COVID-19 vaccination for patients with primary immunodeficiency

Chaim M. Roifman, CM, MD, FRCPC, FCACB[a,b*] and Linda Vong, PhD[a]

Introduction

The worldwide tally of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, causing novel coronavirus disease 2019 (COVID-19), currently approaches 149.7 million (as of 30 April 2021) (Government of Canada 2021*a*). Canada's cases amount to 1 211 083 confirmed infections and 24 169 deaths (Government of Canada 2021*b*). In the midst of the pandemic and a third wave of infections, programs aimed at widespread vaccination against COVID-19 remain an essential stop-gap to slow the spread of infection and help achieve protective herd immunity (Fontanet and Cauchemez 2020). Patients with primary immunodeficiency (PID) have impaired immune responses and may be at greater risk of severe illness due to COVID-19, thus, are strongly recommended to avoid interactions with those outside of their immediate household "bubble", practice hand hygiene, and wear masks when spending time outside or in enclosed spaces where close contact with other people cannot be avoided (Roifman 2020).

With the ongoing rollout of COVID-19 vaccinations, we provide here recommendations for patients with PID. It is important to note that individuals who are immunocompromised should always consult their immunologist for additional considerations/contraindications when reviewing their suitability for vaccination.

Vaccination and the immune response

Vaccination (or immunization) is a safe and effective way to protect against infection from foreign agents such as viruses or bacteria (Plotkin 2013; Siegrist 2018). Vaccines train the immune system by activating the 2 arms of the adaptive immune system—humoral immunity and cellular immunity (Pulendran 2014). Humoral immunity utilizes macromolecules secreted in body fluids to clear extracellular pathogens. Antibodies produced by B cells are the predominate effectors—these specifically recognize and bind to the pathogen or toxin, thereby neutralizing and preventing entry into host cells. Complement proteins participate by "marking" pathogens for clearance by phagocytic cells. In contrast, mobilization of cellular immunity relies on T cell responses. CD8+ T cells kill infected cells and produce antiviral cytokines, while CD4+ T helper (T_H) cell subsets secrete cytokines and provide co-stimulatory signals that are needed to orchestrate the clearance of intracellular and extracellular pathogens, regulate immune tolerance, and maintain protection at mucosal surfaces. Bi-directional interactions between T cells and B cells/antibodies are necessary to ensure robust and long-lasting protective vaccine responses (Igietseme et al. 2004; Crotty 2015).

The introduction of a foreign agent during vaccination leads to the rapid recruitment of immature

[a]Canadian Centre for Primary Immunodeficiency and the Division of Immunology & Allergy, Department of Paediatrics, The Hospital for Sick Children, Toronto, ON; [b]University of Toronto, Toronto, ON

*Corresponding author: Chaim M. Roifman/chaim.roifman@sickkids.ca

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dendritic cells, monocytes, and neutrophils. These cells routinely surveil the body and are equipped with pattern recognition receptors to recognize potential pathogens (Palm and Medzhitov 2009). Detection of vaccine microbial antigens triggers cell activation and the production of inflammatory cytokines and chemokines, resulting in the recruitment of further monocytes, granulocytes, and natural killer cells. Within this proinflammatory milieu, dendritic cells mature and become activated, take up/present small pieces of the antigen on their cell surface (a process dependent on major histocompatibility (MHC) class I or II molecules) (Joffre et al. 2012), and finally migrate to the draining lymph nodes where they encounter and activate resident naïve B and T cells (Randolph et al. 2005; Iwasaki and Medzhitov 2010). Microbial antigens can also reach draining lymph nodes by passive diffusion.

Within the lymph nodes (or other secondary lymphoid organs), naïve B cells that survey the B cell follicle microenvironment bind, internalize, and process the foreign antigen into small segments and present them on cell surface MHC class II molecules. They then migrate towards the B cell-T cell border and engage antigen-specific T_H cells (primed by activated dendritic cells), which provides activating signals needed to elicit B cell differentiation into antibody-secreting plasma cells (Goodnow et al. 2010). During this process, known as the extrafollicular reaction (MacLennan et al. 2003), immunoglobulin (Ig) class-switch recombination occurs (from IgM to IgG, IgA or IgE), producing short-lived, low affinity antibodies within a few days after vaccination (Goodnow et al. 2010).

If sufficient co-stimulatory signals are present, follicular dendritic cells (which trap and retain antigens) and follicular T_H (T_{FH}) cells direct antigen-specific B cells to undergo clonal proliferation in specialized structures known as germinal centers (Goodnow et al. 2010; De Silva and Klein 2015). Here, 2 key steps take place: (*i*) Ig class-switch recombination, and (*ii*) maturation of B cell affinity for specific antigens—a process involving somatic hypermutation of Ig genes. Together, the germinal center reaction selects and enriches for the survival and proliferation of B cells with highest affinity antigen-specific binding (Goodnow et al. 2010). Within this microenvironment, germinal center B cells are provided the necessary cues to support differentiation into large numbers of specific antibody-secreting plasma cells, a process which produces peak IgG vaccine antigen antibodies 4–6 weeks after initial vaccination. Some plasma cells migrate to distinct niches within the bone marrow, allowing them to survive and produce antibodies for years (Good-Jacobson and Shlomchik 2010).

The germinal center reaction also gives rise to long lasting (decade-long) memory B cells (Kurosaki et al. 2015). These cells, when reactivated by an antigen (for example, during the second dose vaccination or exposure to natural boosters), undergo rapid proliferation and differentiation into antibody-secreting plasma cells. The antibodies produced by memory B cells have a higher affinity for vaccine antigens than those produced by naïve B cells and are present in much higher levels (Good-Jacobson and Shlomchik 2010).

T cell-dependent responses play an important role in controlling and clearing pathogens. T cells are produced in the thymus, circulate in the periphery, and are activated in secondary lymphoid organs. Depending on the antigens encountered, naïve T cells differentiate into effector T cells, either (*i*) CD8+ cytotoxic T cells which can kill infected cells through release of lytic enzymes (direct) and antimicrobial cytokines (indirect), or (*ii*) CD4+ T_H cells (Kapsenberg 2003). CD4+ T_H1 cells support cytotoxic CD8+ T cell function and secrete pro-inflammatory interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-β, while CD4+ T_H2 cells secrete IL-4, IL-5, IL-10, and IL-13 (O'Garra and Robinson 2004; Stetson et al. 2004). CD4+ T_{FH} are essential for the development of germinal centers and memory B cell development (Vinuesa et al. 2005).

While the majority of effector T cells die by apoptosis, a small proportion retain their antigen specificity and survive to become long lasting memory T cells (Sallusto and Lanzavecchia 2000). Central memory CD8+ and CD4+ T cells reside in the lymph nodes and can rapidly proliferate in response to re-exposure to specific antigens. In contrast, effector memory T cells surveil the peripheral tissues, ready to generate immediate cytotoxic functions if a specific antigen is detected.

Overall, vaccination primes the immune system against infection to allow rapid detection and re-mobilization of protective responses, without the risk of serious complications that may occur if exposed to the actual pathogen. Importantly, for individuals who cannot produce antibodies, especially those with PID,

T cell dependent responses can still provide a level of protection.

COVID-19 vaccines

Vaccine efficacy, the ability to elicit high affinity antibodies and immune memory, is directly related to the type of vaccine administered: whether it is live (attenuated), killed (inactivated), or contains a subunit of the pathogen. Other determinants include the dose of antigen (Ahman et al. 1999) and whether there are adjuvants present (Spreafico et al. 2010). In general, live vaccines are the most immunogenic, and are extremely efficient at triggering T and B cell activation (Zabel et al. 2013). Nevertheless, most vaccines (aside from those that are capsular polysaccharide-based) have been developed to induce protective T and B cell responses.

It is important to note that vaccines using a live (attenuated) form of the pathogen, such as the measles vaccine, *should not* be administered to individuals who are immunocompromised given the inherent risk of disseminated infection.

The race to produce effective vaccines against SARS-CoV-2 (Zhu et al. 2020), causing COVID-19, that could be (*i*) rapidly developed and (*ii*) deployed on a large-scale has hastened the introduction of novel gene-based vaccines (Pushparajah et al. 2021). These vaccines, utilizing mRNA or vectors containing genetic code, rely on the host immune cell's protein synthesis machinery to produce a key surface protein found on the SARS-CoV-2 virus. The spike protein, a trimeric glycoprotein expressed on SARS-CoV-2, is essential for uptake of the virus into host cells (Letko et al. 2020). Upon entry into the cell, the virus releases its RNA and hijacks the host system to replicate, producing viral copies that can then infect surrounding cells (Fehr and Perlman 2015). The spike protein is therefore an ideal target for the COVID-19 vaccine since neutralizing antibodies would recognize and bind the surface epitopes, preventing SARS-CoV-2 virus entry into cells (Baden et al. 2021).

COVID-19 vaccines based on the mRNA platform (Pardi et al. 2018) contain instructions for cells to make a stabilized version of the SARS-CoV-2 spike protein. The instructions, in the form of mRNA, are encapsulated in lipid nanoparticles to protect and enable them to traverse the cellular membrane of dendritic cells which are recruited to the site of injection. Ribosomes in the host cell cytoplasm translate the mRNA, produce the spike protein, and small fragments are then presented to the cell surface. Together, this triggers both B cell-dependent humoral responses and T cell-dependent cellular responses.

COVID-19 vaccines utilizing non-replicating viral vectors (Pushparajah et al. 2021) are designed to deliver the DNA instructions for the SARS-CoV-2 spike protein into the host immune cell nucleus. The vector, a harmless version of a virus, has been modified to provide only instructions for the spike protein, but cannot replicate to produce copies of itself. Thus, 1 viral vector can only infect 1 host cell. The spike protein is produced by the host immune cell's protein synthesis machinery, processed into fragments and then presented to the cell surface to elicit humoral and cellular responses.

There are currently 4 COVID-19 vaccines authorized for use in Canada. The Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines use mRNA-based platforms, while the vaccines produced by AstraZeneca (ChAdOx1-S, also manufactured by Verity Pharmaceuticals/Serum Institute of India) and Janssen (Ad26.COV2.S, Johnson & Johnson) are non-replicating viral vector-based. In clinical trials, all have been shown to induce humoral and cellular immune responses (Sahin et al. 2020; Baden et al. 2021).

The Pfizer-BioNTech, Moderna, and AstraZeneca COVID-19 vaccines follow a 2-dose schedule. In clinical trials, the first dose of the mRNA-based vaccines resulted in a relatively weak immune response, while the second dose produced a stronger immune response (efficacy against symptomatic COVID-19 after 2nd dose: Pfizer-BioNTech = 94.6%, Moderna = 94.1%) (Polack et al. 2020; Baden et al. 2021). In contrast, AstraZeneca's viral vector vaccine provides comparable immune responses following the first and second dose response, albeit lower than the mRNA vaccines (efficacy against symptomatic COVID-19 after 2nd dose: AstraZeneca = 62.5%) (Voysey et al. 2021). For vaccines requiring 2 doses, there is no evidence to suggest that 1 dose is sufficient to provide long-term protection against COVID-19. Full protection is only achieved 2 weeks after the second dose (CDC 2021). This is important in the context of newly emerging SARS-CoV-2 variants (Mascola et al. 2021), including the B.1.1.7 variant (UK), B.1.617.2 (Delta) variant (India),

B.1.351 variant (South Africa), and P.1 variant (Brazil), as a single dose of the Pfizer-BioNTech COVID-19 vaccine was shown to provide only partial protection against the B.1.1.7 variant (Reynolds et al. 2021).

The Janssen COVID-19 vaccine, approved for use in March 2021, requires only a single-dose to be protective against COVID-19 (efficacy against moderate to severe/critical COVID-19 after 14 days = 66.9%) (Sadoff et al. 2021).

At present, the Moderna COVID-19 vaccine is approved for people who are 18+ years of age. On 5 May 2021 Canada became the first country to authorize use of the Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12+, expanding on Health Canada's previous approval for its use in those aged 16+ years of age. The mRNA vaccines are preferentially recommended over the non-replicating viral vector vaccine types (NACI 2021). Canada's National Advisory Committee on Immunization recently revised their recommendations for the use of AstraZeneca and Janssen's non-viral vector COVID-19 vaccines due to reports of a number of rare cases of serious blood clots known as vaccine-induced immune thrombotic thrombocytopenia (Mahase 2021; Pai et al. 2021). Both the AstraZeneca and Janssen COVID-19 vaccines may be offered those who are 30+ years of age and who prefer to not wait for the mRNA vaccines. All 4 vaccines are planned or currently being trialed in pediatric cohorts.

COVID-19 vaccination of patients with PID

Reports of COVID-19 in patients with PID have highlighted more severe clinical course in those with defects in type I IFN signaling (Bastard et al. 2020; van der Made et al. 2020; Zhang et al. 2020) and greater risk of ICU admission in younger age groups compared to the general population (Meyts et al. 2021). In the United Kingdom, the case-fatality ratio of PID patients with COVID-19 was significantly higher compared to the general population, demonstrating greater morbidity and mortality (Shields et al. 2021). However, in other geographic areas, such as Israel, there is data to suggest that symptoms in some PID patients may be milder (Quinti et al. 2020; Marcus et al. 2021; Meyts et al. 2021), perhaps due to the innate inability to mount appropriate inflammatory responses. Dysregulated or hyperimmune reactions underlie some of the more severe sequalae of COVID-19.

Clinical trials for COVID-19 vaccines have so far involved only a limited number of people who are immunocompromised or have autoimmunity, and no data is available on those who are immunosuppressed or receiving immunosuppressive therapy. By extension, it is not known whether patients with PID will be able to mount the same humoral and cellular immune responses as the general population, or have a diminished protective response, to the vaccine.

The currently available mRNA-based COVID-19 vaccines are considered on par with inactivated vaccines and thus do not present a greater risk to immunocompromised individuals than what would normally be encountered.

Recommendations

1. Given the favorable safety, tolerability, and efficacy data from the COVID-19 vaccine trials, all patients with PID should be vaccinated against COVID-19, especially those who have known biological risk factors and (or) social factors that predispose to severe COVID-19 illness. Experience with other vaccines suggests that patients with PID may have a less robust immune response to the COVID-19 vaccine, and the vaccine may not be as effective. Regardless, the possibility of mild protection against COVID-19 is advantageous compared no protection at all.
2. mRNA-based COVID-19 vaccines are recommended for use in patients with PID (NACI 2021).
3. Caregivers and close contacts should also be vaccinated to limit the risk of exposure to the virus. This is particularly important for caregivers of paediatric (<12 years) PID patients for which COVID-19 vaccines have not yet been approved.
4. Patients with PID who have previously had COVID-19 should still get the vaccine. Vaccination can be delayed until 90 days after the initial infection, since there are few reports of re-infection during this interval.
5. It is important to note that all patients should consult their immunologist or PID physician for specific advice regarding their suitability for the COVID-19 vaccine, including contraindications or allergies to any components of the vaccines.

Common questions

Can immunoglobulin replacement therapy protect PID patients from COVID-19?

Immunoglobulin replacement products contain gammaglobulin (IgG) pooled from the plasma of many donors and provides protection against a wide range of infections. We know that robust levels of neutralizing antibodies against the SARS-CoV-2 virus are produced after infection (Lau et al. 2021). Vaccination also produces protective levels of neutralizing antibodies. Therefore, it is possible that antibody titers against the virus will appear in immunoglobulin replacement products as the number of people who are (*i*) infected by SARS-CoV-2 or (*ii*) vaccinated against COVID-19 increases. However, at present, there is not enough data to guarantee protective antibody levels against the virus in immunoglobulin replacement products.

Will the COVID-19 vaccine benefit PID patients who do not produce measurable antibody titers to other vaccines?

Yes, patients with defects in antibody production may still develop some level of protection against SARS-CoV-2 through T cell dependent responses. Vaccines activate 2 arms of the immune system—humoral immunity (involving antibodies) and cellular immunity (involving T cells). Antibodies, produced by B cells, prevent or reduce infections by blocking their entry into cells. T cells, on the other hand, do not prevent infection but help to control and clear the pathogen.

Will delays in receiving the second dose, beyond the manufacturers' suggested 3–4 week schedule, affect protection against COVID-19?

In clinical trials, the 2-dose COVID-19 vaccines approved for use followed a 21- or 28-day dosing interval. This is the duration between the first and second dose. In practice, delays in the availability of COVID-19 vaccines have meant that most people will be unable to receive a second dose within this time frame. The first dose provides some protection. Preliminary data from the United Kingdom suggests that protection after the first vaccine dose may last 10 weeks (Pritchard et al. 2021; Wei et al. 2021), although it is unclear when protective antibody levels start to wane. Nevertheless, delays in administration of the second dose beyond the range approved by FDA licensing studies are not based on scientific evidence. For this reason, it remains ideal to receive the second dose on time or, if impossible, as soon as it is available.

Can children with PID receive the COVID-19 vaccine?

Children 12 years of age and over are eligible to receive the Pfizer-BioNTech COVID-19 vaccine. Clinical trials for younger pediatric cohorts are in progress or planned. To reduce the risk of infection to younger children, immediate family members and close contacts should be vaccinated, and all members of the household should be vigilant in practicing social distancing measures, regular hand washing, and masking.

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