Vaccines Europe
An industry for healthy lives

Points to consider on the topic of Vaccine Mediated Enhanced Disease (VMED), in anticipation of the joint ACCESS/SPEAC webinar, Sept 10th

Vaccines Europe (VE) welcomes this webinar as an opportunity for the scientific experts in our member Companies to provide questions, comments and proposals on the challenging topic of the VMED.

Vaccines Europe would also like to get the opportunity to formulate questions and possibly further suggestions after the webinar.

As a top line summary, our experts have highlighted that:

- There are many unknowns so far on this theoretical risk, notably on the potential mechanism of action and the possible clinical course on the event.

- Given that there are no known clinical findings, immunological assays or biomarkers that can differentiate severe viral infection (breakthrough cases) from immune-enhanced disease it will difficult to study vaccine-associated enhanced disease (VAED), and particularly difficult if not impossible within electronic health care databases for which information is often incomplete.

- The BC definition is designed for the individual assessments of case reports from clinical trials, where, even if the information is richer than elsewhere, the identification of cases of VMDE will be very challenging (see more below). VE questions the possibility to identify cases of VMDE in EHCR database, where the information is generally much more limited. However, if this would be pursued, then a standard operational version of this case definition should be developed and validated for use in database observational studies.

- A major question is how on an individual basis a severe COVID case can be differentiated from a Vaccine Mediated Enhanced Disease case. The Brighton case definition is basically defining a severe disease case, but cannot attribute the severe disease case for certain to a vaccine enhancement process. In other words, the causal relationship of a severe disease case to vaccination (which would mean a case of VMED) cannot be defined, and more so in studies without a control group. Indeed the BC case definition requires the presence of an "Increased frequency of severe outcomes (...) when compared to a non-vaccinated population". However, this is a population level consideration, not an individual-level consideration.

- If the conclusion is that we cannot differentiate between severe disease and VMED, VE suggests to consider the monitoring of the risk of VMED through monitoring vaccine effectiveness using severe/critical disease leading to hospitalisation/ICU as a proxy, as opposed to an AESI in safety studies. VE also acknowledges that this point may be as much a regulatory than a scientific discussion.

More specific or more detailed points can be found below, including around the questions which were listed in the webinar invitation:

Time windows for VMED monitoring

ADDRESS
EFPIA / Vaccines Europe
Rue du Trône 108 / Troonstraat 108
1050 Brussels – BELGIUM

ONLINE
www.vaccineseurope.eu
@VaccinesEurope
Vaccines Europe

Vaccines Europe
An industry for healthy lives

There are a lot of uncertainties linked with the application of proposed VAED/VAERD case definition in post-licensure setting and especially within RWD. While there are a lot of theories about potential mechanisms on ADE confirmation would require detailed immunological work-up at different time points: serostatus before vaccination, immunological biomarkers post-vaccination (T-cell response, IgG level etc).

Vaccine Mediated Enhanced Disease (VMED; or Vaccine-associated enhanced disease, VAED) in relation to SARS-CoV-2 vaccines is a theoretical phenomenon. The best way to study whether VAED will be observed following SARS-CoV-2 vaccination is through Phase III clinical trials that would collect baseline serostatus information of trial participant (indicating whether there was prior exposure to SARS-CoV-2) and nasal swab throughout the study. Phase III clinical trials will provide at least 1 – 2 years of active follow-up (surveillance) for both placebo and vaccine arms (if integrity of placebo group is maintained). Phase III trials are multi-country and would allow calculation of country-specific SARS-CoV-2 incidence rate in placebo group using active surveillance. Within the Ph III trials, serology will be collected to study immune response and to identify potential VAED, i.e. [severe clinical presentation despite the presence of total IgG, or correlation between the level of IgG and the occurrence of severe forms of Covid-19...] .

Monitoring of VMED may require long follow-up because people may be at risk of VMED after waning of the antibody response.

It should also be clarified whether the case definition will apply after 2 doses of vaccination are completed, similarly to the case definition for vaccine failure. Compliance level in the general population may also be a point to take into consideration.

Background rate of serious/severe COVID-19 disease

It is not possible to distinguish between vaccine failure or lack of efficacy and VMED given that there is no biomarker in immune response to SARS-CoV-2 or S-protein or other component of SARS-CoV-2 vaccine. Assuming background rate of SARS-CoV-2 confirmed infection (by RT PCR or another lab method) normally with vaccine introduction and vaccination uptake in the population > 30-40% we should expect decrease in rates of SARS-CoV-2 infections.

How will "background of serious/severe COVID-19 disease" be defined? Which outcomes to be considered (e.g. death, hospitalization, complications, lab findings, clinical score, ICU duration ...)?

If it is possible to derive any meaningful incidence rates, they should be provided by age group, comorbidity, specific at-risk population (e.g. pregnant women), and per country...

Additional questions include: Will 2020 year be considered background before vaccine introduction in 2021? Will the rate be updated monthly / quarterly, and how should it compare to the real time public health surveillance data for COVID-19 which can also be used (similar to John Hopkins COVID-19 monitor).

Do you recommend observed to expected (O/E) analysis knowing the uncertainties on the COVID-19 disease (knowledge and virus evolving) or to limit O/E analysis to specific outcome (e.g. death)? Do you recommend a minimum number of cases to calculate O/E ratio?

ADDRESS
EFPIA / Vaccines Europe
Rue du Trône 108 / Troonstraat 108
1050 Brussels – BELGIUM

ONLINE
www.vaccineseurope.eu
@VaccinesEurope
Vaccines Europe

Vaccines Europe
An industry for healthy lives

How to identify cases with potential VMED from electronic records (Codes/algorithm)?
How to differentiate VMED from vaccine failure in effectiveness/safety studies? How to assess the risk of VMED in epidemiological studies?

Without biomarker it will not be possible to distinguish between vaccine failure and VMED. Databases will lack prior to vaccination serostatus information. The databases will not have detailed immunological work up (IgG, IgA, T-cell, CD4 count as this information may not be ordered by physician as part of case work up). Also there may be delay in recording immunization status or missing immunization status.

Limitations of the use of administrative databases for calculations of incidence of SARS-CoV-2:

1) Some databases may record only hospitalized cases and may not include outpatient cases (testing may be done by public health laboratories and reported directly to patient. However, the patient may not inform his/her GP);
2) How SPEAC VAED/VAERD definition are applicable in databases? VE suggests that we need a feasibility assessment in the different databases with the availability of the variables, validation of algorithm for VAED BC definition (lack of some lab data in databases) versus medical chart.
   Validity (sensitivity, specificity, PPV) of the proposed algorithm and case identifications strategies will need to be evaluated prior using any of such algorithms.
3) We have observed that lockdown and other measures may decrease the incidence rate of SARS-CoV-2 in population. We have data from Feb – March 2020 with some fluctuations and decrease in May-June and now again increase. What time period will be considered as a background (we don't have full year yet)? We also see changes in age structure of SARS-CoV-2 cases over time (with more cases in younger adults in July- August due to more socializing). Given the novelty of this virus and the fact that epidemiology is still changing background rate should be calculated ideally not before.
4) Delay in processing records in administrative databases: in many countries health system and hospitals were overwhelmed with COVID-19 cases. Even in the US there may be 2-3 months delay in processing COVID-19 cases and their coding in the databases. Calculation of background rates across databases may not reflect actual number of cases treated / diagnosed. Asymptomatic cases will not be captured in administrative databases. How faster it will be possible to obtain updated background incidence rate (quarterly/monthly?)

The risk factor for more severe disease may be prior asymptomatic infection. However, prior exposure to SARS-CoV-2/ COVID-19 asymptomatic will not be captured in admin databases. However, Phase III clinical trials data, pooled Phase III clinical trials, or other existing CoVID-19 surveillance network will help to generate this information.

More generally, and looking forward, will there be systematic medical records review and adjudication of potential VMED cases in the ACCESS studies?

ADDRESS
EFPIA / Vaccines Europe
Rue du Trône 108 / Troonstraat 108
1050 Brussels – BELGIUM

ONLINE
www.vaccineseurope.eu
@VaccinesEurope
Vaccines Europe