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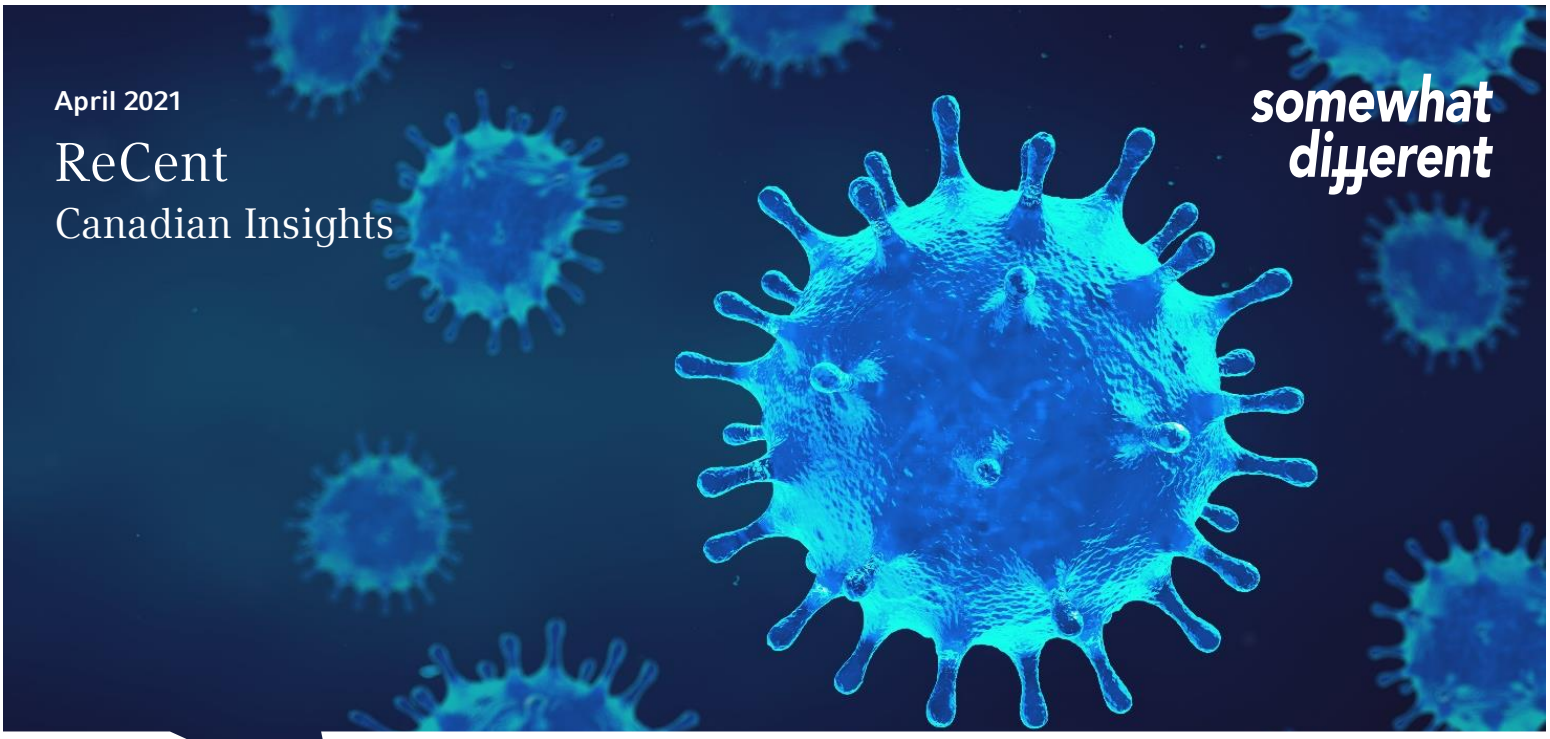

What are the implications for the insurance industry?

# COVID-19 vaccines in Canada

## Introduction

The world has seen many pandemics over the centuries. Small pox, the bubonic plague (also known as the Black Death), and H1N1 strain of influenza (known as the Spanish Flu in 1916), are some of the diseases that have caused pandemics in the past. These diseases no longer exist as a threat to the general population and have a significantly improved prognosis as a result of anti-viral medication, good infectious disease prevention practices but most importantly, vaccines. In fact, the very first vaccine was developed against small pox late in the 18th century.[1] The pandemic caused by the H1N1 strain of influenza took more than 50 million lives in 1916–1918 but that same strain, which caused the pandemic in April 2009, resulted in fewer than 600,000 lives lost due to the effective antiviral medication and vaccine availability.

Since the COVID-19 pandemic announcement in March 2020, more than 3.0 million deaths have been reported worldwide[2] with more than 23,000 in Canada.[3] While there is not yet an effective cure, many recommendations have been developed and proposed over time as vast amounts of information became available. There appears to be some similarities between the viruses causing COVID-19 and Severe Acute Respiratory Syndrome (SARS)[4], however COVID-19 spreads much more easily through community transmission and has consequently had a much greater impact on global health care and the economy worldwide.

Multiple teams from different countries have been racing to develop a vaccine that could provide a lifetime immunity from COVID-19 and/or protect from it for enough time to allow scientists to develop an effective cure. It has been an extraordinary effort worldwide.

Along with the magnitude of research and development activities, we are also witnessing large organizations and regulatory agencies' willingness to adjust administrative parts of vaccine development phases to make the process as flexible and efficient as possible with no negative effect on the quality of the clinical trials.

## How the new vaccines work

The first vaccines to be approved in the US and Canada against SARS-CoV-2 (or COVID-19) were Pfizer/BioNtech BNT162b2 (PBV) and Moderna mRNA - 12173 (MV). These vaccines use the messenger-RNA (m-RNA) of the virus in the process of immune response development. Even though it was only in 2020 when m-RNA vaccines were included in large clinical trials and used in clinical medicine, scientists have been investigating the m-RNA vaccine method for years.[5,6]

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Imagine a virus that looks like a rubber ball with pin-like projections on the surface. The virus uses these spikes to attach to specific areas (Angiotensin II receptors) of human cells. After attaching itself, the virus penetrates the cells with the receptors and starts acting inside.

When the m-RNA of the vaccine enters a body via intramuscular injection, special cells that are part of the immune system, called macrophages, pick up the m-RNA near the injection sites. Based on the information m-RNA contains, a spike protein is made and it appears on the surface of macrophages. The macrophages present the protein to T lymphocytes, specific immune system cells in our bodies that identify these proteins as foreign. As a result, the immune system develops an immune reaction towards these foreign proteins by producing antibodies against them. Our immune system remembers the proteins and is ready to recognize and fight them or anything that contains them in the future. There is no live virus entering a body because of m-RNA vaccination. There is also no viral genetic material entering a nucleus of a human cell to change human DNA.[5,6]

## Why did development of the vaccines take a shorter time than usual?

The vaccine development process usually takes years because it requires preclinical studies and clinical trials containing phases from 1 to 4. Preclinical studies do not involve people. At this stage, researchers test the vaccine on animals to determine basic safety and effectiveness. The phase 1 trial usually includes a small number of healthy adult volunteers to determine the substance's safety and safe dosage. The researchers often start with a small dose and increase it if it proves to be safe. Phase 2 includes more healthy volunteers than phase 1, usually in the hundreds. In this phase, researchers evaluate the effectiveness of the vaccine and further explore side effects. Most pharmacologic studies that enter clinical trials fail at this phase. Phase 3 is a large clinical trial, normally including thousands of people to confirm the effectiveness and common side effects. Phase 4 starts when the vaccine is already approved for use. It includes post-marketing surveillance to find out more about common as well as rarer side effects.[7]

The work that scientists did on other coronaviruses was useful in reducing the time for COVID-19 vaccine development. Similarity of how the viruses causing SARS and COVID-19 attach to human cells helped researchers select the spike protein as the vaccine development target. The information from phase 1 trials of the development of vaccines against SARS saved time for vaccine development against SARS-CoV-2, or COVID-19 as it has become known.[8–10]

During the vaccine development, both Pfizer/BioNTech (PBV) and Moderna (MV) showed transparency by releasing documents with plans and timelines of trials.[11] The well-recognized importance of trial results allowed both research organizations to combine some aspects of 1 & 2 and 2 & 3 phases. As a result, the adjusted process allowed a smooth transition from phase to phase and with significant timesavings.[8] Production started before the phase 3 trial ended, with the manufacturers' understanding of the risk of significant loss if the study failed.[11] It has allowed the companies to save time and deliver the vaccines promptly.

## Efficacy of Covid-19 vaccines currently used in Canada

Large phase 3 clinical trials determine the efficacy of a vaccine. Participants enrolled in such a study are divided into 2 groups. The groups are randomized by different criteria to make them similar by age, gender, and other predetermined characteristics of the study. The first group receives the vaccine as per predefined protocol. The second group is used as a control group, which means the group participants receive a placebo at the same time as the first group receives the vaccine. Vaccine efficacy shows the percentage reduction in disease risk among vaccinated participants relative to the unvaccinated participants. If vaccine efficacy is said to be 80%, it means a vaccinated individual has an 80% less chance of getting the disease than an unvaccinated person.

Both MV and PBV phase 3 clinical trials started at the end of July 2020. The MV trial involved 30,420 volunteers aged 18 and older in the US, divided into 2 randomized groups, which included healthy adults and individuals with a high risk of a complicated course of COVID-19.

The following conditions were documented in the participants: chronic lung disease, cardiac disease (including heart failure, congenital coronary artery disease, pulmonary hypertension, or cardiomyopathies), diabetes, liver disease, HIV infection, and obesity with BMI > 40. The first group of volunteers received 2 doses of the vaccine 28 days apart by intramuscular injection. The second group of volunteers received an intramuscular injection of 2 doses of placebo 28 days apart. After 2 weeks from the second dose, observations demonstrated 94.1% efficacy of the vaccine. The vaccine also demonstrated a different efficacy based on age. It showed 95.6% efficacy in the 18–64 age group and 86.4% in 65 and older group.[8, 12–14]

The PBV phase 3 clinical trial involved 43,548 participants and took place in the US, Argentina, Brazil, South Africa, Germany, and Turkey. The study included participants aged 16 or older. The first group received 2 doses of vaccine 21 days apart, and the second received a placebo in the same time frame. 7 days after the second dose, the vaccine demonstrated 94.6% efficacy. The study included healthy participants and people with stable chronic medical conditions, including but not limited to HIV, hepatitis B, and hepatitis C infection. The study excluded immunocompromised individuals and people on immune suppressant therapy. Additional studies were planned for age groups below 16 and immunocompromised persons.[13,15] The vaccine efficacy was demonstrated to be similar, regardless of gender, race, ethnicity, or pre-existing conditions, including obesity. The PBV study participants with hypertension were reviewed as a separate group and it was determined that the PBV efficacy was 94.6% in participants with hypertension.[8,15] On March 31, 2021, Pfizer-BioNTech announced 100% efficacy of PBV in the age group of 12–15 years based on phase 3 trial involving 2,260 adolescents. The data will be submitted to the food and drug administration (FDA) and European Medicines Agency (EMA) to expand the emergency use authorization.[16]

A third vaccine was approved for use in Canada on February 26, 2021. It was developed through a combined effort of the University of Oxford, AstraZeneca and the Serum Institute of India (AZV). The vaccine uses a chimpanzee adenovirus vector to introduce the spike protein into the human body. Efficacy of AZV against symptomatic disease, based on phase 3 trial using 2 standard doses was 62.1%. There was an arm in the phase 3 trial that demonstrated vaccine efficacy of 90%. These participants received a reduced first dose followed by the second standard dose. Overall, the efficacy after 2 doses was 70.4% against the symptomatic disease. Since the vaccine efficacy after 12 weeks or later after the first dose was higher than at less than 6 weeks from the first dose, the administration of the vaccine 12 weeks after the first dose is considered beneficial.[8]

On March 5, 2021, Health Canada approved the Ad26.COV2.S by Janssen (JJV), also known as Johnson & Johnson. The vaccine uses adenovirus to deliver spike protein and is administered intramuscularly as a single dose. This is the first vaccine requiring only a single dose that has been approved for use. Phase 3 trials involving close to 40,000 participants demonstrated 66.9% efficacy against moderate to severe COVID-19 2 weeks after the vaccination and 85% efficacy against severe desease 28 days after vaccination.[8, 17]

Vaccines provide efficacy against the COVID-19 virus.

## Side effects of the vaccines

Based on the trials to date, neither the MV nor the PBV has demonstrated significant safety concerns. Most frequently noted side effects were pain of the injection site. Local, as well as systemic side effects such as fever, headache, or fatigue were transient, lasting only a few days. Both local

and systemic side effects were more frequently seen in the younger participants and more pronounced after the second phase dose in comparison with the first dose. A higher number of participants in the vaccine group reported symptoms of allergic reaction in comparison with the placebo group. Observation of adverse events of the study participants will be ongoing for 2 years after the administration of the second dose.[13–15, 18]

**Adverse event reports by age group and sex up to and including April 9, 2021 (n=3,444)[19]**

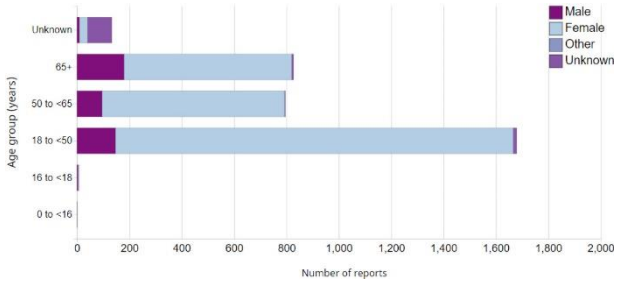


Figure by Health Canada. Reported side effects following Covid-19 vaccination in Canada. Retrieved from https://health-infobase.canada.ca/covid-19/vaccine-safety/#a5

Now that vaccinations have started in Canada, more detailed information can be found on the Health Canada web page, which includes updates every week about all the side effects that have been reported. Based on data from March 19, 2021, the information about side effects was similar to those described in the results of phase 3 trials. It was also noted that younger females demonstrated more frequent side effects than males of the same age group and both genders of higher age groups (See graph).[19]

Shortly after the approval in Canada, several European countries temporarily halted the use of AZV due to cases with thromboembolism within 14 days following vaccination, but many of them since resumed using the vaccine. EMA Safety Committee investigated the circumstances. The committee concluded that the vaccine did not increase the overall thromboembolic risk. However, the reviewed cases demonstrated a slightly higher number of 2 specific conditions, disseminated intravascular coagulation (DIC) and cerebral venous sinus thrombosis (CVST). Both of the complications were noted in individuals under 55. It is important to mention that there were only 7 cases of DIC and 18 of CVST in 20 million people vaccinated with AZ (1 in 800,000). We know that severe COVID-19 itself is associated with significant thromboembolic complications. Based on the above-described facts, the committee concluded that AZV might be related to rare cases of clots associated with thrombocytopenia such as DIC and CVST, but the benefits of the vaccination still significantly outweigh the risks. The National Advisory Committee on Immunization (NACI) of Canada recommends AZV use in individuals of 55 and above, although provincial health authorities are allowed to make individual decisions and reduce the age. Ontario and Alberta recently started offering the vaccine to individuals age 40 and above. The vaccine side effects are under close monitoring.

The JJV vaccine demonstrated no significant adverse events during the phase 3 trial involving more than 39,000 participants. Fever, allergic reactions such as urticaria (5 in the vaccine group), thromboembolic events (15 in the vaccine group vs. 10 in the placebo group), and tinnitus (6 in the vaccine group) were the notable side effects.[8] JJV administration process was temporarily paused in the US for concerns related to six cases of thromboembolic events post-vaccination after administering 6.8 million doses. JJV is not yet distributed in Canada.

## How long will the vaccines continue to provide protection?

As we have previously indicated, both the MV and the PBV phase 3 clinical trials only started in late July of 2020. Data cut off was in October 2020 to make conclusions about efficacy. The time between those dates was not sufficient to draw conclusions regarding the durability of the response. Based on the continued study of MV phase 1 trial participants, the data analysis, published in January 2021 suggested at least 3 months durability of the protection after the second dose of the vaccine. [20,21] A recent analysis of the serums of the same phase 1 trial participants demonstrated no significant drop in antibody titres and maintained live-virus neutralizing activity, suggesting the protection durability over 6 months following vaccination.[22] Trials that will give us more information on the duration of protection are ongoing. These observations should give us a better idea of how long the immunity towards the virus will last for each vaccine, what booster doses will be required, and within what time frame.

## Will the vaccines work against new strains?

Scientists all over the world are following the development of new strains of the virus. As we know, the virus mutates its genetic structure, and some mutations may make strains that can spread more easily, are more difficult to treat, or both. At the time of the start of clinical trials, the highly transmittable strain of the COVID-19 virus that was first detected in the UK in September 2020 had not yet been isolated. The concern was that the spike glycoprotein (S), used as a target in the vaccine development process, might have experienced a genetic mutation in the strain. Information is fast evolving. There are currently 3 modified variants of the original, dominant virus of 2020 known to have a mutation of the area used in the vaccine development process. These variants are B.1.1.7, described above (UK variant), B.1.351 – first identified in South Africa (SA variant), and P.1 lineage, first seen in Brazil (Brazil variant). There are preliminary reports at this time, and some of the conclusions have not yet been published in peer-reviewed journals. Based on initial reports, both PBV and MV show activity against the described strains. However, it is not entirely clear whether they will provide adequate protection against the variant identified first in South Africa.[23,24] It is also unclear if the vaccines will be protective against other possible genetic changes affecting the spike protein of the virus. Based on the similar studies, not published in peer-reviewed journals, AZV was protective against UK variant.[25] However, it has been proven that AZV does not prevent mild to moderate disease caused by South African strain, while the efficacy against severe disease is undetermined.[26] JJV efficacy was 66% in Brazil and 52% in South Africa. It was noted that vaccine efficacy in South Africa against severe COVID-19 was 72% after 2 weeks post vaccination and 83% after 4 weeks following the vaccination.[8] Based on these results, we may presume JJV provides protection against the strains dominant in Brazil and South Africa, however precision is lacking, as we do not know what percentage of cases were caused by the primary dominant variant in these countries during the observation period vs. new strains.

## Vaccination process

By April 10, more than 19% of population of Canada received at least 1 dose. The NACI released a document in November of 2020 outlining the guidance on the population that would be considered a priority for vaccination. There is detailed information available about 3 stages and priorities on Health Canada website.[27]

AZV and JJV can be stored in 2°C to 8 °C range which is somewhat of an advantage because the MV recommended storage temperature before stocking is minus 20°C and for PBV it is minus 70°C. PBV and MV should be transported frozen and then thawed at a clinic. Here, storage temp is 2°C to 8 °C and storage time is 30 days for MV while only 5 days for PBV. Once a vial of any of the vaccines is opened, it should be used within 6 hours.

## Insurance industry

The insurance industry responded quickly to the initial challenge and is continually adapting to the circumstances as more information becomes available. Evidence-based data about COVID-19 has given the industry a good perspective on who carries a low or high risk of a severe course of COVID-19, and the more significant complications resulting from the infection.

### Since the vaccination process has been rolled out nationally, is it now time to make adjustments to our current guidelines?

As described earlier, while there was significant victory in developing the vaccines in a short time frame that demonstrated high efficacy, some aspects preclude us from disregarding the risk at this time.

Limited observation data and unknown duration of protection from the dominant strain is the first concern.

The second concern is a lack of certainty associated with adequate protection against the South African variant. We have only limited preliminary conclusions. However, the information should become available as more individuals are diagnosed. The third and likely more significant concern is the fast emergence of new, potentially dangerous strains. Some of these strains will likely require boosters, and it seems inevitable that a time gap will exist between the emergence of a new strain and the protection afforded by a booster vaccination.

Based on the current data, it is still too soon to say whether the vaccines will completely eliminate COVID-19 related risks. However, we have witnessed an incredible collaboration in the development of the vaccines. We have seen the high efficacy based on successful phase 3 trials of both m-RNA vaccines, and the continued demonstration of safety. Based on the studies, we may conclude that the m-RNA vaccines are effective for at least 6 months after the second dose against the dominant strain. There is also some promise in the preliminary reports related to protection against current strains. All these factors suggest that a few more months of testing will likely provide us with sufficient information and much-awaited reassurance that will allow the removal or reduction of underwriting restrictions associated with the risk of a severe COVID-19 infection or its consequences.

Scientists all over the world are following the development of new strains of the virus.

## Case studies

### Case No 1

A 70-year-old non-smoking female of normal build would like to buy life insurance for CAD 2 million. She is on immunosuppressive medication for rheumatoid arthritis diagnosed 15 years ago. Her last rheumatology consultation in 2020 was done via internet and the consult indicates she has no complaints and her condition has been stable for the last 4 years. Her bloodwork including markers of disease activity are normal. She has received 2 doses of vaccination against COVID-19 in Canada. The second dose was 2 weeks ago.

### Can we offer her life insurance?

We know that our applicant has a higher risk of more severe COVID-19 disease due to the fact that her immune system is suppressed. However, we also could see that her arthritis is stable and without a flair for years. As we may recall, people on immunosuppressive medication were excluded from the PBV trial. We had no such information from MV trial, although arthritis was not specifically mentioned in the list of chronic conditions affecting the study participants. Both MV and PBV showed fewer neutralizing antibodies in people above 65. Considering her condition and medications, her protection may not be as robust and expected effectiveness of the vaccine may be lower than PBV and MV efficacies demonstrated in phase 3 trials for her age group (91.7% PBV, 86.4% MV).[8] We also do not know how long the protection lasts beyond 6 months after the second dose and if it protects from the SA strain. While offering insurance will largely be determined by the risk appetite of an individual insurance company, there are several favorable factors to note: In this case, vaccination is still beneficial for our candidate improving her chances of avoiding severe COVID-19 in the next 6 months, if not longer. Her compliance with medical recommendations suggests that she will get a booster, if it is recommended in the future. Good control of her chronic conditions demonstrated by regular follow up and disease

severity markers is also beneficial, even though a face-to-face assessment did not take place in 2020.

**An offer can be made based on the information provided in this case.**

## Case No 2

A 48-year-old non-smoking male with mildly elevated BMI is applying for CAD 5 million life insurance. He has chronic hepatitis B and has been well followed. He has had normal liver function tests (LFTs) for the last several years, and the yearly abdominal ultrasound is normal. He drinks a glass of wine a couple of times a year. His insurance bloodwork shows positive Hep B S Ag, positive Hep B C Ab, Negative Hep Be Ag, Negative Hep B s Ab. His viral load is 2500 IU and has been in the similar range over the last 5 years. He has never been treated for Hep B. He has received 2 doses of COVID-19 vaccination with a "new type" vaccine. His last dose was in January 2021. He is looking after a parent who lives in the nursing home. The applicant also has hypertension and is on medication but he has no other medical conditions and no significant family history. His insurance physical blood pressure is normal and he has normal LFTs on his insurance bloodwork.

**Can we offer him life insurance?**

The PBV study included people with hepatitis B and the MV trial included people with chronic liver disease. Both vaccines demonstrated efficacy above 94% in this age group and no difference was identified in efficacy or side effects due to liver disease. We also know that PBV trial separately assessed people with hypertension and the efficacy was similar to others in this age group. The applicant's bloodwork shows Hep B carrier. Normal LFTs, low viral load, normal ultrasound are all favorable factors. Even though we do not have information about vaccine durability beyond 6 months after the second dose, or sufficient evidence against all strains, the applicant's age and low case fatality associated with his age group are reassuring.

**An offer can be made in this case based on the insured's medical history.**

## Case No 3

A 34-year-old non-smoking female, who is currently pregnant, is applying for CAD 1 million life insurance. She had a vaccination against COVID-19 a month ago with MV and had a fever for a day after a second dose but no other complications. Her BMI was normal before pregnancy and currently her weight gain is within expected normal limits. It is her second pregnancy. Her previous pregnancy had no complications and lasted full term. She is well followed, and has no pregnancy complications to date. Her most recent labs are from her obstetrician, and include all required data for insurance as well as a CBC. Labs are appropriate for the trimester of her pregnancy. Her blood pressure is normal.

**Can we offer insurance to her?**

Based on Centers for Disease Control and Prevention (CDC), current evidence suggests that the pregnant females are at higher risk of complicated course of COVID-19 in comparison of same age non-pregnant females.[28,29] M-RNA vaccine efficacy in this age group is expected to be high, exceeding 94%, which is a favourable factor. It is also favourable that the applicant has no chronic conditions or any known current or prior pregnancy complications. We learned that MV is effective at least 6 months after the second dose and this information is also helpful. Theoretically, there is no reason to suspect that m-RNA vaccine would cause harm to an expectant mother or to a child since there is no live virus entering the body and spike protein production from m-RNA is not happening in the nucleus. Preclinical studies did not demonstrate any pregnancy related complications. Pregnancy was one of the exclusion criteria for all phase 3 trials so there are no large-scale results available, however, PBV and MV phase 3 trial documentation included a small number of pregnant

women, inadvertently exposed to the vaccines. There were no adverse events reported related to pregnancy. Moreover, based on a publication in March 2021, we learned that antibody titters developed after COVID-19 m-RNA vaccination process were similar in pregnant, non-pregnant and lactating women.[30] The Center of Disease Control of the US (CDC) is in agreement with College of Obstetricians and Gynaecologists, and recommends that vaccination be made available to pregnant individuals. Health Canada acknowledges the lack of information but still recommends vaccination where risk of exposure or severe disease is high. More information will be available by Pfizer and BioNTech who are conducting an international clinical trial to evaluate the vaccine in pregnant woman.

**Based on research and what we know of the insured's medical history, an offer can be made in this case.**

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