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An Evaluation of Influenza Immunization

Influence of Route of Administration and Vaccine Strain *

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A field study was undertaken in Tampa, Fla., to assess the efficacy of subcutaneous and aerosol methods of administering vaccine, and to compare the protection afforded by bivalent (A2 and B) influenza virus vaccine and by A2/Hong Kong/68 virus vaccine. Further objectives of the study included a comparison of the effectiveness of single-dose and 2-dose immunization. Approximately 2100 volunteers received, in a double-blind manner, both an injection and an aerosol administration on 2 occasions 3 weeks apart. The results showed that aerosol administration gave a lower over-all protection rate, although the booster dose seemed to have a marked effect. The protection afforded by A2/Hong Kong/68 virus vaccine was considerably greater than that afforded by the bivalent vaccine, particularly when administration was subcutaneous. Results are also given on the occurrence of side-effects and on the correlation between cigarette smoking and the occurrence of influenza-like illness.

Recent studies have demonstrated the presence of a secretory immunological system that may act as a " first line of defence " in protecting mucous surfaces against invasion by pathogens, and that may be the only defence against pathogens that infect only the mucous surfaces (Tomasi & Bienenstock, 1968; Small & Waldman, 1969). Thus, it has been shown in man that nasal secretion antibody is more closely related to protection against infection with parainfluenza virus (Smith et al., 1966) and rhinovirus (Cate et al., 1966) than is serum antibody. Inactivated influenza virus inoculated into the respiratory tract of mice stimulates higher levels of bronchial antibody than does parenteral immunization, and this is correlated with resistance to challenge (Fazekas de St. Groth & Donnelley, 1950). In man, aerosol immunization with inactivated influenza vaccine has been shown to stimulate higher levels of respiratory secretion antibody than does subcutaneous immunization (Waldman et al., 1968; Fulk et al., 1969). In an influenza vaccine field trial carried out in the winter of 1967–68, the influenza illness rate was significantly lower among persons immunized by aerosol than among persons immunized subcutaneously or among unimmunized controls (Waldman, Mann & Small, 1969).

OBJECTIVES

Because of these findings, the field trial reported here had as its first purpose a comparison of the protective efficacy of aerosol and subcutaneous methods of immunization. A second objective was to compare the protective efficacy of the " old " bivalent (A2 and B) influenza virus vaccine [1] and the A2/Hong Kong/68 influenza virus vaccine. This comparison was undertaken partly as a result of the finding that aerosol immunization with the classical A2 virus vaccine led to significantly more heterologous neutralizing antibody against A2/Hong Kong/68 influenza virus in respiratory secretions (IgA) than in serum (IgG) (Waldman, Wigley & Small, 1969).

Further objectives of the study were to obtain the following information: (1) the comparative protection afforded by booster immunization and by a single immunization, (2) the inapparent infection

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[1] Containing 150 CCA units of A2/Japan/170/62, 150 CCA units of A2/Taiwan/1/64, and 300 CCA units of B/Massachusetts/3/66 per ml.

rate during the Hong Kong influenza epidemic of 1968–69, (3) the effect of cigarette smoking on the incidence and duration of respiratory illness, and (4) the comparative side-effects of aerosol and subcutaneous and of air-gun and needle immunization procedures, and of A2/Hong Kong/68 vaccine, bivalent vaccine, and placebos.

MATERIALS AND METHODS

The volunteers for the field study were approximately 2100 school teachers from the Hillsborough County (Tampa), Fla., school system. The volunteers were randomly divided into 9 groups, as shown in Table 1. Factors such as age, sex, race, smoking habits, and influenza serological status showed that the randomization process distributed the volunteers in such a way that susceptibility to influenza was equal for each of the 9 groups. Vaccine and placebo were administered in a double-blind manner on 2 occasions 3 weeks apart. The commercial bivalent and monovalent A2/Hong Kong/68 vaccines were used.[1] Approximately one-half of the volunteers gave serial blood and nasal wash samples, the latter obtained by a method described by Rossen et al. (1965). Prior to immunization, a brief history was obtained from each volunteer, who then kept a daily record of symptoms for the next 11 weeks. The study was completed by 99% of the volunteers. Shortly after the initial immunization, the peak of an A2/Hong Kong/68 influenza epidemic occurred. The etiology was determined by virus isolations and antibody rises (Chanock et al., 1958) and the epidemic curve was traced by increased absenteeism in the local industries, military installations, and schools as well as by official morbidity and mortality registration. Confirmed cases of influenza occurred as late as the first week of February 1969.

TABLE 1

DISTRIBUTION OF VOLUNTEERS, INFLUENZA IMMUNIZATION STUDY, TAMPA, 1968–69

Study group	Volunteers per group	First administration (12–13 December 1968)		Second administration (3 January 1969)	
		Injection [a]	Aerosol [a]	Injection [a]	Aerosol [a]
1	235	H	S	H	S
2	230	H	S	S	S
3	231	B	S	B	S
4	240	B	S	S	S
5	240	S	H	S	H
6	239	S	H	S	S
7	237	S	B	S	B
8	234	S	B	S	S
9	237	S	S	S	S

[a] S = saline; B = bivalent vaccine; H = A2/Hong Kong/68 monovalent vaccine.

[1] The vaccines were kindly provided by Lederle Laboratories, Pearl River, N.Y.

RESULTS

Over 2.5 million data provided by the teachers regarding vaccine side-effects and illness, and 2000 laboratory data were collected and put in a form suitable for analysis by computer.

Initially, influenza illness was defined in 8 different ways and acute respiratory illness rates were determined. The over-all illness rate for the 2100 volunteers varied from 35.2% to 20.2%, depending on the definition of influenza-like illness. The highest rate was found when the following criteria were used: (1) a temperature higher than 100°F (37.8°C), a feverish feeling, or chills; (2) one of the following symptoms: cough, sore throat, or coryza; and (3) one of the following: headache, malaise, chest pain, or muscle or joint pain. The lowest rate was found when the criteria used were a temperature higher than 100°F (37.8°C) plus 2 of the following symptoms: cough, coryza, sore throat, or muscle or joint pains. Varying the definition of illness changed the attack rates but changed them to the same extent in all the vaccine groups—i.e., varying the definition of illness had a slight quantitative effect but not a qualitative effect on the data. Nevertheless, one definition of illness had to be selected in order to make the data manageable, and since there was so little qualitative difference between rates based on the preliminary serological data shown in Table 2 and those based on over-all attack rates, it was decided to use the definition arrived at before the study began—i.e., fever noted objectively (a temperature greater than 100°F [37.8°C]) or subjectively (a feverish feeling) plus any 2 of the following symptoms: sore throat, muscle or joint pain, cough, and stuffy or runny nose.

A2/Hong Kong/68 virus neutralization tests on serially collected sera from 36% of the volunteers in the placebo group indicate that during the period of

TABLE 2

CORRELATION OF SEROLOGICAL AND CLINICAL OBSERVATIONS, INFLUENZA IMMUNIZATION STUDY, TAMPA, 1968–69

Illnesses and rates	Titres of serum neutralizing antibody to A2/Hong Kong/68			
	All persons other than those receiving A2/Hong Kong/68 vaccine by injection (200 persons)		Control group (saline) (85 persons)	
	⩽1:8	>1:8	⩽1:8	>1:8
No. of persons ill [a]	20	31	8	13
No. of persons well	112	37	54	10
Rates Calculated from the Above Data				
Inapparent illness rate	37/200 = 18.5%		10/85 = 11.8%	
Infection rate	(31 + 37)/200 = 34.0%		(13 + 10)/85 = 27.1%	
Illness rate	(20 + 31)/200 = 25.5%		(8 + 13)/85 = 24.7%	
Non-influenza illness rate	20/200 = 10.0%		8/85 = 9.4%	

[a] Illness defined as (1) having a fever of at least 37.8°C or feeling feverish, and (2) having 2 or more of the following symptoms: sore throat, cough, stuffy or runny nose, and muscle/joint pains.

study there was an A2/Hong Kong/68 inapparent infection rate of 12%, a non-influenza acute respiratory illness rate of 9.4%, and a clinical influenza illness rate of 15%.

The illness rates and the protection afforded by the different vaccines are shown in Table 3. Eliminating illness in the first week of the study as occurring too early for any vaccine to have taken effect, the over-all attack rates for weeks 2–11 of the study are shown in column 3. When these figures are compared with those for the control (saline) group, the over-all uncorrected protection rates (column 4) are obtained. However, as mentioned above, the serological data suggest a background (non-influenza) acute respiratory illness rate of 9.4%. The acute respiratory illness rate for the whole group during the last 4 weeks of the study, a period when there would be expected to be little influenza, was 1.3% per week. This indicates that the 9.4% figure obtained from the placebo group—i.e., 0.94% per week for the 10-week period—is probably not unreasonable. When allowance is made for this factor, the corrected protection rates shown in column 5 of Table 3 are obtained. From these rates and from the corrected weekly protection rates shown in columns 7, 9, and 11, the following conclusions can be drawn.

(*a*) The injected A2/Hong Kong/68 vaccine gave excellent protection, greater than that reported in most influenza vaccine field trials. Even when the background illness is not subtracted, during the peak period of the epidemic (weeks 2–3) the protection rate was 74%. When the correction for background illness is made, the group that received 2 injections of this vaccine showed a protection rate of 97%.

(*b*) The aerosol A2/Hong Kong/68 vaccine gave a lower over-all protection rate, but the booster immunization seemed to have a marked effect. This could have 2 possible explanations, as discussed below. The booster effect is even more impressive when illnesses during weeks 2–3 are eliminated from the results for the group that received the booster (this group became a separate group only at the time they received the booster). During weeks 4–7 the protection rate for the group that received 2 aerosol immunizations of A2/Hong Kong/68 vaccine was 95%.

(*c*) Some protection was provided by the bivalent vaccine given by injection: the rate was 40% in the group that received 1 injection and 52% in the group that received 2 injections.

(*d*) A single dose of aerosol bivalent vaccine gave very poor protection (19%), whereas 2 doses gave fairly good protection (53%, a figure that would generally be considered good in influenza field trials). These data lend support to the finding, mentioned above, that respiratory secretion antibody may be

TABLE 3

ATTACK RATES AND PROTECTION RATES, INFLUENZA IMMUNIZATION STUDY, TAMPA, 1968–69

Inoculation	No. of people	Attack rate [a] (%) for entire period	Protection rate [b] (%) for entire period		Average weekly attack rates (%) and corrected protection rates [b] (%)					
					Weeks 2–3		Weeks 4–7		Weeks 8–11	
			Uncorrected	Corrected	Attack rate	Prot. rate	Attack rate	Prot. rate	Attack rate	Prot. rate
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Saline	237	27.9	0	0	5.9	0	2.1	0	1.9	0
A2/Hong Kong vaccine, injection										
1 dose	230	12.6	55	83	2.0	79	1.1	86	1.1	83
2 doses	235	9.8	65	97	1.1	97	0.7	100	1.2	73
Bivalent vaccine, injection										
1 dose	240	20.4	27	40	3.5	48	2.2	0	1.1	83
2 doses	231	18.2	35	52	3.0	58	2.1	0	1.0	94
A2/Hong Kong vaccine, aerosol										
1 dose	239	22.6	19	29	2.5	64	2.8	0	1.6	28
2 doses	240	15.8	43	65	3.3	52	1.0	95	1.3	63
Bivalent vaccine, aerosol										
1 dose	234	24.4	13	19	3.4	50	2.8	0	1.8	10
2 doses	237	18.1	35	53	3.4	50	1.8	26	1.1	83
Average	236	18.9			3.1		1.8		1.3	

[a] The criteria used to determine the presence of illness were those noted in footnote *a*, Table 2.

[b] The protection rate is obtained by subtracting the attack rate in the vaccinated group from the attack rate in the control (saline) group, and then dividing by the attack rate in the control group. This gives an uncorrected protection rate. Corrected protection rates are obtained by first subtracting, from the attack rates for both groups, the estimated attack rate for non-influenza acute respiratory disease. This correction factor is 0.94% per week, or 9.4% for the entire 10-week period.

Example: During weeks 2 and 3 the uncorrected average weekly attack rate in those receiving 1 injection of A2/Hong Kong 68 vaccine was 2.0%. Subtracting 0.94% gives a corrected attack rate of 1.06%. Similarly, subtracting 0.94% from 5.9% (the uncorrected attack rate for the control group) gives 4.96% as the corrected control-group attack rate. The corrected protection rate is then given by:

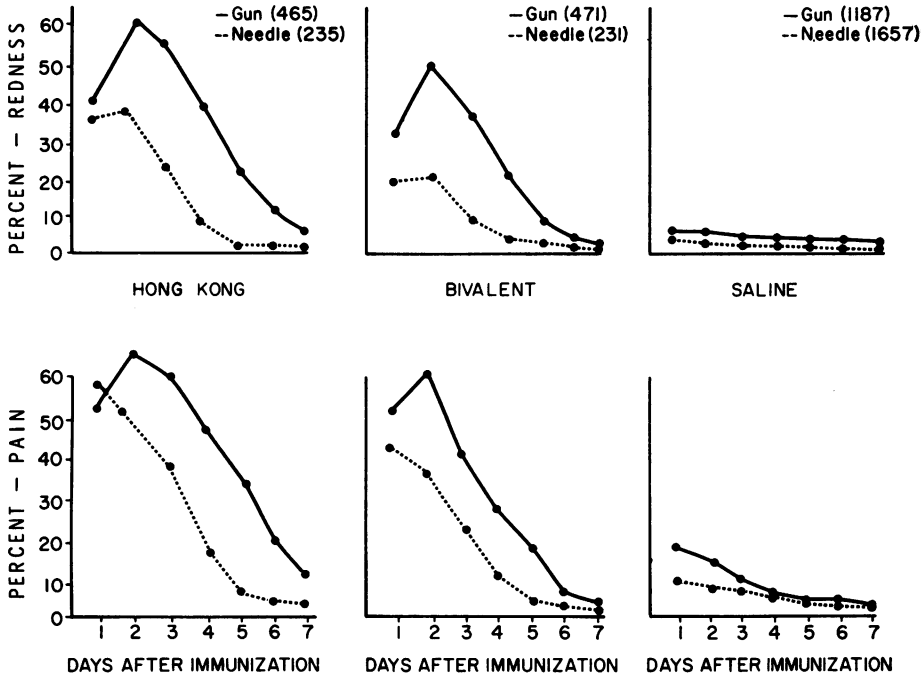
$$\frac{4.96 - 1.06}{4.96} \times 100 = 79\%.$$

less specific than serum antibody. Dissimilar influenza antigens, detectable by humoral antibody systems, may provide some protection through secretory antibody cross-reaction.

There are at least 2 possible explanations of the facts that 1 aerosol dose of A2/Hong Kong/68 or bivalent vaccine afforded poor protection and that 2 doses afforded relatively good protection: (1) 2 doses might have been required to stimulate the antibody response, possibly because this was a relatively " new " antigen, whereas previous aerosol influenza vaccine studies have been carried out with " old " antigens (i.e., classical A2 or B viruses); and (2) the first aerosol immunization, which was administered by nurses who had never used the procedure before, might have been carried out in a technically inadequate manner, and the technique might have been corrected when the second immunization was given.

The following conclusions can be drawn from the data on the side-effects of the immunization procedures: (1) Use of the air-gun injector led to a

LOCAL SIDE-EFFECTS CAUSED BY INJECTOR-GUN AND BY NEEDLE, INFLUENZA IMMUNIZATION STUDY, TAMPA, 1968–69



higher incidence of local side-effects than injection with an ordinary syringe and needle (see the accompanying figure). (2) Injected vaccines led to a higher incidence of systemic side-effects, such as fever and headache, than did aerosol vaccines (those who received the latter did not show a higher reaction rate than the placebo group). (3) There was no difference in local respiratory tract side-effects in any of the groups—i.e., the aerosol administration of influenza vaccines led to no greater an incidence of nasal stuffiness, sore throat, or cough than did the aerosol administration of normal saline.

The data on the effect of cigarette smoking on the incidence of influenza-like illness are shown in Table 4. The incidence of acute respiratory illness was 23% among non-smokers, 19% among those who smoked less than one-half pack of cigarettes per day, 30.5% among those who smoked one-half to 1 pack per day, and 27.5% among those who smoked 1–2 packs per day. Those who smoked more than 2 packs per day were too few in number for valid conclusions to be drawn. These results indicate that smoking more than one-half pack of cigarettes per day increases the risk of influenza-like illness. The duration of illness, as defined by the duration of fever, did not vary with the amount of smoking.

TABLE 4

EFFECT OF CIGARETTE SMOKING ON ILLNESS,[a] TAMPA, 1968–69

Extent of smoking	No. of people	No. of persons ill	Mean duration of illness (days)	Attack rate (%)
Non-smokers	1 534	349	2.74	22.8
0 to ½ pack/day	206	40	2.65	19.4
½ to 1 pack/day	262	80	2.98	30.5
1 to 2 packs/day	69	19	2.74	27.5
>2 packs/day	5	0	—	0
No information	47	11	4.18	23.4
Total	2 123	499		23.5

[a] As defined in footnote *a*, Table 2.

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