

## **Ghosts of vaccines past**

**In 1976, a swine flu scare led to a huge, hurried inoculation effort. That time, however, the shots were worse than the flu.**

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When the men fell ill, doctors thought the cause was something minor. But the lab analysis shocked them: The culprit was an anomalous strain of influenza that was killing its victims at a much higher rate than normal.

Health authorities shuddered, remembering that a new strain of flu killed 675,000 Americans in 1918. Federal health agencies convened emergency meetings, drawing in Congress and the White House. Pharmaceutical companies agreed to make a new vaccine.

The director of the CDC warned that the whole U.S. population "is probably susceptible to this new strain."

That sounds like a catalog of events in the United States since avian influenza H5N1 began surging through poultry flocks in Southeast Asia in December 2003, eventually infecting humans and killing more than half of its 139 known victims.

Sounds like — but is not. Instead, it describes the last time the United States prepared to face a potential pandemic of influenza: the swine flu of 1976.

That outbreak, which began on an Army base in New Jersey 30 years ago next month, is remembered less for its 13 known cases of flu than for the more than 500 illnesses and 32 deaths caused by a rare vaccination side effect.

As the United States prepares for the possibility of an avian flu pandemic, the assumptions, accidents and missteps of 1976 still cast doubt on the government's credibility in forecasting epidemics and recommending vaccination. And some historians and health planners say authorities still have not attended to some of the lessons of swine flu.

"All epidemics contain missed opportunities," said Dr. Howard Markel, director of the University of Michigan's Center for the History of Medicine. "The 1976 epidemic exposed mistakes and problems in vaccine production and distribution that still have not been addressed."

The swine flu episode started with a cluster of respiratory illnesses — congestion, coughs and fever — in a batch of new recruits who reported to Fort Dix, N.J., in early 1976. One of them, Pvt. David Lewis, collapsed during a 5-mile nighttime march and died the next day of pneumonia.

Tests on samples from Lewis and other soldiers revealed they had flu, but not the flu strain that dominated the United States that winter. Instead — no one could say how — they were infected with a virus that had not circulated for 50 years.

The discovery had an electric effect at the CDC. The virus was believed to pass from pigs to people, but the Fort Dix soldiers had had no contact with pigs. Instead, it appeared one soldier had infected the others.

A second set of tests showed more than 200 Fort Dix personnel had been exposed to the flu strain. That suggested that a virus known for jumping once between species and then stopping had gained the ability to pass easily from person to person.

If the swine strain could spread easily in the population, the CDC thought, widespread illness would result, because no one under 50 had any immunity to it. That reinforced the apparent resemblance to the 1918 epidemic, which was also believed to have been caused by a returning strain of virus and had killed mostly the young. And like the 1918 illness, the 1976 outbreak appeared to kill a higher proportion of those who fell ill than annual flu did.

The CDC's director, Dr. David Sencer, wrote a lengthy memo to his federal superiors setting out the elements that had the agency worried: the new strain, the lack of immunity and the scientific belief that pandemics recurred every decade — and that it had been nearly that long since the last one.

On March 24, six weeks after the swine virus was identified, President Gerald Ford declared the government would vaccinate "every man, woman and child" in the United States and asked Congress for an emergency \$135 million appropriation.

"Given the knowledge we had at that time, I think we made the right decision," Sencer, who still lives in Atlanta — and who lost his job as CDC director in the vaccination campaign's wake — said last week. "We had not had a pandemic since 1968. We had a new strain. We had a susceptible population. We had time to make vaccine. If we really believed in preventive medicine, we had no choice."

The path to vaccination was bumpy. In May, the insurance companies that covered the four flu shot manufacturers announced they would not extend liability protection to the new vaccine.

In June, investigators revealed that the vaccine failed in clinical trials to protect children and young adults, those believed to be at most risk. In July, one manufacturer admitted it had used the wrong virus to make its first 2 million doses.

In August, 221 members of the American Legion fell ill with an unknown respiratory infection at a Pennsylvania convention and 34 died, sparking fears that a swine flu outbreak had begun. (The cause of the Philadelphia illness, dubbed Legionnaires' disease after its victims, was not identified until the end of the year. It was a bacterium with no relation to the swine flu virus.)

The mysterious Philadelphia outbreak sharpened fears of what a new flu strain might do and gave fresh impetus to the desire to vaccinate against it. Ten days after the first cases of Legionnaire's were discovered, Ford signed a new law that would protect the manufacturers from liability once the new fiscal year started on Oct. 1.

No more swine flu cases had been discovered, leaving it unclear whether the outbreak had ended or merely gone underground, as flu does most summers. Some scientists called for a pause in the program, stockpiling the new vaccine until there was proof the new strain persisted. Others said any delay would be unwise because flu spreads so rapidly.

"It was the classic public health dilemma," said Dr. J. Lyle Conrad, who in 1976 headed the division of the CDC that dealt with state health departments. "You always have to make decisions on inadequate data in an insufficient amount of time."

On Oct. 1, 1976, the swine flu vaccination program began. In six weeks, almost 45 million people were vaccinated.

On Nov. 12, the Minnesota Department of Health reported a case of Guillain-Barre Syndrome — a paralysis that rises rapidly up the body and is a rare known consequence of vaccination and infection — in a vaccine recipient. Other reports piled in rapidly from other states.

On Dec. 16, the vaccination program was suspended. On Feb. 7, 1977, Sencer was fired by Joseph Califano, who had become secretary of health, education and welfare three weeks before when President Jimmy Carter took office.

When the whole episode of the 1976 swine flu scare was analyzed, 532 cases of Guillain-Barre and 32 deaths were found among vaccine recipients, many times more than in the general population. There were no more known cases of swine flu.

### **CDC embarrassed**

Swine flu was a grave embarrassment for the CDC. An initial assessment, written for Califano, called it a "fiasco"; a second analysis published in 1981 likened it more charitably to a Greek tragedy.

It is also an enduring mystery: Flu vaccinations have been given every year since, but no significant Guillain-Barre outbreaks have accompanied them. (Five cases of the disorder occurred last summer in recipients of meningococcal vaccine.) Two years ago, the Institute of Medicine — a nonpartisan federally chartered group that advises Congress on health policy — recommended the CDC launch lab research to uncover the still murky cause-and-effect of vaccination and Guillain-Barre.

The two-year study at the University of Pennsylvania is using mice to uncover whether components of the vaccine trigger production of an immune-system protein that has been implicated in Guillain-Barre paralysis because it attacks the covering of certain nerve cells.

Researchers are using a stash of 25 long-forgotten vaccine vials that investigators uncovered in the back of a lab freezer in Houston. Together the vials held no more than a pint of liquid. The researchers scoured the country to find them; they are the last known viable samples of the roughly 100 million doses that remained unused at the end of 1976.

Guillain-Barre "is the sword of Damocles dangling over our head as we enter every flu vaccination season," said the CDC's Dr. Sean Shadomy, a CDC epidemiologist on the project. "We are always concerned with whether we will see a repetition of the experience of 1976."

The swine flu shadows flu vaccination in more subtle ways as well.

### **'From crisis to crisis'**

Some historians and health planners say the swine flu experience made the CDC far more cautious, leaving it reluctant to address future pandemic threats in any bold way.

The timeline supports that view. The first federal pandemic-planning task force was formed in 1978; the government's complete pandemic flu strategy was released last month — 27 years later.

But even with the complete strategy on the table, infectious disease experts say the key lessons of the swine flu experience may not have been heeded.

"We are not in any better situation to tackle the decision-making process — who would we need, how would we proceed — than we were back then," said Dr. Brian Currie, senior medical director at Montefiore Medical Center in the Bronx, who received the 1976 shot with no ill effects as an epidemiology graduate student. "We don't yet have the infrastructure to deal with pandemics. We don't even have a very strong infrastructure to deal with regular influenza activity."

Recommendations made immediately after swine flu — that the federal government support flu vaccine manufacturing by guaranteeing both annual vaccine purchases and liability protection — were not enacted. Scientists have called for such measures whenever flu vaccine problems recur, as they did in the past two years.

"We lurch from crisis to crisis, and in between we forget about the issues," Markel said. "In the downtime, we should be thinking about a national — maybe even an international — vaccine agency that develops stockpiles and is indemnified from frivolous lawsuits."

There have been 10 influenza pandemics in the past 300 years, all believed to have been caused by new strains of flu, but swine flu marked the first in which science could give early warning of a new strain's arrival. That allowed for a number of rapid accomplishments, including developing a new vaccine, making and delivering millions of doses, and setting up a surveillance and adverse-events tracking system.

But students of swine flu argue that planners failed in one key step: building in pauses to re-evaluate the program as it proceeded.

"They showed us what not to do by pulling the trigger on vaccination far too early," said Dr. Paul Offit, a vaccine researcher at Children's Hospital of Philadelphia. "They did a lot of things right — setting up surveillance, arranging the vaccine manufacturing — right up until the point of giving the vaccine."

That same mistake was repeated in the rapidly launched smallpox vaccination program that followed the anthrax attacks of autumn 2001. According to Institute of Medicine analyses, the smallpox program — operated in part by the CDC — should have paused to assess both adverse reactions and poor public acceptance of the vaccine.

### **Too cautious today?**

Some planners worry the swine flu experience left the federal health establishment overly cautious, an attitude they say could impair efforts to counter avian influenza H5N1 if it becomes a pandemic strain.

That novel virus has spread persistently for two years, moving from Asia through Russia and into Europe, causing the deaths or preventive slaughter of some 150 million chicken and other birds and killing at least 51 percent of its known human victims.

The threat is more substantial than in 1976, said Dr. Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, who was working in that state's health department when the Guillain-Barre cases developed.

"It would be an equal mistake to be too cautious" now, he said. "History will be much more unkind to us for not acting, given what we know about the current threat, than it will be to those who overreacted in 1976."

Some public health leaders have long felt that Sencer — whose staffers from years ago still speak of him with respect — was treated unkindly.

Sencer himself will publish his first reflections on the 1976 experience next month, in a special issue of the CDC journal *Emerging Infectious Diseases*. In an advance glimpse, he offered that the important lesson for the next pandemic is to allow it to be handled by the experts who understand it best.

"Decisions should be made on a scientific basis, not a political basis," he said. "Because once you enter the political arena, it becomes very difficult to make changes. You don't have the flexibility to respond to new knowledge."