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Serological Characteristics of a "New" Serotype of Influenza A Virus: the Hong Kong Strain

N. MASUREL [1]

Serological studies in the Netherlands have shown that exposure to A2 influenza viruses during the period 1957–67 increased the level of haemagglutination-inhibiting (HI) antibody against A/Equi-2 virus in the sera of persons aged 60 years or more and against A2/Hong Kong/68 virus in sera from persons less than 60 years old. On the other hand, HI antibody titres against A/Swine/30, A/PR/8/34 and A1/Nederland/49 viruses were not reinforced by exposure to A2 viruses.

From these and other findings, the author concludes that the influenza virus strains of the A/Swine era are distantly related antigenically to those of the A2 era, that the pandemic virus of 1889 most closely resembles that of the 1957 pandemic, and that the Hong Kong-type virus appeared in man about 1900 and is probably responsible for A/Equi-2 antibodies found in human sera.

The presence of antibody against a human or animal influenza virus in the sera of persons of a certain age-group suggests that such a virus or a related virus has circulated in man in the past (Masurel, 1967). An increasingly complete picture of the epidemiology of influenza has been obtained during the past 12 years and it seems highly probable that in the near future it will be shown that the succession of antigenic variants over time runs a circular course.

There is general agreement among many investigators that the influenza pandemic of 1918 was caused by the swine virus isolated by Shope in 1930. All influenza A strains that prevailed in the period 1918–57 show an antigenic relationship with this swine virus. The late Professor Mulder called this period the "A swine era" (Mulder & Masurel, 1958; Masurel & Mulder, 1962), and the view was put forward that a new period started with the Asian influenza virus of 1957.

It was suggested, first, that the A2 virus was responsible for the pandemic of 1889; secondly, that the A2 virus might be the parent strain for the variants of influenza virus during the period from 1889 to 1918; and thirdly, that the next variant of the A2 virus might be expected about 8 to 12 years after the pandemic of 1957.

On the basis of the hypothesis of the late Dr Thomas Francis (1960), who stated, *inter alia*, that a limited number of antigenic components are present in the influenza A virus, Mulder & Masurel (1958) suggested that the present "A2 era" might see an antigenic shift of A2 virus similar to that which may have taken place in an earlier "A2 era" from 1889 to 1918.

In 1963 and later, many investigators showed the presence of antibodies against the A/Equi-2 virus in sera obtained from old people (Dowdle et al., 1964; Minuse et al., 1965; Schild & Stuart-Harris, 1965; Masurel & Mulder, 1966; Davenport et al., 1967). These antibodies are found with the highest frequency in the sera of human beings 10 years younger than those in which the highest frequency of A2 antibodies are found.

The suggestion has been made that, if the hypothesis is correct that the pandemic of 1889 was caused by the Asian virus, then an Equi-2-like virus could have started epidemics of influenza in man 10 years later, i.e., around the beginning of the century. Thus, the first large shift of the A2 virus must have occurred at that same point in time. By analogy, it was suggested that a new variant might also be expected in the present era after the same interval (Masurel & Mulder, 1966; Masurel,

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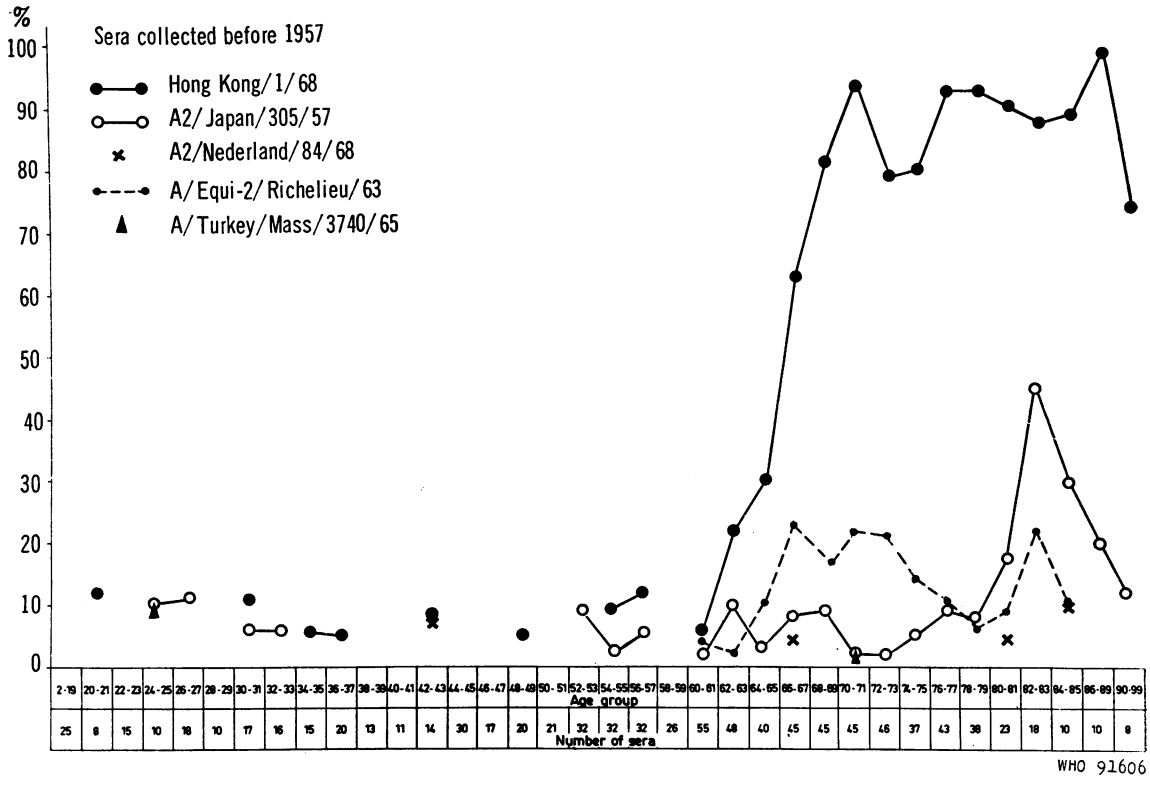
FIG. 1

HI ANTIBODY FREQUENCIES FOR HUMAN, EQUINE AND AVIAN INFLUENZA VIRUSES IN HUMAN SERA COLLECTED IN 1956–57 [a]



[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

1968a); likewise, the new variant could be a virus related to the Equi-2 strain.

In 1968 the Hong Kong strain was isolated. A Hong Kong antibody pattern has been found in sera collected in the Netherlands from human subjects in 1956–57, 1958 and 1967.

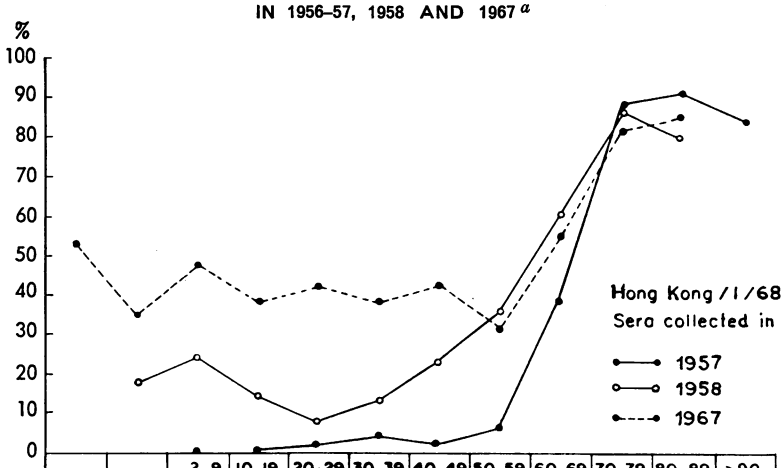
Fig. 1 demonstrates that at least 70% of sera collected in 1956–57 and obtained from persons aged 68 years or over contained haemagglutination-inhibiting (HI) antibody against the Hong Kong strain; a few human sera in the 20–60-year age-groups also showed low titres. Antibodies against against Equi-2 and 1957 A2 strains were also first found in low frequency in the 60-year age-group and were regularly present above this age. Only a few sera in the collection showed a low antibody titre with the A/Turkey/Massachusetts/3740/65 strain or with the A2 virus of the 1968 epidemic (A2/Nederland/84/68).

The Hong Kong antibody curve exhibits a changed pattern in sera collected in 1958 and 1967 (Fig. 2). Antibody against the Hong Kong strain appeared with increasing frequency, though at low titre values, in sera of people of the age-groups under 60 years. After the A2 pandemic of 1957, 20% of the sera contained low-titred antibody against Hong Kong virus; however, there is an increase to 40% in the 1967 sera. This increase correlates with the relationship between the A2 and Hong Kong strains found by cross HI tests in ferret sera and by vaccination experiments in man and animals (Masurel, 1968b).

The A2 epidemics of the period 1957–68 have also influenced the antibody level of Equi-2 virus (Fig. 3).

FIG. 2

HI ANTIBODY FREQUENCIES FOR A2/Hong Kong/1/68 VIRUS IN HUMAN SERA COLLECTED IN 1956–57, 1958 AND 1967 [a]



		2-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	≥90
	0-2	3-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	≥81	
0-8	9-11	12-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	≥90	
Age group (top line, 1957; second line, 1958; bottom line, 1967)											
		7	18	61	81	92	143	233	209	61	8
	54	160	200	200	200	117	120	118	96	17	
37	18	123	186	281	398	422	323	156	52	7	
Number of sera (top line, 1957; second line, 1958; bottom line, 1967)											

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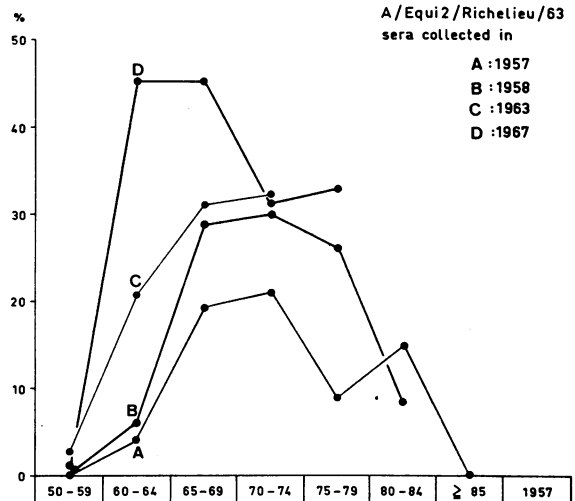
[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

FIG. 3

HI ANTIBODY FREQUENCIES FOR A/Equi-2/Richelieu/63 VIRUS IN HUMAN SERA COLLECTED IN 1957, 1958, 1963 AND 1967 [a]

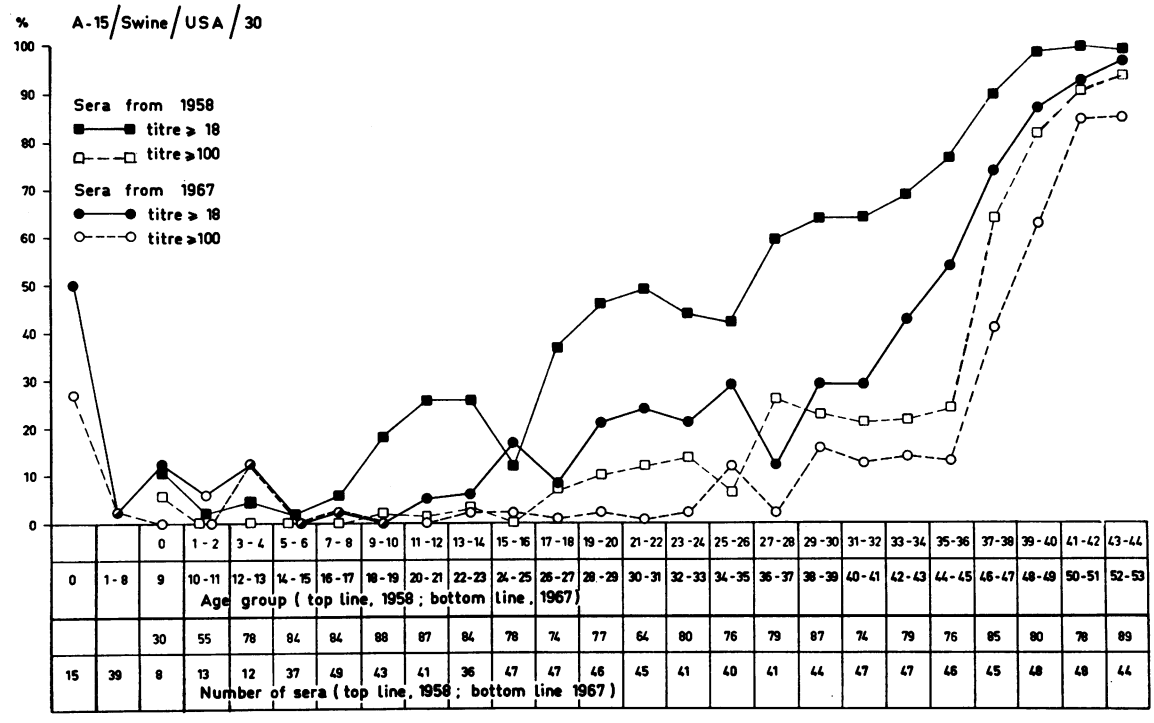


50-59	60-64	65-69	70-74	75-79	80-84	≥ 85	1957
51-60	61-65	66-70	71-75	76-80	81-85		1958
56-65	66-70	71-75	76-80	81-85			1963
60-69	70-74	75-79	80-84	85-89			1967
Age group							
143	130	103	110	99	46	23	1957
180	95	96	75	53	24		1958
297	140	16	12	2			1963
348	117	75	48	25			1967
Number of sera							

[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

FIG. 4

HI ANTIBODY FREQUENCIES FOR A/Swine/30 VIRUS IN HUMAN SERA COLLECTED IN 1958 AND 1967 [a]

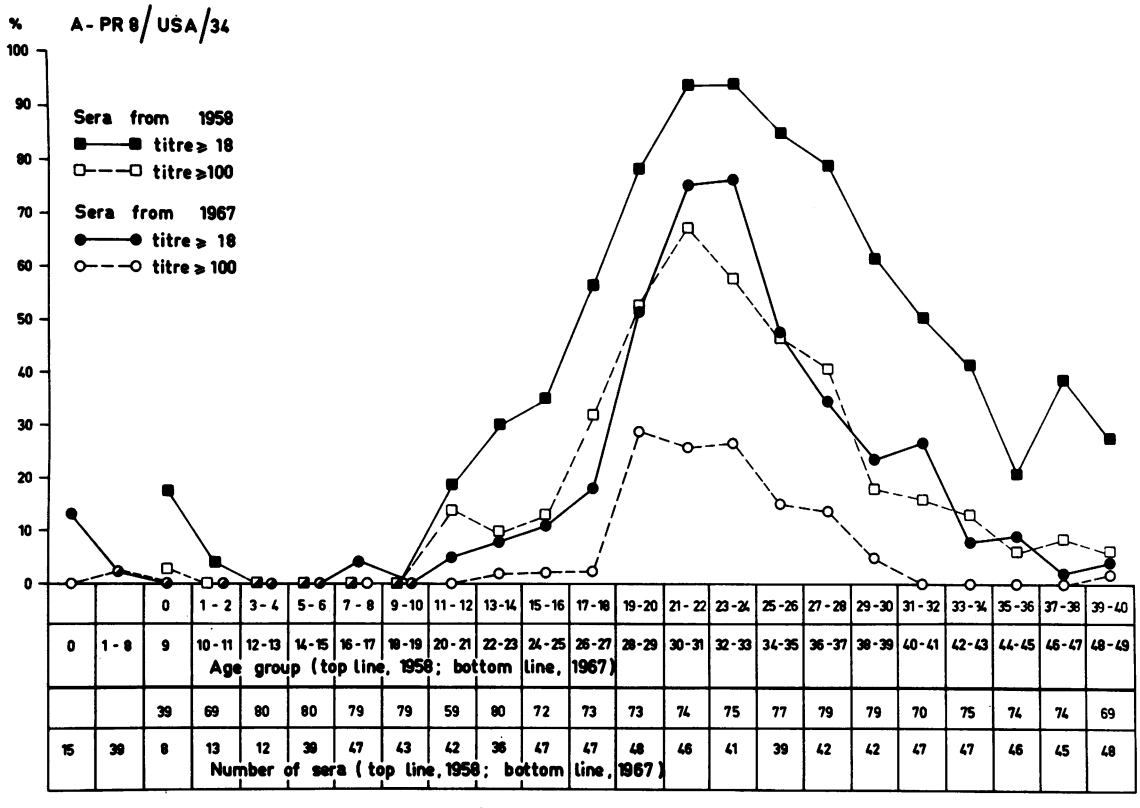


		0	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24	25-26	27-28	29-30	31-32	33-34	35-36	37-38	39-40	41-42	43-44
0	1-8	9	10-11	12-13	14-15	16-17	18-19	20-21	22-23	24-25	26-27	28-29	30-31	32-33	34-35	36-37	38-39	40-41	42-43	44-45	46-47	48-49	50-51	52-53
Age group (top line, 1958 ; bottom line, 1967)																								
		30	55	78	84	84	88	87	84	78	74	77	64	80	76	79	87	74	79	76	85	80	78	89
15	39	8	13	12	37	49	43	41	36	47	47	46	45	41	40	41	44	47	47	46	45	48	48	44
Number of sera (top line, 1958 ; bottom line 1967)																								

[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

FIG. 5

HI ANTIBODY FREQUENCIES FOR A/PR/8/34 VIRUS IN HUMAN SERA COLLECTED IN 1958 AND 1967 [a]

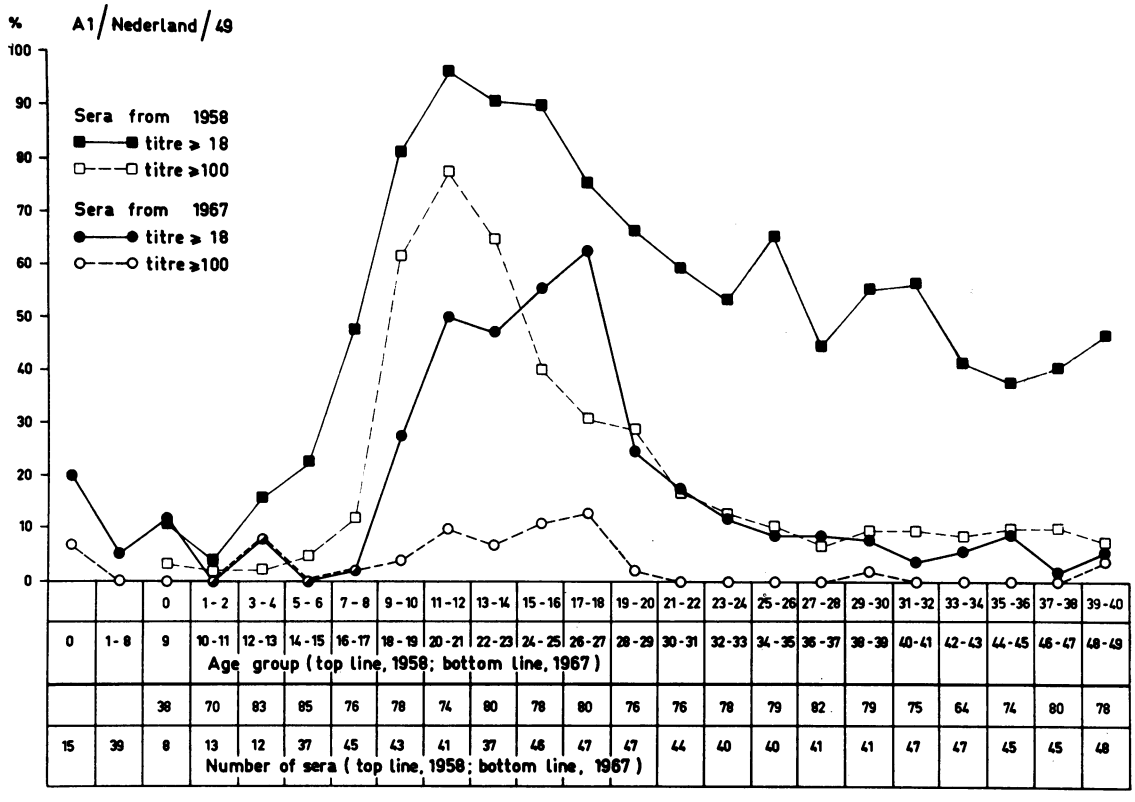


		0	1 - 2	3 - 4	5 - 6	7 - 8	9 - 10	11 - 12	13 - 14	15 - 16	17 - 18	19 - 20	21 - 22	23 - 24	25 - 26	27 - 28	29 - 30	31 - 32	33 - 34	35 - 36	37 - 38	39 - 40
0	1 - 8	9	10 - 11	12 - 13	14 - 15	16 - 17	18 - 19	20 - 21	22 - 23	24 - 25	26 - 27	28 - 29	30 - 31	32 - 33	34 - 35	36 - 37	38 - 39	40 - 41	42 - 43	44 - 45	46 - 47	48 - 49
Age group (top line, 1958; bottom line, 1967)																						
		39	69	80	80	79	79	59	80	72	73	73	74	75	77	79	79	70	75	74	74	69
15	39	8	13	12	39	47	43	42	36	47	47	48	46	41	39	42	42	47	47	46	45	48
Number of sera (top line, 1958; bottom line, 1967)																						

[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

FIG. 6

HI ANTIBODY FREQUENCIES FOR A1/Nederland/49 VIRUS IN HUMAN SERA COLLECTED IN 1958 AND 1967 [a]



		0	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24	25-26	27-28	29-30	31-32	33-34	35-36	37-38	39-40
0	1-8	9	10-11	12-13	14-15	16-17	18-19	20-21	22-23	24-25	26-27	28-29	30-31	32-33	34-35	36-37	38-39	40-41	42-43	44-45	46-47	48-49
Age group (top line, 1958; bottom line, 1967)																						
		38	70	83	85	76	78	74	80	78	80	76	76	78	79	82	79	75	64	74	80	78
15	39	8	13	12	37	45	43	41	37	46	47	47	44	40	40	41	41	47	47	45	45	48
Number of sera (top line, 1958; bottom line, 1967)																						

[a] The ordinate indicates the percentage of sera with corresponding HI antibodies.

The frequency of antibody among persons 60 or more years of age increased from 13% in 1957 (Masurel & Mulder, 1966) to 40% in 1967. The increase is most striking in the 60–64-year age-group—namely from 5% in 1957 to 45% in 1967. No antibody to the Equi-2 virus has appeared in the age-group under 60 years, in contrast to the appearance of Hong Kong antibody in this age-group. It seems that antibody titres to Equi-2 increased both in frequency and in height in consequence of exposure to Asian influenza viruses. In the near future it will be very interesting to investigate what response the Equi-2 antibody will show to the Hong Kong virus.

There is a great difference between the increase or appearance of Hong Kong antibody and of Equi-2 antibody resulting from exposure to Asian influenza viruses during the period 1957–67. The reason is probably that the antigenic relationship between the A2 and the Hong Kong viruses is stronger than that between the A2 and the Equi-2 viruses (Masurel, 1968a, 1968b).

Next we may consider the difference in frequency of antibody against the major antigens of other prototype strains in sera collected in 1958 and 1967.

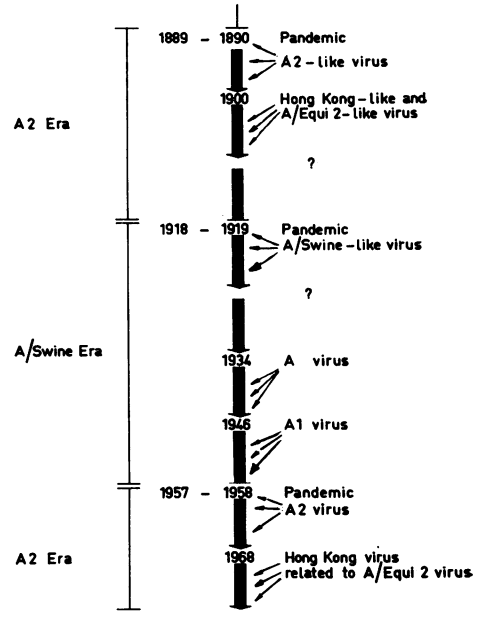
Fig. 4 shows results obtained with the A/Swine/30 strain. Over-all, there is a clear decrease in the frequency of antibody in the 1967 collection as well as a decrease in the frequency of antibody greater than 1/100. In the age-group born before 1918 the decrease is less because the initial antibody is much higher.

Fig. 5 shows data obtained with the PR/8 strain. There is a slightly greater decrease in frequency of high-titred sera than was found with A/Swine/30.

Fig. 6 demonstrates data obtained with an A1 strain. The frequency of sera with a high antibody titre shows an enormous decrease in the age-group 9–18 years—namely, from 55% in 1958 to 10% in 1967. It seems that the titres of antibody against swine, A and A1 viruses have not been reinforced by exposure to Asian influenza viruses, in sharp contrast to the findings with the Hong Kong and Equi-2 strains.

In summary, the results obtained by many investigators with the Hong Kong virus and other human and animal influenza A viruses allows us to reconstruct the influenza eras as shown in Fig. 7.

FIG. 7
DIAGRAMMATIC REPRESENTATION OF INFLUENZA ERAS



It seems reasonable to conclude (1) that the influenza virus strains of the A/Swine era are antigenically only distantly related to those of the A2 era; (2) that the pandemic virus of 1889 most closely resembles the pandemic virus of 1957; and (3) that the Hong Kong-type virus first appeared in man about 1900, as a successor to the A2-type strains of 1889–90, and is probably responsible for Equi-2 antibodies in human sera. This virus is strengthened by the fact that the Hong Kong strain is the only human influenza virus antigenically related to Equi-2.

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