STAT

The short-term, middle-term, and long-term future of the coronavirus

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By Andrew Joseph *and* Helen Branswell March 4, 2021

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When experts envision the future of the coronavirus, many predict that it will become a seasonal pathogen that won't be much more than a nuisance for most of us who have been vaccinated or previously exposed to it.

But how long that process takes — and how much damage the virus inflicts in the interim — is still anyone's guess.

"The most predictable thing about this coronavirus is its unpredictability," said Howard Markel, a historian of medicine at the University of Michigan, who has studied other pandemics.

However long it takes, the transition to a mild endemic virus is unlikely to be a straight line. Some infectious disease researchers envision a healthier summer — with low circulation of the virus and more people vaccinated — but a more tenuous fall. Other factors, like how long protection provided by vaccines will last, what percentage of people gets them, and whether variants of the virus sap the strength of vaccines, will determine the outcome.

These are not predictions that people fed up with the pandemic will want to hear. But at the same time, some experts are optimistic that the end of this phase — the crisis phase — is within sight, at least in this country, as vaccines reach more people and protect them from the worst outcomes of Covid-19.

The challenge might be recognizing what the "end" looks like. Some experts might mark it when daily deaths fall below a certain threshold or when hospitals are no longer facing crushes of cases. But there won't be a single moment, like jolting awake from a nightmare, and we won't be finished for good with SARS-CoV-2, the virus that causes Covid-19. Gradually, fewer people will get sick, more activities will be considered safer, and something approaching normalcy will return.

"It's sort of like getting into a cold pool," said virologist Angela Rasmussen of the Georgetown Center for Global Health Science and Security. "You go in and you get a little deeper, and you get a little deeper, and finally you're in the pool and it feels normal."

The short term

The U.S. right now seems to be at an inflection point. Cases have plummeted from peaks earlier this year, but have more recently plateaued at levels that remain dangerous. There is still a lot of virus circulating in the U.S.; over the past week, the country has averaged more than 65,000 cases per day, which is more than twice the number of cases, *in total,* that Australia has recorded since the start of the pandemic. Vaccines are being rolled out — with a third option authorized last weekend — but supply for now remains limited.

Worrisome variants of the virus are also growing more prevalent. One, known as B.1.1.7, is more transmissible and deadlier than other forms of the virus and is expected to become the dominant strain in the U.S. later this month. But it's not clear how that will have an effect on case counts.

"The variants are a bit of a curveball," said Caitlin Rivers, an infectious disease epidemiologist at the Johns Hopkins Center for Health Security. "I could see a scenario where B.1.1.7 could slow down our progress and maybe precipitate resurgences in some communities," though perhaps not throughout the country.

Conditions may be ripe for a better summer, however. Vaccine supplies should be flowing more freely, at least in the U.S.; the Biden administration now expects enough vaccine doses in hand for all adults by the end of May. With most vulnerable populations protected, there should be fewer hospitalizations and deaths. And with warmer weather, people can return to outdoor life.

Widespread transmission of the virus could be replaced by more sporadic and localized outbreaks. There's also growing evidence that vaccines don't just protect people from getting symptomatic Covid-19, but can reduce transmission.

The country will not reach herd immunity over the summer — that is, the point at which there are so few susceptible to the virus that it can't find new hosts to infect. Kids and adolescents, who make up nearly a quarter of the U.S. population, won't be vaccinated yet in large numbers, and a still unknown

number of adults will resist getting the shot. But experts stress that if the country can reduce transmission, as well as take the bite out of the most severe consequences of the disease through immunizations, the future will look different than the past year has.

“If you look at a country like Australia, or other countries that have really controlled spread, they are doing normal things, and it’s not because they’ve reached the herd immunity threshold,” Rasmussen said. “It’s because they’ve controlled transmission.”

Then comes the fall. Two factors — people spending more time indoors plus colder weather — could allow SARS-2 transmission to pick up again among those who remain susceptible, a potential threat if vaccine uptake is limited. What’s more, some experts have raised the possibility that even people who have been vaccinated or who have been previously infected could be vulnerable to infections if variants are able to evade some of the immune system’s defenses and circulate more widely. The top threats now appear to be B.1.351 (first seen in South Africa) or P.1 (first seen in Brazil), but other variants could appear as well, particularly if vaccines are not provided globally and transmission persists.

B.1.1.7 “could result in more of a wave in, say, April, May, than we would have expected otherwise, but I still do suspect that things will be brought under control in the summer, and there will be very little Covid circulating, with a combination of all these infections that have occurred, all this vaccination that’s occurring,” Trevor Bedford, a computational biologist at the Fred Hutchinson Cancer Research Center, said at a briefing last week. “What I am concerned about is that we could have something of a fall wave” caused by these variants.

Generally, people who have been reinfected by viruses like SARS-2 or been infected after being vaccinated tend to experience mild illness; even if their immune systems can’t block the virus entirely, they have enough experience with the pathogen to recognize it and prevent more severe disease. In clinical

trials, Covid-19 vaccines that were put to the test against B.1.351 did not fare as well at preventing mild illness as they did against other forms of the virus, but they still seemed to prevent hospitalization and death.

It's possible then that any fall wave driven by variants could bring a spike in mild infections but not a surge of severely ill people crowding into hospitals. But that scenario depends on getting more people vaccinated — and the virus not evolving in a way that further undermines the effectiveness of vaccines. It also depends on the vaccines providing protection that lasts, even — especially — among older adults, whose immune systems are in decline and don't generally develop as strong a response to vaccines as children and younger adults.

For a fall wave, "is it going to be big and devastating, or is it going to be a little hump? I don't know," said infectious disease researcher Jennie Lavine of Emory University. "We really need to know how severe disease is going to be after vaccination or upon reinfection, and with different strains."

Michael Mina, an epidemiologist at Harvard's T.H. Chan School of Public Health, worries not just about the public health toll of a potential fall wave, but the psychological and societal ones as well.

"Fall comes along and people have gotten so excited about being back in school and doing this and that without what happened last year," Mina said. "And then we start to see spread again. And I just think it's going to be demoralizing. And it's going to happen swiftly. My hope is that it will not happen in such a way that we see the type of death [we saw previously], but I do think we will start seeing deaths again because the older people who are vaccinated early are going to be losing their immunity at that point." (Researchers don't know for sure that protection provided by Covid-19 vaccines will wane faster in older people, but that is the case with some other immunizations.)

Even in the absence of a big fall surge, public health authorities will likely continue to recommend mask-wearing in certain settings, particularly because the situation is fluid and because children and adolescents — among those at the end of the vaccine line — may still be in the process of being inoculated.

“I really believe that until we get kids being vaccinated, that the smart thing to do is to wear a mask,” said Anna Durbin, a vaccine researcher from the Johns Hopkins Bloomberg School of Public Health.

It’s possible that children don’t contribute to transmission much once most adults are vaccinated, Durbin added, but “until we have 70%, 80% of the population vaccinated — and that includes kids — we don’t know if we’re going to be able to affect transmission enough that it’s essentially going to go away.”

Not everyone is embracing that kind of recommendation. Already, at least four governors have ended mask mandates, and some never instituted them even in the worst parts of the pandemic. Responses in other states have varied widely. In some places, people have been back to barhopping and movie theaters, whereas gyms just reopened in San Francisco, with 10% capacity.

“The sad fact is, we’re going to do that experiment in different states and we’re going to learn from states that take more risks, how risky that is,” said Tom Frieden, a former director of the Centers for Disease Control and Prevention and the CEO of the global health initiative Resolve to Save Lives.

The middle term

Herd immunity has been portrayed by some as a logical endpoint of the pandemic. But that goal, even if attainable, is likely fleeting.

That’s not to say that the country, or the world, will still be in a crisis phase over the next couple years. But even if the U.S. reaches herd immunity through vaccinations, it’s unlikely to last, experts note. Neither a Covid-19

infection nor vaccination is believed to confer lifelong immunity that blocks infections entirely. Instead, people will once again become vulnerable, either because their immunity wanes or the pathogen evolves in ways that allow it to infect even people who have protection against earlier strains. Newborns will also add to the pool of susceptibles.

“Susceptible replenishment,” as it’s known, is why some experts expect seasonal waves going forward. The virus might hover at low levels, passing mostly among people who are unvaccinated, but rear up again as even the vaccinated become vulnerable and seasonal factors give it a boost. Some regions or countries could eliminate the virus through widespread immunizations, but they could also face reintroductions.

How serious future outbreaks will be in terms of disease will be influenced by whether vaccines can continue to prevent severe outcomes, as well how many people are vaccinated, how long vaccine-derived immunity lasts, and how the virus evolves. Those factors will also shape how often people need vaccine booster shots and whether vaccines need to be adapted to better match a changing virus, a possibility that vaccine makers are already exploring.

Ben Cowling, an epidemiologist at the University of Hong Kong, said he thinks Covid-19 could cause more deaths than flu over the next decade, in part because of the continued emergence of variants.

“I think we’re still going to face the problem that hospitals are going to be flooded with Covid cases,” Cowling said. “But maybe we’ll be better at coping with that, with the experience from Covid, better prepared for what happens if there’s a big surge. And maybe health departments, city mayors, and state governors will also have better plans in place to react and know what they should or shouldn’t do if there is a sign of a surge coming.”

Others are more sanguine. Vineet Menachery, a coronavirologist at the University of Texas Medical Branch, described a scenario in which 70% to 75% of a population gets vaccinated. That would drastically minimize spread

of the virus and keep people protected from infections. Even if vaccine uptake was somewhat lower than that, it should still avert a lot of worst-case outcomes, he said.

For Menachery and others, the durability of vaccine protection remains an open question. If vaccines aren't able to provide as much protection against certain variants, "maybe the durability isn't going to be as long. Maybe it's going to be one to two years versus three to four," Menachery said.

Experts hesitate to make predictions about viral evolution; after all, variants emerge as the result of random mutations.

But for a number of reasons it's possible the evolution of SARS-2 might lose some pace going forward. For one, there will — or at least, there should — be less transmission. The fewer people the virus cycles through, the fewer chances it has to mutate. More generally, when a virus spills into a new host, as SARS-2 did into humans in 2019, there are more avenues for it to morph in ways that give it an advantage in infecting host cells and replicating — "low-hanging fruit," as virologist Adam Lauring of the University of Michigan explains it. Over time, there should be fewer ways for an altered SARS-2 virus to outcompete other forms and undermine vaccines.

"It's perfectly reasonable to think that a couple years from now, it might be evolving more slowly," Lauring said.

The long term

Years from now, SARS-CoV-2 could join the ranks of OC43, 229E, NL63, and HKU1— the four endemic, seasonal coronaviruses that cause a chunk of common colds every year. Essentially, our immune systems — primed by vaccines, boosters, and previous encounters with the coronavirus — will be ready to knock back SARS-2 when we see it again, potentially blocking an infection or leading to one that causes no symptoms or maybe just the sniffles.

We tend to lump cold-causing viruses in with influenza when describing “cold and flu season”; after all, they’re all respiratory pathogens and have overlapping seasonal arcs. But experts stress that having SARS-2 join the ranks of flu viruses would be a most unwelcome outcome. While most people don’t see the flu as an existential threat, it still kills tens of thousands of people in the U.S., and hundreds of thousands around the world, every year. (This year was a notable and welcome exception due to the ways in which Covid-19 restrictions inhibited spread of flu.)

“It would be a damn shame to have another influenza,” said Sarah Cobey, an epidemiologist and evolutionary biologist at the University of Chicago.

But many experts think SARS-2 is more likely to behave in the way we regard cold-causing coronaviruses, which would make it mostly an irritant.

Veteran coronavirus researcher Stanley Perlman of the University of Iowa raised the idea that viral evolution could perhaps even play to our advantage. It’s possible, he said, that SARS-2 mutates in ways that actually weaken how sick it makes people, pushing it toward becoming a virus that causes colds for the vast majority.

“But right now,” Perlman cautioned, “that’s just a hope.”

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