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Vaccination against COVID-19: Rationale, modalities and precautions for patients with haemophilia and other inherited bleeding disorders

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While COVID-19 is far from being eradicated, the first COVID-19 vaccine has now been approved in the U.K., the European Union, Canada and the United States, and vaccinations have been initiated as of December 8, 2020 in the U.K. Additional vaccines have been licenced in the United States, the U.K. and India. Approvals in other jurisdictions and the arrival of additional effective vaccines are imminent. The success of vaccination campaigns will depend on the number of people effectively vaccinated. The vaccinated population will limit the spread of the SARS-CoV-2 virus.

In addition to the logistical challenges of large-scale vaccination, good information, understanding, and confidence in the vaccines will determine their adoption by the entire population. Some people have doubts about the efficacy and safety of vaccines or do not acknowledge the need to be vaccinated, either due to legitimate concerns or misinformation. People with haemophilia or other haemorrhagic diseases are no exception to this reality. Here we present a factual perspective to help healthcare providers and people with bleeding disorders make informed decisions on vaccination.

The rationale behind vaccination is to provide every vaccinated person with protection against the SARS-CoV-2 virus. This protection is achieved by stimulating the immune system to

produce antibodies against the virus and to develop lymphocytes that will retain memory and the ability to fight off the virus for a long time. Individuals infected with SARS-CoV-2 mount the same kind of response to the virus, but can develop severe and potentially fatal complications. The vaccine acts as a decoy for the immune system, which it stimulates to react and produce protective antibodies without causing the disease.

Vaccination consists of exposing the immune system of the recipients to structural proteins of the virus that will elicit a response. This is achieved by administering recombinant viral proteins (protein vaccines), or genetic information encoding those proteins (messenger RNA) that will make the cells of the vaccinated person produce the proteins of the virus (mRNA vaccines),[1] or using another weakened virus into which proteins of the SARS-CoV-2 virus have been introduced (vector vaccines).[2] The first two approved vaccines are mRNA vaccines.[3–5] Prompting the cells to produce viral proteins mimics what the virus does in the course of natural infection to replicate itself but without causing morbidity. The mRNA vaccines do not contain a live virus and do not carry a risk of causing disease in the vaccinated person. Also, mRNA from the vaccine does not enter the nucleus of the cell and does not affect or interact with a person's DNA. The mRNA technology has been studied for more than a decade which helped speed up the vaccine development.

Importantly, the vaccines currently being approved have been tested in tens of thousands of people in worldwide clinical trials and there have been no serious adverse reactions. They should be considered extremely safe. Haemophilia patients are not at greater risk of contracting the virus and developing COVID-19; however, when they develop the disease and require hospital admission, ICU transfer, ventilation, and management are very complex.[6,7] Even though recent large clinical studies have not included patients with haemophilia or hereditary haemorrhagic diseases, these patients should be vaccinated like everyone else. However, certain precautions and additional information are relevant and are detailed below.

1. People with bleeding disorders are not at greater risk of contracting COVID-19 or developing a severe form of the disease, and so they are not considered a priority group for vaccination. The general selection rules will apply to people with haemophilia. Haemophilia patients belonging to risk groups according to their age, state of health, or occupation will be vaccinated as a priority like others in the general population with the same risk profile.

2. There is currently no reason to select a particular type of vaccine for bleeding disorder patients. Some vaccines under development and one that has just been approved in the U.K. and India (Oxford University/AstraZeneca ChAdOx1 nCoV-19 or AZD1222), use an adenovirus.[8] Adenovirus is unrelated to adeno-associated viruses (AAV) and is not being used in haemophilia gene therapy, thus there is no contraindication for using it in the bleeding disorders population. No vaccines against SARS-CoV-2 using AAV viruses are currently in clinical trials, but caution may be required for the future. People with bleeding disorders who are contemplating AAV gene therapy in the future or have received it in the past should avoid any future vaccines using modified AAV. This type of virus is widely used as a vector for gene therapy treatments.

3. The vaccine should be administered intramuscularly. The smallest gauge needle available (25-27 gauge) should be used, if possible.[9,10] Some vaccines must be administered using the accompanying needle-syringe combination, and so the use of an alternative needle may not be possible or desirable. Pressure should be applied to the site for at least 10 minutes post-injection to reduce bleeding and swelling.[10,11] Additionally, self-inspection/palpation of the injection area several minutes and 2-4 hours later is recommended to ensure that there is no delayed hematoma. Discomfort in the arm felt for 1-2 days after injection should not be alarming unless it worsens and is accompanied by swelling. Any adverse events (e.g., hematoma, allergic reaction) should be reported to a haemophilia treatment centre. Anticipatory guidance should be given to patients to contact their physician immediately or go to the nearest hospital emergency room right away if they experience an allergic reaction (fever, warmth, redness, itchy skin rash, shortness of breath, or swelling of the face or tongue) as it can be life-threatening.[12,13] Patients with a history of allergic reactions to extended half-life clotting factor concentrates containing polyethylene glycol (PEG) should discuss vaccine choice with their physician because some vaccines contain PEG as an excipient.[14] People with haemophilia and other bleeding disorders who have had a history of allergic or anaphylactic reactions to blood products, including factor concentrates, plasma and cryoprecipitate, but have not had reactions to previous vaccines, are at no greater risk than the overall population for a reaction to a COVID-19 vaccine.

4. We recognize many individuals with bleeding disorders may not have ready access to haemostatic therapies prior to vaccination. In these cases, make efforts to access WFH Humanitarian Aid program or other clotting factors if possible. Alternatively, follow the

instructions above making sure the smallest possible needle is used and maintain pressure for more than 10 minutes.

5. For patients with severe/moderate haemophilia or Type 3 von Willebrand disease (VWD) (regardless of whether they routinely receive prophylaxis or on-demand treatment) the injection should be given after a FVIII or FIX injection, or following a von Willebrand factor-containing injection, respectively. Vaccinations have not been shown to prime FVIII or FIX inhibitor formation in patients with haemophilia.[15] In particular, vaccines against viruses with RNA genomes (influenza, mumps, measles, rubella), like SARS-CoV-2, did not enhance inhibitor formation in an animal model.[16] Mild haemophilia patients with baseline FVIII or FIX levels below 10% may also need haemostatic treatment prior to vaccination and should consult their haemophilia treatment center. For patients with a basal FVIII or FIX level above 10%, no haemostatic precautions are required. Similarly, patients on emicizumab (with or without an inhibitor) can be vaccinated by intramuscular injection at any time without extra haemostatic protection. Depending on their baseline VWF activity levels patients with Type 1 or 2 VWD should use therapies (ie, DDAVP if available, tranexamic acid), in consultation with their haemophilia treatment center. All rare bleeding disorder patients (including those with thrombocytopenia and/or platelet function disorders) should be vaccinated. Haemostatic support would depend on the severity of the disorder and should be decided in consultation with their treatment center.

6. There are no specific contraindications to vaccination related to complications of haemophilia and other bleeding disorders or their therapies. Immune tolerance, treatment of hepatitis C and HIV and other conditions do not contraindicate vaccination. However, the U.K. Medicines and Healthcare Products Regulatory Agency and the Centers for Disease Control and Prevention have advised caution in using the Pfizer/BioNtech vaccine in people with a history of significant allergic reactions. Specific recommendations for people with a history of allergic/anaphylactoid reactions can be found in advisories published by both agencies.[17,18] Other potential contraindications should be discussed individually with the physician because recommendations vary in different jurisdictions due to lack of data in special populations (e.g. pregnant or breastfeeding women).

7. Vaccination is not contraindicated for patients on immunosuppressive agents (cortisone, other immunosuppressive drugs), but their immune responses and protection from infection may be reduced.

8. For patients in a clinical study, vaccination should be discussed with and reported to the study investigators.

9. It is important that haemophilia treatment centres, in close collaboration with patient associations, take action to inform patients about the vaccines and contribute to an effective vaccination program.

Vaccination against COVID-19 is a major public health challenge, including for the community of patients with inherited haemorrhagic diseases. It is paramount to ensure an effective and rapid vaccination program with the adherence of the largest number of well-informed patients worldwide.

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