

Avian flu may tax vaccine makers

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By David P. Hamilton, The Wall Street Journal

Amid fears that a deadly avian influenza in Southeast Asia could trigger a global pandemic, researchers are readying an experimental vaccine that might protect people against infection.

But developing and deploying it could turn out to be one of the biggest challenges in public health today.

The new vaccine for the avian-flu bug designated H5N1 is one of the first produced via a new gene-swapping technique, and no one knows if it will work. Even if the vaccine is effective, manufacturing enough to protect more than a fraction of the world's people would quickly overwhelm today's rickety vaccine-production infrastructure. Vaccine makers already have said they won't produce pandemic vaccine in quantity without government incentives, such as promises to buy unused doses.

In fact, the issues raised by a potential H5N1 pandemic point up many of the same issues — a scarcity of surplus capacity, long production lead times and few corporate or government officials committed to improving matters — raised by recent unexpected blows to the vaccine industry. Late last year, the U.S. faced a sudden shortage of seasonal flu vaccine after U.K. health officials abruptly shut a contaminated Chiron Corp. factory in Liverpool, England, that produced a vaccine called Fluvirin.

“These are daunting, daunting problems,” says Myron Levine, a vaccine expert at the University of Maryland. Adds Luc Hessel, an executive director at French drug maker Sanofi-Aventis SA, a major maker of flu vaccines: “We're still in the learning curve.”

Chiron, in fact, had previously committed to produce test lots of the H5N1 vaccine at the same location, although not in the same facility. It is now more than a month behind in supplying the H5N1 vaccine; a Chiron spokeswoman said the company deliberately delayed production “in response to the Fluvirin situation.” Production of the H5N1 vaccine is now under way, although Chiron says the total delay will be “a few months.”

U.S. health officials involved in the H5N1 trial say the holdup isn't likely to have a major effect on the trials, in part because Sanofi-Aventis is supplying half the vaccine.

Those trials are now scheduled to get under way in March. Scientists will inject 4,000 healthy volunteers with the vaccine, which consists of inactivated copies of the virus designed to elicit an immune response that can prevent infection or limit its damage.

The H5N1 bug first emerged in Hong Kong in 1997, but early efforts to make a vaccine against it didn't work well. Researchers concluded they had used the wrong strains of the virus, partly because they couldn't get more dangerous varieties to grow in the laboratory.

Since then, scientists have placed their bets on a new technique known as “reverse genetics,” in which they swap the most lethal of the flu bug's eight genes with less-dangerous counterparts

from other strains. The resulting “seed” virus poses relatively little threat to human health and grows well in the special chicken eggs used to produce flu vaccines.

Just how potent an immune reaction the new vaccine will produce isn’t clear. The killed virus in ordinary flu vaccines often stimulates the immune system’s “memory” of prior flu infections, boosting the antiviral response. But most people have never encountered an avian virus like H5N1, so the new vaccine will have to start from scratch.

Scientists such as Ruben Donis, section chief of the influenza branch at the U.S. Centers for Disease Control and Prevention, worry that full protection against avian flu might require multiple doses of vaccine. Immunization campaigns might cost more and be less effective as a result, particularly if many people failed to take all their shots.

Finding a working vaccine, however, may be the easy part. If an H5N1 superflu started to spread and flu-vaccine manufacturers converted their entire production to H5N1 vaccine, the World Health Organization estimates it would take six months to make enough vaccine for 10 percent to 20 percent of the U.S. and Europe. After one year, companies could produce almost one billion doses, not even enough to cover the at-risk Chinese population. What’s more, children and the elderly would be exposed to ordinary seasonal flu during that time.

Building up vaccine stockpiles might be one solution, but few governments are yet headed in that direction. The U.S. government recently purchased two million doses of the experimental H5N1 vaccine from Sanofi-Aventis, but it did so to help the company identify potential bottlenecks in its commercial-production process, not to build a stockpile.

At this stage, in fact, no one even knows if the vaccine will remain potent if stored. The making of stockpile vaccine must also be sandwiched into crowded production schedules. Sanofi, for instance, says its facilities can only spare four to eight weeks in the summer when they aren’t making seasonal flu vaccine.

Yet manufacturers aren’t eager to invest in new production facilities unless governments help them cover the cost, an idea still in its infancy. Also, building new factories isn’t a quick fix. If it started construction now, Sanofi figures it would take about five years to build a new manufacturing site for a pandemic flu vaccine.

“The problem of the fragility of the vaccine enterprise is a rather substantial one,” says Anthony Fauci, director of the U.S. National Institute for Allergy and Infectious Diseases in Bethesda, Maryland. Fixing it, he says, will require a complex mix of incentives that could include guaranteed vaccine purchases, tax credits and indemnification of liability in case vaccines lead to unexpected side effects. “All those things are multifaceted and will take time,” he says.

Some governments are starting to address the issue, although their efforts are still in the early stages. The National Vaccine Program Office, run out of the U.S. Department of Health and Human Services, is working to provide some vaccine-industry incentives, although so far they tend to be small-scale programs to assist with research-and-development costs or the expense of clinical trials.

The same office made the bulk order of H5N1 vaccine, reasoning that it was better to address any production problems “now rather than in a crisis,” says director Bruce Gellin.

Even if global health officials manage to find workable solutions to such problems, they will find even bigger questions awaiting them. Will industrialized nations reserve their vaccines for their own citizens, or should they distribute them in developing nations where the need might be greatest? When, exactly, should mass vaccinations begin, given that imperfect forecasting might easily result in immunizing too early _ or worse, too late?

“How many cases do you need to see before you’re really sure it will spread?” asks John Treanor, a microbiologist at the University of Rochester in Rochester, New York. “Or once you see it, will it be too late? That’s the dilemma of dealing with a flu pandemic.”

