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Recycling of H1N1 influenza A virus in man – a haemagglutinin antibody study

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SUMMARY

Sera from people born between 1883 and 1930 and collected in 1977 were tested for the presence of HI antibodies to A/FM/1/47 (H1N1) virus and three recently (1977 and 1978) isolated influenza A-H1N1 viruses. The highest frequency of high-titred antibody to the four H1N1 viruses was detected in sera from people born in 1903–4, i.e. 42, 54, 38, and 22% had antibody against A/FM/1/47, A/Hong Kong/117/77, A/Brazil/11/78, and A/Fukushima/103/78 respectively. The birthdate groups 1896–1907 showed a higher percentage of HI antibody titres $\geqslant 18$, $\geqslant 50$, $\geqslant 100$ or $\geqslant 1600$ against the four H1N1 viruses than the birthdate groups 1907–30. This indicates the existence of an era, 1908–18, in which, apart from the H3N2 virus (1900–18), the H1N1 virus was epidemic among the human population.

INTRODUCTION

Since 1953 the basis for retrospective epidemiologic studies of influenza viruses has been the doctrine of the 'original antigenic sin', introduced by Francis, Davenport & Hennessy (1953). This theory states that the first contact with an influenza virus leaves an imprint of its particular antigens on a person's immunologic memory. During the individual's lifetime specific antibody production is boosted by similar or related influenza strains.

Antibody determination in sera collected in 1958 and 1967 showed that persons with haemagglutination inhibition (HI) antibody titres $\geqslant 100$ against A/Nederland/49 (H1N1) were born between 1939 and 1949 (Masurel, 1976). This birthdate cohort was optimally primed for the H1N1 virus, which circulated between 1947 and 1957 (Masurel & André, 1978). Thus, in sera from older people taken in 1956 it could be established that the influenza viruses A-H2N2 and A-H3N2 which started to circulate in 1957 and 1968, respectively, had caused epidemics seventy years earlier (Mulder & Masurel, 1958; Davenport *et al.* 1969; Fukumi, 1969; Masurel, 1969*a*).

Since 1947 it has been known that following the appearance of a new epidemic subtype of influenza A virus, the present virus disappears as a causative agent of human influenza. By contrast, in 1978 two viruses very different in antigenic composition were simultaneously found: the A-H3N2 virus present since 1968, and the A-H1N1 virus, which had also caused epidemics from 1947 to 1957. In our

earlier studies (Masurel, 1969*b*; Masurel & Marine, 1973) a strict order of influenza A subtypes with serological relation within but not between the 'swine era' (1918–57) and the 'A2 era' (1957–now) was suggested. The appearance in 1977 of the A-H1N1 subtype ('swine era') in the 'A2 era' was contradictory to our hypothesis. The present study was undertaken to discover whether similar contradictory results would be found for the 'A2 era' of 1890–1918. Therefore, the frequency of antibodies against the haemagglutinin component of the H1N1 virus was investigated in sera from persons born before 1930.

MATERIALS AND METHODS

Human sera

Sera from persons born between 1883 and 1930 were collected just before the reappearance of the H1N1 subtype in the Netherlands. In the autumn of 1977, 728 blood samples were supplied by Dr J. Rechsteiner (Central Public Health Laboratory, Bilthoven). The sera were stored at −20 °C.

Influenza viruses

Influenza A-H1N1 viruses used were A/FM/1/47, A/Hong Kong/117/77, A/Brazil/11/78, and A/Fukushima/103/78. The 1947 virus strain was mouse-adapted, the more recent strains were egg-adapted.

Haemagglutination inhibition (HI) test

Before testing, the sera were treated with *Vibrio cholerae* filtrate for 18 h at 37 °C and subsequently heated for 1 h at 56 °C to remove non-specific inhibitors (Masurel, 1962). HI tests were carried out by the microtitre method as described previously (Masurel, 1976). Titres were expressed as the reciprocal of the serum dilution giving 50 % haemagglutination of chicken red cells by four agglutinating units of virus. In all experiments reference antisera were included.

RESULTS

Fig. 1 A shows the percentage of HI antibody $\geqslant 18$ against the H1N1 virus strains A/Hong Kong/117/77, A/Brazil/11/78, and A/Fukushima/103/78 in sera from persons born between 1883 and 1930. One hundred per cent of people born in 1903–4 possess antibody against the H1N1 strains. Peaks of antibody frequency to the three strains are found at a lower level in sera from persons born in 1909–10 and 1925–26.

Fig. 1 B shows the percentage of HI titres $\geqslant 50$ against the same H1N1 viruses. Antibody against all three influenza strains is found in high percentage among sera from people born in 1903–4, i.e. 86, 65, and 61 %, respectively, against the virus strains A/Hong Kong, A/Fukushima, and A/Brazil. The percentage of antibody titres against A/Hong Kong in sera from people born between 1907 and 1930 remains below 40. In these birthdate groups antibody against A/Fukushima and A/Brazil is at most 16 and 15 %, respectively.

The percentages of HI titres $\geqslant 100$ (Fig. 1 C) are highest in sera from people born in 1903–4, i.e. 54, 38, and 22 % respectively, against A/Hong Kong, A/Brazil, and

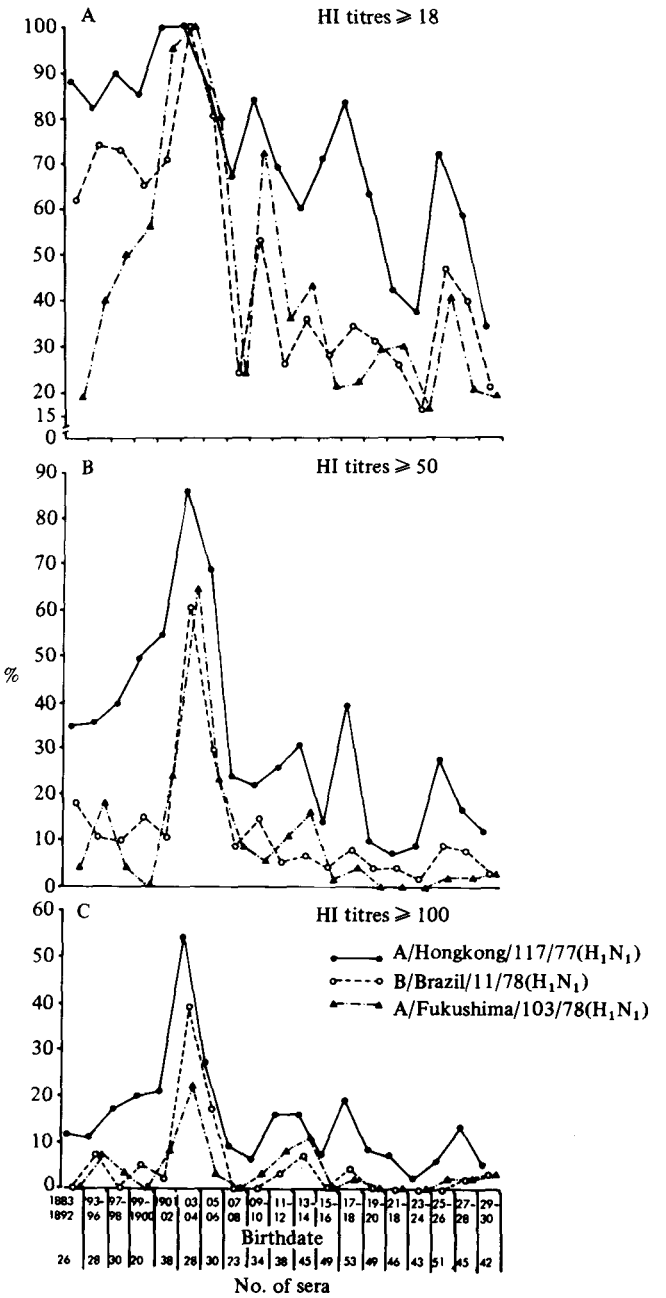

Fig. 1. Percentage of HI antibody titres ⩾ 18 (A), ⩾ 50 (B), and ⩾ 100 (C) against human influenza viruses A/Hong Kong/117/77 (H1N1), A/Brazil/11/78 (H1N1), and A/Fukushima/103/78 (H1N1) detected in sera collected in 1977 from persons born in 1883–1930.

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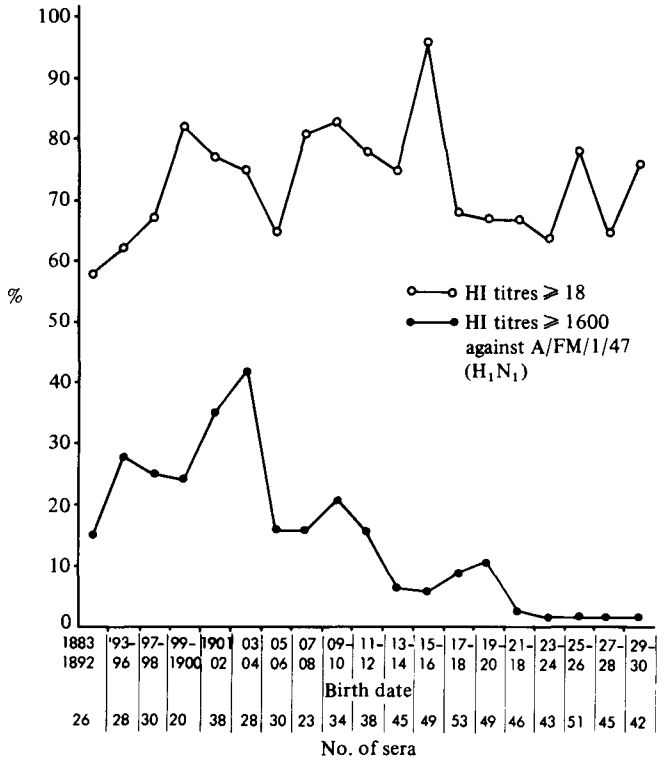

Fig. 2. Percentage of HI antibody titres ⩾ 18 and ⩾ 1600 against the human influenza virus A/FM/1/47 (H1N1) detected in sera collected in 1977 from persons born in 1883–1930.

A/Fukushima. Persons with later birthdates show an abrupt decrease in the frequency of antibody.

Fig. 2 shows the percentage of antibody titres ⩾ 18 and ⩾ 1600 against A/FM/1/47 (H1N1), the representative of the initial epidemic period 1947–57. In the population studied, the percentage of titres ⩾ 18 varies between 65 and 85 in almost all age groups. However, in sera from persons born in 1915–16 a peak of 96 % is reached. Titres ⩾ 1600 against the A/FM/1/47 virus are most frequently found in persons born in 1903–4, i.e. in 42 %. The age groups with birthdates of 1904 and later show an abrupt decrease in percentage of antibody titres ⩾ 1600.

DISCUSSION

The present study indicates that a high percentage of high-titred HI antibody against all four H1N1 viruses, and especially against A/FM/1/47 and A/Hong Kong/117/77 is present in sera from people born in 1903–4. For the first-mentioned virus the levels of antibody are higher. This may be caused by the fact that A/FM/1/47 virus is mouse-adapted and readily inhibited by antibody.

In particular the recently isolated H1N1 viruses exhibit an antibody pattern in which the highest percentage of detectable HI titres is found in sera from people born in 1903–4. This phenomenon is less clearly present with regard to antibody

against the A/FM/1/47 virus. This may be due to an extreme avidity of this virus for homologous and cross-reative antibody. In the 10 birth-years prior to 1907 a higher frequency of HI antibody titres against the mother strains A/FM/1/47 and A/Hong Kong/117/77 can be found as compared to birth-years after 1907. The degree to which antibody to H1N1 virus is present among birthdate-groups 1896–1907 suggests an era in which the H1N1 virus was epidemic among human populations. By analogy with earlier studies (Masurel, 1969*b*; Masurel & André, 1978) we propose that the birth-years 1896–1907 are linked with the period 1908–18 in which viruses of the subtype A-H1N1 were prevalent. Rekart *et al.* (1982) also explained the higher level of HI antibody to H1N1 strains in the old age-groups by the prevalence of a similar epidemic virus early in the century.

Infection with a particular influenza A virus may produce antibody to an antigenically related virus (Monto & Maassab, 1981). However, the high antibody frequency to the haemagglutinin component of the H1N1 virus among birth-years 1896–1907 cannot be traced to the Hsw1 pandemic of 1918, since all birthdate-groups between 1896 and 1918 show Hsw1 antibody titres $\geqslant 100$ in at least 80% of the sera sampled in 1967 (Masurel, 1969*a*). This extensive cohort does not correspond with the period of 1896–1907 in which a high frequency of H1N1 antibody is present in sera sampled in 1977. There is no reason to assume that these very people, born between 1896 and 1907, would have developed HI antibody as a result of Hsw1 infections in 1918 and afterwards. It is obvious that in people primed for H1N1 virus and born between 1896 and 1907, existing HI antibody may have been boosted by the epidemic subtypes Hsw1, H 0 and H 1, circulating in the era 1918–57.

The epidemiologic situation in the period 1968 to the present shows remarkable resemblance to that of the era 1900–18. It would be unwise to conclude that there is an exact timing in the recycling of influenza A viruses, but by analogy with epidemiologic findings of the period early in the century it seems reasonable to suggest that the emergence in man of an A-Hsw1-like virus can be expected around 1986.

In this and former studies evidence is presented or recurrent epidemics of influenza A-H1N1 viruses in the periods 1908–18, 1947–57, and 1977–now. Moreover, it is suggested that around 1908 the H1N1 virus was co-circulating as an epidemic agent with the H3N2 virus. The mechanisms causing this phenomenon remain to be further investigated.

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