Response PE & PV network to question from EMA April 30, 2020 related to tender EMA/2017/09/PE/09

The table on page 18 contains a list of data sources. The tenderer is requested to clarify the data lock point, the frequency of update and the lag time for these databases.
Please clarify whether the databases mentioned in page 18 and the analyses in workstream 1 will be run prospectively.

We would like to explain that for the proposed work there are different types and levels of participation of data sources.

1) Electronic health care data sources (collecting data for routine care and not for research), this data can be used retrospectively or prospectively (workstream 1). We distinguish between
    a. Those participating in background rates (table below and described under 1 a)
    b. Those available for research that will be characterized but are not participating in background rate estimations for this tender (described by headers 1b below)
2) *De novo* prospective data collection from patients specifically for research (workstreams 2 and 3)

Data sources for 1a were identified before submission of the proposal, data sources under 1b and 2 will be identified and described as part of the final report, as it will depend on the protocols and the data collection requirements.

Country	Organization	Name Data source	Lag time	Last data available when data are extracted at data lock point September 1, 2020
(10)(2a)			1-2 years	2018
			9 months for hospital, several weeks for GP	2020 (partial)
			9 months	2019
			1 year	2019
			6 months	2019
			Several months	2020 (partial)
			Several weeks	2020 (partial)
			Several months	2020 (partial)
			Several months	2020 (partial)
			1-2 years	2018 (2019 data available in October-November-December 2020)

We explain the type of data and analyses for data sources listed as part of workstream 1 in more detail

1a. Data sources to generate the background rates of AESI

See below the table with data sources that will be used for the generation of background rates of AESI in workstream 1. We assume that the data lock point will be September 1, 2020.
Background rates will be provided from 7 countries, data from (10)(2a) will

1 b: Electronic health care data sources not delivering background rates by December 2020

Norway (which was listed in the table of the proposal on page 18) knows that it will not be able to get permissions rapid enough to participate in the production of the background rates for the report in December 2020. However, the University of Oslo participates will provide meta-data, data dictionaries and conduct the ETL design for the transfer of data into the Common Data Model, so that they will be ready to participate and generate background rates later when permission is obtained.

In addition to Norway and beyond the sources listed in the table there are several additional electronic health care data sources that will be asked by the VAC4EU secretariat for meta-data, data dictionaries and characteristics in order to create *the required readiness to monitor benefits and risks of COVID-19 vaccines*. All these meta-data will be uploaded onto the VAC4EU catalogue to create readiness to participate in studies and described to EMA in the final report.

These electronic health care data sources include data accessible by VAC4EU members and other related networks

- (10)(2a)

We anticipate that by

1) Delivering a protocol for the background rates and posting the protocol on the EU PAS register;
2) having a ready common data model and statistical analysis plan;
3) Having R-scripts to generate rates rapidly

That will be produced as part of this tender, additional data sources identified as part of this group 1b may produce background rates to create readiness by using the tools, later.

1 b: Clinical sites able to participate in hospital based self-controlled case series studies by using medical charts

As part of workstream 1 we will also create a protocol that describes the design and requirements for hospital-based conduct of SCCS or case crossover studies. This design is useful in all countries and not contingent on the availability of large electronic health data sources. It will allow for rapid data collection and detailed case validation which was proven in the multinational VAESCO studies in Europe on GBS during the 2009 pandemic (see Romio et al) and the WHO multi country studies (see

Perez-Vilar) and described as feasible in the Global Roadmap by FDA (Izurieta).
Under this tender proposal we:

- Create the protocol for such prospective studies,
- Describe the criteria for validation and
- Describe the requirements for participating clinical sites (regarding ability to select cases unbiased from hospital records, and obtain unbiased exposure data).
- We will solicit willingness to participate by clinical sites and the costs through ENCePP and VAC4EU
- Provide a list of 'eligible' sites as part of the final report.

The actual conduct of the studies is not part this tender as it will be implemented after launch of the vaccines.

Question EMA: Please clarify whether the databases mentioned in page 18 and the analyses in workstream 1 will be run prospectively.

Response: The data sources that are listed in table 18 (participating in workstream 1) are all electronic health care data sources that *collect real world data prospectively and* electronically (independent of a study question) as part of routine care.

To address the question:

- Yes, the data sources mentioned in the table (1a) will be used to generate background rates of AESI over a prior 2-year period to comply with the request of EMA for this proposal, this is part of the tender. The data is collected prospectively but study conduct is retrospective (the events have already occurred when the protocol is written)
- Yes, each of those data sources (1a or 1b) may also be able to analyze and run those incidence rates *prospectively*, when data become available, during 2021. This is part of the ecological analyses described in the protocol that will be created for rapid monitoring of safety after vaccine introductions (see task description 1.10 page 10: *Rapid assessment of population impact of signals: Population level comparison of rates of events, prior to COVID-19, during COVID-19 and during vaccination*)
- Yes, each of the data sources listed in table 18 may also be able to participate in prospective effectiveness or safety studies (definition of prospective is: the question is posed prior to the occurrence of the event/exposure) evaluating safety/benefit, coverage. The protocol for prospective coverage, benefit and risk monitoring based on electronic health care databases will be delivered as part of the proposed work (see task descriptions for 1.10, task 1.12 and 1.13, pages 10-11) and describe eligible data sources (based on fit for purpose assessments (see task 4.2).

Workstreams 2 and 3 are *prospective* by nature and will describe the methods and sources to collect data *de novo and real time* specifically for this research from patients directly.

- As part of the tender we will describe the protocols and tools for data collection and the requirements for participation.
- We will also do an enquiry and describe in the final report which sites/countries are ready and willing to participate:
    - Through the IMI-DRIVE consortium for workstream 2 to assess real-time vaccine effectiveness based on test-negative designs) (see task 2.2 page 12)
    - Through pharmacovigilance centers /ENCePP to collect real time online patient-reported safety data in workstream 3. (see task 3.2 page 14)

Question EMA Page 1, Item 4.1: Collectively we can access data from 8 countries from northern, southern, western and more eastern Europe: The Netherlands (PHARMO), UK (CPRD), Norway, Denmark, Germany (GePaRD), Spain, Italy, France (SNDS), Norway will prepare access but will not have approvals quick enough to provide rates. Can the tenderer clarify if there should be a semicolon after 'France (SNDS)'?

Yes, the semicolon should be after (10)(2a) (10)(2a) knows already they cannot make it in time, but will provide all the documentation about the data source, and conduct the ETL design so that data may be made available rapidly whenever possible.

Question EMA: Page 10, Task 1.11: The tenderer is requested to clarify where hospital data will be collected.

As part of workstream 1 we will create a protocol that describes the design and requirements for hospital-based conduct of SCCS or case crossover studies. This design is useful in all countries and not contingent on the availability of large electronic health data sources, there it may be conducted in any of the EU countries.
This design will allow for rapid data collection and detailed case validation which was proven useful and feasible in the multinational VAESCO /WHO studies in Europe on GBS during the 2009 pandemic (see Romio et al 2014, Dodd CN et al. 2013) and the WHO multi country studies (see Perez-Vilar 2018 & Guillard-Maure 2018)) and described as feasible in the Global Roadmap by FDA (Izurieta et al 2013).

As part of this tender we:
- Create the protocol for such prospective case-based studies
- Describe the criteria for validation
- Describe the requirements for participating clinical sites

Typically (based on our experience during VAESCO and WHO studies) these are hospitals/sites that are
- Willing and allowed to participate (after ethical review)
- Able to retrieve medical charts on certain events of interest in a systematic manner (ie. They have a list of all diagnoses in the hospital)
- Willing to extract information from the charts and to provide this
- Able to access patient level vaccination information on their patients in an unbiased manner (from registries, not from patient reports)

Since exploration of the willingness and capacity to participate will depend on the protocol, which is written during the conduct of this tender, we do not yet know which hospitals may participate to such studies. We will provide a list of potential 'eligible' sites as part of the final report.

References for examples of multi-country hospital based SCCS studies using data from hospitals

- Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, Zuber P, Hua W, Bonhoeffer J, Buttery J, Crawford N, Deceuninck G, de Vries C, De Wals P, Gutierrez-Gimeno MV, Heijbel H, Hughes H, Hur K, Hviid A, Kelman J, Kilpi T, Chuang SK, Macartney K, Rett M, Lopez-Callada VR, Salmon D, Gimenez-Sanchez F, Sanz N, Silverman B, Storsaeter J, Thirugnanam U, van der Maas N, Yih K, Zhang T, Izurieta H; Global H1N1 GBS Consortium. International collaboration to assess the risk of Guillain Barré Syndrome following Influenza

A (H1N1) 2009 monovalent vaccines. Vaccine. 2013 Sep 13;31(40):4448-58.

- Guillard-Maure C, Elango V, Black S, Perez-Vilar S, Castro JL, Bravo-Alcántara P, Molina-León HF, Weibel D, Sturkenboom M, Zuber PLF; WHO Global Vaccine Safety-Multi Country Collaboration. Operational lessons learned in conducting a multi-country collaboration for vaccine safety signal verification and hypothesis testing: The global vaccine safety multi country collaboration initiative.nVaccine. 2018 Jan 8;36(3):355-362.
- Izurieta HS, Zuber P, Bonhoeffer J, Chen RT, Sankohg O, Laserson KF, Sturkenboom M, Loucq C, Weibel D, Dodd C, Black S. Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines. Vaccine. 2013 Aug 2;31(35):3623-7.
- Perez-Vilar S, Weibel D, Sturkenboom M, Black S, Maure C, Castro JL, Bravo-Alcántara P, Dodd CN, Romio SA, de Ridder M, Nakato S, Molina-León HF, Elango V, Zuber PLF; WHO Global Vaccine Safety-Multi Country Collaboration. Enhancing global vaccine pharmacovigilance: Proof-of-concept study on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps containing vaccination. Vaccine. 2018 Jan 8;36(3):347-354.
- Romio S, Weibel D, Dieleman JP, Olberg HK, de Vries CS, Sammon C, Andrews N, Svanström H, Mølgaard-Nielsen D, Hviid A, Lapeyre-Mestre M, Sommet A, Saussier C, Castot A, Heijbel H, Arnheim-Dahlström L, Sparen P, Mosseveld M, Schuemie M, van der Maas N, Jacobs BC, Leino T, Kilpi T, Storsaeter J, Johansen K, Kramarz P, Bonhoeffer J, Sturkenboom MC. Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccines: a multinational self-controlled case series in Europe. PLoS One. 2014 Jan 3;9(1):e82222.