Preparing for the Next Influenza Pandemic: A Reemerging Infection

If a foreign army invaded the United States and in a few months ravaged the population, killing 22 000 men, women, and children and then leaving, the loss would be overwhelming, and the nation would turn its collective efforts to preventing such a tragedy from occurring again (1). In fact, this invasion occurs almost every year in the United States, but the foreign invader is a pestilence: a new strain of influenza virus. And we are not shocked by the tragedy, and we do not make every effort to prevent its recurrence. While "emerging" infectious diseases—such as those caused by the Ebola virus in Africa, the hantavirus in the United States, and multidrug-resistant bacteria everywhere—hog the headlines, we need to be reminded that a "reemerging" infectious disease, influenza, takes an even greater toll in lives (2, 3). This awareness should prod us to cope more effectively with the almost annual epidemics of influenza while, at the same time, we begin to plan for the next influenza pandemic.

Four influenza pandemics have occurred in the 20th century, and they are a study in contrasts. The 1918 Spanish influenza was the most devastating: It killed 550 000 persons in the United States and 20 million persons worldwide. The 1977 Russian influenza had a relatively minor effect and did not increase mortality (4). The 1957 Asian influenza and the 1968 Hong Kong influenza had effects in between those of the Spanish and Russian influenzas. The expected 1976 swine influenza pandemic never materialized. These events have been considered at recent meetings held to prepare for the next influenza pandemic, which is expected to be the result of a new influenza subtype that can cause worldwide illness on a massive scale, potentially affecting its victims during a short period and creating serious health consequences (5).

Reduced to its essentials, pandemic preparedness requires that we be able to do the following:

1) Rapidly recognize new virus strains.

2) Establish an adequate surveillance network to detect new strains and assess their effects on populations.

3) Identify the origination of new strains from the animal population.

4) Define the target groups for vaccination.

5) Clarify the role of antiviral drugs.

A successful pandemic plan also requires that an interpandemic plan be implemented before the pandemic occurs to increase awareness of vaccine benefits, enlarge the vaccinated population, and improve existing vaccines. This will help to reduce the serious effect of the almost annual influenza epidemics.

Recognizing the occurrence of a new strain of influenza virus is central to commencing implementation of a successful pandemic plan. We now know that of the two influenza types that commonly cause epidemics—influenza A and influenza B—only influenza A has been associated with pandemics. The main components of the virus that confer immunity are the two surface antigens hemagglutinin (HA or H) and neuraminidase (NA or N). Hemagglutinin has been more thoroughly studied. We have learned that "antigenic drift" results from minor changes (<1%) in the nucleotide sequence of the hemagglutinin or neuraminidase gene and causes epidemics every 1 to 3 years, but we know that it does not cause pandemics. Thus, antigenic drift from influenza A/Beijing/94 (H3N2) to influenza A/Johannesburg/95 (H3N2), still conserves the same hemagglutinin and neuraminidase subtype. Major changes (>50%) in the nucleotide sequence of the hemagglutinin or neuraminidase genes occur at larger, undefined time intervals. These major changes result in antigenic shift, yielding a new hemagglutinin or neuraminidase subtype that has the potential to cause a pandemic. Thus, we go from influenza A/Aichi/57 (H2N2) to influenza A/Hong Kong/68 (H3N2), two subtypes that differ in the hemagglutinin antigen: H2N2 compared with H3N2.

Detection or surveillance methods have improved immensely in recent decades, in part because of an interlocking network of laboratories connected under the auspices of the World Health Organization (WHO). Central laboratories in the United States, the United Kingdom, and Australia coordinate the efforts of 110 WHO laboratories worldwide. Recently, six United States–supported laboratories in mainland China began to collect respiratory specimens in a search for new influenza strains. Lookout posts in Asia are critical because many new strains originate on that continent.

Once a new subtype is identified, it is essential to show that it has epidemic potential for geographic spread in the susceptible civilian population. Swine influenza lacked this potential in 1976. Although swine influenza (A/New Jersey/76 [H1N1]) represented an antigenic shift from the previous H3N2 strains to an H1N1 strain, caused an epidemic at Fort Dix, and epitomized a strain to which the population born after 1957 was susceptible, it did not spread beyond Fort Dix to the civilian population. In addition to having the capacity for geographic spread, a new strain must be virulent enough to cause substantial morbidity and mortality. The 1977 Russian influenza, for example, had the ability to spread geographically, but it caused no excess mortality.

What is the origin of new influenza A subtypes? From animal studies in pigs, birds, and horses, we now know that at least 15 hemagglutinins exist but that only 3 of these (H1, H2, and H3) have infected humans (6). Monitoring the animal population and humans closely associated with animals, especially in China, may give us an early warning of the next pandemic strain.

Once a new subtype is identified and its potential for geographic spread is established, preventive measures for stemming a pandemic need to be implemented. Both influenza vaccine and antiviral drugs will play a role. In recent years, the inactivated influenza vaccine has been shown to be effective in reducing the rate of respiratory illness in young adults and elderly persons, and it has repeatedly been shown to be effective in reducing the rates of pneumonia, hospitalization, and mortality in elderly persons during influenza epidemics (7, 8). Newer influenza vaccines are being tested that may enhance the immune response through the addition of adjuvants or even by replacing the current vaccines with naked DNA vaccines or a live attenuated virus vaccine (9–11), but the current inactivated influenza vaccine remains our main tool for prevention. Antiviral drugs, such as amantadine and rimantadine, are effective against influenza A strains, but the need for prolonged use while influenza is spreading can make the cost prohibitive and may foster the development of resistant strains (12). Nevertheless, these drugs may be needed for high-risk patients.

In a pandemic, the vaccine to be produced would be a monovalent vaccine containing only the new strain, as opposed to the current trivalent influenza vaccine that contains influenza A (H3N2), influenza A (H1N1), and influenza B strains. In the United States, annual vaccine production currently yields approximately 70 million doses of trivalent vaccine. This could be converted to more than 200 million doses of monovalent vaccine. We do, therefore, have the productive capacity to make almost one

dose of vaccine for each citizen of the United States.

Lurking in the background, however, are several major problems.

First, it normally takes as long as 6 months to produce, package, and distribute the vaccine each year, and it takes 1 to 2 additional months to administer it. The first wave of a virulent pandemic strain will almost certainly start spreading widely in less than 6 months. The first challenge, then, is to shorten the production–distribution cycle.

Second, the current vaccine is produced in embryonated chicken eggs. Unfortunately, the egg supply is not stable throughout the year. If the new influenza strain is discovered when the egg supply is low, vaccine production will be delayed. A new growth medium, such as tissue culture or the use of recombinant DNA technology, could replace eggs and would both speed vaccine production and be available at any time.

Third, most vaccine is now administered by private physicians. During the 1976 swine influenza vaccine campaign, vaccine was also administered by local, state, and federal governments, helped by government purchase. For the next pandemic, a national plan combining both the private and public sectors will be most appropriate.

Fourth, will one dose of vaccine be sufficient? During the swine influenza vaccine trials, single doses of different concentrations proved to be either too reactogenic or not adequately immunogenic (13). A need for two doses injected 1 month apart would increase the demand for production and make it almost impossible to vaccinate the entire population of the United States. Under these circumstances, it would be necessary to administer vaccine selectively according to a priority list; for example, preference could be given to high-risk groups and persons responsible for keeping public services functioning.

Fifth, other nations may depend on the United States for vaccine; U.S. companies currently manufacture vaccine for several other countries. In the interest of world health, the United States cannot plan to produce vaccine only for its own population.

Sixth, any mass immunization campaign has the potential to be associated with adverse events, such as the Guillain-Barré syndrome (14). Relief from legal liability will need to be supplied by the government to alleviate such concerns.

The next pandemic cannot be the sole focus of a pandemic plan. In the past 50 years, more persons have died in the aggregate during regularly recurring influenza epidemics than during the few pandemics that have occurred. In the United States, at least 10 000 to 22 000 persons die annually when influenza is epidemic (15). Therefore, we physicians need to sensitize ourselves and our patients to the importance of immunizing now to prevent influenza rather than waiting for a pandemic strain to appear. Hence, we need to implement an interpandemic plan well before the next pandemic. In addition, appropriate risk groups should be immunized now with pneumococcal vaccine to eliminate one of the common causes of secondary bacterial pneumonia after infection with influenza virus (16).

During the interpandemic period, research efforts should focus on the following:

1) Developing vaccines with enhanced immunogenicity.

2) Improving methods for rapid vaccine production and administration.

3) Searching for a "common epitope" that would provide broad "generic" protection against a wide range of type A variant strains.

4) Developing a library of animal hemagglutinin subtypes 4 to 15 that could be grown rapidly for vaccine production (so-called high-yield reassortants).

5) Improving methods for reaching the poorly immunized segments of our population.

6) Adding more surveillance sites for the detection of new strains and the identification of virulence factors and additional susceptibility determinants.

To succeed in all this, cooperation between the private sector and government agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, the National Institutes of Health, and the state and territorial health departments, will be necessary. Success will also require the creation of a national infrastructure for surveillance and control of influenza. International coordination through the WHO will assure global cooperation for what is assuredly a global problem. Such cooperation is already under way in the drafting of pandemic and interpandemic plans and in the global alert program for identifying new influenza strains (Cox NJ, Patriarca PA. Personal communication). Options for worst and best case scenarios need to be considered (17). Careful planning and dissemination of information during the interpandemic periods will prove cost-effective and will minimize the likelihood of inefficient crisis management when the pandemic appears (18).

We currently have the knowledge—clinical, epidemiologic, and technologic—to prevent the worst ravages of this everyday invader. All that is required now is the social engineering—administrative, political, and financial—to translate this knowledge into practice.

Peter A. Gross, MD
Hackensack University Medical Center
Hackensack, NJ 07601-1991

Requests for Reprints: Peter A. Gross, MD, Department of Internal Medicine, Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, NJ 07601-1991.

Ann Intern Med. 1996;124:682-685.

References

1. **Farr W.** Cholera epidemic 1848-49. In: Humphreys NA, ed. Vital Statistics: A Memorial Volume of Selections from the Reports and Writings of William Farr. London: The Sanitary Institute of Great Britain; 1885:333-4.
2. **Lederberg J, Shope RE, Oaks SC Jr, eds.** Emerging Infections: Microbial Threats to Health in the United States. Washington, DC: National Academy Pr; 1992.
3. **National Center for Infectious Diseases.** Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States. Atlanta: Centers for Disease Control and Prevention; 1994.
4. **Kilbourne ED.** History of influenza. In: Influenza. New York: Plenum; 1987: 3-22.
5. Experts warn of possibility of outbreaks of new strains of flu. New York Times. 17 Dec 1995:29.
6. **Webster RG, Schafer JR, Süss J, Bean WJ Jr, Kawaoka Y.** Evolution and ecology of influenza viruses. In: Hannoun C, Kendal AP, Klenk HD, Ruben FL, eds. Options for the Control of Influenza II: Proceedings of the International Conference on Options for the Control of Influenza, Courchevel, 27 September–2 October, 1992. New York: Excerpta Medica; 1993:177-85.
7. **Nichol KL, Lind A, Margolis KL, Murdoch M, McFadden R, Hauge M, et al.** The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med. 1995;333:889-93.
8. **Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA.** The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med. 1995;123:518-27.
9. **Donnelly JJ, Ulmer JB, Liu MA.** Immunization with DNA. J Immunol Methods. 1994;176:145-52.
10. **Lin R, Tarr PE, Jones T.** Present status of the use of cytokines as adjuvants with vaccines to protect against infectious diseases. Clin Infect Dis. 1995;21: 1439-49.
11. **Maassab HF, Shaw MW, Heilman CA.** Live influenza virus vaccine. In: Plotkin SA, Mortimer EA Jr, eds. Vaccines. 2d ed. Philadelphia: WB Saunders; 1994:781-801.
12. **Hayden FG, Couch RB.** Clinical and epidemiological importance of influenza A viruses resistant to amantadine and rimantadine. Reviews in Medical Virology. 1992;2:89-96.
13. **Gross PA.** Reactogenicity and immunogenicity of bivalent influenza vaccine in one- and two-dose trials in children: a summary. J Infect Dis. 1977; 136(Suppl):S616-25.
14. **Hurwitz ES, Schonberger LB, Nelson DB, Holman RC.** Guillain-Barré syndrome and the 1978-1979 influenza vaccine. N Engl J Med. 1981;304: 1557-61.
15. **Glezen WP.** Emerging infections: pandemic influenza. Epidemiol Rev. 1996; [In press].
16. **Fedson D.** Immunizations for health-care workers and patients in hospitals. In: Wenzel RP, ed. Prevention and Control of Nosocomial Infections. 2d ed. Baltimore: Williams & Wilkins; 1993:214-94.
17. **Dowdle WR.** Past, present, and future of influenza control: opening remarks. In: Hannoun C, Kendal AP, Klenk HD, Ruber FL, eds. Options for the Control of Influenza II: Proceedings of the International Conference on Options for the Control of Influenza, Courchevel, 27 September–2 October, 1992. New York: Excerpta Medica; 1993:3-8.
18. **Sechrest L, Backer TE, Rogers EM.** Synthesis of ideas for effective dissemination. In: Sechrest L, Backer TE, Rogers EM, Campbell TF, Grady ML, eds. Effective Dissemination of Clinical and Health Information: Conference Summary. AHCPR Pub. No. 95-0015. Rockville, MD: Agency for Health Care Policy and Research; 1994:187-196.