COVID-19 outcomes in immunocompromised individuals: seroconversion and vaccine effectiveness

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

As we round the corner on the 6th coronavirus disease 2019 (COVID-19) wave amid gradual lifting of social distancing and masking restrictions, it is timely to review the guidance measures for individuals with compromised immune systems, particularly those with primary immunodeficiency (PID) (Roifman 2020). The clinical spectrum of COVID-19 varies from those who are asymptomatic, experience mild symptoms such as fever, cough, and dyspnea, to more severe outcomes including acute respiratory distress, pneumonia, renal failure, and death. Comorbidities predisposing to complications and severe illness include older age (>65 y), males, obesity, cancer, serious cardiovascular disease, chronic obstructive pulmonary disease, type II diabetes mellitus, and immunodeficiency (including PID) (Chen et al. 2020; Huang et al. 2020; Li et al. 2020).

Over the past 2 years since the pandemic took hold, those with PID have been advised to practice rigorous social distancing, hand hygiene, and if appropriate — COVID-19 vaccination, given the possibility of more severe outcomes (Roifman and Vong 2021*b*, 2021*a*). During this period, studies examining the effectiveness of the COVID-19 vaccine and longevity of antibody titers have been instrumental in guiding the need for additional 'boosters', allowing for additional protection due to insufficient seroconversion — the development of specific antibodies following vaccination (or exposure to an infectious agent), or waning immunity. In Canada, individuals with moderate to severe PID have been advised to a receive 3-dose primary series with the Pfizer-BioNTech mRNA vaccine (or a 2-dose primary series using the Moderna adenoviral vector-based vaccine), and 2 booster doses — up to 5 doses in total.

Early clinical trials demonstrated the safety and efficacy of mRNA and adenoviral-vector based COVID-19 vaccines, including against symptomatic SARS-CoV-2 infection and more severe outcomes (Baden et al. 2021; Voysey et al. 2021). Seroconversion was shown to be high regardless of the type of vaccine administered (Eyre et al. 2021; Wang et al. 2021). Further, several studies supported the use of neutralizing antibody titers as surrogate markers of protection (Khoury et al. 2021; Garcia-Beltran et al. 2021). However, such data rarely extrapolate to subpopulations with immune deficits especially given that immunocompromised individuals were excluded from evaluations of vaccine effectiveness. In Canada, 4–5 times more immunocompromised individuals, including those on immunosuppressive medications, solid organ transplant recipients, malignancy, and PID, have been hospitalized or admitted to hospital with COVID-19 than the general population (NACI 2021).

More recently, case series and reports of disease course in those with PID indicate variable outcomes, from those who remain asymptomatic to severe

[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: Linda Vong/linda.vong@sickkids.ca

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complications. Nevertheless, seroconversion rates remain lower than the general population suggesting the need for continued caution.

There remains limited data on efficacy following the 3-dose vaccine primary series in PID, with most studies reporting outcomes following a 2-dose schedule. This likely reflects the initial lack of access to sufficient doses/boosters of COVID-19 vaccines globally and the lag time during transition from a 2-dose to 3-dose schedule. In a U.S. study, among 100 immunocompromised individuals who received a 2-dose mRNA vaccine, half were able to produce an antibody-mediated (humoral) immune response while 69% raised a cell-mediated (interferon-γ release) response (Ramanathan et al. 2021). Separately, an Italian study reported that 7 out of 34 (20%) patients with common variable immunodeficiency (CVID) with no prior exposure to SARS-COV-2 were able to produce IgG and IgA antibody responses to the COVID-19 vaccine spike protein, while 6 out of 7 who had previously been infected showed boosted antibody responses after vaccination. Spike protein antibodies were absent in patients with X-linked agammaglobulinemia, although reassuringly, in 5 out of 6 of this cohort, vaccination specific T cell responses were still detectable (Salinas et al. 2021). Similarly, an Israeli study of 26 patients with PID reported that 18 were able to develop specific antibody responses following the Pfizer-BioNtech COVID-19 vaccine, while 19 raised specific T cell responses (Hagin et al. 2021). Overall, a recent meta-analysis assessing seroconversion rates among immunocompromised individuals reported significantly lower rates between the first and second dose of the vaccine (Lee et al. 2022). A third dose boosted antibody levels, although some may not respond to a fourth dose.

Real-world data describing the severity and level of protection following vaccination against COVID-19 in patients with PID continue to emerge, and paint a conflicting scenario. It is noteworthy that, given the assumption of severe outcomes, many with PID have remained vigilant in sheltering from exposure, resulting in relatively low infection rates. Further, the presence of COVID antibodies in antibody replacement products likely confer some additional level of protection (Karbiener et al. 2021; Romero et al. 2021). Some regions have documented only mild COVID-19 symptoms (Drabe et al. 2021; Goudouris et al. 2021; Deyà-Martínez et al. 2021), perhaps due to the innate inability of those with PID to mobilize inflammatory responses. Marcus and colleagues reported minimal impact of COVID-19 in a cohort of 19 patients with PID from Israel — none were hospitalized (Marcus et al. 2021). However, with a high proportion of asymptomatic cases and most on antibody replacement therapy, this cohort is hard to assess. Our own experience with a cohort of pediatric patients (including those with humoral immunodeficiency, combined immunodeficiency and phagocytic defects) revealed similarly mild COVID-19 disease course (fever, sore throat, nasal congestion, and rhinitis) which resolved without complications (Roifman et al. unpublished observations).

In contrast, globally, overall rates of hospital admissions stand at closer to 50% of reported PID cases of COVID-19 (Fill et al. 2020; Van Damme et al. 2020; Soresina et al. 2020; Ahanchian et al. 2020; Jin et al. 2020; Quinti et al. 2020; Delavari et al. 2020; Ho et al. 2021; Mullur et al. 2021; Meyts et al. 2021; Esenboga et al. 2021; Shields et al. 2021; Castano-Jaramillo et al. 2021; Goudouris et al. 2021). Shields and colleagues reported the outcome of 60 patients with PID, with just over half requiring hospital admission and overall higher case fatality ratios compared to control (Shields et al. 2021). A study by Delavari and colleagues reported 10-fold higher mortality rate in those with PID compared to the general population, despite only 1.23-fold higher COVID-19 infection (Delavari et al. 2020). What is clear is that a more severe clinical course is documented in patients with defects in type I interferon signaling (Bastard et al. 2020; van der Made et al. 2020; Zhang et al. 2020), including those with defects in IFNAR1, IFNAR2, STAT1, STAT2, TICAM1, TRAF3, TBK1, TLR3, and IRF3.

It would be of paramount importance to obtain stratified data on the impact of COVID-19 over the 2-year period of the pandemic. Currently, patients with PID are more protected now with an effective vaccine, effective anti-viral treatments, and gradual enrichment of immunoglobulin products with neutralizing anti-SARS-CoV-2 antibodies.

We propose to differentiate between PID patients who responded well to vaccination with sustained antibody levels and/or those receiving immunoglobulin replacement, from non-responders, especially if they have significant T cell deficiency or an interferon-γ pathway defect.

We also believe that after a prolonged period of home schooling for children with PID, further extension of this practice may be more harmful than exposure to the virus. We recommend that with the advice and guidance of an immunologist, many of these children could relatively safely attend physical school. Yet, we still advise they adhere to masking at school, hand hygiene, and distancing as much as possible. The introduction of new preventative and therapeutic medications renders this transition to normal life easier.

In summary, despite gradual lifting of COVID-19 mandates, continued evidence of impaired immunity and COVID-19 disease course in individuals with PID indicate that this population should continue to remain cautious — but with gradual and selective relaxation of practices.

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