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Influenza Immunization Program

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Since 1961, Advisory Committees of the Public Health Service have recommended annual influenza immunization for those considered at high risk of complication or death from influenza. High-risk individuals include those with chronic underlying illness and the elderly. There has been remarkable consistency in these recommendations although there have been some variations as to whether or not pregnant women should be considered at high risk and whether or not the age for immunization should be set at 45 rather than 65, which has been the standard. In spite of the consistency of these recommendations, the U.S. Immunization Survey showed, in the early 1970's, that no more than 20 percent of high-risk individuals actually received influenza immunization in any given year. With the continuing toll exacted by influenza during epidemics, there was a growing feeling in the public health community that Government support for influenza immunization would be necessary if there was to be substantial improvement in the levels of protection. California was the first State to make a major commitment to support influenza immunization. In 1974, the California Legislature appropriated funds to provide influenza vaccine to elderly individuals in California.

At the national level, no definitive action to support influenza immunization was taken until 1976, when a major antigenic variant of influenza A (the swine flu) was discovered at Fort Dix, New Jersey. A high proportion of the American population had no antibodies against this strain and, in consequence, a program was undertaken to immunize virtually the entire American population against swine flu. The program was truncated by discovery of an increased risk of Guillain-Barré syndrome in those who had received vaccine. In less than 3 months, however, more than 40 million Americans had received influenza immunization. Among high-risk groups, the proportion immunized rose to over 40 percent, approximately double the levels previously attained.

Following termination of the swine influenza program, a conference convened by Secretary Califano concluded that annual influenza immunization of high-risk individuals continued to be an important preventive measure and recommended that the Government be involved to an extent greater than it had been prior to the swine influenza program.

In December 1977, the Soviet Union reported that a new influenza variant (Russian flu) had appeared and was causing epidemics of disease among children and young adults. These reports stimulated the convening of two technical conferences in December 1977 and January 1978, and two public conferences on policy in January and July 1978. Each of these conferences affirmed the need for annual influeuza immunization of high-risk individuals, whether or not major antigenic shifts occurred. Additionally, the public policy conferences both recommended Federal support for influenza immunization programs administered through State and local health departments.

Following consultation with State health officers about the magnitude of programs which might be feasible in the first year and the character of Federal support, a request was submitted to Congress in March 1978 for $15 million, representing $10.9 million in grant funds and $4.1 million in direct operations funds for the three Public Health Service agencies involved: the Center for Disease Control, the National Institutes of Allergy and Infectious Diseases and the Bureau of Biologics. This level of support envisioned the provision of 8-9 million doses of influenza vaccine to high-risk individuals in the 1978-79 influenza season, raising immunity levels in the high-risk groups from their usual level of approximately 20 percent to nearly 40 percent.

The initial request was predicated on early receipt of funds. As time went on, it became apparent that the number of immunizations in the first year would be lower the later the program got underway. For example, a survey of State health departments in July indicated that if funds became available in mid-August, approximately 4.5 million doses of vaccine could be administered and that if the funds did not become available until mid-September, only 3.5 million doses would likely be administered. The request for funds was accordingly decreased and on August 25, Congress appropriated $6.4 million in grant funds and $1.8 million in direct operations funds in the PHS agencies. Because the States had submitted grant requests in anticipation of a possible appropriation, rapid action on the requests was possible and on September 28-29, $5.1 million in project grant funds was awarded to 43 grantees. These included 28 States, the District of Columbia, 2 territories and 7 large cities. Contracts were rapidly completed for all vaccines except the childhood formulation and vaccine was shipped to the projects beginning October 4. Because of delays in completing a contract for the childhood formulation, all vaccine was not received in the project areas until the beginning of December.

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As a result of the delayed arrival of funds and of vaccine, most projects did not commence vaccine administration until much later than originally anticipated and, in consequence, the total amount of vaccine administered in the first year of the immunization projects is lower than expected. Preliminary data indicate that in the period October 1978-January 1979, a total of 992,486 doses of influenza vaccine was administered through the Federally-supported program.

A survey of the 48 project grantees was carried out at the end of January 1979 to ascertain the factors felt most important in the relatively low performance. Forty-three of the 48 reported that delay in availability of funds was an important factor. Insufficient public information and education at the national, State and local level was mentioned as a major factor by 29 and competition between influenza immunization activities and the Childhood Immunization Initiative was mentioned as a major impediment by 28. Local inability to hire personnel, issues of vaccine liability and the complexity of the vaccine recommendations were mentioned as important factors by 17 projects each.

For the 1979-80 influenza season, the situation is as follows: Congress has authorized up to $15 million in influenza immunization grants but has stipulated that certain reports must be submitted before any funds can be disbursed. The continuing resolution enacted by the Congress appropriated $6.4 million in grant funds and $1.8 million for direct operations. A supplemental request for $8.6 million in project grant funds is presently being considered by the Congress to bring the total up to the maximum authorized $15 million. This level of support is estimated to provide influenza immunization in 1979 to 8-9 million high-risk individuals who would not otherwise receive it. The Administration request in the 1980 budget is for $15 million in project grant funds and $5 million in direct operations. Steps are presently underway to try to ensure the timely distribution of the $6.4 million presently available to avoid problems resulting from delay in receipt of funds.

Production and Delivery of Influenza Vaccine

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The production and delivery of influenza vaccines are becoming increasingly complex issues. This development is in part due to the unpredictable nature of the virus and its capacity for frequent change. In addition, the vaccines have become a political issue because of questions of government liability for side effects and because of pressures on the government to support the delivery of needed vaccine to high-risk individuals. In the brief time allotted I will try to summarize the complex sequence of events that precedes the administration of influenza vaccine to individual recipients.

Much of the difficulty involved in production relates to the frequently changing antigenic make-up of the virus. When a new type or subtype of influenza virus is noted to be the cause of disease, there are often only a few months before vaccine must be available for public use. This problem is illustrated in Table 1, which describes the availability of vaccine in relationship to the epidemic of Hong Kong Flu in 1968-69. Within three months of confirmation of the antigenic make-up of the virus as an H3N2 virus, the first lots of vaccine were released for distribution. However, by the time most of the vaccine was ready for release the epidemic was abating and much of it went unused. This unfortunate situation occurred despite the fact that vaccine was produced with extreme expediency. So it is worth noting what the events are that determine the time required between virus identification and vaccine distribution.

TABLE 1

VACCINE AVAILABILITY IN THE USA FOR THE INFLUENZA EPIDEMIC IN 1968-69

Sequence of Events	Days
Outbreak of Respiratory Illness in Hong Kong, July 1968	0
First Variant Sent by DBS to Manufacturers	30
High-Yielding Variant Sent by DBS to Manufacturers	50
First Lot Released (One Million Doses)	120
Five Million Doses Released (Epidemic Began)	140
Fifteen Million Doses Released	165
Twenty Million Doses Released (Epidemic Abated)	180

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In December 1977, there was excitement when news was received that a widespread outbreak of infection due to an H1N1 strain of influenza virus occurred in Russia. This development was important because it marked the emergence of an antigenic type that differed markedly from the H3N2 strains which had been circulating for nearly a decade, and because it was the first time in the modern era of virology that a subtype of influenza had reemerged as a cause of epidemic disease after its absence for a period of many years. The events surrounding subsequent vaccine development are particularly illustrative and are depicted in Table 2. After receipt of the virus in December, the first step in the process of vaccine development consisted of confirmation and characterization of the antigenic nature of the new strain. The details of this process are summarized in Table 3. Stocks of a number of isolates must be prepared by inoculation of embryonated hens' eggs and the virus harvested and used to immunize animals, usually ferrets, for production of specific antibody. The antibody and virus stocks are then studied to determine the cross-reactivity of antigens of the new strain with those of older ones. This process must be accomplished with utmost efficiency, since the decision to produce a new vaccine cannot be made until the tests are completed.

TABLE 2

THE RUSSIAN FLU VACCINE STORY

1. December 9, 1977	Report of H1N1 Influenza Epidemic, USSR
2. December 1977 – January 1978	Confirmation and Characterization of Antigenicity of New Strain
3. January 12, 1978	Surgeon General's Conference on Influenza Vaccines
4. January 26, 1978	Distribution of High-Yield A/USSR Virus to Manufacturers by Bureau of Biologics
5. April 3, 1978	Submission of Experimental Vaccine Lots to Bureau of Biologics
6. April 18, 1978	Release of Experimental Lots for National Clinical Trials

Returning now to our Russian Flu vaccine story (Table 2), we can put these studies in perspective. Approximately on an annual basis, the Surgeon General conducts an influenza workshop session, the purpose of which is to determine the composition of vaccines to be used during the following influenza season. Considered at this meeting are data of the kind just described, and results of epidemiologic surveillance conducted by the Center for Disease Control. The participants include representatives of the Bureau of Biologics, the CDC, the Public Health Service's Advisory Committee on Immunization Practices (ACIP), Manufacturers' Representatives, and a number of expert scientists hired as consultants by the government. In 1978 this workshop was conducted on January 12. At this time, outbreaks of Russian Flu had not yet occurred in the United States. As a consequence, a specific decision regarding vaccine composition was actually postponed for a few more weeks. Thus, as in 1978, unusual epidemiologic circumstances may cause significant delay in vaccine production.

The manufacture of influenza vaccines is outlined in Table 4. After the antigenic content has been determined and high-yield strains of the respective viruses have been obtained, vaccine production may begin. The first and most critical step is the decision to commit capital. The expenditure involves substantial risk. For example, in 1978 a federal program was proposed, but funding was uncertain, and manufacturers did not know whether the government would purchase vaccine. In addition, if an epidemic does not occur, there is less public interest in vaccine and much of that produced may go unused. In this context of uncertainty each manufacturer must decide how much to produce. The next formidable problem they face is the procurement of embryonated hens' eggs, several hundred thousand per manufacturer. The vaccine virus or viruses must then be grown, harvested, and processed, and the resultant vaccine then tested for safety and potency. Once this process is completed, the material is submitted to the Bureau of Biologics for testing and possible release. The manufacturing process requires approximately six to eight weeks.

Potency testing of influenza vaccines has also become more complex in recent years (Table 5). In the past the in vitro assay used for potency standardization was the chick cell agglutination (CCA) test, a measurement which depends upon the capacity of influenza virus hemagglutinin to agglutinate red blood cells. This assay is performed in the same fashion for all influenza viruses, but the results do not correlate well with vaccine antigenicity. On the basis of studies performed in 1976 with Swine influenza vaccines, and on the recommendation of the World Health Organization, the CCA test has been replaced with a new assay which measures the amount of hemagglutinin more directly. The results of this assay correlate very well with vaccine antigenicity, but the conditions used for testing of each new vaccine strain must be determined individually. The methodology is developed by the Bureau of Biologics, then both the vaccine manufacturers and the Bureau perform potency testing on each lot to be released.

At times, in vitro potency testing must be extended by in vivo testing in the form of vaccine clinical trials. When such is the case, the first lots of vaccine released are experimental, and the distribution of vaccine for general use must be postponed until the trials are completed. The 1978 clinical trails were needed to confirm that the immunogenicity of the H1N1 vaccine viruses, measured in terms of hemagglutinin content, was similar to that previously determined in clinical trials of A/New Jersey and A/Victoria, and to determine if different

TABLE 3

CONFIRMATION AND CHARACTERIZATION OF THE ANTIGENIC CHARACTERISTICS OF A NEW STRAIN OF INFLUENZA VIRUS

1. Preparation of Egg-Grown Stocks of Several Recent Isolates
2. Immunization of Animals (Ferrets, Goats, etc.)
3. Serological Testing for Cross-Reactive Antigenicity of Old and New Strains
4. Confirmation of Findings by Use of Human Sera

TABLE 4

MANUFACTURE OF INFLUENZA VIRUS VACCINE

1. Guidelines Received from Regulatory Authorities Regarding Vaccine Content and Nature of Federal Program
2. Decision by Manufacturer to Make Capital Investment to Produce X Amount of Vaccine in X Amount of Time
3. Availability of Embryonated Hens' Eggs for Vaccine Production
4. Inoculation of Eggs with High-Yield Influenza Virus; Harvesting and Processing
5. Safety and Potency Testing
6. Submission to Bureau of Biologics for Testing and Possible Release

TABLE 5

POTENCY TESTING OF INFLUENZA VACCINES

1. Chick Cell Agglutination (CCA) Test
2. Qualitative Determination of Viral Hemagglutinin
   - A. Purification of Hemagglutinin
   - B. Immunization of Animals
   - C. Determination of Appropriate Assay Conditions
3. Clinical Field Trials

vaccine dosages would be needed for different age groups. It was anticipated that young people who had not been alive during the previous H1N1 era would require two injections, since influenza vaccines tend to produce poor responses in unprimed individuals. An example of the kinds of results obtained is shown in Figure 1 which depicts pre- and post-vaccination antibody titers for each of the strains included in the 1978 vaccines. Note that those under 26 years of age responded much less well to the USSR antigens than older individuals. Over 2,000 volunteers were eventually studied; although all aspects of the trials were not completed until the fall, sufficient data were available by early July so that the ACIP was able to meet and make recommendations for vaccine formulations to be given to those 13 years of age and older (Table 6).

At this time Congress was considering recommendations by the ACIP that the federal government sponsor a program designed to aid in the delivery of vaccine to high-risk individuals. In mid-July the funding for this program was rejected in Committee. On July 26, the Secretary of HEW convened a meeting to reevaluate the status of influenza vaccines, including the topics of vaccine virus strains to be used, dosage recommendations, safety, delivery, target populations, and liability. The outcome of the conference was that the recommendations of the ACIP were upheld. In response to this decision the question of a federal program was raised again in Congress and limited funding was approved on August 4.

During this time pediatric clinical trials were continued. Two additional ACIP conferences were held to consider the adequacy of the existing data on children and on September 26 it was finally possible to make formal recommendations for the pediatric dosage. The direct effect of the fluctuation in government posture on the existence of a vaccine program and the necessary delay before pediatric recommendations could be advanced was that vaccine manufacturers could not prepare the material in final containers. Thus, vaccine lots could not be released by the Bureau for distribution until the end of September or early October. The preferred deadline for vaccine release, in order to facilitate maximum effective distribution, is mid-August. Fortunately, nature was kind and the first influenza outbreaks in the United States were reported in California in October.

Table 7 summarizes the outcome of the Russian Flu vaccine story. Presently, several million doses of A/USSR vaccine remain unused. Moreover, the California outbreak was apparently caused by a strain which differed somewhat antigenically from A/USSR, and is more closely related to a strain isolated in Brazil last spring. On February 12 the Surgeon General convened a meeting again, to determine vaccine recommendations for the 1979-80 season and the results of that meeting were reconsidered on March 6 at a meeting convened by Secretary Califano. Fortunately, clinical trials will not be necessary this year, and influenza vaccine should be available in a more timely fashion.

Figure 1.

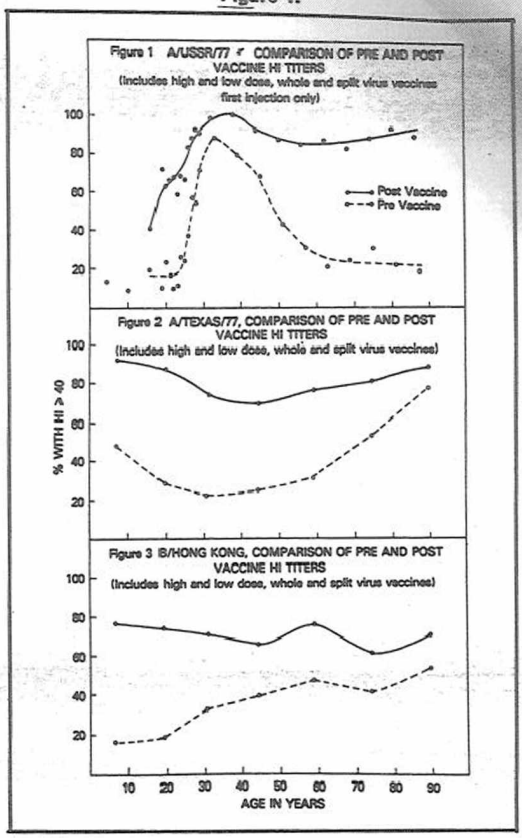


TABLE 6

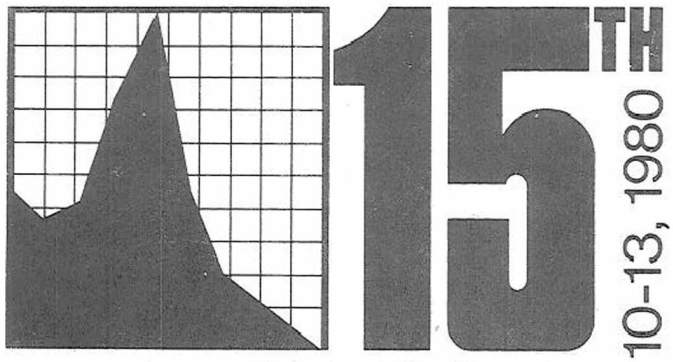
THE RUSSIAN FLU VACCINE STORY: POLITICS

7.	July 6-7, 1978	ACIP Evaluation of Clinical Trials
8.	July 20, 1978	Federal Program Stopped in House Committee
9.	July 26, 1978	Secretary's Conference on Influenza Vaccines
10.	August 4, 1978	Congressional Funding of Federal Program
11.	September 26, 1978	ACIP Recommendations Finalized

TABLE 7

THE RUSSIAN FLU VACCINE STORY: FINALE

12.	September 22, 1978	First Vaccine Lots of Youth Formula Released
13.	October 1978	Influenza Outbreaks in US: A/Brazil and A/California
14.	February 12, 1979	Surgeon General's Conference on Influenza
15.	March 6, 1979	Secretary's Conference



15TH IMMUNIZATION CONFERENCE PROCEEDINGS

March 10-13, 1980

DENVER, COLORADO

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Center for Disease Control
Bureau of State Services
Immunization Division
Atlanta, Georgia 30333

September 1980

Review and Update of Influenza Grant Programs

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The Federally supported Influenza Immunization Program was developed through a vigorous scientific and public review process. A scientific briefing was held on December 22, 1977, followed by a Surgeon General's workshop on technical issues on January 12, 1978. On January 30, 1978, the Secretary's Conference on Influenza A/USSR/77 (HINI), a broad based panel of scientists, consumer representatives, public figures, and academicians recommended:

> ". . .the development of suitable vaccines and their administration to those at high risk of severe illness or death. Federal support of influenza immunizations (provided through the States) will be essential if a substantial portion of those in need are to receive vaccine. Federal participation in influenza immunization should not be regarded as a one-time expenditure but as the beginning of a long-term commitment to support annual influenza immunization of those at highest risk."

This strategy was reaffirmed through a similar public process in the summer of 1978 and again in early 1979. Numerous congressional hearings have also been held.

The Federal proposal developed in response to recommendations from the various public influenza conferences was to provide limited support to State health departments to offer influenza vaccine to high-risk persons in the population who are not currently able to secure it. The program was targeted on high-risk groups and was intended as the first step in developing a continuing system for providing annual influenza immunization. The program would not supplant provision of vaccines by the private sector, but would gradually build up the Nation's capacity to provide influenza immunization on an ongoing basis rather than attempt to mount a massive program on a one-time basis. The program would focus on those individuals who are most vulnerable to serious complications of influenza, rather than attempt a wholesale vaccination of the entire population.

The initial budget request for the 1978-79 program was $15 million, of which $10.9 million was for grants and $4.1 million for direct operations. However, because of funding delays, HEW revised the budget request to $8.2 million, including $6.4 million in grants. Congress approved the program at the revised level, and the President signed the legislation on September 8, 1978. On September 28 and 29, 1978, grant awards totaling $5.1 million dollars were made to 38 States, the District of Columbia, 2 territories, and 7 local areas. Other States did not apply, due primarily to delays in the availability of grant funds.

Contracts for the purchase of 3.3 million doses of vaccine were signed on September 21, 1978, with Connaught Laboratories and Merck, Sharp and Dohme. Because of contract difficulties, the Parke-Davis and Company contract for the purchase of 0.2 million doses was not signed until November 15, 1978. Distribution of influenza vaccine began on October 4, 1978, 1 week after the first influenza immunization grant was awarded, and was completed on November 29, 1978.

Because of the delay in negotiating a contract with Parke-Davis and Company, no youth formulation split-virus vaccine (one of the formulations recommended for those aged 13-25 years, and the only formulation recommended for those under 13) was shipped until November 27, 1978.

A total of 3.4 million doses of influenza vaccine were distributed to State and local health agencies. In addition to project grantees, small amounts of vaccine were distributed to the Indian Health Service and selected Health Services Administration grantees, for use in "high-risk" populations in those States without immunization project grants, and to the Department of Defense and the State Department on a reimbursable basis to immunize "high-risk" American dependents overseas.

Projections of expected vaccine administration were submitted to the Center for Disease Control (CDC) by individual States in mid-August; these served as a basis for establishing vaccine and grant funding needs. Because of initial uncertainties as to the date that vaccine would be available, few grantees scheduled active programs for October. During that month, 182,526 doses of vaccine were administered.

For the period October 1978 through March 1979, a total of 1,033,073 doses was administered.

The 1979-80 Influenza Immunization Program was based on a continuing resolution in which a total of $5.8 million was awarded on September 21, 1979 to 43 States, the District of Columbia, 2 territories, and 7 local health agencies.

Grant funds could not be awarded until the following requirements included in the Health Services and Centers Amendments of 1978 (Public Law 95-6-26) were met:

1. Provision of a complete report on the results of influenza program activities in 1978 and 1979 including information with respect to adverse effects associated

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with influenza immunization, any known liability arising out of such immunization, and other reports relating to safety and effectiveness of the vaccine.

2. A report on the current status of the swine influenza program of 1976 including the status of any claims still pending under the program and the Secretary's plans for dealing with such claims.
3. As they become available, all reports and information with respect to liability arising out of personal injuries or death in connection with immunization programs and interim recommendations of the Secretary with respect to these matters.
4. A copy of the information which will be distributed to individuals before they receive any influenza immunization under a preventive health service program for which a grant is made.

Contracts for the purchase of 2.4 million doses of vaccine were signed on August 24, 1979 with Merck, Sharp and Dohme and Parke-Davis and Company.

Distribution of vaccine began on October 2, 1979 and was completed on October 15, 1979.

Because of the ACIP's recommendation that vaccine prepared the prior year could be used during the 1979-80 influenza season, many projects began their programs prior to shipment of the new vaccine.

Most projects have reported more influenza immunization activity than last year. Some have had exceptional programs. For instance Massachusetts distributed over 213,000 doses of vaccine for use in public clinics through October of 1979.

The total reported number of doses of public sector influenza vaccine administered September 1979 through January 1980 was 1,418,986. In addition 264,843 doses were distributed to private physicians.

Legislation authorizing influenza grant support expired September 30, 1979. The 1980 continuing resolution does not cover influenza. Consequently, new influenza grant funds will not be available in 1980 to fund 1980-81 programs.

The Center for Disease Control requested guidance from the Association of State and Territorial Health Officials (ASTHO) regarding efforts they should make relative to continuation of this program. In response ASTHO sent out a questionnaire to State Health Officials asking for their opinions regarding the future of the influenza program. Thirty-eight agencies responded. Included in the questionnaire were the following questions:

1. Do you favor continuation of Federally supported influenza immunization programs for high-risk individuals? Twenty-nine said yes, eight said no, one was neutral.
2. Would you recommend that CDC pursue renewed authorization and appropriation for influenza immunization project grant programs? Twenty-seven said yes, ten said no, one was neutral.
3. If yes, would you plan to support such activity through contact with your own Congressional Delegation? Twenty-five said yes, seven said no.
4. Even without additional project grant funds, it may be possible for CDC to establish a consolidated Federal contract for influenza vaccine, through which States could purchase vaccine using other Federal funds (314(d), etc.) Would you purchase influenza vaccine through a consolidated Federal contract if there were no continuing project grant program? Eleven said yes, twenty-two said no.
5. It is possible that CDC could purchase influenza vaccine directly and distribute this to States even without a grant program. However, this possibility (as No. 4 above) would provide no additional support to you for program coordination or execution. Would you want to receive influenza vaccine if you did not have to purchase it and if there were no financial support for program coordination (other than what might be available by carry-over from your present grant or through other existing 314(d) funds, etc.)? Twenty-nine said yes, eight said no.

In a study conducted in the fall of 1979 by the Bureau of Health Education, CDC, the following observations were made concerning the relevant attitudes and knowledge of private physicians regarding influenza immunization program activities.

1. Those physicians (91%) regarded the 1978-79 influenza season as a light or average year. Only 13% of the physicians felt that an influenza outbreak during the 1979-80 influenza year would be likely in their own community.
2. The vast majority of physicians (92%) believe that annual influenza shots are necessary for those people with chronic conditions and the elderly.
3. Only 30% of the physicians felt that the average adult needed influenza vaccine. However, if the average adult were to have influenza illness 53% of the physicians thought the disease would be serious.
4. Approximately 10% of the physicians felt that influenza immunization was necessary for children.

Therefore, the Center for Disease Control is exploring the following possibilities:

1. Extensions of existing grants for an additional 12-month period. It is anticipated that some unobligated funds will be available from FY 1978 & 79 awards. This will allow States to maintain limited programs for the coming year.
2. Authorization of local purchase of influenza vaccine by project grantees.
3. Investigation of the possibility of purchasing vaccine nationally to distribute to State projects.

If an influenza program is to be funded for FY 81, authorizing legislation must be introduced in Congress and supplemental appropriation requests prepared and submitted through

PHS, HEW, and OMB to Congress.

On January 30, 1978, former Secretary Joseph Califano convened a public meeting in Washington, D.C. seeking specific policy recommendations for influenza. One of the conclusions reached at that meeting was:

"Federal support of influenza immunizations (provided through the States) will be essential if a substantial portion of those in need are to receive vaccine. Federal participation in influenza immunizations should not be regarded as a one-time expenditure but as the beginning of a long-term commitment to support annual influenza immunization of those at highest risk."

Thus far that conclusion has not become a reality.