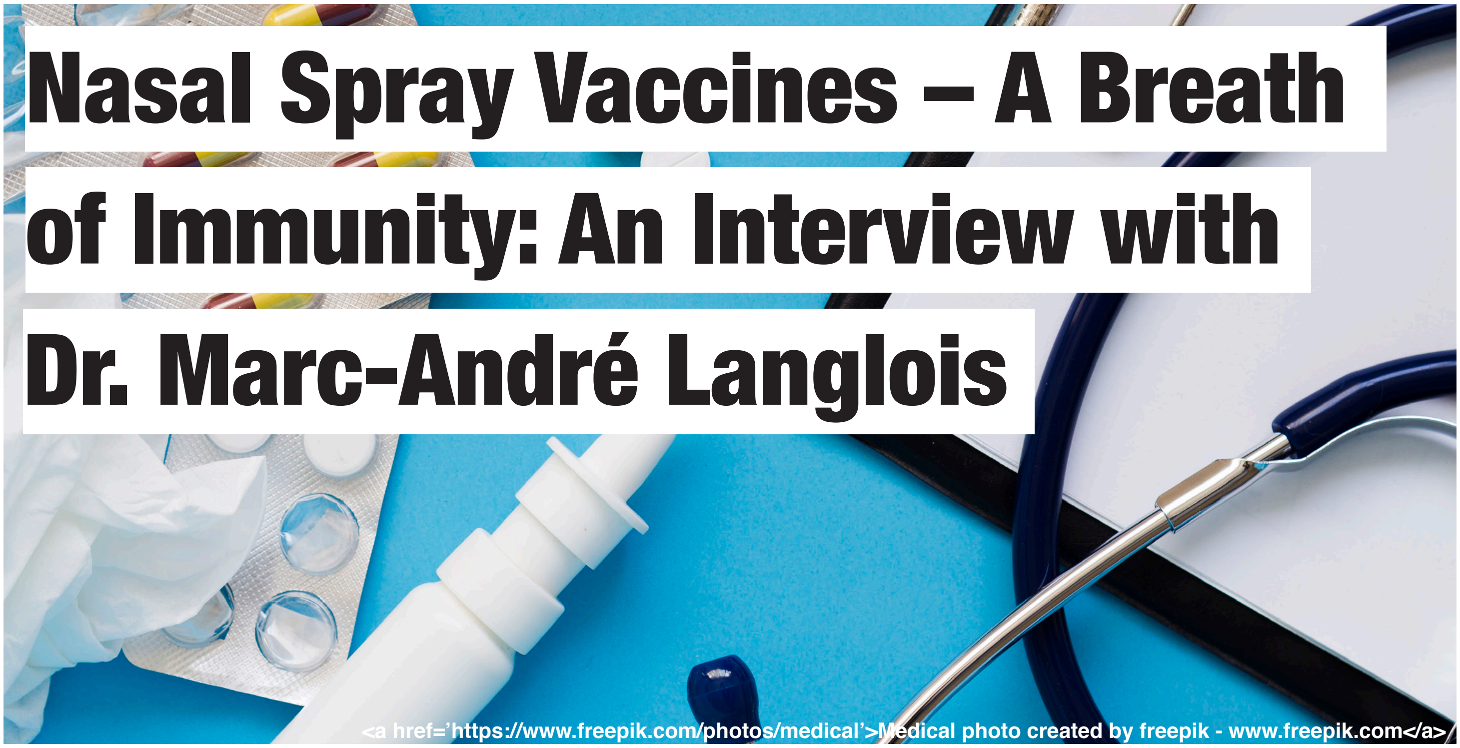
Nasal Spray Vaccines – A Breath of Immunity: An Interview with Dr. Marc-André Langlois



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ABSTRACT

Dr. Marc-André Langlois, a cutting-edge virologist, Canada Research Chair in Molecular Virology and Intrinsic Immunity, and Professor in the Department of Biochemistry, Microbiology and Immunology at the University of Ottawa, received 1 million dollars in Canadian Institutes of Health Research (CIHR) funding to develop a nasal spray COVID-19 vaccine. We had the privilege of meeting with him virtually and having a fascinating and informative conversation on the COVID-19 pandemic, vaccines, and its effect on society.

RÉSUMÉ

Dr Marc-André Langlois, virologue renommé, titulaire de la Chaire de Recherche du Canada en Virologie Moléculaire et Immunité Intrinsèque, ainsi que professeur au sein du Département de Biochimie, Microbiologie et Immunologie de l'Université d'Ottawa, a reçu un million de dollars des Instituts de Recherche en Santé du Canada (IRSC) afin de mettre au point un vaccin contre la COVID-19 sous forme de vaporisateur nasal. Nous avons eu le privilège de le rencontrer virtuellement et d'avoir une conversation fascinante et instructive à propos de la pandémie, des vaccins et de l'effet de la COVID-19 sur la société.

Keywords: *Interview, virologist, COVID-19, pandemic, vaccine*

Can you please say a few words about your academic background? How did you choose your career in virology research?

Well, ending up in virology was a little bit of serendipity. During my bachelor's degree in Microbiology, I became very interested in immunology and allergy. So, I did my Master's in immunology. To learn more technical approaches, such as modifying genes and expressing proteins, I did a PhD in molecular and cell biology so that my career could move forward. During my PhD, I learned cloning techniques and worked with viral vectors for gene delivery. After that, I looked around for top labs working on antibody affinity maturation and class switching and ended up doing a postdoc with Dr. Michael Neuberger in Cambridge, UK. His lab had just discovered a new protein part of the innate immune system, among the first retroviral restriction factors found called APOBEC3. I thought the field of retroviruses was fascinating. The whole sphere around retroviruses and how the immune system restricts them fascinates me. This is what my lab studied until the COVID-19 pandemic. When the pandemic hit, I refocused our efforts on what was immediately necessary at the beginning of the pandemic, such as viral detection and serological assays. My lab's activities pivoted quite significantly at that point.

In what ways is the COVID-19 pandemic similar to other previous viral pandemics?

We haven't had many pandemics in our lifetime. There was the HIV pandemic. However, HIV is not as easily transmitted as an airborne respiratory virus. Influenza is also a pandemic virus, but we have vaccines for it. COVID-19 is so different because it's the first time humans are exposed to such an infectious virus that causes severe morbidity and high mortality levels. And, we had no vaccines for this virus when it started spreading. So, in this instance, the coronavirus is very different from the other viruses so far because we were unprepared for it.

We can make comparisons to the Spanish flu; this is what is done very frequently. However, over a hundred years ago, medical advances were not what they are now. In 1918, the world was coming out of a war and hospitals were filled with injured soldiers. So, the socio-demographic, economic situation was very, very different back then. This is probably why the virus spread so quickly. There were many injured people in dense shelters after the bombing, so the virus could easily be transmitted; there were no vaccines for influenza back then. Therefore, the virus caused a lot of damage and deaths.

The circumstances are entirely different now. The world has a much higher population density. Cities are highly populated, and there's a lot of public transport with a high density of people. In some ways, the current pandemic has its own unique challenges that we were not faced with before, such as air travel. We've realized how reliant we were on air travel to go to conferences and holidays to visit families. And all of a sudden, there's no more air travel. Those are the implications of having a pandemic virus that is airborne and transmitted through aerosols. These viruses are highly transmissible and infectious.

What do you think are the possible reasons that COVID-19 has a differential effect on people across different age groups or people with different comorbidities or characteristics?

We know that if you have an underlying health condition and you're infected with this virus, you will do less well than healthy individuals. Therefore, individuals in long-term care are often afflicted with multiple comorbidities and are impacted much more. We also know that COVID-19 is an inflammatory disease, so it causes severe inflammation in the lungs. Why does it do that more than other viruses? We do not exactly know yet. However, we can observe that most children infected can be carriers of the virus and transmit the virus, but they don't appear to have severe symptoms in most cases; they don't appear to have high levels of inflammation. There are differences in how the virus propagates and causes disease in younger humans, adults, and the elderly. A possible reason is that the angiotensin-converting enzyme levels in children are lower than in an adult. However, it has not been formally demonstrated yet as a probable cause for the difference in infection.

In general, there are a lot of factors that can affect how humans will experience an infection. Indeed, the genetics of the immune system could be a component. We all know that T cell responses are closely linked to human genetics and how these antigens are presented on the surface of T cells. Another parameter that can affect the severity of the disease is pre-exposure to other coronaviruses. There are seasonal coronaviruses that regularly infect us and cause the common cold. We don't make much of them because they usually don't cause severe disease; we cough, have a runny nose and still go to work (when we shouldn't!). These exposures to the seasonal coronavirus do appear to be protective to some degree. If you have had a recent infection of another coronavirus, there is evidence that you could be protected against severe symptoms of COVID-19. So, suppose you look at the complete landscape. In that case, many factors will contribute to whether or not you will be very sick or you will be asymptomatic. Still, we haven't discovered all the factors that are involved in COVID-19 disease severity.

So, you have received massive funding to lead a national group in the development of the nasal vaccine Congratulations, by the way. Could you tell us a bit

more about that project? What are the advantages and disadvantages to nasal vaccines compared to injected vaccines?

A year ago, we received funding to develop a nasal spray vaccine. We were well aware that several companies were developing injected vaccines. The new mRNA vaccines and the vector vaccines would also be coming out very quickly, given the relative simplicity of the Coronavirus. The Coronavirus has one huge antigen on its surface called the spike. All these vaccines are designed to stimulate your immune system to recognize that spike protein, neutralizing it and preventing the virus from infecting new cells. We were well aware that most vaccine approaches would be a standard injection, so we wanted to take another approach to stimulate mucosal immunity in the airways. Given that this is a respiratory virus, you have to inhale it to get infected.

Mucosal immunity is very localized. And, in the case of a nasal spray, it would be just in the upper respiratory tract. This is where the virus comes in. These are the first cells that are infected. When these cells are infected, the viruses can then go down and make their way to the lower respiratory tract. That's when one would get really sick. The idea is that if you can block the virus at the very early stages, at the very entrance to your respiratory tract, you'd have a better chance of neutralizing that virus. The nasal spray vaccine has the advantage of stimulating the immune system exactly where the virus comes in.

Further, vaccine hesitancy is a real impediment to herd immunity, even with very safe vaccines. We expect no more than 65, maybe 70% of the population, will accept both doses of the vaccine. So that exposes 30 to 35% of the people that want nothing to do with the vaccine. A nasal spray vaccine is seen as generally less invasive. There's no needle. It's just a spray; people take sprays for allergies all the time, for instance. Hence, it is seen as generally non-invasive. It almost doesn't feel like a vaccine for most people. And we felt that by developing such a nasal vaccine, we were basically filling the gap in the vaccination campaigns.

Furthermore, the vaccines you receive intramuscularly enable you to develop a potentially severe response. But this immunity wanes over time. So, let's say you took your last shot of COVID vaccines 14 months ago, and you have to take the plane. Perhaps, if you had a nasal spray vaccine that you could get over the counter, you could take it a week or two before boarding the plane. In that case, you could stimulate that mucosal immunity in your upper respiratory tract, which might just give you enough added protection.

Current coronavirus vaccines that are out right now do not necessarily provide sterilizing immunity, which means to protect completely from infection. But by using both vaccine strategies together, you would be stimulating a robust IgA response in the upper respiratory tract and standard neutralizing IgG responses in the lower respiratory tract and blood. So, if you inhale a virus, you can neutralize it at the entry point, and you would have the backup of a standard vaccine. This is how we imagined a nasal spray vaccine to be beneficial; it's not competing with vaccines from giant pharmaceutical companies.

Would this vaccine also be RNA based?

It is a protein-based vaccine, we are expressing parts of the surface spike protein, and we are doing that in plants. Another major issue with vaccines is the global access to vaccines. These mRNA vaccines need to be maintained frozen, and it's challenging to maintain this cold chain if you're going into Africa and Asia. So, there are large populations of humans that would struggle to access these vaccines. Protein-based vaccines have the advantage of being more stable at warmer temperatures and are easier to ship. By developing nasal spray protein-based vaccines made in plants, countries could technically produce their own supplies. The complexity of creating them is much less. There are several advantages for global distribution and accessibility.

Now we're at a stage where we successfully produce the proteins in these plans. We've tested the proteins compared to proteins made in human cells. They're performing just as well in ELISA (enzyme-linked immunosorbent assay) and neutralization assays. It is a very promising approach, but it is still at the experimental stage.

What candidate viruses do you fear the most for future pandemics?

Influenza and coronaviruses are highly infectious airborne viruses. We have seen that such viruses that infect the lungs create tremendous complications in hospitals and broader society. Specialized protective equipment and stringent protocols are needed to treat such diseases, such as N95 masks, visors, ventilators, and isolation areas. You're also putting all your staff at risk every time you treat a patient; that patient might cough and create more aerosols, and there could be multiple transmissions. There are massive complications with airborne viruses.

In contrast, blood-borne viruses, such as HIV, have much more limited transmission. They can't quickly spread without direct and intimate contact. I think respiratory viruses will be something that will be on everyone's radar for a very long time.

Will our daily lives go back to normal?

The definition of normal will change. The new normal for the future will incorporate the lessons that have been learned. The first lesson is that many of us do not need to go to work every day physically. We've realized that the overall productivity of the human population has not gone down from working at home. In most cases, people are honest and give a genuine fair day's work at home. The advantages of not commuting to work are clear. Suddenly, you gain one to four hours a day of your life by being at home, where you can be productive for yourself and your family. Some individuals do need to physically go to work due to the nature of their employment or for their mental health. Still, overall, we realize that a lot can be done at home. People won't travel as much for conferences and business. Companies have realized they're saving money by not holding all their meetings in person.

The norm will also change concerning sanitary measures in public spaces. Will there be a mandatory mask-wearing time in metros or buses? Next time its flu season, we might be asking everyone to wear a mask inside public buildings. Wearing a mask will now have become part of our norm. It's not a strange thing anymore. So, there will be all these small changes throughout society and in our everyday routine.

In 10 or 15 years, when the next generation who have not lived through the pandemic become teenagers, it will mostly be a historical event for them. The fear of the pandemic will dissipate because it will not be something observable. However, the way the pandemic has changed the population's perspective may remain. The awareness of contagion and transmittable diseases will become ingrained in society, similar to the current culture in Asia. When you go to Japan, you see many people wearing masks in high-density public areas. It is perceived as a good hygienic practice and part of the culture to wear a mask when entering high-density environments, especially if you have sniffles.

What is very particular about this pandemic is that everything has been documented in great detail because of the widespread use of digital media If faced with the dangers of a new pandemic, future generations will have the opportunity to go back to these archives and evaluate what worked and what did not. Hopefully, they will make better decisions regarding promptly imposing the wearing of masks in public and shutting down borders and travel to avoid worldwide spread.