COVID-19 vaccine related AESI active surveillance: additional pharmacovigilance activities

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Plan of the presentation

1. Vaccine safety: detection, strengthening, confirmation

2. Signal strenthening

3. Signal confirmation

   - Bias and confounding

   - Study designs

4. Pregnancy registers

5. International collaborations

Vaccine safety

- **Signal detection** - information that **indicates a potential link** between a vaccine and an event previously unknown or incompletely documented, that could affect health

  - Spontaneous reports, data mining

- **Signal strengthening** - to assess the **plausibility of a signal**, yet without achieving the rigour required of signal confirmation

  - Observed-expected (O-E) analyses

  - Self-controlled analysis of spontaneous reports

- **Signal validation/confirmation** - **evaluate the strength of evidence** for a specific signal

  - Specifically designed studies

NB: Cannot use the same dataset for signal detection and confirmation!

Signal detection: routine PV activities

- Previous talk

Signal strengthening: often sequential methods

- No fixed time/sample size, but accumulating evidence until a threshold is reached at which point a decision is reached

- Useful for monitoring recently introduced vaccines (or new schedules), for which extensive past data are unavailable, yet early results are needed

- Methods:

  - Sequential Probability Ratio Test (**maxSPRT**) frequently used

  - Monitors the likelihood ratio which is updated at regular intervals, and results in a decision to accept or reject the null hypothesis of no association, once the likelihood ratio reaches a pre-determined boundary

Implementation: influenza vaccine/GBS
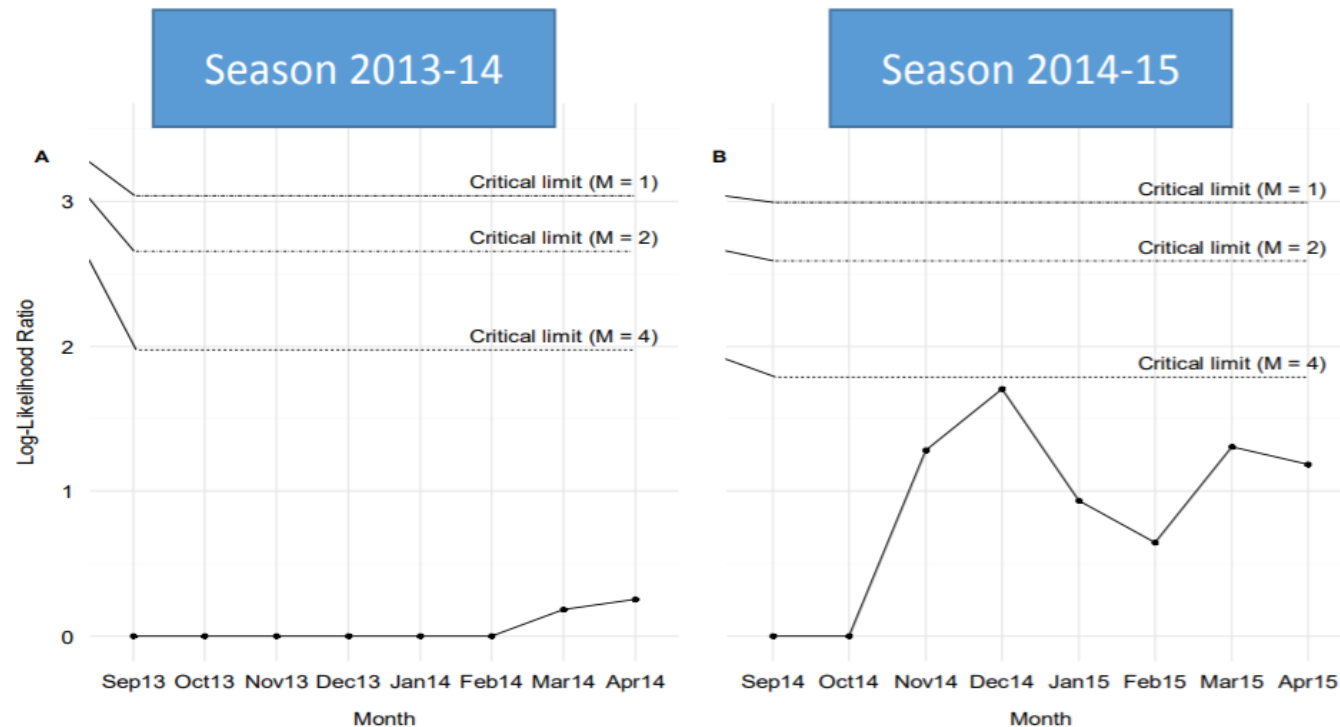
No signal detected in any of the seasons

Signal validation/confirmation: pharmaco-epidemiological studies

- More thorough evaluation of the **strength of the association** between the exposure of interest (vaccine) and the AESI using pharmaco-epidemiological studies (also called observational studies)

- **Observational studies**: exposure is not randomized (unlike in clinical trials) and the assessment of the association (let alone causality) is more complicated

- **Bias and confounding** are threats to observational studies

Sources of bias and confounding

- **Selection bias**: arises from systematic differences in selecting and following study groups
  (in case-control study if selection of cases and controls is based on differing criteria that are related to exposure status; in cohort studies if selection of exposed and unexposed in based on related to developing the outcome)

- **Disease misclassification**: subjects wrongly classified as diseased or non-diseased

- **Exposure misclassification**: subjects wrongly classified as vaccinated or unvaccinated

- **Confounding**: variable that is independently related to both the risk of disease and vaccination status

Confounding

Age

Confounder

Exposure ——————— ? ——————— Disease

AESI
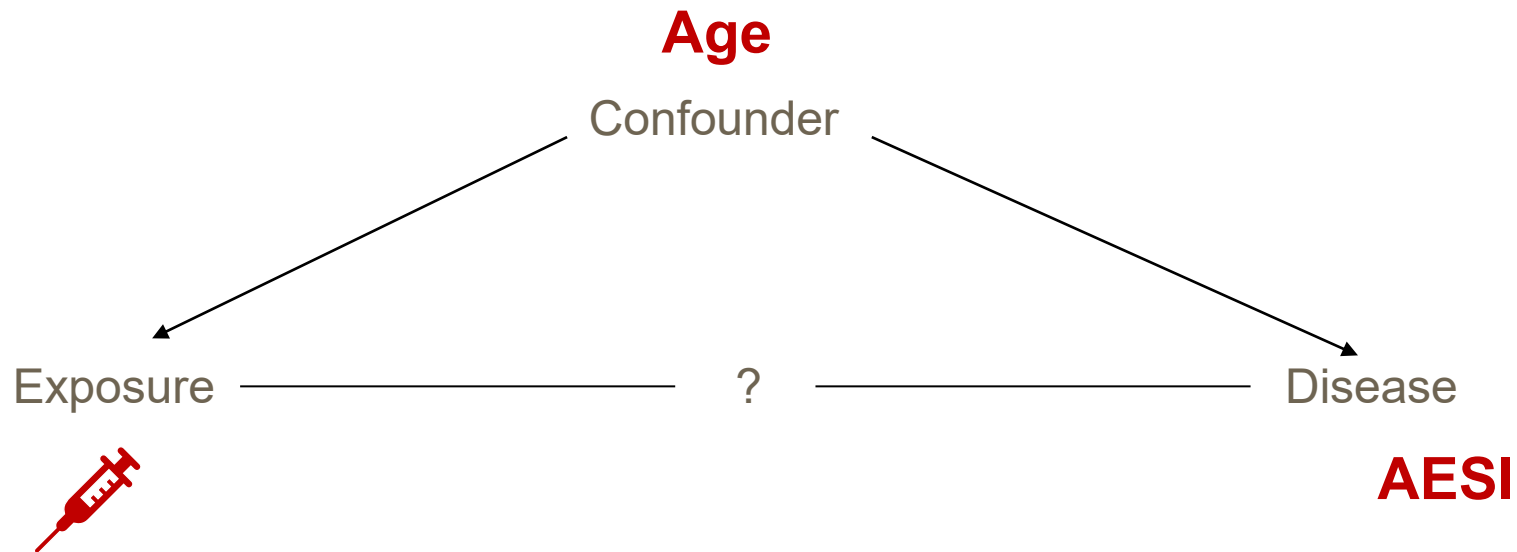
The confounder is associated both with the exposure/vaccination status and the disease, but it is not an intermediate step in the casual pathway between exposure and the disease.

Certain confounders can vary over time, others do not change

Data sources

Primary data collection - data source was specifically created to answer a research question

- Control over the information to be collected, but typically expensive and hence limited in sample size

- Examples: prospective cohort study

Secondary use of existing data- data that was originally collected for other purposes than the research question

- No control over the data to be collected, more errors in the data, but typically lots of information on many subjects ("quantity over quality"), provides the necessary sample size to study rare events

- Examples: medical records at primary care, hospital data (also called Electronic Health Record data, EHR), claims data

Study design

Study design is chosen in function of

- **AESI incidence**: common disease or rare disease

- Presence of a **risk window:** e.g. vaccine-induced anaphylaxis is expected to occur within a few days after vaccination

- Presence of **comparator group**: is there an unvaccinated group comparable to the vaccinated group apart from the vaccine of interest

- **Confounders**: concern about confounding? E.g. patients from high risk groups are more likely to be prioritized for vaccination.

- **Speed to results**: e.g. in case of a health crisis, fast evidence is required

- **Data availability**

- **Financial resources**

Common designs for vaccine safety evaluation

- **Cohort design**:

    - Vaccinated subjects are followed over time starting from vaccination and compared to unvaccinated subjects that have been followed over time as well

    - not suited to study rare events, takes time in case of primary data collection

- **Case-control design**:

    - Subjects with the AESI ('cases') are identified and their exposure to the vaccine of interest is retrospectively assessed. The same is done for subjects without the event of interest ('controls'). Comparing the exposure in 'cases' to that in 'controls' allows to measure the strength of the vaccine-AESI association

    - Suited to study rare events

- **Self-controlled design**:

    - Subjects act as their own comparison, comparing the occurrence of events within the 'risk window' after vaccination to a control period

   - Nicely adjusts for time-invariant confounding

Cohort design

- **Single-arm cohort design, cohort event monitoring (CEM)**:

  - First vaccinated cohorts are closely followed for all potential safety events

- **Two-arm cohort design**:

  - Vaccinated and unvaccinated cohorts are followed and number and severity of AESI are compared between the cohorts

- **Prospective or retrospective**:

  - Prospective: primary data collection, enroll subject at time 0 and follow-up till some time in the future

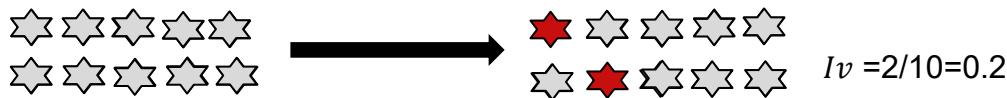 - Retrospective: secondary data use of data covering several years in the past

Cohort design

Two-arm cohort design

Iv =2/10=0.2

Iu =9/10=0.9
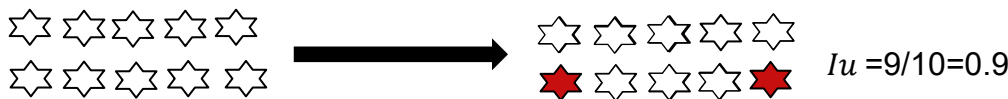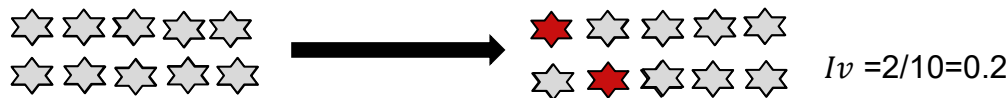
RR = 0.2/0.2 = 1

Single-arm cohort design

Iv =2/10=0.2

Compare to known background rates (e.g. from trials, from literature) or apply self-controlled designs to measure the strength of the assocation

Cohort design

- **Advantages:**

  - Easy to explain (follows natural 'time' direction)

  - Easy to collect all information on exposure (for primary data collection)

  - Can be used to study multiple outcomes

  - Can be used to obtain 'absolute' risk estimates

  - Can include nested studies

- **Disadvantages:**

  - Potential for missing study outcomes

  - Potential for bias due to differences in healthcare seeking behavior

  - Might be time and resource consuming (for primary data collection)

  - Insufficient to study rare outcomes (for primary data collection)

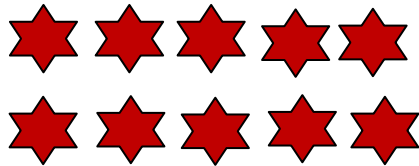 - Long time to results (for primary data collection)

Case-control design

- Compares the vaccination coverage in a group of 'AESI cases' to the vaccination coverage in the control group

- Controls should provide an accurate estimation of the vaccination coverage within the population given rise to the cases

- Several options to select the control group:

  - Hospital controls

  - Community controls

  - External control group (also called case-coverage or screening method)

- Primary data collection or secondary data use:

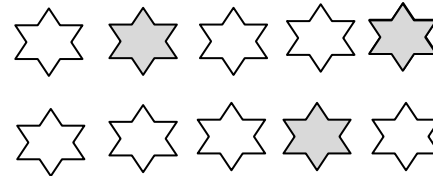 - Case-control studies can also be applied when doing a database study
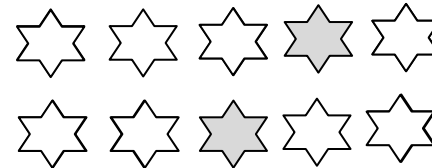
Case-control design

cases   vaccination coverage?

controls   vaccination coverage?

time

Case-control design

- **Advantages:**

  - Can be used to study rare outcomes

  - Fast to results (also for primary data collection)

  - Less resource intensive

  - Less sample size required

- **Disadvantages:**

  - Difficult to explain (does not follow natural 'time' direction)

  - Potential for errors in vaccination exposure ascertainment

  - Cannot be used to obtain absolute risk estimates

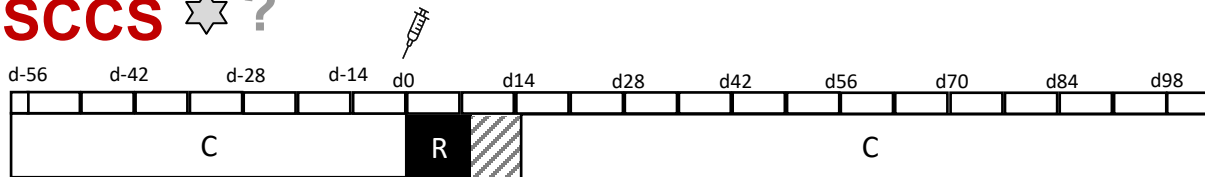 - Selection of controls not always easy

Self-controlled design

- Subjects act as their own control

- Only includes cases

- Not subject to time-invariant confounding

- Different types of self-controlled designs

  - Self-controlled case series (SCCS)

  - Self-controlled risk interval (SCRI)

  - Case-cross over (CCO)
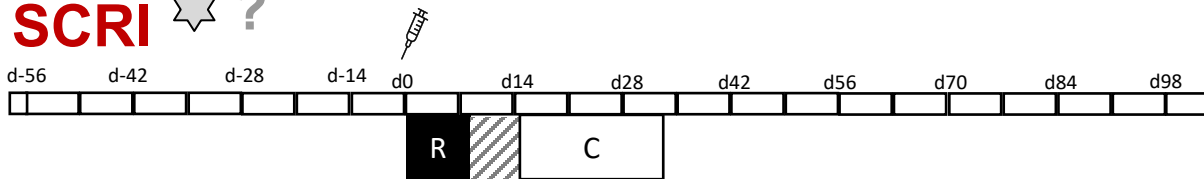
SCCS

Time at vaccination determines risk window
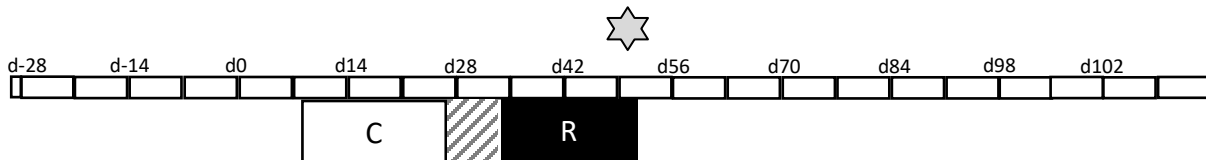
When did event happen wrt vaccination date?

SCRI

Simplified version of SCCS

CCO

Time at event determines risk window

When did event happen wrt vaccination date?

Self-controlled designs

- **Advantages:**

  - Adjusts for time-invariant confounders

  - Can be used to study rare outcomes

- **Disadvantage:**

  - Requires knowledge of post-vaccination risk window

  - Only works for AESI with acute onset

Which design you would select:

- You want to start primary data collection and want to study a rare outcome.

- You want to make sure you do not have time-invariant confounding in your study.

Pregnancy registries

- Lack of pre-clinical developmental and reproductive toxicity (DART) studies

- Pregnancy woman excluded from clinical trials

- Clinical trials in pregnant women are difficult, slow to recruit

- Pregnancy registries study post-licensure inadvertent/off-label vaccine use in pregnancy

- Pregnancy registries to show that vaccine is safe in pregnant women, to not refuse pregnant women beneficial pharmaceutical products

Pregnancy registries

- Prospective collection of data on exposure in pregnancy AND on pregnancy + infant outcomes (often til age 3-12 months)

- Outcomes: e.g. spontaneous abortion, stillbirth, major birth defects
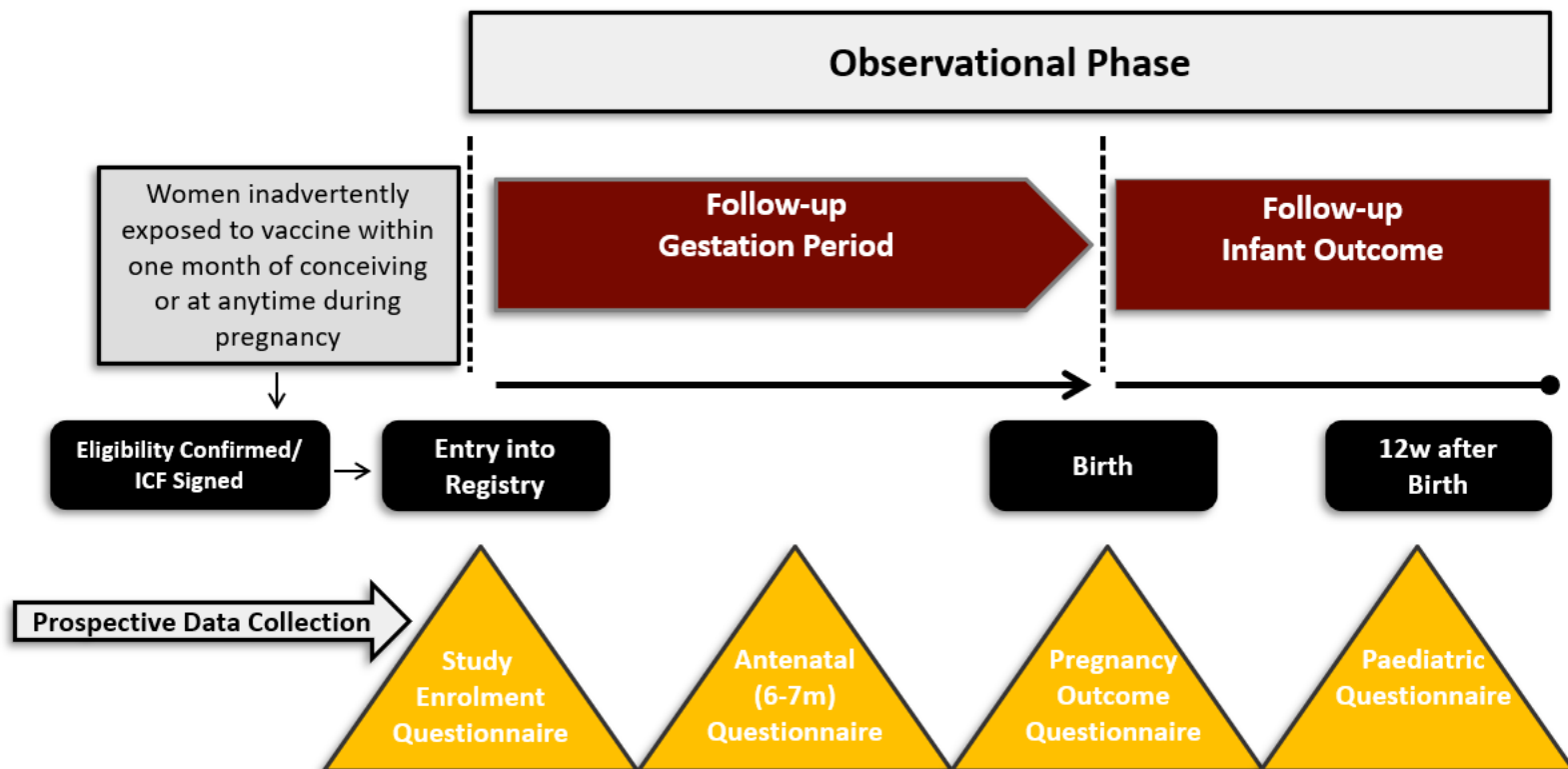
International vaccine collaborations

- Especially to study rare adverse events, international collaboration are required as no national study is large enough

- Examples: https://www.globalvaccinedatanetwork.org/

The Global Vaccine Data Network

Continents 6

Countries 17

Sites 21

290 million — People
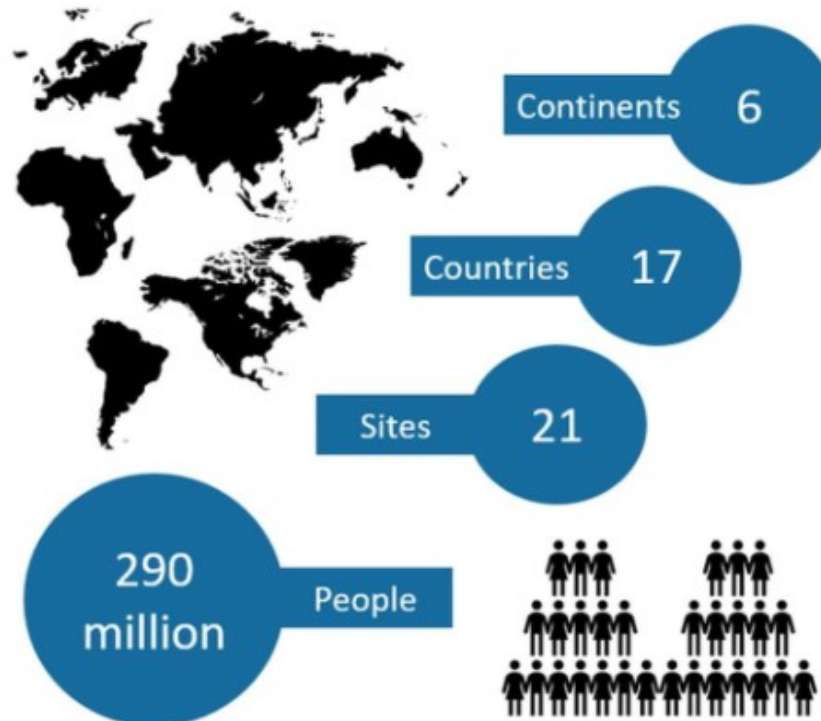
The SOMNIA study – cohort

- **Study design**: a dynamic retrospective cohort study to assess narcolepsy incidence rates (IR) before and during pH1N1 virus circulation, and after pH1N1 vaccination campaigns

- **Data sources**: population-based electronic health record databases from general practitioners (Spain, Netherlands, UK) or claims/record linkage databases (Canada, Denmark, Sweden, and Taiwan)

- **Study population**: individuals registered in the database for at least one year prior to start of follow-up; 540 million person-years

- **Exposure definition**: adjuvanted pH1N1 vaccination (Pandemrix-AS03, Arepanrix-AS03 or Focetria-MF59)

- **Outcome definitions**: narcolepsy with or without cataplexy (case finding algorithm validated using Brighton Collaboration case definition; or or diagnostic code + reimbursement claim for multiple sleep latency test)

- **Potential confounders**: none considered. Stratified by age and sex.

Links to manual and protocols

- COVID-19 vaccines: safety surveillance manual (WHO) https://apps.who.int/iris/bitstream/handle/10665/338400/9789240018280-eng.pdf?sequence=1&isAllowed=y

- Protocol templates for cohort event monitoring and for electronic health records studies (ACCESS project) https://vac4eu.org/covid-19-vaccine-monitoring/

- CDC protocols and standard operating prodcedures for COVID-19 vaccines https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html#anchor_1607961664745