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**Summary of the view of all ERNs on priorities and contra-indications for COVID-19 vaccinations**

2021 will be marked by the vaccination programs against SARS-CoV-2. Currently, various Member States are setting priorities in the vaccination programs for specific groups of patients, including those with rare diseases. On the other hand, there are some rare disease patients for whom vaccination can be contraindicated.

As European Reference Networks (ERNs) are formed by experts in rare diseases, we asked all ERNs to provide their opinion on the priorities and contraindications for patients with a rare disease within their network. The results are summarized in this document and were discussed during the internal ERN-Coordinator group meeting of January 27th, 2021.

First of all, we advise that the general recommendations of the EMA regarding new medicines need to be followed. Unfortunately, the recommendations below will not be complete, and only apply to the adult population. Moreover, these recommendations are based on the expert opinion as evidence is lacking for the majority of rare diseases. When evidence is available this is mentioned in the statement. It is very important that evidence is gathered regarding rare disease patients in the vaccination program, even better will be to set up clinical trials.

This expert opinion-based document with recommendations for adults only, can be no more than a start with the ultimate goal to have a complete overview of recommendations within the years to come, and therefore will need very regular updates. Up to date positions will be available on the websites of many ERNs.

**Rare disease patients with priorities for COVID-19 vaccination:**

**Related to respiratory problems:**

- Patients with a rare disease of the respiratory system, such as alpha-1-antitrypsin-deficiency, pulmonary hypertension, Interstitial lung diseases, especially in those with severe manifestation of the disease and with impaired pulmonary function.
- Patients with upper airway obstructions that require respiratory support (CPAP, BiPAP, tracheostoma etc): specifically, Apert, Crouzon and Pfeiffer syndrome, facial dysostosis (e.g. Treacher Collins, Nager and Miller syndrome), Robin sequence, laryngeal and tracheal cleft and stenosis.
- Patients with rare neuromuscular diseases with respiratory compromise due to weak respiratory muscles and/or deformities of the chest wall or upper airways; and patients with rare bone diseases affecting chest wall abnormalities consequently causing respiratory insufficiency.

**Related to Cardiovascular problems:**

- Patients with primary arrhythmia syndrome and a history of symptomatic arrhythmias, including patients with Brugada syndrome.
- Patient with cardiomyopathy (or congenital heart disease) and risk factors (reduced left ventricular systolic function, heart failure, NYHA III/IV or pulmonary hypertension).
- Patient who carry a (probable) pathogenic variant in the cardiac sodium channel gene SCN5A.
- Patients with collagenopathies which cause cardiovascular complications.

**Related to immunodeficiency or cancer:**

- Patients with rare cancer within 2 years after diagnosis.
- Patients with treated haematological malignancies, starting by those who received allogeneic hematopoietic stem cell transplantation (after engraftment) or patients with comorbidities, and older patients (>65years).
- Patients on immunosuppressive therapy and advanced chronic kidney disease.
- Patients being planned or after solid organ transplantation or chronic allograft dysfunction.
- Patients with disorders of calcium and phosphate complicated with hypocalcaemia and/or chronic renal disease and/or immune deficiency.
- Patients with APECED/APS1 or auto-immune poly endocrinopathy type 1.
- Patients with auto-immune blistering diseases (AIBD) as they use high dosages of corticosteroids and immunosuppressive drugs, which highly increase risk and severity of infection by COVID-19.
- Patients affected with chronic haemolytic anaemia with splenectomy.

**Related to endocrine diseases:**

- Patients with primary hyperaldosteronism.
- Patients with Cushing's syndrome: comorbidities (hypertension, diabetes mellitus) with shown increased risk for severe course of COVID-19.
- Patients with adrenal insufficiency (all kinds of adrenal C14 Addison's, CAH, SAI): In general we **do not** consider patients with adrenal insufficiency being at higher risk for COVID-19 or at a particular risk for a severe course of COVID-19. But as patients with adrenal insufficiency are at a higher risk of mortality in case of infections due to the additional risk of adrenal crises, we agreed that they should be one step up in the priority list for vaccination and get the respective certificates.
- In general, patients with rare thyroid disorders should **not prioritized**. Exceptions to this advice are patients which are severely debilitated, such as patients with MCT8 deficiency and severe forms of RTH-alpha.

**Other Rare Disease patients:**

- Patients with Rare Eye Diseases as they are at higher risk to be contaminated by the COVID-19 virus in daily life, as they cannot apply barrier gestures.
- Patients with advanced liver cirrhosis.
- Patients affected by amino and organic acids-related disorders (AOA).

- Patients affected by disorder of pyruvate metabolism, Krebs cycle defects, mitochondrial oxidative phosphorylation disorders, disorders of thiamine transport and metabolism (PM-MD).
- Patients affected by carbohydrate, fatty acid oxidation and ketone bodies disorders (C-FAO).
- Patients affected by lysosomal storage disorders (LSD).
- Patients affected with haemoglobin disorders as sickle cell disease or thalassaemia major / intermedia with comorbidities.
- Patients with systemic forms of epidermolysis bullosa and skin fragility diseases.
- Patients with cutaneous Auto immune Bullous diseases (Pemphigus, Pemphigoid) (Joly P et al. J Am Acad Dermatol (under publication)).
- Women with incontinentia pigmenti are at risk for severe COVID-19 infection, as 25% of them have high concentrations of autoantibodies directed against type I interferons, causing a more severe (resuscitating) form of COVID-19 (Bastard et al. Science. 2020 Oct 23;370(6515):eabd4585).
- Patients with difficult-to-treat epilepsies are at higher COVID-related risks than the general population, independently of its underlying aetiology. This opinion is based on the (small) case series on COVID-19 and epilepsy, showing that people with epilepsy appear to have more often COVID-19 infections and that outcome is worse (Cabezudo-García et al. Neurology. 2020 Sep 8;95(10):e1417-e1425) and that people with epilepsy suffer more frequently from pneumonia (standardized mortality ratio 6.6; Neligan et al. Brain. 2011 Feb;134(Pt 2):388-95).

**Others related to rare disease patients:**

- Parents or guardians of children undergoing intensive chemotherapy and / or stem cell transplantation.
- Parents or guardians of new-borns with a congenital malformation.
- Parents or guardians of children with autoimmune disorders receiving intensive immunosuppression.
- Family members of children with congenital or acquired immunodeficiencies.
- Parents or guardians of children who are hospitalised for a long period of time.

**Contra-indications for COVID-19 vaccination:**

Almost all ERNs indicated that none of rare diseases included within their ERN have a contra-indication for COVID-19 vaccination. The exceptions are listed below:

- Patients with rare neuromuscular diseases who may have an option with AAV9 treatments should avoid AAV virus mediated vaccines.
- In general caution should be taken with patients involved in gene therapy trials.
- Some patients participating in clinical trials may have contraindications dependent on the kind of clinical trial.
- Please note that COVID-19 vaccines neither are tested for the paediatric age group nor are vaccinations recommended in the paediatric age group undergoing intensive chemotherapy or allogeneic haematopoietic stem cell transplantation for reasons of lacking or incomplete immune response.

We would like to ask you to consider our expert opinion in setting priorities in the vaccination program of COVID-19. We will be happy to discuss this summary during one of the meetings of the Health Security Committee. Although we realise that this document is incomplete, we do wish that it can be of help.

Yours sincerely on behalf of all ERN coordinators,

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