The Vaccine Issue

Season's Greeting everyone. I was holding off putting out the next COVID newsletter until more information on the COVID vaccines became available but we are fielding so many questions in the office about the vaccine it's time to put something out.

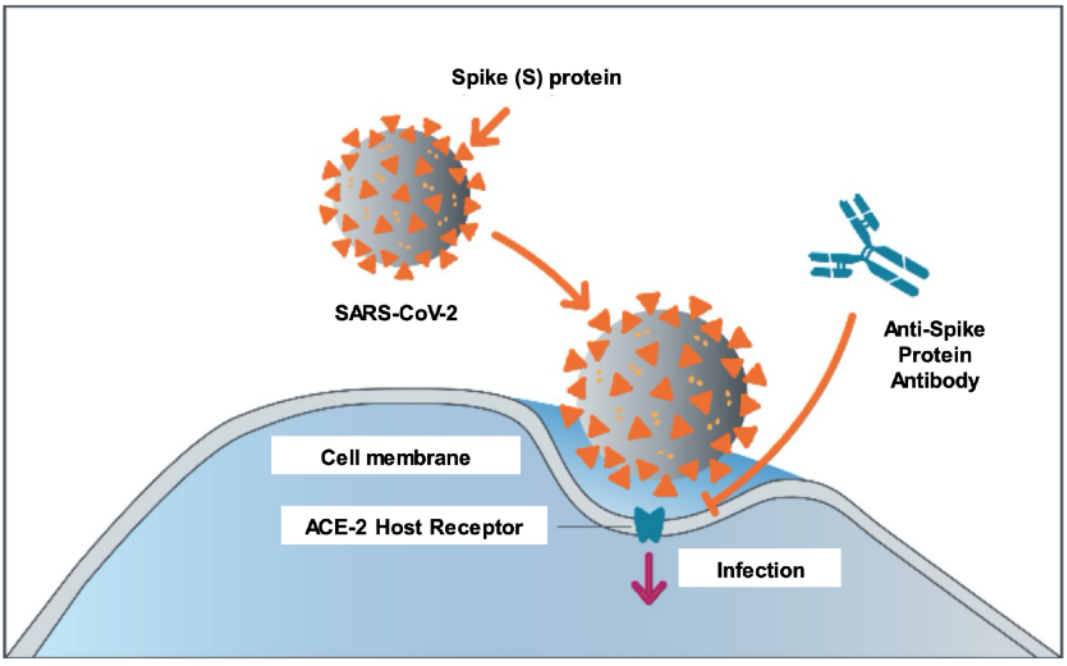
Things are changing so quickly that I must emphasize that what I say stands true for today. Things may very well change as more information comes out.

Presently we have two COVID-19 vaccines approved by Heath Canada under emergency use authorization. The Pfizer-BioNTech vaccine and the Moderna vaccine (mRNA vaccines). I expect the Janssen/Johnson & Johnson and Astra Zeneca / University of Oxford vaccines (Viral vector vaccines) to also be approved for use within the next couple months.

To get from discovering the genetic code of the SARS COV-2 virus to an effective vaccine in arms in 11 months is an awe inspiring scientific triumph. But there are so many questions about the vaccines. Are we rushing the vaccines? Are they safe? When will I be able to be vaccinated? I will try to try to explain what we do know and what we still don't know.

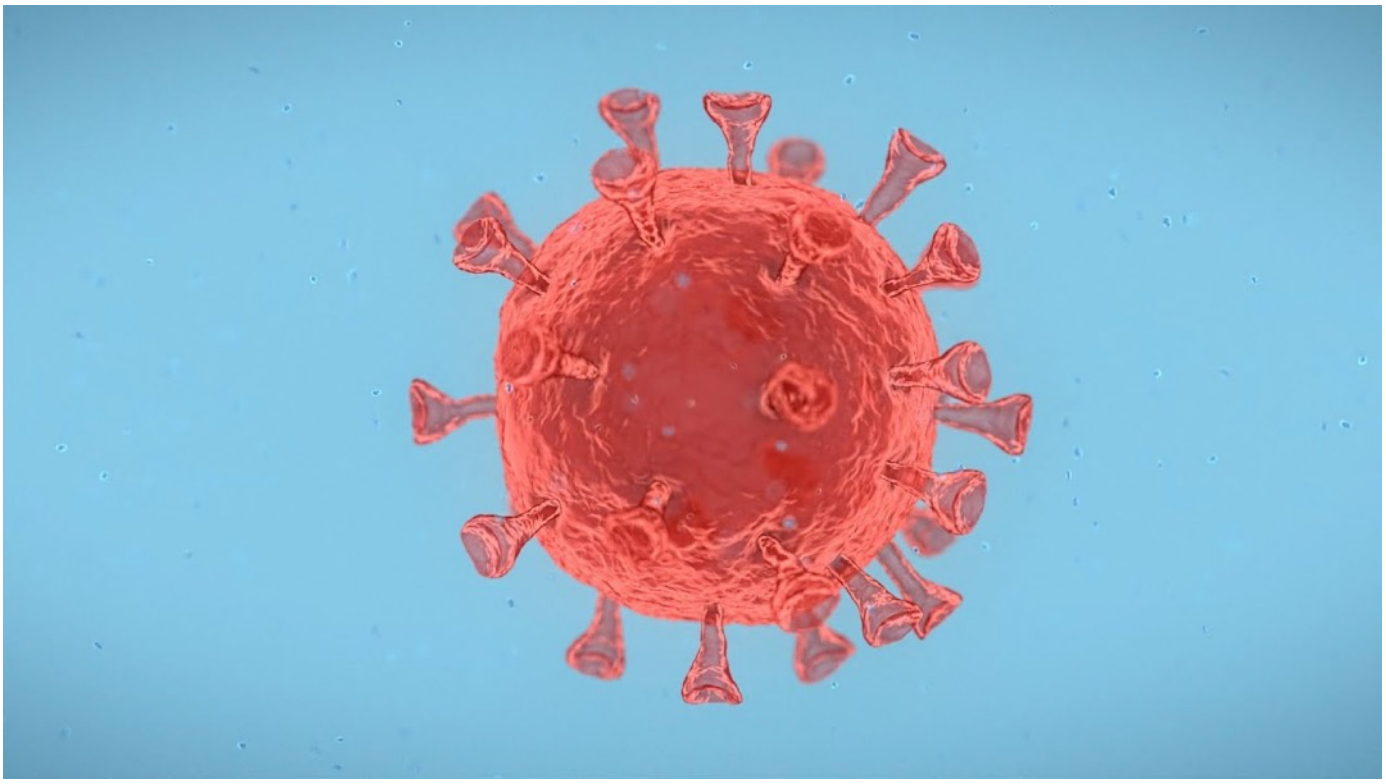
WARNING: The next two pages will be boring, geeky discussions of the virus and the vaccine!

All vaccines in development have a common end point; have the body's immune system able to make antibodies and activate certain immune cells to attack the the virus (usually the spike protein). The spike protein is what binds the virus to our cells and allows entry into the cell where it then does the work of replicating itself.



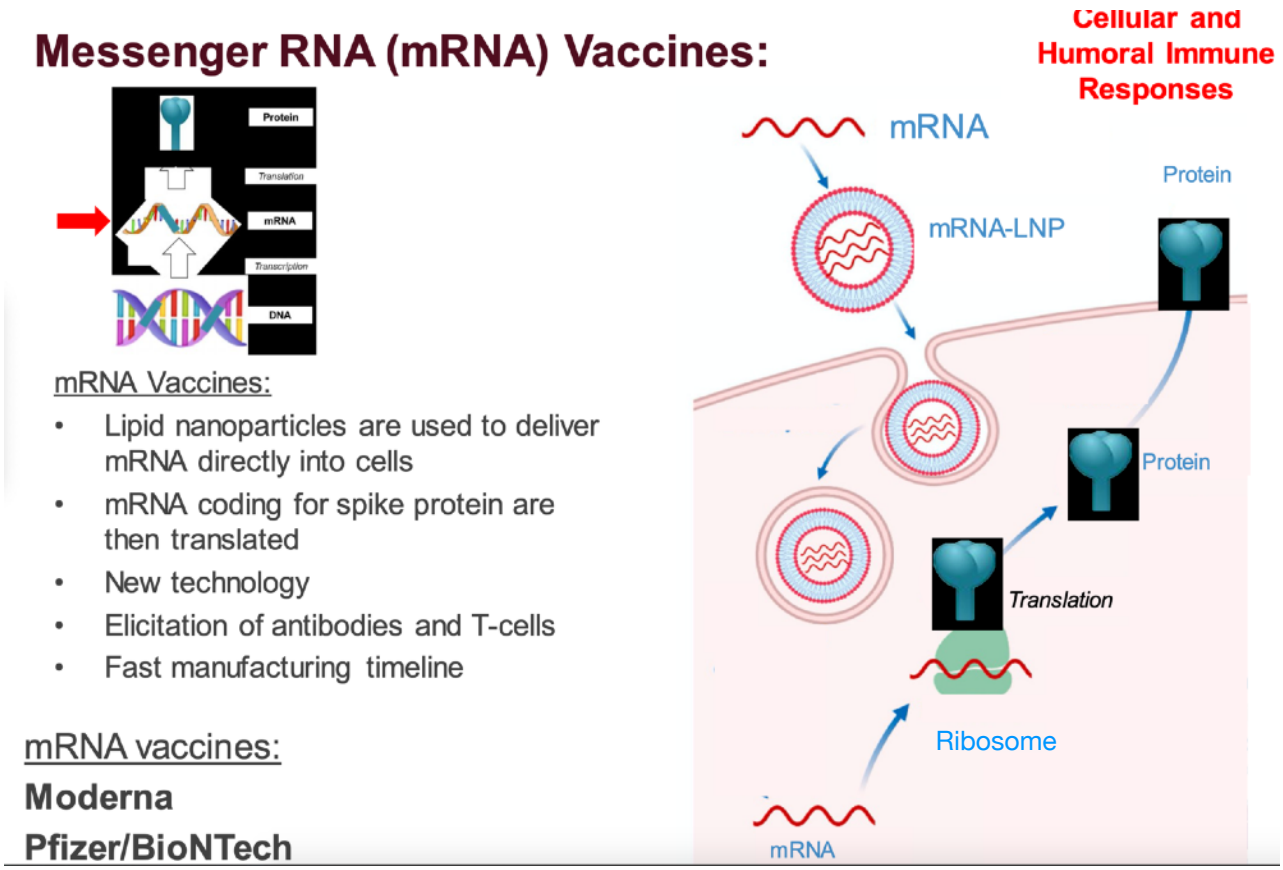
- Spike mediates contact between the virus and the host cell to cause infection
- One way to prevent infection is to block the interaction between spike and ACE-2 via the production of **anti-spike antibodies**

Here is a good video of the various types of vaccine platforms in development. Please click on image below. You may have to click twice.



mRNA vaccines. :

- The purpose of any vaccine is to mimic the infection; get the body to build immunity to the virus but not cause the illness. The vaccine will train the immune system to recognize COVID-19 and respond quickly if you are ever exposed to the actual COVID-19 virus.
- mRNA is something we already rely on in our bodies. On a regular basis, mRNA (messenger RNA) carries genetic messages from the DNA to the ribosomes (the “kitchen” of each cell) where the proteins we need for everyday life are made. mRNA is the recipe that carries information for protein production.
- A COVID-19 mRNA vaccine contains the genetic material to make the “spike protein”. The spike proteins made are then pushed out to the surface of our cell where the immune system sees it and makes protective antibodies against it. Now the immune system is ready if it gets exposed to the actual COVID virus.
- This spike protein does not cause disease. It’s not making a full car (IE. the full active virus). It’s only making the hood ornament. (Hard to drive a hood ornament home!) The vaccine does not stay in your body and does not change your own body in any way. After the protein is made, the cell breaks down the recipe instructions (mRNA). Only one copy of the spike protein can be made from one copy of mRNA,



Enough of the technical stuff.

What does this mean for you?

The first thing is that the mRNA vaccine is very fragile. Pfizer's vaccine has to be stored at minus 75 degrees Celsius and Moderna's at minus 20. Once thawed, the vaccine has a limited time in the refrigerator and all doses (5 or 10) need to be used within 6 hours of mixing. This will likely limit the ability of GP offices to vaccinate with these vaccines. We simply don't have those kind of freezers. People will likely need to travel to the hospitals where vaccination clinics are presently being set up.

The Johnson & Johnson (J&J) and Astra Zeneca vaccines can be stored like traditional vaccines; in our fridges. If the J&J and Astra Zeneca vaccines show to be safe and effective and get approved for use, I suspect that those vaccines will be the ones that doctors offices and pharmacies will be administering.

But I digress. Back to the Moderna and Pfizer vaccines. They are the only ones that are approved for use now

How new is this mRNA technology?

Actually the technology was first developed way back in the early 1990's. The thought was it could be used to develop vaccinations and possible cancer cures. Decades of work and research have been done. It just took a pandemic to launch the technology into prime time.

How effective is it?

Based on the 2 studies with a total of over 73,000 participants, very, very effective. Both vaccines showed a greater than 94% reduction in positive COVID cases. Remember we are overjoyed if we can get 60% efficacy with the flu vaccine.

How did this happen in 11 months without cutting corners?

A pre-COVID normal process from development of concept of vaccine to approval for use usually takes 4-6 years. Post-COVID was an accelerated process but there were no skipped steps. Everything was just done faster.

1) Funding was not an issue. Operation "Warp Speed" was a success (say what you want about President Trump). Securing funding often causes years of delay. That was erased with billions of dollars of support.
2) COVID was so prevalent during the study period, they were able to reach their infection targets only weeks after enrolment.
3) Allowance of a rolling submission. Study data was being filed for review as soon as data became available. Toxicologists, microbiologists, ID specialists and biostatisticians reviewed all the data. They had earlier access to the data and far more hands on deck to look at things.
4) Unlike with other vaccines that go one step at a time and then plan the next step, for the COVID-19 vaccines, governments invested in having companies plan all the steps at the beginning and build up their manufacturing capacity right away.

The only "corner" that was "cut" was the long term safety data. I'll get into that next.

How safe is it?

The mRNA vaccinations do cause short term reactions. Many people complained about fever, muscle aches, joint pains headache, fatigue, chills. Almost everyone complained of at least some injection pain. Most of these symptoms were gone in 24 hrs and the rest by 48 hours. The sore shoulder was gone by 72 hours. Symptoms were deemed mild to moderate (didn't impact function the next day). It's important to know that these are not allergic reactions or side effects. It's the immune system revving up in response to the vaccine. This is a good thing. It's sort of like what happens with the shingles vaccine but even more so. There was no difference in serious reactions between the vaccination group and the control group (that group just got a saline placebo injection).

One important thing to consider: Between the two studies, over 35,000 people got vaccinated. We don't know if there are very rare reactions which weren't picked up in the study. Let's say a severe reaction is seen only in 1/250,000. It could be missed in these studies where 35,000 got the vaccine. Time will show if this is the case or not. Even if there is a rare reaction, I would say the net benefit outweighs the harm.

Let's say 1/100,000 get a terrible adverse (and as of yet unknown) reaction. We know that even in the 20-25 year age group, the risk of death from COVID is about 1/20,000. A vaccine with a rare side effect would still be safer than getting COVID even in this lowest risk population. I am heartened that our government said they would cover the

costs of any long term harms caused by the vaccine. (This is all theoretical as, again in the studies, there have been no long term injuries from the vaccine)

I would assure you though that, if there is a signal of harm, it will be picked up. All countries are monitoring for side effects of people getting the vaccine. This is called a phase 4 study.

At the time of me typing this, the study groups have been followed for 3 months for reactions. Not a lot of time but most side effects do occur within the first few weeks of getting the vaccine. As part of the original study plan, all the people in the study will be followed for 2 years to see if there are any long term effects of the vaccine.

Hasn't there been some reported cases of anaphylaxis?

At the time of me typing this, there have been 9 worldwide reported cases of life-threatening allergic reactions (anaphylaxis) to the Pfizer vaccine and 1 case reported from the Moderna vaccine. All were treated and discharged. In the USA alone, over a million people have been vaccinated so this probably falls into one of those rare events. Most, but not all, had a history of anaphylaxis. The offending agent is thought to be Polyethylene Glycol. It's a common substance used in many products including laxatives.

New guidance from Health Canada states not to give the vaccine to someone if there is a history of anaphylaxis to polyethylene glycol or anaphylaxis with no causative agent identified. Otherwise you are OK to take the vaccine but must stay 15-20 minutes for observation.

What about Bell's Palsy?

One of the studies reported 4 cases of Bell's Palsy (facial weakness) in 22,000 people vaccinated. This number of Bell's Palsy cases is consistent with the expected rate in the general population and did not suggest it was caused by the vaccine. It will be watched in phase 4 trials to make sure it was nothing more than chance.

I heard the vaccines will change my DNA?

Nope. The mRNA never enters the nucleus of the cell where the DNA lives. mRNA cannot be written into the DNA code without an enzyme called *reverse transcriptase (*which does not exist in the human body) and mRNA is broken down immediately after the protein is made on the ribosome. It cannot effect any other cell organelle either.

Can I get COVID from the vaccine?

No. It is only making the spike protein, not the entire virus. (It's not making the car; just the hood ornament)

Does the vaccine contain Mercury, Formaldehyde, aluminum or fetal cells?

No, It contains none of the above.

I heard the vaccine makes women infertile

Untrue. Women conceived in the study after vaccination. Also, no reported cases of increased infertility as a result of COVID-19 infection.

Who Can't Get the Vaccine?

There were groups of people who were NOT included in the studies, and therefore no assumption of either safety or efficacy can be made.

The assumption is that there will be future studies done on these populations.

1) Age under 18 for the Moderna vaccine and age under 16 for the Pfizer vaccine
2) Currently pregnant, planning to become pregnant or breast feeding.
3) Those with suppressed immune systems from medications (prednisone or cancer meds) or medical conditions (Auto-immune diseases).
4) Those that have an allergy to Polyethylene Glycol , had a severe reaction to the first COVID injection, or have unknown cause of anaphylaxis.

What else do we NOT know about the vaccines?

We know they do a great job at protecting the individual getting vaccinated. What we do not know is how long that protection will last. We think and hope for at least a year but we can only continue to follow the people in the studies. We also do not know if getting the vaccine protects us from infecting others. It is possible we could have COVID in our noses and mouths that we keep at bay thanks to the vaccine but may still shed to others that have not been vaccinated yet.

So who get the vaccines and when?

That's not my call (Thank God). NACI (The National Advisory Committee on Immunizations) have given general guidelines but it's really up to the provinces and their local public health officials to determine prioritization. Nursing home residents, staff at nursing homes, hospital workers with direct patient care and native communities will likely be first. After that? Those 80 and up (probably)? Those 70 and up (likely)? Type 2 diabetics and other high risk chronic medical condition? Fire fighters and police? Other essential workers? Meatpackers? Cashiers? Bus drivers? Teachers? Those Incarcerated? "Hot spot" neighbourhoods?

Allocation of a scarce resource will require trade offs. Where will the maximum benefit to society lie?

As for when, I would expect things to ramp up as we get more vaccines approved and in the system. For most people in this practice, that will mean late spring 2021 or later. For some that are still hesitant, that will give you 9 -10 months of vaccine safety data available. I would advise if your "turn" comes up though not passing up the vaccine, just to "see" how others are doing. Society will not return to normal until we get enough people protected from this virus

Which brings me to my second last point. Although there is light at the end of this COVID tunnel, it's imperative that we realize that our situations will not change much until the fall of 2021. That is probably when we will have sufficient herd immunity to reduce the spread of the virus to a trickle. It will get better in the summer 2021 when we can get outside again, but it won't be normal again until we get enough people with protective antibodies through vaccination (preferred) or infection (definitely NOT preferred) Until then, it's keeping our distance, washing our hands often, wearing masks out in public.

In conclusion, I hope this letter gives you some insight and things to think about. When I weigh the risks vs the benefits of getting the vaccine I think the decision is clear. I will be getting this vaccine when my number is called.

Sincerely Yours.

Dr. Sean Gartner

And as an added Christmas bonus, I have included an article in todays globe and mail that describes the potential impact of the new SARS CoV-2 strains in Britain and South Africa.

Anyone curious to see evolution playing out in real time need look no further than NextStrain.org, a website that depicts the ever-sprouting family trees of different pathogens residing in the human population.

Maintained by a collective of computational biologists, NextStrain is currently displaying more than 3,500 genetically distinct branches of SARS-CoV-2, the virus that causes COVID-19. Those are just a selection of all the variations that have been seen. More are showing up all the time, thanks to the immense opportunity for diversification that the virus has gained by infecting about 80 million people this year.

Mostly, these dissimilarities lead to identical behaviour in the virus. Like fingerprints, their genetic codes are useful for identification and for tracing the history of various outbreaks. But the disease they cause is the same.

That is not the case for a pair of new variants spotted in Britain and South Africa earlier this month. Based on epidemiology and preliminary lab reports, one or both may be shifting the character of COVID-19 enough to make a difference in how the disease spreads and who catches it.

This has caused concern not only because of the potential for the pandemic to accelerate, but because a changing virus may become harder for standard COVID-19 tests to spot and for newly approved vaccines to defend against.

The two variants, as well a third reported in Nigeria, are not closely related but they share a change in their viral genomes that relates to how the virus latches on to human cells. The fact that they have arisen independently after hitting upon some of the same

genetic mutations makes it more likely that those mutations are doing something beneficial for the virus.

> "When you start to see parallel evolution of certain mutations that rise in frequency, then that's a sign that there's a real biological advantage to them," said Jeffrey Joy, a research scientist in evolutionary genetics at the BC Centre for Excellence in HIV/AIDS.

So far, the new variants have not be seen in Canada, though the search is on in earnest to discover if they are present in samples that have been gathered but yet to be sequenced so that their individual genetic codes can be read and identified.

In a statement, Gary van Domselaar, chief of bioinformatics at the National Microbiology Laboratory in Winnipeg said "we are conducting an analysis of Canadian cases of COVID-19 to identify if this variant has been previously observed in Canada."

The laboratory, which is part of the Public Health Agency of Canada, is now heading up daily meetings of a working group that includes representatives from regional centres in Quebec, Ontario, Alberta and British Columbia where much of the sequencing of virus genomes in Canada has taken place.

Earlier this week, reporters pressed federal officials to say if enough was being done to screen for the variants. To date, Canada has sequenced about 25,000 viral genomes since the pandemic began. As a straight total, this is about one fifth of what has been done by Britain. But those involved in the Canadian effort point out that it amounts to about the same fraction of cases as Britain has sequenced, which is about five per cent.

Such numbers reveal that even if sequencing was vastly ramped up, the pandemic is too widespread to surveil in a comprehensive way with existing resources. So if Canada can only screen a fraction of its total case count for genetic variants of the virus, those doing the sequencing are faced with having to choose which fraction.

Until now that has involved dividing resources about 50-50 between watching for changes in the virus coming in from abroad versus those that might arise naturally within Canada, said Catalina Lopez-Correa, executive director of the Canadian COVID Genomics Network.

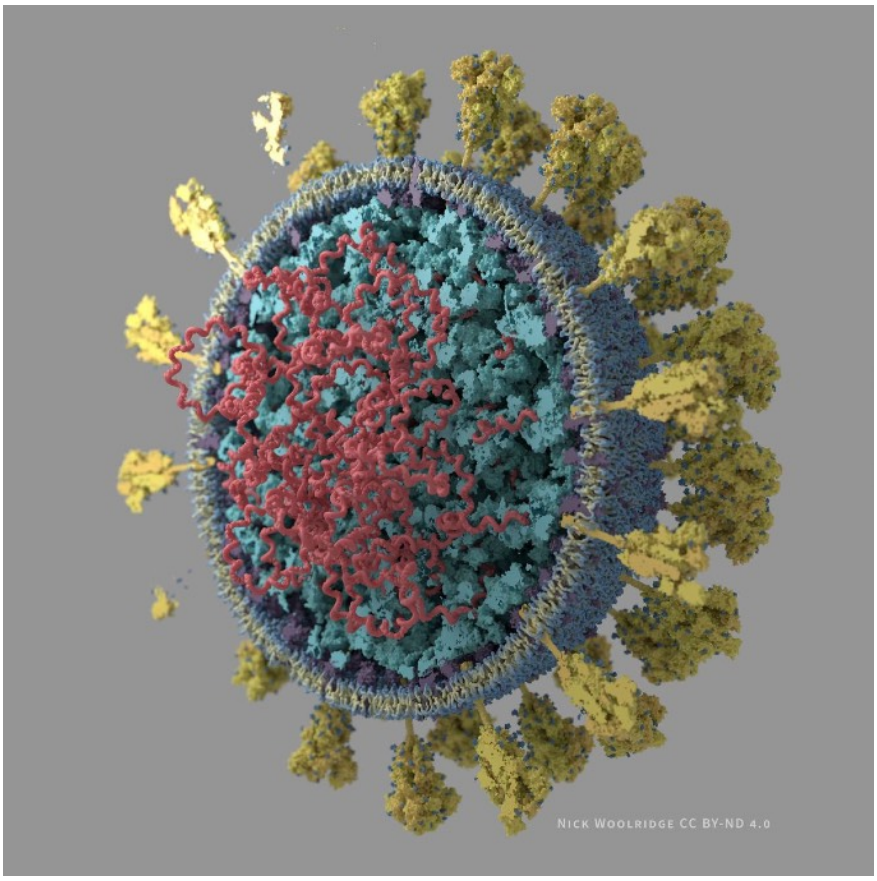
This week, the working group has been sorting out how to shift priorities to address the threat of the new variants. That will certainly include an emphasis on international travellers and their close contacts who have tested positive for COVID-19. It may also involve looking at the viral genomes from "superspreaders" that could help a new variant to gain traction after it arrives.

"This week has really put genomics in the spotlight," Dr. Lopez-Correa added.

The British variant, known as B.1.1.7, raised alarm bells last weekend because it is associated with an increase in cases in the southeast of England, where it likely originated and where it has outpaced other versions of the virus. This prompted Canada to suspend incoming flights from Britain until Jan. 6. It is also another clue that evolution is shaping the trajectory of the variant.

Genetic variants can easily become ubiquitous when they spread through a population where there is no other version of the virus around, a phenomenon known as at the "founder effect." But B.1.1.7 managed to take over in an environment with lots of coronavirus already around. That means whatever it's doing, it's doing it better.

This is is probably due to the large number of mutations the new variant carries – 23 in all, with 17 of them leading to physical changes in the viral proteins. Typically, the SARS-CoV-2 virus accumulates one or two genetic mutations per month.



The viral RNA packed into the core.

NICK WOOLRIDGE/BIOMEDICAL COMMUNICATION

"This suggests that there was a higher rate of molecular evolution in the branch of the family tree immediately before B.1.1.7," Dr. Joy said.

Those changes would have arisen in a single individual, possibly an immune-compromised patient undergoing therapy for a prolonged bout of COVID-19. A study published earlier this month in the New England Journal of Medicine demonstrates the potential of such a scenario to repeatedly challenge the virus and favour the emergence of a rare genetic combination. Evidence is mounting that in the case of B.1.1.7, the result is higher rates of infection.

One of the mutations slightly alters the structure of the virus's spike proteins – the protrusions that stick out of the coronavirus – at precisely the place where they can fix onto human cells. The South African and Nigerian variants also exhibit this change, called N501Y, and it has turned up elsewhere before. The change has been shown to increase transmission in laboratory studies. Other tweaks may improve the odds of the spike protein being in the right configuration when it makes contact with host cells as well as its ability to seal the deal by efficiently fusing with its target.

Marceline Côté, a molecular virologist at the University of Ottawa, said she expects to start studying some of the changes in her laboratory to determine precisely how they might be benefiting the virus. She added that the details of how the spike protein of SARS-CoV-2 behaves are notoriously complex and not entirely understood, despite initially appearing genetically similar to that of the original SARS virus.

"It has a lot of tricks up its sleeve that we didn't necessarily expect," Dr. Côté said.

A key question is whether the new variants alter the spike protein enough to thwart the efficacy of the first round of COVID-19 vaccines. While the question must be put to the test, Dr. Côté noted that the vaccines are made to stimulate a response to multiple parts of the spike, not just the few areas that have changed in the variants. With luck, many of the antibodies that the vaccines stimulate will still serve to lock up the virus and prevent if from infecting cells.

In a statement, vaccine-maker Moderna Inc. expressed confidence that the change would not affect the immune response to the the spike protein induced by its vaccine, approved by Health Canada on Wednesday. The company added that, "We will be performing additional tests of the vaccine in the coming weeks to confirm this expectation."

The impact of a slight change to the spike has been observed before, most notably when a European variant of the virus took over from the one that began the pandemic. That version became dominant in Canada early in the pandemic.

According to Sandrine Moreira, a bioinformatics specialist with Quebec's public health lab, the European variant arrived early on, before travel restrictions were imposed. During that time, "we observed huge diversity" in the genetics of the virus as infections arrived from different parts of the world. That diversity later decreased during lockdown, and Dr. Moreira said that the analysis has yet to be done for summer and fall when some international travel resumed.

"What I suspect is that we'll see increased diversity because of new introductions," she said.

A modelling study posted online Wednesday by researchers at the London School of Hygiene and Tropical Medicine shows why this matters. The analysis estimates that the new variant is 56 per cent more transmissible. That does not mean the disease is more severe – the study found no clear evidence on this point, either way.

But the authors note that higher transmission means more cases overall with the public-health measures that are currently in place, which means more people in hospital and more deaths because of COVID in 2021.

"It may be necessary to greatly accelerate vaccine rollout to have an appreciable impact in suppressing the resulting disease burden," the authors point out.

Epidemiological data in Britain also indicates that the new variant may be more able to infect children. That would fit with the evidence that the new variant is more easily able to bind to human cell receptors. The change would amount to a "levelling the playing field" for infection as a function of age, said Wendy Barclay, a virologist at Imperial College London, during a Q&A session with reporters on Tuesday.

Jesse Papenburg, a pediatric infectious disease specialist at the Montreal Children's Hospital, said the theory hangs together but he cautioned that there are many other factors that may influence why children tend to be less susceptible to COVID-19. One of those is the yet-to-be-determined impact of previous infections by other human coronaviruses.

"I think that may be one of the missing links that, with time, we'll be able to figure out."

In the short term, however, the implications of the new variants could put public-health officials in a no-win situation, said Jason Kindrachuk, a medical microbiologist at the University of Manitoba. If they turn up in Canada in the next couple of weeks, the concern over a more transmissible version of COVID-19 that can also more easily infect children may prompt new measures, such as school closings, to keep it at bay.

Reflecting on the situation – almost as a metaphor for the entire year – Dr. Kindrachuk added, "It's frustrating, it's complex, it's intriguing … and we're trying to temper all of that in some fashion to be able to learn what the hell is going on."