Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1969, **41**, 623-628

The Roles of Early Alert and of Adjuvant in the Control of Hong Kong Influenza by Vaccines

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The major antigenic changes in influenza A virus that occur at 10-year intervals reduce the effectiveness of existing vaccines and pose a problem for the control of pandemics by vaccination. These difficulties may be obviated in two ways. First, by detecting the emergence of a new variant sufficiently ahead of its general spread for it to be possible to produce a corresponding vaccine in good time; the World Health Organization is widely depended upon for this early warning. Secondly, by the improvement of existing vaccines to increase and broaden their antigenicity; here, their modification by, for instance, adjuvant 65 may contribute significantly.

Aqueous influenza vaccine may be quite effective in the control of the disease. The minor antigenic variations in the virus which occur during the interpandemic periods can usually be handled adequately by periodic revision of the strain formula of the vaccine. However, the major antigenic change in influenza A virus which occurs at approximately 10-year pandemic intervals nullifies the usefulness of the vaccine of the previous formula and taxes the ingenuity of those who would hope to control pandemic influenza by vaccines. There are two principal approaches to the solution of this predictable and continuing dilemma. One is to detect the emergence of a new variant in one part of the world as far in advance of its general spread as is possible, in order to produce as much vaccine as possible and to carry out a vaccination programme. The other is to improve the utility of the old-formula, prepandemic vaccine to afford at least some degree of protection against the new strain before its major pandemic spread in the population. Both of these approaches were put to the test in the 1968 Hong Kong influenza pandemic.

VACCINE PREPARATION

The first warning to our laboratories of the existence of the new Hong Kong influenza virus came in a circular letter from the World Health Organization in Geneva on 16 August 1968. By 13 September, new facilities were being readied for production, and actual production of vaccine began in our laboratories on 23 September. The problem of low yield of virus in embryonated hens' eggs from the new strain was solved by Dr H. Fukumi, who furnished a well-adapted high-yielding Hong Kong influenza strain. The first lot of vaccine made in our laboratories was released on 19 November, and 6 167 000 doses were released by the end of 1968. A total of 9 750 000 doses were released by 20 January 1969. A total of 21 900 000 doses were produced by all vaccine manufacturers in the United States of America combined. Meantime, the pandemic itself had progressed rapidly in the population and had largely spent itself by the end of 1968. Hence, for the vast majority of persons in the USA, the new Hong Kong influenza vaccine was too little and too late. The amount of vaccine produced in time for use, in spite of heroic efforts, was far less than in the 1957 Asian influenza pandemic, when there was a 5-month warning prior to the pandemic event, in contrast with the short 3-month warning of the Hong Kong influenza pandemic. Vaccine prepared too late for use in the USA was, however, in good time to be used in the southern hemisphere, where the seasons are reversed, and in certain parts of Europe in which the main outbreak was delayed.

ADJUVANT 65 VACCINE

One means for improving the performance of influenza vaccine is incorporation of the aqueous material into an adjuvant. The example has been

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provided in adjuvant 65 which we have studied in relation to influenza virus vaccine during the past 10 years (Hilleman, 1966; Peck, Woodhour & Hilleman, 1968; Peck et al., 1964; Porter & Titus, 1967; Stokes et al., 1964, 1969; Weibel et al., 1967, 1969; Woodhour et al., 1964, 1966, 1967, 1969a, 1969b).

As shown in Fig. 1, modified from Stokes et al. (1964), aqueous killed influenza vaccine emulsified in peanut oil (adjuvant 65) generally increases the antibody response 4–16-fold, even when the antigen dose is reduced 4-fold or more. This makes it possible to stretch the vaccine supply 4-fold or more in time of urgent need. Such increased antibody may persist for long periods of time, at least for 6 years following the last dose of vaccine, as shown in Fig. 2 and 3 (from Weibel et al., 1969) for types A1 and B influenza viruses.

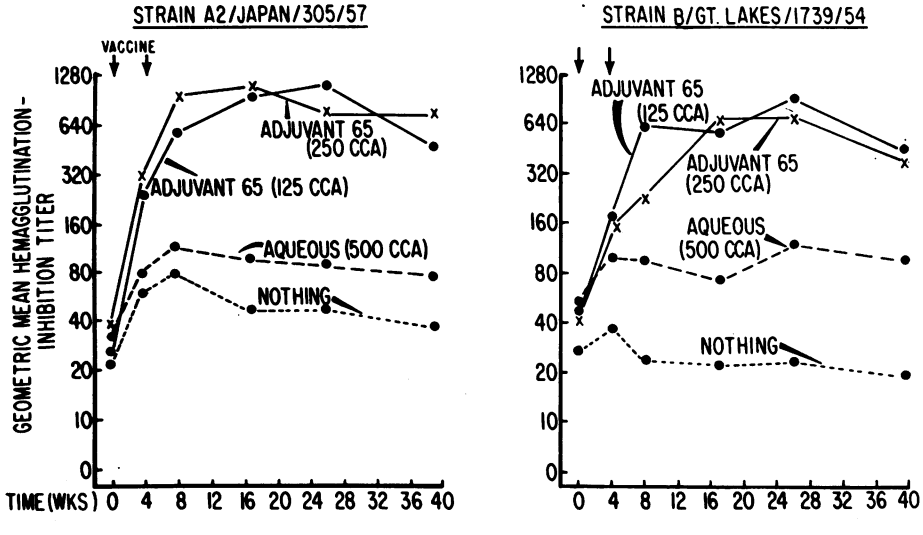
An important consideration is that incorporation of influenza vaccine in adjuvant effects a considerable broadening of antibody response against diverse serotypes. In the example shown in Fig. 4 (from Weibel et al., 1967), incorporation of 1962 A2 vaccine in adjuvant provided high-level antibody against the 1957 and 1964 forms, rendering the changes in antigenic structure unimportant from the immunization standpoint.

An extreme example of broadening of antigenic response was shown for the recent Hong Kong influenza in which there was major antigenic change (10-year cycle) and a resultant pandemic spread of virus throughout the world. The table (see Woodhour et al., 1969b) shows that only 1.4% of the persons who received aqueous vaccine containing 1967 pre-Hong Kong virus developed antibody against 1968 Hong Kong virus. By contrast, 55% of persons given the same vaccine in adjuvant 65 responded with production of antibody against the Hong Kong virus. The antibody titres against Hong Kong virus ranged from 1 : 10 to 1 : 160, and it seems reasonable that general application of the old 1967 vaccine in adjuvant 65 might have afforded substantial protection against Hong Kong influenza in a significant portion of the population had it been used in 1968.

Another example of enhancement of antibody response to influenza vaccine in adjuvant 65 was recently demonstrated in studies employing added polynucleotides which are inducers of interferon and which enhance antibody responses in the short term when given alone with antigen. In the example shown in Fig. 5 (see Woodhour et al., 1969a), adjuvant 65 alone caused substantial enhancement of antibody response in monkeys to influenza vaccine. This was

FIG. 1

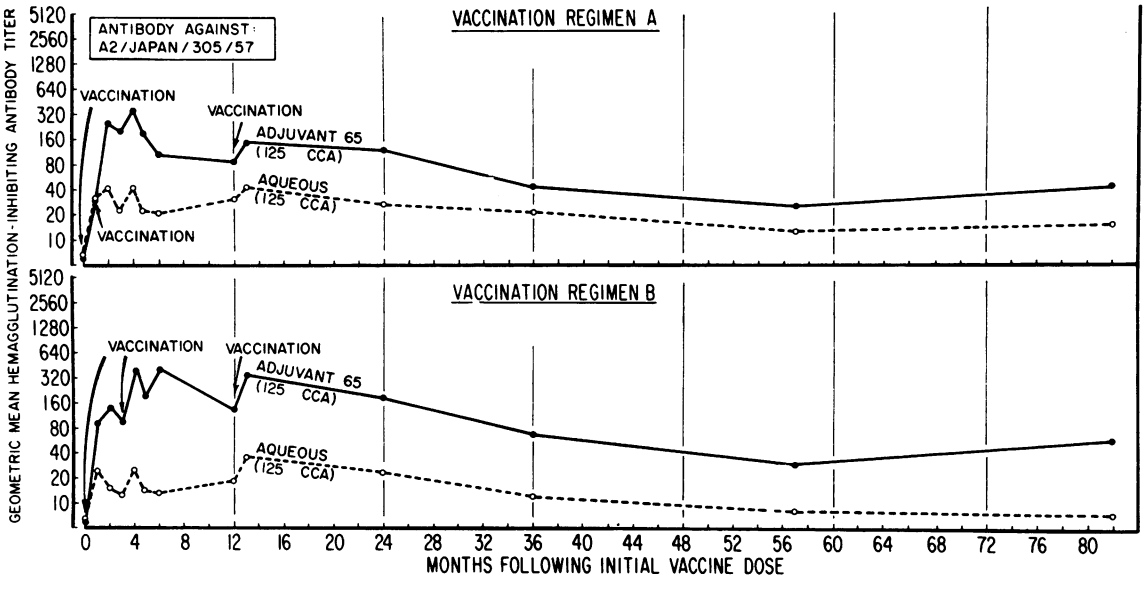
ANTIBODY RESPONSES TO A2 AND B INFLUENZA VIRUSES FOLLOWING ADMINISTRATION OF TETRAVALENT AQUEOUS AND ADJUVANT 65 INFLUENZA VACCINES [a]



[a] Modified from Stokes et al. (1964). 17–20 persons per vaccine group.

FIG. 2

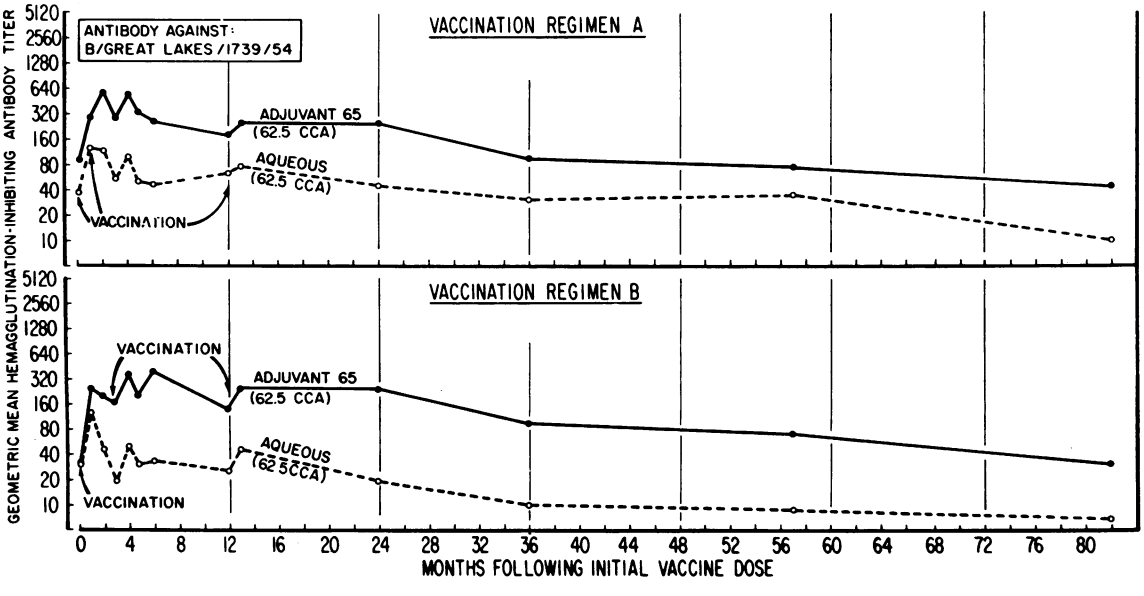
LONG-TERM OBSERVATIONS FOR HI ANTIBODY AGAINST A2/Japan/305/57 INFLUENZA VIRUS VACCINE GIVEN TO HUMAN SUBJECTS IN AQUEOUS OR ADJUVANT 65 FORMULATIONS [a]



[a] See Weibel et al. (1969).

FIG. 3

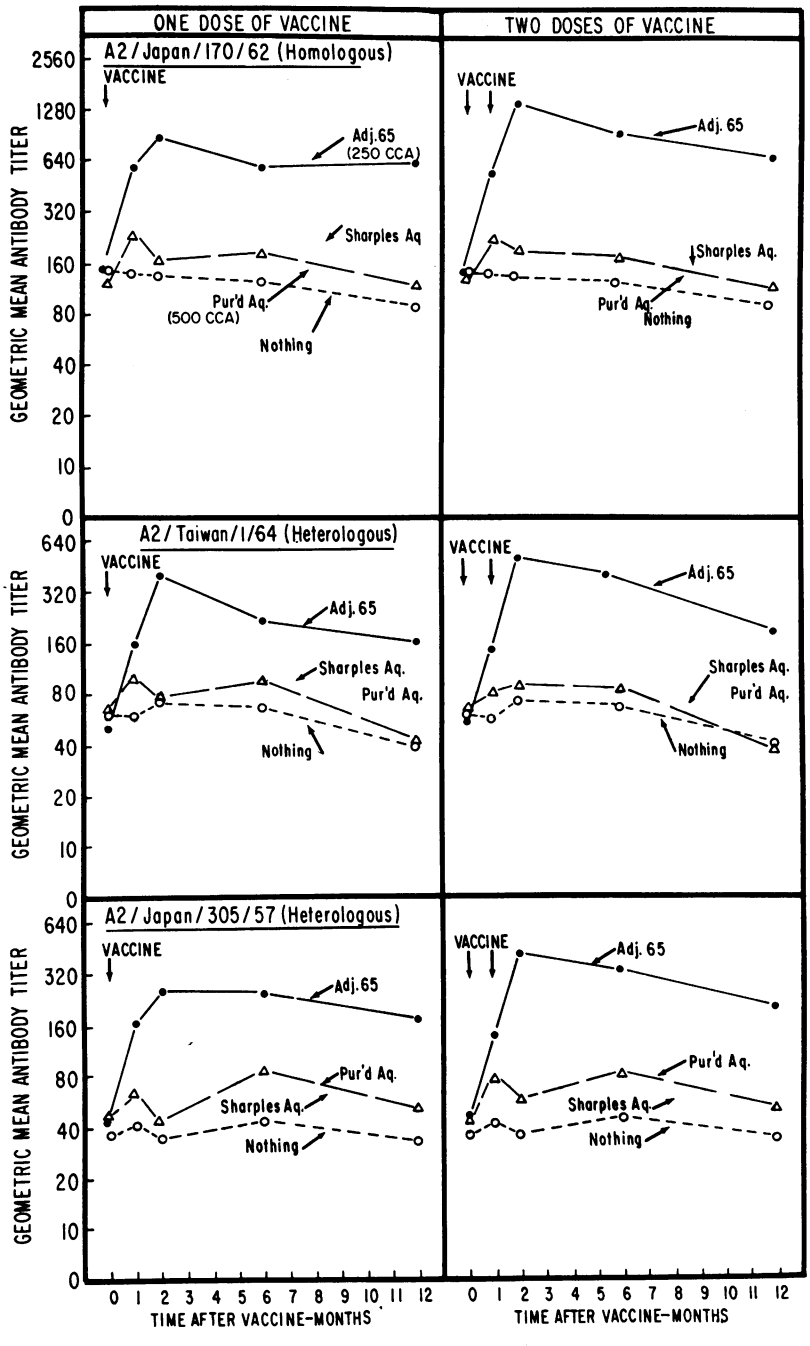
LONG-TERM OBSERVATIONS FOR HI ANTIBODY AGAINST B/Great Lakes/1739/54 INFLUENZA VIRUS VACCINE GIVEN TO HUMAN SUBJECTS IN AQUEOUS OR ADJUVANT 65 FORMULATIONS [a]



[a] See Weibel et al. (1969).

FIG. 4

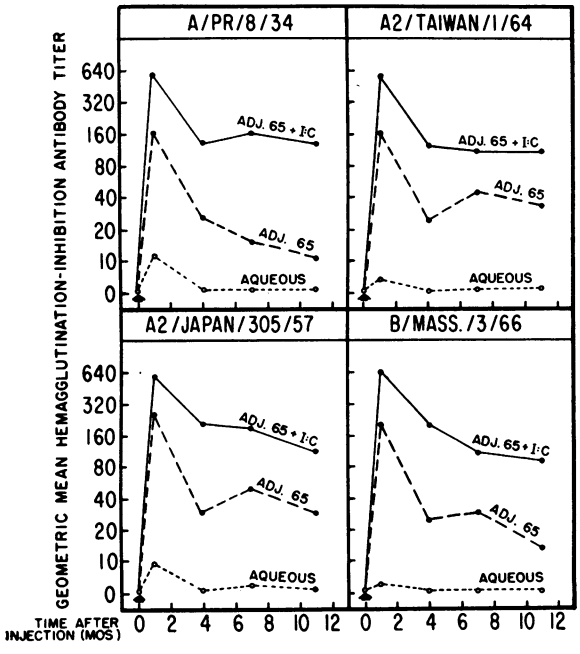
BROADENING OF ANTIBODY RESPONSE TO INFLUENZA A2 ANTIGENIC VARIANTS BY USE OF BIVALENT INFLUENZA A AND B VACCINE IN ADJUVANT 65 [a]



[a] From Weibel et al. (1967). 20–26 persons per vaccine group.

FIG. 5

ANTIBODY RESPONSES IN GRIVET MONKEYS INOCULATED WITH QUADRIVALENT INFLUENZA VACCINE IN AQUEOUS, ADJUVANT 65 OR ADJUVANT 65–POLYNUCLEOTIDE FORMULATION [a]



[a] See Woodhour et al. (1969a). 5 monkeys per group.

DISTRIBUTION OF ANTIBODY TITRES AGAINST HONG KONG VIRUS AMONG INITIALLY SERONEGATIVE PERSONS 2 MONTHS FOLLOWING ADMINISTRATION OF THE FIRST OF 2 DOSES OF AQUEOUS OR ADJUVANT 65 VACCINE

Antibody titre	Numbers of persons with titre following:	
	Aqueous vaccine (600 CCA)	Adjuvant 65 vaccine (600 CCA)
<10	70	30
10	0	5
20	1	17
40	0	9
80	0	4
160	0	2
No. responding / Total	1 / 71	37 / 67
Percentage responding	1.4	55.2

further increased 4–8-fold when polyriboinosinic-polyribocytidylic (poly I·poly C) complex was incorporated in the emulsion. The implications of this synergistic hyperpotentiation of antibody response are obvious. The activity of the poly I·poly C in this instance was separate and distinct from its capacity to induce interferon.

Influenza vaccine in adjuvant 65 has been given to more than 16 000 persons to date without untoward effect. In a recent follow-up of 504 persons given adjuvant 65 influenza vaccine in 1–3 doses up to 5 years previously, only 3, or 0.6%, showed very small persistent nodules which were barely palpable. In addition, no pyrogenic or other systemic reaction has been noted to follow vaccine in adjuvant 65 in contrast to the reaction which sometimes follows aqueous vaccine.

CONCLUSION

In conclusion, there is much existing technology to permit improvement of influenza vaccine and its performance. First and foremost is the matter of early detection of the significant antigenic variant prior to its widespread occurrence in the world population. The activities of the World Health Organization are depended upon for this. Second is the matter of obtaining the highest antibody levels of longest duration and broadest coverage using the least amount of antigen. Here, an adjuvant, such as adjuvant 65, appears to afford a substantial contribution.

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