Joint statement on the current coronavirus pandemic

SARS-CoV-2 — COVID-19 in children and adult patients with

Primary Immunodeficiencies (PID)

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5th update as of 2021, 28 October)

Recent updates are highlighted in yellow.

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Coronavirus

In December 2019, a cluster of pneumonia cases was reported in Wuhan, Hubei Province, China, linked to a novel coronavirus (SARS-CoV-2, leading to COVID-19 disease). Coronaviruses are common in many different animal species and it is rare that they infect people and spread between them, but it happens. Recent examples include Severe Acute Respiratory Syndrome (SARS-CoV-1—CoV, for coronavirus), and Middle East Respiratory Syndrome (MERS-CoV). The SARS-CoV-2 is distinct from the previous two coronaviruses and causes COVID-19 disease.

Current situation

The situation is constantly changing, and we encourage you to monitor the latest advice applicable to your area.

Visit the COVID-19 Dashboard from Johns Hopkins University for the latest global data.

The spread and severity of this viral outbreak has been met by a fast comprehensive, and collaborative response from the public and private health sectors. Beside the virus itself, and the development of multiple variants one of the biggest threats is the overwhelming of the healthcare systems/hospitals due to the rapid spread and severe forms of COVID-19 as well as the difficulty in many countries to access vaccination and the lack of herd immunity in the general population.

Transmission

The transmission mode of COVID-19 is similar to previous coronavirus outbreaks, spreading from person to person through:

- Liquid particles spreading when coughing, sneezing, speaking, singing or breathing heavily. These particles can vary in size from larger respiratory droplets to smaller aerosols.
- Close personal contact with an infected person (shaking hands or touching)
- Touching contaminated surfaces and then touching eyes, nose or mouth with unwashed hands.

SARS-CoV-2 RNA has been detected in faeces, blood, serum, saliva, nasopharyngeal specimens, urine, ocular fluid, breast milk and in placental or fetal membrane samples.[1] Findings have also demonstrated that children may release virus in the stools up to 15 days after recovering from COVID-19. This means that keeping distance, cough etiquette and frequent hand washing should be applied even after clinical recovery.

The incubation period for COVID-19 is currently estimated to range from one to fourteen days, with a median incubation period of five to six days. The onset and the duration of viral shedding

[1] European Centre for Disease Prevention and Control. Infection. 10 August 2020. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/infection [Accessed 27-11-2020].]

is not yet fully established, but reports show that the virus has been identified in respiratory specimens a few days before demonstrated symptoms (pre-symptomatic), peaking in the second week after infection (day 3-6 after onset of symptoms). A high viral load close to symptom onset points to SARS-CoV-2 being easily transmissible early in the infection. So far, reports do not demonstrate a significant difference in viral load in asymptomatic and symptomatic patients, indicating the potential virus transmission from asymptomatic patients.[2] Further studies are needed to establish their role in transmission.

A small number of cases of animals testing positive to COVID-19 after contact with infected humans have been reported. It is recommended that people who are sick with COVID-19 and people who are at risk limit contact with animals. When handling and caring for animals, basic hygiene measures should always be implemented.[3]

Clinical symptoms due to COVID-19 infection

Human coronaviruses commonly cause mild to moderate illness in the general population. So far, the main clinical signs and symptoms reported in this outbreak vary from no symptoms at all to fever, fatigue, dry cough and runny nose. Some patients also experience aches and pains, myalgias, nasal congestion, sore throat and/or diarrhea. Reports also demonstrate transient loss of taste and smell. These symptoms are usually mild and begin gradually. Approximately 80% of the affected people recover from the disease without needing any special treatment. About 15% become seriously ill and require oxygen, with 5% becoming critically ill and needing intensive care.[4]

A SARS-CoV-2 infection is often divided into three phases (I: Early infection, II: Pulmonary phase, III: Hyperinflammation phase), with a minority of the patients transitioning to the third phase. Severe COVID-19 cases may progress to acute respiratory distress syndrome (ARDS) as a result of an aggressive inflammatory response, a cytokine storm, (mimicking hemophagocytic syndrome) during phase III, for which transfer to intensive care unit (ICU) for non-invasive (face respiratory mask) or invasive (mechanical artificial ventilation) might be needed. Thus, the severity of the disease is not only due to the virus itself, but to the hyperinflammatory response to the infection.[5] This usually occurs after 6 to 10 days.

It has been reported that evolution to a more severe stage of the disease, requiring urgent medical care, can be very rapid (within a few hours).

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[2] European Centre for Disease Prevention and Control. Infection. 21 September 2021. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/infection [Accessed 28-10-2021]

[3] Centers for Disease Control and Prevention. What You Should Know about COVID-19 and Pets. 18 October 2021. https://www.cdc.gov/healthypets/covid-19/pets.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fdaily-life-coping%2Fpets.html [Accessed 28-10-2021]

[4] World Health Organization. Coronavirus disease (COVID-19). 13 May 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19 [Accessed 28-10-2021].

[5] Tay, M.Z, Poh, C.M, Rénia, L. et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol (2020). 28 April 2020. Available at: https://doi.org/10.1038/s41577-020-0311-8

Some patients suffering from a more severe course of the infection have also developed thrombotic complications. In addition to this, cardiac damage (cardiomyopathy), acute kidney injury (AKI), encephalitis and skin vasculitis have been reported. Most people fully recover, but some patients might experience sequelae. There have also been reports of patients suffering a complete or partial permanent loss of smell and taste, chronically impaired lung function and neurological sequelae such as encephalopathy, and acute ischemic stroke.[6]

Studies have shown that specific antibodies against SARS-CoV-2 are generated after a COVID-19 infection, but further research is needed to establish if this will result in long-term immunity. [7] However, based on experiences from MERS-CoV and SARS-CoV-1 (previous coronaviruses), it is possible that patients who recover from SARS-CoV-2 will develop long-term, but not life-long, antibodies.

Long-term symptoms

Although most people recover well from a SARS-CoV-2 infection, some individuals experience a range of post-COVID symptoms that can last weeks or months after first being infected. Long term COVID can happen to anyone who has had COVID-19, even if the illness was mild, or if they experience no symptoms at all. People with long COVID-19 report different combinations of the following symptoms: tiredness or fatigue, difficulty concentrating or thinking, headache, loss of smell or taste, dizziness, heart palpitations, cough etc.[8] More research is needed to identify how common these long-term effects are, and how these symptoms will evolve over time.

Variants

Multiple variants of the SARS-CoV-2 are circulating globally. All viruses evolve over time and when they replicate, they sometimes mutate into a new variant of the original virus. This is more likely to happen the more a virus circulates and causes infections in a population. Depending on where the changes are located in the virus's genetic material, they may affect a virus's properties, such as transmission (for example, it may spread more or less easily) or severity (for example, it may cause more or less severe disease).

Stopping the spread at the source remains important. Current measures to reduce transmission – including frequent hand washing, wearing a mask, physical distancing, good ventilation and

[6] European Centre for Disease Prevention and Control. Clinical characteristics of COVID-19. 17 August 2020. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical [Accessed 05-05-2021].

[7] Long, Q., Liu, B., Deng, H. et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 29 April 2020. Available at: https://www.nature.com/articles/s41591-020-0897-1 ; Xiang F, Wang X, He X, et al. Antibody Detection and Dynamic Characteristics in Patients with COVID-19.19 April 2020. Clin Infect Dis. Available at: https://pubmed.ncbi.nlm.nih.gov/32306047/

[8] Centers for Disease Control and Prevention. POST-COVID Condition. 6 September 2021. Available here: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html#:~:text=Long%20COVID%20is%20a%20range,or%20they%20had%20no%20symptoms. [Accessed 28-10-2021].

avoiding crowded places or closed settings – continue to work against new variants by reducing the amount of viral transmission and therefore also the opportunities for the virus to mutate. [9]

Multisystem Inflammatory Syndrome in Children (MIS-C)

It has become clear since the start of the pandemic that in rare cases some children suffer from a post-inflammatory syndrome known as multisystem inflammatory syndrome in children (MIS-C), sometimes requiring intensive care approximately 2-4 weeks after primary COVID-19 infection Patients with MIS-C usually have a history of recent SARS-CoV-2 infection, epidemiologic link, and/or antibody responses demonstrating prior infection. These children frequently had asymptomatic or mildly symptomatic primary infection. While rare, some children have died from MIS-C and the cumulative MIS-C incidence in children is estimated at ~2/100,000 based on a study in the United States[10]. MIS-C has been observed in children around the world, and rates have been observed to increase following COVID-19 surges. The presenting symptoms frequently include fever, abdominal pain, conjunctivitis (redness of the eyes), rash, irritability, headache and in severe cases shock and cardiac involvement [11,12] Treatment is supportive, and may include anti-inflammatory agents such as IVIG and steroids, and other medications to reduce the risk of clotting[13] The syndrome has features similar to Kawasaki disease (KD), but also features of toxic shock syndrome (TSS). Although the number of cases is more limited, similar symptoms have also presented in adult patients[14]. The precise triggers of the exaggerated inflammatory response after COVID-19 have not been identified, and there is no evidence that therapy for acute COVID-19 prevents or increases the risk for MIS-C.

Tests for COVID-19

The test for active SARS-CoV-2 infection usually consists of a nasal (nasopharyngeal) swab, possibly more sensitive than an oral (oropharyngeal) swab or saliva testing. This is sent to a dedicated microbiology laboratory for detection of the virus (by polymerase chain reaction (PCR)

[9] The World Health Organization. The effects of virus variants on COVID-19 vaccines. 1 March 2021. Available at: https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines [Accessed 19-05-2021].

[10] Belay ED, Abrams J, Oster ME et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. JAMA Pediatr. 2021 Aug 1;175(8):837-845. doi: 10.1001/jamapediatrics.2021.0630. PMID: 33821923; PMCID: PMC8025123.

[11] Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). 20 May Accessible: https://www.cdc.gov/mis-c/ [Accessed 26-10-2021].

[12] Wu EY, Campbell MJ. Cardiac Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C) Following COVID-19. Curr Cardiol Rep. 2021 Oct 1;23(11):168. doi: 10.1007/s11886-021-01602-3. PMID: 34599465; PMCID: PMC8486157.

[13] Centers for Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). 20 May Accessible: https://www.cdc.gov/mis-c/ [Accessed 26-10-2021].

[14] Davogustto GE, Clark DE, Hardison E, Yanis AH, Lowery BD, Halasa NB, Wells QS. Characteristics Associated With Multisystem Inflammatory Syndrome Among Adults With SARS-CoV-2 Infection. JAMA Netw Open. 2021 May 3;4(5):e2110323. doi: 10.1001/jamanetworkopen.2021.10323. PMID: 34009351; PMCID: PMC8134998.

method, within a few hours). However, in some cases, a negative PCR does not rule out infection ("false negative"). Efforts are being made to develop additional forms of PCR testing.

The setting for tests may vary from country to country and the availability of health care professionals to perform these tests depend on national circumstances. The waiting time to schedule a test and receive the results may also vary.

Serology tests, i.e. testing through detecting antibodies (IgG and IgM) against SARS-CoV-2 in the blood, are becoming increasingly available. Such tests will reveal whether a person has made a detectable antibody response after being infected with the virus. There are currently various serology tests including some rapid tests being made available online for people to do in their homes, but many of these tests have not been carefully validated and may not be reliable to the highest standards. We recommend only using validated home tests.

Rapid tests including antigenic tests are also increasing available. Their performances may vary from one another but overall they seem to have a higher sensitivity in symptomatic patients. Hence, a negative test should not rule out COVID-19 infection as this is not the gold-standard test.

Another important point is that antibody deficient patients seem to have a higher risk of longer PCR positivity. In this context it should however also be mentioned that PCR positivity may not necessarily mean that the person is still infectious, especially if the CT value is 30 and higher.

Should PID patients get systematically tested for COVID-19?

The situation is constantly changing, and we advise you to follow the latest advice applicable to your area.

For patients with PID who are not able to produce antibodies (such as patients with agammaglobulinemia or other defects of antibody production), serology tests will not be useful. For other forms of PID (including those treated with Ig replacement therapy), this test may also not be of help to assess the patient's response, as immunoglobulin preparations, depending on the date of collection, now contain anti-SARS-CoV-2 IgG.

For PID patients who have tested positive for COVID-19, it is recommended to perform a second screening after the patient has clinically recovered, as it may be that some PID patients, especially patients with a Combined Immune Deficiency (CID), might struggle with clearing the infection. These patients may remain positive longer and risk remaining a source of infection to their environment. On the other hand, it is not clear if PID patients have been tested positive for COVID-19 are able to build a sufficient memory response to protect themselves from recurrent infections.

Treatments

Medicines

The National Institutes of Health provides The Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, offering access to regularly updated information, with systematic review of published results. The World Health Organization also continuously updates a living guideline on Therapeutics and COVID-19.

Use of the antiviral drug remdesivir for the treatment of COVID-19 in adults and children has been approved for use in some countries, however, its efficacy has been contested [15, 16]. We recommend referring to national guidelines for use of this drug.

Dexamethasone is a corticosteroid medication that has been used in different indications for several decades. International RCCTs such as the RECOVERY trial, have shown that dexamethasone plays an instrumental role in reducing mortality and evolution to a severe form of COVID-19.

Additionally, there are a number of human monoclonal antibodies authorised or in development for the treatment of mild-to-moderate COVID-19 in high-risk patients for progressing to severe COVID-19 and/or hospitalisation. See NIH COVID Treatment Guidelines.

Additional drugs and drug combinations are being investigated in randomised controlled clinical trials (RCCTs). Results of these RCCTs should be awaited before a treatment could be recommended.

Plasma derived COVID-19 treatments

Convalescent plasma (plasma with antibodies from recovered COVID-19 patients) is being investigated as a treatment option for seriously ill patients. Results from a PLACID trial in India showed that convalescent plasma was not associated with a reduction in progression to severe COVID-19.[17] In another update from the Cochrane Database Systematic review the researchers were unable to properly assess the efficacy and they remain uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.[18] However, its use in subjects

[15] World Health Organization. WHO recommends against the use of remdesivir in COVID-19 patients. 20 Nov 2020. Available at: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients [Accessed 28-10-2021].

[16] Dyer O. Covid-19: Remdesivir has little or no impact on survival, WHO trial shows. 19 Oct 2020. Available here: https://pubmed.ncbi.nlm.nih.gov/33077424/

[17] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). 22 Oct 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/33093056/

[18] Chai KL et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 12 Oct 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/33044747/

with severe antibody defects and a prolonged course, was associated with clinical improvement and diminished inflammatory markers.[19]

It should also be noted that efforts have been deployed by the plasma industry to accelerate the development of COVID-19 treatments (**hyperimmune globulins**). A group of 10 world-leading global pharmaceutical companies active in the plasma industry have joined together in an attempt to accelerate the development of an unbranded anti-SARS-CoV-2 polyclonal hyperimmune immunoglobulin medicine. In April 2021 the alliance announced that the Phase 3 ITAC did not meet its endpoints. No serious safety signals were raised in the trial.[20]

In addition, other plasma industry companies are also working on similar research programmes.[21]

There are also clinical trials that are studying **high doses (HD) of intravenous immunoglobulin (IVIG)** as a potential treatment for COVID-19. So far there is no conclusive evidence that HD-IVIG is an effective treatment for patients infected with SARS-CoV-2 and more research is needed. Regardless of the outcomes of clinical trials, we emphasize the importance of continuity of Ig replacement therapy for PID patients whose life relies on a continuous life-long and stable supply of immunoglobulins.

COVID-19 clinical trials at a glance

- COVID-19 clinical trials listed on TranspariMED.
- COVID-19 NIH clinical trials registry.
- Living mapping and living network meta-analysis of COVID-19 studies.
- Anticovid

Vaccination

COVID-19 vaccination is an important tool to help stop the pandemic. There are several types of vaccines and all of them aim to prepare our immune systems to recognize and fight the SARS-CoV-2 virus that causes COVID-19. Sometimes this process can cause side effects, but they are generally mild. All COVID-19 vaccines that are in development are being carefully evaluated in clinical trials and will be authorized or approved by European Medicines Agency (EMA) or FDA only if they are able to prevent COVID-19 in the majority of people and if they do not cause major side effects.

[19] Jin et al. Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma. Journal of Clinical Immunology. 15 Sep 2020. Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7490621/

[20] Takeda. CoVIg-19 Plasma Alliance Announces Topline Results from NIH-Sponsored Clinical Trial of Investigational COVID-19 Hyperimmune Globulin Medicine. 2 April 2021. https://www.takeda.com/newsroom/newsreleases/2021/covig-19-plasma-alliance-announces-topline-results-from-nih-sponsored-clinical-trial-of-investigational-covid-19-hyperimmune-globulin-medicine/ [Accessed 28-10-2021].

[21] Grifols. GRIFOLS FACING THE COVID-19 CHALLENGE. 2020. https://www.grifols.com/en/covid-19 [Accessed 06-05-2021]. ; Kedrion Biopharma. KEDRION-KAMADA, ANTI-COVID IG DEVELOPMENT UPDATE. 21 April 2021. https://www.kedrion.com/kedrion-kamada-anti-covid-ig-development-update [Accessed 28-10-2021].

Visit WHO's COVID-19 vaccine development landscape tracker for latest status on vaccines.

Data is also continuously collected to understand the impact on the vaccinations on new viral variants that are circulating. The COVID-19 vaccines that are currently in development or have been approved provide some protection against new virus variants because these vaccines elicit a broad immune response involving a range of antibodies and immune cells.[22]

There are several platforms for how to produce a vaccine such as: Protein subunit, Viral Vector (non-replicating), DNA, Inactivated Virus, RNA, Viral Vector (replicating), Virus Like Particle, VVr + Antigen Presenting Cell, Live Attenuated Virus and VVnr + Antigen Presenting Cell (More info here.)

Some vaccines have been linked to very rare but significant severe side effects (specific form of unusual blood clots with low numbers of platelets in the blood), these include AstraZeneca and Janssen vaccines. In both cases the EMA has stated that "The reported combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects." [23],[24]

Great efforts have been deployed to speed up the vaccine production, however access remains challenging in some world regions. Importantly it should be highlighted that this has not been done at the expense of science. Rigorous quality and safety guidelines are being followed to ensure the production of a safe vaccine.

Vaccination for patients with PID

Disclaimer: The situation is rapidly evolving with regularly updated vaccine recommendations. Patients / care givers should refer to their national/local recommendations and consult their PID expert physician before receiving vaccinations.

Even after full vaccination, people should remain vigilant and continue to follow hygiene guidelines (masks, handwashing etc.) until herd immunity is reached.

Currently, there is not enough validated data to establish the mid-term to long-term efficacy and tolerability/side effects for the approved COVID-19 vaccines in the population, including patients with PID. However, based on the very good tolerability and efficacy in clinical trials in the general population, the general recommendation is that all patients with PID should be vaccinated,

[22] The World Health Organization. The effects of virus variants on COVID-19 vaccines. 1 March 2021. Available at: https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines [Accessed 28-10-2021].

[23] European Medicines Agency. COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 20 April 2021. Available at: https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood [Accessed 28-10-2021].

[24] European Medicines Agency. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 7 April 2021. Available at: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood [Accessed 28-10-2021].

especially those with known risk factors for severe COVID-19 (provided that they are not live attenuated viral vaccines for those in whom these would be contra-indicated). It is also recommended that their close contacts get vaccinated.

Patients who do not respond to vaccines by measurable antibody titers (such as patients with an antibody deficiency including patients with a profound hypogammaglobulinemia or agammaglobulinemia) should still be considered for vaccination, as the vaccines have been shown to activate cellular immunity via T-lymphocytes, which may provide some protection against COVID-19. This principle also applies to patients who received B-cell depleting therapy (such as rituximab).

Patients (including children) with specific PIDs such as: AIRE deficiency (APS1/APECED), NFkB2 deficiency as well as diseases leading to alterations of the type 1 interferon pathways should be highly prioritised for this vaccination. Patients who were infected with SARS-CoV-2 and have now recovered are still recommended to be vaccinated against COVID-19. Current evidence suggests that reinfection is uncommon within 90 days after the initial infection and vaccination may be postponed until the end of this period.

There are also countries where a third dose of a COVID-19 vaccine will be given to a very limited number of immunocompromised patients. To date, this is not a general/common recommendation and patients / care givers should refer to their national/local recommendations and PID expert for advice.

Research on COVID-19 vaccines for patients with PID

A number of studies have been launched with the aim to explore the immune response to natural COVID-19 infection and vaccination in patients with antibody deficiency [25,26,27]. Initial findings have found that most PID patients respond to COVID vaccines, evidenced by the generation of specific antibodies (except in patients with agammaglobulinemia) and T cells. However, the long-term efficacy of the vaccines, and durability vaccine-induced immunity against SARS-CoV2 infection in PID patients, is unknown (same as for the rest of the population).

Unpublished early data also indicates that good results have been observed in Argentina, regarding the Sputnik vaccine in adults and in patients with PID/IEI. They have observed COVID IgG antibodies in some patients, and those who became infected after vaccination did not require hospitalization and presented a moderate evolution without major complications.

[25] University of Birmingham. Study launches to investigate immune response to SARS-CoV-2 infection in patients with antibody deficiencies. 11 May 2021. Available at: https://www.birmingham.ac.uk/news/latest/2021/05/covid-antibody-deficiencies-immune-response-study.aspx?fbclid=IwAR3JtaPKD1CM9R71CFXI3er5d5RO8DqiAW4u-XowVc1gN4rBAVpu6xg5UC8 [Accessed 19-05-2021].

[26] Ottavia M et al. Antibody responses to the SARS-CoV-2 vaccine in individuals with various inborn errors of immunity, Journal of Allergy and Clinical Immunology, 2021, ISSN 0091-6749, https://doi.org/10.1016/j.jaci.2021.08.016.

[27] David Hagin et al. Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in patients with inborn errors of immunity, Journal of Allergy and Clinical Immunology, Volume 148, Issue 3, 2021, Pages 739-749, ISSN 0091-6749, https://doi.org/10.1016/j.jaci.2021.05.029.

Risks associated with COVID-19 vaccines (excl. allergies)

Children: The situation is rapidly evolving with regularly updated vaccine recommendations, including those for children and teenagers. Patients / care givers should refer to their national/local recommendations and PID expert for advice.

Individuals with COVID-19 risk factors (severe chronic lung disease, diabetes, obesity (body mass index ≥30kg/m2), high blood pressure, cardiovascular disease, old age): Until now, phase 2/3 clinical trials of mRNA vaccines have not shown any significant adverse effects in this group.

Immunocompromised persons: See early data on patients with antibody deficiencies [28,29,30]. There is no reason to believe that immunosuppression will promote the occurrence of adverse effects, the problem is rather that the vaccine may be less effective. Additionally, B-cell depleting therapies, mycophenolate, fingolimod, chemotherapy are treatment regimens that influence immunogenicity of the vaccines.

Immunosuppressed people may receive RNA vaccines if they have no contra-indications to vaccination. According to CDC Advisory Committee on Immunization Practices (ACIP; U.S.) and the Joint Committee on Vaccination and Immunisation (JCVI; U.K.) recommendations, patients should be counselled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for reduced immune responses. It is strongly recommended that patients continue preventive anti-infection measures, as the level of protection after vaccination is not known for an immunodeficient individual. In the phase 3 trial of the AstraZeneca/University of Oxford chimpanzee non-replicant adenoviral vector-based vaccine, immunosuppression was an exclusion criterion for participation.

Regarding adenovirus-based vaccines, there might be some degree of immune response against the adenoviral vector that could hamper the specific immune responses to vaccination.

Vaccination and hematopoietic stem cell transplantation (HSCT)

For patients who might undergo a hematopoietic stem cell transplantation (HSCT), there might be a minimum distance between a planned procedure of HSCT and vaccinations in general. The European Society for Blood and Marrow Transplantation has issued a statement mentioning that if the transmission rate in the surrounding society is high, vaccination could be initiated at the earliest three months after HCST.

Patients are recommended to consult their PID expert physician and HSCT expert physician to discuss this matter.

[28] University of Birmingham, 2021.

[29] Ottavia M et al. 2021.

[30] David Hagin et al, 2021.

Precautions

Any respiratory virus that can be spread from person-to-person may be a risk for PID patients. Therefore, PID patients should be cautious and keep track of developments of COVID-19 in their region. Whilst immunoglobulin (Ig) replacement therapy provides protection against a wide range of infections, it does not guarantee immunity against coronavirus. The World Health Organization's (WHO) [31] and the Centers for Disease Control and Prevention's (CDC) [32] recommendations to reduce exposure to and transmission of COVID-19 include, but are not limited to, the list below.

- The MOST IMPORTANT means to prevent infection are:
    - Wash hands frequently (every hour) with hand rub or soap and water for 20 seconds, (if not possible use alcohol-based hand rub), especially after direct contact with ill people or their environment
    - Avoid touching eyes, nose and mouth
    - Avoid close contact (at least 1 meter) with people suffering from acute respiratory infections
    - Avoid close contact (at least 1 meter) with anyone who has fever and cough
    - For extra precaution, avoid close contact (at least 1 meter) with other people when leaving your home
    - Avoid greeting people by shaking hands, kissing or hugging
    - Respect the confinement measures wherever these are applicable

- People with symptoms of acute respiratory infection should practice cough etiquette (maintain distance, cover coughs and sneezes with disposable tissues or clothing, and wash hands) and wear a respiratory mask if instructed by their local health care provider. It is strongly recommended for people with symptoms to get tested.

Additional measures

Masks can be effective if the person wearing one has the appropriate training for a good fitting mask, but if not used appropriately they can pose a risk for contamination. The mask needs to be replaced regularly. Guidance from the WHO[33] on the appropriate way of wearing masks includes:

- Before putting on a mask, wash your hands (with alcohol-based hand rub or soap and water for 20 seconds).

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[31] The World Health Organization. Coronavirus disease (COVID-19): How is it transmitted? 13 Dec 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted [Accessed 28-10-2021].

[32] Centers for Disease Control and Prevention. How to Protect Yourself & Others. 13 Aug 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html [Accessed 28-10-2021].

[33] The World Health Organization. Coronavirus disease (COVID-19): Masks. 1 Dec 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-on-covid-19-and-masks [Accessed 28-10-2021].

- Cover mouth and nose with mask and make sure there are no gaps between your face and the mask.
- Avoid touching the mask while using it; if you do, clean your hands with alcohol-based hand rub or soap and water.
- Replace the mask with a new one as soon as it is damp and do not re-use single-use masks.
- To remove the mask: remove it from behind (do not touch the front of mask)
- Discard immediately in a closed bin; clean hands with alcohol-based hand rub or soap and water.

Many countries have taken measures for citizens to wear masks when spending time outside their homes and we advise that national guidelines be followed. If you are not able to wear a facemask (for example, because it causes trouble breathing), then you should do your best to cover your coughs and sneezes, and people who are caring for you should wear a facemask if they enter your room. If a shortage occurs, masks should be reserved for hospital staff and people experiencing symptoms.

For extra precaution, clean and disinfect frequently touched surfaces daily, including tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks.

Questions regarding daily life (school attendance, work, travel…) depend on the local epidemiological situation and the underlying PID and needs to be discussed with the PID expert physician. This becomes especially relevant during the time of moving out of confinement (see below) when decisions regarding returning to work, school, or living with people in the same household who are returning to normal life become immediately relevant. For patients with higher risk for a severe course of the disease it may be considered to continue working from home, to not send the children back to school and to wear special masks (FFP2) for increased personal protection. However, many of these measures present a strong confinement to life and the cost and benefit needs to be balanced.

<u>If you feel unwell and experience symptoms such as fever, cough and/or difficulty in breathing, stay home and seek prompt medical assistance from your health care provider.</u>

Moving out of confinement

It is important to understand that de-confinement measures do not mean that the virus has been extinguished. Confinement/curfew is the strategy in many countries to “flatten the curve” of infections and to avoid overwhelming the health care systems. In many of these countries there is still only a small proportion of the population that has been exposed to the virus so far and de-confinement may lead to a further increase in infections. Hygiene measures and social distancing are still key to protect PID patients during and after de-confinement.

As the population vaccination progresses in many countries and borders start to gradually reopen, taking a decision about travelling abroad or domestically should be done carefully and with due regard to national, regional and international authorities travel recommendations.

COVID-19 in PID patients

To date (28-10-2021), global surveys aimed at collecting data on COVID-19 in PID patients do not point to an increased risk of COVID-19, especially not in its severe form, although some cases have been reported. However, certain PID patients might be at higher risk than others to be infected or develop a more severe course of disease and patients with PIDs should take extra care to avoid getting this infection.

Patients with PID have generally suffered a less severe course than expected, however the rate of severe disease in younger age groups, as well as rates of admission to ICU, are higher for patients with PID versus the general population.

Data from approximately 600 patients with PID has been published, stating that "Remarkably, the risk factors, severity of disease, and case fatality rate following SARS-CoV2 infection in patients with IEI were not too dissimilar to that observed for the general population. However, the type I interferon (IFN) signaling pathway - activated in innate immune cells in response to viral sensing - is critical for anti-SARS-CoV2 immunity. Indeed, genetic variants or autoAbs affecting type I IFN function account for up to 20% of all cases of life-threatening COVID-19." [34]

Additionally, Italian researchers published a study covering 21 centres in the IPINET national registry, in a cohort of 3,263 adult and pediatric patients. In the 1-year study period, 131 cases of SARS-CoV-2 infection were notified among 3,263 patients with IEI, 33 of them 18 years or younger. The asymptomatic condition, revealed by the screening of patients attending the hospital sites, and of household contacts, was reported in 36.3% of patients 18 years or younger, and 24.5% of patients older than 18 years.

Mean age was similar in asymptomatic, mild/moderate, or severe COVID-19 patients, and in patients who died from COVID-19, with the exception of asymptomatic adult patients who were younger than adult patients with severe COVID-19. Patients with IEI with severe COVID-19 and patients who later died from COVID-19 had a limited spectrum of IEI diagnosis: Common Variable Immune Deficiency (CVID), Del 22q11, and Good's syndrome. At the end of February 2021, the cumulative incidence per 100,000 of confirmed infections was 4.01 in patients with IEI/PID and 5.22 in the general population. Only the incidence in pediatric age was significantly lower in patients with IEI (2.36) in comparison to that in the Italian pediatric population (4.11; $P < .001$). The overall infection-fatality rate was 3.81% in IEIs, compared with 3.28% in the Italian population ($P = .61$) and 5.10% in adult patients with IEI compared with 3.68% in the adult general population

[34] Tangye S, Bucciol G, Meyts I. Curr Opin Allergy Clin Immunol. 2021 Sep 7. doi: 10.1097/ACI.0000000000000786. Online ahead of print. PMID: 34494617

(P = .5). Nonetheless, the fatality rate among Italian patients with IEI is lower than previously reported from other IEI cohorts, ranging from 9.57 to 25%.[35]

The Latin American Society for Immunodeficiencies (LASID) has also opened a special registry for PID/IEI patients infected with SARS-CoV-2. The evolution of these patients was, in general, similar to that reported by other groups.

A second-tier survey aimed at collecting more data is open for entering cases. "COPID19" is the more detailed second phase of the worldwide survey of COVID-19 in PID patients and is directed to physicians who manage PID patients.

Recommendations for PID patients

Patients with PID living in areas of high prevalence should take every precaution and adhere to local, regional and national recommendations (staying at home, teleconsultation, work from home, etc..).

Beyond the precautions mentioned above, we advise prompt phone contact with a doctor if an infection is suspected (should it be your PID expert, or your GP who should let your PID expert know about your condition in order to provide the best advice for each PID patient's specific condition). Patients should always keep the details of their PID diagnosis and medical charts, medications, PID expert doctor and next of kin at hand, in case urgent medical care is needed.

PID patients with lung and/or heart complications, solid organ transplant recipients, previous organ damage, recent recipients of hematopoietic stem cell transplantation or gene therapy, PID patients undergoing treatment for a cancer (malignancy), as well as patients under immunosuppressive or immunomodulatory drugs (for autoimmune, inflammatory, or autoinflammatory conditions complicating the PID course) should remain on their specific therapy until recommended otherwise by their PID expert physician. Immunosuppressive drugs (in particular corticosteroids), might limit signs of infections (fever and other clinical symptoms). It is thus recommended to contact your PID expert physician in case of any unexplained changes in clinical status including your well-being.

PID patients with overweight, old age, cardiovascular disease, diabetes mellitus and/or significant respiratory issues (severe asthma, bronchiectasis or chronic respiratory failure) should receive special attention (as for any risk of respiratory infection).

Impaired Type I interferon (IFN) signalling is emerging as an important factor for control of SARS-CoV-2, from large studies of infected patients. Both the presence of antibodies that neutralize type I IFN and genetic variation in the type I IFN pathway have been demonstrated to be

[35] Milito C, Lougaris V, Giardino G, et al. Clinical outcome, incidence, and SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. 21 April 2021. *J Allergy Clin Immunol Pract*. 2021;S2213-2198(21)00457-8. doi:10.1016/j.jaip.2021.04.017 Available at: https://pubmed.ncbi.nlm.nih.gov/33894392/

associated with severe COVID-19. [36] Thus, patients with forms of PID that result in reduced type I IFN signaling should be considered at high risk of severe COVID-19.

Special attention should be given to patients with APS1/APECED (Autoimmune Polyendocrine Syndrome) due to mutations in *AIRE*. These individuals develop high titers of serum anti-type1 interferons, that have been found in patients and associated with more severe forms of COVID-19. There are reports of several patients with APS1/APECED being affected by forms of COVID-19 requiring hospitalization (incl. in ICU). We recommend patients with this PID to urgently be contacted by their PID expert (and non PID experts, such as endocrinologists and/or hepatologists) in order to get tested very rapidly in case of early symptoms compatible with COVID-19 (and/or if they are contact cases). In case of symptoms, patients should be closely monitored (and therapies should be promptly initiated).

Keep in mind that it is always essential to continue the regular treatment for your PID. Plasma Derived Medicinal Products (PDMPs), such as immunoglobulins (IVIG or SCIG) are safe and will protect you from many other infections.

For everyone, including PID patients, we strongly recommend you to keep up with the latest information on the COVID-19 outbreak in your region, for example provided by the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC) and by your national and local public health authorities.

National guidelines provided by national health authorities should be followed (the epidemiological situation and the management might differ from one country to another).

We want to stress that your PID expert can give you the best personalized advice.

Patients can also visit the IPOPI website to have full access to the FAQ.

COVID-19 and influenza season

To ensure protection against influenza viruses, it is recommended that most PID patients and their families be vaccinated against seasonal flu by inactivated vaccines. All PID patients consult their PID expert physician about seasonal flu vaccine. Please note that recommendations will vary between PID patients and specialist advice should always be sought before receiving vaccinations.

More info on PID and vaccination available here.

[36] Zhang Q, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 23 Oct 2020. Available here: https://science.sciencemag.org/content/370/6515/eabd4570 ; Bastard P, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 23 Oct 2020.

Plasma Derived Medicinal Products (PDMPs), including Immunoglobulins

According to a statement from the Plasma Protein Therapeutics Association (PPTA) there is no risk of transmission of SARS-CoV-2 by PDMPs.[37]

A study in China has demonstrated the detection of SARS-CoV-2 RNA in blood donations[38], but it should be noted that this does not pose a risk to PID patients in terms of transmission via immunoglobulin therapies. The virus inactivation and removal steps during the manufacturing process of PDMPs ensure the safety of IG therapies.

For PID patients who are on Ig replacement therapy, there is no evidence to date that more frequent dosing of Ig will offer more protection. Whilst Ig replacement therapy provides protection against a range of infections, it does not guarantee immunity against coronavirus.

SARS-CoV-2 neutralizing antibodies in IG therapies

Recent studies have been looking at the levels of SARS-CoV-2 neutralizing antibodies in IG therapies as the pandemic has evolved. Most recently very high SARS-CoV-2 antibody titers have been described in the literature. This is due to the fact that an increasing proportion of the general and therefore plasma donors' population, now carries SARS-CoV-2 neutralizing antibodies, a consequence of either earlier COVID-19 or from vaccination against it.[39]

The study shows that a proportion of immunoglobulin lots fractionated from US-origin plasma now contain higher doses of SARS-CoV-2 neutralizing antibodies than earlier used for therapeutic treatment of COVID-19 by convalescent plasma.

Given the fact that the typical time interval between plasma collection and final IG lot release is 7-10 months, it can be expected that plasma collected now would contain higher SARS-CoV-2 neutralizing antibody titers, which should result in a further increase of SARS-CoV-2 neutralizing potency of IG therapies in the coming months.

Whilst these are encouraging news for PID patients, it is important to point out that the clinically protective dose of IG has not been established and that more observational studies are needed at this stage to be able to draw new potential recommendations in this regard. PID patients on IG replacement therapies should therefore continue to take all additional precautionary and protective measures and follow all recommendations outlined in this statement, their treating physician, and relevant national guidelines.

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[37] The Plasma Protein Therapeutics Association. New Coronavirus (SARS-CoV-2) and Plasma Protein Therapies. 3 April 2020. Available at: https://www.pptaglobal.org/media-and-information/ppta-statements/1055-2019-novel-coronavirus-2019-ncov-and-plasma-protein-therapies [Accessed 06-05-2021].

[38] Chang L, Zhao L, Gong H, Wang Lunan, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis. 3 April 2020. https://doi.org/10.3201/eid2607.200839

[39] Karbiener, M et al. Plasma from post-COVID-19 and COVID-19-Vaccinated Donors Results in Highly Potent SARS-CoV-2 Neutralization by Intravenous Immunoglobulins, *The Journal of Infectious Diseases*, 2021; jiab482, https://doi.org/10.1093/infdis/jiab482

Decline in plasma supply

The decline in blood and plasma donations observed in 2020 now estimated at 20% has continued in 2021 due to the COVID-19 outbreak and associated confinement and movement restriction measures.[40] This has had an impact on the supply of life saving plasma derived medicinal products such as IG therapies. Because it usually takes 7-10 months from the time plasma is collected from a human donor to reach the patients, the consequences of the decrease in plasma collection on supply of IG therapies have been manifesting in recent months with varying degree in different countries and are expected to continue in the coming months.

Various PID stakeholders, such as the Supply and Access for Everyone (SAFE) taskforce, are currently taking measures to react to this development on both national and regional levels so that PID patients are prioritized in case of any supply tensions or shortages associated with the COVID-19 outbreak.

[40] Plasma Protein Therapeutics Association. International Plasma Awareness Week 2021: Donate Plasma. Save Lives. 4 Oct 2021. Available at: https://www.pptaglobal.org/media-and-information/press-releases/1120-international-plasma-awareness-week-2021-donate-plasma-save-lives [Accessed 26-10-2021].

Supporting organisations

About IPOPI

IPOPI is the leading advocate for primary immunodeficiencies' patients worldwide working in collaboration with patients, doctors, politicians, regulators, pharmaceutical industry and other relevant stakeholders. IPOPI is the Association of national PID patient organisations currently representing 68 countries. More info: https://ipopi.org, Facebook, Twitter

About ESID

The European Society for Immunodeficiencies (ESID) is a non-profit organization whose main objectives are to facilitate the exchange of ideas and information among doctors, nurses, biomedical investigators, patients and their families concerned with primary immunodeficiency diseases and to promote research on causes, mechanisms and treatment of these disorders. ESID was established as an informal group in 1983 and became a society in 1994. More info: www.esid.org, Twitter

About INGID

The International Nursing Group for Immunodeficiencies (INGID) works to improve, extend and enhance the quality of nursing care of patients with immune deficiencies and to increase the awareness and understanding of Immunodeficiencies amongst nurses. We do this by working together forming international networks of nurses working with patients with that have immune deficiencies, sharing expertise, knowledge, experience, information and research. More info: www.ingid.org

About APSID

The Asia Pacific Society for Immunodeficiencies (APSID) works to provide PID care, education and research for PID patients, through collaborative infrastructure and various APSID Working Parties. A group of over 60 Asian paediatricians and scientists interested in Primary Immunodeficiency met in Osaka, April 2015 and pledged to establish APSID with the following missions: To care and cure patients with primary immunodeficiency (PID), To share PID experience so as to promote collaboration & education, To improve PID management through understanding its genetics & pathogenesis and To advocate and advance the care of PID patients through engaging governments, patient organizations & industry. More info: https://paed.hku.hk/apsid/

About ARAPID

ARAPID is the Arab Society for PID. Its purpose is to bring together the English-speaking east region of the Arab world, closer to the French-speaking west region, to better serve PID patients from the Arab world who are united by consanguinity, etiological profile of PIDs and culture (awareness).
More info: www.arapid.org/en/

About ASID

The African Society for Immunodeficiency (ASID) is a PID focused scientific society. Its main objectives are to improve PID awareness and care within Africa and has been working on addressing continental African PID peculiarities. ASID strives to support African patients through collaborating with national and international patient groups and works with national societies and other relevant authorities to achieve its objectives. ASID also collaborates with international PID societies and alliances, and the industry to promote better PID care and research. More info: www.asid-africa.org

About CIS

The Clinical Immunology Society (CIS) is based in the United States but has members from around the globe. The mission of CIS is to facilitate education, translational research and novel approaches to therapy in clinical immunology and to promote excellence in the care of patients with immunologic/inflammatory disorders. More info: www.clinimmsoc.org

About LASID

The Latin American Society for Immunodeficiencies (LASID) is a vibrant and inclusive international society. This is the home of all professionals dedicated to the field of Primary Immunodeficiencies aiming to develop and perfect the education, scientific research, and health care within this medical specialty. LASID's mission comprises the following: To increase awareness in Primary Immunodeficiency Diseases (PIDD) at all levels all over the continent, to develop diagnostic capabilities to reach as many as possible patients and to favor the development of centers providing appropriate treatments for PIDD patients. More info: www.lasid.org

About SEAPID

South East Asia Primary Immunodeficiency Network or "SEAPID" is a regional NGO - the South East Asian network of Primary Immunodeficiency Experts. It was established in Bangkok, Thailand on 26th January 2015, following an accord reached by experts from the six South East Asian founding countries, namely, Indonesia, Malaysia, the Philippines, Singapore, Thailand and Vietnam.

About IUIS Inborn Errors of Immunity Committee (IEI)

The IEI Committee consists of experts in all aspects of primary immunodeficiencies. Its missions are: to provide an up-to-date classification of all primary immunodeficiency diseases (IEIs), to assist with the identification, diagnosis and management of patients with these uncommon conditions, to support diagnostic and therapeutic guidelines developed by national societies and others, to assist healthcare providers, to promote awareness, diagnosis and treatment of IEIs in all regions of the world, to produce ad hoc reports on any aspect of IEIs, to assist in the welfare of patients with these conditions.

More info: www.iuis.org/committees/iei/

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