

# Scientists seek super-shot for flu 100 years after pandemic

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Biologist Rebecca Gillespie holds a vial of flu-fighting antibodies at the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. Despite 100 years of science, the flu virus too often beats our best defenses because it constantly mutates. (AP Photo/Carolyn Kaster)

The descriptions are haunting.

Some victims felt fine in the morning and were dead by night. Faces turned blue as patients coughed up blood. Stacked bodies outnumbered coffins.

A century after one of history's most catastrophic disease outbreaks, scientists are rethinking how to guard against another super-flu like the 1918 influenza that killed tens of millions as it swept the globe.

There's no way to predict what strain of the shape-shifting flu virus could trigger another pandemic or, given modern medical tools, how bad it might be.

But researchers hope they're finally closing in on stronger flu shots, ways to boost much-needed protection against ordinary winter influenza and guard against future pandemics at the same time.

"We have to do better and by better, we mean a universal flu vaccine. A vaccine that is going to protect you against essentially all, or most, strains of flu," said Dr. Anthony Fauci of the National Institutes of Health.

Labs around the country are hunting for a super-shot that could eliminate the annual fall vaccination in favor of one every five years or 10 years, or maybe, eventually, a childhood immunization that could last for life.



Dr. Anthony Fauci, director of the National Institute for Allergy and Infectious Diseases, speaks during an interview in his office at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. As scientists mark the 100th anniversary of the Spanish influenza pandemic, labs around the country are hunting better vaccines to boost protection against ordinary winter flu and guard against future pandemics, too. "We have to do better and by better, we mean a universal flu vaccine. A vaccine that is going to protect you against essentially all, or most, strains of flu," said Fauci. (AP Photo/Carolyn Kaster)

Fauci is designating a universal flu vaccine a top priority for NIH's National Institute of Allergy and Infectious Diseases. Last summer, he brought together more than 150 leading researchers to map a path. A few attempts are entering first-stage human safety testing.

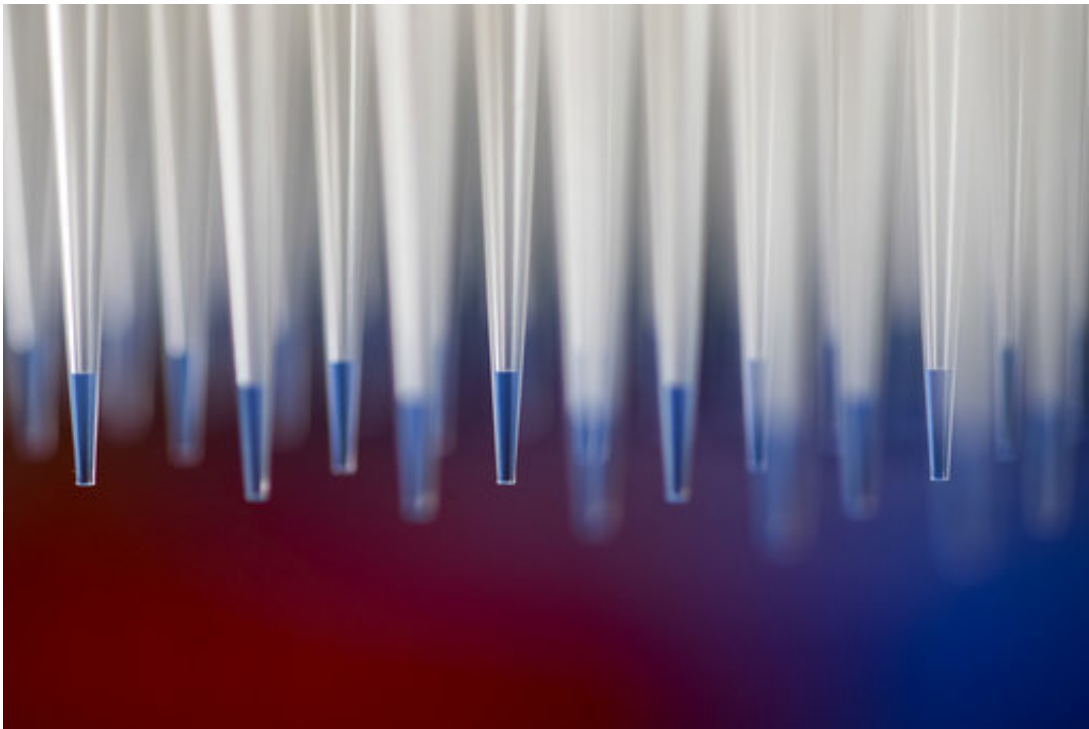
Still, it's a tall order. Despite 100 years of science, the flu virus too often beats our best defenses because it constantly mutates.

Among the new strategies: Researchers are dissecting the cloak that disguises influenza as it sneaks past the immune system, and finding some rare targets that stay the same from strain to strain, year to year.

"We've made some serious inroads into understanding how we can better protect ourselves. Now we have to put that into fruition," said well-known flu biologist Ian Wilson of The Scripps Research Institute in La Jolla, California.

The somber centennial highlights the need.

Back then, there was no flu vaccine—it wouldn't arrive for decades. Today vaccination is the best protection, and Fauci never skips his. But at best, the seasonal vaccine is 60 percent effective. Protection dropped to 19 percent a few years ago when the vaccine didn't match an evolving virus.



Pipettes containing immune cells for testing against possible flu vaccines are seen in the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. There's no way to predict what strain of the shape-shifting flu virus could trigger another pandemic like that of the 1918 influenza or, given modern medical tools, how bad it might be. But researchers hope they're finally closing in on stronger flu shots, ways to boost much-needed protection against ordinary winter influenza and guard against future pandemics at the same time. (AP Photo/Carolyn Kaster)

If a never-before-seen flu strain erupts, it takes months to brew a new vaccine. Doses arrived too late for the last, fortunately mild, pandemic in 2009.

Lacking a better option, Fauci said the nation is "chasing" animal flu strains that might become the next human threat. Today's top concern is a lethal bird flu that jumped from poultry to more than 1,500 people in China since 2013. Last year it mutated, meaning millions of just-in-case vaccine doses in a U.S. stockpile no longer match.

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The NIH's Dr. Jeffery Taubenberger calls the 1918 flu the mother of all pandemics.

He should know.

While working as a pathologist for the military, he led the team that identified and reconstructed the extinct 1918 virus, using traces unearthed in autopsy samples from World War I soldiers and from a victim buried in the Alaskan permafrost.



Biologist Rebecca Gillespie places a vial of flu-fighting antibodies in ice at the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. Scientists now think people respond differently to vaccination based on their flu history. (AP Photo/Carolyn Kaster)

That misnamed Spanish flu "made all the world a killing zone," wrote John M. Barry in "The Great Influenza: The Story of the Deadliest Pandemic in History."

Historians think it started in Kansas in early 1918. By winter 1919, the virus had infected one-third of the global population and killed at least 50 million people, including 675,000 Americans. By comparison, the AIDS virus has claimed 35 million lives over four decades.

Three more flu pandemics have struck since, in 1957, 1968 and 2009, spreading widely but nowhere near as deadly. Taubenberger's research



shows the family tree, each subsequent pandemic a result of flu viruses carried by birds or pigs mixing with 1918 flu genes.

"This 100-year timeline of information about how the virus adapted to us and how we adapt to the new viruses, it teaches us that we can't keep designing vaccines based on the past," said Dr. Barney Graham, deputy director of NIH's Vaccine Research Center.

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The new vaccine quest starts with two proteins, hemagglutinin and neuraminidase, that coat flu's surface. The "H" allows flu to latch onto respiratory cells and infect them. Afterward, the "N" helps the virus spread.



Biologist Jason Plyler prepares to test how immune cells react to possible flu

vaccines at the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. A major push is under way in labs around the country to create a super-shot that could eliminate the annual fall vaccination in favor of one shot every five or 10 years or just maybe, eventually, a childhood immunization that could last for life. (AP Photo/Carolyn Kaster)

They also form the names of influenza A viruses, the most dangerous flu family. With 18 hemagglutinin varieties and 11 types of neuraminidase—most carried by birds—there are lots of potential combinations. That virulent 1918 virus was the H1N1 subtype; milder H1N1 strains still circulate. This winter H3N2, a descendent of the 1968 pandemic, is causing most of the misery.

Think of hemagglutinin as a miniature broccoli stalk. Its flower-like head attracts the immune system, which produces infection-blocking antibodies if the top is similar enough to a previous infection or that year's vaccination.

But that head also is where mutations pile up.

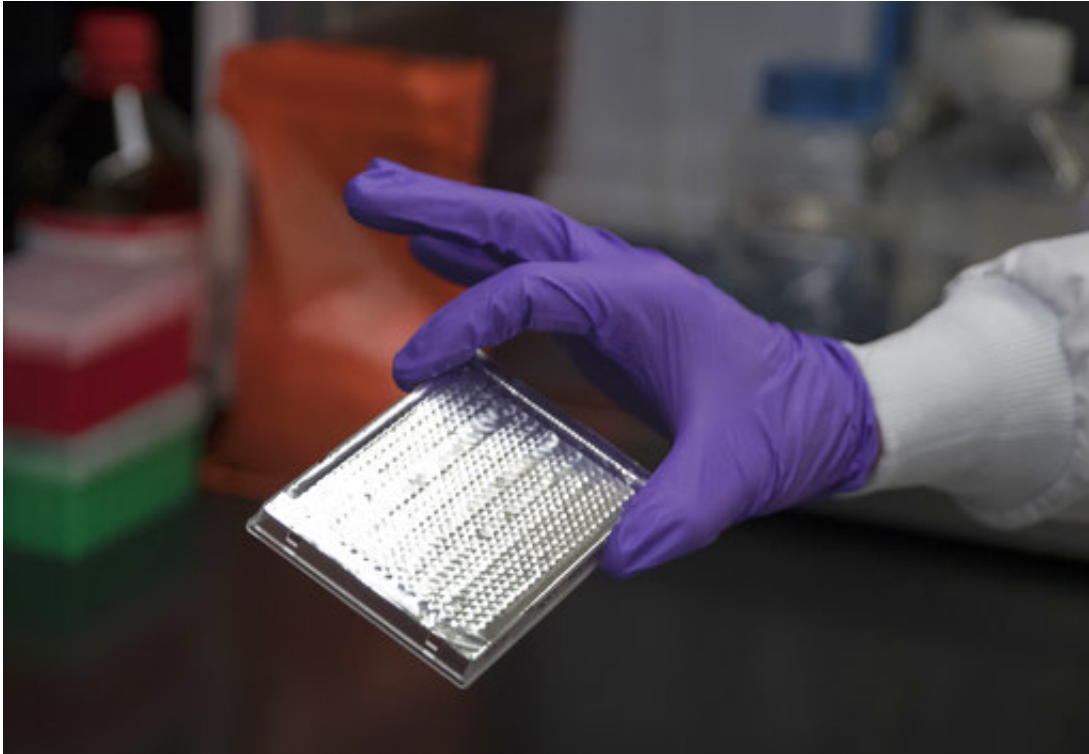
A turning point toward better vaccines was a 2009 discovery that, sometimes, people make a small number of antibodies that instead target spots on the hemagglutinin stem that don't mutate. Even better, "these antibodies were much broader than anything we've seen," capable of blocking multiple subtypes of flu, said Scripps' Wilson.

Scientists are trying different tricks to spur production of those antibodies.

In a lab at NIH's Vaccine Research Center, "we think taking the head off will solve the problem," Graham said. His team brews vaccine from the



stems and attaches them to ball-shaped nanoparticles easily spotted by the immune system.



Biologist Jason Plyler holds a plate containing immune cells ready for genetic analysis at the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. Researchers hope they're finally closing in on stronger flu shots, ways to boost much-needed protection against ordinary winter influenza and guard against future pandemics at the same time. (AP Photo/Carolyn Kaster)

In New York, pioneering flu microbiologist Peter Palese at Mount Sinai's Icahn School of Medicine uses "chimeric" viruses—the hemagglutinin head comes from bird flu, the stem from common human flu viruses—to redirect the immune system.

"We have made the head so that the immune system really doesn't recognize it," Palese explained. GlaxoSmithKline and the Gates Foundation are funding initial safety tests.

In addition to working with Janssen Pharmaceuticals on a stem vaccine, Wilson's team also is exploring how to turn flu-fighting antibodies into an oral drug. "Say a pandemic came along and you didn't have time to make vaccine. You'd want something to block infection if possible," he said.

NIH's Taubenberger is taking a completely different approach. He's brewing a vaccine cocktail that combines particles of four different hemagglutinins that in turn trigger protection against other related strains.

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Yet lingering mysteries hamper the research.



In this October 1918 photo made available by the Library of Congress, St. Louis Red Cross Motor Corps personnel wear masks as they hold stretchers next to ambulances in preparation for victims of the influenza epidemic. A century after one of history's most catastrophic disease outbreaks, scientists are rethinking how to guard against another super-flu like the 1918 influenza that slaughtered tens of millions as it swept the globe in mere months. (Library of Congress via AP)

Scientists now think people respond differently to vaccination based on their flu history. "Perhaps we recognize best the first flu we ever see," said NIH immunologist Adrian McDermott.

The idea is that your immune system is imprinted with that first strain and may not respond as well to a vaccine against another.

"The vision of the field is that ultimately if you get the really good universal flu vaccine, it's going to work best when you give it to a child," Fauci said.

Still, no one knows the ultimate origin of that terrifying 1918 flu. But key to its lethality was bird-like hemagglutinin.

That Chinese H7N9 bird flu "worries me a lot," Taubenberger said. "For a virus like influenza that is a master at adapting and mutating and evolving to meet new circumstances, it's crucially important to understand how these processes occur in nature. How does an avian virus become adapted to a mammal?"

While scientists hunt those answers, "it's folly to predict" what a next pandemic might bring, Fauci said. "We just need to be prepared."

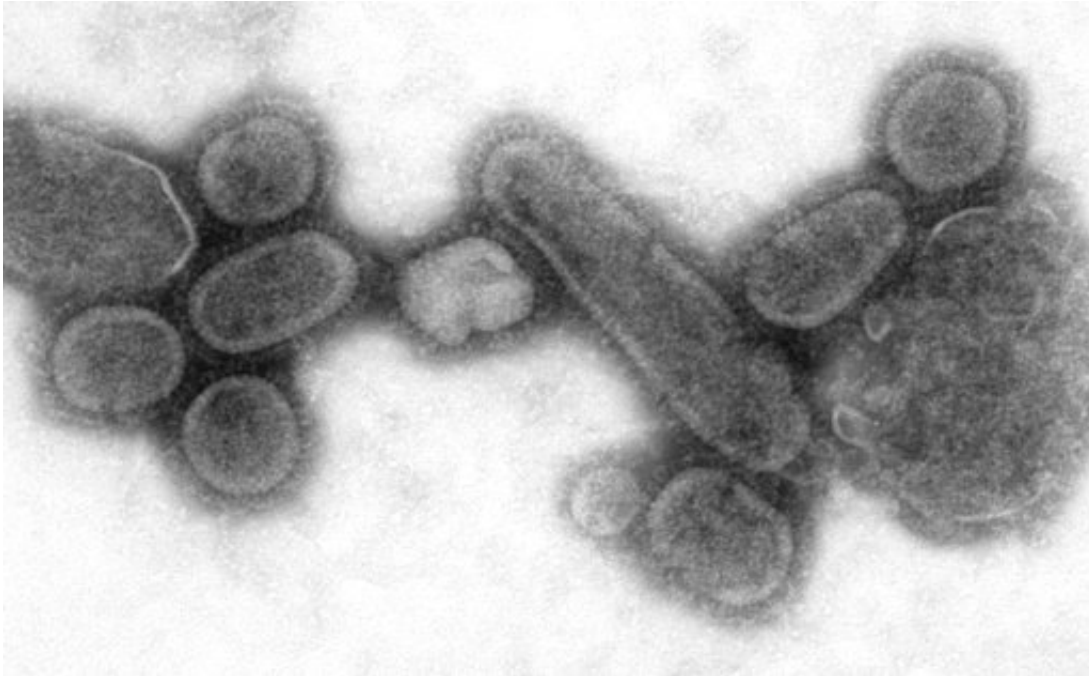


In this 1918-1919 photo made available by the Library of Congress, a conductor checks to see if potential passengers are wearing masks in Seattle, Wash. During the influenza epidemic, masks were required for all passengers. The virus killed at least 50 million people, including 675,000 Americans. Some estimates put the toll as high as 100 million. By comparison, the AIDS virus has claimed 35 million lives over four decades. (Library of Congress via AP)



In this November 1918 photo made available by the Library of Congress a girl stands next to her sister lying in bed. The girl became so worried she telephoned the Red Cross Home Service who came to help the woman fight the influenza virus. No one knows the ultimate origin of that terrifying 1918 flu. But researchers hope they're finally closing in on stronger flu shots, ways to boost much-needed protection against ordinary winter influenza and guard against future pandemics at the same time. (Library of Congress via AP)





This 2005 electron microscope image made available by the Centers for Disease Control and Prevention shows recreated 1918 influenza virions that were collected from a 1918 cell culture. A century after one of history's most catastrophic disease outbreaks, scientists are rethinking how to guard against another super-flu like the 1918 influenza that slaughtered tens of millions as it swept the globe in mere months. Although there's no way to predict what strain of the shape-shifting flu virus could trigger another pandemic, researchers hope they're finally closing in on stronger flu shots, which would boost much-needed protection against ordinary winter influenza and guard against future pandemics at the same time. (Cynthia Goldsmith/CDC via AP)



Biologist Rebecca Gillespie pulls boxes of flu virus strains from a freezer at the Vaccine Research Center at the National Institutes of Health, Tuesday, Dec. 19, 2017, in Bethesda, Md. A major push is under way in labs around the country to create a super-shot that could eliminate the annual fall vaccination in favor of one shot every five or 10 years or maybe, eventually, a childhood immunization that could last for life. (AP Photo/Carolyn Kaster)



In this 1918 photo made available by the Library of Congress, volunteer nurses from the American Red Cross tend to influenza patients in the Oakland Municipal Auditorium, used as a temporary hospital. As scientists mark the 100th anniversary of the Spanish influenza pandemic, labs around the country are hunting better vaccines to boost protection against ordinary winter flu and guard against future pandemics, too. (Edward A. "Doc" Rogers/Library of Congress via AP)

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