow-up questionnaire about specific capacity of an organization to participate in COVID-19 vaccine monitoring studies.

[1]Belgium:
- Federal Agency of Medicines and Health Products (FAMHP): 'We currently explore the possibility of retrospective analysis of background rates of AESI.'

[2]Czech Republic:
- *Fakultni nemocnice* Plzen* answered that they are already engaged in the planning of studies (effectiveness and safety) but didn't choose a protocol.
- *FN Brno**: Didn't choose a protocol.
- *Thomayerova nemocnice** answered: 'Our unit is ready to provide Vaccine Clinical trials of all chosen kind. Depends on the Sponsor needs. As a sponsor study - it depends on approval of sponsor if they agree to share the data.' Already engaged in planning of effectiveness and safety studies. Didn't choose a protocol.
- Motol University Hospital: two different departments responded for the same protocols (Immunology + Infectious Disease).

[3]Finland:
- Vaccine Research Center answered: 'We do not have access to registries, but we are capable of doing other kind of vaccine related studies.'

[4]Latvia:
- *The State Agency of Medicines of Latvia**: 'Only assessment of case reports in national ADR database'. Didn't choose a protocol.

[5]Netherlands:
- RIVM: 'When participating in safety this will be in close collaboration with Lareb'.

[6]Norway:
- University of Oslo responded twice (Dpt of Pharmacy, Pharmacoepidemiology and Drug Safety Research Group + Dpt of Pharmacy) with different contacts and protocols.

[7]Portugal:
- Centro Hospitalar Universitário de São João, EPE: We are willing to participate in collaborative studies, but we don't have the structure to design and coordinate the studies. We have a strong track record of participation in clinical trials and observational studies on drugs (not specifically vaccines)."
- Faculty of Medicine, University of Porto: We are able to actively collect data on adverse events associated to the vaccination. Also, to provide background rates of adverse events of special interest base on pharmacovigilance databases.
- Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS): We are conducting a large scale study to monitor long term cognitive functioning of SARS-CoV-2 infection survivors, using Brain on Track (web-based self-administered test) funded by Gulbenkian Foundation and participate in a National and European register to monitor neurologic complications of COVID-19 patients.

[8]Spain:
- FISABIO answered twice, different protocols.
- Research Triangle Institute: We can leverage expertise and experience in benefit risk evaluations and health preference assessments in therapeutic areas. We do not have exclusive access to data collection tools/data sources. We are interested and able to participate in vaccine studies in other capacity including, leading and coordinating, writing study materials, analyzing data, and related (did not choose protocol). Our concerns are more around the level of "under"-funding of the typical EMA tender studies.

[9]Sweden:
- Karolinska Institute: IF a Covid-19 immunization registers is established in Sweden we can do safety/effectiveness studies linked to national health registers.

[10]UK:
- Public Health England: We are happy to share details of what we are doing and expected outputs to harmonize where possible. We would rather do this than share data unless a clear benefit from doing so can justify the time taken to collaborate given the resources (people) we have who will need to be very focused on producing the analyses we require as fast as possible. This represents the view of the responder and others working closely with them. As for VE we work with IMove on this and would expect to do similar for COVID VE. Did not choose protocol.
- IQVIA: other protocols - CARE registry; IT solutions for engaging vaccine recipients to report outcomes.

5.4.2 Results second round

The follow-up questionnaires were completed by 22 organizations in total (highlighted in table 1), located in 12 different European countries (Figure 4).

Figure 4: Location of organizations that completed the follow-up survey

COVID-19 vaccination strategies in Europe

Each questionnaire started with questions about the COVID-19 vaccination strategy in the country where the organization is located and about how the receipt of COVID-19 vaccinations will be registered. The COVID-19 vaccination strategy and recording in each country are summarized in table 7. It shows that several countries do not yet know, and that multiple sources will be used to register vaccines.

Table 7. COVID-19 vaccination strategy and recording in each country

	Name of the national/regional organization deciding on the COVID-19 vaccine policy	Trusted source for vaccination strategy	COVID-19 vaccination strategy	COVID-19 vaccination registration
Czech Republic (+420)	Ministry of Health in Czech Republic and State Institute of Drug Control	https://www.mzcr.cz/Verejne/obsah/ockovani_4011_5.html	Vaccination plan is to start vaccination with the health professionals and subjects older than 65. GPs will be providing the vaccine to subjects older than 65 and health care workers will be vaccinated by physicians working at hospitals or at outpatient departments.	Primary care records Patient vaccination cards Hospital-based medical records Institute of Health Information and Statistics of the Czech Republic
Denmark (+45)	The Danish National Board of Health	https://www.sst.dk/en/English https://www.sst.dk/-/media/Udgivelser/2020/Corona/Vaccination/Planlaegningsgrundlag-vaccination-COVID-19.ashx?la=da&hash=CA4DE3C330821A104F1383ACDEF47690D962D28B	Likely risk groups (elderly, comorbid, health care workers) will be vaccinated first. Vaccination will most likely take place by centralized mass vaccinations at testing sites. Possibly GPS in de future.	Immunization registry Primary care records Patient vaccination cards Hospital-based medical records
Finland (+358)	National Institute of Health and Welfare of Finland	https://valtioneuvosto.fi/en/-/10616/government-adopts-resolution-on-finland-s-covid-19-vaccine-strategy	In the initial phase, the vaccine will be offered to healthcare and social welfare workers caring for COVID-19 patients and to care home workers, elderly persons and persons at high risk for severe disease due to underlying health conditions. The practical arrangements for vaccination will be coordinated by hospital districts. Municipalities are responsible for organizing vaccination in their areas.	Immunization registry Primary care records National patient archive
France (+33)	Haute Autorité de la Santé	https://www.has-sante.fr/upload/docs/application/pdf/2020-07/note_de_cadrage_strategie_vaccinale_c	To be vaccinated first: 1) health care professionals and persons involved in patient cares 2) patient at risk of severe form.	Immunization registry Primary care records

		ontre_la_covid_19.pdf	Then comes according to the scenario people close to high risk patients, people most likely to be contaminated, professionals providing maintenance of essential activities. The organization of vaccination should be carried out as close as possible to the people concerned. This includes GP, nurses and pharmacists. Actors in occupational medicine, hospitals, and the medico-social world in establishments are also concerned. - "Outpatient" vaccination in doctors' offices, health services and access to vaccines in hospitals for people at risk are also expected.	Hospital-based medical records
Ireland (+353)	National Immunization Advisory Committee (NIAC)	https://www.rcpi.ie/policy-and-advocacy/national-immunisation-advisory-committee/	NIAC has drafted priority groups. National level consideration of optimal approach underway with likely commencement of program in January. Like the UK, it is unlikely that the vaccine will be administered during pregnancy in the initial phases, until more data become available.	Primary care records Hospital-based medical records
Italy (+39)	The national special commission for COVID	http://www.governo.it/it/cscovid19	''In this moment the national and regional strategies are under definition and we are not yet aware of any details.''	Do not know
Netherlands (+31)	RIVM (tasked by the Ministry of Public Health, Welfare and Sports)	https://www.rivm.nl/coronavirus-covid-19/vaccins	Older people, vulnerable people and care workers will be vaccinated first. Vaccinations will take place at 30 vaccination locations throughout the Netherlands. Vaccines will be provided to patients by GPs, institutional physicians, occupational health service and the public health service.	Immunization registry
Norway (+47)	Directorate of Health – based on recommendation from The Norwegian Institute of Public Health (NIPH)	https://www.fhi.no/sv/vaksine/koronavaksinasjonsprogrammet/nasjonal-plan-for-vaksinasjon-mot-covid-19/ (in Norwegian only)	Under development	Immunization registry
Portugal (+351)	Direcção Geral de Saúde	https://covid19.min-saude.pt/#	Overlapping the influenza vaccination strategy	Immunization registry

				Patient vaccination cards
Romania (+40)	National Committee for Coordination of Activities Related to COVID-19 vaccination, under the Govern General Secretary and the Prime Minister	https://vaccinare-covid.gov.ro/	First stage: health care workers at risk (carried out by health units/vaccination centers/mobile vaccination teams) Second stage: older adults in high-risk living situations, groups with comorbidities, personnel working in vital economic functions (carried out by health units/vaccination centers/mobile vaccination teams/GPs)	Immunization registry Primary care records Patient vaccination cards Hospital-based medical records
Slovakia (+421)	Pandemic committee (Ministry of Health and prime minister)	https://www.health.gov.sk/Titulka	Not published yet. Probably vaccination will take place at vaccination centers. First stage: 65+, health care workers, most important employees in the state service (police, fire workers etc). Second stage: general population. Children last.	Not decided yet. Probably: Immunization registry Patient vaccination cards
Spain (+34)	Grupo de Trabajo de vacunación COVID-19 en Andalucía	https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/vacunasCovid19.htm	Andalusian Public Health System-nurses will be providing the vaccines to patients.	In DIRAYA

Capacity of organizations

The collected data from the completed questionnaires will be presented for each type of data collection separately.

App-based data collection

In cohort event monitoring of COVID-19 vaccine safety, vaccine recipients will provide e-consent and be surveyed with a web-based app or other tool available in the participating country.

Four organizations, located in Romania, the Czech Republic and Portugal completed the questionnaire about specific capacity to participate in cohort event monitoring (Table 8).

Table 8. Completed questionnaires for app-based data collection

	1. University of Medicine and Pharmacy Iuliu Hatieganu (+40)RO	2. St. Anne's University Hospital Brno (+420) Czech Republic	3. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) (+351) (PO)	4. Unidade Local de Saúde do Litoral Alentejano (+351) (PO)

If you were to participate, how would you invite COVID-19 vaccine recipients to participate in the study (e.g. health care workers, older adults living in nursing homes)?	Health care workers: Within the hospital it could be done through an email from the hospital management inviting all to complete an online questionnaire. At national level we could also contact (email/ social media) medical societies and National Physicians/ Pharmacist Organization (Colegiul National al Medicilor/ Farmacistilor), National Institute of Public Health. Other patients: through patients' organizations, collecting data through an app or web survey. Will also have to check if we could contact patients from the national registry.	Using advertisement and other tools	Health care workers: through occupational medicine services and approach via e-mail upon vaccination scheduling. Older adults living in nursing homes: this group has low informatics literacy, so we would reach their closest relative. Other: other citizens are reachable trough an App called "Portal do utente ULS Matosinhos".	Do not know yet
Has your organization conducted cohort event monitoring before? Any lessons learned?	Yes[1]	No	Yes[2]	Do not know
Have you used app-based monitoring before?	No	No	Yes	No
If you have used app-based monitoring before, do you have your own app?	Not applicable	Not applicable	No	Not applicable
If you do not have your own app, are you willing to use the web-app of another public organization in Europe (and translate the questionnaire into your own language)?	Yes	Yes	Yes	Yes
In your country, will patients receive a certificate or proof of vaccination, including the type of COVID-19 vaccination?	Yes, a patient vaccination card with personal data of the vaccinated person, stage of vaccination, type of vaccine, batch and series, date of vaccination, date of booster (if applicable).	Do not know	Yes, vaccination is recorded in electronic health record	Do not know
Is there a data source you can access that will contain information on receipt of COVID-19 vaccines?	Yes	Do not know	Yes	Yes
Are you capable to code unexpected AEFIs (Adverse Events Following Immunization) upon data-entry into MedDRA codes?	No, but we are willing to be trained for this	No, but we are willing to be trained for this	Yes, there is an app called SIRAI to record adverse events as well as medication failures	No, but we are willing to be trained for this
Please describe any necessary ethics and/or institutional approvals that your organization would need to obtain to participate in this study, including timelines:	Ethics Committee approval, takes 30 days from application to response	State Institute for Drug Control – ad hoc (individual timelines), Ethics Committee ad hoc (individual timelines)	Local ethics commission and Data Protection Officer	Hospital ethics committee
If the opportunity arises to implement this study for vaccine manufacturers, would your organization be willing to participate?	Yes	Yes	Yes	Yes

Would you like to share any other thoughts or comments on the capability of your organization to participate in this study?	No	No	No	No

[1]Yes. We found a low response rate if the patients are not reminded/ contacted periodically. In the study monitoring the childhood vaccines, parents were willing to participate and collaborative when reminded about the timeline for questionnaire completion. In the study with the healthcare professionals and the H1N1 vaccine we found that having the questionnaires printed on paper helped, but back then smart phones were not that popular. An important lesson was also that patient needs to feel involved and to understand the meaning of the research. Recruitment is more successful if the request is endorsed by an au (e.g unit management for the healthcare workers). Also, people tend not to complete a survey if it's too long or the data filled in at the end of the survey may not be that reliable due to lack of patience and time.

[2]Yes. We are surveying cognitive performance in SARS-COV-2 survivors using an App called Brain on Track. We also have experience with another app for defining individual personal care in a cohort of ambulatory complex chronic patients.

Hospital-based data collection

Hospital-based safety studies would use a case-only approach (e.g., a case-cross-over or self-controlled risk interval design) and would require access to electronic data on discharge diagnoses (using ICD-9/10) and the ability to confirm case status through medical records or other means in your hospitals. Hospital-based COVID-19 vaccine effectiveness studies would use a test-negative case-controlled design and would require the ability to identify patients that are tested for COVID-19 by RT-PCR.

Data on vaccinations should be obtained from patient vaccination cards or though linkage to other secondary data sources. Twelve organizations, located in Romania, the Czech Republic, Portugal, Denmark, Italy, Slovakia and Spain completed the questionnaire about specific capacity to participate in hospital-based studies (Table 4).

Table 9. Completed questionnaires for hospital-based data collection

	1. University of Medicine and Pharmacy Iuliu Hatieganu (+40)	2. St. Anne's University Hospital Brno (+420)	3. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) (+351)	4. Unidade Local de Saúde do Litoral Alentejano (+351)	5. Centro Hospitalar Universitario Lisboa Central – Hospital Santa Marta (+351)	6. Aarhus University (+45)	7. Lazio Regional Health Service (+39)	8. Pharmnet s.r.o. (+420)	9. Pavol Jozef Safarik University (+421)	10.Centro Hospitalar de Lisboa Ocidental (+351)	11. Andalusian Public Health System (+34)	12. Centro Hospitalar de Tràs-os-Montes e Alto Douro – CHTMAD (+351)
Does your organization have a hospital discharge database that captures diagnoses and procedures?	No[2]	Yes	Yes	Yes	Do not know	Yes	Yes	No, we are a CRO	No[15]	Yes	Yes	Yes
Number of bed available in your hospital:	1542	886	400	100	1000	All hospitals in Denmark	Do not know	Not applicable	Depends on which hospital will be available for studies	789	13.955 (Public Health System-region level)	564
Number of admissions in your hospital annually:	Do not know	21.000	10.000	Do not know	30.000	All hospitals in Denmark	About 900.000 in all regional hospitals per year	Not applicable	Depends on which hospital will be available for studies	162.934	3.659.893 (Public Health System-region level)	24.500
How are hospital admissions coded?	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10	ICD-9	ICD-10	ICD-10	ICD-10	ICD-9	ICD-10

Do you also capture codes for outpatient hospital visits?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Who is assigning the discharge codes?	Specialist	Physician	Dedicated others	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist	Specialist	Documentalist	Coding department
How can you access the discharge diagnosis codes?	By signing a collaboration agreement with the hospital that allows us to request the data. Discharge diagnosis codes are included	In hospital database	Through the Chief informatics Officer, ethics commission and administration	In hospital database	Department of codification	Danish National Patient Register data access through Danish Health Data Authority https://pubmed.ncbi.nlm.nih.gov/26604824/	We have access to administrative hospital records, which contain discharge diagnoses	We can sign contracts with hospitals and/or outpatient departments	Monitoring of the discharge records and the hospital database	Using a predefined ICD-10 application	DIRAYA, the regional EHR and ePrescribing system of Andalucía	Information is in database
Are the calendar dates of each hospitalization or hospital visit available?	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization are available	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization are available	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization are available	Yes, when we sign the contracts with hospitals and or ambulatory specialists, we will have calendar dates or hospital visits available.	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization are available	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available	Yes, the admission and discharge date of a hospitalization and the diagnosis date of an ambulatory specialist visit are available
Approximately how long would it take to identify specific events?	Within a week	Within a week	Within a day	Within a week	Within a week	Within a month	Within a month	Within a week	Within a day	Within a day	Within a day	Within a week

What method can you use to assess outcome certainty and onset?	Medical record review	Medical record review Laboratory and other examination	Medical record review	Medical record review Case notes	Medical record review	Medical record review	Medical record review	Medical record review	Medical record review Physician questionnaire	Medical record review	Left blank	Medical record review Physician questionnaire
Is your organization assessing COVID-19 by RT-PCR?	Yes	Yes	Yes	Yes	Yes	No, but data is accessible	Yes	No	Yes	Yes	Yes	Yes
How would you identify subjects that have undergone COVID-19 testing in your hospital?	If testing positive at hospital admission, it would be coded as an admission diagnosis	In hospital database	We ask for the database. We are already monitoring symptomatic and asymptomatic survivors	Consulting hospital database	Medical records	Can be done centrally via registration by the Danish National Board of Health / Statistics Denmark	Regional COVID-19 registry plus discharge diagnosis	Not applicable	We have access to regional public registries were this is recorded	Left blank	Left blank	We have a database of all tests performed
Could the lab involved that conducts the COVID-19 RT-PCR also carry out additional respiratory viruses testing (e.g. influenza, RSV…)?	Do not know	Yes	Yes	Yes	Yes	Yes	Do not know	Do not know	Yes	Yes	Yes	Yes
We need objective and detailed information on COVID-19 vaccination. Would your organization be willing to contact patients to collect written consent to participate in these vaccine safety and effectiveness studies (we would suggest that a hospital collaborator would call the patient or send a letter)?	Yes	Yes	Yes	Yes	Yes	Yes	No, we collect data on regional level, not at hospital level	No, we are a CRO, we cannot contact patients personally	Yes	Yes	Yes	Yes

Will your organization be able to collect information about the following conditions in a patient prior to hospitalization (indicate for hospital health record and GP or patient)?[1]	Yes[3]	Yes[5]	Yes[6]	Yes[8]	Yes[10]	Yes[11]	Yes[12]	Yes[13]	Yes[16]	Yes[18]	Yes[19]	Yes[20]
Would informed consent be needed for you to extract and use data from your hospital (medical records and hospital discharge database) in this study?	Yes	Yes	No	Yes	Yes	No	No	Yes	Do not know	Yes	Do not know	Yes
Would informed consent be needed to request information on the patient from other data sources/health care providers?	Not possible	Do not know	Do not know	No	Do not know	No	No	Yes, the subject needs to be informed about providing their data for studies	Yes, will be discussed with regional or central ethics committee	Yes	Do not know	No
Please describe any necessary ethics and/or institutional approvals that your organization would need to obtain to participate in this study, including timelines:	University Ethics Committee approval would be needed. This can be obtained within 30 calendar days from application submission.	State Institute for Drug Control, Ethics Committee	Institutional review board Board of administrators	Hospital ethics committee	Institutional review board	Regional Patient Safety Board for waiver of informed consent for medical chart review	For observational studies we do not need to obtain consensus for the ethics committee, but have to notify the study and send the protocol to	RA and MEC +LECs approvals. Timelines are after submissions for RA and ECs - 60 days	Local and central ethics committee (30 days)	Institutional review board	Institutional review board	Ethical Committee and Board of Administration

							the ethics committee					
Has your organization participated in other vaccine safety or effectiveness studies? Please provide PMIDs of published studies (up to 5).	http://www.revistafarmacia.ro/201206/issue62012art04.html http://www.revistafarmacia.ro/201906/issue62019art12.html http://www.revistafarmacia.ro/202002/issue22020art5.html	No	No	No	Do not know	PMID 1: 32624249 PMID 2: 31899791 PMID 3: 31187170 PMID 4: 30803841	No	Left blank	No	No	To be provided afterwards	No
	1. University of Medicine and Pharmacy Iuliu Hatieganu (+40)	**2. St. Anne's University Hospital Brno (+420)**	**3. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) (+351)**	**4. Unidade Local de Saúde do Litoral Alentejano (+351)**	**5. Centro Hospitalar Universitario Lisboa Central – Hospital Santa Marta (+351)**	**6. Aarhus University (+45)**	**7. Lazio Regional Health Service (+39)**	**8. Pharmnet s.r.o. (+420)**	**9. Pavol Jozef Safarik University (+421)**	**10.Centro Hospitalar de Lisboa Ocidental (+351)**	**11. Andalusian Public Health System (+34)**	**12. Centro Hospitalar de Tràs-os-Montes e Alto Douro – CHTMAD (+351)**
Given that we would be interested in different events that are treated by different specialties, would you be willing to act as a coordinator to engage with these specialists in your organization and be the principal investigator?	Yes	Yes	Yes	Yes	Do not know	Yes	No	No	Yes	Yes	Yes	Yes

Would you be willing to collect study data in a certified online electronic case record form (e.g. CASTOR, REDCAP)?	Yes	Yes	Yes	Do not know	Do not know	Yes	No	Do not know	Yes	Yes	Do not know	Yes
Would you be able to share pseudonymized data with the central coordinating center, compliant with GDPR (General Data Protection Regulation)?	Do not know. We would need to check this with the hospital. Probably yes but also depending on what data are needed, format.	Yes	Yes	Do not know	Yes	Most likely only in the EU; will need to be determined at the time of the study. Sharing of aggregated data is no problem	Do not know, we can contribute our administrative data to a CDM	Do not know[21]	Yes	Yes	Do not know, we have to check data share issue with the Andalusian Health Service DPO	Yes
Would you like to share any other thoughts or comments on the capability of your organization to participate in this study?	Yes[4]	No	Yes[7]	Yes[9]	No	No	No	Yes[14]	Yes[17]	No	No	No

[1]Influenza-like illness, upper respiratory infections, lower respiratory infections, gastrointestinal infections, race and/or ethnicity, geographic residence of patients, chronic conditions (e.g. diabetes, asthma, cancer), medication use, receipt of other vaccines (e.g. influenza vaccine, childhood vaccines)

[2]Our research center is university based, but we can sign an agreement of collaboration with the county hospital which allows access to their administrative database which was used in previous research. The database captures diagnoses at hospitalization and at discharge, as well as procedures.

[3]Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (GP or patient)

[4]There are some limitations of the available data. We cannot link the hospital data with data at GPs. We cannot link the hospital data to the vaccination status which will be kept in an Electronic National Vaccination Registry (RENV). The hospital database is regional, we can access only the data of patients admitted or monitored in the hospital. This does not exclude the possibility that patients would be treated in other hospitals from Cluj or other surrounding cities. Usually, patients attend this regional hospital when their health issue is more serious, and they may address other hospitals in the region if the health issues are mild.

[5]Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record and GP or patient)

[6] Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (GP or patient)

[7]One of the major institutional strengths is participation in clinical trials. We have a solid infectious diseases department and the hospital is articulated with primary care facilities in the population area of interest.

[8] Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record and GP or patient)
[9]We are a small hospital, we have little personnel, so it will be hard to have a great number of participants.
[10] Influenza-like illness (GP or patient), upper respiratory infections (GP or patient), lower respiratory infections (GP or patient), gastrointestinal infections (GP or patient), race and/or ethnicity (GP or patient), geographic residence of patients (GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (GP or patient), medication use (GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (GP or patient)
[11] Influenza-like illness (hospital health record), upper respiratory infections (hospital health record), lower respiratory infections (hospital health record), gastrointestinal infections (hospital health record), race and/or ethnicity (hospital health record), geographic residence of patients (hospital health record), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record), medication use (hospital health record), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record)
[12] Influenza-like illness (hospital health record), upper respiratory infections (hospital health record), lower respiratory infections (hospital health record), gastrointestinal infections (hospital health record), geographic residence of patients (hospital health record), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record)
[13] Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record and GP or patient)
[14]Pharmnet s.r.o. as CRO participated on many vaccine studies for companies GSK, Pfizer, Sanofi and others in Czech Republic.
[15]Yes. It will be recorded electronically, but this is not a valid electronic system. So what we do when performing studies; first we go into the electronic database and then we compare it to paper medical records. Because each hospital is using different systems, we are not able to just double click and retrieve all the data from all electronic systems. Has to be done on a hospital basis.
[16]Influenza-like illness (hospital health record), upper respiratory infections (hospital health record), lower respiratory infections (hospital health record), gastrointestinal infections (hospital health record), race and/or ethnicity (hospital health record), geographic residence of patients (hospital health record), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record), medication use (hospital health record), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record)
[17]We are part of Ecrin, so we are a network of local clinical trial units (usual hospital). For each type of trial, we set up the suitable hospitals. We can serve as a coordinator, we can serve as a partner for feasibility, contact with a sponsor or organizing institutions, but we are not a hospital itself. But we are based at the university which has its own certified laboratory for COVID-19 testing by PCR. www.ecrin.org
[18] Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record and GP or patient)
[19] Influenza-like illness (hospital health record), upper respiratory infections (hospital health record), lower respiratory infections (hospital health record), gastrointestinal infections (hospital health record), race and/or ethnicity (hospital health record), geographic residence of patients (hospital health record), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record), medication use (hospital health record), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record)
[20] Influenza-like illness (hospital health record and GP or patient), upper respiratory infections (hospital health record and GP or patient), lower respiratory infections (hospital health record and GP or patient), gastrointestinal infections (hospital health record and GP or patient), race and/or ethnicity (hospital health record and GP or patient), geographic residence of patients (hospital health record and GP or patient), chronic conditions (e.g. diabetes, asthma, cancer) (hospital health record and GP or patient), medication use (hospital health record and GP or patient), receipt of other vaccines (e.g. influenza vaccine, childhood vaccines) (hospital health record and GP or patient)
[21] Do not know, as a CRO we can share pseudonymized data after subjects signed ICF, RA/EC approvals and contracts signed with institution, hospital or department

Electronic health record (EHR)-based data collection

Electronic health record (EHR)-based studies, which would use a cohort-based approach, would require access to electronic health data from a variety of sources (hospitalization, outpatient diagnoses, medicines, vaccines and individual level population data) which can be linked to create the necessary analytic dataset. Fifteen organizations, located in Portugal, Denmark, Italy, Spain, Finland, France, Ireland, the Netherlands and Norway completed the questionnaire about specific capacity to participate in EHR-based studies (Table 5).

Table 10. Completed questionnaires for electronic health record (EHR)-based data collection

	3. Unidade Local de Saúde de Matosinhos (Hospital Pedro Hispano e ACeS) (+351)	5. Centro Hospitalar Universitario Lisboa Central – Hospital Santa Marta (+351)	6. Aarhus University (+45)	7. Lazio Regional Health Service (+39)	11. Andalusian Public Health System (+34)	13. Finnish Institute for Health and Welfare (THL) (+358)	14. Rotunda Hospital (+353)	15. PRA Health Sciences (+33)	16. PELyon (+33)	17. Université de Bordeaux (+33)	18. RIVM (+31)	19. Agenzia Regionale di Sanità della Toscana (+39)	20. Spanish Agency of Medicines and Medical Devices – AEMPS (+34)	21. Societa Servizi Telematici – Pedianet (+39)	22.Oslo University (+47)
What is the name of the data source you can access?	SONHO and SClinico	SClinico	All data sources hosted by the Danish Health Data Authority or Statistics Denmark	Regional administrative health care data	DIRAYA-electronic health record (EHR) and ePrescribing system of the Andalucía n public health System	Multiple national health registries	Maternal & Newborn Clinical Management System	Prism eSource	SNDS (National French claims data)	SNDS	Left blank	ARS	BIFAP Base de datos para la Investigación Farmaco-epidemiológica en Atención Primaria	Pedianet and Family pediatrician database (about 4000 primary care pediatricians)	SYSVAC, MSIS, NorPD, Death Registry, NPR, KUHR, Statistics Norway (among others)
How would you classify the type of data sources you have access to	Surveillance data, claims data, electronic medical	Electronic medical records	Claims data, electronic medical records, registries,	Claims data, registries	Electronic medical records Registries	Surveillance data, claims data, registries, primary	Electronic medical records	Electronic medical records	Claims data	Claims data, electronic medical records, registries	Surveillance data, registries	Surveillance data, claims data, registries	Electronic medical records, registries	Surveillance data, electronic medical records, prospecti	Surveillance data, claims data, electronic medical

(indicate all that apply)?	records and registries		disease and hospitalization registries			care visits register								ve HCWs (pediatricians) cohort	records, registries, social data
What is the approximate number of unique individuals contributing to the data source in 2019?	300.000	1.500	5.8 million	6 million	8.5 million	5.5 million	27.000	None	60 million	67 million	Left blank	3.5 million	15 million	4000 primary care pediatricians	5.4 million
When does a person enter in the data source (what determines the population?	At birth (majority)	Registration with a medical practice	Registration in a country	Registration with a medical practice	Registration in a country	National health insurance for all permanent citizens	On booking for antenatal care in the maternity unit	Registration with a medical practice	Registration in a country	From birth to death, even when a subject changes occupation or retires	Registration in a country	Registration with the regional health care service to be assigned a primary care physician	Registration with a medical practice	Part of our cohort	Registration in a country
What is the geographic area covered in the catchment area of the database?	Regional	National	National	Regional	Regional	National	Regional	European	National	National	National	Regional	Multiregional	National	National
How often is the database updated and made	Continuously	Continuously	Varies per type of data set	Varies per type of data set	Continuously	Continuously	Infrastructure not yet established	Continuously	Varies per type of data set[24]	Varies per type of data set[27]	Continuously	Varies per type of data set[33]	Every six months and for a subset of regions	Continuously	Varies per type of data set[43]

available for research?													every two months		
Is the data source held in your organization or do you need to receive permission from other organizations to access the data?	Some are within my organization and others are outside of my organization, but can be accessed and linked	Some are within my organization and others are outside of my organization, but can be accessed and linked	All data reside outside of my organization, but can be accessed	Some are within my organization and others are outside of my organization, but can be accessed and linked	All within organization	Some are within my organization and others are outside of my organization, but can be accessed and linked	Information on governance and ethical approval would be required. External linkage to other sources e.g. immunization registry, has not been done yet	All data reside outside of my organization, but can be accessed	Regulatory approvals are needed	All data reside outside of my organization, but can be accessed	Some are within my organization and others are outside of my organization, but can be accessed and linked	We receive a copy of the data automatically, with specified transmission protocols [34]	All within organization	All within organization	All data reside outside of my organization, but can be accessed
Will the data source you can access contain information on receipt of COVID-19 vaccines?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Do not know	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Will the following data elements regarding COVID-19 vaccine administration be available in your data source?[1]	Yes[4]	Yes[7]	Yes[9]	Exact date of vaccination, probably brand and dose, hopefully batch	Yes[13]	Yes[16]	Dependent on linkage and degree of coverage of national immunization dataset	Yes[22]	COVID-19 vaccine brands, vaccine dose, vaccinator type/ Identity	Exact date of vaccination, COVID-19 vaccine brands	Yes[32]	Yes[35]	Yes[38]	Yes[40]	Exact date of vaccination, COVID-19 vaccine brands, vaccine dose

If exact date of vaccine receipt is not available, are imputed or partial dates available?	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Do not know	Do not know	Yes	Do not know	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Please indicate if the following information can be retrieved in your data source (check all that apply):[2]	Yes[5]	Yes[8]	Yes[10]	Yes[12]	Yes[14]	Yes[17]	Yes[19]	Yes[23]	Yes[25]	Yes[28]	Dates of hospitalizations, date of death, dates and results of laboratory test, COVID-19 testing	Yes[36]	Yes[39]	Yes[41]	Yes[44]
What type of coding system is utilized for diagnosis coding in the data sources you can access (check all that apply)?	ICD-9 CM ICD-10 CM Primary care codification system	ICD-10 CM	ICD-10 DK SNOMED only for pathology data (Denmark does not use ICD-10CM)	ICD-9 CM	ICD-9 CM ICD-10 CM SNOMED	ICD-10 CM ICPC	SNOMED	ICD-10 CM	ICD-10 CM	ICD-10 CM	Notifications by law registration	ICD-9 CM ICD-10 CM SNOMED	ICD-9 CM ICD-10 CM ICPC SNOMED	ICD-9 CM	ICD-10 CM ICPC
Please indicate if the following information about patient characteristics is available in your data source:[3]	Yes[6]	Race and/or ethnicity, geographic residence of patients	Yes[11]	Receipt of other vaccines, geographic residence of patients, socio-economic	Yes[15]	Yes[18]	Geographic residence of patients, socio-economic information, body mass	Body mass index, smoking status	Receipt of other vaccines, geographic residence of patients	Yes[29]	Receipt of other vaccines, geographic residence of patients, health care	Yes[37]	Receipt of other vaccines, body mass index, smoking status	Yes[42]	Yes[45]

				information			index, smoking status				worker status				
Please describe any necessary ethics and/or institutional approvals that your organization would need to obtain to participate in this study, including timelines:	Local ethics commission and data protection officer	Ethic and institutional approvals	Mandatory registration with Danish Data Protection Agency; data access through government servers/data custodians (timeline: months)	For studies based on administrative healthcare data, we do not need to obtain approval from ethics committee, but we have to notify them about the study and send the protocol to the ethics committee	Andalusian Health Service DPO and the Ethical Committee	Findata register authority approval, 3 months	National level information governance and ethical approvals [20]	EC and SNDS approvals. Timelines difficult to assess as they include negotiations with hospitals to install EDC (PrismeSource)	Agreement from Health Data Hub: 1 month after the submission of a protocol. Agreement from CNIL (data privacy body): 2 months after Health Data Hub approval	CESREES, CNIL[30]	GDPR	We need to assess whether this study is included in the provision fo our regional law. We are confident it is, and assessment should be available in few weeks	BIFAP Scientific Committee approval and Ethics Committee approval	Not needed	Regional ethics board, data protection officer approval, approvals from all registry holders[46]
Would you be able to extract the study specific data and	Yes	Do not know	Yes	Yes	Yes	Do not know	No	Yes	No	Yes	Yes	Yes	Yes	Do not know	Yes

transform this locally into a pre-defined data model (CSV files)?															
Do you have experience in conducting multi-database studies using a common data model and common analytics?	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Would you be able to run a R-script to analyze the data and share aggregated results on a central secure platform in Europe?	Yes	Do not know	Yes	Yes	No	Yes	No	Do not know	Do not know	Yes	Yes	Yes	Yes	Yes	Yes
Would you like to share any other thoughts or comments on the capability of your organization to participate in this study?	The center (Unidade Local de Saúde de Matosinhos) already participates in pan European EHR	No	No	No	No	THL will conduct extensive safety follow-up. Collaboration with others is needed to validate	Yes[21]	We have the technology to enable automated data collection through all types of EHR	Yes[26]	Yes[31]	A lot of the work is in progress	We need each study to be compliant with the ENCePP Code of Conduct	BIFAP will not be available for companies sponsored studies	No	NIPH can probably obtain data faster than UOSL. Maybe they should have the first

	projects such as EHDEN and EUCLIDES					and compare the results.									option as DAPs for Norway in COVID-19 vaccination studies.

[1]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity

[2]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage, COVID-19 testing

[3]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), race and/or ethnicity, geographic residence of patients, socioeconomic information, health care worker status, skilled nursing facility; nursing home; or extended care facility stays, body mass index, smoking status

[4]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity

[5]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage, COVID-19 testing

[6]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), race and/or ethnicity, geographic residence of patients, socioeconomic information, health care worker status, skilled nursing facility; nursing home; or extended care facility stays, body mass index, smoking status

[7]Exact date of vaccination, COVID-19 vaccine brands

[8]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine prescriptions (outpatient care), COVID-19 testing

[9]Exact date of vaccination, COVID-19 vaccine brands, vaccine dose, vaccinator type/identity

[10]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, pregnancy start and end dates, mother-child linkage, COVID-19 testing

[11]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), race and/or ethnicity, geographic residence of patients, socioeconomic information, health care worker status

[12]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and type of procedures (outpatient care), medicine dispensing, mother-child linkage, COVID-19 testing

[13]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity

[14]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, COVID-19 testing

[15]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), geographic residence of patients, skilled nursing facility; nursing home; or extended care facility stays, body mass index, smoking status

[16]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity

[17]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and diagnosis of primary care visit, medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage

[18]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), geographic residence of patients, socioeconomic information, health care worker status, country of birth

[19]Dates of hospitalizations, discharge diagnosis from hospitalizations, dates and diagnosis of outpatient specialist visit, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage

[20]This dataset is relatively new- it relates to an EHR that has been implemented on a phased basis since 2016 which now covers 40% of Irish births. National level information governance and ethical approvals would be required and resourcing would be necessary to establish the processes for extracting data.

[21] We are keen to collaborate, but as this is a new dataset, there would be considerable work involved in establishing our processes. It is also uncertain to what extent there will be exposure to the vaccine during pregnancy in Ireland in the initial stages of the vaccination program.

[22]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose

[23]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, medicine dispensing, pregnancy start and end dates, COVID-19 testing

[24]Primary care: every month. Secondary care: every year but could be fast track circuit for COVID studies (every 3 months or every month).

[25]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, dates and type of procedures (outpatient care), medicine dispensing, pregnancy start and end dates, mother-child linkage, COVID-19 testing

[26]Many details will become available in coming weeks, following strategic decisions of the Governement (December 2020) regarding vaccination strategy, etc.

[27]Outpatient data (SNIIRAM) are uploaded to the SNDS throughout the year. It is admitted that a lag of around 6 months is required to catch 90% of the dispensings. Inpatient data (PMSI) are uploaded in one time, at the end of the following year. Hence, we consider that complete SNDS data of year Y are available in January of the year Y+2. SNDS access is regulated.
[28]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage, COVID-19 testing
[29]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), geographic residence of patients, socioeconomic information, skilled nursing facility; nursing home; or extended care facility stays
[30]Each study and data extraction need approval from the CESREES (Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé) in charge of assessing scientific quality of the project, and authorization from the CNIL (French data protection commission), and then contracts with the SNDS data holder (CNAM) for data extraction. This process may be long, lasting generally from 6 to 12 months, but the recent changes in the process may reduce this timeframe especially for COVID-related studies for which an accelerated procedure is expected.
[31]BPE has been using SNDS and the data of the 66 million persons it contains for over 15 years, carrying out more than 50 SNDS-based national and international studies in many therapeutic areas. BPE is a member of the Vaccine Monitoring Collaboration for Europe (VAc4EU) and is actively involved in several European projects such as ConcePTION, ACCESS and CONSIGN. BPE researchers have published more than 120 articles in peer-reviewed journals since 2014. BPE is ISO 9001:v2015 certified for its activities in pharmacoepidemiology research. The platform has a highly secured IT infrastructure that is accredited to host SNDS data extraction. BPE has been registered with ENCePP since ENCePP's creation.
[32]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity
[33]Many data banks are updated on a bi-monthly basis, some daily (eg COVID registry), and we may request monthly updates if needed
[34]Use of data for observational research is regulated by regional law. Linkage with clinical data may be allowed upon permission of the ethical board of the hospital
[35]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose (if data collection for COVID-19 vaccines will follow the usual pathway)
[36] Dates of hospitalizations, discharge diagnosis from hospitalizations, date of death, dates and diagnosis of emergency department visit, dates and type of procedures (outpatient care), medicine dispensing, pregnancy start and end dates, mother-child linkage
[37]Receipt of other vaccines, geographic residence of patients, socioeconomic information, skilled nursing facility; nursing home; or extended care facility stays. BMI and smoking status is only available for women who had a recent delivery
[38]Exact date of vaccination, COVID-19 vaccine brands, vaccine batch number, vaccine dose, vaccinator type/identity
[39]Dates of hospitalizations, discharge diagnosis from hospitalizations, date of death, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, COVID-19 testing
[40]Exact date of vaccination, COVID-19 vaccine brands, vaccine dose, vaccinator type/identity. We could add all the information that we need
[41]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, date of death, dates and diagnosis of emergency department visit, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), mother-child linkage, COVID-19 testing
[42]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), race and/or ethnicity, geographic residence of patients, health care worker status, body mass index, smoking status. Being a prospective study, we will include all the needed information
[43]COVID-19 may be prioritized through a new Data Analysis Platform (almost real time). Some registries 3 months lag time (NorPD), some up to a year (Birth registry)
[44]Dates of hospitalizations, discharge diagnosis from hospitalizations, intensive care unit admissions, ventilator use, date of death, cause of death, dates and diagnosis of emergency department visit, dates and diagnosis of outpatient specialist visit, dates and diagnosis of primary care visit, dates and result of laboratory test (outpatient care), dates and type of procedures (outpatient care), medicine dispensing, medicine prescriptions (outpatient care), pregnancy start and end dates, mother-child linkage, COVID-19 testing
[45]Receipt of other vaccines (such as influenza vaccine, childhood vaccinations), geographic residence of patients, socioeconomic information, health care worker status, body mass index, smoking status, emigration, family clusters and households
[46]Regional Ethics Board (3 months), Data Protection Officer approval (DPIA) (1 month), Approvals from all registry holders (4 -6 months). After all approvals are in place, registries deliver data to the Norwegian Institute of Public Health (NIPH) (3 months). When all data has been received, NIPH has 60 days to anonymize and deliver data to researchers. All in all, the entire process may take 1 - 1,5 years.

Discussion

To prepare a European infrastructure for the monitoring of the COVID-19 vaccines and for conducting specific studies in a collaborative manner across EU countries, the VAC4EU performed a capacity assessment of organizations in Europe to participate in COVID-19 vaccine monitoring studies. To assess the capacity of these organizations, multiple surveys were designed. The first survey was completed by 82 responses from 74 organizations, located in 17 different European countries. These organizations were followed-up with a more specific questionnaire to assess their capacity to participate in EHR-based, hospital-based and/or app-based data collection.

These follow-up surveys were only completed by 22 organizations in total (22/74), located in the Czech Republic, Denmark, Finland, France, Ireland, Italy, the Netherlands, Norway, Portugal, Romania, Slovakia and Spain. The responses show that there is capacity in Europe beyond the organizations in ACCESS, for participation in any of the proposed studies, but that there is lack of responsiveness without clear proposal.

A limitation of this capacity assessment is that not as many organizations as desired completed the follow-up surveys. Possibly, this was because the questions were very specific and sometimes difficult to answer. Also, a significant portion of the information about the vaccination strategy and registration is still to be published in many countries, which also made it complicated for organizations to answer some questions in de surveys.

Because of this low response rate, organizations were invited to an online interview to complete the questionnaires. In the end, not every organization that responded to the initial survey completed the follow-up questionnaires, which makes this capacity assessment less extensive than desired.

6.Governance for implementation of protocols

As stated above ACCESS will not implement the studies beyond the background rates. Implementation can occur through different routes but preferably the Vaccine Monitoring Collaboration for Europe as it is geared to respond to vaccine questions. For EMA framework tenders VAC4EU joins the EU PE&PV network.

The Vaccine monitoring Collaboration for Europe (VAC4EU) https://vac4eu.org is a non-for-profit international association registered in Belgium. It was initiated as a sustainable solution of the Innovative Medicines Initiative funded ADVANCE project, which had 47 partners across academics, vaccine manufacturers, public health organizations and regulatory agencies, including the European Medicines Agency (EMA) and the European Centre for Disease prevention and Control. VAC4EU implements the blueprint for a vaccine monitoring system that was written by ECDC for the ADVANCE project. VAC4EU vision is best scientific evidence on vaccine coverage, benefits and risks in Europe to support data-driven decision making. The mission of VAC4EU is to access, characterize and analyse available and newly collected health data to allow for evidence-based decisions by people, who need to either regulate, advise, prescribe or decide on vaccines (https://vac4eu.org). Its statutes are publicly available through the following link
Since its registration in January 2020, 18 organizations (research and public health organizations) across Europe have joined VAC4EU, subscribing to the vision and mission and recognizing the need to work together to monitor vaccines.

Members

VAC4EU Members (as of December 1, 2020) are:

1. **University Medical Centre Utrecht**, the Netherlands, academic medical centre with ample expertise in vaccine studies, pre-licensure and post-licensure. Host of the VAC4EU secretariat. Coordinator of the ACCESS project. https://www.umcutrecht.nl/nl
2. **Sciensano**, national public health agency Belgium, with ample expertise in vaccine studies, pre-licensure and post-licensure. https://www.sciensano.be
3. **LAREB,** Netherlands national pharmacovigilance center, https://www.lareb.nl. Ample expertise in regular pharmacovigilance and intensive monitoring of influenza and pneumococcal vaccines
4. **RIVM**, the Dutch national public health institute, ample expertise in vaccine coverage, effectiveness and safety studies with primary data collection and secondary use of data. https://www.rivm.nl
5. **Leibniz Institute for Prevention Research and Epidemiology** – BIPS, Germany. Home to the German Pharmacoepidemiologic Research Database (GePaRD), claims data from statutory health insurance providers and currently includes information on about 25 million persons. https://www.bips-institut.de
6. **Societa Servizi Telematici,** Italy. Home to the PEDIANET database covering primary care paediatricians in Italy http://pedianet.it/en/primary-health-care-project
7. **Bordeaux PharmacoEpi (BPE)**, France, is a research platform of the Université de Bordeaux specialized in real world evidence with extensive experience in conducting fields studies and studies based on the French national healthcare database (SNDS). https://www.bordeauxpharmacoepi.eu
8. **Research Triangle Institute Health Solutions (RTI-HS), Spain** a private non-for-profit research organization. Pharmacoepidemiology and Risk Management expertise including EMA-

mandated safety and utilization studies. https://www.rtihs.org/

9. **Lazio Regional Health Service,** Italy. Regional public health agency. Expertise in vaccine studies and COVID-19 studies, access to administrative health care data (mortality, hospital admissions, ER access, drug claims & vaccines, health care assistance), in Lazio region (6 million residents). https://www.deplazio.net/en
10. **Agenzia Regionale di Sanità (ARS) Tuscany**, Italy. Regional public health agency. Expertise in vaccine studies and COVID-19 studies, access to administrative health care data (mortality, hospital admissions, ER access, drug claims & vaccines, health care assistance), in Tuscany region (6 million residents). https://www.ars.toscana.it
11. **Penta foundation**, a private non-for profit foundation hosting a global pediatric research network, which has coordinated hundreds of multisite clinical trials and cohort studies in infectious diseases in the past 30 years. https://penta-id.org/who-we-are/compliance/
12. **PHARMO Institute**, the Netherlands. A private research organization conducting studies on use and effects of medicinal products. Home to the PHARMO data network, is a population-based network from different primary and secondary healthcare settings in the Netherlands. www.pharmo.nl
13. **IDIAP-Jordi Gol**, Spain. A public primary health care research organization. Home to the SIDIAP database, Information System for Research in Primary Care, electronic health data. https://www.idiapjgol.org/index.php/en/
14. **The Foundation for the Promotion of Health and Biomedical Research of Valencia Region**, Spain FISABIO, is a non-for profit scientific and healthcare entity, whose primary purpose is to encourage, to promote and to develop scientific and technical health and biomedical research in Valencia Region. FISABIO has access to regional data and is leading the DRIVE project http://fisabio.san.gva.es/en/fisabio
15. **University Verona**, Italy. An academic research organization and important regional pharmacovigilance centre for Italy
16. **University Oslo**, Norway. Public academic research organization. Expertise in perinatal pharmacoepidemiological studies using Norwegian linked health care registries
17. **Drug Safety Research Unit**, DSRU, UK. The DSRU is a private research organization in the UK which monitors the safety of medicines and vaccines. The Unit has broad pharmacoepidemiology expertise and has conducted post-authorisation studies on over 120 medicines and vaccines. The DSRU has ample experience of monitoring the post-authorisation safety of vaccines, notably active surveillance on the H1N1 swine flu vaccine and enhanced passive and active surveillance on the children's seasonal influenza vaccine, Fluenz Tetra, for many years.
18. **University of Lyon**

Tools for study conduct

The VAC4EU research infrastructure provides a toolbox and IT services to rapidly conduct studies in a distributed manner where data remain local and the data access provider transforms data in a common data model, that is then analysed with standard R-tools(Fig. 5). This process was tested and very successful in the IMI-ADVANCE proof near real time monitoring studies. For proposed studies we will use two IT dedicated tools to engage the data access providers (DAP) who organize local access to data. The study team will comprise representatives from the DAPs. The toolbox to be utilized are available protocol templates from ACCESS, event definitions, codes and algorithms, as well as the R-scripts that were used to assess quality of data and the incidence rates

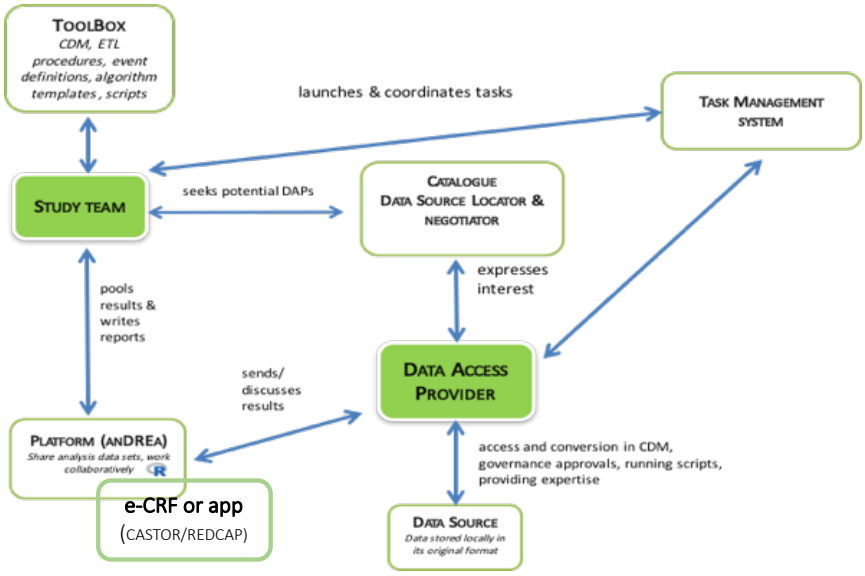

Figure 5: Graphical display how studies can be rapidly conducted using VAC4EU tools

Task management system

This system supports launching and monitoring up of tasks for distributed tasks (e.g. protocol approvals, scripts release)

Remote research environment anDREa platform

The azure Digital Research Environment (anDREa, https://www.andrea-consortium.org/azure-dre/) is a cloud based, globally available research environment where data is stored and organized securely and where researchers can quickly generate workspaces to collaborate in. Within these workspaces, researchers have preinstalled applications at their disposal, as well as the ability to bring own tooling. The DRE facilitates users to collaborate on research projects in a safe, yet flexible computing and storage environment. The architecture of the DRE allows researchers to use a solution within the boundaries of data management rules and regulations. Within the DRE platform each of the projects you are a member of consists of a separate, secure folder, called a 'workspace'. Each workspace is completely secure, so researchers are in full control of their data. Each workspace has its own list of users, which can be managed by its administrators. Each workspace is fully scalable with regard to data quantity and computing power, thereby supporting anything from small to complex multi-center, multisource studies.