Avian flu: Expanding global vaccine production

"If governments are to be prepared for a potential avian-flu pandemic, they must bring pharmaceutical companies and health organizations into the strategic-planning process."

By Kenneth Bonheure, Pierre Keller, and Ken Somers

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With avian influenza spreading from Asia to Africa and Europe, governments are under increasing public pressure to counter the threat of a potentially deadly pandemic. They are already stockpiling antiviral drugs and vaccines, buying options on vaccine production capacity, and even using private-public partnerships to build production plants. Well intentioned though these multibillion-dollar programs may be, however, they are unlikely to help governments protect as many citizens as possible in the most efficient, cost-effective way.

We believe that governments cannot attain this goal if they act alone; only close cooperation with experts from health organizations and the pharmaceutical industry could produce the necessary amount of vaccine for affected areas in the event of a pandemic. The key will be to increase the demand for regular annual flu shots—an effective way of encouraging new vaccine production capacity. Until adequate capacity is built, governments must continue stockpiling vaccines and antiviral drugs to provide at least some stopgap protection.

Thus far, there is no evidence that the avian-flu virus has mutated enough to be easily and sustainably transmitted by humans. As of June 2006 the 226 cases of human infection, which led to 129 deaths, stemmed mainly from contact with infected animals. The several human-to-human cases reported through mid-2006 apparently developed only after close, extended exposure to infected patients and family members. But scientists believe that the virus *will* mutate into a strain capable of entering human cells and replicating easily. They don't know whether this development will take months or years or if the culprit will be H5N1, the current strain of avian flu. Whatever the uncertainties, the World Health Organization (WHO) estimates that in the absence of adequate vaccine capacity, 50 million people could die in an avian-flu pandemic. A virus similar to avian flu caused the pandemic of 1918, which killed 40 million people. Even with epidemiological advances, current government stockpiling plans probably can't achieve adequate coverage.

The five major manufacturers of winter flu vaccine—one in the United States and four in Europe—can produce 300 million dosages annually for the Northern Hemisphere. Pandemics, which occur roughly every 30 years and are therefore not a factor in normal production planning, require at least three times this existing capacity, at least with the currently available technology.

Pandemic vaccines, which are effective at lower doses, are in great demand because manufacturers can produce more of them with the same capacity. The vaccine currently found to be effective against H5N1, however, requires a relatively large dosage—at least 30 micrograms of antigens.[1] If this larger dose remains standard, the capacity available in 2006 would provide inoculations for only 100 million people, or 8 percent of the population of North America, Europe, and Japan, the primary countries where the vaccine is produced.

To keep a country's basic infrastructure working in the event of a pandemic, an estimated 10 percent of the population must be inoculated—including all doctors, nurses, police, and other emergency personnel—as soon as the virus strain is identified and the first batch of vaccine becomes available. The current level of coverage is also far below the 30 percent that, according to the concept of herd immunity,[2] would slow the spread of the virus.[3] Moreover, current capacity can't accommodate the demand from Asia, Africa, and other regions that lack the technology and plants to manufacture vaccines.

The shortfall in production capacity is prohibitively large, but policy makers should not be deterred from starting to close it. The first priority must be to cover 10 percent of the population. This target will be difficult to meet through stockpiling alone—partly because, with a dozen avian-flu virus strains already identified, officials have no guarantee that stocks will be effective against an actual pandemic strain.

By focusing solely on stockpiling dosages of a vaccine, governments overlook the opportunity to prepare the population through preemptive vaccinations against related strains.[4] Although researchers believe that stockpiles of symptom-relieving antiviral drugs will prevent deaths, the vaccines must be ingested

within 48 hours of exposure to be effective. Antiviral drugs are also costly and in limited supply, and they may ultimately prove ineffective, as the virus is likely to become prematurely resistant.[5] Furthermore, the demand created by stockpiling does not spur increases in capacity, because manufacturers in the Northern Hemisphere typically produce vaccines for stockpiling between flu seasons. Similarly, the sale of options on vaccine capacity isn't likely to lead to the industry's expansion; indeed, option prices will probably rise as governments bid for limited capacity.

Recognizing these limitations, some countries are planning to construct costly state-owned vaccine plants that will require the time-consuming transfer of technology from the pharmaceutical industry. (Nordic countries are at the forefront of this trend.) Yet these state monopolies could create excess capacity and destabilize market prices—especially once the perceived threat of a pandemic dissipates.

Instead of acting alone, stakeholders should try to forge an effective global solution, a strategy the United States advocated in its May 2006 report on pandemic planning.[6] First, all parties must agree on the dosage required to limit the spread of the virus. Second, they must increase funding for vaccine research, particularly in antigen-sparing technologies, which would help to produce more vaccine with the existing capacity. Finally, they must build more capacity and stimulate demand for an interpandemic vaccine—that is, inoculations given during a normal winter flu season.

Taking a step in this direction, the WHO has announced that by 2010 one billion interpandemic vaccine dosages will be needed—a number that would require current capacity to triple. An effort by the United States to strengthen its vaccine industry would contribute a portion of this amount. In April 2006 the US government awarded more than $1 billion to five pharmaceutical companies, with the goal of stimulating innovation in cell-based technology, which uses mammalian cells to grow influenza viruses and is speedier and more reliable than the current vaccine technology, which relies on fertilized chicken eggs. Cells can be frozen and stored, whereas eggs are perishable and likely to be in short supply in the event of an avian-flu pandemic, when flocks would be devastated.

To protect as many people throughout the world as possible, the expanded production capacity that the WHO seeks must be geographically coordinated and balanced. Areas with scant production, such as Asia, will require new infrastructure.

Creating demand for the existing winter flu vaccine is the best market mechanism to develop this capacity. Vaccination rates, currently 32 percent in the United States and 17 percent in the European Union, must increase to more than 40 percent. Vaccines for children aged 6 to 23 months should be developed and improved, and adult vaccinations should begin at age 50 rather than 65, as currently recommended. The US market has already begun moving in this direction.

At the same time, pharmaceutical companies should seek government approval and funding to add a fourth flu strain to the current three-strain winter vaccine. This additional one could target H5N1 or any of a dozen related avian-flu strains if regulatory and technical hurdles can be overcome.[7] The new, annually changing four-strain vaccines would not include the precise pandemic virus—indeed they could not, because researchers can't detect it until an outbreak occurs.

These vaccines could, however, mitigate the spread of a pandemic because the injection of strains related to avian flu helps build antibodies against any deadly strain of it that might emerge. Thus a single, more effective vaccination could replace the two flu shots currently required to combat a pandemic. This measure, by itself, would double the production capacity for vaccine manufacturers.

If stakeholders work together, pharmaceutical companies could build enough cell culture-based capacity to satisfy the expanded market for winter flu vaccine by 2012. Progress along these lines would also enable manufacturers to meet the demand for a ten-microgram pandemic vaccine, so Europe, Japan, and the United States could inoculate 30 percent of their populations.

However, to protect people from a pandemic that might occur before this capacity comes on line, governments have only one option: using the spring and summer months, when the regular flu vaccine is not produced, to make vaccines for a potential pandemic. Simultaneously, health officials should begin priming the at-risk population with a four-strain flu vaccine and continue stockpiling treatments such as antiviral drugs.

Savings from higher vaccination rates—and the resulting decrease in levels of illness—would offset the cost of a four-strain vaccine. For each person vaccinated, current winter flu programs achieve annual health care savings ranging from $26.68 in Canada to $46.85 in the United States.[8] If this vaccine were

more widely distributed, the United States could save $3 billion to $5 billion a year in health care spending to treat winter flu sufferers.[9] Indirect costs, such as lost productivity from absent workers, could fall by an estimated one-and-a-half to nine times that amount.[10]

If the market-driven expansion of production capacity left any gaps, governments would have to subsidize the creation of more. That would almost certainly be necessary for governments to reach a 30 percent vaccination rate with a minimum effective dosage of 30 micrograms per shot. However, the building of publicly funded plants should be a last resort because idle capacity would not be cost effective and could cut profits in the private sector, thus limiting the industry's ability to innovate.

Even if governments boost demand for winter flu vaccines, a plan to prime the population could fail because of an ineffective distribution system. Despite the availability of winter flu vaccines, some 34,000 people a year die of flu in the United States. Many of these deaths could be prevented through improved distribution and greater participation in flu shot programs.[11] Stemming a pandemic requires the vaccination of every possible person—a challenge, since in general flu shots are not compulsory.

Governments worry when—not whether—a flu pandemic will occur. To succeed in the fight against a potential flu pandemic, they, together with health organizations and the pharmaceutical industry, must agree on required capacity levels and support research on the reduction of dosages in the event that a pandemic actually breaks out. At the same time, stakeholders must agree on a plan to improve the effectiveness of vaccination programs and coverage, respectively, by promoting awareness and by including a fourth strain in the vaccine. These measures not only make economic sense but will also increase production capacity dramatically. **Error! Filename not specified.**

About the Authors

Kenneth Bonheure is a principal, **Pierre Keller** is an associate principal, and **Ken Somers** is a consultant in McKinsey's Brussels office.

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Notes

[1] An antigen is a foreign substance, usually a protein, that stimulates the body's immune system to produce antibodies. (The name antigen derives from its role in stimulating an immune response—antibody generating.)

[2] Herd immunity refers to the vaccination of a critical level of a population to prevent the spread of infectious disease among the population as a whole.

[3] Thomas A. Reichert, Norio Sugaya, David S. Fedson, W. Paul Glezen, Lone Simonsen, and Masato Tashiro, "The Japanese experience with vaccinating schoolchildren against influenza," *New England Journal of Medicine*, 2001, Volume 344, Number 12, pp. 889–96; and Andrew Fenton, "Early vaccination and appropriate public health intervention impacts, outcome of influenza pandemic management efforts," 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), October 30–November 2, 2004, Washington, DC, Session 120, paper G-1205.

[4] The US government plans to stockpile sufficient quantities of vaccine to immunize 20 million citizens and enough antiviral medications to treat 75 million people, or roughly 25 percent of the population. See the implementation plan of the *National Strategy for Pandemic Influenza*, Homeland Security Council, November 1, 2005, p. 9.

[5] Barry R. Bloom, "Bird flu: Public health and pandemics," Harvard School of Public Health Web seminar, May 16, 2006.

[6] *National Strategy for Pandemic Influenza*, Homeland Security Council, November 1, 2005, p. 3.

[7] In addition, further research is needed to determine the amount of the avian-flu component that should be added to the seasonal vaccine and whether there will be any need for an adjuvant (a chemical additive that enhances the effects of a vaccine at a lower dosage).

[8] Susan C. Wood, Van Hung Nguyen, and Claudia Schmidt "Economic evaluations of influenza vaccination in healthy working-age adults: Employer and society perspective," *PharmacoEconomics*, 2000, Volume 18, Number 2, pp. 173–83.

[9] Peter A. Patriarca, "New options for prevention and control of influenza," *Journal of the American Medical Association*, 1999, Volume 282, Number 1, pp. 75–7.

[10] E. Levy, "French economic evaluations of influenza and influenza vaccinations," *PharmacoEconomics*, 1996, Volume 9, Supplement 3, pp. 62–6.

[11] Barry R. Bloom, "Bird flu: Public health and pandemics," Harvard School of Public Health Web seminar, May 16, 2006.