

*An appraisal of experience for the past three and a half years indicates little progress in control of influenza. The basic assumptions of the control program must be reassessed. There is little evidence that recent vaccines have significantly prevented clinical illness, as well as equally little evidence to evaluate effects on mortality. How long such a program should be continued without better scientific evidence is problematic. Sounder bases are needed for an influenza control program.*

## **THE EPIDEMIOLOGICAL BASIS FOR THE CONTROL OF INFLUENZA**

*Alexander D. Langmuir, M.D., F.A.P.H.A.; Donald A. Henderson, M.D., F.A.P.H.A.; and Robert E. Serfling, Ph.D., F.A.P.H.A.*

IN February, 1960, the Influenza Advisory Committee of the Public Health Service proposed a major modification in the national effort to control influenza by recommending annual immunization of the aged and the chronically ill.<sup>1</sup> The committee urged that primary emphasis should be directed to these high risk groups. Immunization with polyvalent influenza virus vaccines should be performed during the fall months of each year whether or not epidemic influenza was anticipated during the ensuing winter. This proposal was based on three broad assumptions:

1. That excess mortality was the most important consequence of epidemic influenza.
2. That polyvalent virus vaccines had been at least partially effective in preventing clinical illness during most epidemics and therefore presumably would reduce the risk of death among the aged and chronically ill.
3. That epidemics cannot be predicted with sufficient accuracy to permit confident planning of control measures on a year to year basis.

Accordingly, on this realistic and pragmatic appraisal of the situation, it was deemed sound to concentrate efforts on those segments of the population at the greatest risk and to use the best vaccine with the broadest antigenic base possible even though it might be less than ideal.

The Surgeon General accepted this recommendation and assigned responsibility to the Communicable Disease Center for carrying out the program. In the past three and one-half years, promotional programs of increasing intensity have been conducted. Two influenza epidemics have occurred, one due to influenza B virus in 1961-1962, and the other due to influenza A virus in 1962-1963. It is appropriate therefore, at this time, for those charged with the responsibility of carrying out this program to report on their activities, to evaluate such progress as may have been made, and to outline future problems in so far as possible.

It must be reluctantly concluded that there is little progress to be reported. The severity of the epidemic of 1962-1963, in spite of the extensive use of polyvalent vaccine, demonstrates the failure to achieve effective control of excess mortality. Preliminary reports of field studies evaluating the effectiveness of vaccine have been disappointing. The epidemic of 1962-1963 was predicted with considerable assurance but the degree of antigenic drift of the prevailing strain of virus could not be anticipated. Further research will be necessary before a scientifically rational plan for the control of influenza can be devised.

### The Immunization Program

In executing the directive from the Surgeon General in 1960, the plan developed by the Communicable Disease Center concentrated on a program of professional education. The objective was to have the concept of the annual immunization of the chronically ill and of all persons 65 years of age and older become a standard and universally accepted pattern of good medical care, specially of geriatric practice. It was recognized that later a program of general public education would be desirable and even necessary to achieve maximum popular response, but during the first year, at least, promotional efforts should be directed toward the medical and health professions. This was achieved by preparing a fact sheet written in technical terms for the medical reader. This was circulated to editors of medical and health journals and mailed through various professional listings to the practicing physicians of the country. An analysis of excess mortality from influenza according to causes of deaths was published.<sup>2</sup>

The response to this type of promotional program was, as might be expected, rather limited. Records show

that only eight million doses were distributed for civilian use that year.

The Influenza Advisory Committee reviewed the experience of the winter of 1960-1961 and in May of 1961 reiterated its recommendation for annual immunization of the aged and the chronically ill.<sup>3</sup> In its report, the committee also hazarded the qualified statement that either influenza A or B might be epidemic during the following winter season. In a normal news release issued by the Surgeon General's office in October, 1961, this guarded prediction was given headline attention and picked up by the wire services for nationwide dissemination. The effect was dramatic. Within a few weeks, all supplies of commercial influenza vaccine were exhausted and it was too late to manufacture much more. The available vaccine used totaled 20 million doses. Statistics are not available to show what proportion of this was given to the recommended high priority groups in comparison with various strategic and industrial population groups but it was clear that total demand greatly exceeded total supply.

The epidemic of influenza B began in December, 1961, and within the next three-month period, excess mortality was observed in all major geographic divisions of the country.

In May, 1962, the committee met and again reviewed the experience of the previous winter. A more confident prediction was made, "While accurate predictions are difficult, recent and past patterns of influenza A and B indicate that widespread outbreaks of influenza A<sub>2</sub> (Asian) will occur in the United States during the 1962-1963 winter season." The committee also recommended that all persons 45 years of age and over be included in the high risk group needing annual immunization.<sup>4</sup>

This report was released to the press in June, 1962, with the announcement that in view of the prediction an inten-

sive campaign would be inaugurated in September. This information also was brought to the attention of all influenza vaccine manufacturers in the form of an official letter from the Surgeon General urging that adequate supplies of vaccine be stockpiled.

A systematic public education program was conducted including repeated news releases focusing on the prediction of the epidemic and the recommendations for use of the vaccine. A revised influenza fact sheet written in more popular terms was prepared and widely distributed. State and local health departments and voluntary health agencies joined more extensively in the campaign than in previous years. The National Tuberculosis Association adopted this program as one of its major national objectives. From July 1 through December 31, 1962, a total of 42 million doses of polyvalent influenza vaccine was distributed within the United States.

The extent to which this vaccine was used among the important "high risk" groups, i.e., older persons and the chronically ill, is not known with accuracy. Community surveys in Pennsylvania, Oklahoma, and Arizona, however, indicate that between 20 and 25 per cent of those over 65 years of age received the vaccine. Undeniably, a large proportion of the vaccine was again given to various strategic population groups other than the high risk groups recommended by the Advisory Committee.

No attempt has been made to evaluate the relative effectiveness of the various promotional procedures used to attain this broad population response, but there is universal agreement that the most effective single step was the publicizing of the Surgeon General's prediction of an epidemic.

In mid-January, 1963, an epidemic of influenza A began and within the next three months marked excess mortality was observed in all the geographic

divisions except the Pacific Coast States.

In May, 1963, the Advisory Committee met and this time made the following forecast, "widespread outbreaks of influenza A<sub>2</sub> are not anticipated" during the coming winter, with the possible exception of the Pacific Coast States.<sup>5</sup> But in keeping with the basic recommendation first made in 1960, the committee reiterated its advice that older persons and the chronically ill receive annual immunization.

### Excess Mortality

Figure 1 presents the weekly mortality for pneumonia and influenza in 108 cities of the United States from the summer of 1960 to the summer of 1963. As previously mentioned, no epidemic of influenza occurred during the first year of the new program. During the second year, 1961-1962, the excess mortality due to the influenza B epidemic is clearly revealed. A double wave of increased mortality occurred, reflecting the appearance of epidemic influenza B at varying times in different parts of the country. During the third year, 1962-1963, the severe excess mortality due to the influenza A<sub>2</sub> epidemic stands out sharply. Also shown in Figure 1 are the 1962-1963 mortality charts for each of the nine geographic divisions of the country. Excess mortality of marked degree appeared in seven divisions. In the Mountain States, it was less marked and in the Pacific States it was not clearly discernible.

In Table 1 are shown estimates of the excess mortality both from pneumonia-influenza and from all causes during each of the influenza epidemics that have occurred since the winter 1934-1935 when the influenza virus was first demonstrated in this country. These data are presented primarily to provide a basis of comparison of the two recent epidemics with previous experience.

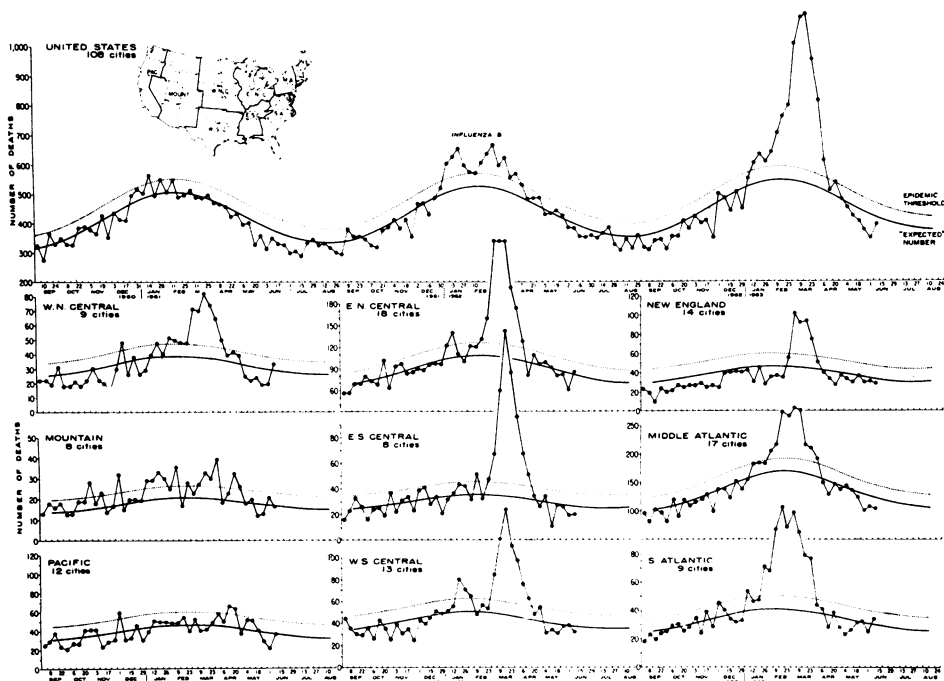


Figure 1—Weekly Pneumonia and Influenza Deaths

The severity of the influenza A epidemic of 1962-1963 is striking. A total of 57,000 excess deaths is estimated, giving a total excess rate of 30.4 per 100,000. With the exception of the pandemic of Asian influenza in 1957-1958, it is necessary to go back to 1943-1944 to find an epidemic of influenza A with greater excess mortality.

The epidemic of influenza B of 1962 was of moderate severity, being associated with an excess of 3,700 pneumonia-influenza deaths and 24,000 excess deaths from all causes. As measured by mortality rates, it was somewhat less severe than the B epidemic of 1945-1946, but distinctly more serious than the relatively minor B epidemics of 1952, 1955, and 1959.

Thus the epidemics of influenza A and B occurring during the past two winter seasons have been fully as serious as measured by excess mortality as

many that have occurred during the last 30 years since the discovery of the influenza viruses. When this fact is related to the present availability of a wide range of antibiotics, of polyvalent influenza vaccine, and of markedly improved medical care, the degree to which influenza remains an unsolved public health problem is emphasized.

#### Effectiveness of Influenza Vaccines

The present commercially available polyvalent influenza vaccines consist of a mixture of inactivated viruses of both A and B types. In theory, the inclusion of representative strains of the major subtypes of these viruses should provide a composite antibody response with a broad base of protection and relative stability.<sup>6</sup>

In the past, most field evaluations of polyvalent influenza vaccines have dem-

onstrated an efficacy of 70 per cent or greater, except when a major antigenic shift in the prevailing strain has occurred. In 1947, with the introduction of the A<sub>1</sub> strain, the polyvalent vaccines then in use were found to be ineffective. In 1957, there was advance warning of the introduction of the A<sub>2</sub> (Asian) strain. Large amounts of monovalent vaccine were produced and this was found to be quite efficacious. Since 1957, the recommended vaccine has again been polyvalent containing representative strains of A, A<sub>1</sub>, A<sub>2</sub>, and B viruses. This was the composition of the 42 million doses of vaccine used in the fall of 1962.

Only a limited number of studies of vaccine efficacy were conducted during the A<sub>2</sub> epidemic of that winter and only

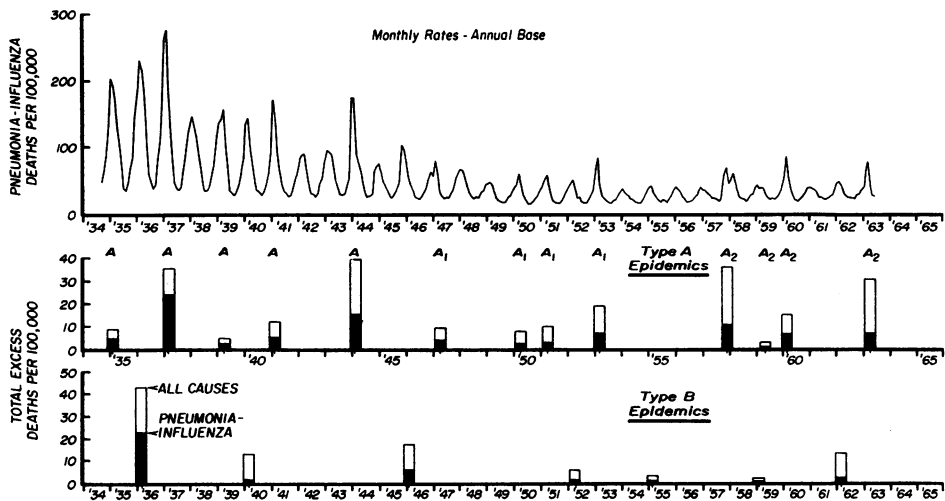
preliminary reports of the results are yet available. The findings are disappointing and point to an efficacy of not greater than 20 to 25 per cent at best. These studies include a placebo control trial in Ohio,<sup>7</sup> a less rigidly controlled study among obstetrical patients in Pittsburgh,<sup>8</sup> and a large scale retrospective study among firemen and their families in Baltimore.<sup>9</sup> A smaller scale evaluation was also conducted at Walter Reed Army Institute of Research.<sup>10</sup>

Immunological comparisons of the strains of virus isolated during the 1962-1963 epidemic revealed that they could clearly be classed within the A<sub>2</sub> subtype of influenza virus, but some degree of antigenic drift was noted.<sup>10,11</sup> Presumably this minor change in antigenic structure accounts at least in part

**Table 1—Mortality Characteristics of Influenza Epidemics in the United States, 1934 through 1963**

Period of Excess Mortality	Type of Influenza	Number of Excess Deaths		Rate per 100,000	
		Pneumonia, Influenza	All Causes	Pneumonia, Influenza	All Causes
Dec.-Jan. 1934-1935	A	5,800	11,000	4.6	8.6
Dec.-May 1935-1936	B	30,000	55,000	23.1	43.1
Jan.-Mar. 1937	A	29,000	46,000	22.4	35.9
March 1939	A	3,100	6,100	2.4	4.7
Jan.-Feb. 1940	B	1,400	17,000	1.1	12.6
Dec.-Feb. 1940-1941	A	7,200	16,000	5.4	12.0
Dec.-Jan. 1943-1944	A	21,000	53,000	15.6	39.8
Dec.-Jan. 1945-1946	B	6,500	23,000	4.8	17.1
Mar.-Apr. 1947	A <sub>1</sub>	4,800	13,000	3.4	9.0
Mar.-Apr. 1950	A <sub>1</sub>	3,200	11,000	2.1	7.5
Feb.-Apr. 1951	A <sub>1</sub>	4,000	15,000	2.6	9.8
Mar.-Apr. 1952	B	2,000	8,500	1.3	5.5
Jan.-Mar. 1953	A <sub>1</sub>	10,000	30,000	6.5	19.0
Jan.-Feb. 1955	B	1,700	4,900	1.0	3.0
Oct.-Mar. 1957-1958	A <sub>2</sub>	19,000	62,000	10.9	36.0
January 1959	B	500	2,400	0.3	1.4
Mar.-Apr. 1959	A <sub>2</sub>	1,500	4,100	0.9	2.4
Jan.-Mar. 1960*	A <sub>2</sub>	12,000	27,000	6.7	15.0
Jan.-Mar. 1962*	B	3,700	24,000	2.0	12.9
Feb.-Apr. 1963*	A <sub>2</sub>	12,100	57,000	6.5	30.4

\* Estimated from 10 per cent sample of United States mortality.



**Figure 2—Pneumonia-Influenza Death Rates by Month and Excess Mortality During Epidemic Periods—United States, 1934-1963**

for the disappointing showing of the vaccine during this epidemic. As a result of these findings, the Advisory Committee recommended the addition of a recently isolated  $A_2$  strain to the mixture for future production of polyvalent vaccine.<sup>5</sup> It is hoped, but by no means certain, that the newly modified vaccine will be more effective in the next epidemic.

There is as yet no scientifically valid basis for predicting the character of the antigenic shifts in virus that appear from time to time. For this reason, widespread use of influenza vaccines for general population groups cannot be justified and has not been recommended by the Advisory Committee. Among the high risk groups, however, it is felt that the continued annual use of a less than ideal vaccine is still justified, and has so been recommended.

### Prediction of Epidemics

Attempts to predict epidemics of influenza are based on assumptions of an underlying periodicity governed by the

balance of immunes and susceptibles in the population.<sup>12</sup> No periodicity was recognized until the influenza viruses were identified. Then a definite although somewhat variable and inconstant periodicity became apparent for epidemics due to both types of viruses.<sup>13</sup> This is shown for the United States over the last 30 years in Figure 2.

From 1934 to 1940, the first four epidemics known to be due to the Type A virus occurred at two-year intervals. Three-year intervals appeared during the 1940's. In 1950 and 1951, small epidemics occurred in consecutive years but for the most part these involved separate geographic areas of the country. Thus, the epidemic due at about this time appears to have been split between two consecutive years, as occasionally is seen in measles epidemics in large cities.

In the winter of 1952-1953, a more severe epidemic of influenza A occurred two, or two and one-half, years after the last one. Then there was a long "salubrious" interval of five years prior to the pandemic of Asian influenza in 1957-

1958. The following year, in 1959, the slight excess mortality due to Type A virus was limited largely to New York City, but in January, 1960, two years after the Asian pandemic, a sharp recurrence of influenza A involved the whole country. This was followed three years later by the epidemic of 1963.

Thus, for an interval of almost two decades, 1934 to 1953, there was a clear tendency for influenza A to recur in a period of two or three years. With the introduction of the A<sub>2</sub> strain of virus after the five-year hiatus, the two- to three-year periodicity has reappeared.

Influenza B also shows a suggestive recurrent cycle of approximately four to six years. Francis first suggested this tendency when he referred to influenza B as a "quadrennial croup."<sup>13</sup> It should be emphasized that epidemics due to this virus are less likely than A epidemics to occur on a nation-wide basis and excess mortality due to influenza B is less severe. It should also be pointed out that the periods of slight excess mortality attributed to influenza B in 1952 and 1955 are borderline in significance. They were not listed by Selwyn Collins in the analyses of weekly mortality in selected cities<sup>14</sup> but have come to light recently in analyses of monthly mortality for the entire country. During these two periods of time, the presence of influenza B virus in the country was known from reports of virus isolations and serological responses.

In 1961, the Advisory Committee made its guarded prediction that either influenza A or B might occur in epidemic form during the following winter on the basis that two years would have elapsed since the 1960 epidemic of influenza A and many years had passed since a significant excess mortality from influenza B had been recorded in the country. It was by no means clear whether Type A or B or possibly both viruses would become epidemic.

When the epidemic was found to be

almost exclusively Type B, then it was possible the next year to make a much firmer prediction that influenza A<sub>2</sub> would recur three years after the 1960 epidemic. The confidence with which this prediction was made was reinforced by the knowledge that A<sub>2</sub> epidemics had recurred at two-year intervals in Great Britain, on the European Continent, and in Japan.

Carrying this reasoning to the future, it was possible for the Committee to predict, with equal confidence, that no epidemics of influenza are to be expected in the United States either of Type A or Type B during the winter of 1963-1964, with the possible exception of the Pacific Coast States that were largely spared in 1962-1963.

These predictions with respect to Type A epidemics have disregarded the question of antigenic shifts of the virus because they do not seem to have been influential. For example, in 1947, the shift from A to A<sub>1</sub> occurred in a cycle that continued without major disruption up to 1952. The introduction of the A<sub>2</sub> virus has been followed in many parts of the world by recurrent two- to three-year cycles. Experience shows that an underlying periodic tendency has repeatedly overridden the antigenic shifts that have been observed so far.

The five-year "salubrious" interval from 1953 to 1957 stands out as an unanswerable challenge to any epidemiologist, no matter how intrepid, who advocates a continuing two- to three-year regularity for influenza A epidemics. Obviously, they dampen off. It is worthy of note, however, that before each of the known pandemics within the past 75 years, in 1889-1891, in 1918-1919, and in 1957-1958, there has been an antecedent "salubrious" period of five or more years of absence or at least relative freedom from severe influenza epidemics. How significant this observation may be is highly speculative. In the future, however, when influenza A

epidemics fail to appear after a three-year interval, in other words when predictions go awry, it would only be prudent for epidemiologists throughout the world to sharpen their surveillance in order to detect the appearance of a new pandemic variant at the earliest possible moment.

## Discussion

From this appraisal of the experience in the past three and one-half years, it is apparent that progress in the control of influenza has not been impressive. A reassessment of the basic assumptions upon which the program was developed is warranted.

There can be little question that the first assumption is valid. Excess mortality is certainly one of the most, if not the most, important consequence of epidemic influenza.

The assumption of at least partial effectiveness of polyvalent vaccines has not been well substantiated. There is little evidence that recent vaccines have significantly prevented clinical illness and similarly little evidence in either direction to evaluate the effect of the vaccine on mortality of older persons and the chronically ill. It is, therefore, problematic how long such a program should be continued without better scientific evidence to justify the major costs to the general public that are entailed.

It is obvious that more basic research on the antigenicity of the influenza viruses and on the determinants of their variability is essential. More extensive field evaluations of specific influenza antigens should be undertaken. Studies employing monovalent vaccines are specially indicated. Field trials to test whether or not annual immunization does reduce excess mortality would be advisable.

The third assumption, that epidemics cannot be predicted, has been at least

partially modified by the recent experience. The increasing confidence with which the Advisory Committee itself has made predictions and used them for recommending action programs warrants the continuation of this practice. Certainly it has been demonstrated that the publicizing of a confident prediction by the Surgeon General is a most effective procedure to achieve community response.

It is obvious that sounder bases are needed upon which to develop a more effective program for the control of influenza. It is necessary to proceed deliberately in a step-by-step manner with constant reappraisal and reevaluation of recommended procedures each year. In developing broad plans for community action, a realistic assessment of recent experience should be weighed equally with older and perhaps more traditional concepts.

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Dr. Langmuir is chief, Epidemiology Branch; Dr. Henderson is chief, Surveillance Section; and Dr. Serfling is chief, Statistics Section, Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, Atlanta, Ga.

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## Disease of Animals and Man

The Annual West-Northcentral Conference on Diseases Common to Animals and Man will be held September 11-12 at the University of Nebraska College of Medicine in Omaha. The conference has three functions: (1) to provide researchers in all branches of the biological sciences in the West-Northcentral states an opportunity to present dates and exchange information on zoonotic diseases; (2) an opportunity for an annual appraisal of the status of these diseases in this region; and (3) to acquaint practitioners in both the medical and veterinary professions with various aspects of zoonotic diseases. For further information write Dr. Norman G. Miller, Department of Medical Microbiology, University of Nebraska College of Medicine, 42nd and Dewey Avenue, Omaha 5, Neb.