The Ultimate Flu Vaccine

A noted immunologist suggests we stop playing year-in, year-out virus roulette and develop a vaccine for all types of influenza

by Jonas Salk

THE controversial program to inoculate Americans against swine influenza is about the best we can do for the moment. The future, however, is quite another story.

As I see it, the rationale for the current program is based on one hard fact and one soft speculation.

The hard fact is that a wide "immunity gap" exists in our population between younger people and those fifty and over. The gap comes about in this way: the influenza virus, like other viruses, carries as part of its protein coating certain antigens that stimulate our immune systems to produce specific antibodies against it; because the swine type of influenza virus has not been in circulation for more than fifty years, people under fifty—and some above fifty as well—lack these protective antibodies and thus would be susceptible if such a virus were to become active again.

The soft speculation—the cause of so much debate—is whether or not the limited outbreak at Fort Dix in January, 1976, might presage a return of the virus to full activity and a pandemic of the 1918–19 variety. Whether it will, in fact, return—and, if so, with what degree of virulence—simply cannot be known with certainty by anyone.

What *can* be known, however, is our state of susceptibility—which is another way of expressing the immunity gap—to this virus. It is a virus that has, after all, given evidence of previous activity (and lethal activity, at that), and it has recently caused an outbreak of the disease—an isolated outbreak, to be sure, but this is often the case when an influenza virus is about to become active. Being thus forewarned, and having no means to assess accurately the true danger, we can at least ask, can we do anything to protect ourselves? If so, is it worth doing? I share the view that we can and should take the protective measures we are now taking—filling the population immunity gap by widespread immunization, using a vaccine containing the swine strain of virus to which there is almost universal susceptibility; and since this is a killed-virus vaccine, it poses no danger of inadvertently causing the disease itself.

Some believe we should wait until there is more evidence of a real epidemic hazard. Others dislike injections; but this concern can be ameliorated by the jet gun now used in mass programs. Still others are opposed on principle to the idea of introducing anything "foreign" into the body or of using procedures that somehow "interfere with nature." In fact, current procedures employ perfectly natural materials that might normally invade the body in their live state and cause the very disease we are attempting to prevent.

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Youngsters, wearing bags of camphor, wait out th

As a participant in the development of flu vaccines, I am completely convinced by available data that vaccination can provide substantial protection. It protects not only individuals but entire groups. In fact, when a high proportion of a given population has been vaccinated, protection is often provided for the unvaccinated, as well as for those who may not have developed as strong an antibody response as others.

Contrary data can also be presented, of course; but we know the reasons for the failures, as well as for the successes. The failures stem from (1) differences in antigenic composition between the strain of virus contained in the vaccine and the epidemic strain—in other words, vaccination against the wrong virus; (2) vaccines of insufficient potency; and (3) insufficiently widespread use of vaccine. Since we can control these factors, such failures do not negate the validity and value of the principle. They simply tell us we must do a better job.

We have thus come to realize that for consistent success from year to year we need a vaccine that will be effective against *all strains* of virus that can cause the disease—not merely against one or another *prevailing strain*. This latter has been our strategy until now. The vaccine, moreover, will have to be employed on a wide scale to prevent epidemics from arising rather than on a limited scale in those groups likely to suffer high mortality if an outbreak were to occur—and who would, in fact, be better protected if the entire population participated in the vaccination program, which would prevent the outbreak at the outset.

When virtually all the people susceptible to a particular influenza virus have been infected and have thus become immune, that strain of virus seems to go "underground" for a time, or it changes its antigenic coat and thus bypasses

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918 pandemic—"The presumed cause was Type A-swine."

the immunity induced by its most recent form. The capacity of the influenza virus to change in this way is the reason why efforts to corner it have been thwarted, whereas unchanging viruses, such as those causing smallpox (one antigenic type) and poliomyelitis (three antigenic types), have been brought under control.

Two conditions contributed to success with smallpox and polio. First, only a small number of virus types, which were antigenically constant, were involved. Second, vaccination was employed on a scale wide enough to interrupt the chain of virus transmission in the population. These conditions led eventually to the eradication of the viruses, since they no longer had a fertile soil in which to become established.

In my view it is theoretically and practically possible to control influenza in any country where the concept of prevention is accepted and practiced effectively. The development of an all-encompassing vaccine against all influenza viruses known to have caused the disease in the past is complicated by the existence of five major families of Type A virus and one of Type B, with variants of each. Nevertheless, we have the basic knowledge for such an achievement—and evidence from prior experimentation that it would work.

The prospect for success lies in our knowledge that immunity to any given strain of influenza virus is associated with a certain level of antibody in the bloodstream. Such levels can be achieved consistently and maintained by use of a vaccine whose immunizing potential is stimulated by use of an immunologic adjuvant—that is, a substance that enhances the effectiveness of an immunizing agent. Such adjuvants (one of those studied is made with mineral oil and an emulsifying agent, another with peanut oil) allow much smaller amounts of the immunizing substance (a killed virus or purified virus protein) to be used than would normally be employed. In the case of the influenza viruses, this use of adjuvants would permit *all* the known major families of types A and B viruses and their variants to be included in a *single* vaccine. The reduced amount of each virus made possible by the adjuvant would also reduce undesirable reactions that might occur if we attempted to combine sufficient quantities of six or more viruses in a single vaccine without the use of a potent adjuvant.

Without an adjuvant, moreover, the levels of antibody induced would not be as high as desirable. A potent adjuvant not only allows a reduction in the amount of virus required to make such a vaccine but also induces levels of antibody high enough to be effective. It also increases the potency of the purified immunizing protein of the virus, in isolation from some of the constituents that may produce undesirable side effects, and from the nucleic acid (the genetic components) of the virus or of the cell in which it is grown. Thus, such a vaccine can be made either of killed virus or of the essential purified viral protein separated from the whole virus, neither of which substances would carry any risk of causing the disease.

What is now needed is a mini–Manhattan Project for a study of the optional adjuvant for this purpose and the optimal quantities of the different influenza-virus antigens. Since the known viruses tend to recycle (the antigens on the Type A-Asian virus, which appeared in 1957, were present on the virus that caused the 1889–90 pandemic; similarly, the Type A-Hong Kong of 1968 appears to have been active in 1900, and the present Type A-swine appears to have been the cause of the 1918–19 pandemic), we would at least be protected against the viruses that have tended to recur in the past and might recur in the future. Any "new" viruses (that is, those that have not yet been observed since influenza viruses were discovered, in 1931, and tracked) would be added to the vaccine as they appear.

THE fundamental assumptions in this approach are that (1) the number of influenza-virus families and variants is finite, (2) a vaccine can be produced that would eventually include all of them, and (3) such a vaccine could be administered to people widely and routinely at an appropriate age. Just as other infectious agents have been successfully dealt with, so, too, by this means, influenza immunity would be maintained and the virus prevented from becoming epidemic.

Influenza vaccine has been used successfully for thirty-three years, but we have never really taken advantage of it as an instrument of preventive medicine. Unless we make control of influenza a national goal, this disease will linger as a chronic threat. It will be the cause of endless debate whenever it is proposed that some effort be made to take another turn on the year-in, year-out flu-virus roulette wheel, as we guess what strain will come up next and whether we can act in such an emergency.

If we focus our attention on the immunity gap and not on the whereabouts of the swine antigen, we will find there is sufficient justification for both the present program as an immediate protective measure and for initiating a mini–Manhattan Project to bring influenza under final control. Every now and then there is a need for decisive action. The cost of such a research and development effort would be inconsequential compared to the gains achieved by reducing mortality, morbidity, and the cost of medical and hospital care. ◉

Vladimir Nabokov
an interview by George Feifer

Wherein a literary genius gives two hours of carefully structured time to an inquiring young novelist

SOMETIMES a journalist should lay his cards on the table at the outset. Few of Vladimir Nabokov's books have moved me as much as the best critics said they should. I have been dazzled by his peerless imagery and language—and his versatility: he has written superbly about everything from the pattern of bathroom tiles to the sensations of wine on a jaded tongue. But his virtuosity often seemed an end in itself and therefore empty, even nihilistic. Behind Pasternak's lyricism, for example, I felt the presence of a great man of powerful passions, whereas Nabokov's exquisite prose might have been produced by some twenty-one-jeweled prose machine. What was he writing *about*? Certain butterflies, I'm told, get themselves up to resemble others for protection. And Russia has a distinguished line of immensely talented, imitative poets whose excellence is in their craft rather than in substance. They describe their private images and visions with ephemerally uplifting brilliance.

But not this, not even my lack of ardor for butterflies, was the principal cause of my nervousness before visiting Nabokov in Montreux. (One relative described him to me as a lepidopterist with a hobby . . . of writing!) I feared that my inadequate enthusiasm for his fiction was my failure rather than his. Some of my best and least pretentious friends have for years professed their love for him, the greatest living novelist writing in English. One has written a doctoral thesis analyzing the very substantive genius I missed. Readers like me, he demonstrated, were either blinded by Nabokov's surface splendor—as the witty author intended—or too unperceptive to sense the deep meanings there.

More to the point, and worse, I hadn't read his complete *oeuvre*. On his own scale for rating reviewers, a delightfully abashing invention that would come in answer to one of my questions, I ranked no higher than a "B." And I had seen him on television, his abrasive *hauteur* cutting through even erudite interviewers like scouring powder through grease in a thirty-second commercial. I had read his comments about great writers—Balzac, Stendhal, Pound, Mann, Dostoevski, Sartre, Lawrence, Camus—whom he not merely disapproved of but contemptuously dismissed as "detestable mediocrities" and "total fakes."

The crowning dreadmaker was his attitude toward the forthcoming interview itself, which required I submit written questions and reproduce his answers verbatim. His own defense of these conditions, based on a desire to transpose his oral "hemmings and hawings" into the prose he is capable of, is the best I'd seen. ("Even the dream I describe to my wife across the breakfast table is only a first draft.") But although it softened some of the humiliation, his conception of an ideal interview—eliminating every element of spontaneity and all semblance of actual talk to achieve a neatly paragraphed essay—was opposite to mine. I was to have no insight through random associations, no opportunity to play my thoughts against his to see when he would reach for the lob or try his dropshot. I was going into literary Wimbledon with the moves preplanned, like some parlor version of tennis for rainy days.

Horst Tappe/NYT Pictures

Nabokov and Véra, at Montreux—"Conversation in half-sentences and gestures."

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