Covid-19 and Bleeding Disorders

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- Preventive measures are the best way to deal with Covid-19, including wearing masks, observing social and physical distancing (at least 6 feet in the case of adults and 3 feet in the case of schoolchildren), washing hands and using 70% alcohol sanitizer, isolating people who have or are suspected of having Covid-19, and isolating people who have been exposed to people with Covid-19. Masks should have at least two layers of breathable fabric and should be worn to completely cover the nose and mouth and to fit snugly against the face.

- A Canadian study of 74,642 individuals who donated blood between May 9 and July 11, 2020, determined that the seroprevalence of SARS-COV-2 (the virus that causes Covid-19) was about 7 per 1000 people. Seroprevalence was lower among whites (6.6 per 1000) and higher among indigenous peoples (9.3), Asians (9.3), and other minorities (10.9). More than blood type or socioeconomic factors, race was a significant predictor of seroprevalence.

- Vaccines work by exposing the body to viral materials or sub-units. The real objective is not just to provoke a short-term antibody response but also to trigger an immune response at the cellular level, so that cells like memory T-cells and B-cells will remain able over a longer term to recognize the virus and release neutralizing antibodies against it.

- As of February, there were over 200 vaccine candidates under development around the world, with considerably fewer having reached the point of human trials. They use any of a number of different platforms, or strategies. The Pfizer-BioNTech and Moderna vaccines, for example, use an RNA-based platform and have now been authorized for emergency use in 42 countries. Fifty-five countries have authorized at least one vaccine based on non-replicating viral vectors, and 25 have authorized at least one vaccine based on inactivated virus.

- Some very novel approaches to vaccines are now being tried. The mRNA approach uses the code of a SARS-COV-2 gene to produce a protein that the body can form antibodies against. Another uses a recombinant SARS-COV-2 surface protein, and a third uses a viral vector like an adeno-associated virus (AAV) to package a SARS-COV-2 gene producing a viral protein to provoke the formation of antibodies.

- As of February 2021, 12 vaccines have been approved for public use by at least one national regulatory authority – 2 based on RNA platforms, 5 on viral vector platforms, 4

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on conventional inactivated virus, and 1 on a peptide platform. They include vaccines manufactured by entities in the United States, China, Russia, Germany, the Netherlands, and India.

- The number of doses of Covid-19 vaccines administered worldwide is now approaching 300 million. With 66 additional vaccines currently undergoing clinical trials – 20 of them already in Phase 3 trials – there should be a number of additional vaccines becoming available in the coming months.

- To be considered effective, a vaccine needs to: elicit an immune response; be safe; stimulate the production of neutralizing antibodies; and confer "adaptive" immunity, meaning that a later exposure to the virus should not provoke a harmful immune reaction.

- Data concerning acute allergic reactions to mRNA-based Covid-19 vaccines were collected from 64,900 Mass General-Brigham employees who received either the Pfizer or Moderna product. 2.2% of the Moderna recipients and 1.95% of the Pfizer recipients experienced acute allergic reactions, most of which were wheezing, skin rash, and other minor reactions. Only 16 employees (7 receiving the Pfizer vaccine, and 9 receiving the Moderna one) experienced an anaphylactic reaction, which represented a rate of 2.47 per 10,000 injections. Fifteen of the 16 were female (it is not clear if this was independently significant or simply due to the composition of the population), 63% had a history of prior allergic reactions, and 31% had experienced an anaphylactic event before, which suggests that people with histories of anaphylaxis or severe allergic response should consult their care providers and take precautions before taking the Covid-19 vaccine.

- Side effects and adverse reactions to vaccines can be reported to the US Vaccine Adverse Event Reporting System (VAERS). The CDC also has a smartphone app called v-safe for collecting such data.

- NHF's Medical and Scientific Advisory Council (MASAC) Document #221, "Recommendations on Administration of Vaccine to Individuals with Bleeding Disorders," provides guidance that persons with bleeding disorders can consult with their caregivers.

- In 2020, a Covid-19 vaccination guidance document was also issued jointly by NHF, the World Federation of Hemophilia (WFH), the European Association for Haemophilia and Allied Disorders (EAHAD), and the European Haemophilia Consortium (EHC). It includes the following points:

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- People with bleeding disorders are not at greater risk of contracting Covid-19 or developing a severe form of the disease. They therefore are not in a priority group for vaccination.

- The smallest gauge needle available (25-27 gauge) should be used if possible, and pressure should be kept on the injection site for at least 10 minutes afterwards. Self-inspection and palpation for delayed bleeding should be done after several minutes and again 2-4 hours later. Adverse events should be reported to one's HTC.

- Patients should notify their physician and go to an emergency room if they experience an allergic reaction.

- Patients with moderate or severe hemophilia should administer FVIII/FIX before receiving the vaccination. Patients with a baseline factor level of 10% or more do not need to pre-treat.

- Patients on emicizumab (with or without inhibitor) do not need to infuse Factor VIII before receiving intramuscular injections.

- Depending on their baseline vWF and ristocetin cofactor activity levels, Type 1 and 2 vWD patients should use therapies (DDAVP if it again becomes available; tranexamic acid; etc.) in consultation with their HTC. Patents with Type III vWD should be given a vWF-containing concentrate.

- Patients with rare bleeding disorders (including thrombocytopenia and platelet function disorders) should be vaccinated. Patients on anticoagulants should have a prothrombin time test within 72 hours before injection. They can be vaccinated if their international normalized ratio is stable and within the therapeutic range.

- There are no specific contraindications to vaccination due to complications of hemophilia or other bleeding disorders, or due to immune tolerance, hepatitis C treatment, or HIV treatment.

- Vaccination is not contraindicated for patients on immunosuppressive agents like cortisone.

- The three currently available vaccines – from Moderna, Pfizer-BioNTech, and Janssen/Johnson & Johnson – are equally effective and available for people with bleeding disorders. It does not matter which one is used.

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- There is no evidence to indicate that hemophilia patients with inhibitors are more likely to have an adverse reaction to the Covid-19 vaccine. The immune response of an inhibitor is an alloimmune response (that is, a response to a foreign protein/antigen), whereas the autoimmune response of concern with Covid is a rejection of one's own antigens. Patients with inhibitors should check with their HTCs but should not forego vaccination.

- With more replication, viruses exhibit "antigenic drift," meaning that they change through mutations. This is why we are seeing new variants of Covid-19. (It is also why, in the case of the flu virus, the annual flu vaccine has to be modified or customized every year.) Until a virus has been eradicated or has few opportunities to replicate (for example, because the human population develops herd immunity), new mutations are going to appear. It is very likely that we will need to receive vaccinations for Covid-19 on an annual or other periodic basis until it is eradicated or brought under sufficient control. This is also a powerful reason why it is important to get vaccinated in the first place and why a high percentage of the global population needs to receive the vaccination.

- A person with a bleeding disorder who contracts Covid-19 could be in a complicated medical management situation. Covid-19 infects and alters the cells in the blood vessels. Rather than facilitating smooth bloodflow, the cells can contribute to the formation of blood clots, necessitating the administration of blood thinners. Managing the delicate balance between preventing clots and maintaining appropriate hemostasis requires the expertise of an ICU associated with an HTC.

- **Articles shared during the presentation for continuing education:**
  - "Management of COVID-19-Associated Coagulopathy in Persons With Haemophilia": https://onlinelibrary.wiley.com/doi/full/10.1111/hae.14191

  - "Vaccination Against COVID-19: Rationale, Modalities and Precautions for Patients with Haemophilia and Other Inherited Bleeding Disorders": https://onlinelibrary.wiley.com/doi/full/10.1111/hae.14271

Additional non-Covid-19 updates from Dr. Valentino:

- World Hemophilia Day (April 17) is approaching. The theme this year is "Adapting to Change: Sustaining Care in a New World." Everyone can contribute to its observation by:

  1) sharing a personal story or video at www.worldhemophiliaday.org;

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2) posting photos on social media and tagging WFH through #WHD2021, #World HemophiliaDay, and #LightItUpRed;
3) supporting the work of WFH at wfh.org/give; and
4) connecting to the global community through wfh.org/connect.

- NHF has modified its Mission Statement to encompass blood disorders (as opposed to bleeding disorders) and to emphasize the objective of enabling affected individuals and their families to thrive. It has also therefore modified its Vision Statement to reflect its vision of "A world without inheritable blood disorders."

- A collaboration among the American Society of Hematology, NHF, WFH, and the International Society for Thrombosis and Hemostasis has produced "Clinical Guidelines for VWD." The emphasis now will be on (1) education of health care workers, the community, payers, policy makers, and other key stakeholders, and (2) collecting data to evaluate the value of the guidelines and whether and how they enable people with vWD to thrive.

- The Bleeding Disorders Conference, to be held virtually on August 26-28, will include among other things: public health sessions focused on women, health equity, and aging; policy/advocacy sessions on insurance, blood safety, and national policy; a nursing pre-con on vWD; and a physician track session exclusively on vWD.

- Dr. Valentino and Dr. Michael Recht, the Chief Science Officer of ATHN, will be co-chairing the NHF State of the Science Summit, which will serve to establish research priorities for NHF and facilitating NHF's research capacity. A Steering Committee of clinicians, researchers, NHF staff, and a patient representative will assist them. Four working groups will focus on research priorities for, respectively, hemophilia, vWD, ultra-rare bleeding disorders, and the health of women, girls, and those with the potential for menstruation. A fifth group will focus on diversity, equity, and inclusion issues in health services research and implementation, and a sixth will concentrate on facilitating and funding priority research in the bleeding disorders community.

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