



## Responding to the Avian Flu Threat: Balancing Risks and Rewards

Vaccine development holds the greatest promise and the greatest challenge for protecting the worldwide population from an avian flu pandemic



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**H**uman infections with avian flu strain H5N1 are occurring in a number of southeast Asian countries that have experienced large outbreaks of avian influenza. How great a risk to the human population is posed by this virus, and what steps can be taken to minimize its impact? Preventive vaccines have great potential to avert the spread of avian flu and other infectious diseases. What are the factors affecting the creation of new vaccines, and how can they be optimized to promote public health?

### RISKS POSED BY H5N1

Human infection with avian H5N1 virus was first noted in Hong Kong in 1997. Of eighteen people known to be infected, six died. All of the infected people had close contact with domestic birds.<sup>1</sup> Data suggest that human-to-human transmission of H5N1 is extremely inefficient, and that avian flu cannot currently be spread among people by coughing or sneezing (small particle aerosol transmission).<sup>2</sup> Instead, transmission to people results from direct contact with infected poultry, although infection through environmental exposure, such as to contaminated water, also seems possible, given the sur-

vival of H5N1 in the environment.<sup>3</sup> Both the popular press and scientific literature have debated the possibility of mutations occurring in the H5N1 virus, allowing it to more easily spread among people.

Experts believe that if H5N1 were to mutate to a more easily transmissible form, the mortality rate would not be as extreme as that of the 1918 pandemic in countries that have mechanisms to control the spread of the disease, as well as the ability to treat it. The 1918 flu pandemic occurred during World War I, which exposed many people to unsanitary conditions that promoted the spread of disease.

However, in the worst case scenario, the human-to-human spread would pave the way for pandemic infection, such as the influenza pandemics of 1918, 1957, and 1969. As the debate continues, it is clear that the risk must be taken seriously, and that we must start preparing for a possible avian flu pandemic now.

### GOVERNMENT RESPONSE

The US government has appropriated \$7 billion to prepare for the threat of an avian flu pandemic, earmarking funds to treat infected populations, contain outbreaks, and — most

importantly — prevention. H5N1 currently can be treated with neuraminidase inhibitor drugs such as Roche's oseltamivir (Tamiflu), and clinical trials are under way for BioCryst's neuraminidase inhibitor Peramivir. But there have been reports of resistance to this type of drug therapy.<sup>2</sup> Government stockpiling of effective antiviral agents and other first-line patient care necessities, such as ventilators, is an important component of the response. Tamiflu is a scarce resource, leading some policy makers to suggest compulsory licensing of Roche's patents on the drug as a way to alleviate the shortage. While the limited amount of the raw ingredient used to produce Tamiflu is considered an impediment to increased manufacture, there is another reason to reject compulsory licensing. It threatens to rob pharmaceutical companies of the returns they need to support their R&D investments that produce other innovative products.<sup>4</sup>

Vaccine development holds the greatest promise of protecting the worldwide population from an avian flu pandemic. Two experimental vaccines (manufactured by Sanofi-Aventis and Chiron) against H5N1 are in clinical trials sponsored by the National

Institute of Allergy and Infectious Disease. Both vaccines are made from inactivated H5N1 viruses.<sup>5</sup> While early results have been encouraging, many challenges remain.<sup>6</sup>

## INCENTIVIZING VACCINE DEVELOPMENT

The ability to use a vaccine to prevent a pandemic hinges on developing a safe and effective vaccine to protect against infection, and on the percentage of the at-risk population that becomes vaccinated. Vaccines are administered to healthy individuals to protect against an uncertain risk. These individuals are unlikely to take a vaccine if they perceive that their risk of falling ill from the infection is less than the risk of being harmed by the vaccine. Concerns about their ability to recover economic damages arising from vaccine-induced harm further reduce the propensity of many individuals to be vaccinated. On the other hand, vaccine manufacturers are unlikely to undertake the economic and technical burdens associated with creating a vaccine if they perceive that an insufficient market exists or that liability exposure reduces their ability to earn a fair return on their investment.

The number of manufacturers producing vaccines for the US market has been waning. In 1967, 26 companies produced vaccines. In 1999, there were four; today, only three remain.<sup>7,8</sup> This decline reflects the risk/reward balance companies must achieve to bring preventive vaccines to market. To tip this balance, the US government implemented three vaccine liability and compensation programs in the last 30 years.<sup>9</sup> These were designed to encourage vaccination by shielding manufacturers from liability while still providing consumers with recompense for vaccine injury.

Under the national Swine Flu Immunization Program of 1976, the US government assumed liability. Claims were filed against the government and award amounts were not limited under the act. The next program is a more limited liability and compensation policy under the National Childhood Vaccine Injury Compensation Act (1986), which created the National Vaccine Injury Compensation Program. Under this program, a two-step mandatory scheme is used. The first step involves no-fault compensation for injuries following administration of included vaccines. Awards are paid by the government and their amounts are capped. Under the second step, a dissatisfied claimant can sue the vaccine manufacturer.<sup>10</sup>

The Phase I Smallpox Vaccination Program was launched in 2003. This program relies on section 305 of the Homeland Security Act of 2002 for liability protection and compensation, but the provisions are unclear and inadequate to address first-responders' concerns of adequate compensation in the event of injury. Consequently, only 40,000 of a targeted 500,000 first responders have been vaccinated.<sup>11</sup>

Proposed legislation to deal with liability for a pandemic flu vaccine is pending in the Senate. That legislation would cover only first responders and health care workers, and would render manufacturers immune from any liability except for willful misconduct.<sup>12</sup> The extent to which this legislation (should it pass in its current form) impedes the public from seeking vaccination depends on whether individuals' fears about succumbing in a flu pandemic outweigh concerns about uncompensated vaccine injury.

Additional economic and technical challenges remain to be solved to encourage production of a safe and effective pandemic vaccine. These include correct prognostication of

the pandemic strain. Because H5N1 is inefficiently transmitted from person to person, a mutated strain would likely be responsible for pandemic infection. Other obstacles include cumbersome and difficult manufacturing methods for producing vaccines, regulatory hurdles, market size, and price. While many of these challenges are not amenable to policy-based intervention, market size and price are two areas in which government policy can make a difference. By initiating contracts that guarantee purchase of significant quantities of vaccine at prices that provide a fair return on investment, the government can encourage development of vaccines to help safeguard the public. ♦

## REFERENCES

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