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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.

AP Photo/Carolyn Kaster

Biologist Rebecca Gillespie pulls boxes of flu virus strains from a freezer at the Vaccine Research Center at the National Institutes of Health, Dec. 19 in Bethesda, Md.

Scientists seek super-shot for flu 100 years after pandemic

By LAURAN NEERGAARD
AP Medical Writer

WASHINGTON — 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.

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.

How soon might one be available? "Years, not decades," he said Friday in an interview with The Associated Press.

"I'm cautiously optimistic, but I am optimistic," he said.

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.

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.

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.

AP Photo/Carolyn Kaster

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, Dec. 19 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

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

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.

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>
> **— Ian Wilson,** flu biologist with The Scripps Research Institute in La Jolla, California.

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.

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.

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.

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.

Yet lingering mysteries hamper the research.

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."