

Race for pandemic flu vaccine rife with hurdles

Animal studies are under way, human trial protocols are taking shape and drug makers are on alert. All the international health community needs now is a human vaccine for the bird flu pandemic sweeping a cluster of Asian countries.

The race for a vaccine began after the first human case emerged in Hong Kong in 1997. This year, a strain of the H5N1 avian flu virus has already claimed 19 lives as of 12 February.

Backed by the World Health Organization (WHO), three research teams in the US and UK are trying to create a seed virus for a new vaccine. Their task is formidable, but researchers remain optimistic. "There are obstacles, but most of the obstacles have been treated sensibly," says Richard Webby, a virologist at St. Jude Children's Research Hospital in Memphis, Tennessee.

The biggest challenge is likely to be the rapidly mutating virus. Candidate vaccines produced last year against the H5N1 virus are ineffective against this year's strain. Scientists will have to constantly monitor the changes and try to tailor the vaccine as the virus mutates, says Linda Lambert, cold and flu program officer for the US National Institute of Allergy and Infectious Diseases.

"You could go down the path of gearing up and testing a vaccine, and six months later find out we're dealing with a different one," Lambert says. "We all agree that we can't wait to see which one comes next."

The urgency stems from fears that H5N1 will combine with a human flu virus, creating a pathogen that could be transmitted from per-



Fast and flu-rious: A human vaccine for avian flu could be ready in a few months.

son to person. But if people have no immunity to the virus, the strain may not mutate as rapidly in people as it does in birds, says Webby. "My personal feeling is that we are not going to see antigenic drift in the first season or so," he says. "There won't be the same pressure on the virus to change that there is on the ordinary flu."

To quickly generate the vaccine, researchers are using reverse genetics, which allows them to skip the long process of searching through reassorted viruses for the correct genetic combination. Instead, scientists clone sequences for hemagglutinin and neuraminidase, the two key proteins in the virus. The sequences are then combined with human influenza genes to create a customized reference strain.

Because products developed with reverse genetics have never been tested in humans, the

candidate vaccines will first have to clear regulatory review. In anticipation, the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) are both preparing pandemic response plans. The EMA has produced a fast-track licensing program, an industry task force and detailed guidance for potential applicants.

In Europe, a reassortant influenza virus—but not the inactivated vaccine—produced by reverse genetics would be considered a genetically modified organism, and manufacturers would need approval from their national or local safety authorities, says John Wood of the UK National Institute for Biological Standards and Control. The WHO has prepared a preliminary biosafety risk assessment of pilot-lot vaccine, which could help speed up the review.

In September 2003, FDA staff met with representatives of the WHO and the US National Institutes of Health (NIH) to evaluate vaccine candidates, establish dose ranges, and identify study populations and clinical endpoints such as immunological assays.

The NIH has also put its virus clinical trial network on alert. A preliminary version of their protocol calls for several hundred subjects, beginning with a group of young adults and gradually expanding to include those most susceptible to the flu—children and the elderly. "If we had product," says Lambert, "it would probably be a couple of months at the earliest before we have early data in healthy adults."

Tinker Ready, Boston

New York consortium to build cooperative mouse house

In New York City, where space for people is at a premium, finding room for mice is no small task. Faced with cramped quarters for their research animals, six local research institutes—including Columbia University and Rockefeller University—are forming a new consortium to create a bigger and better new mouse house.

The institutes hope the new arrangement will help them attract and retain the best researchers. "Every field in biomedical research is highly dependent on the use of transgenic and knockout mice," says Dennis Kohn, director of Columbia University's Institute of Comparative Medicine. A researcher might begin with 50 cages of mice—three to a cage—but within a few years, it is not unusual to need 200 to 300 cages. The consortium plans to build new space for 25,000 to 30,000 additional mouse cages.

"We estimate a projected need of about

500,000 mice for all six institutions combined by the year 2009," says Maria Mitchell, president of the Academic Medicine Development Company, which is leading the consortium's effort.

The new residence will be strictly a breeding facility, and mice will be sent to the institutions for research, says Chris Cosgrove, a vivarium planning specialist with CUH2A, a New Jersey-based company that will help plan the house. The site is likely to be outside Manhattan, but will have good access to public transportation, Cosgrove says.

Work on the new house will begin this year and is expected to be complete by 2006 at the latest. All told, the living space will cost

about \$233 per mouse, and total costs could reach \$15 million.

A mouse house requires more complicated mechanical systems than might be expected, says Cosgrove. "Unlike offices or other labs, housing for mice uses only single-pass air to minimize cross-contamination and maintain a clean environment," he says. "You and I go home at night—the mice don't."

In addition to an air system that provides 100% fresh air, HEPA filtering and tight temperature and humidity control, the building must have backup and emergency power and space for additional maintenance. Such mechanical needs can occupy nearly half of a building compared with a traditional office, which needs only 10–20% additional space.

Vicki Brower, New York

