COVID-19 post-vaccination recommendations for primary immunodeficiency

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

This has been a very difficult and challenging time for humanity to combat the coronavirus disease 2019 (COVID-19) pandemic (Zhu et al. 2020). Science stood up to the challenge in the most admirable manner by producing an unprecedented vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Polack et al. 2020; Sahin et al. 2020; Baden et al. 2021; Sadoff et al. 2021). This highly effective vaccine was also recommended and administered to individuals with inborn errors of immunity that lead to primary immunodeficiency (PID) (Roifman and Vong 2021). While multiple studies have confirmed the efficacy of the vaccine in preventing significant disease in the general public (Dagan et al. 2021; Haas et al. 2021; Lopez Bernal et al. 2021), this protective effect has not been thoroughly evaluated in immune compromised hosts (Barda et al. 2021). In addition to the inherents fault in their immune system, patients with immune disorders were also sheltered from exposure to the virus, making vaccine efficacy evaluation difficult (Meyts et al. 2021; Shields et al. 2021; Quinti et al. 2020; Marcus et al. 2021).

PID encompasses a growing number of patients with a common set of manifestations including recurrent and (or) severe microbial infections, autoimmune features, and increased association or predisposition to cancer (Bousfiha et al. 2020). PID is a highly heterogeneous group of disorders caused by genetic variation in more than 450 different immune-system related genes. Clinical presentation and immune lesions frequently vary widely among different gene defects, different variants in the same gene, and even cases within the same family bearing the same mutation.

While the various components of the immune system normally function interdependently, the humoral and cellular components play a critical role in the response to vaccines (Pulendran 2014). Most immune disorders can be classified as adversely affecting mostly immunoglobulin and antibody production (humoral), predominately T cell deficiency (cellular defect) or a combination of both (combined immunodeficiency) (Roifman et al. 2012). Upon exposure to a pathogen (virus, bacteria), both arms of the immune system cooperate to produce adequate antibodies as well as propagating some T cell populations critical in battling infection in response to microbial exposure or vaccines (Igietseme et al. 2004; Crotty 2015).

The lack of response to vaccination in some extreme cases of profound T cell deficiency, such as severe combined immunodeficiency (SCID), can be predicted. But, in most other immune defects the degree of response and resulting level of protection can be highly variable and difficult to predict, hence, the recommendation by experts to offer vaccination to all these patients (Bonilla 2018).

Evaluation of vaccine efficacy is routinely done by measuring titer levels of specific antibodies and less frequently by studying in vitro T cell responses

[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

Submitted 13 August 2021
Accepted 13 August 2021
Available online 16 August 2021

LymphoSign Journal 8:69–74 (2021)
dx.doi.org/10.14785/lymphosign-2021-0023

(Paris 2020). In the case of COVID-19, these assays have either not yet been standardized (antibody levels) or are not available for clinical use (T cell responses). This limits further the ability to discern the effect of COVID-19 vaccination in patients with PID.

Many patients with PID are treated with immunoglobulins (IgG) for antibody deficiency (Roifman et al. 2008; Betschel et al. 2019). This form of passive immunization encompasses protein fractions extracted from multiple blood donors. Immunoglobulin replacement products (IVIG, SCIG) available in Canada are almost invariably obtained from US donors. Given the widespread infection as well as vaccination rates in the US it is expected that IgG products would contain a significant level of anti-SARS-CoV-2 antibodies (Romero et al. 2021). Consequently, recommendations for PID patients may differ from the relaxing measures offered to the general public.

Precise data on anti-SARS-CoV-2 antibody levels and possible lot-to-lot variations of these products remain scarce, and may be complicated by false-positivity associated with cross-reactive antibodies (Dalakas et al. 2021). While this passive immunization against COVID-19 is a welcome benefit to those patients, it may be dampened by the fact that administration of exogenous IgG can suppress endogenous production of antibodies (Tacke et al. 2013) in response to active immunization with the COVID-19 vaccine.

All these complex issues require individual evaluation of each PID patient by their physician in order to apply the most appropriate course of testing, treatment, or protections measures. In general, it is recommended that until more credible information (scientific evidence) becomes available, patients with PID, in particular those with combined immunodeficiency, should exercise extra precautions as long as COVID-19 and its variants continue to spread in the community (Table 1). This includes proper distancing measures and wearing effective masks (medical grade) in enclosed and crowded spaces (Roifman 2020).

Booster dose of the COVID-19 vaccine

For PID patients, many of whom develop only partial responses to vaccination, a booster dose would provide enhanced protection against COVID-19. On 12 August 2021, the U.S. Food and Drug Administration authorized the use of an additional (third) dose of the Pfizer-BioNTech and Moderna COVID-19 vaccines in people who are immunocompromised (FDA 2021). This group includes patients with PID, individuals on immunosuppressant medications, and the elderly (age >65 y). The third dose can be administered at least 28 d following the second dose of the COVID-19 vaccine. Similarly, on 18 August 2021, Ontario announced plans to authorize third doses of the Pfizer-BioNTech or Moderna vaccines in individuals who are severely immunocompromised (including transplant recipients, those treated with anti-CD20 agents, or undergoing treatment for malignant hematologic disorders), and elderly residents in long-term care homes or high-risk group settings. PID patients should discuss this option with their physician or specialist.

Antibody testing after COVID-19 vaccination

Vaccination against COVID-19 activates the humoral and cellular components of the host immune system, in the same manner as natural exposure to the SARS-CoV-2 virus, leading to the production of B cell-dependent antibodies and mobilization of T cell-dependent pathogen clearance and protective mechanisms (Roifman and Vong 2021). Since the COVID-19 vaccination program began in Canada, over 71% of the population (as of 12 August 2021, https://covid19tracker.ca/vaccinationtracker.html) have received at least 1 dose of an authorized COVID-19 vaccine. It is noteworthy that initial vaccine trials did not include patients with PID, thus, it is not known whether the level of protection seen in the general population would be reflected in this cohort. Nevertheless, COVID-19 vaccination is broadly recommended for those with PID (in consultation with an immunologist) as some measure of protection may still be in place, even if antibody responses remain low/limited.

Specific IgG antibodies against SARS-CoV-2 are generally detectable 14 d after natural exposure, or for the SARS-CoV-2 vaccine, 14 d after the second vaccine dose (Iacobucci 2021; Lou et al. 2020). Antibody (serological) assays which measure specific antibody titer levels can help identify whether an individual is able to mount an immune response following vaccination.

Table 1: **COVID-19 post-vaccination recommendations.**

Protective response to COVID-19 vaccination in PID patients with humoral or cellular defects may be variable or incomplete. Thus:

- Evaluation of the efficacy of the vaccine in PID is desirable and should be pursued once appropriate standardized testing becomes available, or, following discussion with your physician.
- PID patients are advised to continue to exercise precautions, including hand hygiene, social distancing and masking, especially in indoor settings but also in outdoor crowded spaces.
- A boost (third dose) of the mRNA-based COVID-19 vaccine is recommended for immunocompromised individuals, especially PID patients and individuals treated with immunosuppressant drugs.
- Continue to monitor/self-monitor for signs of COVID-19 infection and seek virus testing.
- If tested positive, contact your physician and specialist for implementation of a proper management plan.

It is important to note that, at present, **it is unclear what levels of antibodies are needed to provide protection against COVID-19**. This lack of a defined correlate of protection (a threshold value to serve as a standard) makes it difficult to determine the amount of protection PID patients have against COVID-19, even if specific antibodies are present. Further, antibody titers are just one (of several) indicators of protection. For example, measurement of lymphocyte proliferation in response to antigen stimulation, a process dependent on antigen-specific T cells that develop during initial (prior) exposure, may provide additional clues about an individual's T cell function (Roifman et al. 2012). However, such tests remain research-based and not yet widely accessible.

In Canada, there are currently 22 authorized SARS-CoV-2 antibody assays available for clinical use. These measure antibodies (IgM, IgA, IgG) against highly immunogenic, structural components of SARS-CoV-2, such as the surface spike protein and the intracellular nucleocapsid protein (Wang et al. 2020).

The detection of antibodies against the spike protein (elicited by COVID-19 vaccines as well natural exposure to SARS-CoV-2) can indicate an immune response after vaccination, however, can also indicate previous infection with the virus. Conversely, the presence of antibodies against the nucleocapsid protein suggests previous exposure to SARS-CoV-2, but cannot be used as a marker of SARS-CoV-2 post-vaccination responses.

Results of testing must be interpreted with caution, taking into account the patient's baseline immune function and other temporal contexts. For example, test results for either the spike protein or nucleocapsid antibody may be negative in individuals with immune defects, in which the ability to produce antibodies are hampered. Results may also be negative if there has been insufficient time for antibodies to develop (i.e., test is performed too early after vaccination), or if peak antibody levels have already waned (i.e., test is performed beyond 5 mo post-vaccination) (Aziz et al. 2021). While the clinical utility of post-vaccination testing is not yet fully established, for specific cohorts, particularly patients with PID, antibody titer testing can guide discussions on additional measures needed to protect against COVID-19.

SARS-CoV-2 antibody testing for PID patients

Can be used to measure antibody production in response to COVID-19 vaccination, however, should be interpreted with caution as:

- Levels of antibodies required for protection against COVID-19 are not known
- Clinical utility of post-vaccination testing is not yet established
- Variability in detection exists among available assays

Interpretation of SARS-CoV-2 antibody testing results

Spike protein antibody result: positive

Detectable levels of antibodies against SARS-CoV-2 are present (due to vaccine or exposure to the virus)

Additional:

- PID patients should continue to take protective measures against COVID-19 exposure
- A positive result does not equate to complete protection against COVID-19

- Very rarely, a false-positive result may be present if an individual has been previously exposed to other coronaviruses (the nucleocapsid protein in SARS-CoV-2 has 90% homology with another coronavirus, SARS-CoV-1 (Marra 2003)).

Spike protein antibody result: Negative

No detectable levels of antibodies against SARS-CoV-2 are present

Additional:

- PID patients should continue to take protective measures against COVID-19 exposure
- A negative result can occur if testing was done too early (or too late) after vaccination
- The sensitivity of antibody testing in PID patients is not known
- It is not clear how long antibodies remain after vaccination, and can be different in individuals with PID

Nucleocapsid protein antibody result: positive

Detectable levels of antibodies against SARS-CoV-2 are present due to exposure to the virus

Additional:

- Very rarely, a false-positive result may be present if an individual has been previously exposed to other coronaviruses
- A positive nucleocapsid protein antibody titer result, in conjunction with a positive spike protein antibody titer levels, may indicate an immune response due to exposure to the virus (rather than vaccination)

Nucleocapsid protein antibody result: negative

No detectable levels of antibodies against SARS-CoV-2 are present

Additional:

- Individuals with PID may have false negative nucleocapsid antibody titer results
- A negative result in the context of PID should not be used to rule out prior exposure to the virus or infection status

REFERENCES

Aziz, N.A., Corman, V.M., Echterhoff, A.K.C., Müller, M.A., Richter, A., Schmandke, A., Schmidt, M.L., Schmidt, T.H., de Vries, F.M., Drosten, C., and Breteler, M.M.B. 2021. Seroprevalence and correlates of SARS-CoV-2 neutralizing antibodies from a population-based study in Bonn, Germany. Nat. Commun. **12**(1): 2117. PMID: 33837204. doi: 10.1038/s41467-021-22351-5.

Baden, L.R., El Sahly, H.M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S.A., Rouphael, N., Creech, C.B., Mcgettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Mascola, J., Polakowski, L., Ledgerwood, J., Graham, B.S., Bennett, H., Pajon, R., Knightly, C., Leav, B., Deng, W., Zhou, H., Han, S., Ivarsson, M., Miller, J., and Zaks, T. 2021. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N. Engl. J. Med. **384**: 403–416. PMID: 33378609. doi: 10.1056/NEJMoa2035389.

Barda, N., Dagan, N., and Balicer, B.D. 2021. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. N. Engl. J. Med. **384**: 1968–1970. doi: 10.1056/NEJMc2104281.

Betschel, S., Brager, R., Haynes, A., Issekutz, T., Kim, V.H.-D., Mazer, B., Mccusker, C., Roifman, C.M., Rubin, T., Sussman, G., Turvey, S., and Waserman, S. 2019. Report of the national immunoglobulin replacement expert committee: Algorithm for diagnosis of immunodeficiency requiring antibody replacement therapy. LymphoSign J. **6**: 31–33. doi: 10.14785/lymphosign-2019-0003.

Bonilla, F.A. 2018. Update: Vaccines in primary immunodeficiency. J. Allergy Clin. Immunol. **141**: 474–481. PMID: 29288077. doi: 10.1016/j.jaci.2017.12.980.

Bousfiha, A., Jeddane, L., Picard, C., Al-Herz, W., Ailal, F., Chatila, T., Cunningham-Rundles, C., Etzioni, A., Franco, J.L., Holland, S.M., Klein, C., Morio, T., Ochs, H.D., Oksenhendler, E., Puck, J., Torgerson, T.R., Casanova, J.-L., Sullivan, K.E., and Tangye, S.G. 2020. Human inborn errors of immunity: 2019 Update of the IUIS phenotypical classification. J. Allergy Clin. Immunol. **40**: 66–81.

Crotty, S. 2015. A brief history of T cell help to B cells. Nat. Rev. Immunol. **15**: 185–189. PMID: 25677493. doi: 10.1038/nri3803.

Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M.A., Hernán, M.A., Lipsitch, M., Reis, B., and Balicer, R.D. 2021. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N. Engl. J. Med. **384**: 1412–1423. PMID: 33626250. doi: 10.1056/NEJMoa2101765.

Dalakas, M.C., Bitzogli, K., and Alexopoulos, H. 2021. Anti-SARS-CoV-2 antibodies within ivig preparations: cross-reactivities with seasonal coronaviruses,

natural autoimmunity, and therapeutic implications. Front Immunol. **12**: 627285. PMID: 33679770. doi: 10.3389/fimmu.2021.627285.

FDA. 2021. Coronavirus (COVID-19) Update: FDA authorizes additional vaccine dose for certain immunocompromised individuals. Available from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised [accessed 12 August 2021].

Haas, E.J., Angulo, F.J., Mclaughlin, J.M., Anis, E., Singer, S.R., Khan, F., Brooks, N., Smaja, M., Mircus, G., Pan, K., Southern, J., Swerdlow, D.L., Jodar, L., Levy, Y., and Alroy-Preis, S. 2021. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet, **397**: 1819–1829. doi: 10.1016/S0140-6736(21)00947-8.

Iacobucci, G. 2021. Covid-19: Most UK adults had antibodies after one dose of AstraZeneca or Pfizer vaccine, data suggest. BMJ, **373**: n1274. PMID: 34006531. doi: 10.1136/bmj.n1274.

Igietseme, J.U., Eko, F.O., He, Q., and Glack, C.M. 2004. Antibody regulation of Tcell immunity: implications for vaccine strategies against intracellular pathogens. Expert. Rev. Vaccines, **3**: 23–34. PMID: 14761241. doi: 10.1586/14760584.3.1.23.

Lopez Bernal, J., Andrews, N., Gower, C., Robertson, C., Stowe, J., Tessier, E., Simmons, R., Cottrell, S., Roberts, R., O'doherty, M., Brown, K., Cameron, C., Stockton, D., Mcmenamin, J., and Ramsay, M. 2021. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. **373**: n1088. PMID: 33985964. doi: 10.1136/bmj.n1088.

Lou, B., Li, T.-D., Zheng, S.-F., Su, Y.-Y., Li, Z.-Y., Liu, W., Yu, F., Ge, S.-X., Zou, Q.-D., Yuan, Q., Lin, S., Hong, C.-M., Yao, X.-Y., Zhang, X.-J., Wu, D.-H., Zhou, G.-L., Hou, W.-H., Li, T.-T., Zhang, Y.-L., Zhang, S.-Y., Fan, J., Zhang, J., Xia, N.-S., and Chen, Y. 2020. Serology characteristics of SARS-CoV-2 infection after exposure and post-symptom onset. Eur. Respir. J. **56**: 2000763. PMID: 32430429. doi: 10.1183/13993003.00763-2020.

Marcus, N., Frizinsky, S., Hagin, D., Ovadia, A., Hanna, S., Farkash, M., Maoz-Segal, R., Agmon-Levin, N., Broides, A., Nahum, A., Rosenberg, E., Kuperman, A.A., Dinur-Schejter, Y., Berkun, Y., Toker, O., Goldberg, S., Confino-Cohen, R., Scheuerman, O., Badarneh, B., Epstein-Rigbi, N.A., Etzioni, A., Dalal, I., and Somech, R. 2021. Minor clinical impact of COVID-19 pandemic on patients with primary immunodeficiency in Israel. Front Immunol. **11**: 614086. PMID: 33519822. doi: 10.3389/fimmu.2020.614086.

Marra, M.A. 2003. The genome sequence of the SARS-associated coronavirus. Science, **300**: 1399–1404. PMID: 12730501. doi: 10.1126/science.1085953.

Meyts, I., Bucciol, G., Quinti, I., Neven, B., Fischer, A., Seoane, E., Lopez-Granados, E., Gianelli, C., Robles-Marhuenda, A., Jeandel, P.-Y., Paillard, C., Sankaran, V.G., Demirdag, Y.Y., Lougaris, V., Aiuti, A., Plebani, A., Milito, C., Dalm, V.A.S.H., Guevara-Hoyer, K., Sánchez-Ramón, S., Bezrodnik, L., Barzaghi, F., Gonzalez-Granado, L.I., Hayman, G.R., Uzel, G., Mendonça, L.O., Agostini, C., Spadaro, G., Badolato, R., Soresina, A., Vermeulen, F., Bosteels, C., Lambrecht, B.N., Keller, M., Mustillo, P.J., Abraham, R.S., Gupta, S., Ozen, A., Karakoc-Aydiner, E., Baris, S., Freeman, A.F., Yamazaki-Nakashimada, M., Scheffler-Mendoza, S., Espinosa-Padilla, S., Gennery, A.R., Jolles, S., Espinosa, Y., Poli, M.C., Fieschi, C., Hauck, F., Cunningham-Rundles, C., Mahlaoui, N., Warnatz, K., Sullivan, K.E., and Tangye, S.G. 2021. Coronavirus disease 2019 in patients with inborn errors of immunity: An international study. J. Allergy Clin. Immunol. **147**: 520–531. PMID: 32980424. doi: 10.1016/j.jaci.2020.09.010.

Paris, K. 2020. Assessing antibody function as part of an immunologic evaluation. *In* UpToDate. *Edited by* A.M. Feldweg, and J.S. Orange. Waltham.

Polack, F.P., Thomas, S.J., Jitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck, R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Şahin, U., Jansen, K.U., and Gruber, W.C. 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med. **383**: 2603–2615. PMID: 33301246. doi: 10.1056/NEJMoa2034577.

Pulendran, B. 2014. Systems vaccinology: Probing humanity's diverse immune systems with vaccines. Proc Natl Acad Sci USA, **111**(34): 12300–12306. PMID: 25136102. doi: 10.1073/pnas.1400476111.

Quinti, I., Lougaris, V., Milito, C., Cinetto, F., Pecoraro, A., Mezzaroma, I., Mastroianni, C.M., Turriziani, O.,

Bondioni, M.P., Filippini, M., Soresina, A., Spadaro, G., Agostini, C., Carsetti, R., and Plebani, A. 2020. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J. Allergy Clin. Immunol. **146**: 211–213. e4.

Roifman, C.M. 2020. Managing primary immunodeficiency during the COVID-19 pandemic. LymphoSign J. **7**: 85–89. doi: 10.14785/lymphosign-2020-0009.

Roifman, C.M., Berger, M., and Notarangelo, L.D. 2008. Management of primary antibody deficiency with replacement therapy: summary of guidelines. Immunol. Allergy. Clin. North Am. **28**: 875–876. PMID: 18940580. doi: 10.1016/j.iac.2008.07.003.

Roifman, C.M., Somech, R., Kavadas, F., Pires, L., Nahum, A., Dalal, I., and Grunebaum, E. 2012. Defining combined immunodeficiency. J. Allergy Clin. Immunol. **130**: 177–183. PMID: 22664165. doi: 10.1016/j.jaci.2012.04.029.

Roifman, C.M., and Vong, L. 2021. COVID-19 vaccination for patients with primary immunodeficiency. LymphoSign J. **8**: 37–45. doi: 10.14785/lymphosign-2021-0020.

Romero, C., Díez, J.M., and Gajardo, R. 2021. Anti-SARS-CoV-2 antibodies in healthy donor plasma pools and IVIG products. Lancet Infect. Dis. **21**: 765–766. PMID: 33606999. doi: 10.1016/S1473-3099(21)00059-1.

Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P.A., Truyers, C., Fennema, H., Spiessens, B., Offergeld, K., Scheper, G., Taylor, K.L., Robb, M.L., Treanor, J., Barouch, D.H., Stoddard, J., Ryser, M.F., Marovich, M.A., Neuzil, K.M., Corey, L., Cauwenberghs, N., Tanner, T., Hardt, K., Ruiz-Guiñazú, J., Le Gars, M., Schuitemaker, H., Van Hoof, J., Struyf, F., and Douoguih, M. 2021. Safety and Efficacy of Single-Dose Ad26.COV2.S vaccine against covid-19. New England Journal of Medicine.

Sahin, U., Muik, A., Derhovanessian, E., Vogler, I., Kranz, L.M., Vormehr, M., Baum, A., Pascal, K., Quandt, J., Maurus, B., Brachtendorf, S., Lörks, V., Sikorski, J., Hilker, R., Becker, D., Eller, A.-K., Grützner, J., Boesler, C., Rosenbaum, C., Kühnle, M.-C., Luxemburger, U., Kemmer-Brück, A., Langer, D., Bexon, M., Bolte, S., Karikó, K., Palanche, T., Fischer, B., Schultz, A., Shi, P.-Y., Fontes-Garfias, C., Perez, J.L., Swanson, K.A., Loschko, J., Scully, I.L., Cutler, M., Kalina, W., Kyratsous, C.A., Cooper, D., Dormitzer, P.R., Jansen, K.U., and Türeci, Ö. 2020. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature, **586**: 594–599. PMID: 32998157. doi: 10.1038/s41586-020-2814-7.

Shields, A.M., Burns, S.O., Savic, S., Richter, A.G., Anantharachagan, A., Arumugakani, G., Baker, K., Bahal, S., Bermingham, W., Bhole, M., Boules, E., Bright, P., Burns, S., Cleave, B., Dempster, J., Devlin, L., Dhalla, F., Drewe, E., Duncan, C., Dziadzio, M., Elkhalifa, S., Gennery, A., Goddard, S., Grigoriadou, S., Hayman, G., Herwadkar, A., Huissoon, A., Jain, T., Jolles, S., Johnston, S., Leeman, L., Mahabir, S., Maclochlainn, D., Mcdermott, E., Misbah, S., Morsi, H., Murng, S., Noorani, S., O'Brien, T., Patel, S., Price, A., Tichter, A., Savic, S., Seneviratne, S., Shields, A., Shrimpton, A., Stroud, C., Vaitla, P., and Verma, N. 2021. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J. Allergy Clin. Immunol. **147**: 870–875. e1. PMID: 33338534. doi: 10.1016/j.jaci.2020.12.620.

Tacke, C.E., Smits, G.P., Van Der Klis, F.R.M., Kuipers, I.M., Zaaijer, H.L., and Kuijpers, T.W. 2013. Reduced serologic response to mumps, measles, and rubella vaccination in patients treated with intravenous immunoglobulin for Kawasaki disease. J. Allergy Clin. Immunol. **131**: 1701–1703. PMID: 23498596. doi: 10.1016/j.jaci.2013.01.045.

Wang, M.-Y., Zhao, R., Gao, L.-J., Gao, X.-F., Wang, D.-P., and Cao, J.-M. 2020. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. Front. Cell. Infect. Microbiol. **10**: 587269. PMID: 33324574. doi: 10.3389/fcimb.2020.587269.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, T., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., and Tan, W. 2020. A novel Coronavirus from patients with pneumonia in china, 2019. N. Engl. J. Med. **382**: 727–733. PMID: 31978945. doi: 10.1056/NEJMoa2001017.