Even now, Covid-19 kills over a hundred thousand annually. Here's how to lower the risk

Lynn C. Klotz, Ph.D.
Senior Science Fellow
Center for Arms Control and Non-proliferation
820 1st Street NE, Suite LL-180
Washington, D.C. 20002
Office: 5 Duley Street
Gloucester MA 01930
E-mail: lynnklotz@live.com

Introduction

The New York Times Opinion writer David Wallace-Wells sounded the alarm.

> "probably half of all Covid infections have happened this calendar year — and it's only July. By December, the figure could be 80 percent or more. The gap between cases and severe outcomes is bigger than it has ever been, with the fraction of infections ending in deaths one-tenth that of the pandemic's early stages."

Most COVID-19 infections (Sometimes the CDC website can't be linked, so visit https://covid.cdc.gov/covid-data-tracker/#variant-proportions) are caused by the Omicron subvariant dubbed BA.5 and by subvariant BA.4.6. But the percentages of several other Omicron subvariants with a variety of ancestors is on the rise.

The large number of infections is clearly due to the highly contagious subvariants of Omicron, mainly BA.5. Trevor Bedford, a computational virologist at the Fred Hutchinson Cancer Center in Seattle, is an expert whose opinion Wallace-Wells highly respects, estimates that

> "Right now…around 5 percent of the country is getting infected with the coronavirus each month and…that pattern to largely continue…that as a ballpark estimate…going forward we can expect that every year, around 50 percent of Americans will be infected and more than 100,000 will die."

It is straightforward to calculate the expected high number of deaths. From the October CDC U.S. data the weekly number deaths were 2,566 reported to or identified by the CDC. Cases are trending downward significantly, percent hospitalizations and deaths are leveling off or increasing slightly, but in a background of significantly lower cases.

Assuming the daily averages of deaths holds for the whole year. The number of deaths in 2022 would be 52 weeks per year x 2,566 deaths per day = 133,432 deaths per year. In comparison, there were 45,222 firearm deaths in the United States in 2020, more than 32,000 people were killed in 2013 in auto accidents, and there were 12,000 to 52,000 deaths annually in recent years from seasonal influenza.

Every one of these causes of death is less than the predicted yearly 133,432 deaths caused by the Omicron subvariants.

Dr. Shira Doron, an infectious disease specialist and professor at Tufts University School of Medicine suggests that "the odds of a person dying if they get a COVID infection — what's called the case fatality rate — would be about the same as the flu now, which is estimated to be around 0.1%, or perhaps even lower." Others quoted in the article disagree with Doron saying percent deaths may be higher than 0.1%.

Many people seem to know that they are unlikely to be hospitalized or die. They know this either intuitively and/or are fed up with activity restrictions; so, they go about their daily activities by not wearing masks anywhere. This is a mistake that will contribute to the continuation of high numbers of deaths.

What can be done to reduce the unacceptable number of hospitalizations and deaths?

It seems to me that this is a three-pronged problem: the obvious public-health prong, a therapy prong, and an economic prong. For the public-health part, I analyze others' strategies to keep us safe from infection. For therapy, I analyze the promise of new vaccines and medicines; and for economics, I calculate the dollar cost of sickness and death, which might better get the attention of government. My goal is to make recommendations on how we might eliminate the risk of COVID-19, particularly Omicron subvariants, in the United States. Much of what I will say depends on the careful research or creative ideas of others.

Skeptics will point out that almost everybody everywhere in the United States is unmasked in public and will not change their behavior. It is likely true that their behavior will not change drastically but employing many of the strategies described here could eliminate the Omicron subvariants despite their behavior.

The Yale University immunologist Akiko Iwasaki believes "If we want to contain the spread of the virus, the only way to do that is through mucosal immunity" using nasal vaccines. I agree that nasal vaccines will be an important part of the strategies for preventing the spread of Omicron and its subvariants, but many strategies may be necessary to nearly eliminate the virus, by which I mean the virus likely will not entirely disappear (herd immunity) but will be suppressed to a level that the probability that a single infected person encounters an uninfected person to infect would be very low, called here near herd immunity.

Is disappearance of Omicron subvariants without many strategies by herd immunity possible?

If Professor Bedford is right, 50% of the U.S. population may be infected this year. By the end of next year, more that 90% could by infected, so near herd immunity is possible. Thus, we may not need many strategies.

In a March 2022 but a not yet peer-reviewed study by South African researchers, as many as 97% of people in that country had antibodies from either vaccination, a past infection, or both.

> "The weighted national prevalence of anti-nucleocapsid antibodies (evidence of infection) is 87% and an additional 10% had only anti-spike antibodies (suggesting vaccination and the lack of natural infection)."

In contrast to South Africa, vaccination is the major source of protection against the virus in the United States, not previous infection,.

The idea of reaching near herd immunity is documented in a June 23, 2022 Nature article :

> "But the rise of BA.4 and BA.5 seems to stem, instead, from their capacity to infect people who were immune to earlier forms of Omicron and other variants, says Christian Althaus, a computational epidemiologist at the University of Bern. With most of the world outside Asia doing little to control SARS-CoV-2, the rise — and inevitable fall — of BA.4 and BA.5 will be driven almost entirely by population immunity, Althaus adds, with cases increasing when protection lulls and falling only when enough people have been infected."

In the Nature article, Christian Althaus, a computational epidemiologist at the University of Bern, is arguing for near population immunity (another name for herd immunity).

But we are not out of the woods. In the future, we may see the rise of new deadly pathogens related to or not related to COVID, such as lab-created potential pandemic pathogens. For instance, a new Coronavirus from bats. We will then be starting all over again.

Public-health approaches

The importance of masking indoors

At Boston University, a massive study of SARS-CoV-2 transmission was conducted during the fall 2021 semester. It found only 0.0045% transmitted infections:

> "Participation in class and work activities on a campus with mandated vaccination and indoor masking but that was otherwise fully open without physical distancing during a time of ongoing transmission of SARS-CoV-2, both at the university and in the surrounding counties…Of more than 140 000 in-person class events and a total student population of 33 000 between graduate and undergraduate students, only 9 instances of potential in-class transmission were identified, accounting for 0.0045% of all classroom meetings."

This study dramatically demonstrates the value of indoor masking, at least for college classes that are usually less than one-hour long. For short periods of time, it is reasonable to urge people to wear the highly protective masks indoors and in crowds outdoors using the Boston University study as evidence for the value for masking. N95 and KN95 are readily available at low prices.

The situation is different for K-12 students who will likely sit in a single classroom for three or more hours at a time. In an also massive study of 1,102,039 K-12 students and staff titled *Secondary Transmission of COVID-19 in K–12 Schools: Findings From 2 States*, demonstrated the value of classroom masking:

> "Participating districts in North Carolina and Wisconsin and North Carolina charter schools offering in-person instruction between March 15, 2021 and June 25, 2021 reported on distancing policies, community- and school-acquired infections, quarantines, and infections associated with school-sponsored sports…

> **RESULTS:** During the study period, 1 102 039 students and staff attended in-person instruction in 100 North Carolina school districts, 13 Wisconsin school districts, and 14 North Carolina charter schools. Students and staff had 7865 primary infections, 386 secondary infections, and 48 313 quarantines. For every 20 community-acquired infections, there was 1 within-school transmission event. Secondary transmissions associated with school sports composed 46% of secondary transmission events in middle and high schools. Relaxed distancing practices (<3 ft, 3 ft) and increased children per bus seat were not associated with increased relative risk of secondary transmission. **CONCLUSIONS:** With universal masking, in-person education was associated with low rates of secondary transmission, even with less stringent distancing and bus practices. Given the rates of sports-associated secondary transmission, additional mitigation may be warranted."

K-12 students usually rebel against wearing masks. The universal mask wearing in this K-12 study is surprising to me because there are likely people in every United States community who adamantly oppose masking. Moreover, some states have enacted anti-masking legislation. Most parents know that their children won't wear masks in their classrooms unless forced to do so.

Improving indoor air quality

Dr. Ezekiel J. Emanuel, vice provost for Global Initiatives at the University of Pennsylvania, has a clever idea:

> "COVID also seems to have induced Americans to recalibrate their risk tolerance up — substantially. In exchange for fewer restrictions on masking, travel, and socializing, Americans now seem willing to accept 150,000 to 200,000 COVID deaths annually…This would make COVID the fourth leading cause of death in the United States…Public acceptance of more risk requires increasing thresholds for issuing public health recommendations and restrictions. Accepting the public's position also means forswearing closures of schools, offices, bars and restaurants, and all the other public venues, even when high levels of transmission are occurring or likely. That is what endemic means — living with the virus… But this doesn't mean doing nothing. Public health policy makers need to adopt the air bag model for COVID — safety measures that work in the background without individuals needing to take initiative to get substantial benefit."

Dr. Emanuel mentions first improving indoor air quality:

> "One thing that can be done is to improve indoor air quality. COVID is an airborne illness and improving indoor air quality can reduce transmission and keep people healthy. Mandating schools, public buildings, and other indoor venues to upgrade HVAC systems or use germicidal UV light is critical. Air quality also needs to be improved on planes, trains, buses, and other forms of transportation."

This suggestion is an example of the "air bag model" as it would be working in the background. Rapid air exchange of HEPA filtered air is one system for improving air quality. Since students can pass infections to family members, improving the quality of school air should be tackled early on using President Biden's infrastructure financing. Congress has now passed the Infrastructure Investment and Jobs Act, which provides financing for improving air quality in public places, but it will likely take a year or two for the money to filter down to communities, so they can begin work on improving air quality.

Moving forward minimizing confrontations

So, the question is how do we move forward activities with obvious public-health benefits without politicizing or directly confronting opposition? We should avoid mandating wearing masks, but provide

evidence (e.g., the Boston University study and the K-12 study) for the safety from COVID that masking provides.

Anti-maskers may not allow their children to wear masks in schools. Added to this, K-12 students usually rebel against wearing masks. Thus, K-12 students wearing masks may be in the minority. The masked and unmasked should be placed into different sections of the classroom, with at least six feet separating the two sections if possible.

Vaccines

Background to new vaccines

While there are several vaccines approved or under development for COVID-19, this section will focus only on Moderna's and Pfizer's vaccines for Omicron subvariants. The points I want to make can be covered sufficiently by focusing only on these two vaccines.

In a television interview with Dr. Gabriela Andujar Vazquez of Tufts Medical Center on NBC TV Boston on August 9, 2002, she describes what we know about BA.4.6: "makes us believe that it's gonna behave similar to Omicron…more contagious but not more severe…and we'll know more as days go by." One thing I can conclude from this early data is that BA.4.6 is not showing anything alarming such as high percentages of hospitalizations or the lagging category, deaths. Being optimistic, I am guessing it will follow BA.5 and may not evolve into deadlier strains. Time will tell.

The new Moderna and Pfizer bivalent vaccines protect against both the old and the newer BA.5 and BA.4.6 new variants.

> "The authorized bivalent COVID-19 vaccines, or updated boosters, include an mRNA component of the original strain to provide an immune response that is broadly protective against COVID-19 and an mRNA component in common between the omicron variant BA.4 and BA.5 lineages to provide better protection against COVID-19 caused by the omicron variant."

I argue that BA.4.6 and BA.5 and other new variants may be the end of the line for most if not all virulent Omicron subvariants. Each new subvariant is more contagious because of new mutations in the spike protein, so I assume this implies new mutations in the rest of the viruses' proteins. Thus, a new Omicron subvariant may become much less virulent; indeed, the variant could become non-dangerous when the cumulative mutations reach the point that virulence is stunted. My assumption about considerable mutations is backed up by a multi-authored paper published in December 2021 in the journal Nature that looks at the parent Omicron virus:

> "Various single mutations of Omicron can impair neutralizing antibodies of different epitope groups… In total, over 85% of the tested neutralizing antibodies were escaped by Omicron… our data suggest that infection with Omicron would result in considerable humoral immune evasion."

I take "escaped by Omicron" to mean 85% of polyclonal antibodies don't bind to their epitopes, not that 85% of the epitopes prevent binding of the antibodies. Nevertheless, this publication supports my argument that there are several mutations in all the virus proteins if mutations are somewhat random.

The BA.4 and BA.5 variants should have even more mutations than its Omicron parent, a reasonable assumption.

Of course, this observation says nothing about the virus's virulence. This is a two-edged sword. On the one edge, the Omicron subvariants avoid antibodies; and on the other edge, they become less virulent causing less illness and almost no deaths. Recent case, hospitalization, and death data discussed above are consistent with the thought that as Omicron variants become more contagious, they will become less virulent causing only mild illness and fewer deaths.

To better understand my arguments and see links to supporting publications, consult my two unpublished articles on Omicron and its subvariants that are posted on the Center for Arms Control and Non-Proliferation website. These were written mainly in the spring of 2022 and posted on the CACNP website in mid-July 2022, so are already a bit out of date but not in important ways.

Advantages of nasal vaccines

There are three recent authoritative articles on nasal vaccines that I was able to find: one on the website CNET (August 3, 2022), another in the journal Science Immunology (July 21 2022), another in Scientific American (May 3, 2022). All strongly support nasal vaccines. Both the CNET and Scientific American articles are easy to read for us non molecular biologists/virologists. I leave much of the Science Immunology article to scientists skilled in molecular virology or immunology.

The future for nasal vaccines looks bright:

> "Dr. Joel Ernst, professor of medicine and chief of the division of experimental medicine at the University of California San Francisco…said that many researchers are looking at nasal vaccines as boosters…But the future of nasal COVID-19 vaccines looks fairly bright… While we might need to wait a year or two for clinical trials and authorization in order for nasal vaccines to hit the market: 'I think the prospects are pretty good that we're going to have nasal vaccines'" (From the CNET article)
>
> The mucosal system relies on specialized cells and antibodies within the mucus-rich lining of the nose and other parts of our airways, as well as the gut. These elements move fast and arrive first, stopping the virus, SARS-CoV-2, before it can create a deep infection. 'We are dealing with a different threat than we were in 2020,' says Akiko Iwasaki, an immunologist at Yale University. 'If we want to contain the spread of the virus, the only way to do that is through mucosal immunity.' " (From the Scientific American article)

Below are bulleted points gleaned from the three above sources summarizing the allure of nasal vaccines:

- Injections create a type of immune response known as systemic immunity, which produces what are called immunoglobulin G (IgG) antibodies that circulate throughout the bloodstream and patrol for the virus. Nasal sprays assemble a separate set of antibodies known as immunoglobulin A (IgA). These populate the spongy mucosal tissues of the nose, mouth, and throat. One researcher, Akiko Iwasaki, likens mucosal vaccines to putting a guard at the front door, as opposed to waiting until the invader is already inside to attack.

- While conventional injectable vaccines are generally poor at inducing protective mucosal immunity, nasal vaccines have been shown to trigger both tissue-level mucosal and systemic responses. Injectable vaccines trigger only systemic responses.
- Coronaviruses infect us by latching onto the cells in our upper respiratory tract, including our nose and throat. A nasal vaccine will stop the disease right where it starts.
- Nasal vaccines are much easier to administer as they would be sprayed up the nose at home, not injected by a professional.
- FluMist, reformulated in 2018, the only intranasal vaccine was approved by the Food and Drug Administration.

Concerns and drawbacks of nasal vaccines

Nasal vaccines are not without their concerns and drawbacks, also gleaned from the three sources:

- Because of the nose's proximity to the brain, substances squirted up the nasal passages could raise the risk of neurological complications. In the early 2000s, a nasal flu vaccine licensed and used in Switzerland was linked to Bell's palsy, a temporary facial paralysis.
- Relatively little is known about mucosal immunity. According to epidemiologist Wayne Koff, the human immune system is a black box, and the mucosal immune system is probably the blackest of the black boxes.
- Making nasal vaccines has been slow going because of the challenges of creating formulations for this unfamiliar route that are both safe and effective.
- The prospect of developing an FDA-approved nasal vaccine soon will only be possible with dedicated funding, priority, and breaking down of any regulatory hurdles. What is needed is an operation-warp-speed (OWS) push to reduce significantly delays in manufacturing at scale, regulatory approval, and distribution.
- At present, there is no governmental support for nasal vaccines.
- A nasal spray seems like an easier delivery method than an injection but that is not the case. With intramuscular injections, a needle delivers the vaccine ingredients directly into the muscle, where they quickly encounter resident immune cells. Sprays, in contrast, must make their way into the nasal cavity without being sneezed out, and then must breach a thick barrier gel of mucus and activate the immune cells locked within.

These concerns and drawbacks likely explain the failure of the Oxford/AstraZeneca nasal vaccine.

It may well take more than two years to reach the market. In my opinion, it is unlikely that nasal vaccines will receive Emergency Use Authorization (EUA), delaying market introduction.

The four nasal vaccines beginning or completing Phase III clinical trials

There are four nasal vaccines that are in Phase III clinical trials according to the Journal Science Immunology and eight others in earlier stages of development:

> "Fortunately, there are at least 12 nasal vaccines that are in clinical development and four have reached Phase 3 randomized, placebo-controlled trials: 3 are viral vector (Bharat Biotech, Codagenix and Beijing Wantal Biological),

using a recombinant spike protein or receptor-binding domain or a live, attenuated virus; a 4th is a protein subunit vaccine (Razi Vaccine and Serum Research Institute)." (From the Science Immunology article)

The four, presumably in Phase III, are from the companies Bharat Biotech (India), Codagenix (United States), Beijing Wantal Biological (China), and Razi Vaccine and Serum Research Institute (RVSRI) (Iran). The RVSRI website cannot be linked directly. It was found through the Food and Agriculture Organization of the United Nations.

Each of these companies employ different strategies and therefore their nasal vaccines have different properties. Their strategies are designed to provide vaccines against the BA.4 Omicron subvariant even though no company tests their vaccine on Omicron subvariants, and some companies don't even test on Omicron, testing instead on earlier COVID-19 viruses.

(1) Bharat Biotech strategy and properties

Their vaccine is named ChAdOx1 nCoV-19. In the United States, it is currently in Phase I/II clinical trials with 1,090 participants. The trials are to be completed March 31, 2023. The company claims it has completed Phase III clinical trials in India. In India the vaccine is named BBV154. They have established large manufacturing capabilities at multiple sites across India, so the vaccine could be widely available before the end of 2022, at least in India.

The nasal delivery system has been designed and developed to be cost-effective in low and middle-income countries. The vaccine may be deployed for mass immunization with an easy-to-administer formulation and delivery device. The vaccine is stable at 2-8 degrees Celsius, so it does not require ultralow temperature freezers that might not be readily available in emerging nations.

The vaccine is delivered using a recombinant adenoviral vector construct.

They state that vectored vaccines also enable faster development of targeted vaccines in response to emerging variants of concern.

(2) Codagenix strategy and properties

Their nasal vaccine is named CoviLiv™

Their pipeline diagram indicates that the vaccine has just finished Phase II clinical trials

They employ a live-attenuated delivery virus design, which contains non-spike proteins that are highly conserved across the different Omicron variants of concern indicating potential for immune protection across all subvariants.

They claim they can go from genetic sequence of a wild-type virus to viable candidate vaccine or therapeutic in weeks—and faster, if needed, as new outbreak strains are identified.

(3) Beijing Wantal Biological strategy and properties

Their nasal vaccine is named CA4-dNS1-nCoV-RBD (dNS1-RBD). It is a live attenuated influenza-virus vaccine (LAIV). The influenza vector carries a gene encoding the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2. They do not specify that the spike protein is from Omicron or its subvariants BA.4/BA.5

The vaccine causes a rapid (1 d) humoral and systematic immune response.

As of July 2022, A global multicenter Phase III clinical trial is ongoing and should be completed soon.

(4) Razi Vaccine and Serum Research Institute (RVSRI) Strategy and properties

The development in Iran of the first recombinant protein-based nasal vaccine based on the recombinant SARS-CoV-2 spike protein. The fact that the vaccine was developed in Iran may not make it available in the United States for political reasons

The vaccine is named RAZI-COV PARS. The vaccine was formulated in the oil-in-water adjuvant system named RAS-01 (Razi Adjuvant System-01).

Three different doses of candidate vaccine stimulated remarkable titers of neutralizing antibodies, specific IgG antibodies as well as IgA antibodies. A robust and quick immune response appeared from the third-week post-immunization.

The receptor binding domain (RBD) S1 is a poorly conserved region of the spike protein but represents a promising antigen for induction CoV-specific antibodies. S2 is highly conserved across coronaviruses that induce more cross-reactivity CoV-specific antibodies compared to S1. A specific fragment in the S2 subunit of SARS-CoV-2 was also found to stimulate neutralizing antibodies against SARS-CoV-2 but elicit a longer-lasting and stronger memory response, and also decreases the likelihood of sequence-altering mutations that decrease the efficacy of vaccine.

the production of specific IgG and IgA antibodies is significantly stimulated after the first injection of RAZI-COV PARS vaccine. Antibodies have been detected as early as 28 days after the first dose of vaccination and showed a remarkable increase following the second dose of vaccination from day 35 onwards. The fact that IgA and IgB antibodies take 28 or more days to appear makes the vaccine not an antidote to a just detected infection, immediate use after a person has been infected.

The IgA antibodies in the upper respiratory tract (URT) which are considered a major barrier against viral infection by impeding viral shedding, limiting the degree of spread of infection.

Delivery of nasal vaccines:

> "Akiko Iwasaki is leading one of several research groups in the U.S. and elsewhere that are working on nasal vaccines. Some of the sprays encapsulate the coronavirus' spike proteins—the prominent molecule that the virus uses to bind to human cells—into tiny droplets that can be puffed into the sinuses. Others add the gene for the spike to harmless versions of common viruses, such as adenoviruses, and use the defanged virus to deliver the gene into nasal tissue. Still others rely on synthetically bioengineered SARS-CoV-2 converted into a weakened form known as a live attenuated vaccine." (From the Scientific American article)

General observations about nasal vaccines

Systemic vaccines, such as the Moderna and Pfizer vaccines, must be given well in advance of infection. This is also the case for nasal vaccines except for one exception. According to its developer, Beijing Wantal Biological, their nasal vaccine is an exception as it provides a rapid one-day humoral and systematic immune response. So, if true, this vaccine could be used to eliminate a just acquired infection.

Are the nasal vaccines intended to replace the systemic preventative vaccines or to be used in parallel with them? My guess is that they would be used in parallel, since systemic vaccines have a history of success.

Other nasal vaccines take advantage of conserved sequences in COVID-19 viruses, so the vaccines are likely to work for Omicron subvariants BA.4 and BA.5. The developers are Razi Vaccine and Serum Research Institute (RVSRI) and Codagenix.

The nasal vaccine from the fourth company, Bharat Biotech, doesn't appear to be designed to target Omicron subvariant BA.5. They state that vectored vaccines like theirs enable faster development of targeted vaccines in response to emerging variants of concern, so they can develop a vaccine quickly if necessary.

Medicines

There are medicines on the market and likely several medicines in development.

(1) Pfizer's PAXLOVID is the go-to drug for the treatment of mild-to-moderate coronavirus disease caused by the SARS-CoV-2 virus. PAXLOVID is comprised of two antivirals, nirmatrelvir and ritonavir, which are taken orally. At present, the U.S. government's Health Sciences Authority has granted interim authorization of PAXLOVID. PAXLOVID provides an 89% reduction in the risk of hospitalization and death.

PAXLOVID is a mixture of nirmatrelvir tablets co-packaged with ritonavir tablets. Both are administered together. The treatment course is twice daily for five days, which should be initiated as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset. The cost is $530 for

the treatment course. However, it is being distributed free by the U.S. government or paid for by health insurance carriers. The 5-day treatment course of Paxlovid should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset

Pfizer announced on June 30, 2022 that it has submitted a New Drug Application to the U.S. FDA for PAXLOVID. Pfizer is seeking approval to replace its current emergency use authorization.

One big issue with PAXLOVID is that people who have taken a 5-day course sometimes become reinfected "There isn't much data about the frequency of Paxlovid rebounds. The CDC issued a warning in late May about rebounds, but a Mayo Clinic study in June found them to be rare, with less than 1 percent of study participants experiencing a rebound." Experts say a longer Paxlovid course is needed to prevent rebounds. Pfizer is now studying Paxlovid rebounds.

(2) On August 1 2022, AstraZeneca's antiviral monoclonal antibody, Evusheld, was granted an interim authorization from the U.S. government. This authorization is similar to an emergency use authorization (EUA). Evusheld is comprised of two monoclonal antibodies, tixagevimab co-packaged with cilgavimab. It is administered by intramuscular injection.

Evusheld is authorized for pre-exposure prevention of COVID-19 in adults who have not had a known recent exposure to an individual with COVID-19 infection (pre-exposure prophylaxis) for whom COVID-19 vaccination is not recommended, because they are unlikely to mount an adequate immune response to COVID-19 vaccination due to their moderate to severe immunocompromised state from a medical condition or their receipt of immunosuppressive medications or treatments.

(3) Just announced on August 15 2022 is a new monoclonal antibody that neutralizes all known SARS-CoV-2 variants. In addition, this antibody should be able fight off any viral variant that might emerge. For now, it is named SP1-77. It was developed by researchers at Harvard Medical School and Boston Children's Hospital. The findings were published in Science Immunology on August 11, 2022.
This antibody works in a unique way, by blocking the fusion of the outer membrane of the virus with the membrane of our cells. The fusion site is highly conserved among different variants of concern, which implies that fusion in future variants should also be blocked. Indeed, the antibody neutralized all currently known SARS-CoV-2 variants of concern, including all omicron subvariants in lab tests. So far, it has not been tested in patients. If successful in humans and eventually approved by the FDA, this could be the miracle medicine we have all been hoping for.

There may well be many more medicines in development, but these were the few I came across in my daily activities.

Economics

From the website Money:

> "Fair Health breaks down the hospitalization charges in different states into "complex" and "noncomplex" COVID-19 cases. It defines complex cases as "the most serious" ones, which require admission to an intensive care unit (ICU) and/or a ventilator. Noncomplex cases include hospital admission but not an ICU visit or a ventilator.

Fair Health, a U.S. non-government organization (NGO) recently released an interactive tool that displays state-by-state costs associated with COVID-19 treatment. COVID-19 costs vary considerably depending on the severity of the disease. From the interactive tool: click the button "Click Here to View National Statistics" to find the following data: For a complex inpatient, the average cost is $317,810; for a noncomplex inpatient, the average cost is $74,591; and for an outpatient, the average cost is $2,557.

Clearly, a much higher percentage than 1-0.075=0.925 or 92.5% don't go to the hospital, that is, those from not reported infections. Most infections are not reported, as people quarantine at home, or may not quarantine at all, or may not know they are even infected with COVID-19.

Those who don't go to the hospital have some direct treatment costs. From Fair Health, the average cost of a not-hospitalized, identified patient is $2,557. Added to this, the direct cost for the very large group of not reported infections is much larger. Thus, the yearly cost of treatment reported in this study, $17 billion, is likely a big underestimate.

From JAMA Network Open

> "Among 192,550 adults hospitalized with COVID-19…55,593 (28.9%) were admitted to the ICU, 26,221 (13.6%) died during the index hospitalization, and 5,839 (3.0%) were transferred to hospice care."

The percentage of cases that fall into the outpatient category can be found from CDC data summarized at the beginning of this analysis, where it was found that daily hospitalizations are 5.7% per infection, respectively. Thus, the fraction of infected people that are never hospitalized, the "outpatients," are 0.057; the adjusted fraction of "noncomplex patients" are the people who are hospitalized but don't go to the ICU are (1-0.057)x(1-0.289)=0.654; and the adjusted fraction of "complex patients" that go to the ICU are (1-0.057)x0.289=0.273.

As a check on my arithmetic, these three percentages should add to 1.0: check=0.057+0.654+0.273=0.983, which is close to 1.0 if I account for roundoff error mainly in the 0.057 number. The 0.057 was rounded from .05747, so the 0.983 rises to 0.983x5.747/5.7=0.991 which is much closer to 1.0, the other roundoff numbers likely account for the difference, but the raw data is unavailable to look at its roundoff error.

To calculate the cost for a random infected person in the United States, we will use the just calculated fraction (probability) that that person was either a complex inpatient, a noncomplex inpatient, or an outpatient. From these probabilities and the average cost per person of an infected person picked at random, the average cost multiplied by the estimated number of people infected each year, 133,432 will yield the national cost.

The average cost per person is calculated as (0.057x$2,557)+(0.654x$74,591)+(0.273x$317,810)= $135,690. As I estimated above the yearly death toll is 133,432, the total yearly cost to the United States is $135,690x133,432=$1.7x10^{10} or $18 billion dollars. This should provide considerable incentive to rid ourselves of BA.4, BA.4.6 and BA.5; so, we will not be stuck with Omicron subvariants forever.

Conclusion

I conclude from my analysis that it might take two years to see FDA approval, funding available, and so on to begin implementing many of the strategies identified here to rid ourselves of Omicron and its subvariants. I am guessing it might take an additional two to three years to implement them widely.

I agree with William Hanage, Professor of epidemiology at Harvard's T.H. Chan School of Public Health, quoted in the article. "We can see that there is some immunity out there, and it is interfering with the transmission of the virus. It's just not interfering with the transmission of the virus to make it go away." But we might get lucky. Along with William Hanage's observation, many of the strategies documented in this study will contribute to nearing herd immunity. Also, behavior changes like remote working will contribute. This is a controversial subject debated in an August 29, 2022 Boston Globe article by Camille Caldera.

As noted earlier, my estimate of 10% of the population infected may be low. If Trevor Bedford is right, 50% of the U.S. population may be infected this year, and perhaps 90% could be infected by the end of next year, so nearly approaching herd immunity is possible. This near herd immunity may be enough for practical purposes; that is, it would be difficult for an uninfected person to encounter an infected person.

We will still look to public health and therapeutic strategies to mitigate risk. Even with those, we may not be out of the woods. In the future, we may see the rise of new deadly pathogens related to or not related to COVID; for instance, a new Coronavirus from bats or lab-created potential pandemic pathogens. We will then be starting all over again.