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Perspective

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The Future of SARS-CoV-2 Vaccination — Lessons from Influenza

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After a period of falling Covid-19 illness rates, the recent spread of the delta variant of SARS-CoV-2 was a major disappointment and necessitated a reexamination of some previous assumptions. This reconsideration may, at least in part, be a correction to overly optimistic views of what highly effective SARS-CoV-2 vaccines could accomplish. Some observers had hoped the vaccines could eliminate transmission of the virus, the ultimate goal of reaching herd immunity.[1] A more likely picture of our future with this virus comes into focus if we examine the well-known infection patterns of another respiratory virus, influenza, both in and outside pandemics. That experience can help us reset expectations and modify goals for dealing with SARS-CoV-2 as it further adapts in global spread.

Early results from the clinical trials and observational studies of mRNA vaccines against SARS-CoV-2 indicated that not only were they highly effective at preventing symptomatic infection, but they were also effective in preventing asymptomatic infection and therefore transmission.[2] The basic criterion used for emergency use authorization by the Food and Drug Administration was a standard one: prevention of laboratory-confirmed clinical infection meeting a case definition. The effect on asymptomatic infections was a welcome surprise, because it has been thought that most vaccines for respiratory illnesses, including influenza, are "leaky" — that is, they allow some degree of asymptomatic infection and are better at preventing symptomatic infection.

The initial data on inapparent SARS-CoV-2 infection strengthened the hope that, at a certain level of vaccination, transmission would cease completely. To many of us, this hope appeared overly optimistic, and it seems even more so now; the highly transmissible delta variant causes asymptomatic infections and sometimes illnesses (albeit usually mild) in vaccinated people, probably because of increased growth potential, as well as because of waning immunity, which also involves decreasing IgA antibody levels. Elimination of an illness by means of herd immunity works best when the agent has low transmissibility, and it requires the absence of pockets of susceptible people. Eliminating Covid-19 seemed theoretically possible, because the original 2002 SARS virus ultimately disappeared. That virus, however, did not transmit as well as even the initial strain of SARS-CoV-2. It occurred in limited regions and was characterized by focal spread, including superspreading events. Such a pattern, which was also seen in the early days of SARS-

Summary of World Health Organization (WHO) Process of Virus Selection for Annual Influenza Vaccines.

Overview	Considered Elements and Steps Taken
Disease and virus surveillance	Global surveillance network conducts surveillance to collect specimens with influenza viruses and epidemiologic data.
Virus isolation and antigenic characterization	National Influenza Centers, or Collaborating Centers (CCs), isolate viruses; CCs produce ferret antisera and conduct antigenic characterization to understand the antigenic properties and evolution of the contemporary influenza viruses.
Genetic characterization of viruses	WHO CCs characterize a representative subset of viruses by use of genetic sequencing.
Human serology studies with influenza vaccine viruses	WHO CCs work to understand immune response induced by current vaccines to circulating influenza viruses to determine whether antigenicity of recently identified viruses differs from that of older viruses.
Virus fitness forecasting	Modeling is conducted using genetic and antigenic characterization data to forecast virus fitness.
Vaccine effectiveness	Global network provides vaccine-effectiveness findings from current and prior influenza seasons.
Selection of candidate vaccine viruses	WHO and representatives evaluate data and twice each year make recommendations for the northern and southern hemispheres' seasonal influenza vaccines.

CoV-2, is called "overdispersion" — 10% of cases, for example, may be responsible for 80% of transmission.[3] These dynamics explain why there were great differences in antibody prevalence within a given city and spotty global spread early in the pandemic. Overdispersion was thought to be an unstable trait that would disappear, with transmission becoming more uniform and higher overall. That transition appears to have occurred as newer variants take over.

Given the parade of variants, their varying transmissibility, and continuing concern about antigenic changes affecting vaccine protection, I believe it should now be clear that it is not possible to eliminate this virus from the population and that we should develop long-term plans for dealing with it after the unsupportable surges are fully controlled. Pandemic and seasonal influenza provide the most appropriate models to aid in developing strategies going forward.

As with SARS-CoV-2, when a novel pandemic influenza strain appears, its spread can overwhelm the health care system. Waves of infection go through a city in weeks and a country in months, but there is scant evidence that superspreading events occur. Thereafter, the pandemic virus persists as a new seasonal strain, and antigenic changes occur — albeit probably not as quickly as we are seeing with SARS-CoV-2. The new strain joins the other seasonal influenza types and subtypes that reappear each year. The goal of vaccination becomes managing the inevitable outbreaks and reducing the rates of moderate-to-severe illness and death. Preventing mild disease, though important, is less critical.

Readministration of influenza vaccine has become an annual event for much of the population, in response to both waning immunity and the appearance of variants, termed antigenic drift, necessitating updated vaccines. Even when there is no substantial drift, revaccination is recommended because of waning immunity. But antigenic drift is a constant issue and is monitored globally, with vaccine composition updated globally twice a year on the basis of recommendations from a World Health Organization consultation.[4] As outlined in the table, various criteria are considered in decisions about which strains to include in vaccines. Vaccine effectiveness against laboratory-confirmed symptomatic infection is never higher than 50 to 60%, and in some years it is much lower. Thus, the value of influenza vaccines, now given to as many as 70% of people in some age groups, lies not in eliminating outbreaks but in reducing them and preventing severe complications.

Though there may be similarities between SARS-CoV-2 and influenza, there are also meaningful differences. The most obvious difference is the efficacy of SARS-CoV-2 vaccines, which is currently much higher than we can achieve with influenza vaccines. Whether that degree of efficacy will continue is one of the many open questions that can only be answered over time. It is clear, however, that revaccination will be necessary, for the same reasons that influenza revaccination is necessary: antigenic variation and

waning immunity. Data on the frequency of reinfection with seasonal coronaviruses may not be relevant, but they suggest that protection is relatively short term even after natural infection.[5] Revaccination frequency and consequences will need to be determined.

Let us hope that certain problems with the influenza vaccine — such as the failure of vaccination, in some years, to produce the desired increase in protection in previously vaccinated people — do not occur with the SARS-CoV-2 vaccines. Other issues, such as the variant to be targeted by vaccines, will need to be addressed. The successful public–private collaboration in selecting influenza strains offers a model for dealing with such issues. SARS-CoV-2 vaccines will be used globally, and the strain or strains contained in future vaccines will need to be chosen globally, in consultation with the manufacturers.

Most predictions about the shape of the post–Covid-19 world have been inaccurate — a reflection of rapid changes in knowledge. But we can now see a picture emerging in which use of effective vaccines will continue to be critical over the long term. Increases in asymptomatic infections and mild illnesses in vaccinated people will nonetheless continue to be possible, as variants continue to emerge. Counts of hospitalizations and deaths may be more important in monitoring the overall impact than numbers of cases, as long as the vaccines continue to be largely effective at preventing severe illness. The possibility of severe illnesses in a small proportion of vaccinated people does emphasize one of the greatest unmet needs we currently face: continued emphasis on better therapeutics and antiviral agents, which will not be affected by molecular changes in the virus as much as vaccines are.

The future timing and composition of booster vaccine doses will need to be determined on the basis of observational studies. We currently have few data on non-mRNA vaccines, particularly protein-based vaccines, which may have characteristics different from those of mRNA vaccines, especially in terms of duration of immunity.

Overall, the situation will be fluid, but we will require the continuing use of vaccines to avert severe consequences, even if milder illnesses still occur at a low frequency. We need to learn to live with these illnesses, just as we have learned to live with influenza.

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HISTORY OF MEDICINE

When Women and Children Made the Policy Agenda — The Sheppard–Towner Act, 100 Years Later

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On November 23, 1921, President Warren Harding signed into law the Sheppard–Towner Maternity and Infancy Protection Act, which marked the first time in American history that the federal government asserted responsibility for the health of mothers and children. Passed thanks to intensive lobbying by women, who had newly acquired the right to vote, the Act launched a 7-year policy experiment that continues to pose an intriguing "what if" question: How might health and welfare policy have evolved in the United States had this remarkable program not been defeated by organized medicine and states-rights conservatives?

Sheppard–Towner represented the culmination of the Progressive Era crusade to reduce infant mortality.[1] In 1900, at least 10 of every 100 newborns in American cities didn't live to see their first birthday. Reducing infant mortality became the first mission of the U.S. Children's Bureau after its creation in 1912. The first