1967-1968

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> REPORT NO. 84 SEPTEMBER 15, 1968

NATIONAL COMMUNICABLE DISEASE CENTER

INFLUENZA -RESPIRATORY DISEASE SURVEILANCE

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U.S. DEPARTMENT OF . HEALTH, EDUCATION, AND WELFARE. public health service



PREFACE

Summarized in this report is information received from State Health Departments and other pertinent sources, domestic and foreign. Much of the information is preliminary. It is intended primarily for the use of those with responsibility for disease control activities. Anyone desiring to quote this report should contact the original investigator for confirmation and interpretation.

Contributions to the surveillance report are most welcome. Please address to: Acting Chief, Influenza-Respiratory Diseases Unit, Epidemiology Program, National Communicable Disease Center, Atlanta, Georgia 30333

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I. SURVEILLANCE SUMMARY

A. REVIEW OF THE MECHANICS OF INFLUENZA SURVEILLANCE

From time to time it would seem appropriate to review the methods employed in the surveillance of influenza in the United States, and this portion of the Influenza-Respiratory Disease Surveillance Report briefly summarizes current techniques.

Whereas, the clinical diagnosis of individual cases of influenza is quite difficult and requires laboratory confirmation, influenza epidemics usually are easily recognized. These are heralded by abnormal increases in school and industrial absenteeism, occurrence of multiple clinical cases in the same epidemiologic unit (family, school, or industry), or observation of an unusually large number of cases of febrile respiratory illness by a single clinician or group of clinicians.

Although regular and systematic morbidity (case) reporting of many communicable diseases has been established in the 52 health jurisdictions of the United States (50 States, the District of Columbia, and Puerto Rico), only 26 have established systems for reporting cases of influenza-like illness. Influenza morbidity statistics should not be used to compare the magnitude of activity between two different areas, because the nature of the disease reported varies from state to state and even from region to region within a state. Furthermore, an increasing number of reported cases may be as representative of increasing concern about an epidemic as of the actual amount of influenza within the community. At best, morbidity reports are but an index of influenza activity.

After the onset of an epidemic of febrile respiratory illness, there are usually inevitable delays in the recognition of the outbreak, reporting it to local health officers, to state epidemiologists, and in turn to the National Communicable Disease Center (NCDC). Notwithstanding this time lag, it has been possible to report outbreaks occurring in one area to the responsible public health officials in adjacent and distant areas so that they may be alerted for similar outbreaks.

A few areas in the United States have formal systems for detection of influenza epidemics. These include monitoring of school absenteeism in representative communities, reporting of cases of respiratory illness seen in college infirmaries, and serologic surveys for the presence of influenza antibodies.

In the United States, 122 cities with populations of 100,000 or greater, voluntarily submit weekly reports by postcard listing the total deaths, the primary pneumonia deaths, and the influenza deaths for the past week. These data are plotted against "expected" curves which are projected for one-year intervals on the basis of the preceding 5 years' deaths. The "expected curve" is projected by a computer in accordance with the technique which has been described in the Morbidity and Mortality Weekly Report (MMWR), Volume 14, Number 1, January 9, 1965. The "expected curve" is the central feature of an excess mortality system. Without it, it is impossible to say how many deaths are in excess. A few populous areas in the United States, such as New York City and the state of California, construct their own expected curve and maintain their own excess mortality graphs.

It has been shown¹ that peak deaths from pneumonia and influenza follow the peak occurrence of cases by an interval of 3-4 weeks. Thus, even though the mortality data

can be analyzed very quickly, excess mortality graphs reflect influenza activity which occurred 3-4 weeks previously. Furthermore, since small outbreaks of influenza A and outbreaks of influenza B generally do not produce excess mortality, one cannot depend upon this technique alone to document every influenza epidemic. Nonetheless, excess mortality is an excellent monitor of influenza activity. Comparison of mortality from year to year can be used to assess the severity and extent of an influenza epidemic.

B. U.S. SURVEILLANCE SUMMARY 1967-68

Influenza A

In the last week of October 1967, a marked increase in the occurrence of respiratory illness was observed by physicians of the Student Health Service at Western Michigan University in Kalamazoo. Influenza was suspected; and specimens for virus isolation and paired acute and convalescent sera were obtained by the Michigan State Health Department. Approximately 4 weeks later, on November 30, 1967, the Respiratory Virus Infections Unit, Virology Section, Laboratory Program, NCDC, received a call from the chief of the virus laboratory of the Michigan State Health Department. Although no virus had been isolated, the paired sera demonstrated the occurrence of influenza A infection. On the next day, the Florida state epidemiologist reported a presumptive outbreak of influenza in a school in North Miami.

On Monday, December 4, 1967, the National Communicable Disease Center sent a telegram to all state epidemiologists informing them of the outbreaks in Michigan and Florida. Simultaneously letters were sent to all state health officers and laboratory directors describing the outbreaks in detail. Within a week, four other states had reported possible outbreaks of influenza. An epidemic curve by state is shown in Figure 1.

Influenza activity had been predicted as likely to occur in the eastern part of the country, and the first spontaneous reports of influenza activity were from the eastern and central United States. States were contacted beginning in the eastern and central part of the country. In general, it took less than 2 weeks for a report of an outbreak to reach NCDC (Figure 3). States west of the Mississippi took significantly longer to report the occurrence of outbreaks than the eastern states. States in the west had not originally expected to have as much influenza activity as states in the east, and often obtained confirmation of influenza A before reporting it. In addition, reports from states in the east were solicited by NCDC before states in the west. It should be noted that with the exception of New England, the eastern states tended to be involved earlier than the western states and that influenza A activity, as assessed by the respective state epidemiologists, was more extensive in the east (Figure 2).

When states reported suspected outbreaks of influenza to NCDC they were encouraged to document the actual occurrence of influenza by laboratory techniques. Figure 4 shows the delay between onset of outbreaks of influenza and laboratory documentation of influenza A activity in the 1967-68 epidemic. Included are 40 states in which documentation had been made by February 24, 1968. There was no significant difference in delay of documentation between states east of the Mississippi and states west of the Mississippi. Furthermore, of the five states which documented influenza A activity within 2 weeks of onset of an epidemic, 4 of the 5 tested groups of unpaired sera. No state which used the technique of comparison of groups of unpaired sera required more than 2 weeks to make the diagnosis, even though the average delay in laboratory documentation was 4 weeks.

By May 30, 1968, A2 viruses had been grown from specimens from 32 states, and diagnostic serologic rises in influenza A antibody had been obtained from specimens from 48 states

(all but Idaho and Nevada). Although excess mortality was first noted in New York City in the 50th week of 1967, it was not until the first week of 1968 that excess mortality was observed in any of the nine geographic divisions or in the country as a whole. The onset of excess mortality was observed 4 weeks after the first outbreaks (Michigan and Florida) were reported. Over the first 6 weeks of 1968, pneumonia-influenza mortality, total mortality, and mortality in the group aged 65 and over, demonstrated a sharp rise and fall (Figure 5). Only the Pacific Division did not demonstrate significant excess mortality (Figure 6).

Continuous personal communication with the state epidemiologists and other interested persons was maintained throughout the course of the epidemic; in addition, weekly summaries of current influenza activity were presented in the MMWR (Volume 16, Nos. 48-52; Volume 17, Nos. 1-7). Daily reports of influenza activity by state, which were sent to the office of the Surgeon General, were also used as the basis of information for the press.

Influenza B

There were no confirmed outbreaks of influenza B in the United States in the 1967-68 season (Figure 2). Single isolates of influenza B were reported from California and Hawaii. California, Hawaii, Michigan, Oregon, and Wisconsin each reported at least one diagnostic serology for influenza B.

SUMMARY

In the winter of 1967-68, a major epidemic of A2 influenza occurred in the United States. Forty-six states reported outbreaks of influenza-like illness. The extent of the outbreaks of influenza was much greater in the eastern part of the country. Excess mortality was seen throughout the month of January 1968 for the country as a whole and for eight of the nine geographic divisions. Excess mortality appeared 4-5 weeks after the onset of outbreaks.

¹Langmuir, A. D., Epidemiology of Asian Influenza, American Review of Respiratory Diseases, <u>83</u>:2-14, February 1961.

Figure 1 INFLUENZA ACTIVITY BY STATES UNITED STATES, 1967-1968











Figure 3

INTERVAL BETWEEN FIRST OCCURRENCE OF OUTBREAKS OF INFLUENZA-LIKE ILLNESS AND OFFICIAL REPORT TO NCDC IN 45 STATES



HAWAII NOT INCLUDED

Figure 4

INTERVAL BETWEEN FIRST OCCURRENCE OF OUTBREAKS OF INFLUENZA-LIKE ILLNESS AND LABORATORY CONFIRMATION IN 40 STATES^{*}



6 ADDITIONAL STATES HAD REPORTED OUTBREAKS OF INFLUENZA-LIKE ILLNESS, BUT THERE WAS NO LABORATORY CONFIRMATION OF THE OUTBREAKS AS OF FEBRUARY 24, 1968.





Figure 6 PNEUMONIA-INFLUENZA DEATHS IN I22 UNITED STATES CITIES



II. SPECIAL STATE REPORTS

A. Pennsylvania

An institution for the aged in Pittsburgh (Allegheny County) reported approximately 185 cases of influenza-like illness among its 215 residents. The illnesses began in late December 1967, peaked during the first week of January 1968, and subsided by mid-January. In the fall of 1967, 80-90 percent of the residents had received commercial influenza vaccine (polyvalent). Six influenza A2 viruses were isolated from a total of 10 specimens submitted from this outbreak to the Allegheny County Health Department Laboratory (Table 1). Vaccine effectiveness could not be measured in this outbreak, since there were not enough nonvaccinated persons to tell whether the attack rate would have been higher in the nonvaccinated group than it was in the vaccinated group. Nonetheless, it is clear that an outbreak of A2 influenza was propagated in a population which had been highly vaccinated.

(Reported by: Shirley E. Johnson, M.D., William G. Lord, D.V.M., Disease Control Division; and Joseph Sarandria, Director of Laboratories, Allegheny County Health Department.)

TABLE 1

Summary of Influenza Virus Isolations At an Institution for the Aged - Pittsburgh, Pa.

PATIENT NUMBER	VACCINE HISTORY	SERUM ACUTE	TITERS (CF) CONVALESCENT	VIRUS ISOLATED
l	lcc polyval en t vaccine Sept.'67	1:20	1:160	A2
2	¹ ₂ cc polyvalent vaccine Oct.'67 ¹ ₂ cc " " Nov.'67	1:5	l:160	A2
3	None	1:5	1:20	A2
4	lcc polyvalent vaccine Sept.'67	1:20	1:80	A2
5	None	1:5	1:160	A2
6	Unknown	1:5	1:320	A2

B. Indiana

An outbreak of disease clinically diagnosed as influenza occurred at a private boys' school in north central Indiana. The initial case was on November 29, 1967. Over the next 2½ weeks, 260 of the 890 students became ill (Figure 1). The students were in grades 9 through 12, and the disease appeared to affect all grades equally.

Although no viruses were isolated from this outbreak, three of four serum pairs showed diagnostic rises in hemagglutination-inhibition antibody against influenza A2 antigens; there were no rises against influenza B antigens.

(Reported by: A. L. Marshall, M.D., Director, Division of Communicable Disease Control, Indiana State Board of Health.)



C. Iowa

On December 4, 1967, the Iowa State Health Department was notified regarding high absenteeism in the Clarinda School System due to an acute febrile respiratory illness. Members of the State Hygienic Laboratory and the State Department of Health obtained symptom histories, throat washings and swabs, and serologic specimens on approximately 40 patients on December 6, 1967. Convalescent sera were obtained 2 weeks later.

The clinical illness was characterized by fever between 100-104°F., cough, sore throat, coryza, headache, photophobia, and a tired feeling in the eyes. Many complained of dizziness, weakness, lethargy, chills, chest pain on coughing, and low backache. Gastrointestinal complaints and myalgia were minimal. Joint pain was absent.

The epidemic occurred through the first 15 days of December. The extent of the illness can be estimated by examining absentee rates for the six schools which compose the Clarinda School System (Table 2). Peak absenteeism during the epidemic period was compared with the average daily absenteeism during the second 9-week period of the previous school year (November 3, 1966-January 16, 1967). The high school and junior high school had the highest absentee rates with approximately one-third of both schools absent at the peak.

TABLE 2

SCHOOL	Enrollment	Average Daily Absenteeism Full Term 1966*	Peak Absenteeism Fall Term 1967	Date of Peak Absenteeism
Configld Condo Cabial	222	2 00	05 00	
Garrield Grade School	228	3.90	25.9%	Dec. 11
McKinley Grade School	317	3.3%	12.9%	Dec. 11
Lincoln Grade School	203	2.6%	21.7%	Dec. 8
Junior High School	226	3.7%	31.0%	Dec. 11
Senior High School	470	4.2%	34.0%	Dec. 5
Western Community College	650		25 - 30%	

Absenteeism in the Clarinda School System

*Average daily absenteeism for 1966 was calculated for the second 9-week period [November 3, 1966 to January 16, 1967] of the 1966-67 school term.

Seven of eight paired sera showed diagnostic rises in CF and HI antibodies against influenza A antigens. There was no rise in CF antibodies against influenza B, Mycoplasma pneumoniae, para-influenza, and adenovirus antigens.

(Reported by: Arnold M. Reeves, Ph.D., Chief, Preventive Medical Service; F. P. Koontz, Ph.D., Chief, Microbiology & Serology Section, and Yau Wai Wong, Principal Virologist, State Hygienic Laboratory, Iowa State Department of Health.)

D. California

During the 1967-68 season, California did not experience epidemic influenza. Scattered cases of influenza type A were observed in many parts of the state, but incidence was moderate in most areas. The first cases of type A2 influenza had onset of illness during the first and second weeks of January. Fourteen of the first 32 cases to be confirmed by complement-fixation tests for influenza A were in students. In many instances these students acquired their infection during the Christmas holiday while vacationing in the East.

Only two outbreaks of influenza were recorded in the state, and these were both in institutions--one a state hospital, the other a recidential school for young adults. Both occurred in early February. The outbreaks affected only a limited number of persons at each instution and infection did not spread to the outside.

Data on school absenteeism during the season were supplied by 14 cooperating local health departments, and covered a school population of over 200,000 children. Although slight rises in absenteeism were noted at different time intervals in different school systems, the rapid, sharp, significant rises in absenteeism which have generally been seen with influenza activity were not observed. There was also no increase in absenteeism in a few industries which were monitored for this purpose. A number of cases clinically described as influenza-like illness were confirmed to be due to Mycoplasma pneumoniae. There was no excess mortality observed in the 11 California cities monitored weekly.

(Reported by: Philip K. Condit, M.D., Chief, Bureau of Communicable Diseases Edwin H.Lennette, M.D., Ph.D., Chief, Viral and Rickettsial Disease Laboratory, California State Department of Public Health; and an EIS Officer.)

III. INTERNATIONAL SUMMARY

A. July 1967-June 1968

Reports published in the World Health Organization Weekly Epidemiological Record form the basis for the 1967-68 International Influenza Summary (Table 1). Because of inherent differences in reporting from country to country, these data can be expected to give only a general appraisal, and omissions, and minor inconsistencies may represent as yet unpublished data or incomplete reports.

TABLE 1

International Influenza Summary July 1967-June 1968

COUNTRY	FIRST RECOGNIZED	ESTIMATED EXTENT OF	LABORA	TORY	PREDOMINANT VIRUS TYPE
		OUTBREAK	Isol.	Serol.	
AFRICA:					
South Africa	July 1967	Widespread	A2	А	А
AMERICA:					
Argentina	Oct. 1967	Isolated	A2	-	А
Jamaica	Nov. 1967	Isolated	-	В	В
United States	Nov. 1967	Widespread	A2,B	А, В	А
Canal Zone	Dec. 1967	Regional	A2	-	А
Canada (Eastern)	Jan. 1968	Widespread	A2	А	А
Chile	Jan. 1968	Widespread	-	А	А
Canada (Western)	Apr. 1968	Regional	A2,B	А, В	в, А
Argentina	May 1968	Widespread	A2	-	А
ASIA-OCEANIA:					
Hong Kong	Aug. 1967	Isolated	A2	-	А
Fiji	Oct. 1967	?	В	-	В
Japan	Nov. 1967	Widespread	A2	А	А
Taiwan	Nov. 1967	Isolated	В	-	В
Japan	May 1968	Isolated	В	В	В
Australia	June 1968	Widespread	A2,B	-	А
EUROPE:					
Norway	Nov. 1967	Widespread	A2	А	А
Denmark	Dec. 1967	Widespread	-	А	А
Italy	Dec. 1967	Regional	A2	-	А
Netherlands	Dec. 1967	Widespread	A2	А	А
United Kingdom	Dec. 1967	Widespread	A2	А	А
Finland	Jan. 1968	Isolated	A2	-	А
Federal Republic of					
Germany	Jan. 1968	Widespread	A2	А	А
Greece	Jan. 1968	Regional	A2	-	А
Hungary	Jan. 1968	Widespread	A2	А, В	А
Sweden	Jan. 1968	Isolated	-	А	А
Yugoslavia	Jan. 1968	Regional	A2	А	A
France	Feb. 1968	Regional	A2	А	А
German Democratic Republic	Feb. 1968	Regional	A2	-	А
Switzerland	Feb. 1968	Widespread	A2	А, В	А
Portugal	Mar. 1968	Regional	A2	А	А
Rumania	Mar. 1968	Isolated	A2	-	А

Most of the influenza seen around the world during 1967-68 was A2(Asian). South Africa had an epidemic in July; Japan, the United Kingdom, and the United States of America, all had large epidemics of A2 influenza in the late fall and early

winter; later many European countries had epidemics of A2 influenza; and in April and May there were epidemics in Chile and Argentina.

During the past year, two occurrences of A2 influenza, 6 months apart, were observed in Argentina. The initial appearance consisted of isolated cases and the subsequent appearance was associated with widespread activity.

Outbreaks of type B influenza were reported from the Far East, Fiji, and Taiwan, in the fall of 1967. In the spring of 1968, some cases of B influenza were reported in Western Canada and in the Western part of the United States; and outbreaks of influenza B were reported in Japan.

B. July 1968 - Present (Preliminary Report)

About July 8, daily reported cases of influenza-like illness from government outpatient clinics in Hong Kong began to rise steadily. Arrangements were made to monitor 10 representative clinics throughout the colony at a time when there were still only 12 to 15 cases per day. The number of patients seeking medical attention increased sharply during mid-July and reached a peak on the 25th and 26th when attendance at the 10 monitored clinics reached 500 to 600 persons daily. During the weekend of July 27-28, additional clinics were established and existing clinics were kept open to render assistance. From material obtained in these clinics, the WHO Influenza Reference Laboratory in Hong Kong isolated well over 100 influenza viruses. Five of these strains were sent to WHO World Influenza Center in London on July 17 for confirmation and further evaluation.

Since mid-August influenza activity in Hong Kong has appeared to be on the wane, and clinic visits have declined. Estimates of the overall attack rate have varied from 15 to 30 percent. Approximately 30 percent of the staff of the American Consulate experienced influenza-like illness during the epidemic. An article in the <u>South China Morning</u> Post on July 25, 1968, estimated that between 10 and 20 percent of the staff of the medical and health department of the Crown Colony had been affected. There is no available information on basic epidemiologic characteristics, such as age-specific attack rates, and similarly, there is very little information on the clinical characteristics of the illness. The disease has been labeled "mild" by most observers and "influenza deaths" have been few. Total mortality figures available only through August 3 do not yet show significant excess mortality for Hong Kong, Kowloon, or the New Territories.

In mid-August, an outbreak of influenza-like illness began in Singapore, and the strains from this outbreak have been reported by the WHO World Influenza Center to be similar to the Hong Kong strains. In the third week of August a large epidemic of influenza-like illness, apparently the largest since 1957, was observed in the Philippines. To date there is no laboratory confirmation of the etiology of this outbreak. Finally, an outbreak of influenza has been reported by the UPI from the Taipei area of Taiwan; a message has been received by WHO that there is influenza-like illness in Indonesia, and another message has been received that there is no influenza-like illness at the moment in Thailand.

It should be mentioned that outbreaks of influenza in April and May in Argentina, Chile, and the Easter Islands, outbreaks in South Africa in May, and outbreaks in Australia and New Zealand in June and July, all appear to have been caused by strains which differ only moderately from the strains isolated in the U.S. last winter. The important question of whether outbreaks in places like the Philippines and Indonesia are being caused by Hong Kong-like strains or by strains similar to those isolated in Australia is as yet unanswered. Furthermore, to date influenza has been reported only from areas which have not had major amounts of influenza A2 activity for at least 2 years. So far no outbreaks of influenza have been reported from Japan, which had a major epidemic of A2 in November 1967 through February 1968.

IV. LABORATORY REPORT

A. July 1967-June 1968

Influenza A2 viruses were submitted to the International Influenza Center for the Americas from widely separated geographic areas including South and Central America, the United States and Canada, England, and Japan, during the 1967-68 influenza season. Some of these viruses were recovered in primary tissue culture; and some were recovered in chicken eggs, the system of choice. In both systems, however, the percent of successful isolations was low. Hemagglutinin titers of newly isolated strains were generally low. The avidity of most strains for specific antibody was moderate and they were not unusually sensitive to non-specific inhibitors in serum. Receptor destroying enzyme (RDE) treatment was satisfactory for removal of inhibitors.

Analyses of strain relationship among viruses received for antigenic characterization were accompanished by reciprocal hemagglutination (HI) tests utilizing allantoic fluid antigens and strain-specific immune chicken sera treated with RDE. Similarity coefficients were calculated from geometric mean titers of duplicate HI tests by the formula of Archetti and Horsfall.¹ The coefficient of similarity between any two strains in which at least one antiserum failed to inhibit the heterologous virus was recorded as indeterminate (i).

Antigenic relationships among 10 influenza A2 strains isolated in the 1967-68 season and 7 type A viruses prevalent previously are compared in Table 1. The A2/New Jersey/1/67 and A2/Georgia/1/67 viruses were isolated at the end of the 1966-67 seasons. With the exception of A2/Texas/2/68, A2/Tokyo/3/67, and A2/England/10/67, the A2 isolates from the past season form a cluster of antigenic variants rather closely related to each other. All showed some antigenic drift away from the A2/Taiwan/1/64 strain, and for most strains there is evidence of some drift from the A2/Japan/170/62 strain as well.

HI titers of 1967-68 viruses and their monospecific immune sera reacting with previously prevalent type A strains are given in Table 2. A2/Japan/305/57 antiserum inhibited poorly the recent isolates, but antisera to A2 strains isolated since 1957 reacted well. Antisera to 1967-68 viruses were broadly reactive with all A2 strains.

Two contemporary type B influenza strains, B/Taiwan/3/67 and B/Hawaii/1/68, were compared antigenically with previously prevalent strains. Similarity coefficients of type B strains in Table 3 indicate both 1967-68 strains are similar to the current vaccine strain, B/Massachusetts/3/66, but vary in their relationships to B viruses isolated in previous years. B/Taiwan/3/67 is rather close to 1962 and 1965 variants whereas B/Hawaii/1/68, like B/Massachusetts/3/66, has moved away from the earlier strains.

Reciprocal HI titers of influenza B strains and their monospecific antisera are given in Table 4. The 1967-68 viruses appear to be less avid than B/Massachusetts/- 3/66 but this may be due to differences in egg passage levels.

Table 1 Strain Relationships* of Type A Influenza Viruses

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1	i	11.3	4.8	6.7	8.0	2.4	∫ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		<u></u>	A. S. S.	/ c	÷ /		\sim				
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1	1	11.3	4.8	6.7	8.0	1.4	3.4	2.8	0.8	1.7	4.0	1.7]	· / _	41.1	'×10	چ ا	
1	1	16-0	9.5	11.3	9.5	5.7	8.0	5.7	2.0	9.5	8.0	4.8	4.8	7 🗟		\hat{z}	Dund	/
t	1	22.6	11.3	13.5	13.5	8.0	6.7	6.7	2.4	8.0	6.7	4.0	4 0	5.7	1	./ _	2.5°	
1	1	11.3	4.0	6.7	4.8	6.7	11.3	2.4	4.0	11.3	4.8	4.0	6.7	4.0	9.5	7 7		

*Similarity coefficients (r) according to the formula of Archetti and Horsfall, J. Exp. Med. 92:441, 1950.

By definition, a coefficient of 1.0 indicates identity; i.e., strains indistinguishable under the test system. i Indeterminate Closely related strains with r values <4.0 are indicated by shading.

Antisera***	A. PR. 8. 34	A1, FM 1, 47	A2. Japan, 305. 57	A2. Japan, 170, 62	A2/Taiwan 1.64	A2/ New Jersey/1/67	A2, Georgia, 1, 67	A2. Montevideo - 2205. 67	A2. (Cordoba - 522, 67	A2, Panama 1, 67	A2 New York City 1/67	A2, Berkeley, 1, 68	A2. 'Albany - 2. '68	A2, Texas, 2, 65	A2. Ann Arbor. 7-67	A2. Tokyo 3. 67	A2 England 10 67
A/PR/8/34	14482	0	0	0	10	10	0	0	0	0	0	0	0	0	0	()	0
A1. FM/1. 47	10	905	0	0	0	0	0	0	0	0	0	0	0	()	θ	0	0
A2/Japan/305/57	0	0	453	640	160	226	80	57	80	57	57	113	80	28	57	-4()	160
A2, Japan, 170, 62	0	0	640	1810	453	1280	320	320	320	160	160	320	226	80	113	57	905
A2, Taiwan, 1, 64	0	0	80	226	1280	160	113	80	57	57	57	80	113	28	57	28	160
A2/New Jersey/1/67	10	0	160	1810	1280	20480	2560	640	640	453	905	905	1810	320	453	320	1810
A2, Georgia, 1. 67	0	0	57	226	160	320	453	320	80	226	320	640	320	226	80	40	160
A2, 'Montevideo, '2208, '67	0	0	57	226	320	453	226	905	160	16()	160	226	453	113	160	160	320
A2/Cordoba/522/67	0	0	320	1280	1280	2560	1280	453	<u>1810</u>	640	1280	1810	1280	453	453	320	1810
A2/Panama/1/67	0	0	80	453	453	905	453	640	320	<u>640</u>	1810	905	1280	640	905	453	453
A2/New York City/1/67	80	0	80	640	905	1280	1810	1280	453	1810	5120	1810	3620	1280	320	320	905
A2/Berkeley/1/68	0	0	40	226	320	453	320	80	320	320	320	<u>1810</u>	640	113	160	160	640
A2, 'Albany, '2, '68	0	0	80	640	320	453	320	113	320	320	640	640	<u>640</u>	226	160	160	453
A2//Texas//2/68	0	0	20	160	160	160	160	113	80	226	226	160	160	<u>160</u>	80	80	113
A2/Ann/Arbor/7/67	0	0	80	453	453	1280	453	226	320	453	453	453	453	226	2560	453	640
A2/Tokyo/3/67	0	0	40	453	453	64 0	320	226	226	453	453	453	453	226	320	<u>1810</u>	320
A2, 'England, '10, '67	0	0	40	226	320	905	113	40	320	160	80	226	160	57	453	113	<u>1810</u>

 Table 2

 Hemagglutination Inhibition: Type A Influenza Viruses*

*Geometric mean titers of duplicate tests.

**Allantoic fluid antigens.

***Chicken antisera treated with receptor destroying enzyme.

 Table 3

 Strain Relationships* of Type B Influenza Viruses



*Similarity coefficients (r) according to the formula of Archetti and Horsfall, J. Exp. Med. 92:441, 1950.

By definition, a coefficient of 1.0 indicates identity; i.e., strains indistinguishable under the test system. i = Indeterminate

Closely related strains with r values <4.0 are indicated by shading.

Hemagglutination Inhibition: Type B Influenza Viruses*										
Antisera***	B/Lee/40	B, GL, 1739 54	B. Maryland, 1, 59	B, Taiwan, 2, 62	B. Colorado, 2, 65	B. Mass. 3, 66	B, Taiwan, 3, 67	B Hawaii/1/68		
B Lee 40	<u>890</u>	15	10	0	0	0	0	0		
B GL 1739 54	20	<u>160</u>	40	0	10	10	0	0		
B Maryland 1 59	80	160	5120	20	40	450	225	150		
B Taiwan, 2, 62	20	40	20	320	110	20	15	10		
B Colorado 2 65	0	40	40	80	160	80	40	35		
B Massachusetts 3 66	0	20	40	20	20	<u>320</u>	150	80		
B Taiwan 3 67	40	20	80	225	80	225	<u>160</u>	100		
B Hawaii 1 68	0	80	320	80	11()	1780	890	<u>640</u>		

 Table 4

 Hemagglutination Inhibition: Type B Influenza Viruses*

*Geometric mean titers of duplicate tests.

**Allantoic fluid antigens.

***Chicken antisera treated with receptor destroying enzyme.

B. July 1968 - Present

Two of five viruses isolated during the recent influenza outbreak in Hong Kong and sent to the International Influenza Center by Dr. W. K. Chang, National Influenza Center, University of Hong Kong, were examined by reciprocal hemagglutination-inhibition tests. Similarity coefficients for Hong Kong/l and Hong Kong/8 with earlier A2 strains indicate a magnitude of dissimilarity which has not been previously observed within this subtype (Table 5). Similarity coefficients for all virus pairs could not be determined (i) because of the poor reactivity of many strain specific antisera with the Hong Kong/l and Hong Kong/8 antigens. Nevertheless, these isolates were still classified as influenza A2 viruses. All five isolates were readily identified with the WHO reference A2 polyvalent antisera; and antisera produced against both Hong Kong/1 and Hong Kong/8 strains clearly demonstrated an antigenic relationship with the earlier A2 viruses (Table 6). These results confirm the findings of the World Influenza Centre in London.² The Hong Kong viruses represent a major antigenic drift and identification may not be possible using specific antisera produced against earlier A2 reference strains.

Of additional interest regarding these new isolates is a low level reciprocal cross with A/Equi-2 strains found in the NCDC laboratories. While a "one way" antigenic relationship with equine strains has been suggested in the past³, this is the first report of a reciprocal cross. Confirmation of these findings by neutralization tests is under way.

Further indication of the magnitude of antigenic difference between the Hong Kong isolates and the previous influenza A2 strains⁴ may be seen in the patterns of antibody response from confirmed cases of influenza occurring during the 1967-68 outbreak in the United States and from persons recently vaccinated. Table 7 shows the results of hemagglutination-inhibition (HI) tests with paired sera from four such groups:

Group I consists of acute and convalescent serum pairs from persons (ages 4-75) with a laboratory confirmed diagnosis of influenza during 1967-68.

Group II consisted of pre- and post-vaccine serum pairs from healthy prison volunteers who received a single dose of the 1967-68 commercial polyvalent vaccine.

Group III consists of pre- and post-vaccine serum pairs from elderly persons (ages 70-74) who received 2 doses of commercial bivalent vaccine.

Group IV consisted of prison volunteers receiving 3600 CCA units of purified A2/Japan/305/57 vaccine.

Group I convalescent sera showed a high geometric mean (GM) titer to A2/Japan/170/62, one of the two A2 strains in the current vaccine; and all serum pairs responded with a fourfold or greater rise. Similar results, although with somewhat lower GM titers, were obtained with A2/Georgia/19/67, the strain representing isolates from the 1967-68 influenza outbreak in the United States. A significant response was also noted with A2/Tokyo/3/67 which is somewhat different antigenically from either of the above viruses and is similar to isolates from the current outbreaks in Australia, New Zealand, and South Africa. However, antibody response to the Hong Kong strain was considerably lower. GM titers of the convalescent sera were <10 and only 19 percent of the serum pairs showed a fourfold or greater increase in titer. The response of the vaccinees in Group II was quite low for all strains, including A2/Japan/170/62. While the individuals in Group III and Group IV had excellent responses to the vaccine strains, their response to the Hong Kong strain was not appreciably increased over that of Group II.

Homotypic and heterotypic antibody responses of vaccinees depend both on the potency of the vaccine and the age and prior influenza experience of the recipient. This is also true to some extent for individuals recovering from the natural disease. While serum antibody titers are only indirectly related to protection, individuals demonstrating peak heterotypic antibody titers following immunization or natural disease would be considered at lowest risk of infection. The antibody responses in all four groups measured with the Hong Kong antigen are minimal.

The results with human sera confirm the previous findings based on reciprocal HI tests with monospecific animal sera. The Hong Kong/8/68 strain represents a considerable antigenic change from earlier A2 influenza isolates.

Few laboratories have had extensive experience in the isolation of the Hong Kong-like virus, but reports to date, in striking contrast to recent years, suggest that virus may be readily isolated in primary rhesus monkey kidney as well as embryonated eggs.

¹Archetti, Atilo & Horsfall, Frank L. Jr.: Persistent Antigenic Variation of Influenza A viruses after Incomplete Neutralization in ovo with Heterologous Immune Serum, J. Exp. Med. 92:441, 1950.

²WHO Weekly Epidemiological Record 43:33, August 16, 1968.

- ³Davenport, Fred M. et al.: Further Observations on the Significance of A/Equine-2/63 Antibodies in Man, J. Exp. Med. 126:1049, 1967.
- ⁴National Communicable Disease Center, Morbidity and Mortality Weekly Report, Volume 17, Number 33, August 17, 1968.

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³⁵imilarity coefficients (r) according to the formula of Archetti and Horsfall, J Exp Med 92:111, 1950. ¹⁵i — indeforminate

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Table 7 HI Antibody Titers to Hong Kong/8/68 and Selected Influenza Virus Strains With Paired Sera From Persons III With Influenza During Winter 1967-68 (Group I), From Persons Vaccinated With the 1967-68 Commercial Vaccine (Group II and III), and From Persons Receiving 3600 CCA Units of A2/Japan 305/57 Vaccine (Group IV).

			Seru	ım 1		Serum 1	*	Serum pairs
Group	Number	Antigen	$\begin{bmatrix} \text{Titers} \\ -\frac{1:10}{\binom{9}{6}} \end{bmatrix}$	GM _t **	Titers 1:10 (**)	GM _t	GMp***	Showing <u>-</u> 4 fold titer rise (%)
I. Illness (all ages)	32	A2 Japan 170 62 A2 Georgia 19 67 A2 Tokyo 3 67 Hong Kong 8 68	75 41 28 3	21 - 10 - 10 - 10	$ \begin{array}{r} 100 \\ 100 \\ 94 \\ 34 \end{array} $	$ \begin{array}{r} 437 \\ 101 \\ 54 \\ -10 \end{array} $	$ \begin{array}{r} 437 \\ 101 \\ 74 \\ 10 \end{array} $	100 100 85 19
II. Vaccine (prison)	57	A2 Japan, 170/62 A2 Tokyo 3/67 Hong Kong 8/68	94 65 11	73 11 ~10	97 70 33	$\begin{array}{c}110\\17\\\cdot10\end{array}$	$\frac{112}{22}$ ~ 10	24 16 11
III. Vaccine (elderly)	36	A2, Japan, 170, 62 A2, Tokyo, 3, 67 Hong Kong, 8, 68	39 25 6	10 + 10 + 10	100 86 36	$\frac{259}{28}$	$259 \\ 48 \\ 14$	92 53 12
IV. Vaccine (prison, high dose A2, 57)	44	A2 Japan 305 57 A2 Japan 170 62 A2 Tokyo 3 67 Hong Kong 8 68	89 84 20 7	$55 \\ 22 \\ -10 \\ -10$	98 98 89 20	$1020 \\ 450 \\ 27 \\ -10$	$ \begin{array}{r} 1300 \\ 510 \\ 33 \\ 12 \end{array} $	90 90 71 11

+Convalescent sera collected approximately 3 weeks after onset. Post-vaccine sera collected 3 weeks after final injection. + + GM_{t} = Geometric mean titers of total group.

 $\operatorname{cont}_{\mathrm{II}}$ = coordination in the original group. *** GM_{D} = Geometric mean titers of positive sera only.

V. A METHOD FOR RAPID DIAGNOSIS OF INFLUENZA OUTBREAKS

Two principal procedures are available to establish the occurrence of influenza: isolation of the virus and a rise in titer of influenza antibody between acute and convalescent serum specimens.

The importance of isolation of influenza viruses cannot be overstressed. Only when a virus has been isolated during an outbreak can the type of influenza virus causing the outbreak and its relationship to previous ones be established with certainty. Even though multiple virus isolates obtained from the same epidemic will undoubtedly confirm that the epidemic is caused by a specific influenza virus, virus isolation is neither a convenient nor practical means of laboratory documentation of epidemics. Often, laboratories spend time working on improperly collected and poorly handled specimens. Theoretically, it should be possible to isolate and identify an influenza virus in as little as 48 hours; but, in practice it may take a week or more before an isolate is identified; multiple blind passages of virus may be required before an isolation is made. Finally, it is much easier to demonstrate a diagnostic rise in antibody than it is to isolate a virus from a single infected person.

Serologic diagnosis of influenza infection is most readily made by the hemagglutinationinhibition (HI) or by complement-fixation (CF) tests. CF or HI tests can be run within a 24-hour period; however, there is considerable time lag in making a serologic diagnosis since collection of acute and convalescent sera from the same individual takes 2 to 3 weeks. To minimize this time lag, a number of investigators^{1,2,3} have compared groups of acute and convalescent sera taken from one epidemic, but from different persons.

By the time the presence of an epidemic has been established, there are usually a number of individuals in the community who are already convalescent from the illness, while a number of other persons are in the early acute stages. At one point in time, 10 or more acute specimens and 10 or more convalescent specimens can easily be collected. Since influenza antibody levels vary by age and by influenza vaccination status, the acute and convalescent groups should be equivalent with respect to age and preferably consist of unvaccinated individuals.

The same serologic test (CF or HI) is performed in a single run on each of the sera in each of the groups. Geometric mean titers are then calculated for the acute and the convalescent groups. Although for any single individual a fourfold rise in titer constitutes a diagnostic rise, a fourfold rise in geometric mean titer is clearly too stringent a criterion for documentation of an epidemic: for instance, if 6 of 10 persons involved in the same outbreak had exactly a fourfold rise in influenza antibody and the remaining 4 had no rise, one would not hesitate in making the diagnosis of an influenza outbreak even though the geometric mean titer rise for the group of 10 was less than fourfold.

Table 1 shows both CF and HI titers obtained on groups of acute and convalescent sera in an outbreak of influenza B in Pinal County, Arizona, in 1967. Both by CF and HI tests, the geometric mean titer of the convalescent group is higher than that of the acute group. One may then ask, "Is the geometric mean titer of the convalescent group statistically <u>significantly</u> higher than that of the acute group?"

For purposes of illustration, Table 2 shows a statistical analysis of acute and convalescent HI titers to B/Maryland/1/59. Columns 1 and 3 list the acute and convalescent titers for two random samples of patients; the corresponding log titers to the base 10 are shown in Columns 2 and 4. Because of the marked non-normality of titer data, it is necessary to analyze log titers rather than the titers themselves whenever a comparison between means is desired. A conventional Student's t test is then performed on the log titers as described (page 25).

TABLE 1

ACUI	TE GROUP		CONVALE	SCENT GRO	OUP
Patient	TIT	ERS	Patient	TI	TERS
lumber	OF	HI	Number	CF	HI
	- 8	10	10.	< 0	10
× •			1 .	< 8	40
3.	< 8	201	12.	<8	80
i.	< 3	10	13.	< 8	10
÷.	< 8	<10	14.	64	40
ô.	< 3	20	15.	16	20
~ .	<.∂	10	16.	128	160
з.	< 8	20	17.	< 8	40
9.	<8	20	18.	256	160
GEOMETRIC			GEOMETRIC		
MEAN	5	17	MEAN	16	38

Titers of 9 Acutely Ill Persons and 9 Convalescents Against Influenza B/Maryland/1/59

TABLE 2

Analysis of Hemagglutination Inhibition Titers (Unpaired Acute and Convalescent Phase Sera)

(1)	(2)	(3)	(4)
Acute	x=log ₁₀ (Acute)	Convalescent	y=log ₁₀ (Convalescent)
10	1.00000	10	1.00000
80	1.90309	40	1.60206
20	1.30103	80	1.90309
10	1.00000	10	1.00000
< 10(=5)	.69897	40	1.60206
20	1.30103	20	1.30103
10	1.00000	160	2.20412
20	1.30103	40	1.60206
20	1.30103	160	2.20412
$\Sigma_{\mathbf{X}}$	= 10.80618		Σ _x = 14.41854
$\frac{1}{x} = \frac{\Sigma x}{n_X}$	$= \frac{10.80618}{9} = 1.20069$	$\frac{1}{y} = \frac{\Sigma y}{n} =$	$\frac{14.41854}{9}$ = 1.60206
$\Sigma \mathbf{x}^2 = 13$.	891.10	$\Sigma_{\rm V}^2 = 24.7$	73051
$s_{X}^{2} = \frac{9(1)}{9(1)}$	<u>3.48103)-(10.80618)²</u> 9(8)	$s_y^2 = 9(24)$	<u>.73051)-(14.41854)²</u> 9(8)
$s_x^2 =$.11327	sy ² = .20	0399

The average acute and convalescent log HI titers to B/Md. were found to be $\frac{1}{x}$ = 1.20069 and $\frac{1}{y}$ = 1.60206, respectively. As shown above, the sample variances of the two log titer samples are given by s_x^2 = .11327 and s_y^2 = .20389. To compare the acute and convalescent geometric mean titers, the usual t statistic is computed, where

$$t = \frac{\bar{x} - \bar{y}}{s_p} \sqrt{\frac{1}{n_x} + \frac{1}{n_y}}$$

 s_p is the pooled standard deviation and is the square root of the weighted average of $s_X{}^2$ and $s_V{}^2;$ that is,

$$s_{p} = \sqrt{\frac{(n_{x}-1)s_{x}^{2} + (n_{y}-1)s_{y}^{2}}{n_{x} + n_{y} - 2}} = \sqrt{\frac{(9-1)(.11327) + (9-1)(.20389)}{9 + 9 - 2}} = .39822$$

where $n_{\rm X}$ and $n_{\rm y}$ are the number of acute and convalescent titers, respectively. For the Pinal County data,

$$t = \frac{1.20069 - 1.60206}{(.39822)} \sqrt{\frac{1+1}{9}} \frac{-.40137}{.18772} = -2.14$$

and there are $n_X + n_y - 2 = 16$ degrees of freedom.

The tabulated value of the t statistic for 16 degrees of freedom is 2.120 at the P=0.05 level and is 2.583 at the P=0.02 level. Since the absolute value of t for the Pinal County data (2.14) is greater than 2.12, the null hypothesis, that the true geometric mean acute and convalescent HI titers are the same, can be rejected at the P=0.05 level. This is strong presumptive evidence of an influenza B outbreak in Pinal County.

Therefore, a diagnosis can be made within 24 to 48 hours of the time when the outbreak is first investigated. In one quick trip not only can acute specimens, which will form the basis for a definitive diagnosis, be collected, but also a type-specific working diagnosis can be made. Care must be taken that the acutely-ill and convalescent persons have (and have had) the same illness.

The comparison of acute and convalescent sera by this technique can apply to most epidemic illnesses for which a diagnosis can be made serologically. One is comparing the most susceptible persons in the population (the acutely ill group) with the most resistant members of the population (the convalescent group). In some instances, when acute specimens are not available one may be tempted to compare persons who did not become ill with persons who are convalescent. This may be possible; however, persons who did not become ill, may have had pre-existing high titers and not have become ill because they were already immune to the agent. In this event the "not ill" group will have a high geometric mean titer and will not differ significantly from the convalescents.

In the surveillance summary it was noted that in 1967-68 four of the five states which obtained laboratory documentation from an influenza outbreak within 2 weeks of onset compared acute and convalescent groups. With the ever-increasing emphasis on prophylaxis and treatment of viral infections, rapid diagnosis is becoming exceedingly important. Comparison of matched groups of acute and convalescent sera is presently a rewarding method for rapid diagnosis of influenza epidemics.

¹Milstone, J.H., <u>et al.:1945</u> Influenza B Epidemic in the Pacific Area, Military Surgeon, December 1946.

²Grist, N.R., et al.: Rapid Serological Diagnosis of an Outbreak of Influenza, Brit. Med. J. <u>2</u>:5249, August 12, 1961.

³ National Communicable Disease Center, Influenza-Respiratory Disease Surveillance Report, No. 82, June 30, 1966.

VI. RECOMMENDATION OF THE PUBLIC HEALTH SERVICE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

In May 1968 the Public Health Service Advisory Committee on Immunization Practices completed the following recommendations on influenza immunization in the civilian population. (Reprinted from the MMWR, Vol. 17, No. 26, Week Ending June 29, 1968.)

INFLUENZA VACCINES - 1968-69

RATIONALE FOR SELECTIVE USE OF INFLUENZA VACCINE

Prevention of influenza in the general population through routine vaccination, although perhaps a goal for the future, is not presently possible. Two of the limiting factors are that influenza occurs at intervals and in patterns which are only broadly predictable and that influenza vaccines are not yet completely adaptable to regular, widespread use. There continues to be a sound basis, however, for recommending **selective** use of influenza vaccine. The rationale for selective use is based on characteristics of the disease, its epidemiology and virology, and the efficacy of vaccines.

Influenza is a generally mild epidemic illness which appears periodically. Its pattern of recurrences provides a basis for yearly forecasts: type A epidemics occur at 2-3 year intervals, and type B epidemics, at 3-6 year intervals. Periodicity is thought to result from antigenic variations in the prevalent influenza viruses and shifts in the balance of susceptibles and immunes in the population. The relative accuracy of influenza forecasts depends on the extent of recent epidemics and the antigenic changes in influenza viruses.

Although our best available preventives of influenza, inactivated vaccines are among the least satisfactory immunizing agents in general use today. They have often been marginally effective, offering rather brief periods of protection. They also produce local and systemic reactions with relatively high frequency. Public health recommendations in recent years have acknowledged these limitations and have encouraged only selective influenza vaccination.

Older and chronically ill individuals in the population are essentially the only ones who have any risk of serious complications or fatality from influenza. Therefore, annual influenza vaccination has been recommended for them while not being recommended for the entire population.

When epidemic influenza is forecast, vaccination programs might reasonably be extended beyond the high risk groups to those providing essential community services. Otherwise, large-scale vaccination programs are not now warranted and should not take precedence over public health activities of already established importance.

The following prospectus for influenza in 1968-69 includes a description of vaccines which will be available and general recommendations for limited influenza vaccination.

INFLUENZA PROSPECTUS - 1968-69 - UNITED STATES

During the late fall and winter of 1967-68, all but four States - Oregon, California, Idaho, and Nevada - reported

outbreaks of influenza-like illness. A sharp increase in pneumonia-influenza deaths occurred coincidentally in eight of the nine geographic divisions of the United States the Pacific Division was the only exception.

Forty States confirmed influenza A2 by laboratory procedures. Viral strains recovered during 1967-68 remain in the general family of type A2 viruses identified worldwide since 1957, but show a moderate antigenic shift from strains isolated in recent years.

No outbreaks of type B influenza were reported in the United States in 1967-68. The country last experienced type B influenza epidemics in 1965-66 (East) and 1966-67 (West). Strains of type B virus recovered in other areas of the world over the past year are antigenically similar to those identified in the United States in 1965-67.

In view of influenza's periodicity, little or no A2 influenza is expected to occur in the United States during the 1968-69 season, except possibly on the Pacific Coast. Scattered type B influenza may be seen, but its total extent should be minimal.

INFLUENZA VIRUSES AND VACCINES

Formulation of current influenza vaccines is reviewed annually by the Division of Biologics Standards, National Institutes of Health, and changes are made when significant shifts have occurred in the antigenic characteristics of prevalent viruses. This regular review is essential, since vaccine effectiveness depends primarily on the antigenicity of component viruses and on how similar they are to viruses occurring in the community.

Optimally constituted influenza vaccines have achieved 60 percent or greater protection against the same or closely related viral strains. However, vaccines in general civilian use often have not appeared to achieve this degree of protection.

Another important factor in vaccine effectiveness is the amount of antigen administered. In an attempt to minimize the frequency of local and systemic reactions associated with influenza vaccines, the Division of Biologics Standards established a limit of 600 chick cell agglutinating (CCA) units of antigen per adult dose of vaccine for civilian use.

Limited quantities of a new, highly purified vaccine of bivalent formulation also with 600 CCA units, were used in 1967-68. This vaccine, which contains substantially less non-viral material than the regular vaccines, caused fewer severe reactions.

INFLUENZA SURVEILLANCE

It should be emphasized that decisions on formulations of influenza vaccines and recommendations for their

U.S. DEPARTMENT OF HEALTH. EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE Health Services and Mental Health Administration, National Communicable Disease Center

SUPPLEMENTARY RECOMMENDATION OF THE PUBLIC HEALTH SERVICE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

The Public Health Service Advisory Committee on Immunization Practices meeting on September 4, 1968, issued the following supplementary recommendations regarding influenza immunization and control in the civilian population, (Reprinted from the Morbidity and Mortality Weekly Report, Volume 17, Number 35, Week Ending August 31, 1968.)

INFLUENZA - 1968-69

In July 1968, an outbreak of influenza A2 was reported from Hong Kong, the largest outbreak in that area since 1957. Although strains of influenza virus from this outbreak cross-react to some extent with some previous A2 strains, they do show a marked antigenic change from previous strains. Similar viruses were subsequently isolated from an outbreak in Singapore.

These developments have led to a re-appraisal of the influenza prospectus for the United States and the following recommendations on the use of influenza vaccine.

INFLUENZA VIRUSES AND VACCINE FORMULATION

The continued change in antigenic characteristics of influenza viruses isolated over the years is well recognized. Minor variations occur almost yearly. Major antigenic shifts occur infrequently. When they do, they may produce widespread disease, as in 1957 when the A2 (Asian) strains first appeared. There have also been instances when a major change in the virus has not resulted in epidemics, such as the initial appearance of the A1 strains in 1947.

It is felt that the present change in the influenza virus increases the probability that influenza A2 will occur extensively in the United States in the 1968-69 season.

As previously forecast, scattered type ${\bf B}$ influenza may be seen.

It is only through intensive surveillance that the true extent of the disease will be determined.

Protection through vaccination depends both upon the antigenic similarity of the vaccine strain to the virus prevalent in the community and upon the amount of antigen administered. Influenza vaccines, under optimal conditions, have achieved 60 percent or greater protection. When A2 influenza virus appeared in the United States in 1957, vaccines containing only VI antigen gave very little protection.

Low levels of antibodies against the current strain ($\Lambda 2$ Hong Kong 68) can be demonstrated in the sera of the persons who had documented influenza during the past influenza epidemic. Similar observations have been made in groups of persons vaccinated with the currently available commercial vaccines. Current vaccines may provide only limited protection against $\Lambda 2$ Hong Kong 68. Better

protection against A2 Hong Kong 68 will require a newly formulated vaccine.

The development and manufacture of a monovalent influenza vaccine containing a Hong Kong strain will take a considerable period of time, and only a limited number of doses will be initially available.

RECOMMENDATIONS FOR VACCINE USE*

It is therefore recommended that currently available bivalent and polyvalent influenza vaccine be given only to persons at highest risk of mortality or severe complications as a result of influenza. When monovalent vaccine becomes available the same groups should be vaccinated or revaccinated with it. High-risk groups include persons with chronic illnesses as defined below and all persons in the older age group:

Chronically III:

Persons of all ages who suffer from chronic debilitating diseases, including cardiovascular, pulmonary, renal, or metabolic disorders:

- patients with rhoumatic heart disease, especially with mitral stenosis;
- patients with such cardiovascular disorders as arteriosclerotic heart disease and hypertension, especially showing evidence of frank or incipient cardiac insufficiency;
- patients with chronic bronchopulmonary diseases such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis.

Older Age Groups:

During major influenza outbreaks, especially those caused by type Λ viruses, increased mortality has regularly been recognized for persons over 45 years of age and even more notably for those over 65. This association has been particularly marked in individuals with underlying chronic disease.

⁴Reaction: and contraindication: are detailed in the Recommendations of the May 1968 meeting of the Committee, a. reported in MMWR, Vol. 17, No. 26, Week Ending June 29, 1968.

use rely on prompt reporting of epidemiologic and laboratory data collected during each influenza season from as many sources as possible.

INFLUENZA VACCINES - 1968-69

As in the 1967-68 influenza season, both bivalent and polyvalent vaccines will be available. Each vaccine contains 600 CCA units, but the bivalent vaccine contains a higher proportion of contemporary strains. Polyvalent vaccine incorporates older strains (types A and A1), hence less of the recent A2 and B antigens. The older strains have not been shown to play a significant role in protecting against currently prevalent viruses; therefore, the bivalent product should provide greater protection.

Compositions of the 1968-69 vaccines are shown below:

Type	Strain PR 8-34	CCA Units Per Adult Dose			
		Bivalent		Polyvalent	
A					100
A 1	Ann Arbor 1-57				100
A 2	Japan 170-62 Taiwan 1-64	${150 \\ 150}$	300	${100 \\ 100}$	200
В	Mass 3 66		300		200
	Total		600		600

RECOMMENDATIONS FOR VACCINE USE

Until consistently high level and durable protection can be expected from influenza vaccines and until their capacity for producing reactions is reduced, routine vaccination of healthy groups of adults and children is not recommended. This recommendation is particularly relevant in 1968-69, because epidemic influenza is not expected to occur.

Annual influenza immunization is again recommended for individuals in groups known to experience high mortality from epidemic influenza. In particular, immunization with bivalent vaccine is recommended for persons in older age groups and for all individuals with chronic illnesses, as defined below:

Chronically Ill: Persons of all ages who suffer from chronic debilitating diseases, including cardiovascular, pulmonary, renal, or metabolic disorders: 1) patients with rheumatic heart disease, especially with mitral stenosis; 2) patients with such cardiovascular disorders as arteriosclerotic heart disease and hypertension, especially showing evidence of frank or incipient cardiac insufficiency; 3) patients with chronic bronchopulmonary diseases such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; and 4) patients with diabetes mellitus and Addison's disease.

Older Age Groups: During major influenza outbreaks, especially those caused by type A viruses, increased mortality has regularly been recognized for persons over 45 years of age and even more notably for those over 65. This association has been particularly marked in individuals with underlying chronic disease.

Vaccination Schedule

All injections should be given subcutaneously.

Persons Vaccinated After July 1963*: Only a single booster of bivalent vaccine at the dosage level specified below is necessary for individuals for whom immunization is indicated and who have been vaccinated as recently as July 1963. This booster dose is best given in early December, which is approximately one month before the beginning of the usual influenza season.

Persons Not Vaccinated Since July 1963*: Persons for whom immunization is indicated and who have not been vaccinated since July 1963 should receive a primary immunization series of bivalent vaccine. The optimal primary series consists of two doses 2 months apart. Even a single dose will afford some protection, and a second injection as early as 2 weeks after the first will enhance the antibody response. Immunizations should be scheduled to be completed by early December.

Vaccine Dose**

Adults and Children Over 10 Years Old: 1.0 ml. on one or two occasions as specified above.

Children 6 to 10 Years Old: 0.5 ml. on one or two occasions as specified above.***

Children 3 Months to 6 Years Old: 0.1-0.2 ml. of vaccine on two occasions 1-2 weeks apart, followed by a third dose of 0.1-0.2 ml. about two months later.***

Reactions

Reactions to regular influenza vaccines are thought to be related primarily to the non-viral components of the vaccine and commonly include erythema, induration, and tenderness at the site of injection. Systemic reactions of fever, headache, and malaise also occur, but less frequently.

For older individuals who should receive influenza vaccine but have experienced severe local and systemic reactions following receipt of regular vaccines, full doses of a highly purified influenza vaccine should be considered. Intracutaneous administration of regular vaccines had previously been used in these older age individuals but is less effective than full doses of vaccine given by the subcutaneous route.

Contraindications

Since the vaccine viruses are propagated in eggs, the vaccine should not be administered to anyone who is hypersensitive to eggs.

^{*}This date represents the last major change in the A2 component.

^{**}The equivalent dose volume of highly purified vaccine is indicated by the manufacturer.

^{***}Since febrile reactions in this age group are common following influenza vaccination, an antipyretic may be indicated.

STATE EPIDEMIOLOGISTS AND STATE LABORATORY DIRECTORS

Key to all disease surveillance activities are the physicians who serve as State epidemiologists. They are responsible for collecting, interpreting, and transmitting data and epidemiological information from their individual States; their contributions to this report are gratefully acknowledged. In addition, valuable contributions are made by State Laboratory Directors; we are indebted to them for their valuable support.

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