

# The Long Road to a Universal Influenza Virus Vaccine<sup>1</sup>

PETER PALESE

Professor and Chair, Department of Microbiology  
Icahn School of Medicine at Mount Sinai

Thank you to the Society for the kind invitation and thank you to symposium moderator Dr. Shenk for the introduction. The title of this talk is “The Long Road to a Universal Influenza Virus Vaccine,” and I want to start out by reminding us all that vaccines are really wonderful—they work very, very, very well—but the road to an effective vaccination that everyone takes is sometimes a long one.

The first table is one you have probably seen (Table 1). We all learned in school that Edward Jenner vaccinated Jim Phipps, a 9-year-old boy living on his estate, with a cowpox vaccine in 1796. The story is quite interesting. Ethical standards were different then and there was no patient consent, but the experiment worked. The young boy was protected against a challenge with smallpox. However, it took 181 years until we had the last smallpox case in Somalia, and only three years later was the World Health Organization able to declare the world free of smallpox. It was a 200-year effort, really; it was not easy.

As a matter of fact, six years after Edward Jenner did the experiment of vaccinating this 9-year-old boy, there were already people saying, “this doesn’t work,” “this is terrible.” Figure 1 is a cartoon from 1802 called *The Cow-Pock—or-the Wonderful Effects of the New Inoculation!* In the cartoon, a physician is vaccinating a patient against smallpox with a coxpox virus; it shows the other vaccinated patients with what looks like cows erupting from their eyes, mouths, ears, legs, etc. You can see all the things here that were unnatural and that people were not very happy about with this vaccination.

Figure 2 is a pamphlet from 1891, almost 100 years later, called *Exposing the Evils of Vaccination*. So, you can see, it took a very, very long time until vaccination against smallpox became commonplace. People did not really accept that this was a good thing to do. Just look at the numbers in Table 2 from the Global Health Council. In the 20th century alone, they estimate that there were more than 300 million deaths. This really happened from 1900 to 1920. The numbers also

---

1 Read 8 November 2019 as part of *The Next Influenza Pandemic* symposium.

<i>Date</i>	<i>Event</i>
May 14, 1796	Jim Phipps vaccinated by Edward Jenner
October 26, 1977	Last case of smallpox discovered in Somalia
May 8, 1980	WHO declares the world free of smallpox

TABLE 1. History of smallpox eradication.

<i>Major 20th-Century Wars</i>	<i>Deaths</i>	<i>20th-Century Smallpox</i>	<i>Deaths</i>
World War I	9.2 million		
World War II	20.0 million		
Korean War	1.5 million		
Vietnam War	2.1 million		
Gulf War	100,000		
<i>Total</i>	32.9 million		>300 million

TABLE 2. The impact of viral disease on human health. Source: Global Health Council.

include the deaths we had in the major 20th-century wars; I think these numbers, deaths by the virus vs. deaths in the wars, are very comparable. Smallpox was a real curse, and I think we should be thankful for Edward Jenner and the vaccine. We have eradicated this disease!

I also want to mention—along the theme that vaccination is really good for us—the polio virus vaccination. Most of you have probably not seen the image in Figure 3. This is a hospital ward with iron lungs for the poor children and infants who had paralytic poliomyelitis. Their chest muscles were paralyzed, and they were put into these mechanic ventilators; you can see there are dozens of those iron lungs. But what very few people know is that few of those patients ever left the iron lungs alive. That’s something which is really terrible, I believe, and drives the point home that this was a very bad situation. By now,



FIGURE 1. *The Cow-Pock—or—the Wonderful Effects of the New Inoculation!*, James Gillray, 1802. This cartoon shows a physician vaccinating against smallpox with a coxpox virus and his patients growing cows out of their bodies.

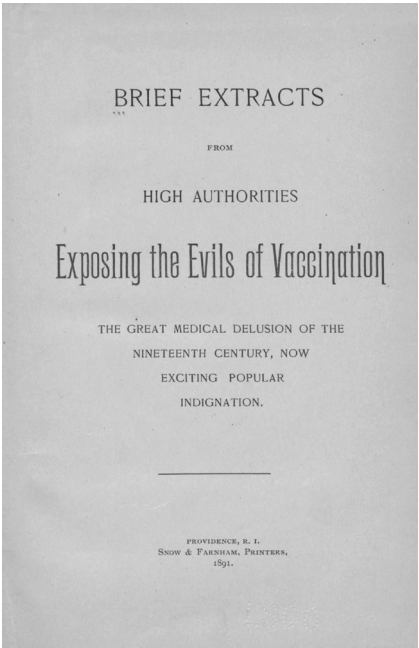


FIGURE 2. 1891 pamphlet, *Exposing the Evils of Vaccination*.



FIGURE 3. Iron lungs were machines that helped children with poliomyelitis breathe. Despite using these mechanical respirators, few of the infected children survived. Source: Smithsonian National Museum of American History.

we have basically eradicated poliomyelitis—polio infections—except for some very rare outbreaks in Nigeria and Afghanistan.

The third example of how vaccines are good for us is the measles vaccine campaign, and the chart in Figure 4 shows it in a very poignant way. The chart lists the 50 states in the United States, and indicates 1960, when the vaccine was introduced. The colors illustrate how many cases of measles were in Alaska, Wyoming, etc. After the introduction of the vaccine, you can see that measles was basically wiped out. You all know that the American Indians were killed by diseases brought by the white man, namely measles, smallpox, etc. I think it can be easily seen here how well the vaccine works.

Let's come back to influenza. We have seen Figure 5 in different variations; in this case, I show it in terms of life expectancy. Here we have the numbers from 1900 up to the year 2000. There was a life expectancy of approximately 47 years in 1900 (and this was for both men and women), whereas a baby girl born in 2019 has a life expectancy of about 85 years. I think the reason we all show this graph is because there was a dip of ~10 years in life expectancy in 1918–1919. This was the result of the 1918–1919 influenza pandemic. Coming back to vaccines, there was a bacterium that was discovered in 1892 called *Bacillus influenzae*; this was thought to be the causative agent of the 1918 pandemic. We had no idea yet that influenza was caused by a virus. You can see from Figure 6 that the famous company Wellcome used the bacterium shown here to make a vaccine against the 1918

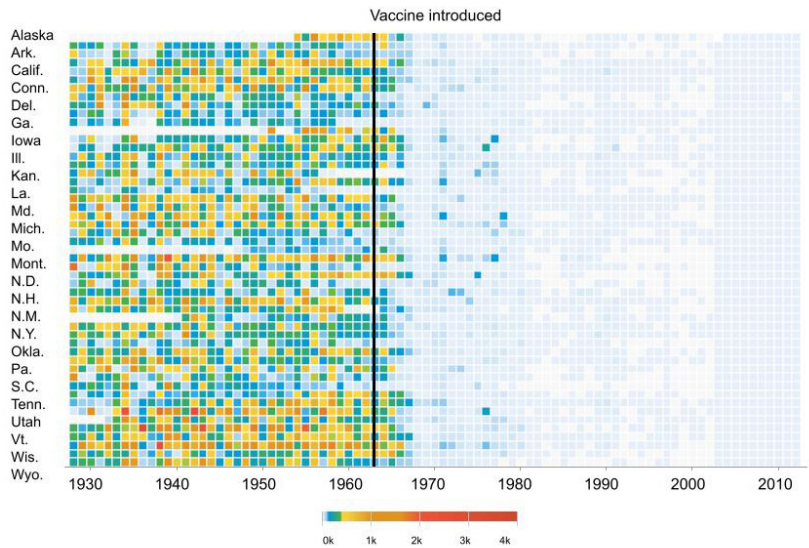


FIGURE 4. Cases of measles in the United States before and after the measles vaccine campaign was introduced. Centers for Disease Control and Prevention (CDC) data from 2003 to 2012 comes from its Summary of Notifiable Diseases, which publishes yearly rather than weekly and counts confirmed cases as opposed to provisional ones.

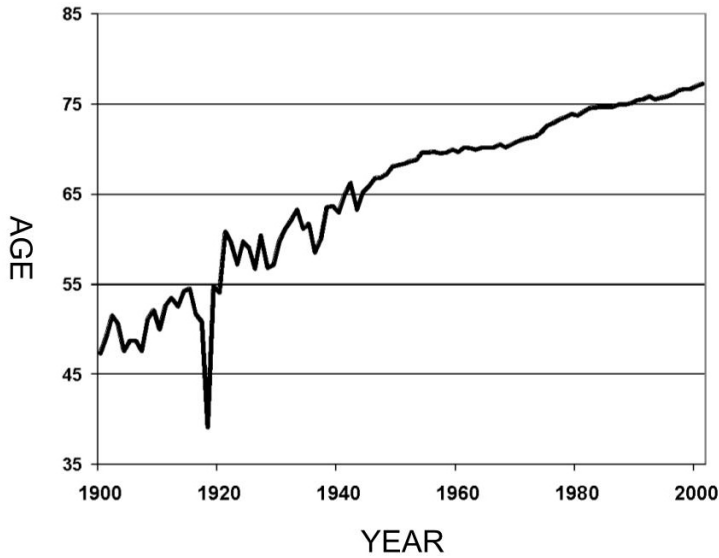


FIGURE 5. The life expectancy in the United States from 1900 to 2000 for both sexes is shown with a dip of 11 years caused by the 1918–1919 influenza pandemic.

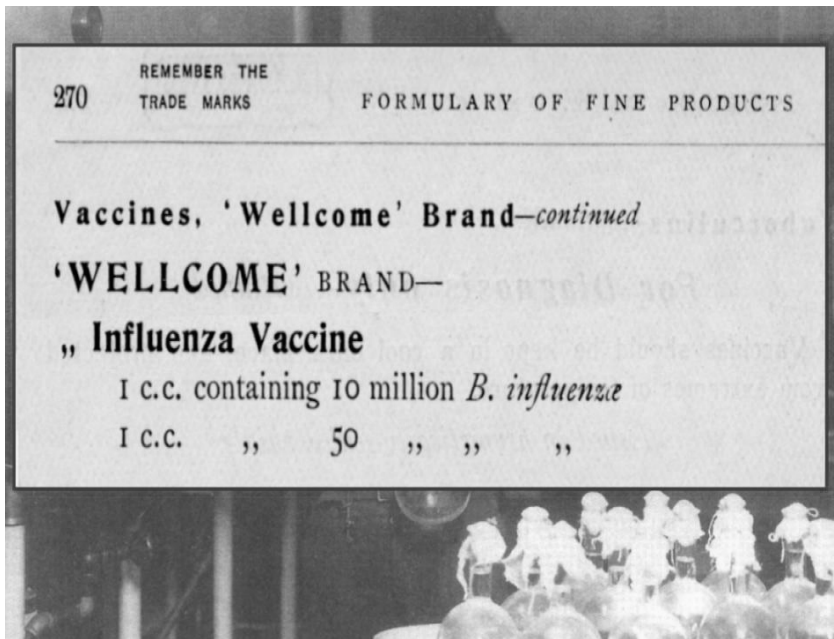


FIGURE 6. Wellcome used bacterium to make a vaccine against the 1918 virus and sold it as a medicine. Source: Mark Van Ranst, Leuven.

virus and sold it as a medicine. It's quite interesting that the successor of Wellcome, GlaxoSmithKline, is still selling influenza vaccines, but today they are the right ones against the circulating viruses (not bacteria). I think it's a fascinating historical fact that we had no idea what the influenza agent was in 1918, but that companies were happy to make vaccines nevertheless.

You have also heard about the current influenza virus vaccines, and I want to say right away that they are good vaccines but underappreciated. Indeed, they are not perfect, and I do think there's a better mouse-trap we can develop in terms of making a vaccine that's as good as the one against smallpox, against measles, and against poliomyelitis. Right now, we have FDA-approved influenza vaccines in this country that involve three different platforms: inactivated, live attenuated, and recombinant.

The first one consists of *inactivated* virus. The virus is grown up, purified, inactivated, and then injected; our immune system makes an immune response against this inactivated virus. It's not inactive, it's inactivated, so there is no disease-causing virus in the vaccine preparation. That's very important. It's just that the virus has been killed by formaldehyde, as Dr. Shenk mentioned in his introduction. There's a

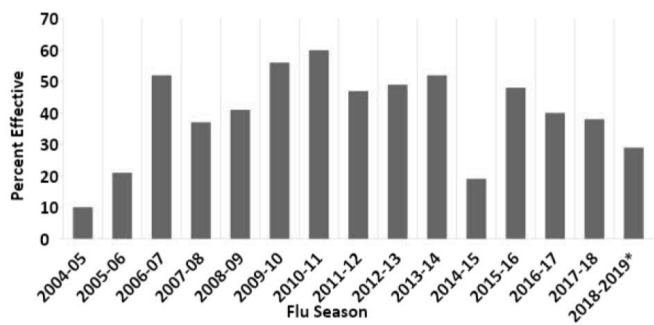


FIGURE 7. Seasonal flu vaccine effectiveness. Source: CDC Seasonal Flu Vaccine Effectiveness Studies, <https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm>.

\*Vaccine effectiveness estimates for 2018–2019 were presented to the Advisory Committee on Immunization Practices (ACIP) on June 27, 2019.

second platform, which consists of a virus that has been changed to be very weakened and only grow in the upper respiratory tract. This platform is very good for children and is called the *live attenuated* platform. And very recently, we have a *recombinant* form, which does not rely on any influenza virus but rather a protein that is actually made by a recombinant DNA technology, so there’s no virus involved. Those are the three platforms that we have. I was very happy to see the many hands going up earlier of people who have already gotten their vaccine. Just do it! It’s a good idea, really. The problem, however, is that we have a vaccine that really has to be given every year, which is unique in terms of vaccines. The reason for that, and we will talk more about it, is because we have this antigenic change of the virus. Again, the vaccine is good. It is actually better than its reputation. If you get vaccinated, it’s likely that if you do get the flu it will be milder than if you had not been vaccinated.

Now, what other problems are there with respect to influenza vaccines? You heard already that they are not perfect. Figure 7 shows data from the Centers for Disease Control and Prevention (CDC). If you look at the y-axis, you can see we have had some seasons where the vaccine was only 10 percent effective, and it never really goes above 60 percent. That’s one of the unfortunate things. Figure 8 shows what has happened from 2000 to 2020. We have two influenza A viruses and two influenza B viruses co-circulating. You can see the different shading, which indicates that from year to year the virus changes. For

the 2019–2020 vaccine, we have four vaccine components: two influenza A virus and two influenza B virus components, as follows:

- A/Brisbane/02/2018 (H1N1)pdm09-like virus
- A/Kansas/14/2017 (H3N2)-like virus
- B/Phuket/3073/2013-like (Yamagata)
- B/Colorado/06/2017-like (Victoria)

The first two components had to be changed, but the two B-virus vaccine components were unchanged from the previous year. This is a problem for the vaccine manufacturers; some years, two components have to be changed, or three, or sometimes all four. That's a nightmare and makes it very, very difficult for the industry to produce protective influenza virus vaccines in light of continuously changing pathogens. So, we would like to have a universal vaccine, something that is given once in a lifetime and protects us against all different influenza strains.

Figure 9 shows the CDC's weekly influenza surveillance report and the percentage of visits for influenza-like illness for the current season in comparison to previous seasons. You can see there are sometimes more or fewer influenza visits at weeks 42 and 48. Sometimes a lot! The curve here shows that 2011–2012 was a very harmless influenza season. This is yet another problem, the timing and also whether it's a bad year. I don't think influenza epidemics are easily predictable.

What we have in Figure 10 is the number of influenza-like visits as well as the time of vaccine distribution. In 2009, the right curve shows when the vaccine was actually shipped out by the manufacturers and the left curve shows when we had most of the influenza activities. It indicates that the majority of influenza virus cases had already occurred when the vaccine was being distributed to pharmacies, Walmart, CVS, pediatric offices, etc. The vaccine came too late!

We have all heard about other threats, such as H7N9 (Figure 11), H10 viruses, and H6 influenza viruses popping up. Fortunately, they are only in China so far and there is no human-to-human transmission yet; it is only chicken to human. This is all in the back of our minds and the question is, how can we do better? Dr. Shenk made a point in terms of the numbers; these are real numbers despite the vaccines, and despite the antiviral. The CDC data (Figure 12) show that annually there were 9.2 million to 60 million influenza cases from 2010 to 2016. The hospitalizations were 140,000–710,000, and the deaths were 12,000–56,000 from 2010 to 2016, per year. Figure 13 shows the virus, which is the pathogen causing flu. Influenza is not the divine



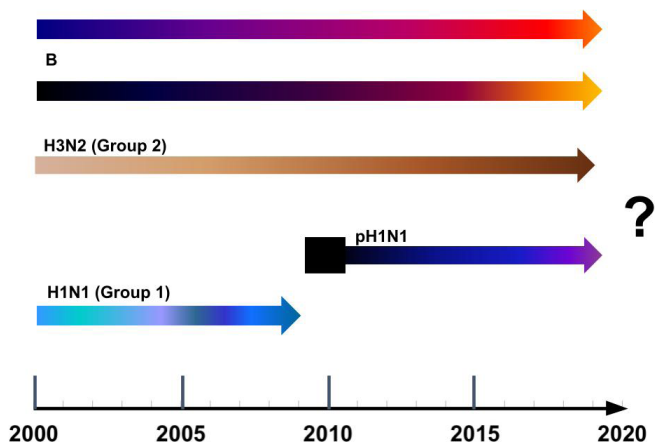


FIGURE 8. Influenza viruses circulating in the human population. Two influenza B viruses have been co-circulating and two influenza A viruses have been isolated over the last 20 years. The different shadings in the arrows over time illustrate antigenic changes in the viruses.

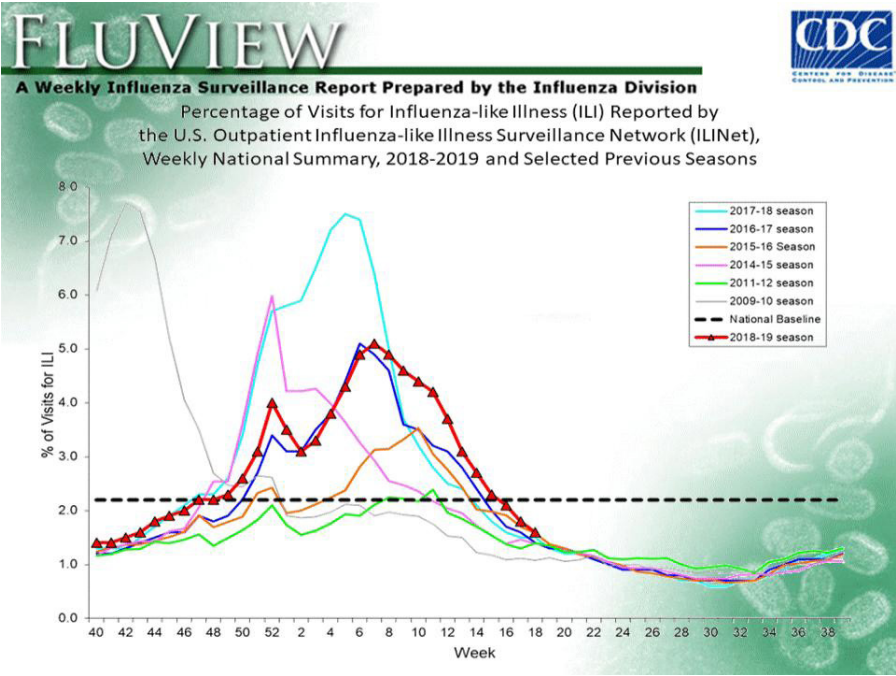


FIGURE 9. CDC’s weekly influenza surveillance report and the percentage of visits for influenza-like illness for the current season in comparison to previous seasons.

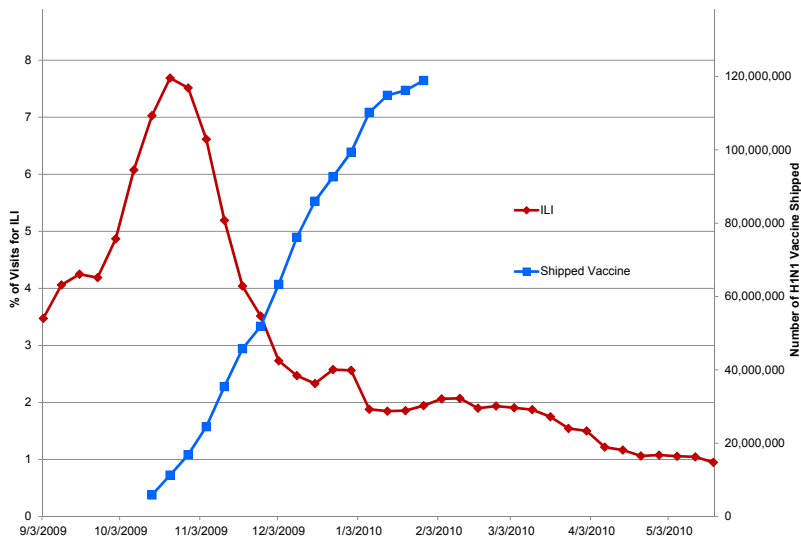


FIGURE 10. Visits for influenza-like-illness (red) and pH1N1 vaccine distribution (blue), September 2009–May 2010. Source: CDC ILI and Vaccine Distribution Data.

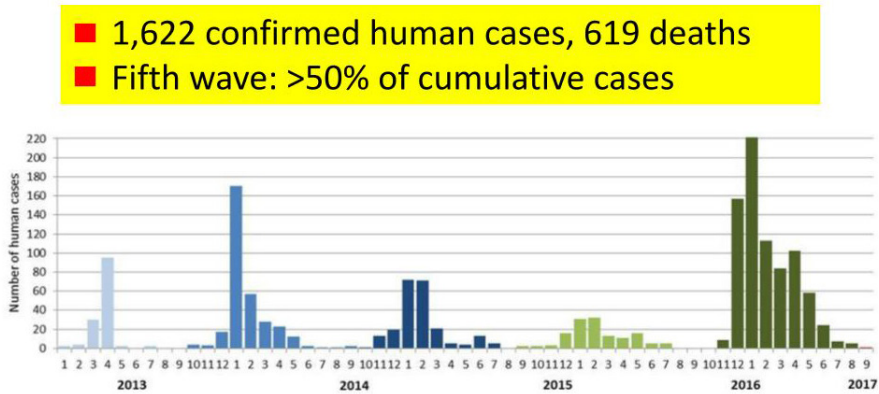


FIGURE 11. Five waves of human H7N9 influenza infections in China, February 2013–present. Source: [http://www.fao.org/ag/againfo/programmes/en/empres/h7n9/situation\\_update.html](http://www.fao.org/ag/againfo/programmes/en/empres/h7n9/situation_update.html).

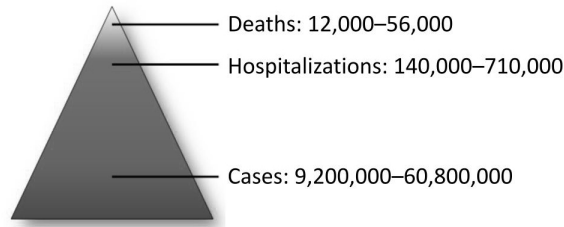


FIGURE 12. Burden of influenza in the United States annually (2010–2016). Source: <https://www.cdc.gov/flu/about/disease/burden.htm>.

visitation upon sinners; it's really caused by something and that something is a virus.

Figure 14 shows a graphic of the virus with the hemagglutinin and the neuraminidase spikes on the outside. You have to think of this electron-micrograph as a very small particle. If you had an infected cell in relation to this blown-up virus, it would probably fill 20 auditoriums like the one we are in now stacked one above the other. And you have to think about one small virus that infects a gigantic cell, and within 8 or 9 hours, we have 100,000 new virus particles. You can see that this replicating virus is not the best for an infected lung, or an infected respiratory tract. It really is this replicating virus that is causing the disease. When we get infected or get a vaccine, we make an immune response mostly against the hemagglutinin on the outside of the virus. That's what the immune system sees. We designed an approach, a way of actually redirecting the immune system toward the conserved domains of the spikes, not toward the highly immunogenic tips of the spikes. You have to think of a spike as a mushroom with a head and a stalk, and it turns out that the stalk is much more conserved than the very tip of the hemagglutinin spike.

There are three independent laboratories within the Department of Microbiology at the Icahn School of Medicine at Mount Sinai that are focusing on a universal influenza virus vaccine: the laboratory of Dr. Florian Krammer, of Dr. Adolfo García-Sastre, and my own laboratory. We designed new vaccine constructs that can be given with different platforms, either as a recombinantly made protein, as a live attenuated, or an inactivated (not inactive) influenza virus vaccine. As you can see in Figure 14, we have two vaccine constructs. On the outside there are the hemagglutinin spikes, and, as I said before, the very tip of the hemagglutinin is the most immunogenic portion of the virus. We have basically, from an immunological standpoint, silenced

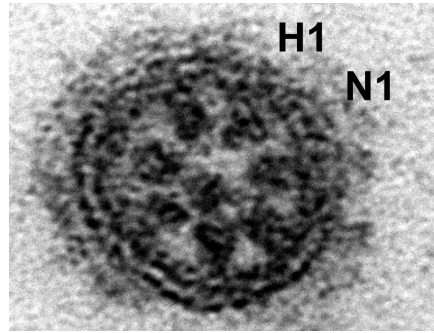


FIGURE 13. Electron micrograph of virus, which is the pathogen causing influenza H1, hemagglutinin subtype 1; N1, neuraminidase subtype 1. Source: Yi-Ying Chou.

these highly immunogenic tips. We fused hemagglutinin-stalks of circulating viruses with tips from exotic hemagglutinins which we, humans, have not yet seen. We refer to these constructs as chimeric hemagglutinins because they have an irrelevant (exotic) head and the stalk of regular human viruses.

Figure 14 shows a chimeric H8/1 hemagglutinin. It has the head of an H8 hemagglutinin and the stalk of a hemagglutinin from a virus circulating in 2019. Then there's the neuraminidase, which is the second viral surface protein. We hope that our approach of removing the immunodominant head of the hemagglutinin will direct the immune system toward the conserved stalk of the hemagglutinin as well as the (conserved) neuraminidase. So, we have two different vaccine constructs. We envision that we will vaccinate first with the chimeric H8/1 and then follow with the chimeric H5/1 construct. We hope that such an approach will actually work in humans. We have been able to use this successfully in protecting mice and ferrets. In fact, it works beautifully in mice. But remember, mice are not men and ferrets are not humans, so the ultimate animal model is unfortunately us. We are happy to say we are in phase I human trials. The trial shown in Figure 15 is funded by the Bill & Melinda Gates Foundation, and there are several arms in the vaccine trials. Preliminary data are very promising, but the jury is still out until we have the results from phase II and phase III trials.

In Figure 15, you can see the different arms of the phase I trial; let me explain. We have this chimeric H8/1 hemagglutinin expressing vaccine construct. Subjects are primed with this vaccine and then boosted with a chimeric H5/1 hemagglutinin-expressing vaccine. The different arms use different platforms, killed virus preparations vs. live

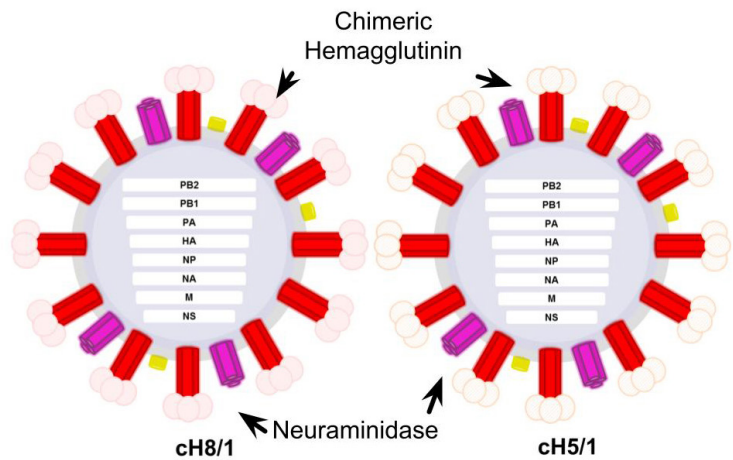
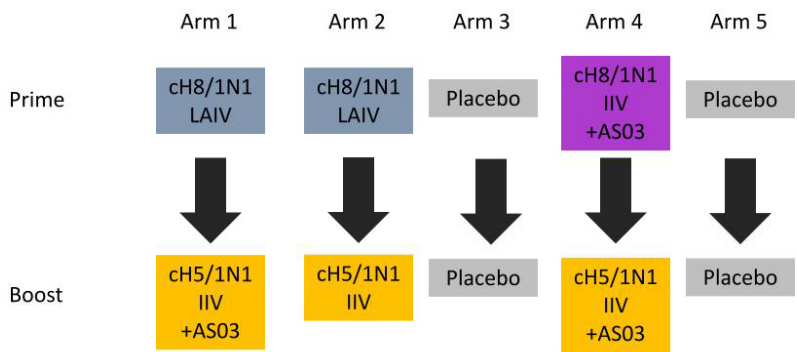


FIGURE 14. Human universal influenza virus vaccine. Source: Florian Krammer, Adolfo García-Sastre, and Peter Palese.



LAIV: Live-attenuated influenza virus vaccine (Leningrad backbone)  
IIV: Inactivated influenza virus vaccine  
AS03: Adjuvant

FIGURE 15. Bill & Melinda Gates Foundation-funded chimeric hemagglutinin-based LAIV-IIV phase I trial.

attenuated virus. Because a live virus is being used, subjects in the trial have to be quarantined in a hospital or in a hotel. They can't leave and have to be checked whether they are shedding any virus, etc. Another variable is vaccination with and without adjuvant. The adjuvant is a way of making the vaccine more immunogenic and broader in protecting against different challenge viruses. However, one cannot give adjuvant every year because of possible side effects. In the present case, we are proposing that the adjuvant be given once in a lifetime or once every 20 years, and hopefully the FDA is okay with that approach. We trust that our chimeric construct plus an adjuvant would give us long-lasting protection against all future strains. So that's our hope. I'm pretty sure we will get there, but again, nothing is easy, as you know.

Let me summarize. Our approach is vaccination with chimeric hemagglutinin constructs, and we were able to protect mice for a year and a half—but that's in mice and not in humans. We can also achieve long-lasting protection in ferrets. Most importantly, we are now in human trials but should also understand that these are only phase I trials and we still need successful phase II and phase III trials. Also, we need three components in the final vaccine formulation. We need two A virus components and one B virus component.

In closing, I will leave you with a statement by Bill Gates about the possibility of the next epidemic in a video from Vox News as found on Vox's YouTube channel.<sup>2</sup>

---

2 Vox, "What Bill Gates Is Afraid Of," May 27, 2015, video, <https://www.youtube.com/watch?v=9AEMKudv5p0>.