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FOR BIOTECH FIRMS, A BOOSTER FLU POINTS TO NEED FOR NEW VACCINES

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Six years ago during the Christmas season, scientists at a small Meriden biotechnology company labored around the clock at the request of U.S. health officials to develop a new vaccine to stave off a potentially devastating flu pandemic.

They succeeded in just eight weeks, even though the feared pandemic of deadly avian flu that had appeared briefly in China petered out before the vaccine was needed.

As the threat waned, so did public and private interest in developing a new generation of influenza vaccines -- vaccines that can be produced quickly to combat rapidly emerging flu viruses such as the one that has circulated over much of the United States this month.

But December's nasty influenza outbreak and the appearance of SARS earlier this year have revived a sense of urgency to create new vaccines.

Scientists at Protein Sciences Corp. in Meriden and other biotechnology companies say the technology now exists to quickly! produce vaccines as effective or better than the current flu vaccine. Producing the current vaccine requires about six months and tens of millions of fertilized chicken eggs.

If the public maintains its healthy fear of flu, then new vaccines may be on their way, said Dan Adams, president and chief executive officer of Protein Sciences.

"Unfortunately, you need an event to bring the issue to the forefront," Adams said.

"With Washington's attention span, problems don't exist when something goes out of the news."

Some of the new technologies used to combat influenza are bizarre, but promising.

Protein Sciences, for instance, uses caterpillar cells to produce the proteins that are the basis of its vaccine, while other researchers use kidney cells from African green monkeys.

All the new technologies employ genetic engineering strategies and share one big advantage over existing manufacturing methods that depend on culturing viral strains in fertilized eggs: They are nimble enough to keep pace with rapidly mutating flu viruses.

The current outbreak that has raised havoc across the nation stems from a relatively minor genetic change in a Type A influenza virus that has circulated in recent years. The so-called Fujian variant was left out of this year's vaccine, which was formulated in February to meet production deadlines. However, the vaccine still offers some protection because of similarities between the viral strains.

Yet no such protection would be available in the event of a worldwide pandemic -- which scientists say is inevitable given viruses' propensity to make occasionally dramatic and dangerous genetic changes.

"The world will be in deep trouble if the impending influenza pandemic strikes this week, this month, or even this year," virologists Richard J. Webby and Robert G. Webster

of St. Jude Children's Research Hospital wrote in a review of pandemic preparedness published in November in the journal *Science*.

In the fall of 1997, world health officials feared they were facing the century's fourth full-fledged pandemic -- the arrival of a deadly new strain of influenza, to which people had no immunity.

The new strain of avian influenza, which apparently jumped from chickens directly to people, showed signs of being particularly lethal. By Christmas, six of the 18 people who contracted the flu had died.

Health officials feared that hundreds of thousands of people could die worldwide, but it was too late to produce a new vaccine using traditional methods. It was impossible to obtain hundreds of millions of fertilized eggs needed to create a new vaccine to protect the U.S. population.

As it turned out, the egg production problem was irrelevant: The avian flu was so virulent it destroyed chicken embryos.

At the request of the National Institutes of Health, Protein Sciences diverted seven scientists to develop a new vaccine. Using a genetic sequence from RNA taken from the avian flu, they engineered a virus adept at infecting caterpillar cells to produce a protein unique to the avian flu virus.

They then introduced the modified virus into caterpillar cells grown in a bioreactor. The infected caterpillar cells produced flu protein, which was extracted and used as a vaccine. The immune systems of those inoculated would recognize the protein and if exposed, be able to fight off the flu virus.

From early December 1997 through January 1998, the company managed to produce 1,700 doses of vaccine, Adams said.

Fortunately, they weren't needed. The avian flu proved to be difficult to transmit from person to person and was contained after the slaughter of millions of chickens, ducks and geese in Hong Kong markets.

As the immediate threat of avian flu ended, so did the will to help develop a new generation of flu vaccines, Adams said.

"There are a hell a lot of regulatory obstacles" in developing new vaccines, said Dr. Maurice Hilleman, an early flu vaccine pioneer and now director of the Merck Institute for Vaccinology. "The question is, what is the incentive to develop them?"

The existing vaccine has been around for decades and has a track record of safety. It also is relatively inexpensive -- doses wholesale for less than \$9 a shot.

Developers of new vaccines must show that their product is at least as safe and effective and can be produced as economically. Fear of lawsuits also makes the development of new vaccines unattractive, as does the need to raise large initial investments needed to create large-scale manufacturing capabilities, Adams said.

Those obstacles slowed development of the caterpillar-based vaccine at Protein Sciences, which has concentrated on selling a variety of proteins for pharmaceutical and research use.

However, early trials of the company's flu vaccine show that it appears to be safe and may offer elderly patients more protection from the flu than the existing vaccine. Adams is optimistic that the company will get government help to fund the larger-scale trials it needs to confirm those findings.

"The [U.S. Food and Drug Administration] is serious about getting out of eggs," he said.

Adams said that if the larger trials prove successful, the company could have the vaccine ready to market by 2006, possibly even 2005. He said there is no reason the company couldn't produce new vaccines effective against emerging flu strains within eight weeks. Experts hope the timetable for developing new vaccines will be faster than nature's ability to spin out virulent new flu strains.

For instance, the emergence of SARS in March overshadowed the death of a young Hong Kong girl a month earlier -- from avian flu.

``Nature's ongoing experiments with [influenza] may be the greatest bioterror threat of all," concluded Webby and Webster. ``The time for talking is truly over."

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