REFLECTION
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Addressing COVID-19 vaccine hesitancy - healthcare workers and trainees must be equipped for discussions about vaccines

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ABSTRACT

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has challenged our world throughout the past year. As we end 2020 conversing with loved ones, the topic of COVID-19 vaccination is inevitable. Throughout the next year, our gradual return to a more familiar society will be influenced by vaccine compliance. It is therefore paramount that healthcare professionals and trainees are equipped with current knowledge to address the questions and concerns of our loved ones. The Holidays should be viewed as an opportunity to address misconceptions and questions. This brief review outlines some arguments for why a COVID-19 vaccine is necessary and clarifies some features of the current top vaccine candidates. By addressing the questions and concerns of our loved ones before they need to decide whether or not they will receive a COVID-19 vaccine, we lay the groundwork for them to make informed choices.

KEYWORDS
COVID-19, vaccination

1 | REFLECTION

As we reflect on the Holiday season, the world is still grappling with what was a year dominated by personal, professional, economic, and health challenges. We have seen how coronavirus disease 2019 (COVID-19) has flipped our society on its head, and we have experienced the tolls of lockdowns to prevent the spread of SARS-CoV-2. We ended the previous year with hopes that a return to normalcy in our society is approaching, prompted by news that vaccine development efforts were charging forward with success. However, this previous year had also been marked by significant political unrest, immense personal and economic sacrifices, and

decreased trust in the very systems that are working to resolve the pandemic. Indeed, vaccine hesitancy is a significant hurdle that must be overcome - it is vaccinations, and not vaccines themselves, that offer us a return to normalcy. As we finished the year having conversations with our loved ones, many of us healthcare trainees and professionals might have unknowingly stepped into a boxing ring where misinformation from social media and inflammatory reporting has ruled victorious throughout the past months. Although it is clear that misinformation on this topic is widespread, some of our family members might also have reservations about the COVID-19 vaccines that stem from uncertainty around how the vaccines work or difficulties in understanding their safety profiles. It is therefore paramount that we, as representatives of the healthcare field, be prepared to address the questions and concerns that will inevitably arise in our future interactions with the people in our personal lives. We should view our conversations with friends and family as an opportunity to lay the groundwork on the role that vaccinations will play in resolving the pandemic. This summary aims to provide health trainees and professionals with current information on COVID-19 and vaccination. This is not an exhaustive review, but rather a small collection of information that will arm healthcare trainees and professionals with knowledge and resources to engage with questions on this topic that might arise from our loved ones.

2 | WHY VACCINES ARE NECESSARY

To understand why a vaccine is our best shot at resolving the COVID-19 pandemic, we need to make note of some disease characteristics. SARS-CoV-2 is an incredibly infectious virus with the capacity to spread uncontrollably in our population. The reproductive number (R_0) – the number of individuals one infected person is likely to infect – is estimated based on how long someone with the virus is contagious, the probability of an infected person passing the virus on to someone they are in contact with, and the frequency of contact with others in society (1,2). The R_0 for SARS-CoV-2 is estimated to be between 2.0 and 3.0 (3), higher than seasonal influenza which is typically around 1.3 (4). To help understand the significance of this difference, if we were to compare a typical influenza with an R_0 of 1.3, and the more conservative estimate of the R_0 for SARS-CoV-2 at 2.0, after ten cycles of infection we would estimate that influenza would affect approximately 56 people and SARS-CoV-2 would affect 2,047 people. A part of why SARS-CoV-2 can spread so uncontrollably in our society is that individuals without any noticeable symptoms or signs of disease can spread the virus (5–7). The incubation period – the time separating exposure to SARS-CoV-2 and the onset of symptoms – ranges from 1-14 days (8) with a median of 4-5 days (9,10). Indeed, many individuals are infectious days before noticing illness (11), making the control of outbreaks logistically complex. The R_0 can be decreased by limiting our contact with others in society (e.g. lockdowns, social distancing, masks) and we prevent the growth of infections only when this number falls below 1.0 (12). COVID-19 has claimed the lives of over 16,000 Canadians since the first death nine months ago (13). Although influenza mortality can be challenging to accurately determine, the mortality of COVID-19 is much higher than the estimated 3,500 Canadians who die from seasonal influenza each year (14). Notably, these deaths occurred while implementing strict containment practices. Between March and June, Canada had an excess of 7,000 deaths aligning well with the first wave of the COVID-19 pandemic (15). To resolve the COVID-19 pandemic, it is clear that our society must achieve a significant degree of immunity.

Early on in the pandemic, social media posts suggesting the use of 'COVID parties' became widespread, advocating that individuals intentionally expose themselves to SARS-CoV-2 so as to 'get their infection out of the way.' There are many reasons why vaccine-mediated immunity is preferable to infection-acquired immunity. Firstly, our healthcare system cannot manage such a rapid influx of patients sick with COVID pneumonia – though our containment efforts help to reduce the number of cases and hospitalizations, COVID-19 has still

managed to place immense stress on our healthcare system. At the time of this article, nearly 700,000 Canadians have tested positive for COVID-19 (16), comprising about 1.8% of Canada's population. The minimum number of immune people needed to protect the whole population from transmission (i.e. 'herd immunity') can be estimated using the R_0 value by the formula 1-(1/R_0) (17). Since the estimated R_0 of SARS-CoV-2 ranges from 2.0-3.0, we can predict that between 50-67% of Canadians (at least 19 million people) would have to contract COVID-19 to reach this objective, and this is likely to be an underestimate. With the current case mortality rate estimated at 2-4%, this would equate to 380,000-760,000 COVID-19 deaths in Canada to reach natural herd immunity. This is assuming that reinfection does not occur, and that immunity following natural infection is long-lasting, which are not valid assumptions given that re-infection has been described in a growing population of patients (18,19). This is also not considering the non-COVID-19 mortality that would result from a lack of resources in a healthcare system overrun with COVID-19 patients. Thus, the massive number of deaths that would result from a pursuit to obtain natural immunity is an unacceptable and preventable cost. Secondly, COVID-19 is a novel disease, and there are many potential long-term health consequences to infection. Indeed, there is an increasing awareness that 'long COVID' will be a significant sequela to the pandemic, and includes a myriad of complications such as prolonged fatigue (20), cognitive impairment (21–23), cardiomyopathy (24,25), lung scarring and fibrosis (26,27), and many other serious consequences of the inflammatory and immunogenic insults of COVID-19 (28,29). These long-term manifestations of COVID-19 infection may very well impact our health system for decades to come, so obtaining targeted immunity without these long-term consequences is ideal. Thirdly, many might have heard speculation that previous infection with seasonal coronaviruses (which cause about 30% of common colds) may confer immunity to SARS-CoV-2. However, a retrospective clinical investigation found that the serum from individuals with previous seasonal coronavirus infection had protection against seasonal but not pandemic strains, suggesting that this immunity is not generalizable (30). Moreover, immunity to seasonal coronaviruses typically lasts approximately 12 months, and reinfection with the same strain of virus beyond this timeline does occur (31). We do not yet know exactly how long COVID-19 immunity lasts, either by vaccination or by infection, but one recent report suggests that immunity following infection lasts for at least six months (32). A recent update on the Moderna mRNA-1273 vaccine demonstrated elevated antibody titers at 119 days following initial inoculation (33). Finally, some have argued that vaccines are not necessary since SARS-CoV-2 will continue to mutate as the pandemic continues, attenuating or becoming less pathogenic over time. Though it is true that this phenomenon is observed for other RNA viruses, such as influenza, the per base mutation rate of SARS coronaviruses is less than that of influenza due to proofreading enzymes and complex mismatch repair machinery that correct errors in replication of the viral genome (34–36). Some experts estimate that effective attenuation of SARS-CoV-2 would take years to develop, with each year infecting millions more. These statements are not intended to intimidate the reader or their family members, but rather to dispel misconceptions about COVID-19 epidemiology and immunology, and to reaffirm why vaccination is being pursued. By creating vaccines, we are effectively able to achieve herd immunity to COVID-19, minimize the number of deaths, hospitalization, and long-term disability, while sustaining immunity safely through the use of boosters if necessary.

3 | VACCINE CANDIDATES: MECHANISMS AND SAFETY

Now that we have discussed some reasons why vaccinations will be so important in resolving the pandemic, we will review some information about the current vaccine candidates. This commentary is not meant to be an exhaustive review of the vaccine candidates themselves – a useful website for staying up to date with the status of all 60 current vaccine candidates is COVID19 Vaccine

Tracker (https://covid19.trackvaccines.org/). The Pfizer and Moderna vaccines deliver a small messenger RNA (mRNA) molecule to our cells which lets them produce a small fraction or a modified version of the viral spike protein without ever having virus in the body. This allows the immune system to naturally react and produce antibodies against these proteins so that if the virus does ever enter the body the immune system can attack and clear it before infection can happen. The Oxford vaccine uses an adenovirus that does not cause disease in humans to deliver some of the SARS-CoV-2 genetic material to the body, so that the body can produce a small fraction of the viral protein and build immunity through almost the same mechanism as the mRNA vaccines. Although all of these vaccines work by introducing a small amount of viral genetic material into the body, this material is not stable and is degraded a short time after vaccination and does not enter the nucleus of cells or change the host's DNA (37). The benefit of these technologies is that a person is never exposed to the unmodified or disease-causing parts of the virus. In the opinion of the authors, they are the most technologically advanced and controlled vaccines ever made. Early phase III trial data from these vaccine candidates have shown at least 90% efficacy in preventing infection, and one showed 100% efficacy in preventing severe COVID-19 (38,39). Better efficacy estimates will be determined as more data becomes available, but this data is very encouraging since there was a chance that none of the candidates would show efficacy. Importantly, this does not mean that the pandemic is over, and we must remain vigilant to reduce the spread of COVID-19 throughout the next year.

With any new treatment or intervention, safety is a top priority. These will be the first vaccines to use this type of technology in humans, and care must be taken to develop them and test their safety and effectiveness. As physician-scientists in training, we have watched in awe at how rapidly the scientific community has learned about SARS-CoV-2 and COVID-19. However, when taking the perspectives of those outside of science, we can appreciate why many may observe this incredible velocity with skepticism. Indeed, many will question whether vaccine development was rushed, and if safety was sacrificed due to urgency. To understand why this is not the case, we need to briefly discuss the process of vaccine development. Vaccines are developed and distributed in numerous stages, including pre-clinical scientific investigation, animal studies, human trials with increasing numbers of participants (phases I-III), approval, manufacturing, distribution, and monitoring. Although this development course typically takes approximately 10-15 years before the monitoring stage, there are factors that have contributed to increasing the efficiency of this process for COVID-19. Firstly, research and development into pandemic coronaviruses had already begun prior to the existence of SARS-CoV-2. This is because the related coronaviruses, SARS-CoV and Middle Eastern respiratory syndrome (MERS) coronavirus already had ongoing vaccine development efforts. Indeed, the technology that had been developed to vaccinate against MERS allowed for the efficient focused scientific investigation of vaccines against SARS-CoV-2 (40). Recruitment of volunteers for human trials can take a long time, but due to the global influence of COVID-19 many were eager to volunteer, willing to aid in the testing of vaccines. Due to the urgent need for a vaccine, research programs were able to overlap different phases of human trials, beginning phase II trials at the time that phase I trials were being completed, for example. Manufacturing is labour-intensive and costs billions of dollars, and thus it typically only begins once phase III trials have been completed and approval has been granted. The need for a vaccine to be available to the public once it has been definitely demonstrated to be both safe and effective meant that manufacturing could begin early for promising candidates. This was done with the complete acceptance that millions of doses will be disposed of if the candidate is not definitely demonstrated to be both safe and effective. All of these factors have greatly increased the efficiency of vaccine development, without sacrificing any assessment of safety. Vaccines are only approved if they meet incredibly high standards of safety.

With over 20,000 participants involved in the individual clinical trials for any of the approved vaccines, corners are not being cut. It is worth pointing out that due to the large number of participants in these trials, by

the time that a vaccine is made available to the public, thousands of volunteers have taken it and those in earlier trial phases have now been monitored for months. The clinical trials also boast diverse patient populations (38,41), so the utility of the vaccines for different populations is well-determined. It is also of paramount importance to point out that while there may be side effects of drugs that are used for diseases, many of which have been overlooked historically, vaccines are arguably the safest, and most effective medicines in human history. These vaccines are no exception and rely on the same natural action of the human body to build an immune response against this virus. They just use a different delivery system – they allow our immune systems to react to an incomplete part of the virus in a controlled way, avoiding the serious complications that uncontrolled infection can have on multiple organ systems.

This controlled activation of our immune systems by vaccination may be associated with side effects such as headache, fever, body aches, pain at the injection site, and very rarely, allergic reactions (38,42). To help illustrate how rare severe allergic reactions are, consider the example of anaphylaxis following COVID-19 vaccination, which has an incidence of 11.1 cases per million doses (43). If a healthcare worker vaccinated one person every minute of every day throughout an eight-hour shift, they would expect to see one case of vaccine-induced anaphylaxis after six months of work. This case would be rapidly identified and treated effectively. If you were to alternatively expose people to COVID-19 at the same rate, you would expect between 10-20 deaths due to COVID-19 every day throughout a six-month period. The benefits of vaccination far outweigh the low risk of serious allergic reactions to vaccines, despite their media presence. These side effects are possible in other vaccinations which are given to millions of people safely each year (e.g. measles, polio, influenza). Side effects from vaccination are a product of the vaccine activating our immune systems and the vast majority resolve within a few days. Importantly, the side effects advertised as possibly occurring due to a vaccine can also occur from infection itself, and the incidence of some (e.g. Guillain-Barre Syndrome) is an order of magnitude more likely to occur from infection than vaccination (44).

The hope with this new technology is that it will allow for a more targeted and effective immune response and faster vaccine production. These are technologies which scientists around the world have been developing for years, being catapulted to the forefront of the medical frontier today because of dire need. This is not the first time that science has answered a call of extreme urgency with incredible leaps forward, and it will not be the last.

4 | CONCLUSION

As we reflect on the COVID-19 pandemic last year and wonder what the current year holds, it is important that health professionals and trainees remain informed about this global disease. With vaccines now being administered at a record pace, vaccine hesitancy should be addressed before hesitant individuals are asked to get in line for their shot. Our return to normalcy will not occur over night - it will occur gradually throughout a logistically complex national vaccination campaign and depend on the degree of immunity that we are able to develop and maintain in our population. This will take time and there will be delays, but these delays can be reduced significantly if we have good vaccine compliance throughout the entirety of this vaccination campaign. We have discussed some points that we believe will be useful for healthcare professionals and trainees when addressing some of the concerns of their family members.

Approaching conversations on this topic should be done with great care and should be tailored to one's audience. Though the information in this commentary may help you to construct answers to some of the questions your family members might have on this topic, providing this information will likely not be sufficient to convince someone who is vaccine-hesitant to jump to the front of the line when vaccines are made available to them. However, the tactful communication of this knowledge will allow you to address some of the concerns and perhaps misinformation on this topic that would prevent

individuals from making informed decisions regarding vaccination. Laying the groundwork now means preparing our loved ones for the decisions they will need to make throughout the next year regarding vaccination. The pandemic has placed a massive stress on many aspects of our society, and we must listen carefully to the concerns of our loved ones, empowering them to make informed choices. The pandemic will end with vaccination, and as we write this article both Pfizer's and Moderna's mRNA COVID-19 vaccines have been approved by Health Canada and are being administered to citizens. The authors will gladly line up to receive any approved COVID-19 vaccines as soon as they are made available to us. We encourage our colleagues and loved ones to place similar trust in the rigorous systems involved in vaccine development and approval in Canada.

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