Comparative Incidence of Influenza A-Prime in 1953 in Completely Vaccinated and Unvaccinated Military Groups

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This research differs from other influenza vaccination studies in several respects. Completely vaccinated and unvaccinated groups are compared and several factors encountered which may affect results are evaluated. The effect of differences in housing is an entirely new finding.

Most of the studies on the efficacy of influenza virus vaccines, as carried out by members of the Commission on Influenza, were designed to include a fixed proportion of pseudovaccinated controls in all military units in which vaccine was given. The protective effect of a vaccine was then measured by comparing the incidence of influenza in those receiving vaccine with that in the controls receiving pseudovaccine.

In 1945 an opportunity was afforded for a different type of study. All members of ASTP units were vaccinated against influenza in the fall of that year, while none of the personnel of Navy V-12 units received influenza vaccine. The protection ratios found in these totally vaccinated and totally unvaccinated populations were the highest that have been observed in any of the studies by the commission.[1-3]

However, it is not clear whether the high protection ratios of the 1945 studies were obtained because influenza B, which was prevalent in that year, is more easily controlled by vaccination than influenza A or A-prime, or perhaps, as was previously suggested,[4] a comparison of attack rates in completely vaccinated populations with those in completely unvaccinated groups gives a better demonstration of the full effectiveness of a vaccine.

In order to explore further these aspects of the problems of immunization against influenza another experiment on the efficacy of vaccination of a total population was planned for 1953, a year in which influenza A-prime was expected. This study is reported in detail not only because the results reinforce the concept that the maximum effectiveness of a vaccine is shown by vaccination of a total population, but also because it was possible to demonstrate the influence of other factors, such as differences in housing, in the incidence of concomitant noninfluenzal disease, and in the number of blood samples obtained, which may affect the evaluation of vaccination experiments.

Materials and Methods

Vaccine—The principal vaccine employed was prepared in a commercial laboratory and contained 750 CCA units per ml, made up of equal parts of FMI A-prime, Cuppett A-prime, and Lee B strains of influenza virus. Virus was concentrated and partially purified by

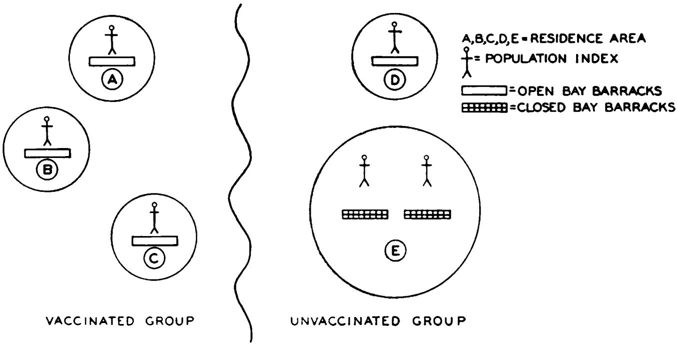

Figure 1—Sampson Air Force Base

centrifugation and inactivated with formalin. A volume of 1 ml was given subcutaneously. A small proportion of the population under study received the same dose of one of two other vaccines of different formulas. All, however, are considered as a single group.

Plan and Conditions of Study—The individuals participating in the study were recruits assigned for basic training to Sampson Air Force Base, Geneva, N. Y. Upon arrival they were formed into flights of 64–72 airmen. Each flight was housed, fed, and trained as a unit for a 12-week period. Flights were allocated on alternate days to one of two training commands. Hence, the strength of each was approximately the same. The trainees in Command I were housed in Areas A, B, and C (Figure 1). Those in Command II were housed in D and E areas. Areas A, B, C, and D contained approximately the same number of recruits in equal numbers of open bay * barracks; Area E contained about twice as many recruits and barracks as any of the others. The barracks in Area E were closed bay in type. When fully occupied each type of barrack contained the same number of men. Trainees were acquired by and lost from each area to approximately the same extent throughout the study period. As indicated by the curved line in Figure 1, the installation of the permanent base complement separated the two commands. Each command used separate buildings for classrooms and was served by separate mess halls and dispensaries. Contact between the recruits in the commands was limited by these circumstances to occasional associations at post theaters, churches, or dayrooms during off duty hours. Recruits assigned to Command I were vaccinated on the third

* Open bay barracks were not partitioned, while closed bay barracks were divided into rooms capable of accommodating six persons.

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day after arrival at Sampson. In order to provide an opportunity to compare the incidence of influenza in totally vaccinated or unvaccinated populations recruits assigned to Command II were not vaccinated.

All airmen reporting to sick call with an oral temperature of 100° F or greater were admitted to the base hospital. Acute phase and convalescent blood samples were obtained from all patients with signs or symptoms suggesting respiratory disease. Throat washings were taken from a limited number of patients. Etiologic diagnoses were attempted only in patients hospitalized for respiratory disease.

Diagnoses: Influenza—A serologic diagnosis was employed to ascertain the incidence of influenza. The hemagglutination-inhibition test, as recommended by the Committee on Standard Procedures in Influenza Testing,[5] was used to measure antibody and antibody rise. The Group A antigens used were PR8 (1934), Rhodes (1947), and Burman (1953), a strain isolated at Sampson during the epidemic. Lee (1940) was selected as a representative Type B strain. Antibody titers are expressed as the reciprocal of the dilutions employed. A fourfold or greater rise in antibody was considered diagnostic of influenza.

Streptococcal Infection—Diagnosis was based on sore throat, pharyngeal exudate, isolation of hemolytic streptococcus by throat culture, or recognition of the clinical syndrome of scarlet fever.

Other Respiratory Disease—Aside from a small number of cases considered to be primary atypical pneumonia or pneumonococcus lobar pneumonia, the majority of the remaining cases of respiratory disease were undifferentiated. For convenience these will be referred to as acute respiratory disease (ARD).

Calculations—The populations observed in this study were continually changing in make-up, with a gradual but progressive increase in size. The population figure used to compute weekly rates was the average number of persons present during that week. The course of the epidemic was charted by weekly rates. In order to summarize the total experience of the epidemic period, average weekly rates for each respiratory disease were calculated by dividing the sum of the weekly mean populations into the number of cases in each diagnostic category hospitalized during the epidemic period.

Owing to circumstances beyond control disproportionate numbers of patients admitted for respiratory disease from the two commands were not bled in convalescence. In consequence, 10.6 per cent of the cases in the vaccinated Command I and 17.8 per cent in the unvaccinated Command II were lost from the study. To correct for this inequality the cases lost from each command were distributed into the major diagnostic categories under consideration. The basis for distribution was the presumption that the same proportion of each disease would obtain in the lost cases as in the known cases.

Results

Serologic Response to Vaccination—Antibody response to vaccination was measured by comparing pre- and postvaccination titers in sera obtained from 168 recruits. Bleedings were done at two-week intervals. The data presented in Table 1 are similar to previous observations. A moderate antibody rise to PR8 was noted even though that strain was not included in the vaccine.[6] This finding emphasizes the antigenic relationship of A and A-prime strains. An excellent response was measured with Rhodes, while postvaccination titers obtained with Cuppett were the lowest observed. The response to Lee was greatest.

Table 1—Serologic Response to Vaccination

Antigen	Geometric Mean H.I. Titer * Pre	Post
PR8 A 1934	204.8	307.2
Rhodes A′ 1947	174.1	752.6
Cuppett A′ 1950	<32	134.4
Lee B 1940	128.0	952.3
	Unvaccinated	Vaccinated
Burman A′ 1953	48.6	248.3

* Hemagglutination inhibition titer

An estimate of the capacity of this vaccine to induce antibodies against a strain of virus isolated during the epidemic at Sampson (Burman 1953) was obtained by comparing antibody levels in vaccinated and unvaccinated recruits hospitalized prior to the epidemic (Table 1). Sera were available from 99 vaccinated and 75 unvaccinated persons. The average titer against Burman was fivefold higher in vaccinated than in unvaccinated patients. As with the Cuppett strain postvaccination antibody levels to Burman strains were lower than to the older strains, PR8 and Rhodes. Relatively low postvaccination levels of antibody to recent isolates have been frequently observed.[7,8] Nevertheless, the degree of protection afforded by influenza vaccines in this and in other recent studies has been consistently high.[8-10]

Isolation of Virus—Four strains were isolated at Sampson during the epidemic period. Antibody rise was observed in the recruits from whom the isolations were made. The isolates were influenza A-prime virus and appeared antigenically similar to strains isolated elsewhere in the same year.[11]

Epidemic Period—The first portion of Figure 2 represents the weekly incidence of all respiratory disease hospitalized for the period November 1, 1952, through January 2, 1953, from the vaccinated and unvaccinated groups. In this interval the attack rates in both populations were approximately the same, which indicates they were at equal risk. Ten per cent of all sera collected during this period was tested in the

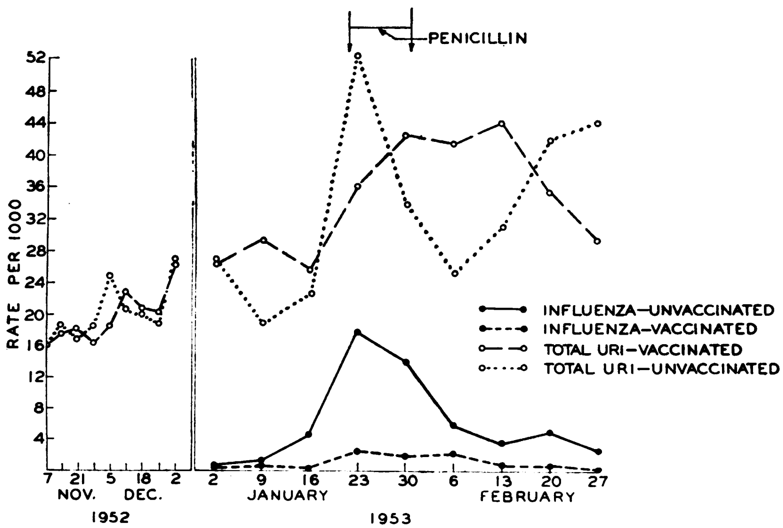

Figure 2—Weekly Incidence of Respiratory Disease

laboratory and no serologic evidence of influenza was found. Early in January the appearance of influenza at Sampson was recognized clinically and this impression was promptly confirmed by isolation of virus and serologic findings. The incidence and distribution of influenza were determined by testing all sera collected from December 27 through February 27 by hemagglutination-inhibition. A sample of the sera was also tested for complement-fixing antibodies using as antigens allantoic fluid or membranes from eggs infected with Spirup A-prime (1948) * strain or Burman strain (1953). The technic used has been previously described.[12] Excellent agreement was found in results of the two methods.

The epidemic appeared to be of brief duration, the course being shown in the second portion of Figure 2. Weekly rates of total respiratory disease in vaccinated and unvaccinated groups during the epidemic period are also presented. The epidemic of influenza as observed in the unvaccinated population was characteristic in that the ascending limb of the curve of incidence rises abruptly and the duration of maximal incidence was brief. The descending limb appears somewhat prolonged due possibly to a constant addition of susceptibles to the population in consequence of the daily arrival of new recruits. It is apparent in Figure 2 that the disparity in incidence of influenza in the vaccinated and unvaccinated groups is not reflected in the relative incidence of total respiratory disease in these populations except for the week ending January 23. For example, during the week ending January 30 total respiratory disease was markedly reduced in the unvaccinated command even though the incidence of influenza remained high. In contrast, the incidence of total respiratory disease in the vaccinated command continued to rise, although the attack rate of influenza was low and stationary.

This paradox is in part explained by the fact that for the purpose of a study on streptococcal disease, conducted independently at Sampson, oral penicillin was given to all members of the unvaccinated command for a 10-day period beginning January 22. The vaccinated command was not given penicillin and served as a control. As reported by the investigators reponsible for the oral penicillin experiment,[13] the incidence of streptococcal infection in the penicillin-treated, unvaccinated command was greatly reduced, while the streptococcus rate in the untreated, vaccinated recruits continued at a high level. The use of penicillin correlates with the sharp drop in total respiratory disease in the unvaccinated command beginning on January 23.

It should also be noted that the continued rise in total cases of respiratory disease in vaccinated recruits is attributable to disease other than influenza. The disparity in distribution of non-influenzal disease during the outbreak of influenza made it impossible to measure the efficacy of vaccination in this investigation by comparing the incidence of total hospital admissions from the vaccinated and unvaccinated commands. Reliance, therefore, had to be placed upon serologic diagnosis. Confidence in the validity of serologic diagnosis as a basis for comparison of attack rates in vaccinated and unvaccinated groups stems from past experiences. In previous vaccination studies it has been shown that the attack rate of noninfluenzal disease was essentially the same in vaccinated and unvaccinated groups, even though serologic methods were used for the diagnosis of influenza.[4, 7-9] If vaccination, by raising antibody levels, masked the serologic response to infection in a significant number of persons, a disproportionate incidence of non-

* Kindly furnished by Dr. E. H. Lennette of Berkeley, Calif.

influenzal disease would have been found in the vaccinated groups.

Protective Effect of Vaccination: The Influence of Disparities in Collection of Blood and in the Incidence of Non-influenzal Illnesses Upon the Protection Ratio—The average weekly incidence of all respiratory disease in vaccinated and unvaccinated recruits for the epidemic period is presented in Figure 3. The amount of respiratory disease in the vaccinated command was slightly greater than in the unvaccinated. The greater incidence of streptococcus infection and of ARD in the vaccinated command is apparent. The former has been explained as due to the fact that penicillin was not given to vaccinated recruits. It also seems likely that some of the patients in the vaccinated command diagnosed as ARD may well have been hospitalized as the result of streptococcal infection, since the incidence of streptococcal disease was high during this period and criteria for that diagnosis included but a single throat culture. Therefore, it would appear that disproportions in the incidence of non-influenzal disease between the two commands can be accounted for satisfactorily and that the risk of respiratory disease was equal during the epidemic period.

The protective effect of vaccination is clearly shown when the incidence of influenza in the vaccinated and unvaccinated recruits is compared. The average weekly rate in the vaccinated command was 1.06 per 1,000 (S.D.=0.14) and in the unvaccinated, 6.35 (S.D.=0.36), yielding a protection ratio of 6.0–1. However, this summary statistic does not accurately reflect the full protective effect of vaccination in the study. It will be noted in Figure 3 that, by chance, convalescent sera were obtained from a lower percentage of persons hospitalized from the unvaccinated command. Therefore, a disproportionate number of cases of identifiable influenza probably was lost to the study from this popula-

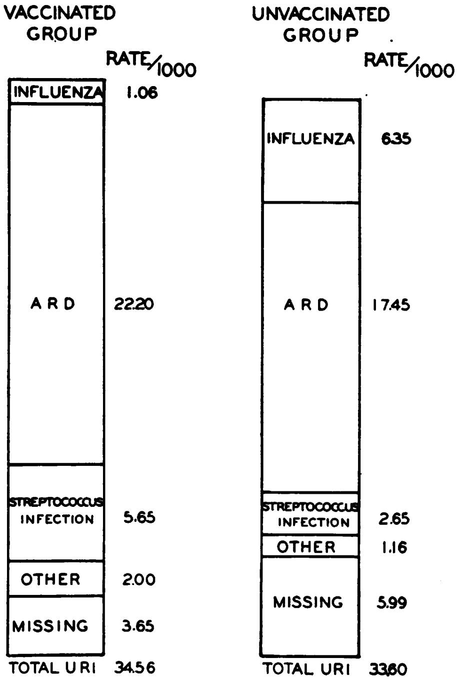

Figure 3—Average Weekly Rate of Respiratory Disease from January 2 to February 27, 1953

tion. When the cases missing from each command were distributed into the major diagnostic categories, influenza, ARD, and streptococcal infection, in the proportions observed, a corrected number of cases was derived for each disease. With these corrections the average weekly rate of influenza in the vaccinated command becomes 1.17 per 1,000 and, in the unvaccinated, 7.73 per 1,000. The protection ratio becomes 6.6–1.

During the influenza epidemic period many patients were hospitalized who suffered more than one infection. In most instances the organisms responsible for these double infections were hemolytic streptococcus and influenza virus. In general, it was impossible to decide on clinical grounds whether patients infected simultaneously with these two agents sought hospitalization because of their reactions to infection with streptococcus, with influenza virus, or were responding to both agents. Since subclinical infection with either pathogen can be expected during coexistent epidemics of both, a disproportionate incidence of either disease in the two study groups would affect the incidence of the other as determined by laboratory findings. Thus, a high incidence of influenza A would increase the laboratory diagnosis of hemolytic streptococcus infection.

Conversely, a high incidence of streptococcal disease would cause hospitalization of a number of recruits subclinically infected with influenza virus and their serologic response would include them as cases of influenza. The purpose of the present investigation being to measure the degree of protection afforded by vaccination against influenza, it seemed pertinent to estimate the influence that the greater number of streptococcal infections in the vaccinated command had upon this study. To accomplish this, all cases of double infection with streptococcus and influenza virus were set aside and the rate of influenza alone in both remaining populations was calculated. At the same time, an adjustment was made for inequalities in the number of cases lost due to failure to obtain convalescent sera. On this basis the rate of influenza in the vaccinated group became 0.81 per 1,000 and in the unvaccinated 6.38. Utilizing these rates, the protection ratio becomes 7.9–1.

Influence of Housing Upon the Protection Ratio—Since the unvaccinated recruits in E area lived in closed bay barracks while in D area they lived in open bay buildings, an opportunity was available to estimate the influence of type of housing upon the transmission of influenza. Pertinent data are summarized in Table 2. It will be recalled that E area contained twice as many recruits and barracks as D area. The per cent of barracks in which infection occurred was the same in both areas, indicating that opportunities for the introduction of influenza into these populations were equal. However, the average weekly incidence of infection was significantly greater in troops housed in open bay barracks in D area (P=0.01). Moreover, the average number of cases in barracks where influenza occurred was lower in the closed bay type. It would appear then that spread of influenza within a barrack was impeded by the closed bay type of construction.

Table 2—Influence of Type of Barracks Upon Spread of Influenza

Type of barracks	Area D Open Bay	Area E Closed Bay
Ratio of population and number of barracks	1	2
Per cent of infected barrack units	77.3	80.5
Average weekly rate of influenza per 1,000 for epidemic period	7.81	5.56
Average number of cases in infected barrack units	8.24	5.36

The vaccinated population lived in open bay barracks, while only one-third of the unvaccinated recruits were similarly housed. Hence, it seems valid to correct for bias introduced by the fact that two-thirds of the unvaccinated airmen appeared to obtain partial protection against the spread of influenza by the physical nature of their barracks. For this purpose the comparison in the rate of influenza between vaccinated and unvaccinated recruits was restricted to those similarly housed. Corrections were simultaneously made as in data previously presented for double infections and lost cases. The corrected rate in unvaccinated recruits housed in open bay barracks was 6.6 per 1,000. The rate in vaccinated trainees was 0.81 per

1,000. The protection ratio using these adjusted rates was 8.1–1. It seems probable that this figure most closely approximates the protective effect of vaccination operative during this study, since it is derived after correcting for recognized inequalities in the conditions of the experiment.

Discussion

In a recent summary of previous vaccination tests carried out by members of the Commission on Influenza,[3] in which control and vaccinated subjects were mixed in the same study groups, the protection ratios found when the attack rates were as stable as those in the present study ranged from 3.6–1 to 5.2–1. In the present investigation a comparison of the incidence of influenza A-prime in a totally vaccinated population with that of a totally unvaccinated population yielded a crude protection ratio of 6.0–1 and a corrected ratio of 8.1–1. Protection ratios of 8.3–1 or greater [1, 2] have been observed in experiences with vaccination of total populations against influenza B.

From these data it is apparent that a greater divergence in attack rates of vaccinated and unvaccinated persons was found when vaccinated individuals were segregated, and that this effect obtained whether the prevailing disease was influenza A-prime or influenza B.

It seems probable that several factors may contribute to the low protection ratios obtained when control and vaccinated subjects are mixed. In these circumstances the attack rate in controls may be lower than the expected incidence in an entirely untreated population, since vaccination of a portion of a unit may offer partial protection to unvaccinated persons in that group.[4] Moreover, the risk of the vaccinated persons is not reduced to a minimum when highly susceptible persons are allowed to mingle with the immunized. Nevertheless, the results of this type of study probably provide the best estimate of the degree of protection to be expected for persons in the population at large who seek vaccination. On the other hand, complete vaccination of a population would capitalize fully upon the advantages of herd immunity. At the same time this procedure would not influence the attack rate in a segregated untreated population. Hence, it seems logical to conclude that a better measure of the full protective capacity of a vaccine can be obtained by comparing the incidence of infection in totally vaccinated and unvaccinated populations. The fact that higher protection ratios have been found in studies where total vaccination was the practice lends support to this view. Finally, the results of studies in completely vaccinated populations provide a basis for a rational estimate of the value of vaccination for institutions, military units, and other groups who are relatively separated from the community at large.

Summary

A high degree of protection against influenza A-prime in 1953 was observed in a field trial with influenza virus vaccine carried out at Sampson Air Force Base. The plan of the study was to compare the incidence of influenza A-prime in a totally vaccinated group with that found in another group which was not given vaccine. The groups were relatively isolated from each other. The degree of protection observed was higher than that found in other vaccine experiments where controls were mixed with vaccinated persons. A similar result was found following vaccination of segregated populations against influenza B in 1945. The theoretical advantages of complete vaccination of a population seem substantiated by these experiences. Studies with totally vaccinated populations appear to give a better measure of

the full protective power of influenza vaccines.

Data were presented which indicate that partitioning of barracks limits the spread of influenza. Other unavoidable inequalities encountered in the experiment were disparities in the incidence of noninfluenzal disease and in the number of blood samples obtained. The crude protection ratio was 6.0–1. After correcting for these circumstances the ratio was 8.1–1.

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Indian Health Service to USPHS

On July 1, the health and hospital health program for Indians was transferred from the Department of the Interior to the Public Health Service, in accordance with federal legislation passed in August, 1954. In order to carry out this responsibility a Division of Indian Health has been created in the Bureau of Medical Services. The division head is James R. Shaw, M.D., a Public Health Service officer who has headed the health program in the Interior's Bureau of Indian Affairs for the past two years. Drs. Joseph Dean and Frank French continue to serve as assistant chiefs. About 3,600 employees, largely in western hospital and area offices, have also been transferred.

In announcing the creation of the new division, Surgeon General Leonard A. Scheele pointed out that half of the deaths among Indians on reservations are due to preventable diseases, that the average age at death is only 36 in contrast to 61 among whites. He outlined a twofold program, to expand the medical care program by providing more clinic and hospital services and to step up public health and preventive services. The Service is also carrying out a study as directed by Congress of the entire Indian health problem and ways of meeting it. The report of findings is due in October, 1956.