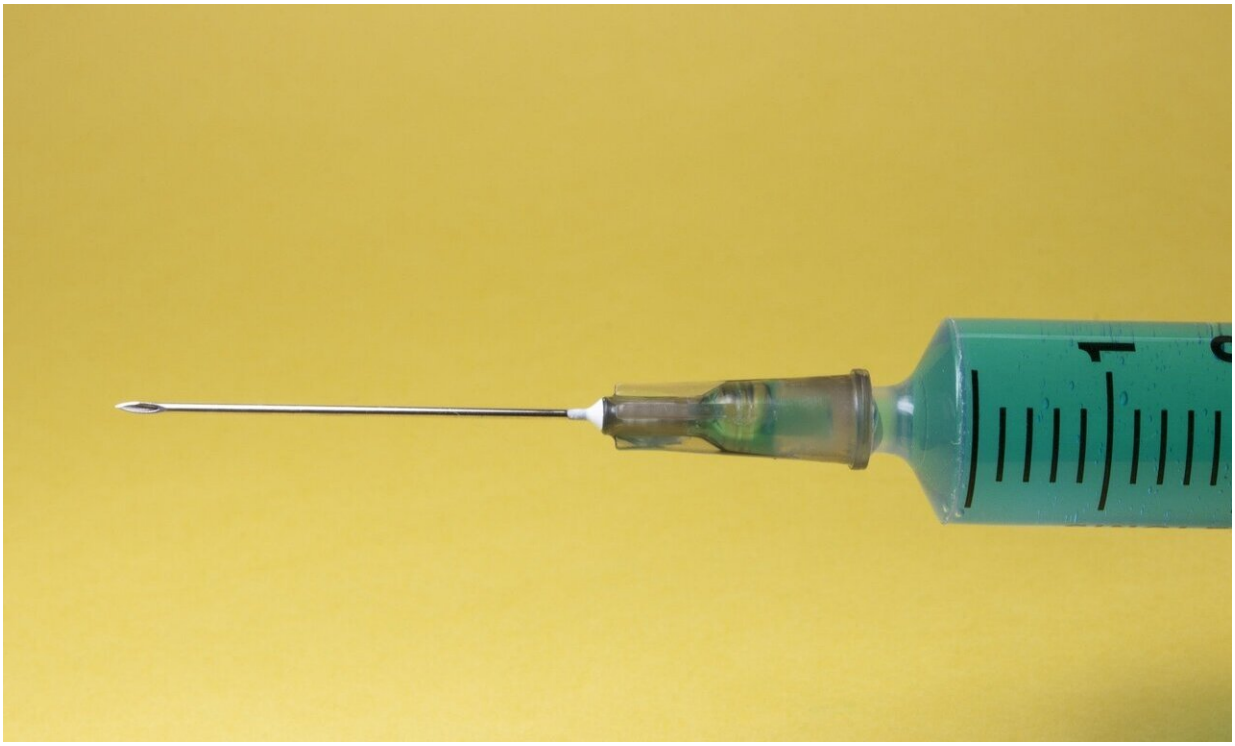
Eight things you need to know about the worldwide hunt for a COVID-19 vaccine

July 27 2020, by Gillian Rutherford



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With more than 100 teams around the world racing to find a vaccine against SARS-CoV-2, including three at the University of Alberta, what are the chances of getting something that works?

The World Health Organization's list shows 21 vaccine projects in either

phase 1 or 2 of clinical trials, and two projects, one in China and the other in the U.K., in phase 3. The top two report they are seeing protective antibodies created in their trials, but even they can't say for sure whether, or when, their vaccines might be ready for widespread distribution.

There's a lot at stake, with nearly 16 million of the world's 7.5 billion people already infected and more than 600,000 dead—and the numbers are growing exponentially. And while public health measures such as social distancing and masks seem to be keeping the lid on the pandemic in Canada, outbreaks continue now that the economy is reopening and fears are mounting about a second wave in the fall.

"We've seen the measures that are needed to slow the virus down are fairly extreme and are not sustainable to the degree that they were started at, although they were totally necessary," said Lynora Saxinger, a U of A infectious diseases specialist and co-chair of Alberta Health Services' Scientific Advisory Group on COVID-19. "It's hard to figure out how to keep the virus from spreading without a vaccine."

Some U of A experts, such as virologist David Marchant and biological scientist David Wishart, are on the record expressing doubt about the chances of ever finding a vaccine—because of the technical and safety challenges, not to mention production and distribution obstacles—while others, such as virologist Michael Houghton, medical microbiologist David Evans and oncologist John Lewis, are forging ahead with solid funding and high hopes for their vaccine approaches.

Folio asked the U of A's leading experts in viruses and infectious diseases, medical ethics and drug manufacturing to map out what it will take to develop, test, manufacture and administer an effective vaccine against COVID-19.

1. There is cause for cautious optimism

A typical vaccine can take a decade or more to develop, and for some diseases, such as HIV/AIDS and hepatitis C, nothing has yet been approved despite decades of work. That said, vaccines have been developed for more than 20 life-threatening diseases, preventing millions of potential deaths each year from smallpox, diphtheria, measles and polio, among other diseases. The pressure for success—scientific, economic, political, social and humanitarian—has never been so intense. Never before have so many scientific teams dropped everything and pivoted to study a single global problem.

"We just can't afford to wait 10 years," said Tom Hobman, a cell biologist and former Canada Research Chair in RNA virus host interactions.

"There are some people who said we should have let the virus run its course," rather than bringing the world to a halt with public health measures to prevent the spread and spending billions on research to find vaccines and antiviral treatments, he said. "I don't agree with that approach.

"If you look at it strictly from a biological standpoint—in the animal world, that's what happens—but as humans we don't do that. I'm really encouraged by the news that we're hearing (about promising projects) and I'm cautiously optimistic."

Saxinger said one cause for optimism is the sheer force with which COVID-19 has hit the world.

"One of the reasons that vaccine development is historically really slow is that a lot of the diseases that we are making vaccines for are not very common in the community, so enrolling enough people into the trial to

test efficacy takes many years," she said. "The trials for COVID will recruit very quickly and have results quickly because it's basically tearing around the globe and creating havoc.

"It's just such an explosive epidemic in so many places that I think we'll get answers more quickly," she said. "This is not our usual vaccine situation."

Saxinger's reading of the science is that thanks to the huge international co-operative effort, enough is already understood about the immune response to the virus that it is probable a vaccine will be found to provide protection.

"We're not sure for how long the protection will last," she cautioned. "But there's a very good chance that we'll have a vaccine."

2. More than one vaccine may work

Another reason for optimism is the number of projects underway and the variety of technological approaches being taken. At its basic level, a vaccine's job is to prime the immune system so it is ready to mount a powerful defence as soon as it encounters a virus. But there are many ways to do that. Each technology presents its own advantages and disadvantages.

The traditional approach is to give a small dose of weakened or inactivated pathogen, or just a part of it, so your body will recognize the real thing when it shows up. These vaccines can take time to develop and may require large manufacturing facilities, which don't exist in the numbers required to inoculate the world.

A newer technology involves using another harmless virus as a "vector" or delivery vehicle for a part of the COVID-19 virus, but again, this kind

of vaccine may be relatively complex to manufacture and there is concern about the safety of repeated doses, which may be required to "boost" immunity. Nucleic acid (DNA and RNA) based vaccines look promising because they are relatively cheap and easy to make, but no such vaccine has yet been approved for human use against other diseases, although many have been in development with promising results. Concerns remain about potential changes to recipients' chromosomes, so these vaccine options will have to pass critical safety hurdles.

Hobman said it is a plus that so many different platforms are being tested, because it creates a competitive incentive. He pointed out that there are several manufacturers of influenza vaccines who take different approaches to the annual cocktail that is given to prevent the most prevalent strains of flu each year. Those vaccines are often far from perfect, providing less than 30 percent efficacy, he said.

"They still do provide benefits by reducing transmission and lessening the course of the disease," he said. "It doesn't have to be perfect."

He said a likely scenario is that one or two types of vaccine will be ready first and will provide some immunity, but because it seems that immunity does not last long even among those who have had COVID-19, a booster inoculation will likely be required, possibly using one of the technologies that is slower to develop.

"I actually would be really happy if multiple vaccines are proven to work, and they were all manufactured in different ways, because then there's less likely to be bottlenecks in production that would affect our ability to scale up," Saxinger said.

"Billions of doses will be needed and anything that will help diffuse the manufacturing, and allow countries to make their own, would be

excellent," she said.

3. It won't happen quickly

Much media coverage has speculated about getting a vaccine ready to go by the end of this year, but Saxinger believes the very best-case scenario would be to have vaccines ready for widespread public inoculation of Canadians by the end of 2021.

"All of these various factors about how they are made and how they work and how they can be tested make it a complex playing field," she said.

Hobman pointed out that while finding a viable vaccine candidate is challenging enough, the testing takes time and can't be rushed, although some testing phases can be done in parallel. Then there's the licensing process, manufacturing and distribution of billions of doses, all of which present huge logistical challenges.

"It's not trivial," said Hobman, whose lab is working on interferon and other potential antiviral candidates to treat patients until a vaccine is ready to go.

Hobman explained the safety and efficacy testing for a vaccine involves numerous steps, none of which can be skipped. It starts with preclinical testing in small animals such as ferrets and mice. Then phase 1 testing evaluates whether the vaccine is safe for healthy individuals and whether it can induce an immune response. In phase 2, you're looking at a larger group of people to monitor safety and to see how dosage affects antibody production. Then in phase 3 you do large-scale testing with thousands of people to see whether the vaccine really does provide protection against the virus. How many people who are vaccinated get sick, how severe are their symptoms, are there side-effects and how well

can those be managed?

"Vaccines are like any drug," he said. "Some people do react poorly, but it's usually a very small percentage, and we have to assess that risk against the benefit on a population basis."

Saxinger said that while testing steps can't be missed, there are other parts of the process that can be expedited. For example, the U.S. government has already ordered 300 million doses of the Oxford University/AstraZeneca vaccine candidate even before phase 3 trials are complete, at a cost of up to US$1.2 billion.

"If it turns out they work the way you need them to, they'll be ahead of the game," Saxinger said. "I hope they bet on the right horse.

"I see real efforts to try and shorten the time it will take to get a vaccine to the public and a real willingness to invest in that."

4. Some healthy people may have to take a risk before the rest of us get protected

The testing phases of vaccine development can't be rushed because there is so much potential harm if things go awry. Hobman recounted how researchers for a dengue virus vaccine uncovered a frightening phenomenon in which some vaccinated people actually experienced more severe illness than non-vaccinated individuals when they became infected with dengue virus. This is the exact opposite of what COVID-19 vaccine researchers hope to achieve, but the only way to find out whether their vaccines induce this response is to test them out ... on a lot of people.

This summer, 30,000 healthy American volunteers will be recruited for

that U.S. phase 3 trial as part of the government's "Operation Warp Speed" on vaccine development, while 9,000 Brazilian health-care workers will be asked to try a different vaccine being developed by Sinovac. Medicago of Quebec City began phase 1 testing in 180 volunteers earlier this month, while CanSino's vaccine candidate has been approved for human trials in Canada and is enrolling 696 people for phase 1 and 2 trials at Dalhousie University. The Dalhousie researchers report being overwhelmed by volunteers who want to take part in the trials.

In all the trials announced so far, participants are given either a dose of the prospective vaccine or a placebo and then are monitored for at least two months and up to four years, depending on the phase. The volunteers may or may not encounter the SARS-CoV-2 virus while going about their normal lives. If the vaccine works, the people who received it would develop fewer, or at least less severe, illnesses than the control group and the general population in the region.

Meanwhile, a movement in the U.S. known as "1 Day Sooner" is promoting so-called "challenge trials," which would purposely expose the volunteers to the active virus, effectively speeding up the time it takes to get results. The pressure to go this route is so intense that the World Health Organization has come out with key ethics criteria for challenge trials during COVID-19.

"We need to encourage public dialogue around challenge studies and who would be first to receive vaccines," said Michael van Manen, a pediatrician who is the Endowed Chair of Health Ethics and the director of the John Dossetor Health Ethics Centre at the U of A.

Whether people sign up for a challenge trial or a regular trial, van Manen noted that ethics boards and governments oversee trials, so it's never "just anything goes."

"Vaccine research receives significant ethical oversight," he said. "This is particularly important in our current situation where there is a great deal of public and political pressure to develop treatments and vaccines. Still, we need to pause to reflect.

"Yes, people who choose to engage in such risks (by signing up for a clinical trial) should be able to decide for themselves, especially if it's something they believe in."

However, the problem is that the risks of intentionally exposing healthy individuals to SARS-CoV-2 are really unknown. With no sure, effective treatment, there is no guarantee you will fully recover if you become severely ill. Not enough time has passed since the illness first appeared for the long-term side-effects of COVID-19—including brain, lung or kidney damage—to be fully understood. And because you can be contagious before you even develop symptoms, you could unwittingly share the disease with family or friends who did not sign up for the trial.

5. We'll be able to manufacture the vaccines we need right here at home

It will take more than four million doses to immunize every Albertan once a successful drug or drugs are found. Whether the winning formulae are developed in Canada or internationally, those doses for Albertans will likely be prepared at the Alberta Cell Therapy Manufacturing (ACTM) facility on the U of A campus, one of just six publicly funded Good Manufacturing Process (GMP) facilities in Canada.

Built with clean rooms to ensure no bacterial contamination, it was opened by surgery professor and scientific director Greg Korbutt in 2015 thanks to a total of $26 million from the Canada Foundation for

Innovation, the Government of Alberta and the U of A. The ACTM is already working on a number of boundary-pushing projects, including preparing a hepatitis C vaccine for human trials led by virologist Michael Houghton and CAR-T immunotherapy cells for oncologist Michael Chu, and hopes to soon begin making islet stem cells for surgeon James Shapiro.

"They're unable to do that type of research without our facility," said Korbutt.

Until now, the ACTM has produced cell therapy products for phase 1 clinical trials, but Korbutt said the facility has the capacity to make enough vaccine doses for all Albertans. ACTM has the equipment to put doses of vaccine in vials so they can be stored properly, distributed to clinics, drawn up in syringes and injected. Having that start-to-finish production capability allows the facility to charge for future commercial projects and become financially self-sustaining.

"We would be able to make thousands of vials in a day," Korbutt said, which would allow the facility to supply Alberta and beyond.

6. Once we have a vaccine, who will get it, and when?

The global Vaccine Alliance, Gavi, has been spearheading the conversation about what it will take to vaccinate the world against COVID-19. State governments, philanthropists and pharmaceutical companies came through with billions of dollars for vaccine research, manufacturing and distribution at a global pledging summit last month. One of the biggest concerns is for lower-income countries that won't be able to make or buy their own supply of vaccines.

"If particular individuals—for example, the taxpayers of a particular country—bore certain burdens to develop a vaccine, then it could

potentially be argued that they should get it first," said Michael van Manen. "But we must also look at who is most vulnerable or who is most likely to transmit the virus should they become infected.

"There are so many considerations with the ethics of limited resources and large population needs. We need to ensure we deploy the vaccine to save the most lives across the globe while making necessary and fair choices and recognizing that some individuals live with more hardships than others."

In Canada, Saxinger said modelling would likely be done to determine who gets the vaccine first to ensure the most benefit for the entire population.

"You may be looking at where outbreaks are the most active so you can try to cool those areas down, and also who is most at risk of severe disease so you can protect them first," she said.

"Another thing to look at is if there's a particular group that is responsible for a lot of the transmission, because you might focus on that group early.

"There are different factors but it would not just be, 'Hey, everybody line up,' it would be a matter of triaging as supply of the vaccine comes in," Saxinger said.

7. You may be "strongly encouraged" to get the shot once it's your turn

Saxinger indicated that most experts feel around 70 percent of us will need to get the shot to stop the march of COVID-19 based on the R-naught factor (R0), which is the average number of other cases caused

by each infected person. In Canada, without public health interventions in place, it is believed to be between 2.0 and 3.0. By comparison, influenza's R0 factor is around 1.3. Saxinger explained that the coronavirus is so much more dangerous than the flu in part because we have absolutely no background or residual immunity to the brand-new disease.

"There's no archived immunity in the population, which is why it's been so devastating," Saxinger said. "The stakes are much, much higher to get good uptake of the COVID vaccine."

Last year, 1.4 million doses of influenza vaccine were administered to Alberta's population of 4.3 million people over the course of a six-month campaign. Saxinger said the campaign to get everyone vaccinated against COVID-19 would be bigger and more sustained, with lots of promotion and education. She suggested "encouragement programs" and outreach for those who are reluctant to get vaccinated, such as linking vaccination to child benefit payments, as had been done elsewhere.

"I would be in line with my sleeve up pretty darn quick, but I worry the situation could be ripe for an increase in anti-vaxx sentiment," she said. "That kind of thinking seems to be contagious to a certain part of the population."

Though Saxinger supports education over coercion, she said she would support making inoculation mandatory if not enough people were willing to step up voluntarily. Van Manen said such a public policy discussion would have to balance the principle of minimizing government intrusion into people's lives and respecting what could be legitimate safety concerns against the risk to the community. He noted that, for example, people in Canada can be forced to take treatment for tuberculosis because it is highly contagious, although most people opt to take treatment to benefit themselves, so it is uncommon to need to turn to the

law.

"Individuals can't just walk around the streets with active TB, but that's in part because they are placing other individuals at risk," he said.

"What should be considered in the case of a vaccine is, by requiring vaccination, to what extent are you really decreasing the risk of spread? Generally, we allow people to make risky choices for themselves, such as going bungee jumping, smoking or other risky activities."

Van Manen hopes we can get to 70 percent of the population vaccinated without having to infringe on the liberties of those who choose not to get the shot.

8. While we all wait for a vaccine, this is what you can do to protect yourself and others

Estimates suggest between five and 10 percent of Canadians have already been exposed to the SARS-CoV-2 virus. While that number will continue to rise until a vaccine is found, it's a long way from what's needed to reach so-called herd immunity, which means virtually everyone is protected (at least for a while) whether they have been inoculated or not, because the disease can't circulate through the population effectively. While there are numerous promising antivirals and other treatments in the works, Saxinger pointed out that most are aimed at shortening the illness or keeping those with severe illness alive.

"All this stuff will help people once they get sick, but the improvement will be modest, and it won't affect the march through the community," she said. "I think of COVID-19 as being like a bonfire that's spitting sparks. We're all just walking around as pieces of tinder, and there's still lots of tinder."

Like Hobman, Saxinger argues against letting the virus rip through the community and just trying to protect the most vulnerable.

"People are attracted to this seemingly easy idea of just keeping the frail people safe, but no one has succeeded in doing that," she said. "Sweden tried and failed."

"Also, many young healthy people have gotten devastatingly ill or died. They have lower risk, not no risk."

Until a vaccine is widely available, Saxinger said it's on all of us to strictly adhere to public health practices—such as social distancing, reducing contacts, frequent handwashing, staying home when you're sick and wearing a mask in public indoor spaces—to "keep a lid" on the virus. It's essential, she said, for saving lives and protecting the health-care system.

Saxinger suggests keeping a log of all of the people you come into contact with on a daily basis.

"I usually can't remember what I had for breakfast," she commiserated. "But if you turn out to get sick or if you come into contact with someone who is sick, you need to be able to give a good accounting for who you've been around."

Saxinger said our best hope to avoid another peak in cases and another potential shutdown of the economy is to watch vigilantly for localized outbreaks, then quickly trace anyone who might have been exposed, isolate them and contain the spread.

"People are frustrated because it seems like we don't know everything about this virus, but we know a heck of a lot given that it's only been around for six months," she said. "It's kind of remarkable how much we

do know and how much we're continuing to learn."

Provided by University of Alberta