Observations on Excess Mortality Associated with Epidemic Influenza


One of the classic epidemiologic descriptions frequently applied to influenza is embodied in the phrase "high morbidity, low mortality." This remains true in the present era, just as it was true of many influenza epidemics of past centuries. Such a description, however, tends to lose sight of the fact that morbidity in epidemic influenza may be so high that even the relatively low associated mortality may itself reach grave proportions. Although no influenza epidemic in recorded medical history has ever approached the catastrophic pandemic of 1918-1919 in terms of total mortality, the lethal potential of the disease has not been lost.

Sir Macfarlane Burnet emphasized the problem of excess influenza-associated mortality several years ago when he wrote:

Whenever an epidemic of influenza passes through a community, there is a sharp peak of deaths from various causes among the aged. Any elderly person rendered frail by physical disability is likely to succumb to an attack of influenza. This was heavily underlined during the 1951 influenza outbreak in Great Britain. In Liverpool the epidemic passed like an angel of death amongst the old. During the peak week there were more deaths than in the worst week of the 1918-19 pandemic. An investigation of the saving of life that might be effected by appropriate immunization of the aged against influenza would seem to be a very worthwhile project.

This problem has been reemphasized during the past 3 years. Two epidemics of Asian strain influenza have occurred in the United States since the identification of this new antigenic variant in May, 1957.

The first epidemic occurred in 2 distinct waves from September through December 1957, and from January through March 1958; a total of almost 40,000 excess deaths was recorded during the first wave and of 20,000 during the second wave. During the first 3 months of 1960 a second major epidemic occurred, resulting in approximately 27,000 excess deaths. A total of 86,000 deaths in excess of the expected number thus occurred in the United States as a result of Asian influenza epidemics in the 3-year period since the introduction of the strain.

A total of 86,000 deaths in excess of the normally expected number occurred in the United States as a result of the 3 epidemic prevalences of influenza in the period 1957-1960. It was deemed important to characterize these 86,000 excess deaths further in order to define, as accurately as possible, those individuals at highest risk of death from influenza. The high-risk groups were demonstrated to be persons over 65 years of age, persons with certain associated chronic diseases, particularly cardiovascular disease and broncho-pulmonary disease, and pregnant women. It may be anticipated that some benefit, in terms of saving of lives, would accrue if these high-risk groups were routinely immunized against influenza.

It is important to characterize these 86,000 excess deaths further and to determine, if possible, in how many of these deaths the influenza was merely a terminal event in an already severely debilitated patient, and in how many the influenza and its accompanying pneumonia may have killed a person in active, productive life, albeit in an older age group, or with definite but compensated chronic disease.

Although these questions may be difficult to answer, the present contribution is an attempt, through the examination of standard mortality data, to define the nature and extent of excess mortality due to influenza, to identify those groups at special risk of death from influenza, and to estimate the possible benefit, in terms of saving of lives, that might be realized by adequate immunization of the population at risk.

Source of Data

Standard mortality data from the National Office of Vital Statistics have been used as the basis for the tables and figures in this contribution. These data are of 3 types: (1) the weekly reports of deaths

due to influenza and pneumonia received from 108 major United States cities; (2) final mortality data for specific causes of death for years up to and including 1958; and (3) the 10 per cent sample of death certificates taken by the National Office of Vital Statistics to obtain estimated death rates for major causes of death for the years 1959 and 1960. Use of the 10 per cent sample was necessary because of the lag in publication of final mortality figures.

Mortality Due to Influenza and Pneumonia

The most sensitive statistical measure of the extent of an influenza epidemic is the number of deaths due to influenza and pneumonia in excess of the usual seasonal expectancy. The late Dr. Selwyn Collins made thorough studies of mortality due to epidemic influenza in the United States from 1887 to 1956. Using a modification of Collins' methods, the Communicable Disease Center has employed the weekly reports of influenza and pneumonia deaths from 108 cities in the United States as a surveillance technique to evaluate the trends of epidemic influenza since 1957. These data are presented graphically in Figure 1, for the country as a whole and for the 9 major geographic regions individually, from September, 1957, to May, 1960. The numbers of deaths reported each week are shown as small circles connected by a straight line. The solid, smoothly curved line defines an average seasonal expectancy determined from recorded data for the period September through August of 1955-1956, 1956-57, 1958-59. Dashed "epidemic threshold" line allows for chance variation in weekly numbers of deaths. Area between recorded deaths and trend line represents excess mortality due to influenza and pneumonia.

![Figure 1. Weekly pneumonia and influenza deaths in 108 U.S. cities, 1957-1960. Small circles connected by straight line show number of deaths reported each week. Solid, smoothly curved (base or trend) line defines average seasonal expectancy determined from recorded data for period September through August of 1955-56, 1956-57, 1958-59. Dashed "epidemic threshold" line allows for chance variation in weekly numbers of deaths. Area between recorded deaths and trend line represents excess mortality due to influenza and pneumonia.](image-url)

The epidemic year 1957-1958 was not included in the calculation of this base line. The dashed "epidemic threshold" line, parallel to the base or trend line, allows for chance variation in weekly numbers of deaths. Experience has shown that an elevation of observed deaths above the "epidemic threshold" for 2 or more weeks usually indicates a rise in mortality of epidemiologic significance. The area between the recorded deaths and the trend line is considered to represent excess mortality due to influenza and pneumonia.

The 2 waves of excess mortality in the fall and winter of 1957-1958 are evident in this figure. Some geographical variation in the severity of the epidemic was present, especially noticeable during the period of the second wave of deaths early in 1958. The Mountain and Pacific regions, in particular, had relatively less mortality than other regions in

<table>
<thead>
<tr>
<th>Age, Yr.</th>
<th>Expected</th>
<th>Observed</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>28,720</td>
<td>29,320</td>
<td>600</td>
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<tr>
<td>1-14</td>
<td>8,350</td>
<td>9,520</td>
<td>1,170</td>
</tr>
<tr>
<td>15-24</td>
<td>9,240</td>
<td>7,240</td>
<td>1,900</td>
</tr>
<tr>
<td>25-44</td>
<td>20,170</td>
<td>39,770</td>
<td>8,600</td>
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<tr>
<td>45-64</td>
<td>105,200</td>
<td>113,900</td>
<td>8,700</td>
</tr>
<tr>
<td>65+</td>
<td>194,820</td>
<td>237,280</td>
<td>42,460</td>
</tr>
<tr>
<td>All Ages</td>
<td>457,000</td>
<td>447,100</td>
<td>9,900</td>
</tr>
</tbody>
</table>

The table below shows the estimated excess mortality by age, United States, 1957-58 and 1960.

Table 1.—Estimated Excess Mortality by Age, United States, 1957-58 and 1960

<table>
<thead>
<tr>
<th>Age, Yr.</th>
<th>Expected</th>
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<th>Excess</th>
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</thead>
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<td>All Ages</td>
<td>457,000</td>
<td>447,100</td>
<td>9,900</td>
</tr>
</tbody>
</table>

the first wave and virtually no second wave. During
the following winter and spring, sporadic outbreaks
of both influenza A₂ and B were frequent through¬
out the country, but resulted in little excess mor¬
tality. This excess was localized almost entirely to
the Middle Atlantic region in March and April,
1959. During the first 3 months of 1960, a much
more severe epidemic in terms of excess mortality
occurred on a nationwide basis. The degree of
excess mortality recorded during this epidemic was
comparable to either of the epidemic waves in
1957-1958. Of interest is the fact that the Mountain
and Pacific regions had severe epidemics, as meas¬
ured by excess mortality, in 1960, whereas the
Middle Atlantic region had virtually none. This is
in contrast with the situation in 1957-1958, when the

Table 2.—Estimated Excess Mortality by Selected Causes,
United States, 1957-58 and 1960

<table>
<thead>
<tr>
<th>Causes</th>
<th>October-December, 1957</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Observed*</td>
<td>Excess</td>
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<tr>
<td>Pneumonia-influenza</td>
<td>22,349</td>
<td>24,549</td>
<td>12,100</td>
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<tr>
<td>Cardiovascular-renal</td>
<td>231,000</td>
<td>246,350</td>
<td>24,900</td>
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<tr>
<td>All other causes</td>
<td>174,000</td>
<td>188,020</td>
<td>8,020</td>
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<tr>
<td>All causes</td>
<td>428,329</td>
<td>447,670</td>
<td>29,341</td>
</tr>
<tr>
<td></td>
<td>January-March, 1958</td>
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<td></td>
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<tr>
<td>Pneumonia-influenza</td>
<td>26,140</td>
<td>27,740</td>
<td>6,600</td>
</tr>
<tr>
<td>Cardiovascular-renal</td>
<td>235,100</td>
<td>258,100</td>
<td>13,000</td>
</tr>
<tr>
<td>All other causes</td>
<td>160,100</td>
<td>170,100</td>
<td>1,000</td>
</tr>
<tr>
<td>All causes</td>
<td>421,320</td>
<td>448,920</td>
<td>39,200</td>
</tr>
<tr>
<td></td>
<td>January-March, 1960</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia-influenza</td>
<td>18,270</td>
<td>20,670</td>
<td>10,000</td>
</tr>
<tr>
<td>Cardiovascular-renal</td>
<td>266,300</td>
<td>298,200</td>
<td>12,000</td>
</tr>
<tr>
<td>All other causes</td>
<td>174,600</td>
<td>182,800</td>
<td>8,200</td>
</tr>
<tr>
<td>All causes</td>
<td>459,170</td>
<td>491,600</td>
<td>36,430</td>
</tr>
</tbody>
</table>

* 10% mortality sample.

Middle Atlantic region experienced a severe out¬
break and the Mountain and Pacific regions re¬
corded relatively mild epidemics.

Mortality Due to All Causes

As shown by Collins and Lehmann,² ⁵ the force
of an influenza epidemic extends far beyond the
deaths ascribed to influenza and pneumonia. A
better measure of the total impact of an epidemic
is provided by the total excess mortality, even
though this index is somewhat less sensitive an
indicator than deaths due to influenza and pneu¬
monia alone.

The calculations presented in Tables 1 and 2 and
in Figure 2 show total mortality in the United
States in excess of seasonal expectancy. Seasonal
expectancy was calculated ⁶ by a linear projection
of mortality data for comparable months from 1953
to 1959, excluding the epidemic periods in 1957,
1958, and 1960. For example, linear estimates of
expected deaths in the 65-year and older age group
in February of 1958 and 1960 were made from a
straight line fitted to the data for February of 1954,

Table 1 and Figure 2 describe the age distribu¬
tion of total excess deaths in the 3 epidemic pre¬
valences of Asian influenza. The shape of the histo¬
gram of age-specific mortality due to influenza and
pneumonia is in general a skewed “U,” with peaks
at either end of the age spectrum. This type of
curve has characterized recorded influenza epi¬
demics ⁷ with the single exception of the 1918-1919
pandemic. The marked mortality among young and
middle-aged adults in that pandemic resulted in a
unique “W”-shaped curve.

It is apparent that the population over 65 years
of age pays by far the heaviest toll in excess deaths.
Although during the first epidemic period only
slightly over one-half of the excess deaths occurred
in persons 65 years and older, this proportion in¬
creased in succeeding epidemics; in the 1960 epi¬
demic, 80 per cent of the excess deaths occurred
among individuals in this age group.

Table 2 presents the estimated excess mortality
during the 3 epidemic periods by 3 broad causes.
Of the excess deaths, almost 85 per cent were
attributed to 2 broad categories: pneumonia-influen¬
za and cardiovascular-renal disease. Indeed, car¬
diovascular-renal disease alone accounted for over
one-half of the 86,000 total excess deaths during the
3 epidemic periods. It is apparent that elderly per¬
sons, particularly those with associated cardiovas¬
cular-renal disease, are at highest risk of death from
influenza.

It need not seem paradoxical that an epidemic of
influenza should cause a distinct wave of excess
deaths said to be due to cardiovascular-renal dis¬
ease, or to some condition other than influenza or
pneumonia. The explanation of these “epidemics”
of chronic disease lies in the fact that deaths in the
United States, as well as in most other countries,
are coded and tabulated by “primary” cause of
death, defined as the cause that initiated the train
of circumstances which eventually resulted in death.
A typical example is a patient with arteriosclerotic
heart disease who then develops influenza,
followed by pneumonia, and finally death. Death is
likely to be due to the heart disease, since that was
the first or “initiating” cause.

Effect of Chronic Disease

In order to characterize the excess deaths due to
diseases other than influenza and pneumonia fur¬
ther, it seemed pertinent to examine the mortality
due to certain specific chronic diseases in detail.

Figure 3 presents mortality rates by month, as
estimated from the 10 per cent sample of death
certificates, for a number of major causes of death.
A crude index of seasonal expectancy was ob¬
tained by computing a 2-year average for each
disease category, from data of comparable months
of the nonepidemic years September, 1956, through
August, 1957, and September, 1958, through
August, 1959.
The death rate by month due to influenza and pneumonia presents a vivid picture of the epidemic periods, the last quarter of 1957, the first quarter of 1958, and the first quarter of 1960. The death rate due to all causes is clearly higher during the epidemic periods than would have been anticipated had there been no epidemic.

Major cardiovascular-renal disease, as defined in the World Health Organization's international classification of diseases, injuries, and causes of death, is a broad group including all diseases of the heart, vascular diseases of the kidney and central nervous system, as well as diseases of the remainder of the vascular tree. Again, death rates due to major cardiovascular-renal disease were markedly higher during the epidemic periods than in the correspond-

<table>
<thead>
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<th>Month</th>
<th>Excess Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct-Dec 1957</td>
<td>1,800</td>
</tr>
<tr>
<td>Jan-Mar 1958</td>
<td>1,500</td>
</tr>
<tr>
<td>Jan-Mar 1960</td>
<td>1,000</td>
</tr>
</tbody>
</table>

October, 1957, suggests the desirability of studying the possibility of influenza-associated excess mortality in this category further.

Another observation may be made from Figure 3 that deserves comment. In the death rates due to all causes—major cardiovascular-renal disease, arteriosclerotic heart disease, vascular lesions of the central nervous system, hypertensive heart disease, and generalized arteriosclerosis. It should be noted that a gradual decrease in the death rate for hypertensive heart disease is evident over the 4-year period of the graph; an abnormal increase in the death rate is

In one cause of death included in Figure 3, malignant neoplasms, no definite influenza-associated increase is demonstrable. Collins and Lehmann demonstrated previously that the death rate due to malignant neoplasms was an essentially straight, although gradually ascending, line, with no demonstrable seasonal variation, or influenza-associated excesses. The data of Figure 3 are in agreement with those of Collins, although a small peak in

![Figure 3](image_url)
1958. This deficit is small in each case; nevertheless, the consistency of this finding suggests that it represents a real phenomenon. The opinion is occasionally expressed that influenza kills primarily those individuals who would die of their primary disease alone, in the absence of epidemic influenza, within 6 to 12 months. The deficits observed in this figure may represent a “compensatory” phenomenon—a result of the premature death, due to epidemic influenza, of those individuals who might have died within 6 to 12 months of their primary disease alone. It should be noted, however, that the amount of such “compensatory” deficit is small in each case and accounts for only a small proportion of the preceding excess. This suggests that most victims of an influenza epidemic are those who might have lived considerably longer had influenza not claimed them, rather than severely debilitated patients in whom influenza is merely a terminal event.

Another group of chronic diseases, less frequent as causes of death but yet of great clinical importance, were found to have a strong association with epidemic influenza in terms of increased risk of death, and are presented in Figure 4.

Final mortality figures per month from 1955 to 1958 are presented in this figure, with a direct comparison of the number of deaths during the epidemic period in the fall of 1957 and winter of 1958 with the corresponding period one year before. This type of comparison was made because final mortality figures are available only through 1958. It should be noted, in the interpretation of these graphs, that number of deaths per month due to certain diseases, e.g., rheumatic mitral valvular disease, pulmonary tuberculosis, and chronic nephritis, appears to be decreasing gradually. The number of deaths due to diseases of the respiratory system other than influenza and pneumonia, on the other hand, appears to be increasing gradually. The number of deaths in each category during the fall and winter of 1956-1957 therefore may be considered only to approximate normal seasonal expectancy.

Some degree of increase in the number of deaths during the epidemic period may be noted in each of the disease categories. This increase is marked in deaths due to asthma and diseases of the respiratory system other than influenza and pneumonia; moderate in deaths due to diabetes mellitus, rheumatic heart disease and its sub-group, rheumatic mitral valvular disease; and mild but definite in deaths due to cirrhosis of the liver, pulmonary tuberculosis, and chronic nephritis.

Comment

These data demonstrate excess mortality in certain chronic disease states during the known epidemics of Asian influenza, 1957-1960, in a manner similar to the classic studies by Collins and Lehmann 4,5 of influenza epidemics from 1918 to 1951. Polak 6 reported a similar study of excess mortality associated with Asian influenza in the fall of 1957 in the Netherlands. He was able to demonstrate an increased risk of influenza-associated death among individuals with multiple sclerosis, paralysis agitans, cardiac valvular lesions, bronchial asthma, tuberculosis, kyphosis, scoliosis, and diabetes mellitus.

Excess influenza-associated deaths due to asthma, diseases of the respiratory system other than influenza and pneumonia, and pulmonary tuberculosis probably occur primarily in patients whose pulmonary function is significantly compromised. The lives of diabetics are jeopardized by influenza not only by their increased risk of bacterial superinfection and increased incidence of cardiovascular-renal disease, but also by the increased risk of acidosis and coma during an acute infection.

An increased risk of influenza death in association with certain conditions is better demonstrated by clinical studies than by analysis of reported mortality data. The association of rheumatic heart disease and influenza-associated death, particularly rheumatic mitral stenosis and fatal influenza-virus pneumonia, for example, is so well documented in the literature that its occurrence seems well beyond the realm of chance. In a study of the pul-
monary complications of influenza seen at the New York Hospital during the fall of 1957, 10 of 21 patients who developed pulmonary complications had underlying rheumatic heart disease, mitral stenosis being the most common lesion. Of these 10 patients, 4 developed primary influenza virus pneumonia; 3 of the 4 died. In an analysis of influenza-associated deaths in Boston, 16 the patients in 5 of the 32 fatal cases had rheumatic heart disease. In a report of 103 influenza-associated deaths from the Netherlands, 16, 9 of 10 patients with mitral stenosis succumbed to an abacterial influenza-virus pneumonia. As has been indicated, 16 this marked association of influenza-virus pneumonia and mitral stenosis suggests that pulmonary hemodynamic factors may be of significance in the pathogenesis of the syndrome.

An association of influenza-associated deaths and pregnancy is a common clinical impression. Collins 1 demonstrated that death rates due to puerperal septicemia and other acute complications of pregnancy and childbirth showed influenza-associated excesses in earlier years, 1931 and before. In the 1918 pandemic, for example, women in the childbearing-age groups frequently developed complicating pneumaticia, with resulting high mortality rates. In general, however, epidemics of influenza since 1931 have been less severe and have caused no demonstrable mortality excesses in this category. This is true also for the recent epidemics due to Asian influenza. Furthermore, the present system of registration and coding of deaths would result in the death of a pregnant woman due to influenza or pneumonia being coded as due to influenza and pneumonia, regardless whether pregnancy was noted or not. If such an association did exist, it would be demonstrable only by a special study of mortality among women of childbearing age in which the presence or absence of pregnancy was noted on each death certificate.

Evidence in support of such an association may be found in several clinical studies. The study of influenza-associated deaths in Boston 14 revealed that 4 of the 32 deaths occurred in pregnant women, at from 4½ to 8½ months' gestation. Of these 4 women, 3 were otherwise in good health prior to contracting influenza; one, however, also had myasthenia gravis. Of 139 influenza-associated deaths reported in 1957 from the New York State Health Department to the Communicable Disease Center, 15 6 occurred in pregnant women. Of 1,230 fatal cases of influenza reported from the Netherlands in 1957, 16 11 occurred in pregnant women, resulting in a mortality rate from influenza which was twice as high among pregnant women as compared with non-pregnant women in the same age group. One can only speculate on the possible pathogenic factors of significance in this association.

There is thus a significant body of evidence that the lethal potential of epidemic influenza is still present and still to be reckoned with. Rather than recurring in a mild form, as might have been anticipated as the over-all immunity of the population increased, the most recent outbreak in 1960 resulted in excess mortality which exceeded that of the second wave of the 1957-1958 epidemic and approached that of the first wave.

This analysis serves to underscore the fact that certain individuals are at increased risk of death from influenza. Three broad groups can be identified, 2 of which overlap: persons over 65 years of age, persons with certain associated chronic diseases, and pregnant women. Associated chronic illnesses of significance include cardiovascular-renal disease, particularly rheumatic heart disease; chronic pulmonary diseases, e.g., bronchial asthma and pulmonary tuberculosis; and metabolic diseases such as diabetes mellitus.

It would seem entirely reasonable to believe that the prevention of influenza in these high-risk groups would, in turn, result in a corresponding reduction of excess influenza-associated mortality. No direct evidence exists to either support or refute this belief. A number of reports in the recent literature 18-21 do provide evidence that immunization with influenza vaccine is from 60 to 75 per cent effective in preventing influenza. It may be inferred, therefore, that annual immunization of such high-risk groups against influenza, in order to provide continuing protection, might well be highly effective in reducing the disquieting toll of excess deaths periodically exacted by epidemic influenza.

Summary

A total of 56,000 excess deaths are estimated to have been caused by Asian influenza during the 2 epidemics that have occurred since its introduction in 1957. Close to 40,000 of these deaths occurred during the first epidemic in the fall and winter of 1957-1958; 27,000 more excess deaths occurred during the second epidemic in the first 3 months of 1960.

The relationship of age and certain chronic disease states to the excess mortality associated with these epidemics of influenza was investigated. Over two-thirds of the excess mortality occurred in persons aged 65 years and over. Excess influenza-associated mortality was demonstrated in persons with cardiovascular-renal disease, certain bronchopulmonary diseases, and diabetes mellitus.

Mortality data as well as clinical studies confirmed a strong association of rheumatic heart disease with influenza-associated deaths. The increased risk of influenza-associated death in pregnancy was supported by clinical studies.

Immunologic protection through the routine use of influenza vaccine in such high-risk groups may be of great value in reducing the extent of influenza-associated excess mortality.
The authors wish to express their appreciation to Drs. Alexander D. Langmuir and E. Russell Alexander, Epidemiology Branch, Communicable Disease Center, for their helpful advice and encouragement.

References


INFLUENZA IMMUNIZATION.—Vaccination against influenza still poses an important problem because of frequent strain variation, and the search continues for antigens of sufficient breadth to cover all emergent virus variants. It is felt that this problem can be overcome by selection of vaccine strains which contain adequate quantities of different antigenic components. By including sufficient amounts of all the constituent antigens shared by influenza A virus, for example, it should be possible to include in a vaccine all the antigens of which a mutant A strain might possibly be composed. Presently employed polyvalent influenza vaccines contain the standard 4-strain formula with a total of 500 CCA units per milliliter. Recently Jensen et al. have shown that injection of a 6-strain preparation, with a total of 1,000 CCA units, while producing no greater incidence of undesirable side-effects than lower doses, repeatedly stimulated superior antibody responses than with the standard 500 CCA 4-strain formula. Use of the 6-strain vaccine should provide greater protection against new influenza virus mutants. For establishment of basic immunity the adult immunizing dose consists of two 1-ml. inoculations administered subcutaneously with an interval of 7 days between injections. The intradermal route has also been advocated to reduce side-reactions, but antibody titers obtained through this method have not been comparable to those of the aforementioned routes. Since the duration of protection following immunization is not known but probably does not exceed 12 months, it is recommended that vaccination be repeated annually.—Menzin, A. W.: Treatment in Internal Medicine: Current Immunization Methods and Materials, Arch Intern Med 107:409-429 (March) 1961.