

Monitoring the use and performance of authorized COVID-19 vaccines in the EU/EEA

Reflections document and questionnaire for the Health Security Committee

Background

Through the [EU vaccine strategy](#), a large portfolio of COVID-19 vaccine candidates is being selected to accelerate their development, manufacturing and deployment. All vaccines expected to be authorised and used for protection against COVID-19 are *newly* developed and for most, the production platform technologies (mRNA, non-replicative vector-based, subunit VLP) have not been authorised to date. In addition, no vaccine has ever been developed and authorised to protect humans against any of the seven known coronaviruses that cause disease in humans, including SARS-CoV-1, MERS and SARS-CoV-2 that cause severe disease.

The Commission Communication on [“Preparedness for COVID-19 vaccination strategies and vaccine deployment”](#) underlines that developing and swiftly deploying safe and effective vaccines against COVID-19 remains an essential element in the management of and eventual solution to the COVID-19 pandemic. It stressed that safety; quality and effectiveness are fundamental requirements for any vaccine, or medicinal product, to reach the EU market. Thus, whilst the need for a vaccine is urgent, the safety requirements for COVID-19 vaccines remain as high as for any other vaccine in the EU. Once authorised, safety and the effectiveness of vaccines should be monitored. As part of the monitoring, public authorities responsible for vaccination programmes are usually conducting such studies.

This Communication also announced that the European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA), in close collaboration with the Commission, Member States, European and international partners are establishing enhanced vaccine effectiveness, coverage, safety and impact monitoring activities specifically for COVID-19 vaccines. This includes the development of a structured post marketing monitoring platform for vaccines, including COVID-19 vaccines.

Outcomes and type of studies

Performance of new vaccines is expected to be monitored carefully when they are rolled out in larger populations, including to populations that have not been included in the phase 3 trials that served as the basis for EU authorization. Several stakeholders beyond the vaccine developers, such as regulatory agencies, public health agencies, ministries of health and NITAGs have largely similar post-authorisation data needs, which then may be used for different monitoring purposes and can be listed as follows:

1. Vaccine coverage /exposure

There is a need to prepare ahead of the upcoming large COVID-19 vaccination campaigns. Unfortunately, less than half of the EU/EEA MS have electronic immunisation registries. For vaccine monitoring studies (addressing immunogenicity,

safety, or effectiveness), validation of vaccine product and batch number will be necessary and must be made available in settings where studies will be conducted. Documentation of vaccination in individuals and at population level will be needed in all MSs and barcodes to facilitate such documentation are expected, according to EMA. Reporting of coverage/exposure data by age and other target groups to public health and regulators at

the EU-level will support evaluation of impact of vaccine recommendations made by National Immunisation Technical Advisory Groups (NITAGs) or equivalent advisory groups. It would also serve as denominator should a vaccine safety signal occur in e.g. observed versus expected analyses of known medical entities.

2. Immunogenicity (short- and long-term)

Assessment of immunity during clinical trials should be followed by monitoring of duration of immunity over time by vaccine product. Over time, also identification of correlates of protection will hopefully be acquired utilising both standardised antibody and T-cell immunity assays.

3. Safety

Following clinical trials, safety should be assessed through routine, enhanced and active surveillance by vaccine product. Mobile apps may serve as modern helpful tools and complement earlier study tools, including monitoring through telephone or letters. Possible adverse events of special interest (AESI) should be monitored. These can include known complications to natural COVID-19 disease, or known possible adverse events following immunisation such as anaphylaxis. Preparedness for assessment of possible vaccine safety signals should be in place (either among one of the pre-specified AESI or an entirely new safety signal) as well as requests from affected individuals on compensations. Safety may also need to be monitored carefully if booster doses are required and soon comparative safety studies will be of great interest to programme managers.

4. Effectiveness

Vaccine effectiveness is commonly assessed in observational studies. These studies will be key to understand if the authorised vaccines provide protection against severe disease in the vaccinated individual or also provide protection against transmission in the population. Different study designs and study populations will be needed for these two research questions and are currently under discussion. Study designs that are under discussion are cohort studies, case-control studies, self-case control studies, case-cohort, case-crossover that can be prospective or retrospective. Study populations under discussion are health care workers, staff and residents in long-term care facilities, hospitalised COVID-19 patients and controls, and outpatients with COVID-19 and their controls. Finally, comparative effectiveness studies will also be of great interest to programme managers.

5. Vaccine acceptance

The success of the immunisation programmes are dependent upon high vaccine uptake/ acceptance. In recent surveys conducted by [IPSOS](#) vaccine hesitancy has been reported up to approximately 40% among survey participants. More information on vaccine hesitancy is forthcoming from the 2020 EU-wide survey of the Vaccine Confidence Project and a behavioural insight study currently conducted by the Joint Research Centre. Reasons for low uptake must be better understood.

The importance of multi-county studies

Studies mentioned above are likely conducted at the national level. However, multi-country studies using the same study protocols, case-definitions and case report forms would enhance safety-monitoring activities. Any new post-marketing information centrally collected, identified and evaluated can ensure that appropriate regulatory actions are taken in a timely manner to protect patients and safeguard public health.

If possible, application of ethical approvals for studies to be conducted in all EU MSs are recommended should a need arise since epidemiology of the COVID-19 outbreaks may

guide the geographical setting for conduct of in particular vaccine effectiveness studies. Time to the initiation of a study could then be shortened significantly.

The role of the EU/EEA NITAG Collaboration network

The [EU NITAG COLLABORATION](#) is organising a series of webinars to discuss options for prospective and retrospective study designs and study populations. It is possible that several study designs will be recommended due to biases affecting all study designs. Studies assessing the first year of vaccination when priming an immune response will be initiated and studies that will assess duration of immunity and subsequent need for booster doses and safety upon revaccination will be equally important for policy-recommendations by EU/EEA NITAGs. Germany has offered to conduct a living systematic review of the literature starting 2020 and a working group with experts from approx. 10 EU/EEA MS will be created under the EU/EEA NITAG COLLABORATION to monitor the results. However, reviewing the evidence in the scientific literature is dependent upon scientifically sound studies having been conducted and reported.

ECDC's current plans for monitoring of COVID-19 vaccines

A small study on vaccine effectiveness is planned by ECDC and will include building of an infrastructure of settings capable to conduct studies as well as study protocols.

For this highly unusual situation with many new vaccines and many different age and target groups, including health care and front-line workers, individuals 70+ and other identified risk groups for severe disease in the initial phase of roll out, it is essential to conduct studies to inform public health, regulators and the public. Careful statistical analysis of sample size is needed to provide *product-specific safety and effectiveness* that should be the basis for assessments of these new vaccines and their use short- and long term. There are no shortcuts to be made since many view this virus to be here to stay in the human global population.

Questions to the Health Security Committee:

1. Is your country planning national / sub-national studies to monitor the safety and effectiveness of (a) COVID-19 vaccine(s), once available?
2. If yes, what kind of study/studies are you planning and what will you monitor?
 - a. Vaccination coverage
 - b. Vaccine acceptance
 - c. Safety
 - d. Effectiveness
 - e. Immunogenicity
 - f. Other things
3. Are you interested to participate in multi-country studies that would be coordinated by ECDC and EMA?