

Medical Countermeasures for Pandemic Influenza: Ethics and the Law

Lawrence O. Gostin, JD

SERIOUS OUTBREAKS OF AVIAN INFLUENZA A (H5N1) have occurred among birds in Asia, with cases now reported in Europe.¹ Although H5N1 is highly contagious among birds, it is rare in humans due to a significant species barrier.² As of January 7, 2006, 146 cases were reported with 76 deaths.³ Human-to-human transmission has occurred, but transmission to date has not continued beyond one person.

The prevalence of H5N1 is currently very low and pales in comparison with pandemics of human immunodeficiency virus, malaria, and tuberculosis. However, recent evidence that the 1918 "Spanish" flu was caused by an avian influenza virus lends credence to the theory that current outbreaks could have pandemic potential.^{4,5} Extrapolating from the 1918 pandemic, which killed an estimated 20 million to 50 million people in a less-populated planet,⁶ modeling studies indicate that 500 000 to 1 million Americans could die, with tens of millions of deaths globally.⁷ In response, the US government^{8,9} and the World Health Organization¹⁰ recently issued strategic plans.

Therapeutic countermeasures (eg, vaccines and antiviral medications) and nonpharmaceutical interventions (eg, infection control, social separation, and quarantine) form the 2 principal strategies for prevention and response.¹¹ This Commentary focuses on the medical countermeasures.

Planning and Market Incentives

The vast majority of proposed expenditures in the \$6.7 billion federal influenza plan is devoted to medical countermeasures with \$4.7 billion allotted for cell-based vaccine technology and stockpiling of experimental vaccine, and \$1.4 billion for antiviral medicine (oseltamivir).⁸ Despite the promise of medical countermeasures, there is a well-known history of a chronic mismatch of public health needs and private control of production. Vaccine production has been unreliable even for seasonal influenza—eg, the United States lost half of its supply in 2004-2005 when the United Kingdom withdrew Chiron Corporation's license due to bacterial contamination.¹²

The United States' goal must be to build a system that ensures stable and economically viable vaccines to meet potentially massive public needs. Strategies that integrate public and private sectors rather than relying solely on private markets are most likely to succeed.¹³ Market forces create disincentives for manufacturers that inhibit vaccine development: high investment costs, limited or variable markets, and regulatory compliance. Vaccine manufacturers are leaving the industry and, therefore, are creating the risk of

severe shortages. In 1967, 26 companies were licensed to manufacture vaccines in the US market; today only 4 companies supply influenza vaccine, with only 2 manufacturing domestically—MedImmune (live attenuated influenza virus, intranasal) and Sanofi Pasteur.¹⁴

The Institute of Medicine has recommended a national vaccine authority to advance the development of vaccines.¹⁵ With or without a national vaccine authority, government can create incentives by boosting demand through seasonal vaccine awareness programs, issuing purchasing contracts, and providing price guarantees or subsidies. Recognizing the need, the G7 Finance Ministers announced a pilot advance market commitment for vaccines of public health importance.¹⁶

Even if vaccination supplies were adequate, distribution to the population is problematic. Pandemic influenza would require mass vaccination within a short timeframe. Federal stockpiles must meet local needs, requiring systems for transportation, storage, and safe administration of the vaccine. If 2 doses are required to achieve immunity, a callback system or immunization registry may be necessary. The federal strategic plan leaves these vital issues unresolved, delegating them to the states.

Regulation, Intellectual Property, and Liability

The vaccine industry faces multiple, overlapping regulatory hurdles. These regulations are intended to improve safety and efficacy but they also increase costs and delays. On the federal level, the US Food and Drug Administration licenses vaccines, conducts regular inspections (Current Good Manufacturing Practice), and requires each lot of vaccine to be tested for contaminants before public release. Two states ban thimerosal (a mercury preservative), although the Institute of Medicine has not found a causal link to autism.¹⁷ California's statute commences in July 2006 and Iowa's law exempts influenza vaccine; bills are pending in other states. This legislation could undermine federal plans because influenza vaccines contain thimerosal. In addition to federal and state regulation, agencies in other countries regulate vaccines. Recognizing the problem of overlapping regulatory requirements, the Food and Drug Administration and the European Medicines Evaluation Agency published pathways for licensing of pandemic vaccines.¹³ Since manufacturers must rapidly begin mass commercial production, regulatory requirements should be timely, efficient, and well-coordinated.

Author Affiliations: Center for Law and the Public's Health, Georgetown University, Washington, DC; and Johns Hopkins University, Baltimore, Md.

Corresponding Author: Lawrence O. Gostin, JD, Georgetown University Law Center, 600 New Jersey Ave, NW, Washington, DC 20001 (gostin@law.georgetown.edu).

Potential patent disputes have significant cost implications for commercial vaccines. The H5N1 virus is most effectively grown in fertilized chicken eggs after modification through reverse genetics,¹⁸ which is a patented technology. Similarly, newer cell-based technologies that promise more efficient mass production are subject to intellectual property protection. Although intellectual property affords incentives for innovation, it can also impede timely and large-scale vaccine production in a public health emergency.

The Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS, Art. 31)¹⁹ allows countries to grant compulsory licenses (affording a right to produce a product without the patent holder's authorization) in a public health emergency. To ensure adequate production capacity, some have called for compulsory licenses for oseltamivir. The federal government plans to stockpile 81 million courses of oseltamivir, an amount sufficient to treat one fourth of the US population. At a cost of more than \$1.4 billion, the states must bear a high proportion of the costs.⁸ Hoffmann-La Roche Inc, the patent holder until 2016, has stated that the global demand largely exceeds production capacity.²⁰ However, the company opposes compulsory licensing, arguing that the raw materials are scarce, the manufacturing process is complex, and patent protection is necessary to create incentives.²⁰

Whatever the merits of compulsory licensing, antivirals have only limited utility. Oseltamivir should be taken within 48 hours of the onset of symptoms, giving patients little time to obtain a prescription and commence treatment.²¹ It is only partially effective against H5N1 and may not be effective if the virus mutates. Given the potential for mass use and patient nonadherence with the 5-day course of treatment, there is a risk of drug resistance.²² Consequently, reliance on stockpiling antivirals, although probably helpful in reducing hospitalizations, will not significantly impede a pandemic.

Liability protection for industry and fair compensation for patients offer a sound dual approach to vaccine policy. Such a system already exists under the national Vaccine Injury Compensation Program (VICP), but needs reform. The VICP created a no-fault system that pays for injuries caused by specific immunizations; Congress added influenza to VICP in 2004. Special masters at the Federal Claims Court adjudicate compensation based on a vaccine injury table. To recover damages, claimants must show that a listed vaccine caused their injury. A compensation trust fund is financed by a tax on each dose.

Patients can choose not to participate in VICP, which has led to a sustained critique that legal liability represents a major disincentive for the industry. The president's influenza plan virtually bans lawsuits (except for willful misconduct) and assigns liability determinations to a political figure (the US Department of Health and Human Services secretary).⁸ The political critique, however, overstates the negative influence of liability on vaccine production. Influenza vaccine litigation has been rare, with 10 reported jury verdicts or judicial decisions during the past 20 years and most with small verdicts.²³

Mass use of an untried vaccine during a public health emergency could result in numerous adverse events. Health care workers and patients would be less likely to volunteer without a fair compensation system as the failed smallpox vaccination campaign demonstrated.²⁴ A no-fault system such as VICP would provide relief for injured patients and greater certainty for the industry. Experimental H5N1 vaccines currently are not covered under VICP, so the new vaccine would need to be added. Moreover, VICP in its current state has become adversarial, burdensome on claimants, and time-consuming. A reformed system would have to take account of important issues: an overwhelmed program, resulting in delays; insufficient money in the compensation trust fund; and injustices caused by excessive burdens placed on patients injured by a new vaccine. In return, the industry should be spared lawsuits based on strict liability, but should answer to claims of gross negligence or recklessness.

Ethical Allocation of Scarce Resources

There will almost certainly be extreme scarcity of countermeasures in the short term. Companies will not meet mass needs for vaccines without dramatic improvements in production facilities and technologies (eg, cell-based cultures and dose sparing). The same scarcity will occur with antivirals given complex production processes and trade law that affords a single company exclusive manufacturing rights. The United States has limited capacity with only 2 domestic vaccine suppliers and no priority over purchasing orders for oseltamivir.

The most challenging question facing bioethics is how to ration scarce, life-saving resources: "Who shall live when not all can live?"²⁵ Blind justice might dictate a random allocation of scarce interventions (eg, a lottery or first-come first-served system). Yet, this seems unsatisfying when life-saving countermeasures can be targeted more cost-effectively. Given the devastating social and economic ramifications of a pandemic, other rationing criteria are worth consideration.

Prevention/Public Health. The historic mission of public health is prevention, so countermeasures to impede transmission should be a high priority. Thus, where feasible, rapid deployment of vaccines or prophylaxis to groups at risk of acquiring infection should be used to contain localized outbreaks. For example, ring vaccination of contacts in a family, congregate setting, or local community could be an effective intervention that would maximize lives saved.

Scientific/Medical Functioning. If the first political priority is public health, then it is essential to protect individuals who innovate, produce vaccines or antivirals, provide treatment, and protect the public's health. These are critical social missions necessary to save lives and provide care for the sick. Consequently, priority should be given to key personnel in developing countermeasures (scientists, laboratory workers), delivering health care (physicians, nurses, hospital staff), and devising public health strategies (epidemiologists, health officials).

Social Functioning/Critical Infrastructure. In a large-scale pandemic, key sectors of society may not be able to func-

tion. Many public and private actors are necessary for the public's health and safety: first-responders (ambulance, fire, humanitarian assistance), security (police, national guard, military), essential products/services (water, food, pharmacies), critical infrastructure (transportation, utilities, telecommunications), and sanitation (undertakers, cemetery workers, garbage/infectious waste personnel). Continued functioning of governance structures similarly would be important such as the executive, legislative, and judicial systems.

Medical Need/Vulnerability. Medical need is a widely accepted rationing criterion. It focuses on reducing serious illness and death among individuals and, therefore, targets those who are most vulnerable. It requires a scientific or epidemiologic judgment about at-risk groups that may vary. Seasonal influenza disproportionately burdens infants and the elderly, but highly pathogenic strains may affect young adults, as occurred with Spanish flu.

Intergenerational Equity. Medical need often favors the elderly because they are most vulnerable to influenza complications. However, there may be reasons not to routinely favor this age group. Interventions may be less beneficial for the elderly than to younger, healthier populations.²⁶ All human lives have equal worth, but interventions targeted toward the young may save more years of life. Would a "fair innings" principle militate in favor of children, young adults, and pregnant women?

Social Justice/Equitable Access. The allocation of benefits should not favor the rich, powerful, or politically connected. The Gulf Coast hurricanes seared into the American consciousness the inequities that could ensue in a public health emergency—evacuation and relief services disfavored the poor and people of color. Special efforts, therefore, should be made to ensure fair distribution of life-saving countermeasures to traditionally underserved populations.

Global Perspective. Realistically, resources will go to those countries where products are owned and manufactured. Major influenza vaccine producers operate and distribute almost exclusively in Europe, North America, and Asia.¹⁴ This reality can have devastating consequences for resource-poor countries that cannot compete economically for expensive countermeasures. Consequently, there is a strong moral justification for fair rationing from a global perspective. Even from a less altruistic perspective there are reasons to invest in poor regions. Improved surveillance and response can help in early detection and containment of outbreaks, affording universal benefits.

Civic Engagement/Fair Processes. Public cooperation in a health emergency is more likely if citizens accept the fairness and legitimacy of allocation decisions. Advance discussion of ethical principles keeps the public informed and engages it in a participatory decision-making process. A pilot project on civic engagement found that stakeholders and citizens at-large, at a high level of agreement, chose a functioning society and reducing deaths as priorities in vaccine allocation.²⁷ This altruistic consensus is comforting, but may not reflect real behavior in a time of crisis, which could involve

hoarding, stockpiling, and black marketeering. Citizens will agree to fair allocation if they believe the allocation process is fair. However, if they believe that others are jumping the queue due to influence or money, they will be less likely to behave selflessly. This is all the more reason for fair and transparent decision-making processes in advance of a pandemic.

Planning for an influenza pandemic is vital to success. It requires scientific innovation, modern laws, and ethical action. Private markets working alone cannot create stable supplies of life-saving countermeasures or ensure fair allocations. Rather, constructive partnerships among nations, government, industry, and the community are essential to maximize survival and socioeconomic functioning in an impending crisis.

Financial Disclosure: None reported.

REFERENCES

- Rosenthal E. Bird flu spreads westward in Turkey; new human case found in eastern villages and Ankara. *The International Herald Tribune*. January 9, 2006.
- The Writing Committee of the World Health Organization. Avian influenza A (H5N1) infection in humans. *N Engl J Med*. 2005;353:1374-1385.
- World Health Organization. Cumulative number of confirmed human cases of avian influenza A/H5N1 reported to WHO. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_01_07/en/index.html. Accessed January 9, 2006.
- Taubenberger JK, Reid AH, Lourens RM, et al. Characterization of the 1918 influenza virus polymerase genes. *Nature*. 2005;437:889-893.
- Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*. 2005;310:77-80.
- Barry JM 1918 Revisited: lessons and suggestions for further inquiry. In: *The Threat of Pandemic Influenza: Are We Ready?* Washington, DC: National Academies; 2005.
- Osterholm MT. Preparing for the next pandemic. *Foreign Affs*. 2005;84:24-28.
- US Dept of Health and Human Services Web site. HHS pandemic influenza plan. Available at: <http://www.hhs.gov/pandemicflu/plan/>. Accessed January 9, 2006.
- White House Web site. National strategy for pandemic influenza. Available at: <http://www.whitehouse.gov/homeland/nsipi.pdf>. Accessed January 9, 2006.
- World Health Organization. *WHO Global Influenza Preparedness Plan*. Geneva, Switzerland: World Health Organization; 2005. Publication WHO/CDS/CSR/GIP/2005.5.
- World Health Organization Writing Group. Nonpharmaceutical interventions for pandemic influenza, international measures. *Emerg Infect Dis*. 2006;12:81-87.
- Stohr K, Esveld M. Will vaccines be available for the next influenza pandemic? *Science*. 2004;306:2195-2196.
- World Health Organization. *Vaccines for Pandemic Influenza*. Geneva, Switzerland: World Health Organization; 2004. Publication WHO/CDS/CSR.GIP/2004.3.
- Danzon PM, Pereira NS, Tejwani SS. Vaccine supply: a cross-national perspective. *Health Aff (Millwood)*. 2005;24:706-717.
- Institute of Medicine Council. *Statement on Vaccine Development*. Washington, DC: National Academies; 2001.
- G-7 Finance Ministers. Center for Global Development Web site. Vaccines for development, G7 to pilot advance market commitments. Available at: http://blogs.cgdev.org/vaccine/archive/2005/12/g7_to_pilot_adv.php. Accessed January 9, 2006.
- Institute of Medicine. *Immunization Safety Review: Vaccines and Autism*. Washington, DC: National Academy Press; 2004.
- Check E. Avian flu special: is this our best shot [published online May 25, 2005]? *Nature*. doi:10.1038/435404a. Accessed January 9, 2006.
- World Trade Organization Web site. Agreement on trade-related aspects of intellectual property rights, article 31. Available at: http://www.wto.org/english/docs_e/legal_e/27-trips.doc. Accessed January 9, 2006.
- Zamiska N, Dean J. Generics challenge Roche's Tamiflu claims. *Wall Street Journal*. November 3, 2005.
- Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med*. 2005;353:1363-1373.
- Moscona A. Oseltamivir resistance—disabling our influenza defenses. *N Engl J Med*. 2005;353:2633-2636.
- Mello MM, Brennan TA. Legal concerns and the influenza vaccine shortage. *JAMA*. 2005;294:1817-1820.
- Institute of Medicine. *The Smallpox Vaccination Program: Public Health in an Age of Terrorism*. Washington, DC: National Academy Press; 2005.
- Arras JD. Ethical issues in the distribution of influenza vaccines. *Yale J Biol Med*. In press.
- Gardner EM, Gonzalez EW, Nogusa S, Murasko DM. Age-related changes in the immune response to influenza vaccination in a racially diverse, healthy elderly population [published ahead of print October 14, 2005]. *Vaccine*. 2005.
- Public Engagement Pilot Project on Pandemic Influenza. *Citizen Voices on Pandemic Flu Choices*. Washington, DC: National Academy Press; 2005.