





# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
CENTER FOR DISEASE CONTROL

TO : Director  
Center for Disease Control

DATE: May 17, 1978

FROM : Chairman  
Interagency Work Group on Pandemic Influenza

SUBJECT: Plan for Pandemic Influenza

Attached is "A Plan for Pandemic Influenza" which has been prepared by the Interagency Group.

The first draft of this report was circulated within the Public Health Service in October and November 1977. A revised version was nearing completion on December 14 when reports were received from the World Health Organization of isolates of H1N1 influenza virus in the USSR. The Work Group met on December 16 to review available information on the H1N1 virus and recommended that, while too little data on A/USSR/77 were available to permit the formulation of a specific response, a general public briefing of what is known should be provided to interested parties as soon as possible. This briefing was held at CDC on December 22, 1977, and a summary of the meeting has been widely distributed.

The Work Group met again on January 4, 1978, to review additional data on the epidemiology of A/USSR/77(H1N1) influenza and took the following actions:

1. Finalized the "Summary of Conclusions and Recommendations" section of the "Plan for Pandemic Influenza" and transmitted it to you on January 5 for discussion with Dr. Lashof on January 6.
2. Recommended that estimates be developed for technical issues which must be addressed before broad policy issues are decided. These technical issues included:
  - a. The expected impact of spread of H1N1 virus in the United States, including expected demands on the medical care system.
  - b. The segments of the population expected to be at high risk from the new strain.

- c. The efficacy and risks of influenza vaccines incorporating the new strains.
- d. The possibility, if any, of having any appropriate vaccine available this influenza season.
- e. The advisability of including other influenza antigens in vaccines to be prepared, and of other alternative interventions such as administration of viral inhibitors, etc.
- f. The opportunities presented by the anticipated pandemic for research on influenza and its prevention.
- g. The particular needs of the military with respect to prevention of H1N1 influenza.

It was recommended that these questions be addressed by personnel within the agencies of the Public Health Service or, alternatively, by existing outside advisory groups. This latter option was adopted, and on January 12, 1978, a Public Health Service Influenza Virus Vaccine Workshop was held at NIH. In attendance were representatives from the Viral and Rickettsial Disease Panel (BoB), the Advisory Committee on Immunization Practices (CDC), University Medical Centers, Health Departments, the Armed Forces, the Pharmaceutical Industry, and the Public Health Service. A copy of the report of this meeting is attached.

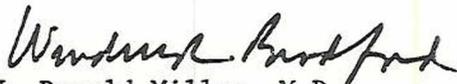
- 3. Recommended that key policy issues (the extent of immunization to be carried out, the role of the Federal Government in carrying out programs, and related issues) be addressed by a broad-based group in a public forum sometime in January, but after the development of technical estimates as outlined above. As you know, the Secretary convened such a group on January 30.

The attached "Plan for Pandemic Influenza" was a useful guide in developing a response to A/USSR/77. However, it has not been updated to reflect the events which have occurred since December 1977, particularly the epidemiology of A/USSR/77 which is proving to be unique in many respects. We will continue to revise the Plan to include knowledge gained as a result of the reintroduction of this particular influenza virus, and as a result of the implementation of the proposed immunization programs this fall. We view the attached Plan as part of an evolving public health strategy for addressing influenza. We would emphasize that one of the major conclusions of the Work Group was that the best method of dealing with pandemic influenza is to establish an ongoing influenza

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immunization program in the public sector during interpandemic periods. This conclusion was underscored by the appearance of A/USSR/77, and the current proposal before Congress will accomplish this needed step.

We suggest that this report be circulated within the Public Health Service and the Department for comments in order to seek counsel in particular on those recommendations which have not yet been acted upon. The Work Group will continue to meet regularly during the coming year to ensure communication and coordination among the PHS agencies and the Department of Defense in carrying out the proposed high-risk influenza program, and to revise contingency plans for pandemic influenza based on the experiences of this year.

  
J. Donald Millar, M.D.

2 Attachments

PLAN FOR PANDEMIC INFLUENZA  
INTERAGENCY WORK GROUP ON INFLUENZA  
DECEMBER 1977

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PLAN FOR PANDEMIC INFLUENZA  
INTERAGENCY WORK GROUP ON INFLUENZA

DECEMBER 1977

Part I. Background

On August 17, 1977, Dr. Joyce Lashof, Deputy Assistant Secretary for Health (Programs) in the Department of Health, Education, and Welfare asked the Directors of the National Institutes of Health, the Center for Disease Control, and the Commissioner of the Food and Drug Administration (NIH, CDC, FDA) to develop an influenza pandemic contingency plan which "should cover aspects of how we will detect a new variant, decide on likelihood of pandemic potential, reach decisions regarding vaccine formulation, and field testing . . . Specific decision points should be identified as well as probable decisionmakers." This responsibility was delegated to the NIAID in the NIH and to the BoB in FDA with CDC being the lead agency. Subsequently, representatives from the Department of Defense were invited to participate in the work of the group.

In preparing this report, the work group reviewed the history of influenza, vaccine production and vaccination practices in the United States, and current efforts in surveillance and research. Particular attention was given to Federal responses to threats of pandemic influenza in 1957, 1968, and 1976, including the decision-making process, the timetable under which decisions were made, and the outcomes of these decisions. Since the question of liability for vaccine-associated adverse reactions extends to immunization

programs in general and is being reviewed by other groups within the Department, the work group did not specifically address this issue.

## Part II. Summary of Conclusions and Recommendations

### A. Conclusions

Major antigenic variants of influenza A virus will continue to emerge periodically. These events will typically be accompanied by rapid, worldwide (pandemic) spread of the variants with high morbidity and increased mortality. Initial pandemic spread may occur as a single wave or as two waves (either in the same year or in successive flu seasons). Following the initial pandemic wave(s), the same variant may cause periodic epidemics for several years. Thereafter, lesser antigenic variation, or drift, may be anticipated, and these variants may cause epidemics every 1-4 years until the next major antigenic variant, or shift, occurs. Epidemics following the initial pandemic wave(s) have historically caused morbidity and mortality to cumulate to much greater totals than accompanied the initial pandemic. As a consequence, efforts to reduce the impact of new antigenic variants must deal not only with the initial pandemic wave, but also with successive waves during the inter-pandemic period.

At the present time, the major weapon available to minimize the impact of influenza is annual vaccination of all or part of the population. Although influenza vaccine is safe and effective, it is imperfect both in the degree of protection afforded and in

the desired freedom from untoward reaction. The appropriate role of antiviral agents such as amantadine or other drugs such as the pneumococcal polysaccharide vaccine has not yet been fully ascertained.

B. Recommendations

Given the above considerations (which are dealt with in detail in the body of the report), recommendations for the Department of Health, Education, and Welfare are as follows:

1. Initiate a federally-supported program of annual influenza immunization for those persons at high risk of severe complications of the disease.

This approach will serve the dual functions of protecting the high-risk population during interpandemic periods of influenza and of establishing an ongoing level of production and administration of influenza vaccine which will facilitate any needed expansion in production volume or changes in the character of the vaccines in the face of anticipated pandemics.

Some prerequisites to initiating such an annual program include:

- a. Legislative authorization both for an ongoing program and for emergency expansion (if needed).

b. Resolution of the problem of liability for serious injury resulting from public participation in immunization programs. There is serious concern about the availability of vaccines for public programs in the absence of such resolution.

2. Strengthen and extend national and international influenza surveillance.

This will afford the earliest recognition of antigenic variants, allow the acquisition of more definitive data on the socioeconomic impact of influenza, provide better estimates of the costs and benefits of immunization or other control measures, and allow monitoring of adverse reactions to these control measures.

3. Expand influenza clinical and laboratory research activities. This will facilitate rapid and definitive testing of vaccines derived from new variants, improvement in existing vaccines, and development and testing of live vaccines which may be more quickly and economically produced and offer longer and better protection. Investigation into the proper role of antiviral agents and other vaccines is imperative. A major obstacle to the execution of much of this needed research (which requires the use of human subjects) is the problem of

compensating subjects who might be injured in the course of the research. This problem has been reviewed by a Secretarial (DHEW) Task Force and is also under separate consideration relative to research subjects in general.

4. Establish a continuing, formal mechanism to develop plans and make policy recommendations regarding influenza, including preparations for potential pandemic influenza.

This is viewed as a three-tiered process:

- a. A governmental working group is needed to coordinate the continuing refinement of plans, to evaluate the impact of strain variation and use of vaccines, and to coordinate research activities. This group should include representation from agencies of the Public Health Service, the military medical departments, and the Veterans Administration.
- b. Outside technical review and advisory bodies are needed to evaluate information about new variants and data regarding vaccines, and to make recommendations regarding vaccine formulation, dosage schedules, and populations most in need of vaccination. These bodies presently exist as the Viral and Rickettsial

Vaccine Panel (of the Bureau of Biologics), the Advisory Committee on Immunization Practices (of the Center for Disease Control), the Microbiology and Infectious Diseases Advisory Committee (of the NIAID), and the Armed Forces Epidemiological Board.

- c. Outside public policy development and review is necessary to deal with the larger national policy issues involved in response to potential pandemics. This could be done by a standing National Commission on Immunization Policy as recommended by the National Conference on Immunization in 1977, or by convening one or more ad hoc public meetings of representatives of appropriate public policy groups.

### Part III. Report of the Interagency Work Group on Influenza

#### A. Introduction and Background

For the past 400 years, epidemics resembling influenza have been recorded in many countries. Epidemics from as early as the 16th Century in England and the 18th Century in the U.S.A. are recognizable as influenza, even in the absence of precise knowledge of their causative viruses. The pandemic of 1918, attributed to what is now known as swine influenza virus, was the largest in recent history, causing an estimated 500,000 deaths in the United States and 20 million worldwide. In more

modern times, since 1957, influenza in the U.S.A. is estimated to have caused nearly 400,000 excess deaths (deaths exceeding the expected number in a specific time period associated with a known influenza epidemic). Of the total, 70,000 and 30,000 were associated with the pandemics of 1957 and 1968, respectively. The remainder were associated with epidemics of influenza A which occur every 1-3 years, often producing disease in up to 30 percent of the population in many areas. Excess mortality has been observed in conjunction with influenza epidemics or pandemics in 13 of the past 20 years. Deaths continue to occur despite the fact that antibiotics are available for treatment of secondary bacterial infections and that influenza vaccines have been in limited use for over 30 years.

The influenza viruses are unique in their ability to circumvent immunity by gradually undergoing alteration of their two surface antigens (drift). Influenza A virus may also undergo a complete and abrupt change in one or more of its surface antigens (shift). Antigenic drift has been attributed to the selection of preexisting mutants by the pressure of increasing immunity in the human population. Antigenic shift is not as well understood, but some evidence suggests that "new" influenza A viruses may arise from reservoirs in horses, pigs, birds, or through genetic recombination of such strains with current human strains.

Viruses arising by antigenic drift tend to cause epidemics, whereas viruses exhibiting shift cause pandemics. This distinction is useful since it implies a major difference in the anticipated rapidity of virus spread and public health impact. Viruses undergoing antigenic drift encounter partial immunity in the population which provides some resistance to virus spread. Viruses undergoing antigenic shift historically have encountered little or no immunity, and the result is an explosive outbreak affecting all age groups and geographic regions.

Recent influenza A pandemics occurred in 1918, 1957, and 1968. In the first two instances, the viruses exhibited changes in both surface antigens (hemagglutinin and neuraminidase). In 1968, the antigenic shift occurred only in the hemagglutinin, and the spread of the virus may have been somewhat muted by partial immunity in the population through antibody to the unchanged neuraminidase surface antigen.

However, despite this useful distinction, viruses demonstrating antigenic drift may also cause pandemics in the strictest epidemiological sense of the word. For example, worldwide epidemics (pandemics) occurred with the influenza A viruses of 1972, 1974, and 1975. Although these viruses had only gone through an

an antigenic drift, they could also be traced around the globe, usually completely replacing the previously prevalent strains, and often reaching all areas in a period of less than a year. Therefore, while the relationship between antigenic change and epidemics is complex, presumably involving multiple factors attributable to the host as well as to the viruses, antigenic drift or shift is the most readily identifiable marker of epidemic potential. Consequently, virus surveillance remains the most important component of early warning and defense against influenza epidemics.

Since 1918, pandemics of influenza A have occurred at intervals of 39 and 11 years. They cannot be predicted. The causative virus of pandemic influenza, by definition, cannot be completely determined until at least the first phases of the pandemic are underway (as the 1976 experience documented). Therefore, pandemic prediction, even under the most efficient and extensive surveillance system, must operate under a serious handicap, and the period of time available for vaccine production will always be limited unless major breakthroughs occur in surveillance or vaccine production technology.

At the present time, the only effective means of reducing morbidity and mortality due to epidemic or pandemic influenza is through the use of a vaccine. However, vaccination programs

in pandemic years have been too limited to evaluate conclusively their effectiveness. Kavet has shown that routine annual vaccination of those at high risk of severe complications of influenza is a cost beneficial strategy,<sup>1</sup> and annual immunization has greatly reduced influenza incidence in military populations. Antiviral drugs such as amantadine have not been sufficiently studied in large population groups to evaluate their effectiveness.

In response to the isolation of an influenza virus with pandemic potential in May 1957, surveillance systems were strengthened and, later, an emergency fund was authorized by Congress in the event the health care system became severely taxed in caring for the ill. The PHS developed recommendations for influenza vaccination, but vaccine production and distribution were left to the private sector. While over 50 million doses were ultimately produced and released for distribution, less than 20 million doses were in the distribution system when the peak of influenza activity was reached in mid-October. Although the number of doses actually administered is not known, manufacturers reported that large surpluses existed in February 1958 representing considerable financial loss.

<sup>1</sup>Kavet, J.: Influenza and Public Policy, Unpublished Dissertation, Harvard University, 1972.

In 1968, isolation of a new strain of influenza virus did not occur until mid-August, leaving, as it turned out, even less time to produce and administer vaccine prior to the peak of influenza activity in the United States (late December). Again, PHS made recommendations about vaccination, and over 40 million doses were ultimately produced. Based on U.S. Immunization Survey data, Kavet estimates that 21 million persons were immunized, of whom 3.5 million were above the age of 64.<sup>2</sup>

In 1976, the Federal Government, faced with the threat of a possible swine influenza pandemic, introduced the largest influenza vaccination program in history. Over 40 million persons were vaccinated, including nearly 48 percent of individuals at high risk. These figures dwarf those achieved in any previous year.

Fortunately, in 1976, the pandemic did not occur. However, the absence of a pandemic and the criticisms of the program, both within and without the Federal Government, may create an environment in which decisions will tend to be overly cautious and conservative. It is the purpose of this paper to review the past experience of the PHS response to influenza and to discuss alternatives for future actions.

<sup>2</sup>Kavet, J.: Influenza and Public Policy, Unpublished Dissertation, Harvard University, 1972.

## B. Present Activities

### 1. Surveillance

In general, influenza surveillance is composed of two principal elements: (1) Identification of unusual levels of illness or mortality in community settings (school and workplace absenteeism, visits to outpatient facilities with upper respiratory symptoms, regular household interviews on health status, changes in expected death rates), and (2) collection and analysis of specimens from persons with influenza-like illness for laboratory identification of the causative virus. Data on these surveillance elements are obtained through five general surveillance networks, each reporting on one or more elements: State and local health departments, World Health Organization collaborating laboratories, National Center for Health Statistics Health Interview Surveys, special study centers funded by the National Institute of Allergy and Infectious Diseases, and military installations. The Center for Disease Control draws on each of these systems to collect, analyze, and distribute information on the status of influenza in the United States and the world, and serves as a principal laboratory for virus isolation and characterization for most of the Western Hemisphere. Influenza surveillance information is published regularly

in the World Health Organization Weekly Epidemiologic Report, in the Center for Disease Control Morbidity and Mortality Weekly Report, and during the "influenza season," in a special CDC Influenza Surveillance Report. Health Interview Survey data are published periodically by the National Center for Health Statistics (weekly summaries were published during the swine flu program).

2. Assessment of Vaccine Use

Questions about influenza vaccine have been included since 1963 in the annual U.S. Immunization Survey conducted by the Bureau of the Census for the Center for Disease Control. Vaccine production and distribution data are obtained through the Bureau of Biologics (FDA) and directly from the manufacturers. Detailed summaries of vaccine administration were obtained from States during the 1976 program.

3. Surveillance of Illnesses Occurring After Vaccination

During the National Influenza Immunization Program (swine flu) in 1976 a surveillance system was established for reporting adverse events which occurred following vaccination. The system was passive in the sense that the vaccinee or the attending physician was relied upon

to initiate a report. Two types of reports were forwarded from State and local health departments to CDC: Illnesses requiring a person to visit a physician or hospital and illnesses which required home bed rest. Deaths and hospitalizations were to be reported by telephone. These, or other serious illnesses, were investigated by State and local health authorities with assistance as needed by CDC (e.g., the deaths in Pittsburgh in early October and reports of the Guillain-Barre Syndrome). During the program, over 4,600 such reports of illness were received by CDC, excluding those cases of GBS uncovered through the active investigation of the syndrome which began in December. No such system had previously been implemented.

4. Decisionmaking on Vaccine Formulation and Recommendations for Its Use

The annual decisionmaking process for influenza immunization has, until now, been vested in two elements of the Public Health Service: The Bureau of Biologics (BoB) of the Food and Drug Administration and the Center for Disease Control. Because of expertise, interest, and considerable financial support to influenza surveillance and to influenza vaccine studies, NIAID has played a significant role in supporting and consulting with the other two agencies. The respective

processes performed by BoB and CDC provide answers to the following questions:

- a. What, should comprise this year's vaccine?
- b. Who should receive the vaccine?

The BoB has led the annual process dealing with the question of vaccine composition by developing recommendations for vaccine formulation. CDC has lead responsibility for developing influenza vaccine administration recommendations. Both agencies have standing groups of "outside" advisors who assist in the process of reaching appropriate decisions. In the case of the Bureau of Biologics, the outside group is the Virus and Rickettsial Vaccine Panel and for CDC, the Advisory Committee on Immunization Practices (ACIP).

In December of each year, the BoB usually calls together its consultants supplemented by staff scientists at CDC, NIAID, some NIAID influenza contractors, the vaccine manufacturers, and other persons with particular expertise or interest in influenza immunization. Data regarding current strains of influenza virus and current epidemiological characteristics are reviewed, and a tentative consensus is reached as to the appropriate recommendations for vaccine formulation for the next year. About a month later, if there are no significant new developments to suggest the need for reconsidering

the tentative recommendations, BoB makes a firm recommendation to the manufacturers for vaccine formulation. The CDC usually convenes the ACIP each May in a public meeting to consider matters related to influenza immunization for the coming influenza season. Those invited include the committee members, CDC staff, liaison representatives from NIAID, BoB, the American Academy of Pediatrics (Redbook) Committee on Infectious Diseases, and other persons who may have particular interest in immunization against influenza including vaccine manufacturers. This group prepares material needed for PHS recommendations for influenza immunization. Although the processes of BoB and CDC are not formally tied to each other, many of the members of one committee also participate in deliberations of the other. In usual circumstances, these deliberations have produced timely recommendations with wide acceptability to manufacturers, medical practitioners, and the public health community. Influenza vaccine recommendations of the Public Health Service Advisory Committee on Immunization Practices (ACIP) for the 1977-1978 influenza season were published in the June 17, 1977, issue of the Morbidity and Mortality Weekly Report. (Appendix A)

The traditional process was supplemented in the 1976 swine influenza program through review by a special group of experts convened by the President, and by subsequent Congressional review. (Pandemic preparedness has always raised policy issues not addressed in "usual" years, and such extra policy-oriented groups were convened in 1957 and 1968, at the request of the then Surgeons General.)

In addition, Secretary Califano convened a special work group on March 11, 1977, to develop recommendations for vaccine use during the 1977-78 influenza season (Appendix B).

#### 5. Vaccine Production and Distribution

In the United States, all influenza vaccines in public use are produced by the pharmaceutical industry. Because of such features as technical complexity of production and low profit margin, relatively few companies now engage in biologics production. The inactivated influenza virus vaccines for the 1975-1976 winter season were produced by six pharmaceutical firms, but in 1976-1977, the number declined to four.

Vaccine production involves growth of the appropriate influenza virus in fertile chicken eggs, harvest of the virus-rich allantoic fluid, and concentration, purification, and inactivation (killing) of the virus. In the final step,

the resultant inactivated virus concentrate is diluted to the level specified as appropriate for human immunization and filled in rubber capped glass vials ready for use. In general terms, one can think of each 0.5 ml human dose as containing about 100 million virus particles and each egg harvest yielding enough virus for preparation of one to three human doses of vaccine.

Each manufacturer has developed an individual production process, and while these methods are generally known, the specifics are considered trade secrets. Some manufacturers use processes that disrupt the virus by chemical or physical means while others prepare vaccines consisting mainly of intact inactivated virions; these products are commonly termed "split" and "whole" products, respectively. No two vaccines are identical in their biologic properties. People, too, are heterogeneous in their response to inactivated influenza virus vaccines. Factors such as recipient age and previous immunologic experience with influenza viruses are important determinants. Consequently, each year there must be a selection of the most appropriate dosage and type of vaccine for the various age groups in the population. Influenza vaccine production in a "normal" year follows a predictable annual cycle: Eggs are ordered in the fall; decisions on formulation are made in January; and vaccine

is produced in the winter and spring, distributed in the summer, and used in the fall. This system allows minimum time to monitor for virus change in nature before selection of the most contemporary viruses for vaccine production, but it provides maximum time for vaccine administration prior to the winter respiratory virus season. Dosage has generally been based on the experience of previous years with other vaccine formulations, although special clinical trials were carried out with candidate vaccines prior to the 1976 program.

Influenza viruses are continually changing in antigenic characteristics. Since more than one type of virus may become active during a particular winter, one can postulate population risk but cannot predict the likelihood of exposure of a particular person. The 1976-1977 season serves to illustrate the situation. During that winter, many areas in the United States experienced epidemics of type B influenza (Hong Kong strain), others suffered from type A (Victoria strain) influenza, and although no outbreaks were recognized, one pregnant woman died of type A swine influenza. Additionally, a variant related to A/Victoria/75 (the A/Texas/77 strain) appeared in many parts of the country toward the end of the season. Obviously, a vaccine containing a single type of inactivated virus would not be capable of protecting against all of these threats.

Consequently, influenza vaccines are generally prepared as a mixture of the individual influenza virus type thought most likely to be important during the next winter.

The emergence in nature of a new or markedly changed influenza virus considerably increases the possibility of widespread epidemics. Recognition of this threat creates a demand for more vaccine. With the short time frame available, the capacity of industry to increase production levels is limited primarily by constraints at the production facility and not by the supply of poultry breeding stock and fertile eggs. The most important constraints involve: (1) Finite limits in the supply of skilled personnel, equipment, and facilities required to produce the vaccine; and (2) the element of uncertainty in predicting the market demand for vaccine. This latter constraint applies since in the past most influenza vaccine has been produced for private sector distribution and sales (except in 1976-1977), and often the pattern of public demand is not clear until the production cycle has been completed.

#### 6. Vaccine Control

Inactivated influenza virus vaccines are biologics subject to Section 351 of the Public Health Service Act. Since biologics are also drugs, experimental work with these vaccines is subject to regulation under the investigational new drug provisions of the Food, Drug, and Cosmetic Act. The development, production, and use of vaccines and other

biologics has commonly involved the cooperative efforts of both public and private sectors. Most research on influenza and its control has been supported by public funds. Work during the 1940's that led to the development and licensure of the first inactivated influenza virus vaccines was sponsored by the Department of Defense through the Armed Forces Epidemiological Board and its Commission on Influenza and on Immunization. The improvements in the vaccine since those early years have come about through the continued joint efforts of government, industry, and the biomedical/public health community.

A prospective manufacturer applies to the Bureau of Biologics, FDA, for an establishment license and a product license. The review process involves data review, inspection, and product testing by the Bureau of Biologics as well as the manufacturer. After licensure, monitoring is continued through a system of periodic reinspection of the production facilities, review of clinical data, and batch-by-batch evaluation of vaccine. The manufacturer is responsible for performing the required tests on the batch, but a summary of the production records and samples of the batch are submitted to the Bureau for review and confirmatory testing. Only after the Bureau releases the batch can distribution be initiated.

Once licensed, there are two types of changes in product that periodically occur. One relates to the gradual improvement

in manufacturing methods that results from advances in the "state of the art" or from technical innovation on the part of the manufacturer. The other changes are those necessitated by the alterations of the virus in nature, i.e., substitution of a new contemporary virus for an earlier virus in the manufacturing process. In either instance, the manufacturing changes are procedurally processed as amendments to the existing product license. The amount of information needed to support a proposed license amendment varies with the circumstances.

Manufacturers are given more guidance in the production of influenza vaccines than in the manufacture of most biologics. The same arrangements are true internationally, and stem from the practical realities of dealing with a mutated virus capable of triggering explosive epidemics. Through a public process, national and international consensus is reached on matters relating to vaccine composition, vaccine dose, and recommendations for use. This information is provided to industry. As production gets underway, the Government provides the forum for the identification and resolution of various technical problems and assists in the generation of necessary laboratory and clinical data. It is a flexible system that allows for a "best effort" irrespective of the lead time provided.

With the exception of the 1976-1977 swine influenza experience, the Government has had little control over the amount of vaccine produced or the ultimate distribution and use of the vaccine. The quantity of vaccine produced each year is usually insufficient to provide vaccine for all of the "high risk" population for which vaccine is recommended annually. Moreover, much of the vaccine produced is administered to "normal" individuals, leaving the "high risk" groups relatively under-immunized (no more than 25 percent of this target population was immunized in any year prior to 1976-1977).

7. Research on Influenza and Influenza Immunization

The goal of influenza research is to develop the methodology required to prevent or reduce the impact of this disease on the population of the United States. This is a difficult task for two reasons. First, as noted, the influenza virus differs from all other viruses which affect man in that it is continuously changing its antigenic coat. Second, influenza, the disease, characteristically has a very short incubation period and high attack rate. To develop methods to control this disease and prevent its effects, NIAID supports research which will increase understanding of the pathogenesis, immunology, chemoprophylaxis,

therapy, and epidemiology of influenza and of the basic properties of the viruses. These efforts are closely coordinated with other agencies of the Government (BoB, CDC, DoD). NIAID also has a major focus on development and testing of live influenza vaccines. Theoretically, live vaccines have the following advantages over inactivated vaccines: (1) The number of doses per egg would be more than 100 times that of inactivated vaccines, (2) non-parenteral administration might be possible, (3) live vaccines could stimulate local respiratory tract immunity in addition to humoral immunity, and (4) with live vaccines broader antigenic coverage against variants might be possible, reducing the need for strain changes in the vaccine.

#### C. The 1976 Program

The events of 1976 differed from those in 1957 and 1968 in several key respects:

1. A new influenza virus subtype was first identified in the continental United States.
2. The identification of the new virus occurred during the month of February, near the end of one influenza "season" and well in advance of the next "season."

3. Large-scale field trials were conducted before final potency and dosage recommendations were made.
4. Production was increased by guaranteeing its purchase with public funds, and public vaccination programs were carried out.
5. Reporting systems were established to monitor vaccinations administered and the occurrence of illnesses after vaccinations.

This program was a signal success in several respects:

1. By December 16, more than 45 million persons had been vaccinated, many more than were vaccinated in 1957 and 1968.
2. Approximately 48 percent of individuals at "high risk" from influenza were immunized (including an astounding 69 percent of persons age 45-64 in the "high risk" groups). These figures dwarf those of any year prior to 1976.
3. Influenza surveillance was sharply increased with five times as many reporting sources as the previous year.
4. Vaccine recommendations were tailored to achieve maximum effectiveness in various age groups.
5. The vaccine manufacturers produced over 150 million doses of influenza vaccines, more than 7 times their usual annual output.
6. Special risk and benefit statements were developed and utilized as a routine procedure for the first time in a mass immunization program.

The negative aspects of the program are equally well known:

1. The scope of the program resulted in an unwillingness on the part of the insurance industry to provide liability coverage to the vaccine manufacturers or to many of those who would administer the vaccine. This problem was only resolved through special legislation.
2. Vaccines were delivered later than anticipated, causing State and local health authorities to delay carefully laid plans and to cancel and reschedule clinics.
3. Important segments of the population felt left out of the decisionmaking and information-sharing process.
4. An apparent statistical association between influenza vaccination and the onset of the Guillain-Barre Syndrome was identified, resulting in suspension of the program.
5. The program was carried out against a virus which did not produce a pandemic (or any outbreaks) during the 1976-1977 influenza season. Approximately 70 million doses of vaccine are available for future need, but cannot be used without further legislative action.

These successes and failures provide an excellent opportunity for planning and strengthening future efforts. It is very important to look at both, and also to recognize the complexity of the disease and of the decisions which must be made. First, influenza

is a disease explosive in nature, which, typically when its antigenic makeup changes abruptly, spreads throughout the world in a matter of months. Second, it still represents a major cause of mortality in the United States, even in "non-pandemic" years. Third, its unique epidemiologic and immunologic characteristics are complicated and not clearly understood, and what is known is often difficult to explain to the public.

Each of these characteristics was evident in the real and imagined problems of the 1976 program, and each underlay the somewhat different Federal response in 1957 and 1968. They deserve careful examination.

#### D. Planning for the Pandemic

##### 1. The Timetable

A series of critical action steps and key policy decisions necessary for planning and implementing influenza programs were identified after analyzing the pandemic preparations of 1957, 1968, and 1976. Based on this analysis and an assessment of current vaccine technology and public sector readiness, a timetable which estimates the minimum number of days needed to complete each action step and make key policy decisions was developed.

The action steps and key policy decisions included in the timetable are:

Action Steps:

- a. Identification and epidemiologic confirmation of the survival and spread of the new virus.
- b. Establishment of a "production strain" of the new virus.
- c. Production of vaccine for clinical trials.
- d. Adaptation of the "production strain" to the individual manufacturing requirements of the pharmaceutical companies.
- e. Establishment of vaccine dosage requirements.
- f. Release and delivery of vaccine.

Key Policy Decisions:

Determine vaccine production and delivery goals:

- a. Will the Federal Government assure the purchase of quantities of vaccine over and above what the private sector and the military will distribute alone? If so, how much vaccine?
- b. Will the Federal Government support the public sector costs of administering vaccine among civilians not served by the private sector? If so, what target groups?

A discussion of the minimum time frames available to decision-makers follows and is summarized in Table I.

TABLE I  
 MINIMUM TIME FRAMES FOR COMPLETION OF  
 INFLUENZA PROGRAMS AFTER INITIAL VIRUS CONFIRMATION

<u>ACTION STEP</u>	<u>EARLIEST BEGINNING TIME (DAYS)</u>	<u>EARLIEST COMPLETION DATE (DAYS)</u>
a. Identification and epidemiologic confirmation of the survival and spread of the new virus	1	30
b. Establishment of a "production strain" of the new virus	1	15
c. Production of vaccine for clinical trials	15	60
d. Adaptation of the "production strain" to manufacturing requirements	15	40
e. Development of potency requirements and vaccine recommendations	60	120
f. Release and delivery of vaccine:		
(1) Production of 25 million doses	40	100
(2) Production of additional 75 million doses	100	190
(3) Release of 25 million doses (200 CCA) <sup>1</sup>	130	130
(4) Release of additional 75 million doses	130	190
g. Effective utilization: <sup>2</sup>		
(1) 25 million doses	140	165
(2) 75 million doses	140	215

Table I (continued)

Policy Decisions

Determine vaccine production and delivery goals	1	30
a. Will the Federal Government assure the purchase of quantities of vaccine over and above what the private sector and the military will distribute alone?	1	30
b. Will the Federal Government support the public sector costs of administering vaccine among civilians not served by the private sector?	1	30

<sup>1</sup>Release of first 25 million must await the development of vaccine recommendations (Step e). It is assumed that BoB could release this initial supply of vaccine 10 days after potency requirements were set or shortly thereafter.

<sup>2</sup>It is assumed (1) that a minimum period of 10 days will be required to prepare "released" vaccine for shipment and to complete actual distribution to health providers; and (2) that a maximum of 1 million doses can be administered daily; and (3) that it requires 15 days after vaccination to achieve protective antibody levels.

Action Steps:

- a. Identification and epidemiologic confirmation of survival and spread of the new virus

Because major antigenic variants of influenza A virus are accompanied by rapid, worldwide (pandemic) spread of influenza, it is important that this step be completed quickly. For previous pandemics, this step took approximately 1 month to complete following reports of a possible new virus sub-type. It is estimated that the minimum time frame for completing this step in the future will also be approximately 1 month since epidemiologic confirmation of spread and laboratory confirmation of a new virus requires about 30 days.

- b. Establishment of a "production strain" of the virus

The newly isolated virus often grows and reproduces very poorly in the laboratory situation. Techniques for developing high growth strains through processes of recombination with existing laboratory strains have been greatly improved in recent years. Because of this innovation, the establishment of a "production strain" in 1976 was accomplished in half the amount of time (15 days) required in 1957 and 1968. With

advances in technology, such as recombination, it is anticipated that the minimum time necessary for completing this step in the future will be 15 days following epidemiologic confirmation of a new virus.

c. Production of vaccine for clinical trials

In 1976, the decision was made to conduct large field trials on the swine influenza vaccine before vaccine dosage recommendations were made. This was the first time that large-scale field trials preceded the use of a "new" influenza vaccine. Quantities of vaccine sufficient for the conduct of these trials were available approximately 7 weeks after establishment of a "production strain" of the new virus. The variability in the virus strains and yields makes it difficult to predict the minimum amount of time needed to complete this step. BoB estimates that with improved laboratory techniques, the minimum time needed to produce vaccine for clinical trials in the future will be approximately 45 days after establishment of a "production strain." This amount of time could be shortened to 30 days assuming there were no virus growth or yield problems.

d. Adaptation of the "production strain" to the individual manufacturing requirements of the pharmaceutical companies

After a high growth production strain is available to the manufacturers, some additional time is needed to inoculate eggs, to grow the virus in quantity, and to establish other production capabilities. In 1957 and 1968, this step required 55 and 45 days, respectively, after the availability of a production strain. In 1976, production capabilities were established about 22 days after the production strain had been made available, but liability issues delayed completion of this step for another 143 days. Once liability problems are solved, it is estimated that future decisionmakers should allow at least 25 days after the "production strain" has been made available to complete this step. If there were no virus growth or yield problems, this step could ideally be completed in 15 days.

e. The establishment of vaccine potency and dosage recommendations

Vaccine potency and dosage recommendations can be made after clinical trial data are analyzed. In 1976,

initial vaccine dosage recommendations were made on June 22 (65 days after the beginning of the clinical trials) for most of the adult population. Supplemental vaccine schedules were established about 12 weeks later for high risk children. It took 3 additional weeks (for a total of 15 weeks) to determine dosage recommendations for children in normal health and persons between the ages of 18 and 25. The delay in vaccine recommendations for children was due to the unexpected finding that a second booster dose was needed for adequate immunization because the initial single dose proved existing vaccines inadequate within tolerable limits of reactions. For planning purposes, a minimum of 60 days will be needed to conduct clinical trials which will enable vaccine potency and dosage recommendations to be established.

f. The release and delivery of vaccine

According to BoB, 60 days is the minimum time required to produce the first 25 million doses of influenza vaccine after development of production requirements. Thereafter, 25 million doses can be produced per month. In 1976, vaccine production

and delivery was affected by liability problems which slowed down production, and swine flu legislation (PL 94-380) which forced the release of vaccines to be postponed until October 1. Once liability problems are resolved, BoB's projections will be reliable for use in future pandemic planning.

Key Policy Decisions: Determine vaccine production and delivery goals

Two key policy decisions which must be made are those which determine vaccine production goals (to prompt private sector to begin maximum production of vaccine) and vaccine delivery goals (to permit the development of the programs at the State and local level). In the final analysis, these decisions are: (1) Will the Federal Government assure the purchase of quantities of vaccine over and above what the private sector and the military will distribute alone, and (2) will the Federal Government support the public sector costs of administering vaccine among civilians not served by the private sector? Each of these decisions is discussed in detail below:

1. Will the Federal Government assure the purchase of quantities of vaccine over and above what the private sector and military will distribute alone? If so, how much vaccine?

In order to make this decision, the following factors must be carefully examined: The potential for occurrence of a pandemic; the anticipated impact of a pandemic; the vaccine effectiveness and risk of complications; and the amount of lead time prior to the influenza season. Liability issues are also of prime importance but will not be addressed by this paper.

#### The Potential for Occurrence of a Pandemic

If the following three ingredients clearly exist, the probability of a pandemic is high: (1) An antigenically distinguishable new influenza virus, (2) a susceptible population, and (3) demonstrated capability for human-to-human spread of the virus.

#### The Anticipated Impact of a Pandemic

The impact of pandemic influenza is measured by comparing the number of pneumonia and influenza deaths occurring during the outbreak with the

number usually expected during that period. Although it is not possible to assess the virulence of an influenza virus in advance of its epidemic occurrence, any pandemic can be expected to cause thousands of excess deaths and millions of cases of illness.

#### Vaccine Effectiveness and Risk of Complications

When a mutant virus is identified with markedly new antigens, it is possible to develop a highly effective, specific antigen vaccine. Improved techniques in vaccine purification also result in fewer side effects than vaccines of the past.

#### The Amount of Lead Time Prior to Influenza Season

Vaccine manufacturers normally produce 20 million doses of influenza vaccine in interpandemic years. If more vaccine is needed, a decision must be made to permit the manufacturers time to gear up for increased production. For example, a decision to produce 100 million doses must be made no later than the middle of April to allow manufacturers sufficient production time. This means that the epidemiologic confirmation of the survival and

spread of a new virus must also be completed by mid-April. This time frame assumes that the ultimate dosage recommended will be based on the production of vaccine at a potency of 200 CCA's (chick cell agglutination units). If 400 CCA units are required, vaccine production will be roughly halved, leaving only 50 million doses. Since the decision on CCA concentrations cannot be made sooner than 3-4 months after confirmation of the virus, Congressional action must precede firm knowledge about the exact amount of vaccine which can be produced.

This timetable underscores the difficulties which will confront any attempt to outrace the first wave of a pandemic with an essentially population-wide or other major vaccination program. Virus confirmation, according to the preceding analysis, must occur very early and each of the steps must be accomplished in minimum time. The key policy decisions must be made in April. Even then, vaccine production must often take place after the normal production cycle of the manufacturers has been completed, and vaccine production and delivery goals must be set before the final production estimates are established (contingent upon the development of potency

requirements). Final decisions must be made during the time of the year when influenza activity in the northern hemisphere is typically low.

2. Will the Federal Government support the public sector costs of administering vaccine among civilians not served by the private sector? If so, to what target groups?

Several factors must be considered before making this decision: Potential Occurrence of an Epidemic and the Anticipated Impact of a Pandemic; and the Availability of State and Local Resources. Again, liability issues play a key role but are not addressed in this paper.

Potential for Occurrence of an Epidemic and the Anticipated Impact of a Pandemic

As discussed above, a new virus strain along with a susceptible population and human-to-human spread are the ideal ingredients for a pandemic. Any pandemic will result in thousands of deaths at a tremendous cost to society. As the cost to society increases, Federal support becomes more justifiable. It is generally accepted that routine influenza recommendations (immunization of the population at

high risk--elderly and chronically ill persons) would not forestall a flu pandemic. Routine actions would have to be supplemented.

#### Availability of State and Local Resources

Prior to 1976, the public sector had limited involvement in administering influenza vaccines. If a decision to involve the public sector in the administration of influenza vaccines is made, State and local health agencies must be allowed enough time to establish delivery systems. In terms of costs, there are three possibilities:

- (1) State legislatures could appropriate the funds - Some State legislatures meet only every 2 years so this alternative could present some timing problems. In addition, it is unlikely that all States would be able to afford the costs of a major immunization program for a pandemic.
- (2) State and local agencies could divert resources from ongoing programs to an immunization program - this alternative would have a high amount of opportunity costs associated with it. If

resources were diverted, there would be costs to society resulting from reduced commitment to the ongoing program.

- (3) The Federal Government could support the public sector costs - there would be greater certainty of participation by all States and fewer lost opportunity costs to other programs if this alternative were selected. The scope of resources would be expanded and would allow better utilization of all delivery points.
- (4) A combination of all three, as is the practice for other immunization programs and was the case in the swine flu program.

With proper planning, a Departmental recommendation to OMB can be made very soon after there is sufficient epidemiologic and laboratory evidence of a new virus subtype. It is assumed that at least 30 days would be required to obtain OMB and Congressional approval. Therefore, production and delivery goals can be established as early as 30 days after the epidemiologic confirmation of virus survival and spread. This might be shortened somewhat if

Congressional review of the issues occurred simultaneously with Departmental planning as soon as the virus is first isolated.' It will be lengthened if authorizing legislation and the liability issue must be addressed by Congress, in addition to appropriations.

#### SUMMARY

Some technological advances in vaccine production have shortened the time frames required in preparing for influenza pandemics, but public decisions will continue to be made against severe time pressures. Several actions could ease the time pressure significantly.

- a. The establishment of an ongoing influenza immunization system in the public sector, directed toward high risk groups. This system coupled with childhood immunization programs already established, could be fairly easily expanded to provide immunizations to the entire population. A federally supported influenza immunization system would be directed on a continuing basis at interpandemic, or epidemic, preparedness. This is the best way to assure pandemic preparedness, for it maintains the essential research, production, and distribution base. Though neither the time of

arrival nor the antigenic structure of the next major influenza A variant can be foretold, the complex of scientific and service mechanisms that will recognize it, adapt it for use as a vaccine, and distribute the vaccine is the same complex essential to the surveillance and control of influenza at all times.

- b. A decision not to attempt to outrace the first wave of a pandemic, but to provide immunizations primarily to ameliorate a second wave of the pandemic (if any) and to prime individuals against the subsequent strains of the virus which will occur through antigenic "drift."
- c. A decision to broaden immunization with the objective of preventing morbidity as well as mortality. This, too, would prime more individuals against subsequent strains while maintaining higher levels of protective antibody in the population.
- d. An expansion of worldwide morbidity and virus surveillance systems under the auspices of the World Health Organization.
- e. The development of an "all antigen" influenza vaccine.

## 2. Discussion

If the objective of the Public Health Service is to reduce morbidity and mortality associated with influenza, steps must be taken to:

- a. Improve the public's understanding of influenza and its prevention.
- b. Establish a decisionmaking process which can respond to the unpredictable nature of influenza and which opens up decisionmaking to a wide (but potentially definable) group of professionals and nonprofessionals.
- c. Remove known obstacles to the production of vaccine and the conduct of immunization programs.
- d. Strengthen surveillance systems and expand research directed toward a better understanding of the influenza virus, methods of reducing the impact of epidemics and pandemics, and methods of vaccine formulation and production.

Public understanding. A series of public attitude surveys were undertaken monthly throughout the swine flu program, and followup surveys have recently been completed. These surveys are very useful in evaluating public understanding of and attitudes toward swine influenza and the 1976 program.

They suggest that 57 percent of adults had decided to be vaccinated against swine flu in August 1976 (prior to the initiation of the vaccination phase of the program), and that 1 year later (August 1977) 53 percent of the population wanted to be vaccinated against influenza in the future if it was "recommended."

Among people not wanting to be vaccinated, the feeling that "it was not necessary" and the fear of adverse effects were the primary determining factors, both in 1976 and 1977.

These surveys also indicated that virtually the entire population was aware of the swine flu threat in August 1976, and was aware that a national program was being developed. However, this general understanding probably belies some very basic misunderstandings of influenza by the public. Such statements as "I had the stomach flu" are common, indicating a general equation of any supposed viral illness with influenza, resulting in considerable skepticism about the seriousness of the disease. On the other hand, the specter of "swine flu" and the frequent references in the press to the 1918 pandemic apparently created an excessive fear of a massive, highly virulent "plague" which was imminent. The failure of this supposed plague to materialize created further skepticism.

Part of the current problem, therefore, is the recent sudden mobilization of the Federal Government to confront a problem which had received little or no noticeable attention in the past.

#### The Decisionmaking Process

During 1976, the CDC, BoB, and NIAID, which have clearly demarcated responsibility for influenza surveillance and control, vaccine formulation and control, and influenza research, respectively, combined forces to collaborate in the coordination of an unprecedented national influenza program. The smooth functioning of the communication processes between the three agencies is a prerequisite to providing the necessary technical information required for a decision on future national vaccine policies and for the necessary program control. In 1976, communication among the three agencies was primarily on an ad hoc basis through workshops, informal meetings, and telephone contacts. There is much to be gained by formalizing the communication among these agencies and bringing the military medical departments and the Veterans Administration into that system. The establishment of an inter-agency working group is desirable. The purpose of this group would be to review and advise

the represented agencies and the Surgeon General on current influenza virus activity, influenza immunization strategy, and research needs.

The work group would also provide information and advice on technical matters to BoB, CDC, and NIAID Advisory Groups which would continue to make formal recommendations for vaccine formulation, use, and research. At the present time, no group is specifically assigned the responsibility to advise on a national pandemic strategy or to answer such questions as: (a) Should there be a major Federal investment in influenza immunization? and (b) should some form of nationwide vaccination campaign be attempted?

In 1976, four dimensions were added to the normal decision processes to answer these questions: (a) The preparation of an HEW recommendation to the White House for a national immunization program, (b) a brief review of this proposal by a selected group of Presidential Advisors, (c) the submission to Congress of a request for funds to carry out the National Influenza Immunization Program, and (d) Congressional action. This process has been vigorously criticized as being "political," "closed," and "lacking input" specifically from State and local health authorities, private medicine, the media, and the public.

Thus, it appears that under interpandemic circumstances, the BoB-CDC processes for producing recommendations on formulation and use of influenza vaccine have been efficient and effective. In potential pandemic situations, however, a broader consensus on national action seems desirable.

In 1957 and 1968, Surgeons General task forces, or analogous groups, were called upon to deal with the broad policy issues provoked by potential pandemic strains. In 1976, HEW hierarchy and an ad hoc panel of Presidential Advisors served this purpose.

These models do not appear to have satisfied the need; in 1957 and 1968, action was late and ineffective and in 1976 the process was severely criticized. Whether any group of individuals selected in any way can establish a sufficiently broad consensus regarding a potential pandemic remains in doubt. However, avenues for approaching this problem seem to be of two types: (a) The Public Health Service National Immunization Conference of April 1977 recommended the establishment of a standing National Commission on Immunization Policy which would deal with pandemic planning as part of its assigned duties, or (b) the selection of a broad-based temporary committee similar to those appointed by Secretary Califano to examine influenza policy for 1977.

The existence of a national commission, derived from various segments of society, would provide a logical organ for dealing with the larger national policy issues involved in response to a potential pandemic. In the absence of such a commission, there seems to be little alternative but to convene a special broad-based ad hoc committee to reexamine the same issues.

Removal of known obstacles to influenza vaccine production and influenza vaccination programs

In 1957, again in 1968, and again in 1976, it was seen that an effective response to a pandemic threat required complex procedures including enormous increases in vaccine production and supplies for vaccination; rapid mobilization of medical, paramedical, and administrative personnel at the Federal and local level; anticipation of the medico-legal, liability problems; and public acceptance of the program. Each of these requirements presented major stumbling blocks. The much-needed resources and expertise were either minimal or unavailable. These problems can be minimized, or even avoided, in the future. What is needed, in addition to a strengthened decisionmaking process as outlined above, is a reassessment of the Federal role in supporting influenza immunization. This role, prior to the swine influenza program, has been limited to making annual recommendations for vaccine

use, with no attempt to support or provide leadership for implementation of these recommendations in the civilian population. A beginning step in this direction was made in March 1977 through the Secretary's Conference on Influenza Vaccine Activity for 1977-1978. This group recommended that the Government do more in 1977-1978 than in the years prior to 1976, such as explore appropriate activities for improving influenza immunity levels. Whether this support should be in the area of vaccine purchase or assistance in vaccine delivery, or both, was not clearly defined by the group, but it was felt that Federal action of some type was needed or the level of immunization would move backward. It was also expressed that the Federal Government needs to explore the need for underwriting liability insurance appropriate for the type of program involved.

A major obstacle confronting the swine influenza program was the need to protect the various program participants from liability which might occur as a result of real or alleged injury resulting from vaccination. A long-range solution to this problem is essential if we are to be able to provide vaccines of all types and if we are to encourage and support their application in public programs.

Other obstacles to the production of vaccine and its administration must be addressed. However, the immediate needs are: (1) To resolve the problem of liability since it directly affects our ability to explore alternative means of improving the production and administration of vaccine; and (2) to establish a technical and policymaking decision process which can address outstanding issues in a careful and timely fashion.

#### Surveillance and Research Needs

Influenza surveillance systems were greatly expanded in 1976-1977, and their sensitivity and responsiveness were improved. These systems are continuing, but need to be strengthened by increasing the number of health care providers participating in a formal program of virus surveillance, expanding animal surveillance activities, meeting training needs of laboratory workers, and adding several key links to international surveillance activities (notably the Chinese mainland).

There are several promising areas of research which need to be exploited. They include:

1. Further development of subunit vaccines for use in unprimed individuals, particularly. The split-virus vaccines current available are less reactogenic in children, but require two doses to be adequately immunogenic.
2. Further testing of 2-dose schedule of small, non-reactogenic whole virus vaccine, with hemagglutinin content standardized with immunologic techniques (e.g. immunodiffusion).
3. Development of improved recombinant viruses for vaccine production.
4. Development of live virus vaccines. To date, it has not been possible to identify the factors responsible for virulence or attenuation. Techniques must be developed to identify them and to reproducibly transfer the attenuation determinants to contemporary antigenic variants.
5. Studies of pathogenesis of influenza.
6. In conjunction with improved animal surveillance, studies of the emergence of new animal strains of influenza and their transmission to humans.

7. Development of chemoprophylactic and chemotherapeutic antiviral agents. Amantadine is licensed and merits further testing in controlled clinical trials. Recent information suggests rimantadine is less toxic, therefore requires controlled studies and clinical testing to determine if it is a preferable antiviral agent to amantadine.
8. Some mechanism to assess the impact of each year's program outcome ought to be developed.

# M M M M R

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### Recommendations of the Public Health Service Advisory Committee on Immunization Practices

#### Influenza Vaccine

##### INTRODUCTION

Influenza occurs in the United States every year, but with great variation in incidence and geographic distribution. It periodically becomes epidemic when the antigens of prevalent influenza viruses have changed enough for a significant proportion of the population to become susceptible. More epidemics are caused by influenza A viruses than by influenza B viruses, and influenza A epidemics are notable for causing mortality in excess of what is normally expected. Furthermore, only influenza A viruses undergo major antigen changes that result in pandemics (worldwide epidemics).

An example of the sudden appearances of antigenically distinctive influenza A viruses occurred in February 1976, when A/New Jersey/76 (swine) influenza virus was identified as the cause of a focal epidemic at Fort Dix, New Jersey. Recognition of the potential of this new virus for supplanting prevalent strains of influenza A, the threat of subsequent pandemic spread, and the Federal program to provide specific swine influenza vaccines in 1976 are well known. The fact that A/New Jersey/76 virus did not spread beyond Fort Dix makes it unlikely that this virus constitutes a risk in 1977-78. Nevertheless, because swine influenza viruses continue to exist in swine in the United States and to cause occasional human cases, primarily in those with agricultural exposures, the swine influenza vaccines remaining from 1976 have been stockpiled in the event of future need.

Thousands of persons have died of influenza in epidemics in the United States in the past 20 years. In the 1957-58 influenza season, when a new influenza A virus (Asian strain) appeared, nearly 70,000 deaths were attributed to it in this country alone. In 1968-69, when the Hong Kong variant caused widespread epidemics in the United States, there were an estimated 33,000 excess deaths. In the intervening years, whenever influenza A epidemics have involved most of the country, 10,000 to 20,000 excess deaths resulted.

Efforts to prevent or control influenza in the United States usually have been aimed at protecting those at the greatest risk of becoming seriously ill or dying. Repeated observations during influenza epidemics have indicated that deaths occur primarily among chronically ill adults

and children and in older persons, especially those over age 65. These "high-risk" persons should be vaccinated annually regardless of the amount of influenza in their geographic areas.

In interpandemic periods, vaccinating the entire population has not been considered to be a reasonable public health objective for several reasons: the limited duration of protection from influenza vaccines, the relatively low attack rates of influenza in community outbreaks, and the usual lack of serious complications of disease in healthy people.

##### INFLUENZA VIRUS VACCINE FOR 1977-78

The Bureau of Biologics, Food and Drug Administration, reviews influenza vaccine formulation regularly and recommends reformulation with contemporary antigens when indicated. Bivalent influenza vaccine for 1977-78 will contain inactivated influenza A and B viruses representative of currently prevalent strains. Each adult dose of vaccine will contain 400 chick cell agglutinating (CCA) units of antigen or its equivalent in the following proportion: 200 CCA units of influenza A virus comparable to the prototype A/Victoria/3/75 (H3N2) and 200 CCA units of B/Hong Kong/5/72 influenza virus.

The 1977-78 vaccine will be available in "split-virus" and "whole-virus" preparations. Split-virus vaccines, which contain antigens produced by chemically disrupting the influenza virus, have been associated with somewhat fewer side effects than whole-virus vaccines, particularly in children. However, the split-virus vaccines appear to be somewhat less effective in eliciting antibodies when given as a single dose to persons who have not been "primed" by exposure to related viruses in nature or through vaccination.

The characteristic side effects and immunogenicity of split-virus and whole-virus influenza vaccines are important in understanding dosage recommendations for various age groups. Adults and older children, most of whom have had experience with influenza antigens related to A/Victoria/3/75 or B/Hong Kong/5/72 either by infection or through vaccination, can be expected to have a good antibody response to a single dose of the 1977-78 bivalent influenza vaccine. Children less than 6 years of age, some of whom have not encountered the currently prevalent viruses, will

*Influenza Recommendations - Continued*

need 2 doses of vaccine given 4 or more weeks apart in order to achieve satisfactory antibody responses. These children will not be adequately protected unless the second dose is given. Furthermore, because children and adolescents tend to experience somewhat more side effects from influenza vaccine than adults, only split-virus vaccines should be given to persons less than 18 years of age.

**VACCINE USAGE**

**General Recommendations**

Annual vaccination is strongly recommended for adults and children of all ages who have such chronic conditions as: 1) heart disease of any etiology, particularly with mitral stenosis or cardiac insufficiency, 2) chronic bronchopulmonary diseases, such as chronic bronchitis, bronchiectasis, tuberculosis, emphysema, and cystic fibrosis, 3) chronic renal disease, and 4) diabetes mellitus and other chronic metabolic disorders.

Vaccination is also recommended for older persons, particularly those over age 65 years, because excess mortality in influenza outbreaks occurs in this age group.

Vaccination may also be considered for persons who provide essential community services and may be at increased risk of exposure. Vaccination of such persons and of patients not specified in the high-risk groups should be made on an individual basis giving consideration to the inherent benefits, risks, and costs.

The accompanying table (see p. 199) summarizes vaccine and dosage recommendations by age group for 1977-78. These recommendations are derived from observations made during the field trials of influenza vaccines conducted in 1976. Because information from the immunization of infants and young children is limited, the dosages recommended for them are conservative.

**SIDE EFFECTS AND ADVERSE REACTIONS**

Side effects of influenza vaccine occur infrequently. Three types of responses to influenza vaccines have been described:

1. Fever, malaise, myalgia, and other systemic symptoms of toxicity starting 6-12 hours after vaccination and persisting 1-2 days. These responses to influenza vaccine are usually attributed to characteristics of the influenza virus itself (even though it is inactivated) and constitute most of the side effects of influenza vaccination. Such effects occur most frequently in children and others who have had no experience with influenza viruses comparable to the vaccine antigen(s).
2. Immediate—presumably allergic—responses, such as flare and wheal or various respiratory expressions of hypersensitivity. These reactions are exceedingly uncommon but can occur after influenza vaccination. They probably derive from exquisite sensitivity to some vaccine component, most likely residual egg

*(Continued on page 199)*

**Table I. Summary—Cases of Specified Notifiable Diseases: United States**

*[Cumulative totals include revised and delayed reports through previous weeks]*

DISEASE	23rd WEEK ENDING		MEDIAN 1972-1976	CUMULATIVE, FIRST 23 WEEKS		
	June 11, 1977	June 12, 1976		June 11, 1977	June 12, 1976	MEDIAN 1972-1976
Aseptic meningitis	51	36	50	857	818	841
Brucellosis	2	2	4	81	117	62
Chickenpox	5,243	5,538	---	139,787	131,017	---
Diphtheria	2	-	2	45	102	102
Encephalitis	16	13	17	268	330	360
	7	4	10	90	130	130
Hepatitis, Viral	341	331	203	7,114	6,447	4,220
	567	651	737	14,078	15,702	19,236
	158	194	---	4,078	3,848	---
Malaria	15	14	7	172	154	124
Measles (rubeola)	2,356	1,518	1,191	44,267	28,827	20,552
Meningococcal infections, total	34	27	25	979	829	753
	34	27	24	974	818	736
	-	-	-	5	11	18
Mumps	459	1,035	1,660	12,897	28,071	38,351
Pertussis	15	10	---	308	420	---
Rubella (German measles)	698	372	651	15,888	9,090	13,003
Tetanus	3	1	1	22	18	28
Tuberculosis	601	648	---	13,352	14,402	---
Tularemia	3	1	4	41	55	46
Typhoid fever	5	11	10	161	142	150
Typhus, tick-borne (Rky. Mt. spotted fever)	52	27	45	269	172	172
<b>Veneral Diseases:</b>						
Gonorrhea	18,062	19,701	---	409,804	425,059	---
	693	417	---	11,827	13,007	---
Syphilis, primary and secondary	391	475	---	3,164	11,045	---
	5	4	---	135	150	---
Rabies in animals	62	70	70	1,248	1,199	1,331

**Table II. Notifiable Diseases of Low Frequency: United States**

	CUM.		CUM.
Chrax:	-	Poliomyelitis, total:	4
Chlamydia: Nev. 1	68	Paralytic:	4
Genital rubella syndrome:	8	Psittacosis: N. Mex. 1, Calif. 1	27
Leptospirosis: Calif. 2	52	Rabies in man:	-
Leptospirosis: La. 1	21	Trichinosis: Conn. 1, Ups. N.Y. 1, Md. 1	49
Plague:	1	Typhus, murine: Ups. N.Y. 2, Tex. 3	30

\*Delayed reports: Leptospirosis: Iowa 1 (1976); Psittacosis: Ark. 1 (1977)

Table III  
Cases of Specified Notifiable Diseases: United States  
Weeks Ending June 11, 1977 and June 12, 1976 - 23rd Week

AREA REPORTING	ASEPTIC MENIN- GITIS	BRUCEL- LOSIS	CHICKEN- POX	DIPHTHERIA		ENCEPHALITIS			HEPATITIS, VIRAL			MALARIA	
						Primary: Arthropod- borne and Unspecified		Post In- fectious	Type B	Type A	Type Unspecified		
						1977	1976	1977	1977	1977	1977		
UNITED STATES .....	51	2	5,243	2	45	16	13	7	341	567	158	15	172
NEW ENGLAND .....	1	7	742	-	-	-	-	2	7	11	9	-	7
Maine .....	-	-	1	-	-	-	-	-	-	-	-	-	-
New Hampshire*	-	-	18	-	-	-	-	-	1	1	-	-	-
Vermont .....	-	-	10	-	-	-	-	-	-	-	-	-	1
Massachusetts .....	-	-	363	-	-	-	-	-	-	1	9	-	2
Rhode Island .....	-	-	106	-	-	-	-	-	-	1	-	-	2
Connecticut .....	1	-	244	-	-	-	-	2	6	8	-	-	2
MIDDLE ATLANTIC .....	8	-	783	-	5	4	1	-	64	59	22	3	42
Upstate New York .....	-	-	606	-	-	-	1	-	11	13	6	1	10
New York City .....	3	-	148	-	5	1	-	-	16	11	6	2	20
New Jersey .....	5	-	NY	-	-	3	-	-	9	13	7	-	6
Pennsylvania .....	-	-	29	-	-	-	-	-	28	22	3	-	6
EAST NORTH CENTRAL .....	-	-	2,149	-	-	2	1	1	53	85	9	-	10
Ohio .....	-	-	256	-	-	1	-	-	17	25	-	-	5
Indiana*	-	-	55	-	-	1	-	-	2	3	3	-	-
Illinois .....	-	-	532	-	-	-	1	1	7	29	-	-	1
Michigan .....	-	-	907	-	-	-	-	-	23	25	5	-	2
Wisconsin*	-	-	399	-	-	-	-	-	4	3	1	-	2
WEST NORTH CENTRAL .....	2	1	172	-	1	-	1	1	16	32	13	3	15
Minnesota .....	-	-	-	-	-	-	-	-	2	1	-	-	4
Iowa*	-	-	81	-	-	-	-	-	3	5	2	-	-
Missouri .....	2	1	4	-	1	-	1	-	2	7	6	3	8
North Dakota*	-	-	11	-	-	-	-	-	-	-	-	-	-
South Dakota .....	-	-	1	-	-	-	-	-	-	1	-	-	1
Nebraska .....	-	-	11	-	-	-	-	-	7	1	2	-	-
Kansas .....	-	-	64	-	-	-	-	1	2	17	3	-	2
SOUTH ATLANTIC .....	13	-	368	-	-	1	1	2	71	92	24	1	26
Delaware .....	-	-	12	-	-	-	-	-	1	3	-	-	-
Maryland .....	-	-	34	-	-	-	-	-	10	11	2	-	7
District of Columbia .....	-	-	4	-	-	-	-	-	2	1	-	-	1
Virginia*	2	-	20	-	-	-	-	-	4	1	5	1	4
West Virginia*	3	-	72	-	-	-	-	-	-	3	-	-	1
North Carolina .....	-	-	NY	-	-	1	-	-	5	6	2	-	4
South Carolina .....	2	-	1	-	-	-	-	-	11	3	5	-	-
Georgia .....	-	-	17	-	-	-	-	-	5	16	-	-	4
Florida .....	6	-	208	-	-	-	1	2	33	48	10	-	5
EAST SOUTH CENTRAL .....	2	1	82	-	-	5	3	-	17	29	4	-	3
Kentucky .....	-	-	64	-	-	-	-	-	-	-	-	-	3
Tennessee .....	2	1	NY	-	-	3	-	-	15	14	-	-	-
Alabama .....	-	-	10	-	-	-	-	-	-	2	4	-	-
Mississippi .....	-	-	8	-	-	2	3	-	2	13	-	-	-
WEST SOUTH CENTRAL .....	9	-	172	-	1	1	-	1	16	49	22	1	9
Arkansas*	1	-	3	-	-	-	-	-	2	19	4	-	-
Louisiana .....	-	-	NN	-	-	-	-	-	2	-	-	-	-
Oklahoma .....	-	-	4	-	-	-	-	-	2	2	-	-	-
Texas .....	8	-	165	-	1	1	-	1	10	23	18	1	9
MOUNTAIN .....	-	-	287	1	2	-	-	-	9	53	13	-	6
Montana*	-	-	9	-	-	-	-	-	-	7	1	-	-
Idaho .....	-	-	14	-	-	-	-	-	-	3	-	-	-
Wyoming .....	-	-	-	-	-	-	-	-	1	2	-	-	1
Colorado .....	-	-	254	-	-	-	-	-	4	2	4	-	4
New Mexico .....	-	-	-	1	1	-	-	-	-	14	-	-	-
Arizona .....	-	-	NN	-	1	-	-	-	4	20	7	-	1
Utah .....	-	-	2	-	-	-	-	-	-	5	1	-	-
Nevada*	-	-	8	-	-	-	-	-	-	-	-	-	-
PACIFIC .....	16	-	488	1	36	3	6	-	88	141	42	7	54
Washington .....	-	-	449	1	34	1	-	-	-	2	1	-	4
Oregon .....	6	-	5	-	-	-	-	-	10	14	4	-	1
California*	8	-	-	-	1	2	4	-	78	112	37	7	44
Alaska .....	-	-	9	-	1	-	2	-	-	31	-	-	1
Hawaii .....	2	-	25	-	-	-	-	-	-	2	-	-	4
Guam*	NA	NA	NA	NA	-	NA	-	-	NA	NA	NA	NA	-
Puerto Rico .....	-	-	17	-	-	-	-	-	-	-	7	-	1
Virgin Islands*	-	-	-	-	-	-	-	-	-	-	-	-	-

NN: Not Notifiable

NA: Not Available

\*Delayed Reports: Asep. Meng.: Iowa delete 11 (1976), Ind. delete 1, W. Va. delete 1 (1977); Bruc.: Iowa delete 3 (1976), Ark. add 3, Mont. delete 1 (1977); Chickenpox: Iowa delete 80 (1976), N. Hamp. add 11, Calif. add 16, Guam add 2 (1977); Enceph. Pri.: Iowa delete 6 (1976); Enceph. Post: Iowa delete 2 (1976), Fla. delete 1 (1977); Hep. B: Iowa delete 6 (1976), Fla. delete 1 (1977); Hep. A: Iowa add 6 (1976), Ind. delete 2, Wis. delete 1, N. Dak. delete 7, Va. delete 1, Nev. add 2, Guam add 1, V.I. add 1 (1977); Hep. Unsp.: Iowa add 3 (1976), Guam add 1, V.I. delete 1 (1977).

Table III-Continued  
Cases of Specified Notifiable Diseases: United States  
Weeks Ending June 11, 1977 and June 12, 1976 - 23rd Week

REPORTING AREA	MEASLES (Rubella)			MENINGOCOCCAL INFECTIONS TOTAL			MUMPS		PERTUSSIS	RUBELLA		TETANUS
	1977	CUMULATIVE		1977	CUMULATIVE		1977	CUM. 1977	1977	1977	CUM. 1977	CUM. 1977
		1977	1976		1977	1976						
UNITED STATES .....	2,356	44,267	28,827	34	377	829	459	12,897	15	698	15,888	22
NEW ENGLAND .....	168	2,114	276	2	41	38	19	551	-	26	1,076	-
Maine .....	51	87	3	-	3	-	2	40	-	-	68	-
New Hampshire* .....	10	474	7	-	3	2	-	86	-	1	231	-
Vermont .....	23	288	-	-	4	3	-	5	-	-	63	-
Massachusetts* .....	29	582	24	1	12	11	4	99	-	14	330	-
Rhode Island .....	13	51	14	-	-	4	1	46	-	-	124	-
Connecticut .....	42	632	228	1	19	18	12	275	-	11	260	-
MIDDLE ATLANTIC .....	456	6,449	5,971	6	140	113	72	952	1	262	4,992	1
Upstate New York .....	147	2,527	2,422	1	35	43	10	176	-	101	2,661	-
New York City .....	84	396	348	3	30	30	14	359	-	10	258	-
New Jersey .....	7	132	544	1	28	16	41	283	-	54	1,623	1
Pennsylvania .....	218	3,394	2,657	1	47	24	7	134	1	97	450	-
EAST NORTH CENTRAL .....	414	8,996	12,074	-	95	101	206	4,498	1	155	3,294	1
Ohio .....	86	905	422	-	35	44	17	590	-	39	1,038	-
Indiana .....	116	4,092	2,551	-	7	4	3	249	-	17	865	-
Illinois .....	75	1,198	1,221	-	17	10	60	731	-	5	245	-
Michigan .....	23	793	4,894	-	24	35	67	1,525	1	82	799	1
Wisconsin* .....	114	2,008	2,986	-	12	8	59	1,403	-	12	347	-
WEST NORTH CENTRAL .....	464	8,933	1,049	1	64	60	45	3,037	1	24	453	3
Minnesota .....	252	2,285	321	-	21	13	-	5	-	5	16	1
Iowa* .....	97	4,183	31	-	5	8	4	1,239	-	2	149	-
Missouri* .....	81	890	12	-	27	18	29	837	-	-	32	1
North Dakota .....	-	16	3	-	1	3	-	11	-	-	9	-
South Dakota .....	1	51	2	-	4	2	1	59	-	12	17	-
Nebraska .....	-	180	40	-	1	3	-	54	1	-	2	-
Kansas .....	33	1,323	640	1	5	13	11	832	-	5	228	1
SOUTH ATLANTIC .....	167	3,343	1,682	9	207	165	28	556	-	56	1,469	7
Delaware .....	-	22	122	-	3	2	1	94	-	1	23	-
Maryland .....	11	297	665	2	15	15	3	40	-	-	5	-
District of Columbia .....	-	1	4	-	-	2	-	5	-	-	-	-
Virginia .....	63	1,820	409	-	12	26	-	69	-	7	543	1
West Virginia .....	10	179	156	-	8	4	3	133	-	1	83	-
North Carolina .....	2	49	-	1	52	31	1	31	-	10	410	-
South Carolina .....	7	137	3	-	20	30	1	10	-	34	200	-
Georgia .....	60	706	-	1	36	13	2	10	-	1	47	-
Florida .....	14	132	323	5	61	42	17	164	-	2	158	6
EAST SOUTH CENTRAL .....	80	1,665	681	4	114	72	21	664	1	41	1,835	2
Kentucky .....	59	988	657	-	19	14	1	79	-	-	66	1
Tennessee .....	16	575	9	3	30	31	16	380	1	34	1,655	1
Alabama .....	4	76	-	1	44	20	3	180	-	7	108	-
Mississippi .....	1	26	15	-	21	7	1	25	-	-	6	-
WEST SOUTH CENTRAL .....	35	1,872	589	2	171	130	24	1,098	1	24	680	3
Arkansas .....	-	26	-	-	9	6	1	27	-	-	1	-
Louisiana* .....	2	73	161	1	64	18	-	30	2	-	23	1
Oklahoma .....	1	52	273	-	6	18	1	400	-	-	25	-
Texas .....	32	1,721	155	1	92	88	22	641	2	24	631	2
MOUNTAIN .....	106	2,034	4,753	2	35	24	4	524	5	15	318	1
Montana .....	26	1,070	189	-	2	3	-	4	-	2	11	-
Idaho .....	53	125	1,994	1	4	3	1	116	-	3	8	-
Wyoming .....	5	9	3	-	1	-	-	-	-	-	2	1
Colorado .....	7	470	201	-	1	4	3	242	-	6	226	-
New Mexico .....	3	17	14	1	17	2	-	93	5	-	8	-
Arizona .....	8	253	222	-	8	7	-	-	-	-	10	-
Utah .....	-	5	2,068	-	1	4	-	62	-	2	46	-
Nevada .....	4	85	62	-	1	1	-	7	-	2	7	-
PACIFIC .....	466	8,861	1,752	8	112	126	40	1,017	2	95	1,771	4
Washington* .....	17	452	191	2	15	20	10	247	-	12	419	-
Oregon .....	15	306	118	-	10	10	3	183	-	3	93	-
California .....	422	8,014	1,441	6	68	85	26	547	2	76	1,247	4
Alaska .....	-	55	-	-	17	9	-	24	-	-	1	-
Hawaii .....	12	34	2	-	2	2	1	16	-	4	11	-
Guam* .....	NA	3	9	-	-	-	NA	1	NA	NA	4	-
Puerto Rico .....	39	677	169	-	-	2	13	425	2	1	21	7
Virgin Islands .....	-	10	5	-	-	-	1	172	-	-	-	-

NA: Not Available

\*Delayed Reports: Measles: Iowa add 10 (1976), N. Hamp. add 9, Mass. delete 11, Wis. add 146, Iowa delete 2, Mo. delete 19, Guam add 1 (1977); Men. Inf.: Mo. delete 1, La. delete 1 (1977); Mumps: Iowa add 9 (1976); Pertussis: Wash. add 1 (1977); Rubella: Iowa add 1 (1976), Guam add 2 (1977)

Table III-Continued  
Cases of Specified Notifiable Diseases: United States  
Weeks Ending June 11, 1977 and June 12, 1976 - 23rd Week

REPORTING AREA	TUBERCULOSIS		TULA-REMIA	TYPHOID FEVER		TYPHUS-FEVER TICK-BORNE (RMSF)		VENEREAL DISEASES (Civilian Cases Only)				RABIES IN ANIMALS		
	1977	CUM. 1977	CUM. 1977	1977	CUM. 1977	1977	CUM. 1977	GONORRHEA		SYPHILIS (Pri. & Sec.)		CUM. 1977		
								1977	CUMULATIVE		1977		CUMULATIVE	
									1977	1976			1977	1976
UNITED STATES .....	601	13,352	41	5	161	52	269	18,062	409,804	425,059	391	9,164	11,045	1,248
NEW ENGLAND .....	27	493	1	2	10	-	3	305	10,536	11,363	16	363	319	19
Maine .....	-	37	-	-	-	-	-	34	779	984	1	9	8	17
New Hampshire* .....	4	15	-	-	-	-	-	27	427	301	-	2	4	1
Vermont .....	-	21	-	-	-	-	-	10	281	271	-	4	2	-
Massachusetts .....	17	268	1	2	7	-	-	206	4,640	5,382	12	270	227	-
Rhode Island .....	2	37	-	-	2	-	2	26	850	775	-	4	12	-
Connecticut .....	4	115	-	-	1	-	1	2	3,559	3,650	3	74	66	1
MIDDLE ATLANTIC .....	114	2,134	-	3	30	2	10	2,228	42,933	47,357	46	1,275	1,868	26
Upstate New York .....	12	335	-	-	4	-	2	491	6,912	7,425	-	112	119	16
New York City .....	43	715	-	1	12	-	-	664	17,696	21,015	28	801	1,194	-
New Jersey .....	34	539	-	2	12	2	2	624	7,115	7,412	10	167	244	9
Pennsylvania .....	25	545	-	-	2	-	6	449	11,210	11,505	8	195	311	1
EAST NORTH CENTRAL .....	94	2,120	3	-	15	-	-	2,449	62,323	67,293	15	969	958	48
Ohio* .....	6	320	1	-	5	-	-	321	15,555	16,237	9	246	231	-
Indiana .....	10	248	-	-	-	-	-	120	5,858	6,205	2	70	52	2
Illinois .....	53	839	-	-	1	-	-	1,003	20,680	25,043	-	501	535	14
Michigan* .....	20	613	-	-	9	-	-	784	14,341	14,002	2	106	129	3
Wisconsin .....	5	100	2	-	-	-	-	221	5,889	5,806	2	46	51	29
WEST NORTH CENTRAL .....	22	459	5	-	12	2	10	1,146	21,563	21,684	4	221	199	289
Minnesota .....	6	94	-	-	3	-	-	184	3,806	3,893	2	67	43	94
Iowa* .....	1	48	-	-	-	-	-	136	2,573	2,728	-	26	19	53
Missouri* .....	5	191	4	-	5	1	7	526	9,174	8,620	2	77	84	22
North Dakota .....	-	12	-	-	-	-	-	13	391	317	-	-	-	39
South Dakota .....	5	22	1	-	-	-	-	31	566	593	-	1	2	59
Nebraska .....	1	18	-	-	1	-	-	134	1,895	1,877	-	21	13	-
Kansas .....	4	74	-	-	3	1	3	122	3,158	3,656	-	29	38	22
SOUTH ATLANTIC .....	121	3,010	8	-	27	32	153	4,202	99,694	103,429	109	2,605	3,314	129
Delaware .....	-	25	-	-	-	-	1	30	1,347	1,359	-	16	35	1
Maryland .....	14	434	1	-	-	4	16	573	12,708	14,101	11	177	269	-
District of Columbia .....	14	150	-	-	-	-	-	284	6,550	7,210	12	275	264	-
Virginia .....	18	334	-	-	6	11	48	405	10,256	10,852	5	251	283	2
West Virginia* .....	4	113	-	-	3	-	1	65	1,467	1,311	-	1	17	4
North Carolina* .....	15	516	2	-	1	14	57	577	14,858	15,165	12	374	635	4
South Carolina .....	15	288	2	-	-	3	12	419	9,298	10,213	6	114	169	3
Georgia .....	10	333	3	-	9	-	18	662	19,080	18,935	27	493	470	85
Florida .....	31	817	-	-	8	-	-	1,187	24,130	24,283	36	904	1,172	30
EAST SOUTH CENTRAL .....	57	1,161	2	-	3	9	38	1,671	36,272	38,034	13	315	436	41
Kentucky .....	12	272	1	-	-	4	5	133	4,835	4,772	-	33	65	12
Tennessee* .....	27	388	1	-	1	5	30	613	14,510	14,935	6	99	176	22
Alabama .....	9	315	-	-	1	-	3	565	10,098	10,863	1	52	86	7
Mississippi .....	9	186	-	-	1	-	-	360	6,829	7,464	6	131	109	-
WEST SOUTH CENTRAL .....	52	1,552	18	-	6	7	54	2,128	52,786	56,788	81	1,294	1,261	433
Arkansas .....	11	175	11	-	-	3	9	168	4,099	5,503	-	29	43	56
Louisiana* .....	4	311	-	-	-	-	-	367	7,952	8,272	15	280	267	4
Oklahoma .....	3	146	4	-	-	4	35	221	4,905	5,158	2	35	49	149
Texas .....	34	920	3	-	6	-	10	1,372	35,830	37,855	64	950	902	224
MOUNTAIN .....	16	353	3	-	14	-	1	648	16,549	17,007	3	191	317	55
Montana .....	1	19	1	-	-	-	1	30	811	839	-	-	3	28
Idaho .....	2	19	-	-	-	-	-	26	799	883	-	4	12	-
Wyoming .....	2	7	-	-	-	-	-	24	419	354	-	13	6	-
Colorado .....	-	54	2	-	7	-	-	158	4,257	4,134	1	55	71	3
New Mexico .....	-	52	-	-	-	-	-	120	2,397	3,278	-	34	86	-
Arizona .....	11	169	-	-	3	-	-	257	4,865	5,129	2	75	101	23
Utah .....	-	15	-	-	4	-	-	33	944	833	-	4	16	1
Nevada .....	-	18	-	-	-	-	-	NA	2,057	1,557	NA	6	22	-
PACIFIC .....	98	2,070	1	-	44	-	-	3,285	67,148	62,104	104	1,931	2,333	208
Washington .....	NA	132	-	-	1	-	-	224	5,133	5,270	NA	76	65	-
Oregon .....	4	93	-	-	3	-	-	162	4,714	4,616	1	57	56	-
California .....	83	1,528	1	-	39	-	-	2,738	53,690	49,315	103	1,765	2,162	197
Alaska .....	-	31	-	-	-	-	-	82	2,152	1,750	-	13	10	11
Hawaii .....	11	286	-	-	1	-	-	79	1,459	1,153	-	20	40	-
Guam* .....	NA	31	-	NA	1	NA	-	NA	96	165	NA	1	1	-
Puerto Rico .....	9	149	-	-	3	-	-	65	1,390	1,175	6	249	248	29
Virgin Islands .....	-	1	-	-	-	-	-	5	89	120	-	3	34	-

NA: Not Available

\*Delayed Reports: TB: N. Hamp. add 1, Ohio delete 1, Mich. delete 1, N. Carol. delete 2, Guam add 2 (1977); Typhoid Fever: Mo. delete 1 (1977); GC: Tenn. delete 2, La. delete 13, Guam add 6 (1977); Syphilis: La. delete 6 (1977); An. Rabies: Iowa add 2 (1976); W. Va. delete 2 (1977)

Table IV  
Deaths in 121 United States Cities\*  
Week Ending June 11, 1977 - 23rd Week

REPORTING AREA	ALL CAUSES					Pneumonia and Influenza ALL AGES	REPORTING AREA	ALL CAUSES					Pneumonia and Influenza ALL AGES
	ALL AGES	65 Years and Over	45-64 Years	25-44 Years	Under 1 Year			ALL AGES	65 Years and Over	45-64 Years	25-44 Years	Under 1 Year	
<b>NEW ENGLAND</b> .....	592	384	138	36	15	32	<b>SOUTH ATLANTIC</b> .....	1,303	568	304	57	43	46
Boston, Mass. ....	157	86	49	7	7	7	Atlanta, Ga. ....	130	74	35	11	4	1
Bridgeport, Conn. ....	36	26	7	2	-	3	Baltimore, Md. ....	127	76	41	2	5	4
Cambridge, Mass. ....	23	17	5	1	-	3	Charlotte, N. C. ....	50	25	17	5	1	2
Fall River, Mass. ....	20	17	3	-	-	-	Jacksonville, Fla. ....	88	55	25	3	3	4
Hartford, Conn. ....	53	33	10	8	-	2	Miami, Fla. ....	102	58	36	3	2	3
Lowell, Mass. ....	18	12	4	1	-	1	Norfolk, Va. ....	57	30	13	9	4	4
Lynn, Mass. ....	21	15	5	1	-	-	Richmond, Va. ....	86	45	31	5	3	10
New Bedford, Mass. ....	29	20	6	3	-	-	Savannah, Ga. ....	49	28	17	1	-	5
New Haven, Conn. ....	47	34	8	4	-	1	St. Petersburg, Fla. ....	65	50	14	-	-	5
Providence, R.I. ....	53	29	15	4	2	7	Tampa, Fla. ....	63	31	21	5	4	3
Somerville, Mass. ....	4	3	1	-	-	1	Washington, D. C. ....	146	73	40	12	16	2
Springfield, Mass. ....	42	25	9	3	3	2	Wilmington, Del. ....	40	23	14	1	1	3
Waterbury, Conn. ....	39	29	7	2	-	1							
Worcester, Mass. ....	50	38	8	-	3	4	<b>EAST SOUTH CENTRAL</b> .....	727	421	195	45	26	34
<b>MIDDLE ATLANTIC</b> .....	2,684	1,641	715	168	76	95	Birmingham, Ala. ....	95	53	27	3	3	4
Albany, N. Y. ....	44	28	8	3	5	-	Chatanooga, Tenn. ....	56	38	12	5	1	2
Allentown, Pa. ....	22	17	3	1	-	1	Knoxville, Tenn. ....	41	25	13	2	-	-
Buffalo, N. Y. ....	95	62	22	2	3	4	Louisville, Ky. ....	112	65	28	5	9	9
Camden, N. J. ....	22	14	3	2	2	2	Memphis, Tenn. ....	171	100	41	11	7	9
Elizabeth, N. J. ....	32	25	5	1	1	1	Mobile, Ala. ....	76	44	18	10	2	2
Erie, Pa. ....	43	31	9	-	2	1	Montgomery, Ala. ....	44	25	13	3	-	2
Jersey City, N. J. ....	42	25	10	5	1	1	Nashville, Tenn. ....	132	71	43	6	4	6
Newark, N. J. ....	52	23	22	3	3	1	<b>WEST SOUTH CENTRAL</b> .....	1,243	690	331	82	69	26
New York City, N. Y. ....	1,296	781	350	96	31	44	Austin, Tex. ....	29	21	3	2	-	1
Paterson, N. J. ....	33	20	9	2	1	2	Baton Rouge, La. ....	46	26	13	3	4	2
Philadelphia, Pa. ....	384	223	110	26	12	11	Corpus Christi, Tex. ....	38	25	9	1	2	-
Pittsburgh, Pa. ....	157	110	64	12	6	11	Dallas, Tex. ....	204	104	54	15	10	4
Reading, Pa. ....	30	23	6	1	-	-	El Paso, Tex. ....	55	35	10	1	6	1
Rochester, N. Y. ....	136	83	34	7	2	6	Fort Worth, Tex. ....	84	46	23	7	6	2
Schenectady, N. Y. ....	23	15	6	2	-	-	Houston, Tex. ....	284	125	92	27	15	7
Seranton, Pa. ....	53	37	13	2	-	2	Little Rock, Ark. ....	54	30	13	3	4	1
Syracuse, N. Y. ....	94	61	22	2	6	2	New Orleans, La. ....	145	91	37	7	6	-
Trenton, N. J. ....	43	31	9	-	1	2	San Antonio, Tex. ....	156	90	41	12	10	2
Utica, N. Y. ....	18	12	6	-	-	1	Shreveport, La. ....	66	37	20	1	5	2
Yonkers, N. Y. ....	25	20	4	1	-	3	Tulsa, Okla. ....	82	60	16	3	1	4
<b>EAST NORTH CENTRAL</b> .....	2,421	1,347	702	162	111	63	<b>MOUNTAIN</b> .....	480	294	97	42	22	27
Akron, Ohio ....	76	45	21	4	3	-	Albuquerque, N. Mex. ....	41	26	7	4	1	3
Canton, Ohio ....	18	10	6	1	-	1	Colorado Springs, Colo. ....	28	16	5	4	-	5
Chicago, Ill. ....	561	306	159	35	37	17	Denver, Colo. ....	99	56	18	13	7	6
Cincinnati, Ohio ....	194	109	63	8	7	3	Las Vegas, Nev. ....	45	21	11	5	3	2
Cleveland, Ohio ....	182	88	67	12	5	2	Ogden, Utah ....	21	13	4	2	-	3
Columbus, Ohio ....	142	74	46	13	3	5	Phoenix, Ariz. ....	100	61	25	6	4	1
Dayton, Ohio ....	108	58	36	8	3	-	Pueblo, Colo. ....	26	23	1	2	-	4
Detroit, Mich. ....	313	167	92	27	14	1	Salt Lake City, Utah ..	46	29	8	3	4	-
Evansville, Ind. ....	67	40	18	3	2	2	Tucson, Ariz. ....	74	49	18	3	3	3
Fort Wayne, Ind. ....	69	34	18	3	6	-							
Gary, Ind. ....	17	5	6	5	-	2	<b>PACIFIC</b> .....	1,775	1,147	415	93	47	48
Grand Rapids, Mich. ....	47	36	10	1	-	8	Berkeley, Calif. ....	17	11	2	2	1	1
Indianapolis, Ind. ....	164	97	40	10	9	5	Fresno, Calif. ....	82	52	18	6	4	-
Madison, Wis. ....	28	15	6	2	3	4	Glendale, Calif. ....	29	22	5	-	1	2
Milwaukee, Wis. ....	137	92	34	3	7	7	Honolulu, Hawaii ....	41	25	9	2	3	-
Peoria, Ill. ....	43	20	9	6	5	-	Long Beach, Calif. ....	87	49	32	1	1	3
Rockford, Ill. ....	43	18	13	4	4	4	Los Angeles, Calif. ....	567	391	116	31	6	23
South Bend, Ind. ....	47	29	14	3	1	2	Oakland, Calif. ....	71	47	14	3	5	1
Toledo, Ohio ....	107	63	30	8	2	-	Pasadena, Calif. ....	32	25	5	1	1	1
Youngstown, Ohio ....	61	41	14	6	-	-	Portland, Ore. ....	129	78	28	7	9	-
<b>WEST NORTH CENTRAL</b> .....	786	487	193	49	27	26	Sacramento, Calif. ....	73	39	24	5	2	-
Des Moines, Iowa ....	58	39	14	2	2	-	San Diego, Calif. ....	146	90	39	5	3	3
Duluth, Minn. ....	31	24	4	1	2	2	San Francisco, Calif. ....	174	108	44	15	3	2
Kansas City, Kans. ....	33	18	6	4	1	2	San Jose, Calif. ....	57	39	7	4	1	1
Kansas City, Mo. ....	142	97	34	7	2	3	Seattle, Wash. ....	171	104	46	8	6	4
Lincoln, Nebr. ....	31	23	7	-	1	2	Spokane, Wash. ....	55	39	12	1	1	4
Minneapolis, Minn. ....	106	58	29	11	3	6	Tacoma, Wash. ....	44	28	14	2	-	3
Omaha, Nebr. ....	84	55	21	1	2	-							
St. Louis, Mo. ....	170	97	42	15	13	5	<b>TOTAL</b> .....	11,711	6,979	3,090	734	436	397
St. Paul, Minn. ....	63	45	12	3	-	4	Expected Number .....	11,224	6,762	2,915	733	374	358
Wichita, Kans. ....	68	31	24	5	4	2							

\*By place of occurrence and week of filing certificate. Excludes fetal deaths.

The Morbidity and Mortality Weekly Report, circulation 67,500, is published by the Center for Disease Control, Atlanta, Georgia. The data in this report are provisional, based on weekly telegraphs to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the succeeding Friday.

The editor welcomes accounts of interesting cases, outbreaks, environmental hazards, or other public health problems of current interest to health officials. Send reports to: Center for Disease Control, Attn.: Editor, Morbidity and Mortality Weekly Report, Atlanta, Georgia 30333.

Send mailing list additions, deletions, and address changes to: Center for Disease Control, Attn.: Distribution Services, GSO, 1-SB-36, Atlanta, Georgia 30333. When requesting changes be sure to give your former address, including zip code and mailing list code number, or send an old address label.

*Influenza Recommendations — Continued*

TABLE 1. Influenza vaccine dosage by age, 1977-78

Age	Product Type	Dose Volume (ml)	Total CCA Units*	Number of Doses
18 years and older	Whole-virus or Split-virus	0.5	400	1
6-17 years	Split-virus	0.5	400	1
3-5 years	Split-virus	0.25	200	2**
6-35 months	Split-virus	0.15	120	2**

\*Representing equal amounts of A/Victoria/75 and B/Hong Kong/72.

\*\*4 weeks or more between doses; both doses essential for good protection.

protein. Although current influenza vaccines contain only a minute quantity of egg protein, they can, on rare occasions, provoke hypersensitivity reactions. Individuals with known or suspected hypersensitivity to eggs should be given influenza vaccine only under the care and close observation of a physician.

- Guillain-Barré syndrome, usually a self-limited paralysis, is observed within 8 weeks after influenza vaccination in approximately 10 of every million persons vaccinated. It also occurs, but less frequently, in unvaccinated persons. Prior to the intensive surveillance of influenza vaccine that occurred during the swine influenza vaccination program in 1976, serious adverse reactions, such as this syndrome, to influenza vaccines had been virtually unrecognized. While the risk is not high, persons who receive influenza vaccine should be aware of it and should recognize that 5-10% of persons with the Guillain-Barré syndrome

have residual weakness to some degree and approximately 5% of them die.

**PREGNANCY**

Elevated rates of maternal and fetal mortality and of congenital anomalies and other fetal effects resulting from influenza infection during pregnancy have been widely discussed. Numerous reports from the 1918-19 influenza pandemic and a few small but better controlled studies in 1957-58, when the Asian influenza pandemic occurred, suggested that influenza can cause increased maternal and fetal deaths. However, a number of more recent, prospective studies have failed to corroborate those findings. Thus, although there are no persuasive data to document that pregnancy is a risk-factor with influenza, the effect of influenza in pregnancy cannot be forecast with assurance. Physicians generally avoid prescribing unnecessary drugs and biologics for pregnant women, especially in the first trimester; however, there are no data that specifically contraindicate influenza vaccination in pregnancy.

Epidemiologic Notes and Reports**Ludwig's Angina — Wisconsin**

A 38-year-old truck driver from Beaumont, Texas, presented at a Wisconsin hospital on June 23, 1976, with dyspnea, fever, and malaise. On admission he was noted to be severely tachypneic. Chest X-ray showed bilateral interstitial pulmonary infiltrates and pleural effusions, and arterial blood gases demonstrated severe hypoxia and metabolic acidosis. Blood cultures were obtained, and the patient was placed on penicillin, gentamicin, and chloramphenicol. Within 24 hours he developed increasing respiratory distress and suffered a cardiopulmonary arrest. Upon being resuscitated, he was transferred to a university hospital.

Examination at this hospital on June 24, 1976, showed the patient to be deeply obtunded and in shock. Severe gingivitis was apparent, and enlarged, matted, cervical, and supraclavicular lymph nodes were noted on the left side. An aspirate of these nodes showed rare neutrophils and one pleomorphic gram-negative rod. Examination of the pleural fluid revealed rare, pleomorphic, faintly staining, gram-negative bacilli.

Because the patient had traveled extensively through an area of the United States where plague is endemic, and be-

cause the clinical picture was compatible, pneumonic plague was strongly suspected. Tetracycline was added to the therapeutic regimen, and the patient was placed in strict isolation. CDC was contacted on June 25 to arrange for fluorescent antibody staining of specimens and to discuss the advisability of treating secondary contacts prophylactically. A recommendation was made that all patients who had had contact with the patient during the past 2 days be placed on prophylactic tetracycline pending confirmation of the diagnosis.

On June 25, it was learned that the patient had had a severe toothache and had seen a dentist one day prior to becoming ill. Cultures of the pleural fluid that had been negative 24 hours after being taken at the first hospital were growing an anaerobic gram-positive coccus, and an aerobic gram-negative rod. It was then strongly suspected that the patient had a dental abscess with a unilateral infection of the deep cervical spaces which had spread intrathoracically. The patient died with refractory shock and hypoxia later that same day.

*Ludwig's Angina - Continued*

Autopsy confirmed necrotizing gingivitis and an extensive putrid phlegmon of the deep fascial planes of the left side of the neck extending into the mediastinum and pleural spaces. Blood cultures taken on admission to the first hospital subsequently yielded *Peptostreptococcus* and *Bacteroides melanogenicus*; cultures of the pleural fluid yielded the same organisms and *Streptococcus viridans* and a *Bacillus* species.

**Editorial Note:** Ludwig's angina is a rare infection, usually of dental origin, which begins in the submandibular and submental spaces and spreads downwards through planes of the deep cervical fascia; it rarely extends into the mediastinum. A dental abscess of the mandibular molars can be identified in most cases. Although alpha-hemolytic strepto-

cocci and staphylococci have been most commonly recovered in culture, the infection usually involves anaerobic organisms from the oral cavity. Treatment involves antibiotics, surgical drainage of the fascial spaces, and supportive therapy. Tracheostomy is often required as sub-mental inflammation characteristically forces the tongue upwards and backwards, compromising the airway.

Reported by DG Maki, MD, WA Agger, MD, University of Wisconsin Center for Health Sciences; and Bur of State Services, CDC.

**References**

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3. Gross BD: Ludwig's angina due to *Bacteroides*. *J Oral Surg* 34: 456-460, 1976

Current Trends**Cigarette Smoking in Teenagers - United States**

Four nationwide surveys of teenage smoking habits reveal that the prevalence of smoking in this group is increasing. The results of these surveys, conducted every 2 years from 1968 through 1974, are shown in Table 2.

Smoking among males 12 to 18 years of age rose from 14.7% in 1968 to 18.5% in 1970, and then stabilized at approximately 16% in 1972 and 1974.

In contrast, the proportion of females who smoked in this age group increased steadily from 8.4% in 1968 to 15.3% in 1974, when the number of females smoking almost equaled the number of male smokers. If the teenage female smoker becomes pregnant there is an increased risk of perinatal mortality (MMWR 26[18], 1977).

Reported by the National Clearinghouse for Smoking and Health, Bur of Health Education, and the Family Planning Evaluation Div, Bur of Epidemiology, CDC.

TABLE 2. Percentage of U.S. teenagers\* 12-18 years of age smoking cigarettes\*\*, 1968, 1970, 1972, and 1974

	1968	1970	1972	1974
Males	14.7	18.5	15.7	15.8
Females	8.4	11.9	13.3	15.3

\*Current regular smoker = smokes one or more cigarettes per week.

\*\*Representative samples were randomly selected by computer from a bank of all possible combinations of area codes, telephone exchanges, and subscriber numbers with a sufficient surplus of selections to allow for the elimination of nonresidence telephones or residences containing no teenagers. The standardized questionnaires, which took approximately 15 minutes to complete, were administered by trained professional interviewers.

**Erratum, Vol. 26, No. 22**

p 177 In the article, "Hepatitis—United States, 1975-1976," first column, second paragraph, last line should read: "The average 4-week incidence of

hepatitis B is 0.50 cases/100,000 population," not "weekly," as written.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE / CENTER FOR DISEASE CONTROL  
ATLANTA, GEORGIA 30333

Director, Center for Disease Control, William H. Foege, M.D.  
Director, Bureau of Epidemiology, Philip S. Brachman, M.D.  
Editor, Michael B. Gregg, M.D.  
Managing Editor, Anne D. Mather, M.A.  
Chief, MMWR Statistical Activity, Dennis J. Bregman, M.S.

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