Bull. Org. mond. Santé } 1969, **41**, 531-535
Bull. Wld Hlth Org. }

Studies with Inactivated Influenza Vaccines Purified by Zonal Centrifugation*

2. Efficacy

S. C. SCHOENBAUM,[1] S. R. MOSTOW,[2] W. R. DOWDLE, M. T. COLEMAN & H. S. KAYE

High (3000 CCA units) and standard low (300 CCA units) doses of the monovalent purified vaccines described in an earlier paper were evaluated in a double-blind manner in 2 adult populations for protective effectiveness against illness caused by the Hong Kong influenza virus. Epidemics in both populations occurred 4–6 weeks after single injections of vaccine were given.

The attack rates among recipients of low or high doses of A2/Japan vaccines in a prison were virtually identical to those among the control groups receiving B/Massachusetts vaccines. The attack rate among those receiving 3000 CCA units of Aichi vaccine was nearly 70 % less than the rate among recipients of A2/Japan or B/Mass. vaccines. Similarly, in a retirement community the attack rate among the recipients of 3000 CCA units of Aichi vaccine was 50 %–70 % lower than the attack rate among the recipients of the A2/Japan vaccine. In both populations, recipients of high doses of Aichi vaccine who later became ill tended to have less morbidity, fewer and lower fevers, and shorter stays in bed. Attack rates among the groups receiving low doses of Aichi vaccine were somewhat lower than rates among those receiving A2/Japan or B/Mass. vaccines, but the effect was not statistically significant. Divalent and polyvalent commercial vaccines were also without protective effect.

The results indicate that optimally constituted influenza vaccines at standard dosage levels have little, if any, effectiveness and that even very large doses of vaccine do not approach the high degrees of effectiveness that have been achieved with other virus vaccines.

The prevention of serious morbidity and excess mortality, which frequently accompany influenza epidemics, should be the objective of influenza vaccine use in civilian populations. However, there has never been a direct demonstration that the use of influenza vaccines can prevent excess mortality. Indirect evidence that influenza vaccine can achieve this objective would be the demonstration that the vaccine is regularly effective in preventing clinical illnesses, particularly in those populations that are at highest risk of complications and death from influenza.

The safety and potency of influenza vaccine can be evaluated with a reasonable assurance of success. However, the evaluation of protective effectiveness requires both an epidemic of influenza and a surveillance system for detecting illnesses. During the 1968–69 season, influenza epidemics occurred in 2 of the 3 previously described vaccinated populations. A sharp influenza outbreak of 3 weeks' duration, with an over-all clinical attack rate of approximately 40%, occurred in late December 1968 among the inmates of Georgia State Prison. The other outbreak, beginning in late December and lasting 5–6 weeks with an over-all clinical attack rate of approximately 10%, occurred among the residents of the retirement community. Although in the school populations some cases of Hong Kong influenza occurred in December 1968 and some cases of influenza B occurred in March 1969, no detectable epidemics occurred.

* From the Respiratory Diseases Unit, Epidemiology Program, and Respiratory Virology Unit, Laboratory Division, National Communicable Disease Center, Atlanta, Ga., USA.

[1] Present address: Peter Bent Brigham Hospital, Boston, Mass., USA.

[2] Present address: Cleveland Metropolitan General Hospital, Cleveland, Ohio, USA.

METHODS

The populations, vaccines, and vaccination procedures are described in Part 1.[1]

At the Georgia State Prison the Chief Medical Officer maintained surveillance. Beginning on 27 December 1968, more than twice the usual number of persons went to sick call because of respiratory illnesses. On 30 December throat swabs and blood specimens were obtained from 42 inmates with acute febrile respiratory illness. The epidemic of influenza lasted until 14 January 1969. On 23 January all vaccinees were interviewed and a prepared questionnaire was used to determine a history of influenza-like illness. At this time a serum sample was obtained from each vaccinee. Finally, medical records of all vaccinees were reviewed to determine who went to sick call for influenza-like illness.

The retirement community is served by a central medical clinic with a staff of 20 physicians plus nurses, physiotherapists, and welfare workers. A medical epidemiologist maintained close surveillance of clinic patients between 12 December 1968 and 14 February 1969. Each day this physician reviewed the records of all patients who visited the clinic for any medical reason. Patients seen early during an acute respiratory illness were identified and throat swabs and/or serum specimens were obtained from them.

On 10 February 1969, a questionnaire was sent to all vaccinees and to a randomly selected group of approximately 900 residents in the retirement community who had not been included in the immunization programme. Each person was asked if he had had an influenza-like illness. If such an illness had occurred, he was asked to provide information on the presence or absence of fever of 99.6°F (37.6°C) or higher, chills, eye pain, muscle aches, headache, or malaise. He was also asked if he had gone to bed because of this illness and if he had seen a physician.

RESULTS

A Hong Kong variant of the influenza A virus was isolated from throat swabs of 30 of the 42 prisoners from whom specimens were obtained. All 42 had diagnostic serological responses to a Hong Kong antigen. Furthermore, 74% of those who went to sick call for respiratory illness and 74% of those who said they had an influenza-like illness on direct interview showed diagnostic rises in antibody to the Hong Kong influenza virus.

A comparison of the attack rates in the different vaccine groups demonstrated several important points (Table 1). (1) Attack rates among prisoners receiving 300 CCA units of the B/Massachusetts vaccine were similar to those among recipients of the same dose of the A2/Japan/170 vaccine. (2) Attack rates among inmates receiving 3000 CCA units of the B/Mass. vaccine were similar to those among recipients of the same dose of the A2/Japan/170 vaccine. (3) Based upon the criteria of a history of febrile illness, going to bed, and attendance at sick call, attack rates among the recipients of 3000 CCA units of either the B/Mass. or A2/Japan/170 vaccines were lower than those among the recipients of 300 CCA units of these vaccines. In no instance was there a statistically significant difference between the attack rates in groups receiving high and low doses of these 2 vaccines. (4) The inmates who received 300 CCA units of the Aichi vaccine showed slightly lower attack rates than any of the recipients of B/Mass. or Japan/170 vaccines, although the difference was not statistically significant ($P>0.05$). (5) Data from both the interview (and questionnaire) and the prison records (sick call surveillance) showed low attack rates among the recipients of 3000 CCA units of Aichi vaccine. Using the combined attack rates among recipients of the B/Mass. vaccines as the base-line, there was a 70% reduction in attack rate among the high dose Aichi vaccine recipients (Table 1). (6) The attack rates calculated from the direct interview data were substantially higher among recipients of the polyvalent vaccine than among recipients of any other vaccine.

Unlike the prison outbreak, the epidemic in the retirement community occurred in an open population and should more accurately reflect the effect of the vaccine in general civilian use. Using as a base-line the attack rates among recipients of 300 CCA units of A2/Japan vaccine, the following observations were made (Table 2). (1) There was very little difference between the attack rates among recipients of low and high doses of the A2/Japan/170 vaccine, although recipients of the high dose showed slightly lower rates. (2) Those who received the commercial polyvalent vaccine again showed the highest rates, although these rates were proportionately lower than those observed at the Georgia State Prison. (3) Those who received the Aichi vaccine experienced

[1] See the paper by Mostow et al. on page 525 of this issue.

TABLE 1

ATTACK RATES COMPUTED FROM QUESTIONNAIRES AND SICK-CALL SURVEILLANCE, GEORGIA STATE PRISON, 1968–69

Symptom	Attack rates (%) among recipients of the following vaccines						
	A2/Aichi/2/68		A2/Japan/170/62		B/Massachusetts/3/66		Polyvalent [a]
	300 CCA units	3000 CCA units	300 CCA units	3000 CCA units	300 CCA units	3000 CCA units	
Questionnaire:							
Illness	32	15	41	41	39	40	68
Fever	26	10	41	38	39	29	59
Confinement to bed	12	3	31	16	32	17	51
Prison records:							
Attendance at sick call	17	10	42	19	43	24	33
Serology (S2-S3):							
4-fold rise to A2/Georgia/25/69 [b]	15	10	62	43	70	47	61
4-fold rise to both A2/Georgia/25/69 and A2/Aichi/2/68	9	5	44	30	59	44	50
No. of persons in group	35	39	41	37	30	38	39

[a] Containing A2/Japan/170/62, A2/Taiwan/1/64, A/PR/8/34, A1/Ann Arbor/1/57, and B/Mass./3/66.
[b] Virus isolated during prison epidemic.

TABLE 2

ATTACK RATES COMPUTED FROM QUESTIONNAIRES AND MEDICAL CLINIC SURVEILLANCE, CALIFORNIA RETIREMENT COMMUNITY, 1968–69

Symptom	Attack rates among recipients of the following vaccines						Attack rates among unvaccinated persons
	A2/Aichi/2/68		A2/Japan/170/62		Commercial		
	300 CCA units	3000 CCA units	300 CCA units	3000 CCA units	Divalent [a]	Polyvalent [b]	
Questionnaire:							
Influenza-like illness	10	6	13	12	12	14	10
Febrile illness	6	4	9	8	8	11	8
Confinement to bed	7	5	12	10	9	12	8
Surveillance:							
Attendance at medical clinic for respiratory illness	5.9	3.3	6.6	5.7	7.0	8.3	5.0
Fever at time of clinic visit	1.2	0.7	2.2	1.8	2.2	3.5	1.7
No. of persons in group	576	596	577	611	600	566	848

[a] Containing A2/Japan/170/62, A2/Taiwan/1/64, and B/Mass./3/66.
[b] Containing A2/Japan/170/62, A2/Taiwan/1/64, A/PR/8/34, A1/Ann Arbor/1/57, and B/Mass./3/66.

the lowest attack rates, although the reduction among recipients of 300 CCA units was not statistically significant. (4) Attack rates were significantly (50%–70%) lower among recipients of 3000 CCA units of Aichi vaccine than among recipients of 300 CCA units of A2/Japan/170 vaccine. (5) Persons who had not been vaccinated, although not a strict control group, showed attack rates in the same range as most of the vaccine groups. Only the recipients of 3000 CCA units of Aichi vaccine showed substantially lower attack rates than the unvaccinated groups.

DISCUSSION

As shown in Part 1 of this paper,[1] neither the B/Mass. nor the A2/Japan vaccines stimulated serum antibody against the Aichi antigen in the 3-week period after vaccination. The essentially identical attack rates observed among recipients of the A2/Japan and B/Mass. vaccines at the Georgia State Prison lend validity to the use of recipients of 300 CCA units of A2/Japan vaccine at the retirement community as a basis for comparison of effectiveness. When recipients of the B/Mass. vaccines and of 300 CCA units of A2/Japan/170 vaccine are used as the base-line for determining protection, a remarkable similarity is seen in the results obtained in these 2 vastly different populations separated by 2000 miles (3220 km).

A large proportion of those who reported illnesses at the interview at the Georgia State Prison had laboratory evidence of infection: of the recipients of A2/Japan and B/Mass. vaccines who reported an influenza-like illness, 80% showed a 4-fold or greater rise in antibody to the Aichi antigen during the epidemic period. However, the interviews failed to reveal a substantial proportion of the infected individuals: 45% of those who reported no apparent illness showed antibody rises indicating infection.

Two effects of vaccine should be considered separately—namely, the prevention of infection and the modification of illness in infected persons. These studies provided some evidence that both may occur as a result of the use of killed vaccine. In both studies, persons who received the high dose of Aichi vaccine had not only fewer illnesses but also milder ones. Among those who were ill, relatively fewer required bed rest or needed to consult a physician; and among those who had fever, relatively fewer had high fevers. Often in studies of vaccine effectiveness the data have been obtained only through a central medical facility (Stuart et al., 1969). Although such a procedure increases the probability of accurate diagnosis, it selects—rather than people who are ill—those ill enough to seek medical attention.

Demonstrating the protective effectiveness of influenza vaccines has frequently been very difficult because of the unpredictability of the occurrence and duration of epidemics, the variability of attack rates, and major antigenic changes in the virus causing the epidemic. Moreover, the clinical diagnosis of influenza is not precise. Reluctance to rely on clinical diagnosis has naturally led to the use of serology as a method for studying vaccine effectiveness. However, persons who have been given a vaccine containing a virus similar to the epidemic strain will have higher titres against this strain than will the control groups. It has been shown that such persons are less likely to have a further 4-fold increase in titre following infection (Rapmund et al., 1959). Thus, if a rise in serum antibody levels is used as the principal criterion of illness, vaccines containing a virus similar to the epidemic strain will invariably be demonstrated to be " effective ".

The Public Health Advisory Committee on Immunization Practices of the US Public Health Service met on 4 September 1968 and recommended that, for civilian use, " currently available bivalent and polyvalent influenza vaccine be given only to persons at highest risk of mortality or severe complications as a result of influenza. When monovalent vaccine becomes available the same group should be vaccinated or revaccinated with it." On 28 September 1968, the Advisory Committee further stated, in reference to the 400-CCA-unit A2/Aichi/2/68 vaccine, that " although effectiveness of the new vaccine can be substantiated with certainty only by field use, a single dose can be expected to afford significant protection, judging from experience with comparably potent monovalent influenza vaccines. If field tests indicate that a booster dose is necessary, further recommendation will be made."

From the results of these studies, it appears that the old A2 vaccine had little demonstrable effect on clinical illness. Furthermore, a standard dose of Hong Kong vaccine was not effective.

Although ideally it might be desirable to give several doses of vaccine, this was completely impracticable in the 1968–69 season. Despite heroic

[1] See the paper by Mostow et al. on page 525 of this issue.

efforts by the manufacturers, present technological limitations on the production of influenza vaccine prevented a substantial portion of the high-risk group from receiving even a single dose before the peak of the epidemic. Even at the retirement community, which was one of the first civilian populations in the USA to receive the vaccines, a second dose—even if given only 3 weeks after the first—would have come just at the onset of the epidemic. Furthermore, single doses of 3000 CCA units of vaccine stimulated as much serum antibody as has been obtained with an optimally spaced series of doses, and generally much more. Even so, 3000 CCA units of Aichi vaccine afforded only moderate levels of protection. Nasal antibody studies now under way may cast some light on the discrepancy between stimulation of serum antibody and protection.

Influenza vaccines are most needed in years when a major shift in the virus occurs. It is then that morbidity and mortality are highest. Producing large quantities of a new accine is difficult. It has always been felt, however, that vaccines produced in response to a major antigenic shift have the greatest chance of being effective because the vaccine strain will be almost identical to the strain prevalent in the population. As stated earlier, the purpose of administering influenza vaccines should be to prevent severe morbidity and excess mortality. Despite extensive use of influenza vaccines in the civilian population, attainment of these goals has never been demonstrated. The present studies indicate that optimally constituted influenza vaccines at standard dosage levels have little, if any, effectiveness and that even very large doses of vaccine do not approach the high degree of effectiveness that has been achieved with other virus vaccines. Attention should be redirected towards finding a more efficacious means of protection.

ACKNOWLEDGEMENTS

The authors express their gratitude to Dr Thomas J. Albert, Chief, Infectious Disease Division, and Dr Charles F. Pait, Chief, Division of Public Health Laboratories, Orange County Health Department, Santa Ana, Calif.; Dr C. D. Warren, former Medical Director, Georgia State Prison, Reidsville, Ga.; Dr Bernard Portnoy, Associate Professor of Pediatrics and Community and Public Health, Infectious Disease Division, Los Angeles County, University of Southern California Medical School, Los Angeles, Calif.; and Dr Michael B. Gregg, Chief, Viral Diseases Branch, Epidemiology Program, and Dr Harvey Matlof, Epidemic Intelligence Service Officer, National Communicable Disease Center, Atlanta, Ga.

REFERENCES

Rapmund, G., Johnson, R. T., Bankhead, A. S., Herman, Y. F. & Dandridge, O. W. (1959) *U.S. armed Forces med. J.*, **10**, 637

Stuart, W. H., Dull, H. B., Newton, L. H., McQueen, J. L. & Schiff, E. R. (1969) *J. Amer. med. Ass.*, **209**, 232