



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Deputy Executive Director

Dear François,

EMA would like to thank EURORDIS and EPF once again for the suggestion to hold a public stakeholder meeting on the development and authorisation of safe and effective COVID-19 vaccines in the EU. We are very pleased to hear that you found it useful.

Thank you for the questions collected from discussions between EURORDIS and the European federations. These highlight the importance of providing adequate information to the public and patients with pre-existing diseases, and of understanding the concerns of the rare disease community on the uncertainties around the use of COVID-19 vaccines in groups of patients not included in clinical trials.

We understand that the rare disease community may have many questions regarding the use of the upcoming COVID-19 vaccines. In particular, rare disease patients at high risk of COVID-19 want to understand how these vaccines could impact their pre-existing conditions or interact with other ongoing treatments. As you know, EMA is evaluating these vaccines and will provide recommendations for use in the prescribing information on the basis of the clinical studies done so far. The Agency has concluded the approval of the first vaccine ([Comirnaty](#)) on Monday 21 December 2020 and the second vaccine ([COVID-19 Vaccine Moderna](#)) on Monday 6 January 2021 and the full product information has been published for both.

While in a regular context the inclusion of rare disease patients in trials may be limited, in the current emergency context, and with vaccines being developed using new technologies, it is expected and understandable that trials have first focused on more homogenous populations and have avoided exposing the most vulnerable patients to an experimental treatment. This will mean that it is likely that there will be limited data in some of the disease-specific settings that you mention, and data will only emerge following authorisation as the vaccines are used in the general population. Bearing all this in mind, we have tried to address your questions below.

We agree on the relevance of the points you raise, and in addition to our exchange, we would suggest that EURORDIS raises these important aspects with relevant bodies responsible for deciding vaccination policy and prioritisation at national level.

Your question:

1. Different age groups

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Vaccines should first be authorised for adults, then data will be available for adolescent from 16 to 18 years of age, and then for younger citizens. It would be important to provide families with estimated timelines on when results in younger age groups will be available to the EMA COVID-19 Task Force, and when the CHMP could extent the indication to these age groups.

Some adults living with a rare disease might opt to defer the vaccination for some reasons explained below, but to protect them, it could be important to propose the vaccine to their children, when available.

EMA response:

At present it is not known whether and when vaccines will be authorised for use in children. Some currently ongoing trials are enrolling some adolescents. In general, the use of COVID-19 vaccines in children will be investigated once there is sufficient information from studies in adults and in adolescents above 16 years of age.

EMA's Paediatric Committee (the PDCO) can grant deferrals of studies in paediatric investigation plans ([PIPs](#)) for some medicines. Deferrals allow a company to delay development of the medicine in children until, for instance, there is enough information to demonstrate its effectiveness and safety in adults. Even when studies are deferred, the PIP includes details of the paediatric studies and their timelines. The PIPs for each vaccine will be published and will include these timelines. Existing PIPs are linked below:

- The date of completion of the [PIP for Pfizer-BioNTech BNT162b2](#) is July 2024
- The date of completion of the [PIP for Moderna \(mRNA-1273\)](#) is December 2024

Your question:

2. Housing as a variable in COVID-19 vaccine trials?

Prioritisation should recognise that a healthy older person who can shelter in place is at different risk from a medically vulnerable older person in crowded housing. It would be important to analyse the efficiency of the vaccines in different settings.

EMA response:

EMA is not involved in setting priority groups for receiving the vaccine. These are under the remit of the relevant national authority, who will consider many factors including the need to protect groups of people at higher risk. As mentioned earlier, we would recommend EURORDIS to address this with the relevant body setting immunisation policies in the member state of interest.

The safety and efficacy of the COVID-19 vaccines are studied in different populations, including different age groups, ethnicities and genders as well as different co-morbidities. The effect of different environmental settings as such has not been specifically addressed, although some trials have enrolled individuals at higher risk of exposure to the virus, such as health care workers.

Studies in specific populations not sufficiently included in trials and longer-term studies will continue after authorisation, as for all medicines. Post-authorisation observational studies of effectiveness will show how well the vaccine works in real-life settings (i.e. outside the controlled setting of clinical trials) and on specific populations, such as in people with certain diseases or living in long-term care facilities for example, which could provide useful information with respect to your question.

Your question:

3. Clinical trial protocols and COVID-19 vaccines

Patients who participate in clinical trials to test an experimental product for their disease: are sponsors of these trials encourage to address the possibility to use the vaccine for all trial participants who would be eligible for the vaccination? Usually authorised concomitant medications are strictly defined in the trial protocol.

EMA response:

The gold standard for demonstrating efficacy and safety of a new vaccine is a randomised placebo-controlled study, which means that half of the study population should receive a saline solution that mimics the vaccine. In this way people won't know what they are getting, and the results are thus more robust. This is required by regulatory authorities worldwide.

After efficacious products are authorised, it may be difficult to continue to conduct studies with a placebo arm for similar medicines for ethical reasons, because individuals would be deprived of a potentially lifesaving medicine.

In the case of COVID-19 vaccines, this is an important consideration. Marketing authorisation holders of authorised vaccines whose trials are still ongoing are bound to offer the vaccine to the initial placebo recipients. This would lead to unblinding of the study subjects, which means that it will be difficult to continue to collect the data as planned in the study protocols until the study end.

It is not mandatory to conduct studies on concomitant administration of COVID-19 vaccines with other medications or with other vaccines before authorisation, as this would delay authorisation. However, these studies are planned to be conducted after authorisation. They will provide information on potential immune interference among co-administered vaccines or issues with safety or reactogenicity.

Your question:

4. The need for comparative information leaflets

Some expressed concerns about a supposed "collusion between the pharmaceutical industry and governments", and other interests than public health would prevail. EURORDIS does not subscribe to this theory, and stresses the importance to be able to choose between different vaccines, after discussing the different options with your own doctor, instead of a mandatory vaccination campaign with one product only. This might not be in the remit of the EMA, however it could be useful to publish a comparative information leaflet, that would combine the elements of the different package leaflets.

EMA response:

Many different types of vaccines for COVID-19 are under development and it is expected that some would be more suited to certain populations. We agree that it would be desirable if patients, including those in the rare disease community could choose among different options. This however is not within EMA's remit and is something we would advise EURORDIS to discuss at national level with bodies responsible for immunisation policy.

Medical advice regarding a choice between the different available vaccines should be made in consultation with the healthcare professional who knows the medical history of the patient and is therefore best placed to provide advice. In addition, the risk of exposure to COVID-19 disease will probably be taken into account. The prescribing information and package leaflet, which are approved as part of the marketing authorisation, are useful to support this decision and consultation.

As for other medicines, EMA will not be able to provide a comparative information leaflet as part of the marketing authorisation. It is not in the remit of the EMA to perform comparative analysis across medicinal products, however this can be done by public health bodies at national or European level.

Your question:

5. Adenovirus used as viral vector

Among different vaccine candidates, some use the viral vector technology, based on an adenovirus. If the same adenovirus is used as the vector for gene therapies to treat some rare diseases, is there a risk to induce an immune reaction to the adenovirus that could make the future use of a gene therapy, using an adenovirus as a vector, ineffective?

If this risk exists, should it be mentioned in the package leaflet of the vaccine in question, and should healthcare professionals and relevant patient organisations be part of a communication campaign about this risk, for example in haemophilia?

Same for patients who used a gene therapy based on an adenovirus already, when they will envisage a vaccine against COVID-19, some clear information should be made available.

EMA response:

We cannot provide definitive answers at this stage because the assessment of the first 2 COVID-19 vaccines based on adenoviral vectors is currently ongoing. The risk of developing immune responses against the vaccine vector is under consideration and will be discussed in light of the available evidence. Theoretically such immune responses might affect how well people may respond to subsequent doses of the vaccine. If such a risk is found, it will be adequately reflected in the EPAR documents. Any contraindications, special warnings or undesirable effects will also be detailed in the prescribing information and package leaflet.

Knowledge on use of adenovirus-based vaccines is also available from other adenovirus-based vaccines currently authorised in EU, most recently the Ebola vaccine Zabdeno. In that context, pre-existing immune responses against adenovirus type 26 (Ad26) used in Zabdeno were assessed in several clinical trials, and in the UK and US studies antibodies were present in few participants (3% - 13%), at low titres, prior to vaccination. Such pre-existing immunity was found not to have any impact on the Ebola-specific antibodies and cell-mediated responses triggered by the vaccine.

EMA is evaluating COVID-19 vaccines in the context of a conditional marketing authorisation. This has all the safeguards and controls in place to enable thorough post-authorisation safety monitoring through the collection of additional data in a planned manner. Such safety monitoring will take place more frequently and will include activities that apply specifically to COVID-19 vaccines. Companies for example will provide monthly safety reports in addition to the regular updates required by the legislation and conduct studies to monitor the safety and effectiveness of COVID-19 vaccines after their authorisation. In addition, [independent studies](#) of COVID-19 vaccines coordinated by EU authorities will give more information on the vaccine's long-term benefit and safe use.

Your question:

6. Definition of vulnerable populations

Different vulnerability levels will probably guide the prioritisation of people to vaccinate.

Age is certainly a criteria that will help define the most at risk populations in whom the initial benefit/risks will be positive with no dispute.

The number of conditions also increases the risk of being hospitalised.

Therefore, all organisations representing rare diseases are questioning whether the people they represent should be defined as vulnerable groups who should be vaccinated soon, or very soon.

Even when not immediately described by one of these conditions, risks could be increased. For example, people with Osteogenesis imperfecta have restricted pulmonary functions (due to scoliosis and shape of the rib cage), so if infected with the coronavirus, the disease might be worse than a normal person.

EMA response:

As mentioned, EMA is not involved in decisions on prioritisation of groups for vaccination. For patients with certain conditions, the risk of developing serious complications with COVID-19 may be increased. Unfortunately, there may not be comprehensive knowledge of the course of COVID-19 in patients with rare diseases and we recommend following the recommendations provided by national authorities and healthcare professionals. It would be logical to apply a precautionary principle when taking clinical decisions, for example for very fragile or vulnerable patients the prescriber will need to consider the benefits and risks of vaccination versus the individual risk of contracting COVID-19 disease.

Your question:

7. Rare epilepsies

As fever seems to be a common side effect to all COVID-19 vaccines, and fever can trigger seizures in patients with rare or common epilepsies, appropriate and close monitoring of this side effect might be needed for this group as part of the pharmacovigilance activities

For Dravet syndrome in particular, one question is about vaccines using the mRNA technology, and to which extend this could interfere with antisense therapies also based on the mRNA technology.

EMA response:

Many patients with rare diseases, such as Dravet syndrome, will not have been specifically studied in COVID-19 vaccine clinical trials. There is also no data available on whether mRNA vaccines might potentially interfere with mRNA therapies. It would be important to highlight all these concerns to the healthcare professional/prescriber to ensure the patient's specific conditions can be taken into account.

Fever is a side effect of the authorised COVID-19 vaccines. Once a vaccine is authorised and starts to be used in the general population, additional data will be generated on the vaccine's side effects, as well as long-term safety and benefit, both via safety studies and enhanced safety surveillance. This will help further informing on the side effects and use in special populations.

Your question:

8. Medical conditions or treatments excluded from the phase III vaccine trials

Hereditary Haemorrhagic Telangiectasia (HHT), rare cancers, immune deficiencies, lupus: blood transfusions and immuno-suppressant are standard of care. Will patient need to stop their treatments before receiving the vaccine, and how long before? When can they resume their treatments safely? Would the recommendation apply to all vaccines equally?

Non-Hodgkin lymphomas in general or Waldenström are other groups that were excluded from phase III trials.

HHT: One clinician wanted to know if there are any specific measures on patients treated with bevacizumab since it could lead to an immunosuppression.

The same questions for Auto-inflammatory diseases: is there a need to stop anti-inflammatory treatment before? How long before, when can they be started again?

Rare cancers, melanomas: trials explicitly excluded people with a history of cancer, therefore no data about how effective and safe the vaccines are in people with any kind of e.g. (rare) melanoma. Immunotherapy is a treatment modality that is being used on rare melanomas and although immune checkpoint inhibitors do not cause immunosuppression, they can cause immune-related adverse effects in organ systems. This could constitute a risk regarding vaccination-related complications.

EMA response:

The efficacy, safety and immunogenicity of the COVID-19 vaccines so far authorised have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of a vaccine may be lower in immunosuppressed individuals. However, although immunocompromised people may not respond as well to the vaccine, there are no particular safety concerns for the authorised vaccines.

As we have noted, there is limited data in many disease-specific settings. We would refer patients with specific diseases to the product information of each vaccine. EMA cannot advise on the management of specific pathologies beyond the information which is available in the product information.

In addition, questions on clinical practice are outside the remit of EMA. Since many rare disease patients will not have been sufficiently studied in clinical trials, it is important to highlight all these concerns to the healthcare professional/prescriber to ensure specific conditions can be taken into account. Questions concerning patient's current treatment for existing conditions, whether they should stop before vaccination or when to resume should be discussed with their healthcare professional based on the information in the product information and in line with available advice at national level.

Your question:

9. Transplanted patients

In many rare diseases, patients benefit from transplanted organs, and take immune-suppressant treatments to prevent organ rejection. Some expressed clear concerns that patients will not immediately consider a vaccine.

EMA response:

Transplanted patients were not included in clinical trials of COVID-19 vaccines. Studies in specific populations not included in trials may be conducted after authorisation, including in ongoing and planned safety studies and observational effectiveness studies.

Your question:

10. Neurological diseases

In the past, some concerns were shared by a large part of the population and by many healthcare professionals on the possible neuro-toxicity of some vaccines, e.g. vaccine for Hepatitis B infection. Even if these risks were further analysed and finally, the perception prevails in the population.

Are specific monitoring measures planned for patients with neurological diseases, to characterise these risks, or the absence of risks?

People who had an episode of Guillain Barre syndrome for example often renounce to vaccines, and struggle to access the information they need.

EMA response:

This has been brought to the attention of EMA's safety committee (the Pharmacovigilance Risk Assessment Committee, PRAC) for consideration during assessment of the Risk Management Plan (RMP).

Safety data will be collected through spontaneous systems and observational studies, both of which will allow for stratified analyses, detailed in EMA's [Pharmacovigilance plan](#) for COVID-19 vaccines.

Your question:

11. Haemophilia(s)

The Federation indicated some information people with haemophilia will need:

Warnings about people with bleeding disorders to alert on the possibility of an intramuscular haematoma. One measure could be to recommend applying pressure or giving factor replacement coverage to prevent bleeding

People with bleeding disorders should still be vaccinated according to their priority group (based on age, co-morbidities and healthcare work)

The vaccine should be administered with a thin needle and very slowly

Having a bleeding disorder should not be a contra-indication to receiving the COVID-19 vaccine.

Any vaccines using AAV can trigger AAV immunity and should only be given to patients who are informed about, and consent to the risk of never being eligible for AAV-based gene therapy

EMA response:

There are no contraindications for the COVID-19 vaccines authorised so far except for hypersensitivity to the active substance or to any of the excipients.

As with other intramuscular injections, the authorised vaccines should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

The Agency is not be able to advise on the management of specific pathologies such as haemophilia beyond the information which is available in the product information.

Also questions on clinical practice are outside the remit of EMA. Since many rare disease patients will not have been sufficiently studied in clinical trials, it would be important to highlight all these concerns to the healthcare professional/prescriber to ensure specific conditions can be taken into account.

We look forward to updating the public with information on COVID-19 vaccines and treatments as it becomes available, through the unprecedented transparency measures we have put in place, and wish to underline again our commitment to public health measures based on scientific evidence and to playing our role in combatting the devastating pandemic crisis.

Yours sincerely,

Melanie Carr

Head of Stakeholders and Communication