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ACUTE RESPIRATORY INFECTIONS IN CIVILIAN ADULTS

II. Clinical and Serologic Observations in a Vaccine Study Group

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In recent years numerous reports have been published concerning the efficacy of killed influenza and adenovirus vaccines in the prevention or modification of illness due to these viral agents. It has been established that such vaccines conferred a significant degree of protection during epidemic outbreaks of acute respiratory infection due to the various types of influenza in civilian and military groups and against adenovirus outbreaks in military recruits.[1-4] It has also been shown that multiple influenza and adenoviruses may be combined in a single vaccine without loss of antigenic efficiency of the individual antigens in the mixture.[5]

A study to determine the clinical efficacy of several polyvalent influenza, adenovirus and parainfluenza vaccines in a heterogeneous adult civilian population group was begun in September, 1959 as part of a continuing respiratory infection investigation program. Four months after the institution of this study, an epidemic outbreak of Asian influenza occured in the Detroit area. This chance happening presented an opportunity to observe the protective rate of the various polyvalent vaccines in prevention of an epidemic illness due to one agent (Influenza A_2) contained in certain of the vaccines under study.

Materials and Methods

Three hundred adult hospital employees volunteeded to participate in the study. Two hundred and forty of the subjects had never received respiratory virus vaccines. They were divided into four equal groups of 60 each by random selection. The remaining 60 subjects received either influenza or adenovirus vaccine or a placebo in the previous two years, but not more recently than 12 months before. These subjects were divided by random selection into two groups of 30 each resulting in a total of six groups. The vaccine administered to each group and the number of subjects completing the study is presented in Table I. The vaccines were coded by the statistician and neither the subjects, clinical observers or laboratory investigators had knowledge of the composition of material given any subject until all clinical and serologic data were completed. Commercially prepared vaccines and a

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Table I

Composition of Vaccines and Division of Subjects into Groups

Test Vaccines	No. of Subjects
Influenza	57
Influenza-Adenovirus	60
Influenza-Adenovirus-Parainfluenza	58
Placebo	59
Adenovirus	28
Parainfluenza	29
Total	291

placebo were employed. The influenza vaccine contained PR-8, A/AA '57, Great Lakes and Asian strains combined in a final concentration of 100, 100, 100 and 200 CCA units respectively per ml. of final vaccine. The pooled adenovirus vaccine contained Types 3, 4 and 7 strains and the Parainfluenza Types 1 and 3 strains. Each vaccine and the placebo also contained 3.5 mg. of $ALPO_4$ per ml. and Merthiolate 1:10,000. Polyvalent influenza, influenza-adenovirus, influenza-adenovirus-parainfluenza or placebo were administered to subjects who had never received prior vaccination. Adenovirus or parainfluenza vaccine was given to the previously vaccinated group.

One ml. of vaccine or placebo was administered to each subject subcutaneously in the left deltoid at the outset of the study (Sept., 1959) and a second injection was given one month later. Blood was obtained for serologic testing at 0, 4 and 8 weeks. In March, 1960 at the termination of the Asian Influenza epidemic, all subjects were again bled and the sera were paired with the previous specimens. Asian influenza hemagglutination inhibition titers[6] of the coded sera were determined in the laboratory of Drs. McLean and Timm. A four-fold increase in titer between the 8th week (Oct., 1959) blood and 24th week (March, 1960) blood specimens was considered to represnt serologic evidence of Asian influenza infection.

All participants were interviewed by a nurse assigned to the study once every two weeks and were also instructed to report to the clinic at the time of onset of any acute respiratory or febrile illness. A special study history form was completed by the nurse at each visit. If the temperature was 100° F or more, the subject was examined by one of us (F. C. or E. Q.) and a throat culture for *Beta hemolytic streptococci* obtained. Based on the history examination and results of the throat culture, a clinical impression was formulated. Subjects who were afebrile with localized acute respiratory symptoms were classified as having a Common Cold. In subjects with a temperature of 100° or above with systemic as well as acute respiratory symptoms, Acute Respiratory Disease was diagnosed. Streptococcal sore throat was not encountered during the study period under analysis. The clinical diagnosis served as a rough estimate of the severity of the acute respiratory illness.

The clinical data were correlated later with the presence or absence of a four-fold rise in Asian influenza titer by employment of computer analysis of the data.* The correlation of clinical illness and antibody titer changes to other antigens in test vaccines will be the subject of a later report.

Results

The 1960 epidemic outbreak of Asian influenza previously mentioned is depicted in Figure 1. The top two graphs illustrate the number of cases of "pneumonia" and "influenza" reported to the Detroit Department of Health**, before, during and after this epidemic. The lower graph shows the biweekly rate of all respiratory illness that occurred in the entire study group between Nov., 1959 and Dec., 1960. A sharp rise in incidence of respiratory illness occurred early in 1960, suggesting that our

*Accomplished by R. R. Gauch, Parke, Davis & Co., Ann Arbor, Michigan.

**Data on the incidence of influenza and pneumonia, and permission to use the data kindly supplied by Drs. Joseph G, Molner and Charles P. Anderson, Detroit Department of Health.

volunteer group had probably experienced the same epidemic outbreak that was observed in the general population.

The incidence of occurrence of a four-fold rise in Asian influenza antibody titer in the hospital study group is presented in Table II. This and subsequent tables give the rate per 100 subjects. or percentage. Those subjects who received placebo or vaccine which did not contain Asian influenza antigen are tabulated in the non-protected group, while those who received a vaccine containing Asian influenza antigen are listed in the protected group. This table also depicts the incidence of serologic evidence of infection in the absence of a respiratory illness and the association of both serologic and clinical evidence of an acute respiratory illness.

Table II

Incidence of Four-Fold Rise in Asian Influenza Antibody Titer between October, 1959 and March, 1960

	Not Associated with Respiratory Illness	Associated with Respiratory Illness
Non-Protected Groups		
Placebo	5%	15%
Adenovirus	7% Aver. 5%	28.5% Aver. 19.2%
Parainfluenza	3%	14%
Protected Groups		
Influenza	7%	7%
Influenza-Adenovirus	0% Aver. 4%	5% Aver. 4%
Influenza-Adenovirus-Parainfluenza	5%	0%
Protection Rate		79.7% (P = .05)

These data indicate that serologic response without clinical evidence of infection occurred with approximately equal frequency in both the non-protected and protected groups. In contrast when both serologic and clinical evidence of acute respiratory infection was observed, the incidence was 19.2 per cent in the unprotected group and 4 per cent in the protected group, representing a protection rate of 79 per cent. This difference is statistically significant. (P value = .05) Among the protected groups it is of interest to note that clinical infection did not occur in the group that received the combined influenza-adenovirus-parainfluenza vaccine while the rate for the other two groups was 7 and 5 per cent. This difference is on the borderline of statistical significance and cannot be explained on the basis of difference in pre-epidemic antibody titer since these titers were essentially similar in the three groups. It is attractive to speculate that the addition of parainfluenza antigen to the vaccine was responsible for the enhanced protection, but the number of subjects is too small to permit this conclusion.

Since acute respiratory illness associated with a four-fold rise in Asian influenza antibody titer occurred in both the non-protected and protected groups (although at a lower rate in the latter) it was of interest to determine if vaccination exerted any

Table III

Severity of Respiratory Illness Associated with a Four-Fold Rise in Asian Influenza Antibody Titer as Determined by the Clinical Diagnoses and Duration of Illness

	Non-Protected Group	Protected Group
1. Clinical Diagnosis:		
Common Cold	33%	36%
ARD-Influenza	60%	64%
Pneumonia	4%	0%
2. Duration of Illness:		
1-3 days	28%	22%
4-7 days	40%	44%
8-17 days	20%	33%
+ 14 days	10%	0%

influence on the severity of the illness when it did occur (Table III). The clinical diagnosis and duration of common cold, acute respiratory disease and influenza was made with approximately equal frequency in both groups. There was one instance of pneumonia in a non-protected subject. Similarly, the duration of illness was essentially the same for the two groups. These data indicate that if a symptomatic respiratory illness associated with a diagnostic rise in antibody titer occurred, vaccination did not modify the severity of the illness.

Table IV

Incidence of Respiratory Illnesses in Absence of Four-Fold Rise in Influenza Antibody Titer between January 1, 1960 and March 15, 1960

Non-Protected Groups		
Placebo	45%	
Adenovirus	28.5%	Aver. 35.8%
Parainfluenza	34%	
Protected Groups		
Influenza	26%	
Influenza-Adenovirus	45%	Aver. 37%
Influenza-Adenovirus-Parainfluenza	40%	

Table IV illustrates the incidence of acute respiratory illness not associated with a rise in antibody titer to Asian influenza (and therefore presumably respiratory illness other than Asian influenza). It is apparent that infection rates were approximately equal for both the non-protected and protected groups.

Summary

In the course of a study concerning the protective value of inactivated polyvalent respiratory vaccines an Asian Influenza epidemic occurred. Of six vaccines employed in this study, three contained Asian influenza antigen. The incidence of

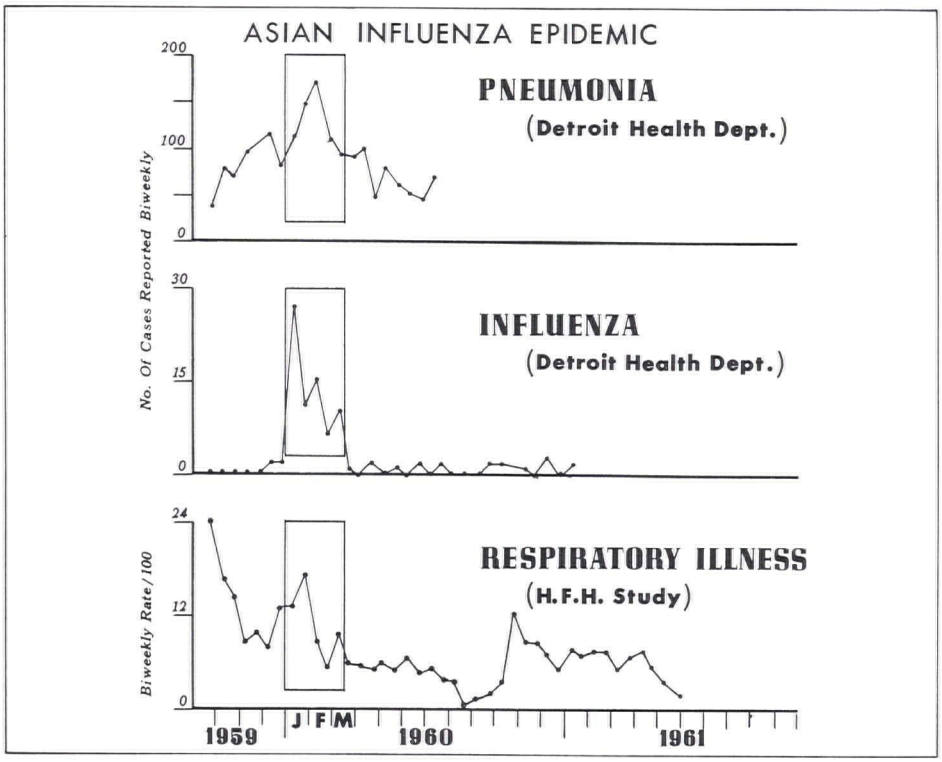

Figure 1

The occurrence of Pneumonia, Influenza and Respiratory Illnesses in Detroit and in the study group.

serologically proven influenza associated with clinical respiratory illness was 19.2 per cent in the subjects who did not receive vaccine containing the Asian influenza antigen and 4 per cent in the group who did, a protection rate of 79 per cent. These figures are comparable to those obtained by other investigators.[1-4] The severity and course of respiratory illness occurring in subjects with four-fold rise in Asian influenza antibody titer were the same in the protected and non-protected groups in this study. Finally, the protection afforded by the vaccine was specific.

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REFERENCES

1. Salk, J. E., Menke, W. J., Jr., and Francis, J., Jr.: A clinical, epidemiological, and immunological evaluation of vaccination against epidemic influenza, Am. J. Hyg. 42:57, 1945.

2. Stallones, R. A., Hilleman, M. R., Gauld, R. L., Warfield, M. S., and Anderson, S. A.: Adenovirus (RI-APC-ARD) vaccine for prevention of acute respiratory illness — Field evaluation, J.A.M.A. 163:9, 1957.

3. Bell, J. A., Hantover, M. J., Huener, R. J., and Loosli, C. G.: Efficacy of trivalent adenovirus (APC) vaccine in Naval recruits. Progress report, J.A.M.A. 161:1521, 1956.

4. Dull, H. B., Jensen, Keith E., Rakich, J. H., Cohen, A., Henderson, D. A., and Pirkle, C. I.: Monovalent Asian influenza vaccine, J.A.M.A. 172:1223, 1960.

5. Cox, F., Jr., Timm, E. A., Quinn, E. L., Colville, J. M., and McLean, I. W.: Acute respiratory infections in civilian adults, Henry Ford Hosp. Med. Bull. 10:27, 1962.

6. Jensen, K. E.: Influenza in American Public Health Association: Diagnostic proceeding for virus and rickettsial disease, ed. 2, New York, The Association, 1956, p. 241.