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Report to Rep. Henry A. Waxman; by Elmer B. Staats, Comptroller General.

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Contact. Human Resources Div.
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Organization Concerned: Department of Health, Education, and Welfare.
Congressional Relevance: Rep. Henry A. Waxman.
Authority: Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). Public Health Service Act, as amended (42 U.S.C. 262). P.L. 94-380. 21 C.F.R. 601.25.

The swine flu vaccine program was predicated on the conclusion by Department of Health, Education, and Welfare (HEW) officials that the vaccine would protect between 70% and 90% of those vaccinated against swine flu outbreak.
Findings/Conclusions: This conclusion was based on a HEW review of antibody response data gathered during the 1976 swine flu vaccine trials and observations of the effectiveness of previous flu vaccines. Since scientists agree that experimental investigations involving deliberate exposure to a new virus strain, such as swine virus, are very difficult to perform and could pose a potentially serious health hazard in the United States, this method was not used to determine the effectiveness of the swine flu vaccine. The swine flu vaccine's effectiveness was estimated through clinical trials that measured the participants' antibody level before and after receiving the vaccine. HEW officials and other flu experts noted that information on possible long-term effects of flu vaccination is needed, but it would be difficult to plan and it would probably not be feasible because no one knows what to look for. As part of the swine flu immunization program, the Center for Disease Control had responsibility for conducting short-term surveillance on vaccine recipients. In addition, the Center is supporting two studies on women who recieved the vaccine to identify unfavorable pregnancy outcomes. (SC)

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

JUN 27 1977

B-164031(2)

The Honorable Henry A. Waxman
House of Representatives

Dear Mr. Waxman:

This is in response to your letters of February 24 and March 3, 1977, requesting information concerning vaccines. In a subsequent discussion with your office it was agreed that our response would address only swine influenza vaccine. We did not request formal comments from the Food and Drug Administration although the report's contents have been discussed with officials of the agency.

To respond to the issues raised in your letters, we obtained information from the Department of Health, Education, and Welfare's (HEW's) Food and Drug Administration, the National Institute for Allergy and Infectious Diseases of the National Institutes of Health, and the Center for Disease Control. We also talked to members of HEW's Advisory Committee on Immunization Practices, Food and Drug's Advisory Review Panel on Viral and Rickettsial Vaccines, researchers at the Mount Sinai School of Medicine, New York City, and others involved in flu vaccine research.

INTRODUCTION

Flu is an infectious disease, which affects the respiratory system, lasting from a few days to 2 weeks. There are two primary types of flu--types A and B--each of which has a number of strains. Strains are the different flu organisms which have been isolated and identified as causing flu infection. Flu virus vaccines are biological products designed to combat the particular strain or strains causing the disease.

The first license for the manufacture and use of flu virus vaccine was issued in 1945. As of December 31, 1976, six establishments were licensed to manufacture the vaccines and four were actually engaged in producing them. Flu vaccine manufacturers use different processes to produce an inactivated or killed virus product. The most striking difference between processes is that two manufacturers produce a "whole" virus vaccine while the other two produce a "split" virus vaccine. In the latter process the virus is split into subunits by a chemical treatment. Recent trials support the

supposition that whole virus vaccine promotes better antibody responses in younger age groups, but that adverse reactions are more frequent and severe than with split virus vaccine.

Flu infection presents a unique problem to practitioners of preventive medicine. Flu viruses usually undergo minor but continuous changes from year to year. With each change, the human body's ability to neutralize the infection and the value of previously prepared vaccine is lessened. This change is significant because the protective value of the vaccine is probably related to its similarity with the invading flu virus. Occasionally, perhaps every 10 to 15 years, the type A virus changes significantly, rendering the existing vaccine, as well as the body's defense mechanisms, virtually worthless. Flu differs from polio, smallpox, measles, and other viral diseases, because the infecting virus for these diseases does not change.

There are two principal theories on how flu viruses with epidemic potential occur. One theory claims that flu viruses undergo cyclical changes, and that a virus which caused disease in the past might reappear in 60 or 70 years. In fact, the 1918 flu pandemic is believed to have been caused by a swine flu virus.

The second theory postulates that major antigenic 1/ changes may result from a genetic recombining of a human virus with one of the many flu strains whose natural hosts are animals or birds. Following its appearance, the "new" virus replaces the "old" virus, which disappears completely. Still, much uncertainty exists regarding the origin and pattern of flu pandemics.

HEW ESTIMATE OF EFFECTIVENESS OF SWINE FLU VACCINE

HEW officials concluded that swine flu vaccine would protect between 70 and 90 percent of those vaccinated against a swine flu outbreak. They based this conclusion on their review of antibody response data gathered during the 1976 swine flu vaccine trials and observations of the effectiveness of previous flu vaccines.

1/Substances found on the surface of flu viruses which are believed to dictate human susceptibility to the virus. They also stimulate the production of antibodies.

HEW officials said that scientists agreed that experimental investigations involving deliberate exposure to a new virus strain, such as swine virus are very difficult to perform and could pose a potentially serious health hazard in the United States. Thus, this method was not used to determine the effectiveness of swine flu vaccine. According to an HEW official, the effectiveness of a vaccine can best be determined if vaccinates are exposed through natural epidemics and the result is compared to a control group whose members were also exposed but did not receive the vaccine. He further added that this method was not used because a swine flu epidemic did not occur.

The swine flu vaccine's effectiveness was estimated through clinical trials that measured the participants' antibody level before and after receiving the vaccine. The trials did not demonstrate how well antibody levels protect against a flu attack, but did measure what levels of antibody vaccine recipients should expect to attain. According to HEW officials, over the past decade or so there has been a general scientific consensus that antibody studies and not deliberate exposure experiments would be sufficient as the indicator of vaccine effectiveness. These officials said that flu experts generally agree that an antibody level of 40 or more is indicative of protection.

HEW officials observed that over the last 25 years, type A flu vaccines have provided between 67- and 90-percent protection. This range was based on vaccine trials conducted by the Department of Defense and was summarized in the following table presented March 21, 1977, at the Conference on Influenza Vaccine Activity for 1977-78.

Effectiveness of Flu Virus Vaccines, 1943 to 1969

Year	Type	Protection rate (percent)
1943	A	72
1947	A1	a/9
1950	A1	68
1951	A1	75
1953	A1	88
1957	A1	82
1957	A2	67
1958	A2	86
1960	A2	90
1968	b/A2	96
1969	b/A2	73

a/A Food and Drug official advised us that the low protection rate for 1947 was due to the fact that a major change in the virus occurred and the wrong vaccine was used.

b/Hong Kong flu.

The Food and Drug Administration also referred us to a report on an outbreak of type A flu which occurred in a Dade County, Florida, nursing home during January 1977, which showed a vaccine effectiveness rate of 83 percent.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) requires that a new drug be approved by the Secretary of HEW for safety and effectiveness before it can be introduced into interstate commerce. The Secretary has delegated this authority to the Food and Drug Administration. The Public Health Service Act, as amended (42 U.S.C. 262), requires that biological drugs must be shipped interstate from a licensed establishment to insure they are safe, pure, and potent as well as safe and effective under the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration administers the Food, Drug, and Cosmetic Act and the drug provisions of the Public Health Service Act.

The Code of Federal Regulations (21 CFR 601.25) set up review procedures for determining the effectiveness of flu vaccine and other biological products licensed before July 1, 1972. The Code states that

> "Proof of effectiveness shall consist of controlled clinical investigations * * *. [This requirement can be] waived on the basis of a showing that * * * an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies, and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists * * *." (Underscoring added.)

Food and Drug's Advisory Review Panel on Viral and Rickettsial Vaccines reviewed the safety, effectiveness, and labeling of flu and other vaccines. The Panel's January 1977 draft report concluded that "Influenza vaccine is relatively (70-80 percent) effective against disease caused by the homologous [vaccine properly matching the infecting virus strain] virus * * *." The Panel added that duration of the protection is limited by continuous changes in the virus.

In its review of data from the four current flu vaccine manufacturers, the Panel concluded that each product was safe and effective. However, it noted that while there is substantial evidence for the safety and effectiveness of whole virus vaccines produced by two manufacturers, "Further efficacy trials must be designed and implemented by the * * * [two manufacturers of split product vaccine]." The draft report adds that the protective efficacy of split flu virus vaccines "is not clearly demonstrated" although evidence "favors the view that protection of vaccines is correlated [to the antibody levels produced] * * * without regard to [whether a vaccine is the split or whole type]."

The Panel also noted that because of the frequent changes in flu vaccines, evidence of effectiveness is difficult or impossible to obtain before the vaccine must be released for use. The Panel further said:

> "Changes in component virus strains [such as was needed to produce swine flu vaccine], dictated by * * * [FDA], do not require efficacy tests for protective effect of each vaccine in human subjects. * * *"

EVALUATION OF LONG-RANGE EFFECTS OF FLU VACCINE

HEW officials and other flu experts noted that information on possible long-term effects of flu vaccination is needed, but it would be difficult to plan and it would probably not be feasible because no one knows what to look for. They pointed out that serious long-term effects of flu vaccines "would certainly have become manifest by this time." It was felt that this was a reasonable conclusion because of the many years of experience with flu vaccines and the millions of persons who have been vaccinated without detection of serious complications.

HEW officials informed us that "Influenza vaccines have been in general use for more than 20 years, and their safety and effectiveness have been studied throughout this period." They were only aware of one study which examined mortality associated with adjuvant 1/ flu vaccine. This Department of Defense-sponsored study was published in 1972 and examined mortality among Army recruits who received adjuvant flu vaccine from 1951 through 1953. The study found no evidence that the risk of death was enhanced among recipients of adjuvant flu vaccine. Also, its findings were essentially negative with respect to malignant growths and allergic diseases. The principal researcher involved said that the study was specifically designed to determine the effects of the adjuvant vaccine and not the effects of standard flu vaccine. He added, however, that the findings are somewhat applicable to flu vaccine in general, to the extent that adjuvant and standard (nonadjuvant) vaccines are the same. This researcher was not aware of any other studies of long-term effects of flu vaccine.

A Food and Drug official said he believes that findings pertaining to adjuvant vaccine would be completely applicable rather than somewhat applicable, because if two things cannot cause tumors together, it is hard to imagine how one can.

The National Institute for Allergy and Infectious Diseases is beginning a 3-year study of possible adverse reactions to flu immunizations. This study will focus on individuals who were vaccinated during the national swine immunization clinical

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1/A substance that, when mixed with an antigen, enhances antigenicity (the promotion of antibodies) and gives a superior immune response.

trials but who had not been previously exposed to the particular flu vaccine or virus. This followup study was considered particularly important for children because of the scarcity of information on possible long-term reactions in children.

As part of the swine flu immunization program, the Center for Disease Control had responsibility for conducting short-term surveillance on vaccine recipients. It was this surveillance effort that identified the occurrence of the Guillain-Barre syndrome among vaccinated individuals. A Food and Drug official said the Guillain-Barre syndrome would not have been discovered without the intensive surveillance which was carried out during the swine flu program.

In addition, the Center is supporting two studies on women who received the swine flu vaccine to identify unfavorable pregnancy outcomes, such as spontaneous abortions, stillbirths, and congenital malformations. These studies will follow reactions in children up to 6-weeks beyond birth, born of women in the studies.

CONSIDERATION OF ADVERSE EFFECTS IN BENEFIT-RISK ANALYSIS FOR SWINE IMMUNIZATION PROGRAM

HEW and its Advisory Committee on Immunization Practices, which annually develops recommendations for the use of flu vaccine, considered the benefits and risks of swine flu vaccination.

At a June 22, 1976, advisory committee meeting that was open to the public, Center officials presented information on adverse effects of flu vaccines. The meeting was held to discuss recommendations for vaccine usage. The reactions discussed were acute allergic reactions; fever, chills, and myalgia; and neurological or nervous system reactions. These were expected to occur within days following vaccination. In summarizing these reactions, a Center official pointed out that fatal allergic and nervous system reactions were reported before 1963 but no such incidents were reported in recent years. He said that reactions manifested by conditions such as fever, chills, and myalgia were reported from 0 to 51 percent of vaccine recipients covered by studies since 1968. The conclusion presented was that the absence of reported fatal reactions in the past 13 years and the low frequency of reports of other nervous system disorders suggests that these complications are extremely rare.

HEW officials and the advisory committee also discussed vaccination risks in special groups, such as children under 3 and pregnant women, before vaccine recommendations were made. However, the National Commission for the Protection of Human Subjects of Biomedical and Behavorial Research 1/ expressed concern that the advisory committees' conclusions regarding pregnant women were based on general observations and not on conclusive studies showing relative benefits and risks.

In some instances, adverse reactions are discovered only after widespread use of the product and surveillance of many vaccines; this was the case with the Guillain-Barre syndrome.

As a method of obtaining information on hazards after a product is in use, the Food and Drug Administration maintains an adverse reaction data system. Food and Drug officials advised us that they did not prepare a formal summation of adverse reactions from flu vaccine based on data from their system. They said that adverse reactions are monitored as they are reported and that Food and Drug officials and others are well aware of what reactions are in this system. According to these officials, most reports are about mild, relatively common reactions, such as fever and myalgia.

According to Food and Drug officials, when evidence of an unusual or significant reaction is found, workshops with flu experts and manufacturers are organized to discuss the problem. They said that workshops were organized on two separate occasions to discuss adverse reactions detected through the Food and Drug system. They said that in one instance convulsions were detected in children and a warning was put in vaccine circulars. In another instance a large number of persons at a Boston utility company became ill after being vaccinated, but the actual cause of the illness could not be determined.

The National Institute for Allergy and Infectious Diseases is doing a 3-year study (see p. 6) which will examine the possibility that flu vaccination may potentiate flu illness (make vaccinates more susceptible to severe natural

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1/Public Law 94-380, which authorized the National Swine Flu Immunization Program of 1976, required HEW to consult with this commission on the content of the program's informed consent form. The law did not require HEW to obtain approval from the commission.

infection than unvaccinated individuals). This consideration was discussed by several HEW officials and flu experts.

Food and Drug's Advisory Review Panel on Viral and Rickettsial Vaccines and the Food and Drug Administration are required to consider the benefit-risk ratio in determining the safety and effectiveness of flu vaccines. In its January 1977 draft report (see p. 5.), the advisory panel stated that "the ultimate approval of a vaccine hinges heavily on the benefit-risk ratio. This term implies a quantitative formula which, unfortunately, is not attainable with exactitude."

In its assessment of the benefit-risk ratio for flu vaccine, the advisory panel concluded that

> "Epidemic influenza is associated with a considerable morbidity [disease] and, in certain groups, an excess mortality [death]. Prevention of such disease and death is highly desirable. The risk associated with present vaccines is small, even including the risk of * * * [Guillain-Barre syndrome]."

The panel also noted that there is a need to study effectiveness in high-risk populations so that the true benefit-risk ratio in those groups can be more precisely assessed.

RESEARCH STUDIES ON PANDEMIC POTENTIAL OF SWINE VIRUS

On October 7, 1976, researchers from the Mount Sinai School of Medicine, New York City, published a study on the swine flu virus isolated from recruits at Fort Dix, New Jersey.

As previously noted, one theory on why a flu virus has epidemic potential is that the virus represents a genetic recombination of a human virus with one whose natural hosts are animals or birds. Although the study recognized possible limitations to making a definitive analysis of the composition of the Fort Dix swine virus, it suggested that this virus was closely related to other swine viruses which have always been evident in swine, and that it likely it was not derived by recombination with a previously unknown human virus.

The study concluded that, if recombination of human and animal strains is generally required for the emergence of new strains virulent for man, the Fort Dix swine virus is an "unlikely candidate for the next influenza pandemic."

Dr. Edwin D. Kilbourne 1/ told us that the study findings were "very provocative" but that he and his staff did not believe it should have altered the continuance of the immunization program. He said that he and his staff decided that since the study involved application of a new technique, it should undergo additional peer review before it was formally presented. Consequently, they did not present the study's findings at the HEW-sponsored June 21, 1976, public meeting on the swine flu vaccine program. Dr. Kilbourne said that on the weekend before the June 21 meeting, HEW officials, clinical trial investigators, and others met to prepare for the public meeting and he mentioned the study to several of those in attendance, which included Food and Drug, National Institute for Allergy and Infectious Diseases, and Center for Disease Control officials. Dr. Kilbourne also said that the study was never discussed by the Advisory Committee on Immunization Practices as an agenda item.

HEW officials said the study was not considered entirely pertinent to the question of vaccination because (1) the researchers' results suggest that the Fort Dix swine virus did not arise through recombination of a swine virus with a recent human virus, but did not prove that recombination could not have occurred with human viruses prevalent several years ago, and (2) the researchers did not consider other known methods of adopting a virus to a new species.

British researchers reached a similar conclusion in a study published July 3, 1976. These researchers exposed six volunteers to the swine flu virus. Volunteers showed mild or moderate reactions, suggesting that the swine virus was less virulent than other recent forms of human flu virus. They noted that the virus was not likely to spread among people and that the outbreak possibly "was an isolated event and that the virus will not become established in man."

HEW officials advised us that this study was discussed in several public meetings and its results were well-publicized. Food and Drug officials questioned the validity of the conclusions reached, stating that the virulence can be affected by transmission in humans or by laboratory conditions.

1/Dr. Kilbourne served as a member of the Advisory Committee on Immunization Practices and as a consultant for the Food and Drug Administration's Advisory Review Panel on Viral and Rickettsial Vaccines. He is Chairman of the Department of Microbiology, Mt. Sinai Hospital, where the research was performed.

We discussed this study in a telephone conversation with a Center official, who also served on the advisory committee. He said that the conclusion of the British study was not surprising because there was no evidence that swine flu virus was extremely virulent. He said that the major concern was that the virus was different from other flu viruses to which persons had been exposed and had protection. As a result, the swine virus was capable of causing widespread illness and subsequent death.

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We are preparing a report to the Congress on the swine flu immunization program which will also address certain questions posed in your letter. A copy of that report will be furnished to you when issued.

We will be in touch with your office in the near future to arrange for release of this report to the Food and Drug Administration.

Sincerely yours,

Comptroller General
of the United States