Bull. Org. mond. Santé } 1969, **41**, 469-473
Bull. Wld Hlth Org. }

Interpretation of Influenza Antibody Patterns in Man

Existence and Significance of Hong Kong Antibody in Old People prior to the Hong Kong Influenza Epidemic

HIDEO FUKUMI [1]

In sera drawn from persons over 72 years of age living in an old people's home in Japan there was found to be a certain degree of antibody to Hong Kong virus before the outbreak of the Hong Kong influenza epidemic in that country. The Hong Kong antibody titres in this group showed no correlation with the titres of simultaneously circulating classical A2 antibody. These findings suggest that some 70 years ago there may have been an epidemic influenza era during which a type of influenza A virus prevailed that was similar in antigenic structure to the Hong Kong type. A similar suggestion was made by workers in the Netherlands in connexion with the classical A2 influenza on the occasion of its appearance about 10 years ago. In view of the time lag between their findings and the present findings in Japan, the author suggests that an " ancient Hong Kong influenza era " may have followed the " ancient A2 influenza era ", which may be supposed to have lasted about 10 years.

The influenza virus—whether of type A or type B—is known to be very apt to change its antigenic structure. In the case of type A, however, the change in antigenic pattern is sometimes quite dramatic, giving rise to a new " era ", in which further minor antigenic changes take place. The appearance of the Hong Kong type of virus seems to suggest the development of a new influenza era.

At the time of the appearance of the classical A2 virus, workers in the Netherlands (Mulder & Masurel, 1958) reported the presence of antibody to that virus in people aged 70 years and over and suggested the existence of an influenza era in which virus antigenically similar to the classical A2 virus had prevailed and speculated that that era had begun with the 1889 influenza pandemic.

Sera from persons in an old people's home in Tokyo, which had been taken prior to the appearance of the Hong Kong influenza epidemic, were tested for antibody titres against Hong Kong virus and it was found that some who were over 70 did have some degree of such antibody. As the Hong Kong virus has a very minor antigen in common with the classical A2 virus, it was to be expected that a small fraction of the population would have some antibody —usually at a titre of 1 : 16 to 1 : 32 or 1 : 64 at most—to the Hong Kong strain a result of infection with the classical A2 virus and that there would be a definite correlation between these titres and their classical A2 antibody titres. However, in the case of the persons over 70 whom we tested, there was no correlation between their Hong Kong and their classical A2 antibody titres.

MATERIALS AND METHODS

Sera

In November 1967, just before the last outbreak of classical A2 influenza in Japan, sera were taken from persons aged 60–92 years in the Yokuhu-yen old people's home, situated in the outskirts of Tokyo.

HI antibody titration

Titration of haemagglutination-inhibiting antibody was made on plastic plates using 0.2 ml of antigen, 0.2 ml of serum and 0.4 ml of chick red blood cells (0.5%). Sera were treated with receptor-destroying enzyme (RDE) just prior to the titration.

Five antigens were employed in HI titration to represent each of the 5 influenza eras:

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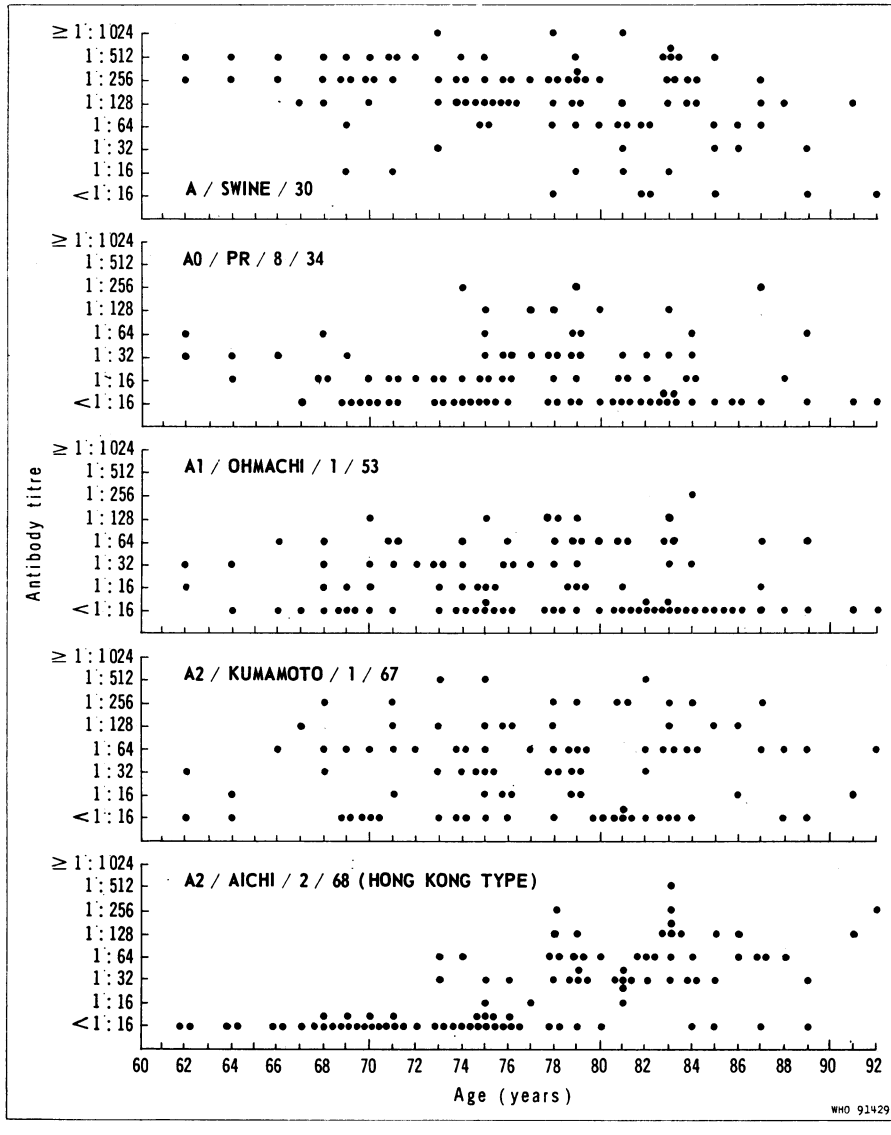
A/Swine/30	for the Spanish influenza era
A0/PR/8/34	for the A0 era
A1/Ohmachi/1/53	for the A1 era
A2/Kumamoto/1/67	for the classical A2 era
A/2/Aichi/2/68 (Hong Kong type)	for the Hong Kong influenza era

RESULTS

Antibody titres against each antigen for the persons in the old people's home were plotted against age as shown in Fig. 1. As can be seen in this figure, in the case of both A/Swine/30 and A0/PR/8/34, the antibody titres drop a little and the percentage of those with a titre of $<1:16$ increases with age, whereas

FIG. 1

AGE DISTRIBUTION OF ANTIBODY TITRES AGAINST REPRESENTATIVE INFLUENZA VIRUS STRAINS IN YOKUHU-YEN OLD PEOPLE'S HOME



with A1/Ohmachi/1/53 and A2/Kumamoto/1/67 the distribution of titres is more equal at all ages. What is most striking is the antibody distribution pattern for A2/Aichi/2/68 (Hong Kong type). Up to 72 years of age, no persons show a clear antibody titre, but at the age of 72 antibody titres $\geq 1:16$ begin to appear and at ages above 77 years rather few show no Hong Kong antibody and fairly high titres (1 : 256 and even 1 : 512) are seen.

The next problem is whether or not there is a correlation between Hong Kong and A2 antibody titres among those aged more than 70 years. Fig. 2 makes it clear that there is almost no such correlation.

FIG. 2

CORRELATION BETWEEN HONG KONG AND CLASSICAL A2 ANTIBODIES IN YOKUHU-YEN OLD PEOPLE'S HOME

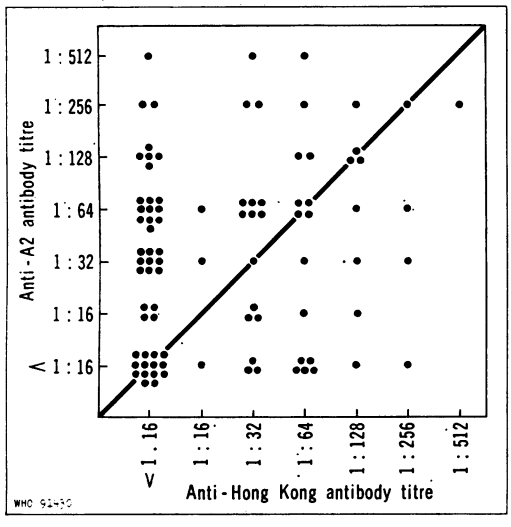


TABLE 1

ANTIGENIC ANALYSES OF HONG KONG INFLUENZA VIRUS STRAINS

Antigen	Ferret convalescent antisera (reciprocal titres)			
	A2/Aichi/2/68		A2/Hong Kong/58/68	
	No. 397	No. 398	No. 394	No. 395
A/Swine/30	<16	<16	<16	<16
A0/PR/8/34	<16	<16	<16	<16
A1/Kohjiya/1/52	<16	<16	<16	<16
A1/Ohmachi/1/53	<16	<16	<16	<16
A2/Adachi/2/57	<16	32	<16	32
A2/Murakami/4/64	16	128	<16	256
A2/Kumamoto/1/65	<16	64	<16	64
A2/Kumamoto/1/67	16	32	<16	64
A2/Tokyo/1/67	16	256	<16	128
A2/Kanagawa/1/67	16	64	<16	64
A2/Tokyo/3/67	<16	256	<16	256
A2/Aichi/2/68	1 024	1 024	1 024	1 024
A2/Hong Kong/58/68	1 024	1 024	1 024	1 024
A2/Hyogo/1/68	1 024	1 024	512	1 024
A2/Hyogo/2/68	512	1 024	1 024	512
A2/Tokyo/2/68	1 024	1 024	1 024	1 024
A2/Kumamoto/2/68	512	1 024	1 024	1 024
A2/Kumamoto/3/68	1 024	1 024	1 024	512
A2/Kanagawa/6/68	1 024	1 024	1 024	1 024
A2/Tokyo/3/68	512	512	512	512
A2/Hiroshima/1/68	512	1 024	512	256

DISCUSSION

The Hong Kong virus is very different from the classical A2 virus in antigenic structure although they do have a minor antigen in common (Fukumi et al., 1968) (Table 1). It is this common antigen that explains why there was a small number of persons in the general population who had some low degree of Hong Kong antibody before the Hong Kong influenza epidemic occurred (Table 2); these persons showed good correlation between their Hong Kong and classical A2 antibody (Fig. 3), that is, those with a relatively high Hong Kong antibody titre also had a rather high A2 titre.

On the contrary, as we have have seen, among old people aged more than 70 years some had fairly high Hong Kong antibody titres which were not correlated at all with classical A2 antibodies. This has been found not only by myself but also by others in Japan (T. Karaki & N. Tsuchiya, personal communication, 1968; K. Takahashi, personal communication, 1968). Persons in 3 other old people's homes were examined by us for their Hong Kong antibody titres, but, although essentially the same results were obtained, the picture is complicated by more recent classical A2 infection, and these studies will therefore be reported in another publication with a detailed discussion.

TABLE 2

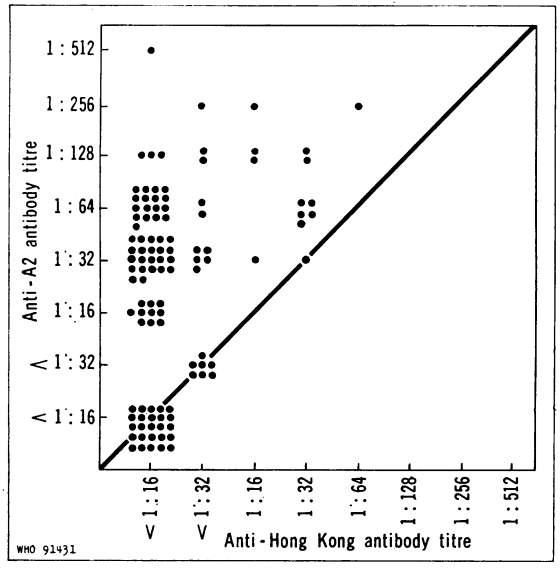
FREQUENCY DISTRIBUTION OF ANTIBODY TITRES AGAINST CLASSICAL A2 AND HONG KONG INFLUENZA VIRUSES IN A TOKYO POPULATION GROUP AGED 20–60 YEARS [a]

Antigen	HI antibody titre							
	<1 : 16	<1 : 32	1 : 16	1 : 32	1 : 64	1 : 128	1 : 256	1 : 512
A2/Kumamoto/1/67	25	7	10	29	24	9	3	1
A2/Aichi/2/68 (Hong Kong type)	77	17	6	7	1			

[a] Sera taken in August 1968, before the epidemic of Hong Kong influenza.

FIG. 3

CORRELATION BETWEEN HONG KONG AND CLASSICAL A2 ANTIBODIES IN A TOKYO POPULATION GROUP AGED 20–60 YEARS [a]



[a] Sera drawn in August 1968, before the epidemic of Hong Kong influenza; same sera as in Table 2.

From the above findings, it is clear that there is a residue of antibody against the main antigen of Hong Kong virus (which is quite different from that of classical A2) among the population more than 70 years old. As mentioned earlier, a similar finding was reported by Mulder & Masurel (1958) in connexion with classical A2 antibody at the time of the first appearance of the A2 virus; this means that about 10 years ago part of the population over 70 had A2 antibodies left over from some event prior to the appearance of the A2 virus. If, as they suggest, this residual A2 antibody was derived from an influenza era during which a virus similar to the classical A2 had prevailed—an era that might have started with the 1889 influenza pandemic and that may reasonably be called the " ancient A2 influenza era "—then, by the same line of reasoning, an era which might be called the " ancient Hong Kong influenza era " may

FIG. 4

RELATIONSHIP BETWEEN INFLUENZA " ERA " AND AGE-SPECIFIC ANTIBODY PATTERNS TO 5 REPRESENTATIVE INFLUENZA VIRUS STRAINS (SCHEMATIC)

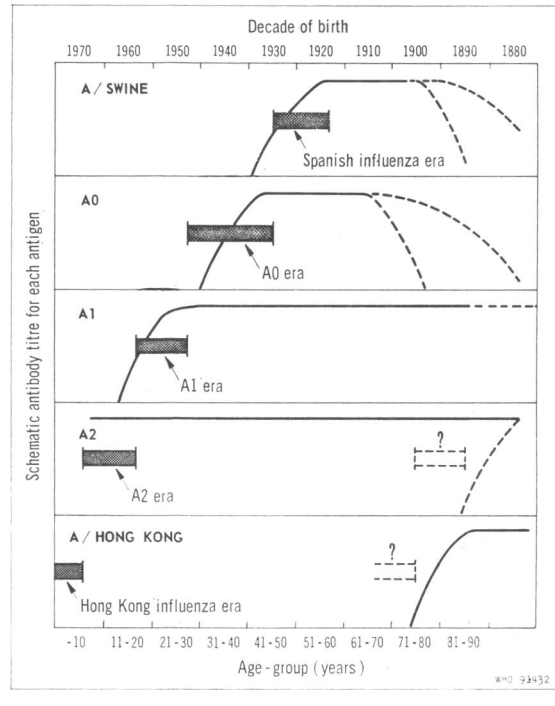


TABLE 3
AGE-SPECIFIC ANTIBODY PATTERNS FOR REPRESENTATIVE INFLUENZA A STRAINS IN 1963

Virus strain	Age-group (years)	No. of sera with indicated antibody titre											
		<1 : 16	<1 : 32	<1 : 64	1 : 16	1 : 32	1 : 64	1 : 128	1 : 256	1 : 512	1 : 1024	1 : 2048	Total
A/Swine/30	≤20	402	4	1	4	4	1						416
	21-30	337	4		3	3	1	1		1			351
	31-40	48	4		9	7	6	4	1				79
	41-50	7	1		2	7	12	13	13	2	1	1	58
	⩾51					3	3	5	8				19
A0/PR/8/34	≤20	378	6	1	8	13	9	1	1				417
	21-30	173			35	60	52	25	1	1			347
	31-40	10	2		11	18	23	12	3	23	4		106
	41-50	18			5	14	13	5	2				57
	⩾51	5			3	2	1	3					14
A1/Ohmachi/1/53	≤20	44	1		49	116	119	72	16	1			418
	21-30	69	1		49	91	82	37	13	3			345
	31-40	31	2		14	18	11	3					79
	41-50	28	1		9	10	7	2					57
	⩾51	5			4	2	2	1					14
A2/Adachi/2/57	≤20	31			17	61	129	124	44	8	3	2	419
	21-30	53	1		19	78	112	62	16	4	2	1	346
	31-40	17	1		9	16	23	9	1	1			77
	41-50	16			8	16	14	4					59
	⩾51	5			2	3	3	1					14

be presumed to have followed upon the " ancient A2 influenza era ".

Several years ago an experiment was carried out by us (Fukumi et al., 1964) that showed the age patterns of antibody titres to 4 influenza antigens representing A/Swine, A0, A1 and A2 viruses in a population of factory workers 15–55 years old in Tokyo (Table 3). Those sera were drawn in 1963, and it is of interest that the age patterns are more or less specific for each antigen.

Fig. 4 has been prepared to show schematically the relationship between the influenza eras and the age-specific antibody patterns for the 5 representative influenza antigens. In the case of the Spanish influenza, A0 and A1 eras, the correlation with the antibody patterns by age is very clear, but there is not such a close correspondence for the " ancient A2 " and Hong Kong eras, accepting Mulder & Masurel's suggestion that the former began with the 1889 influenza pandemic.

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