Current perspectives of influenza

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Physicians frequently use the term "the flu" to explain various symptoms of their office patients, but too often this diagnosis is a catchall term meaning "I don't know what's wrong with you." The disease caused by the influenza virus is not a gastrointestinal syndrome characterized by nausea, vomiting, and diarrhea; it is not the "common cold" characterized by coryza and headache; and it is not generalized aches and pains; nor does it occur in the summer, except rarely and under unusual circumstances.

Influenza is an acute infectious disease caused by an RNA containing myxovirus. This disease begins abruptly with fever, frequently recurring short chills, headache, malaise, retroorbital eye pain especially on eye motion, hacking, irritating, nonproductive cough, and severe myalgias. The paucity of respiratory symptoms relative to the intensity of the systemic symptoms is impressive. As is true with many infectious diseases, influenza may have a wide spectrum of manifestations ranging from inapparent infection (up to 25% of cases) to rapidly overwhelming pneumonia causing death in hours to days. In general, the disease tends to be mild; however, the impact of influenza on the community may be substantial. It is estimated that the 1968 Hong Kong influenza epidemic cost the US economy 3.5 to 5.0 billion dollars. In addition, 30,000 more deaths than the

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number expected for the same time period ("excess mortality") were attributed to the Hong Kong flu virus. Since that time, except for one epidemiologic season, there have been annual outbreaks of influenza resulting in 2,000 to 3,000 deaths, and the loss of millions of dollars. The continued prevalence of this virus, even though vaccines have been available for nearly 35 years, involves two main areas: the inherent mutability of the virus resulting in changes in the antigenic structure of the two surface proteins (hemagglutinin and neuraminidase) and difficulties in producing and distributing enough vaccine once the changes in the virus have been recognized. This paper will review some of the history of influenza vaccines, describe recent developments, and suggest an approach to controlling this disease.

Influenza vaccine was developed shortly after the discovery of the virus.[1] Early vaccines were crude formalinized fluids harvested from the infected allantoic cavity of developing chicken embryos.[2] It was recognized early that there were a number of adverse reactions from these vaccines which also did not contain enough virus to stimulate antibody levels adequate for protection. Therefore, attempts were made to concentrate infected allantoic fluids in the hope of increasing the potency of the vaccine. These concentrated, inactivated, and allegedly purified vaccines were more effective in stimulating antibody,[3] but they also caused an increased number of adverse reactions.[4] Consequently, it was recommended that the dosage of vaccine be limited, mainly to decrease the severity of adverse reactions. We now know that these reactions were mainly due to nonviral impurities in the vaccines. The ability of the older, low potency vaccines to prevent disease remained largely untested, except in closed military populations where variable results were obtained.

In the late 1940s and early 1950s unpredictable results with injected killed vaccines prompted Russian investigators to attempt to prevent influenza by spraying inactivated virus intranasally. This technique proved to be unreliable and led to the development of live, but attenuated vaccines. This approach is currently being used in the USSR again with variable results. In the United States several groups are also investigating live attenuated vaccines, but production yields are quite low and it is difficult to predict when a vaccine virus strain is attenuated enough for use in man. The first large scale trials with these vaccines have been set up for the 1974–1975 season. Even if this technique proves successful, production problems will limit the usefulness of this approach for the near future.

The most promising approach to the control of influenza has been the application of continuous flow zonal ultracentrifugation to the vaccine production process.[5] This has resulted in an inactivated vaccine which is far superior to the older vaccines in terms of purity (freedom from nonviral protein) and does not cause significant reactions at a standard dose.[6] These newer "purified" vaccines stimulated antibody as well as the older vaccines,[7] thus negating the theory that local reactions to vaccine are necessary for their adjuvant effect. However, at standard levels of dosage this degree of antibody stimulation is clearly suboptimal, since the effectiveness of vaccine

for prevention of disease remained quite low ($< 50\%$). Therefore, experiments in animals were performed to assess the effects of increasing the dosage of the newer purified vaccines. These results are quite clear. Removal of nonviral impurities permits the use of very large doses of influenza vaccine without causing severe reactions (death) in mice. Furthermore, the higher the dose given, the higher the level of antibody stimulated, and the greater the protection upon challenge with wild virus.[8] Following these results, similar studies were performed in human volunteers with the dosage of vaccine ranging from the previous "maximum" (300 CCA units) to 16 times that dose in adults and 20 times that permitted in children of school age. The paucity of severe reactions was impressive. Although the number of both local and systemic reactions in the children was nearly twice that of adults, there was no increase in school absenteeism even at the highest dosage levels, attesting to the mildness of the reactions.[9] However, a safe vaccine is of little benefit unless it can provide protection. In recent years, standard doses of potent inactivated influenza vaccines have provided some protection during epidemics caused by influenza viruses closely related to the vaccine strains.[10-13] As has been recently emphasized, protection is related to the level of both circulating serum and nasal secretory antibody, and we now know that these levels are dependent on the dose of vaccine.[14] Increasing the dose of vaccine not only increases the level of antibody, but clearly decreases the attack rate of clinical influenza.[15] A summary of the vaccine trials demonstrating the relationship of protection to dose of vaccine is presented in the *Table*. Also of interest and possibly of greater importance, the influenza vaccines, especially at higher dosage levels, modified the disease in those whom it failed to protect completely. When compared in a double-blind manner to a control group, those receiving appropriate vaccine had fewer fevers, lower temperatures, less confinement to bed, and fewer visits to physicians.[10] These data have resulted in liberalizing the dosage of influenza vaccine to a maximum of 700 CCA units of the type A virus. At this level, better protection can be expected than was previously possible and, in addition, milder disease can be expected in those recipients who do not derive complete protection from infection. Even greater protection would be afforded by further increases in dosage, but the increased cost will probably be a deterrent to recommending such changes in the near future.

Two other areas should be considered in the approach to preventing and ameliorating this disease. The first of these would be to support natural host defenses. It is known that the mucus of both the upper and lower respiratory tract contains both specific antibody which is present after natural infection from or immunization against influenza virus[16, 17] and nonspecific substances, mainly mucoproteins, which are capable of neutralizing influenza virus.[17] During the winter, home and office heating reduces ambient humidity to levels simulating desert conditions, and the protective mucus barriers may be broken. Cigarette smoking probably compounds this problem. Although specific, controlled studies have not been done, it would seem prudent to hu-

midify home and office air and to discourage smoking for high risk patients who might contract influenza.

The second area which merits consideration is the use of antiviral compounds. At present the only antiviral drug available by prescription for the chemoprophylaxis of influenza is amantadine hydrochloride. This compound had been used successfully for both the prevention and modification of infection caused by type A influenza viruses,[18-21] but it is ineffective against type B influenza. The efficacy of this drug for the prevention of influenza is variable and seems to be similar to that achieved with the lower doses of influenza vaccine (50% to 60%). The reduction in signs and symptoms (mainly fever) by the administration of amantadine once infection has been established is real, although not dramatic. To be effective in preventing infection, amantadine must be given prior to and for the duration of exposure to type A influenza virus. This means that frequently it must be administered for several weeks. Although the cost is not unreasonable (approximately $8 a month) the drug has a rather low toxic/therapeutic ratio. In other words, adverse reactions are seen at dosage levels (blood levels) very near or at the level required for therapeutic effectiveness. The adverse reactions mainly affect the central nervous system and most are amphetamine-like responses. However, more serious reactions including hallucination, severe anxiety, blurred vision, slurred speech, and withdrawal symptoms have occurred. In the elderly, convulsions have been reported when the recommended doses of 100 mg twice a day are exceeded.

When should amantadine be used? One must be selective, knowing that adverse reactions may be associated with its use, but I feel that it should be given to those patients who are at greatest risk of death from influenza, especially those persons who are not or cannot be vaccinated for a variety of reasons. In addition, amantadine might be useful if a virus mutation would render "current" vaccines ineffective. Newer, hopefully less toxic, anti-influenza drugs are being developed, but currently, and for the near future, amantadine is the only drug available.

The safest, most reliable method of preventing or modifying influenza in chronically ill persons at risk of death is immunization with influenza vaccine in the late autumn. In the United States, the number of persons who should receive influenza vaccine is estimated to be between 40 and 50 million. Only 10% actually are immunized. The remainder of the 20 million doses produced each year are given to healthy young adults. If enough vaccine were available, vaccination of most healthy adults and children theoretically might prevent the spread of an epidemic. However, this theory has never been tested and the supply of vaccine is limited. Therefore, the use of vaccine should be strictly limited to those at greatest risk of death.

A major reason that a sufficient number of doses of vaccine of adequate potency are not produced is an economic one. The inherent mutability of the influenza virus results in a vaccine which is always slightly "out of date," because the antigenic structure of the wild virus is constantly changing, whereas the vaccine virus is static and unchanging. Occasionally the antigenic change in the wild virus

is of such magnitude that existing influenza vaccines become instantly obsolete, and the vaccine producers have large stocks of worthless vaccine which cannot be marketed. Consequently, each year they produce only a relatively small amount of vaccine as a hedge against the risk of losses secondary to a major change in the virus. In addition, new strains of influenza grow poorly in eggs. Therefore, when a mutation in the virus requires a new vaccine, an individual egg produces fewer doses causing lower profit margins and decreased incentive to produce vaccine. This decreased incentive results in underpromotion of the product which results in fewer sales, and a cycle is established which results in underutilization of vaccine, especially in the groups at greatest risk of death should they develop influenza.

The solution to the problem is as complex as the factors causing it. Ideally, production of influenza vaccine should be undertaken by the Public Health Service either directly or indirectly by financial support. A vaccine would at least be available. Increased education of primary physicians as to whom to vaccinate and when to vaccinate could also be included. The Public Health Service could also underwrite the development of high yielding viruses for vaccine production—the methodology already exists.[22, 23] This would result in fewer eggs required to produce vaccine, and in lower production costs while increasing the total volume of vaccine. Although this is a theoretical prediction, the availability of reasonably priced vaccine should result in increased promotion leading to increased numbers of patients being immunized. The end result could be a decreased number of overt cases and decreased morbidity and mortality from influenza—something never achieved in the United States to date.

Unfortunately today's physician has today's vaccine which is in very limited supply. The physician should use the vaccine wisely. In other words, do not advise that healthy children and adults receive influenza vaccine. All chronically ill patients with respiratory, cardiovascular, renal, and endocrinologic diseases should be selectively vaccinated. From the data in the *Table,* one could argue for a double or triple dose of vaccine, since reactions will be

Table. Modification of febrile respiratory disease by influenza vaccine, 1968–1969*

	Reduction of attack rate by low and high doses of Hong Kong vaccine					
	Middle aged prisoners			Elderly retirement community		
	300 CCA units	3000 CCA units	Controls	300 CCA units	3000 CCA units	Controls
Clinical influenza	18%	62%	0	23%	54%	0
Fever	33%	74%	0	33%	56%	0
Confinement to bed	63%	91%	0	42%	58%	0
Visit to physician	60%	77%	0	11%	50%	0

* Adapted from Mostow et al.[15]

minimal and protection would be significantly greater. However, the limited supply of vaccine precludes such a recommendation and, therefore, it is advised that the dosage recommended by the Public Health Service Advisory Committee on Immunization Practices be given. This is a single 0.5 ml dose given either subcutaneously or intramuscularly, depending on which brand of vaccine is used. The package insert gives directions on the proper route of administration.

In conclusion, influenza vaccine is now safe, and reactions commonly seen with older vaccines have been virtually eliminated with the newer purification processes. Influenza vaccines are effective both in preventing and in modifying disease in those persons it fails to protect completely, but this is clearly dose related. Finally, the current shortage of vaccine and the constraints on permitting larger doses are secondary to a lack of profitability for the vaccine producers. Therefore, influenza vaccine production should be underwritten by the Public Health Service. Only then, will an adequate amount of vaccine be available, so that the physician can achieve his goal—the reduction of morbidity and mortality from influenza.

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