Home Remedies: How Should Canada Acquire Vaccines for the Next Pandemic?

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Online Appendix: Vaccine Production Platforms

The active ingredients produced using the different vaccine production platforms, illustrated below, work in the same basic way: each presents (either directly or indirectly) the immune system with an antibody generator or "antigen" that primes the immune system to neutralize the virus among those who subsequently become exposed.

The first and oldest method is to grow whole viruses, in fertilized chicken eggs or other live animal cell cultures in large-scale fermenters. The vaccine viruses are weakened or attenuated so they cannot produce disease but still cause the body to mount an immune response against the virus.

The second method also grows the target virus in cell cultures; but the viruses are then inactivated, using either heat or a chemical treatment, rendering them unable to infect and replicate. Some approaches split the inactivated virus into pieces. The body still recognizes the pieces of the virus and mounts an immune response that blocks any future infection by the actual virus.

The remaining vaccine production platforms do not require the propagation of the target virus in large-scale fermenters. Instead, they use lab created, or "recombinant" DNA. DNA sequences, or genes, contain the code that instructs cells to make one or more proteins. The protein-based platforms deliver this instruction set into a cell that is cultured in a lab; this could be an animal, insect, plant or microbial cell. Once inside this cell, the DNA is converted within the cell's cytoplasm into RNA, which instructs the cell to produce the small but important pieces of the virus envelope that the human immune system can recognize and respond to. For SARS-CoV-2, the spike protein, which sticks out of the virus envelope, is commonly used. The viral proteins manufactured in these cells are then harvested, purified and injected into a human; the immune cells recognize it as foreign and develop a protective immune response.

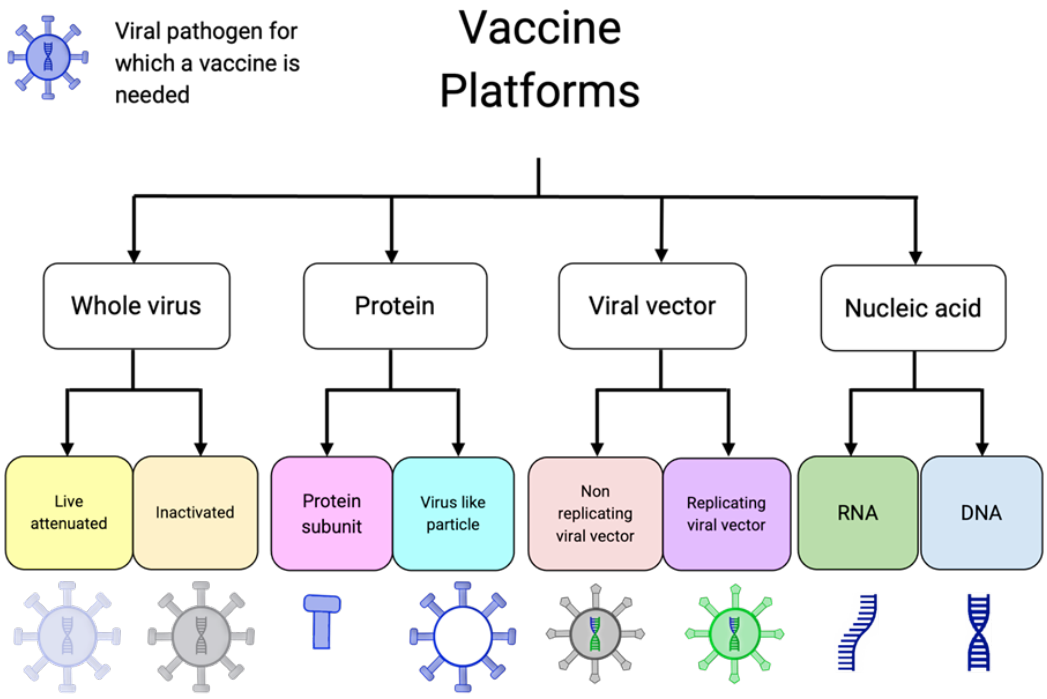
These cell-made virus proteins, including the spike protein, can also be expressed on the outside of a particle that is about the size of a virus. As it also has the shape and size of a virus, the expectation is that the protein delivered on a virus-like particle would induce an even broader response by the body's immune cells.

The vaccine production technologies described above – the whole virus and virus protein platforms – require the in vitro propagation of either the virus itself or its proteins, which are then formulated into vaccines. The remaining vaccine platforms use a different tact. These vaccines do not contain the inactivated virus or virus proteins but instead contain the genetic code for the viral proteins. This vaccine, once injected, delivers this genetic code to the inoculated person's own cells, which in turn produce and introduce the protein of interest to the immune system. In essence, the person's own cells are making the vaccine.

This genetic code is contained using lab-manufactured DNA or RNA. If DNA is introduced into the cells of the inoculated person, the DNA moves to the cell nucleus where the code is transcribed to make mRNA (m for messenger) that takes the message to the body of the cell where it acts as the template to make the protein of interest, such as the SARS-CoV-2 spike protein.

RNA vaccines skip the DNA step, and transport mRNA directly into a person's cells. The mRNA directly codes the production by the host cell of the protein of interest that will induce an immune response against the virus. Self-amplifying RNA (saRNA) adds the ability to direct the cells to produce more copies of mRNA, thereby reducing the dose requirement.

Figure A1: Different Vaccine Platform Descriptions



Source: Adapted from COVID-19 Vaccine Tracker https://covid19.trackvaccines.org/vaccine-types/ (Accessed May 10, 2021).

Different platforms use different ways of delivering the genetic code into the cells of the inoculated person. The viral vector vaccine platforms get the DNA code into human cells using a non-pathogenic virus shell to carry and "infect" the inoculated person's cells. The most common vector is an adenovirus (one of many common cold viruses) that has had DNA to code for the spike protein integrated into its own DNA, in the lab. The manufacturing process involves growing the transporting, or "vector," viruses in cell cultures. The virus shells that transport the DNA can be ones that do not replicate in human cells; these are called replication incompetent. The virus shells can also be weak viruses that can replicate a few times without causing disease; these are called replication competent viral vectored vaccines. The nucleic acid platforms aim to get either DNA or RNA into the cells of the inoculated person without requiring a virus shell to transport them.

A detailed description of the mRNA technology and its manufacturing process is described in a review article by Jackson et al. (2020). But, briefly, the manufacturing process for mRNA vaccines begins with a DNA plasmid which contains the genetic code for the protein antigen used to stimulate an immune response, such as the SARS-CoV-2 spike protein. The DNA plasmid is used to transcribe the genetic code into mRNA molecules in chemical reaction vessels. The mRNA are subsequently purified and formulated with lipid nanoparticles to make the mRNA vaccine, which is filled into vials for storage and distribution. The lipid nanoparticles protect the fragile RNA while it

is transported and facilitates its entry directly into a person's cells.

The DNA technology also starts with a plasmid of DNA that contains the genetic code for the protein antigen. In this case the purified DNA plasmid is injected directly into the recipient. The key challenge for DNA vaccines is getting the DNA into the patients' cells. Many techniques have been tried but so far, the most effective technique seems to be electroporation – delivering short pulses of electrical current to the patient with the vaccine. The electricity creates temporary pores in a patient's cell membranes, enabling the DNA to enter the cells and ultimately the cell nucleus, where it uses the cell's protein manufacturing mechanisms to produce the spike protein antigen (Nabel 2008).

The RNA technology has been used in the COVID-19 vaccines developed by Pfizer and Moderna. To date, however, DNA technology has not been used in any licensed vaccines intended for human use.