COVID-19 Forum Questions and Answers
May 20th, 2020

The May 20th members only Forum was focused on vaccine development and COVID-19 recovery and a number of questions were posted by participants.

We have compiled the questions, and provided answers from experts within our field, with guidance that is applicable in the Canadian context. With limited published evidence, most answers represent consensus of expert opinion and were considered current at the time of the May 20th

COVID-19 Vaccine Development

1. There are a number of vaccine types described- are there advantages to one over another- for the ability to be effective in the face of mutation, or immunogenicity, etc?
   - Hopefully, eventually, there will be enough clinical trials to allow for comparison between vaccines for all sorts of outcomes. That said, there are advantages and disadvantages to all types of vaccines. Vaccines that use a viral platform as the delivery system (i.e. adenovirus 5) present the antigen in another non-replicating virus, to which the immune system has a strong signal. The downside is that if there are pre-existing antibodies to the viral platform used, the immune response may be lower, which may impact effectiveness.
   - Some of the DNA vaccines are very targeted and generate a very strong immune response; the downside is that, to date, there has not been any licensed vaccines using those technologies.

2. Are any of the vaccine candidates similar to other existing vaccines that we currently recommend or 'use if indicated' in pregnancy?
   - Some platforms use a live virus, but it’s been attenuated, others use a live virus that is not able to replicate in the host (humans). The vaccine we will test at the Phase I study at the Canadian Center for Vaccinology is live and attenuated – it cannot replicate in the host.
• Most vaccines look at the spike protein as the most important antigen. The purified protein will be safe in pregnancy, but non-neutralizing antibodies may develop that could cause antibody enhancement. In general, it is important to have neutralizing antibodies and to use adjuvants that don’t drive a TH2 response but rather a TH1 or balanced TH1/2 response. Other companies are looking at using different adjuvants that have been shown to be safe in pregnancy.

3. **Can you provide clarity about immunity?**
• The goal for immunity is to have a neutralizing antibody against a receptor binding domain or spike protein. Humoral immunity is works by binding the part of the virus that binds to the cell and thereby preventing the virus from entering the cell; cellular immunity occurs after the virus enters the cell. The most effective immunity involves a combination of cellular and humoral

4. **Which kinds of tests for immunity will be used for this COVID-19 vaccine trial?**
• This trial is doing an enzyme immunoassay to quantify the antibodies, as well as pseudoviral neutralization and measuring T-cell immunity. On a subset of participants, SARS-CoV-2 neutralization test will be performed; these tests have to be performed in level 3 conditions.

5. **There has been talk about using serum from those who have recovered from COVID-19 illness to induce immunity – is this possible?**
• This has not been proven with evidence yet; there is a trial across Canada currently underway where plasma is being isolated from recovered volunteers and is being used to test this hypothesis.

6. **What are the challenges and possible strategies for protecting our elderly, with their less robust immune systems- is it all about adjuvant?**
• It’s not all about adjuvant, but adjuvant is certainly important. Other vaccines show that different adjuvants are more effective in older populations. This COVID-19 vaccine study does not use adjuvants but is specifically looking at the immune response in older individuals, as well as frailty and its effect on immunogenicity.
• Other strategies include increasing the amount of antigen used in the vaccine for the elderly and immunizing everyone around the frail.
7. **How is the general information from vaccine trials extrapolated to pregnancy?**

- There are no current protocols that include pregnant women or children in COVID-19 vaccine Phase I trials; it would be very unusual to have a pregnant individual in Phase I because committing to not being pregnant during the duration of the study (often several months long) is a condition of participation. In later phases of clinical study, one would have to enroll pregnant women as an intended population in order to have a large enough sample with enough power to assess adverse outcomes. If female participants happen to become pregnant during the study, the numbers will be very low and insufficient to draw any conclusions (although those women will be followed very closely). Once there are sufficient safety data from Phase II studies, it may be possible to expand Phase II or to include a separate group (pregnant women) in Phase III.

**COVID-19 Vaccine Approval/Regulatory Process**

8. **What is the normal expectation for efficacy for regulators to approve a new vaccine, and how might that differ for COVID-19? How efficacious will a vaccine need to be in order to be licensed?**

- Phase I is a very difficult period. There are a number of potential vaccines that appear very promising in animal models, but don’t work in clinical trials. In general, about half of vaccines in Phase I studies make it to Phase II or III.

- There are no specific targets for efficacy that regulators require for a completely new vaccine – their goal is to determine if this vaccine is effective compared to a comparator (i.e., placebo). However, once a vaccine is licensed, subsequent ones have to be at least as efficacious as the previous ones. This is particularly difficult with COVID-19 because there are a lot of concerns with the immune response – especially with how would this affect the ageing population. The WHO has suggested that a COVID-19 vaccine should have at least 50% efficacy (lower end of the 95% confidence interval should be >50%).
9. **Given the number of COVID-19 vaccine candidates and the accelerated vaccine trials, what is a reasonable estimate of when a vaccine will be available for clinical use?**

- We are hoping for a telescoping design for the vaccine development process; an accelerated process to shorten the timeline so that Phase II studies could follow 2-3 months after Phase I. For Phase III, the timeline depends on the circulation of the virus at the time, since it consists of comparing the incidence of infection-related outcomes between treatment and placebo groups. If the circulation of COVID-19 is low at that time, it will take longer to collect the data. If the results from Phase II studies look promising, Health Canada can choose to do an emergency release/authorization prior to the vaccine officially receiving its marketing authorization. Efficacy data is possible to collect while using the vaccine (as was the situation with the Ebola vaccine) if regulators make that decision and Public Health officials decide to take that route.

10. **How long will it take to produce millions of doses of the COVID-19 vaccine?**

- For DNA type vaccines, huge amounts of doses can be manufactured very quickly. The government is going to have to make a choice as to which potential candidates go on from Phase I to Phase II and III studies, and some decisions will be made on availability, cost and production in Canada. The production of multimillions of doses are planned for this year.

11. **What are the steps for implementing vaccination after a vaccine for COVID-19 is approved?**

- Plans for implementation of vaccination and vaccination programs and policies are unknown at this point. The National Advisory Committee on Immunization will likely provide guidance as to priorities for immunization.

The Public Response

12. **Does there seem to be increased acceptance of vaccines in general, especially by the vaccine hesitant, with all the talk of vaccination around COVID-19?**

- Unfortunately, this is not being observed in regular practice. That said, COVID-19 has re-introduced the topic of infectious disease into peoples’ minds – a change in perception may be a good outcome from the COVID-
19 crisis! Healthcare providers may have to be very persistent in their messaging about vaccination, and build on the ripe mindset of their patients.

13. With respect to COVID-19 recovery – what are your thoughts on opening up things based on epidemiological approaches?
   - The expectation at this point is that things are looking better and Canada has come over the hump of the initial wave, although there is still an expectation for what could be looming ahead with relaxation of the public health restrictions. The response by public health will differ according to jurisdiction.

14. Why did SARs and MERs seem to disappear- and why are vaccinologists not thinking that COVID-19 will follow a similar pattern of demise?
   - SARs was lethal but its infectivity was not as high as COVID-19’s. MERS was also more lethal, but not as widespread. COVID-19 may behave differently in its persistence, because it is so adapted and transmits so well. There are regional differences and, without travel limitations, this becomes more difficult. Small jurisdictions are easier to control.