Research

Influenza A virus recycling revisited*

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Current textbooks link influenza pandemics to influenza A virus subtypes H2 (1889–91), H3 (1900), H1 (1918–20), H2 (1957–58) and H3 (1968), a pattern suggesting subtype recycling in humans. Since H1 reappeared in 1977, whatever its origin, some workers feel that H2 is the next pandemic candidate. This report reviews the publications on which the concept of influenza A virus subtype recycling is based and concludes that the data are inconsistent with the purported sequence of events. The three influenza pandemics prior to 1957–58 were linked with subtypes through retrospective studies of sera from the elderly, or through seroarchaeology. The pandemic seroarchaeological model for subtype H1 has been validated by the recent recovery of swine virus RNA fragments from persons who died from influenza in 1918. Application of the model to pre-existing H3 antibody among the elderly links the H3 subtype to the pandemic of 1889–91, not that of 1900 as popularly quoted. Application of the model to pre-existing H2 antibody among the elderly fails to confirm that this subtype caused a pandemic in the late 1800s, a finding which is consistent with age-related excess mortality patterns during the pandemics of 1957 (H2) and 1968 (H3). H2 variants should be included in pandemic planning for a number of reasons, but not because of evidence of recycling. It is not known when the next pandemic will occur or which of the 15 (or more) haemagglutinin subtypes will be involved. Effective global surveillance remains the key to influenza preparedness.

Keywords: disease outbreaks; history; forecasting; influenza A virus, immunology, isolation, and purification; retrospective studies; seroepidemiological studies.

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Introduction

Influenza pandemics and the emergence of new haemagglutinin antigen (HA) subtypes of the influenza A virus have become synonymous in modern day virology. With little or no population immunity to the novel surface antigen(s), the virus spreads rapidly, resulting in increased morbidity and excess mortality (*1*) worldwide. Epidemics and pandemics in the pre-virology era are more difficult to recognize. Historic pandemics are characterized as periods of excess mortality that coincided with global accounts of disease that are epidemiologically and clinically compatible with influenza A. Six pre-virology influenza A pandemics are listed by Potter (*2*) for the last 300 years: 1729–33, 1781–82, 1830–33, 1889–91, 1900 and 1918–20. Vivid descriptions of the devastating effects of influenza-like disease worldwide leave little doubt that the first four were true pandemics, separated from each other by about 50 years. During the 1889–91 pandemic, morbidity and mortality were greater than had been seen in decades, with three successive waves occurring through most parts of the world (*3*). The 1918–20 pandemic, also with three successive waves, was unequalled in recorded history (*4*). The outbreak in 1900 was deemed a pandemic only in retrospect (*5*). Excess mortality was reported in North America (Massachusetts) and in England and Wales during the winter of 1900–01, but historic accounts of influenza epidemics occurring elsewhere in the world are absent. On the basis of the criteria for all other pre-virology pandemics, 1900 would not qualify (*2, 3*).

The pandemics of 1889–91, "1900", and 1918–20 occurred prior to the isolation of the first influenza virus type A from humans in 1933 (*6*), and were linked to subtypes on the basis of retrospective studies of sera from the elderly, or "seroarchaeology" (*5, 7, 8–13*). The concept of influenza A virus subtype recycling arose from these reports. For nearly 30 years, textbooks and reviews have stated that subtype H2 first appeared in about 1889, H3 in about 1900 and H1 in 1918, and that H2 also appeared in 1957 and H3 in 1968. This suggests that the number of subtypes capable of infecting humans is finite. Since H1 reappeared in 1977, whatever its origin, some workers feel that H2 may be the next pandemic candidate. This article critically reviews the data on which the concept of influenza A virus recycling is

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based and the implications of recycling for pandemic planning.

Principles of seroarchaeology

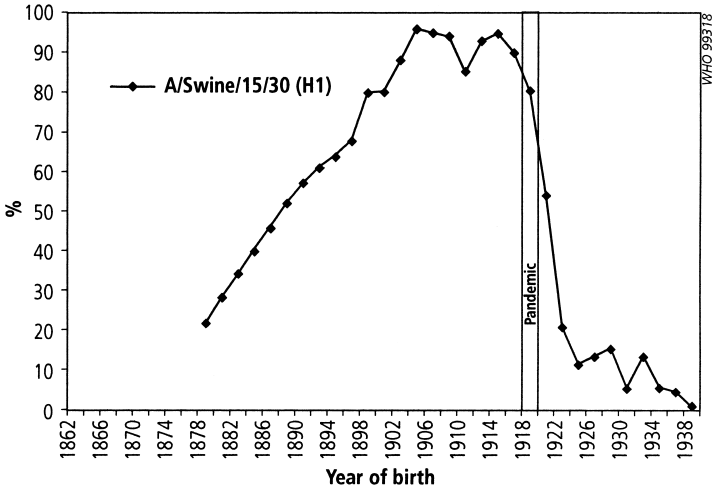
The "doctrine of original antigenic sin" (*14*) states that the first infection with an influenza virus leaves a lifelong immunological imprint, reinforced by later infections with antigenically related strains. That is, the highest antibody titres in an age group appear to reflect the dominant antigens of the virus responsible for the childhood infections of the group. Antibody reinforcement or heterologous anamnestic antibody responses within a subtype depend on the existence of cross-reactive determinants on the original priming haemagglutinin and the secondary stimulating haemagglutinin (*15, 16*). Heterotypic anamnestic antibody responses between H2 and H3 subtypes have been attributed to shared neuraminidase (N2) antigens (*17–19*).

In practice, seroarchaeology is not an exact science. Spurious haemagglutination inhibition (HI) heterotypic responses between subtypes often occur for which there are no obvious immunological explanations (*9, 13, 20, 21*). Age-related HI seroprevalence patterns may be influenced by a number of conditions, including immunological experience with influenza viruses, the presence of non-specific serum inhibitors, the choice and quality of treatment to destroy inhibitors, "avidity" of the influenza virus test strain for antibody, and the minimum titre selected as baseline. In addition, the higher the selected baseline antibody titre, the sharper the seroprevalence peak. Despite these variables, the agreement on some seroarchaeological findings is remarkable.

The 1918–20 seroarchaeological model

Detection of high levels of antibodies to the newly isolated influenza viruses from humans (*7*) and swine (*8*) in persons over 10 years of age in 1935 suggested that the devastating pandemic of 1918–20 was caused by the same or a closely related virus. The birth dates associated with the peak prevalence of swine virus (H1) antibodies did not change in sera collected 12, 17 or 20 years later (*10*). To illustrate the relationship of swine virus HI antibody to the 1918–20 pandemic period, the data reported by Masurel (*22*), which were originally presented by age, have been rearranged and presented in Fig. 1 by year of birth. A sharp increase in the prevalence of H1 (swine) antibody in sera collected in 1967 from the elderly begins with those born in 1924 and reaches a peak of nearly 95% among individuals born in 1914. An H1 antibody prevalence of $\geqslant 80\%$ occurs among persons born between 1888 and 1919. The presence of swine antibodies in persons born in the post-pandemic period 1921–24 may reflect a circulation of the pandemic strain over the subsequent 3-4 years,

Fig. 1. **Distribution of HI antibody titres of 100 or > 100 to A/Swine/15/30 (H1) in human sera collected in 1967 (adapted from Masurel (*22*))**



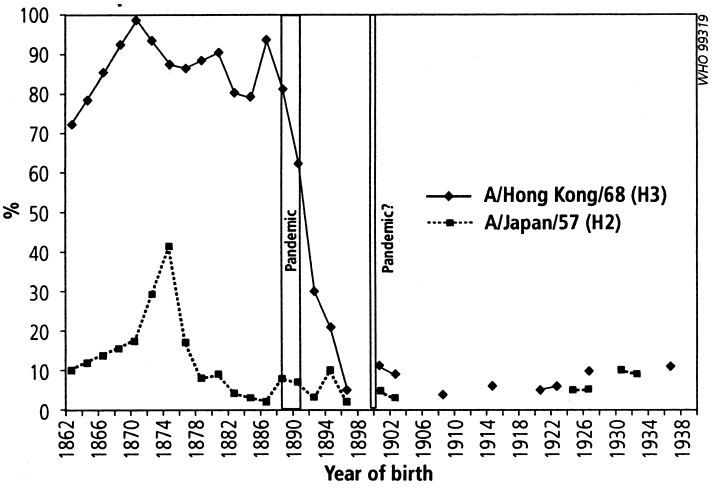
similar to that observed following the pandemics of 1957 (H2) and 1968 (H3) (*3*). In summary, these findings suggest that the swine virus (H1) emerged in 1918–20 and left a lifelong immunological imprint on most persons who were aged $\leqslant 25$ years at the time.

More recently, the swine virus (H1) has been linked to 1918–20 through complete sequencing of the HA gene recovered from persons who died of influenza during the pandemic (*23*). These findings validate the H1 seroarchaeological pattern as a model for other pandemic periods.

Application of the 1918–20 seroarchaeological model to H3 antibodies found in the elderly

The presence of pre-existing H3 antibody among the elderly prior to the H3 pandemic of 1968 was a common observation (*5, 11–13, 21*). H3 antibody prevalence in sera collected in 1956–57, originally analysed by age by Masurel (*24*), have been reformatted and presented here (Fig. 2) according to year of birth, using the same scale as in Fig. 1. The antibody prevalence curve for H3 (Fig. 2) is virtually the same as that for H1 (Fig. 1). H3 antibody prevalence begins to increase sharply among those born about 1894 and peaks at a birth date of about 1887. In addition, as in the H1 seroprevalence pattern (Fig. 1), H3 antibody prevalences of $\geqslant 80\%$ persist over an age range of about 20 years, among those born from about 1868 to 1889. The 1889–91 pandemic bar shown in Fig. 2 — but not the 1900 bar — intersects the steep antibody prevalence curve at virtually the same point as in the 1918–20 model (Fig. 1). Antibody prevalence may vary for those born after 1894, depending on whether the sera were collected in 1957, 1958 or 1967, but the H3 antibody prevalence peak remains unchanged (*12*). As in the

Fig. 2. **Distribution of HI antibody titres for A/Hong Kong/68 (H3) and A2/Japan/57 (H2) in human sera collected in 1956–57 (adapted from Masurel (*12*))**



1918–20 model, the H3-like virus in 1889–91 left a lifelong immunological imprint on ⩾80% of those who were aged ⩽21 years at the time.

Inspection of the overlapping seroprevalence curves in Fig. 1 and Fig. 2 suggests that about half of those born in 1893 were primed to H3 during the pandemic and the remainder were primed to H1, 25 years later.

The H3 seroprevalence data published by Davenport et al (*5*) on human sera collected in 1958 and 1966, and converted to the same scale as in Fig. 1 and Fig. 2, are also consistent with 1889–91 as pandemic years (data not shown). The specificity of the HI results was confirmed by a complex photometric method designed to distinguish the reaction of virus with homologous antibodies from that encountered when virus reacts with heterologous antibodies (*25*).

Seroarchaeological studies of neuraminidase antibodies suggest that the surface antigens of the virus in the late 1800s were H3N8 rather than H3N2, as in 1968–69 (*26, 27*).

Additional evidence linking an H3-like virus with the 1889–91 pandemic is provided by the sharp decrease in expected excess mortality seen among the elderly during the H3 pandemic of 1968–69 (Fig. 3), indicating a high degree of protection among persons born prior to 1893 (*28*). Protection during the H3 epidemic of 1970 was complete; no excess mortality occurred in persons born prior to 1885. Additionally, the influenza attack rate in 1968–69 among persons born prior to 1890 was about one-third the rate among those born after 1899, providing additional confirmation of the powerful protective effect of pre-epidemic H3 antibody (*29*).

If the validated seroarchaeological model is accepted for 1918–20, it must also be accepted that an H3-like virus caused the pandemic of 1889–91, but not of 1900 as is commonly held.

Application of the 1918-1920 seroarchaeological model to H2 antibodies found in the elderly

Unlike the universal findings of pre-existing H3 antibody among the elderly, there was less agreement on the independent origin of pre-existing H2 antibody. In the 1950s and 1960s three laboratories did not find an orientation in H2 antibody towards any particular age group (*30–32*), while three did (*9, 10, 33*). One laboratory in Europe (*9*) and one in the USA (*10*) were the primary sources of H2 seroprevalence data, and their findings differed by nearly eight years.

Masurel (*12*), in the Netherlands, performed HI tests for H2 and H3 antibodies on the set of human sera collected in 1956–57 (Fig. 2). An increase in H2 antibody prevalence begins in persons born about 1876 and drops off sharply among persons born before 1870. Masurel & Marine (*34*) found that 29% of persons born between 1857 and 1877 possessed pre-epidemic H2 antibodies, many at low titres, whereas 90% possessed pre-epidemic H3 antibodies. Persons born between 1878 and 1891 possessed only pre-epidemic H3 antibodies. The H2 seroprevalence curve (Fig. 2) is totally different from the H3 and H1 (Fig. 1) curves.

Davenport et al. (*5*) in the USA reported the highest prevalence of H2 antibodies among persons born in years for which Masurel found little or none. Conversion of the data reported by Davenport et al. to the same scale as in Fig. 2 suggests two peaks in antibody prevalence: a small, sharp peak between 1892 and 1898, and a higher and broader peak for those born between 1878 and 1886 (Fig. 4). Because of the small number of sera (25 or less) tested for each age group, the peak between 1892 and 1898 is accounted for by the presence of HI-positive reactions in three additional sera. The higher 1878–86 peak occurs almost 8 years later than that reported by Masurel (Fig. 2), with low numbers of HI titres persisting among those born in the early 1900s (Fig. 4). Taken at face value, the data from Davenport's laboratory suggest that H2 appeared in the USA about eight years after it appeared in Europe and co-circulated with H3 for nearly 20 years.

Specificity of pre-existing H2 antibodies

The lack of agreement among investigators raises questions about the specificity of the HI test for H2 antibodies. Human serum inhibitors were a particular problem in performing HI tests with early H2 strains, and may have influenced the seroprevalence data. Several treatment methods for the removal of nonspecific serum inhibitors were in use at the time (*35*). The most common serum treatment described in the studies under discussion was receptor-destroying enzyme (RDE). RDE was prepared from *Vibrio*

cholerae filtrates (*36*) by individual laboratories, often with variable results in the absence of universal reference standard materials.

Clarke et al. (*32*) in the United Kingdom found no particular orientation of pre-pandemic H2 titres towards any age group in sera treated with RDE, but noted that the numbers of positive HI titres varied with the batch of RDE used: the weaker the batch, the greater the number of positive sera. They further noted that the serological response to H2 infection during the 1957 pandemic was relatively uniform, regardless of age, as would be expected if the H2 virus had not been experienced previously by those who became ill.

Hilleman et al. (*30*) in the USA also found no orientation in pre-pandemic H2 titres towards any particular age group when untreated sera were tested by HI. Instead, they reported a gradual increase in H2 titres among those born up to about 1900, with little further change among those born earlier. However, upon treatment of the same sera with RDE, all H2 titres were eliminated except for one person born after 1900 and 6 of 72 (<10%) born between 1887 and 1862.

Davenport et al. (*10*) examined pools of pre-1957 human sera in two-year increments using the photometric test (*25*) for homologous H1 (swine) and H2 antibodies. The H1 (swine) photometric test results were remarkably consistent with the HI data (Fig. 1), being uniformly positive over the expected range of birth years. Unlike these confirmatory results for H1 (swine) antibodies, only 6 of 11 pools were sporadically positive for H2 antibodies by the photometric test over the range of birth years from 1901–02 to 1877. Furthermore, only 17% of 60 sera recorded as positive for H2 antibodies by the HI test in Davenport's laboratory were positive with the photometric test for homologous antibodies in a second laboratory (*10*).

Of the 16 sera (80%) found by Masurel to be H2 positive in the HI test, 13 were positive in the photometric test (*10*). About half of the 52 sera positive for H2 by the HI test in Mulder & Masurel's laboratory were positive in the mouse protection test (*9*) at dilutions of 1:2. Thus, H2 neutralizing antibody at its highest peak was present in only approximately 15% of persons born between 1857 and 1877.

Although the number of sera found positive by the photometric or mouse protection tests was considerably less than that found by the HI test, the two former tests confirmed that sera from some of the elderly contained antibodies reactive with the H2 antigen. Masurel & Marine's data (*34*) also suggest that the influenza experience of the 1857–77 birth-date cohort was different from that of the 1878–91 cohort in terms of its independent response to H2 antigens. The absence of a correlation between H2 and H3 antibody titres (*21*) and the inability of H3 virus absorption to completely remove H2 antibodies in sera from the elderly are cited as further evidence of specificity (*13*). However, interpretation of findings from these two studies is complicated by

Fig. 3. **Excess mortality by age, from all causes during two influenza epidemics (adapted from Housworth and Spoon (*28*))**

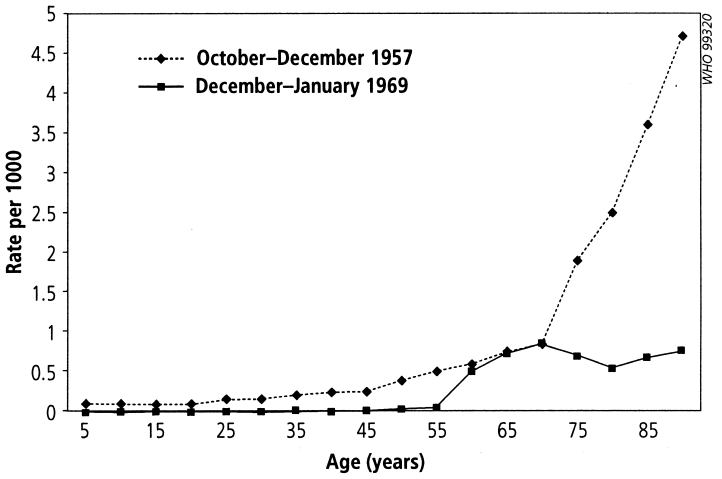
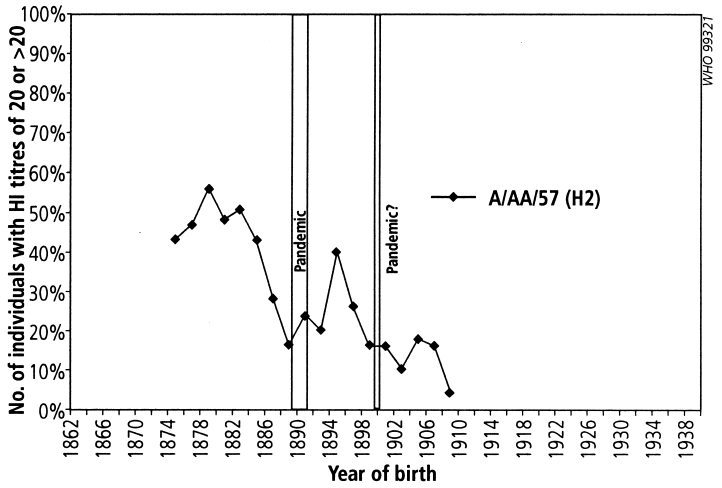


Fig. 4. **Distribution of HI antibody titres for A/Ann Arbor/57 (H2) in human sera collected in 1957 (adapted from Davenport (*5*))**



the likelihood of subjects having been infected at sometime during the H2 era of 1957–67.

Evidence against specificity or, at least, an abundance of H2 antibodies among the elderly is the absence of any observed protective effect among persons who were aged ⩾ 80 years during the 1957–58 pandemic (Fig. 3). This is in stark contrast to the strong protective effect observed for pre-pandemic H3 antibodies in 1968–69 (*28, 29*) and H1 antibodies in 1977 (*3*).

Discussion

Application of the validated H1 seroarchaeological model to pre-existing H3 antibodies found in the elderly and the excess mortality patterns of 1968–70 confirms that an H3-like virus caused the pandemic of 1889–91, but not of 1900. As would be expected the virus (H3) with the highest peak antibody prevalence (>90%) in the elderly resulted from a

pandemic (1889–91), not an epidemic (1900). It also stands to reason that the virus (H2) with the lowest seroprevalence (15–29%) was an unlikely cause of the most severe influenza event of the late nineteenth century (1889–91).

What then were the reasons for linking H2 to 1889–91 and H3 to 1900? First, the reports of pre-existing H2 antibody in the elderly predated the H3 findings by 10 years. Because there was no knowledge in 1957–58 of H3 outbreaks yet to come, H2 antibodies were attributed to the 1889–91 pandemic, the only accepted pandemic around that period (*9*). Thus, when pre-existing H3 antibody was recognized in 1968, the 1889–91 pandemic slot was already taken.

The second reason for linking H3 to 1900 was the assumed time lag in acquiring antibody after birth. This "1–5 year lag rule", which was derived from H1 interpandemic clinical experience (*37*), pushed the pandemic forward from the year of birth of the last cohort, i.e. to about 1900. Whereas the lag rule may have applied at a time of diminished influenza activity, there is no reason to assume it holds for a pandemic. Even during interpandemic periods, antibody may be found in about half of the children within the first year of exposure to influenza (*38*). Moreover, the lag rule does not allow for continued circulation of the pandemic strain before major antigenic variants appear 3-4 years later (*3*).

Not all investigators at the time concurred with the prevailing thought on the dates for the initial appearance of H2 and H3 subtypes. Marine et al. (*11, 13*) and Schoenbaum et al. (*29*) favoured 1889–91 for H3. Fukumi (*21*) described the "absence of a close correspondence" of his data with the hypothesis that H2 emerged in 1889–91 and H3 in 1900. Masurel & Marine also stated that, on strict mathematical grounds, 1889–91 must be favoured as the time of emergence of the H3 virus (*34*).

The origin of pre-existing low levels of H2 antibody among the elderly remains an open question. Marine et al. proposed that minor haemagglutinin antigens shared between H3 and H2 may explain the prevalence of H2 antibodies in the pre-1957 epidemic sera from the elderly (*13*). Justification for an antigenic relation between the two was the almost universal anamnestic H2 antibody response following immunization with H3 virus. This theory lost favour when it was reported that the low-level cross-reactions between H2 and H3 antigens in the HI test were due to shared neuraminidase (N2) antigens (*17*). H2/H3 heterotypic anamnestic responses were thought to be due to B-cell orientation through the shared N2 antigens (*18*). No evidence was found of a prominent relationship between H2 and H3 antigens (*19*). Still unexplained, however, is the occurrence of robust heterotypic anamnestic antibody responses to contemporary H2 antigens in humans after immunization with the equine virus (H3N8), where there is no neuraminidase in common (*39*). Also unexplained are the animal experiments demonstrating reciprocal, but asymmetric, heterotypic anamnestic antibody responses between H2 and H3 recombinants with discordant neuraminidases (*40*).

On purely epidemiological grounds, and given the low prevalence of H2 antibodies among the elderly, stimulation of H2 antibody by the H3 virus (by whatever immunological mechanism) cannot be totally dismissed. Assumptions about H2/H3 antigenic relationships in the nineteenth century have been based on viruses that were isolated nearly 80 years later. The hypothesis of Marine et al. (*13*), coupled with incomplete removal of nonspecific serum inhibitors, remains as a possible explanation for the widely differing H2 findings in different laboratories (*5, 9, 30–33*), including the inability to reproduce HI results (*27*), and the remarkable parallel between H2 and H3 seroprevalence presented by Davenport et al. (*5*).

Another possible explanation is that H2 antibodies may have been produced by infection with an as yet unidentified but antigenically related virus that circulated prior to 1889–91. For example, low levels of antibodies to the equine-2 virus were found in the elderly shortly after the virus was isolated from horses in 1963. To some workers, these findings suggested that the equine-2 virus had circulated among humans before 1900 (*41, 42*). Only after the pandemic of 1968–69 was it recognized that the newly emerged H3 virus and the equine-2 virus (currently classified as H3) were antigenically related. Thus, antibodies to equine-2 (H3N8) in the elderly were concluded to be cross-reactions, representing only a tip of the seroprevalence "iceberg" from the H3 pandemic of 1889–91 (*5, 13*).

Finally, it is also possible that the low-level titres of pre-existing H2 antibodies in the elderly may correspond to the end of a pandemic era, rather than the beginning. The H2 seroprevalence pattern in the Netherlands closely resembles an epidemic during an interpandemic period (*12, 20, 21*). The small H2 seroprevalence peak found by Mulder & Masurel (*9*) in the Netherlands (but not found by Clarke et al. (*32*) in the United Kingdom) coincides with the 1875 epidemic in continental Europe (*43*). The virus antigens that stimulated H2 antibodies in the latter half of the 1800s may have exhibited considerable drift from the parent H2 variant, which may have emerged as early as the pandemic of 1830–33. Minor epidemics occurring at the end of a long H2-like era may also explain the absence of protection among the elderly in the 1957 pandemic and subsequent H2 epidemics. Persons initially infected with a possible H2-like virus in the pandemic period of 1830–33, or subsequent regional epidemics in 1847–48 or 1850–58, were unlikely to have been alive in 1957.

But all this is speculation. There is no simple explanation for pre-existing H2 antibodies in the elderly. The independent origin or the significance of pre-existing H2 antibodies among persons born in the late 1800s in Europe, North America and Japan is uncertain. The only certainty is that, in the second half of the nineteenth century, an H2-like virus was

not associated with an influenza event comparable to that of H3 in 1889–91 or H1 in 1918–20.

Another means of testing the virus recycling hypotheses is through the protective effect of pre-existing antibody, as observed in 1968–70 for H3 (Fig. 3) and in 1977 for H1. The steep, uninterrupted increase in excess mortality with age in 1892 (*44*) (Fig. 5) suggests that the population at that time had no prior experience with H3, at least as far back as about 1800. The excess mortality rate for 1957–58 also provides no evidence of protection of any specific age group (Fig. 3). The well-known "W" excess mortality curve for 1918 is somewhat more difficult to interpret (Fig. 5). Excess mortality was elevated for all ages, with the rates being highest for ages below 2 years, young adults and those aged $\geqslant 80$ years. These data are more consistent with an extraordinary vulnerability of young adults (*4*) than with protection of older adults through pre-existing H1 antibody.

Thus, age-related excess mortality patterns alone suggest that H3 has circulated twice in the past 200 years, from 1889–91 to some undetermined time prior to 1918, and from 1968 to the present; H2 has circulated once in the past 130 years, from 1957 to 1967; and H1 has circulated twice in the past 170 years, from 1918 to 1956, and from 1977 to the present. However, evidence suggests that the 1977 H1 virus may not have been a natural event but the reintroduction of the virus to humans from a frozen source (*45, 46*).

Years for which there is strong evidence of influenza pandemics, with subtype etiology, are listed in Table 1.

Fig. 5. **Deaths from pneumonia and influenza in USA in three influenza pandemics (adapted from Dauer & Serfling (*44*); data for 1892 for Massachusetts only)**

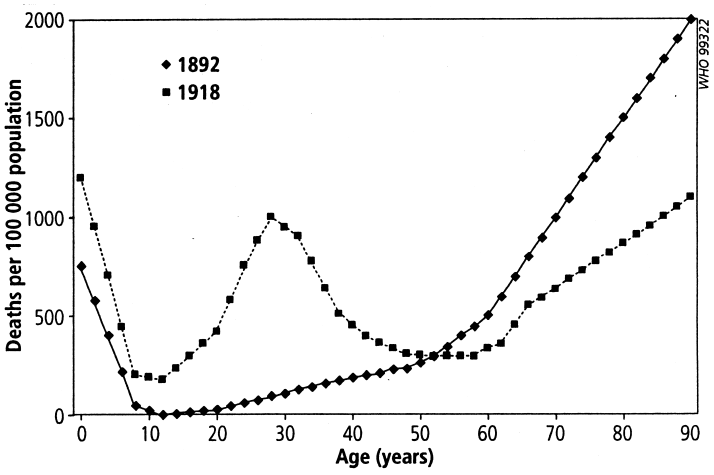


Table 1. **Historically recognized pandemics attributed to influenza[a]**

Years of occurrence	HA subtype	No. of years since last pandemic
1729–33	—	?
1781–82	—	49
1830–33	—	48
1889–91	H3[b]	55
1918–20	H1	27
1957–58	H2	37
1968–69	H3	10
1977[c]	H1	9

[a] Modified from Potter (*2*).

[b] Determined through retrospective serological studies (seroarchaeology).

[c] No excess mortality.

Conclusions

This review of the evidence for influenza A virus recycling supports claims for recycling of the H3 subtype, which first appeared in the pandemic of 1889–91 and nearly 80 years later in the pandemic of 1968–69. No firm evidence was found to link the H2 subtype to a pandemic other than that of 1957–58. Thus, there is no firm basis for predicting the sequential reintroduction of H2 on grounds of recycling. However, the inclusion of H2 as one of the potential candidates for pandemic planning would be prudent. H2 variants continue to circulate widely among aquatic birds (*47*). H2 is also one of only three of the 15 influenza A virus subtypes known to have caused a pandemic, and the possibility remains that the number of subtypes transmissible to humans may be restricted (*48*). On the other hand, reintroduction of an H2 variant into the human population within the next few years would not be expected to produce a pandemic of disastrous proportions. Virtually everyone born before 1967 has had some immunological experience with H2 antigens.

Pandemic planning must be open to any possibility. It is not known when the next influenza pandemic will occur, or which of the 15 (or more) haemagglutinin subtypes will be involved. Effective global surveillance remains the key to influenza preparedness. ■

Acknowledgements

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Résumé

Le point sur la réémergence cyclique du virus grippal A

Les pandémies grippales de 1889-1891, 1900 et 1918-1920, survenues avant l'isolement du premier virus grippal de type A chez l'homme en 1933, ont été associées à des sous-types sur la base d'études rétrospectives du sérum de personnes âgées, ce qu'on appelle l' «archéosérologie». La notion de réémergence cyclique des sous-types du virus grippal A provient de ces observations. Pendant près de 30 ans, les manuels et mises au point bibliographiques ont indiqué que le sous-type H2 est apparu pour la première fois vers 1889, H3 vers 1900, H1 en 1918, H2 et H3 réapparaissant respectivement en 1957 et 1968. Comme H1 est réapparu en 1977, quelle qu'en soit l'origine, certains chercheurs pensent que la prochaine pandémie pourrait être due à H2. Le présent article examine de manière critique les données sur lesquelles est basée la notion de réémergence cyclique du virus grippal A et ce que cela implique pour la prévision des pandémies.

Les résultats des tests d'inhibition de l'hémagglutination sur le sérum recueilli chez des personnes quel que soit leur âge montrent que le virus porcin (H1) apparu en 1918-1920 a laissé une empreinte immunologique définitive chez la plupart des personnes âgées à l'époque de 25 ans au plus. Le profil archéosérologique de H1 a été validé comme modèle pour d'autres périodes de pandémie par les récentes observations du gène HA du virus porcin chez des personnes décédées de la grippe au cours de la pandémie 1918-1920. L'application du modèle aux courbes de séroprévalence obtenues à partir des résultats de l'inhibition de l'hémagglutination sur les sérums recueillis avant 1968 associe la pandémie de 1889-1891 à un virus de type H3 et non de type H2 comme on le croyait généralement. Comme pour le virus porcin H1, le virus H3 en 1889-1891 a laissé une empreinte immunologique définitive chez la plupart des sujets âgés à l'époque de 21 ans au plus. Un autre indice d'un lien entre un virus de type H3 et la pandémie de 1889-1891 est la surmortalité bien inférieure à la surmortalité attendue chez les personnes âgées au cours de la pandémie de 1968-1969 due à H3, ce qui révèle une forte protection des personnes nées avant 1893.

On ne dispose pas d'un ensemble de données analogues concernant l'origine indépendante de l'anticorps anti-H2 préexistant chez les personnes âgées. Trois des six laboratoires n'ont constaté aucun lien entre l'anticorps anti-H2 et une classe d'âge déterminée. Un laboratoire en Europe et un aux Etats-Unis sont à l'origine des données de séroprévalence concernant H2; leurs constatations diffèrent de près de 8 ans. L'origine indépendante ou la signification des anticorps anti–H2 préexistants chez les personnes nées à la fin du siècle dernier est incertaine. Il apparaît toutefois clairement qu'au cours de la deuxième moitié du XIX^{e} siècle, un virus de type H2 n'était pas associé à un phénomène grippal comparable à celui de H3 en 1889-1891 ou H1 en 1918-1920.

La seule surmortalité liée à l'âge révèle que H3 a circulé deux fois au cours des 200 dernières années, de 1889-1891 jusqu'à une date indéterminée antérieure à 1918, et de 1968 jusqu'à l'époque actuelle; H2 une fois au cours des 130 dernières années, de 1957 à 1967; et H1 deux fois au cours des 170 dernières années, de 1918 à 1956 et de 1977 jusqu'à la période actuelle. Il se peut toutefois que la réémergence de 1977 n'ait pas été naturelle, mais qu'il se soit agi d'une réintroduction du virus chez l'homme à partir d'une source congelée.

Si rien ne permet de prévoir la réémergence de H2 sur une base cyclique, il paraît prudent de considérer H2 comme l'un des agents potentiels aux fins de la prévision des pandémies. Les variants de H2 continuent à circuler largement chez les oiseaux aquatiques et il se pourrait que le nombre de sous-types transmissibles à l'homme soit limité. On ignore quand surviendra la prochaine pandémie et lequel des 15 sous-types d'hémagglutinine (ou davantage) sera concerné. Une surveillance mondiale efficace reste l'élément clé des efforts de préparation face à la grippe.

Resumen

Nuevas consideraciones sobre la recirculación del virus gripal tipo A

Las pandemias de gripe de 1889-1891, 1900 y 1918-1920 se produjeron antes del aislamiento del primer virus gripal tipo A en el hombre, en 1933, y se han relacionado posteriormente con diversos subtipos mediante estudios retrospectivos del suero de las personas ancianas entonces afectadas, en lo que vendría a ser una suerte de «seroarqueología». El concepto de «recirculación» de los subtipos del virus A procede de esos estudios. Durante casi 30 años se ha señalado en libros de texto y artículos de revisión que el subtipo H2 apareció por primera vez aproximadamente en 1889, H3 aproximadamente en 1990 y H1 en 1918, y que H2 reapareció en 1957, y H3 en 1968. Puesto que el subtipo H1 reapareció en 1977, cualquiera que fuese su origen, hay quienes creen que H2 es el mejor situado para provocar la próxima pandemia. En el presente artículo se revisan críticamente los datos que fundamentan el concepto de recirculación del virus gripal y su repercusión en la previsión de las pandemias.

Los resultados de las pruebas de inhibición de la hemaglutinación (IH) llevadas a cabo con sueros de personas de todas las edades muestran que el virus porcino (H1) apareció en 1918-1920 y dejó una huella inmunológica de por vida en la mayoría de las personas que tenían entonces $\leqslant$ 25 años. Las características seroarqueológicas del virus H1 han sido validadas como modelo para otros periodos de pandemias por el reciente hallazgo del gen HA del virus porcino en personas que fallecieron a causa de la gripe durante la pandemia de 1918-1920. La aplicación del modelo a las curvas de

seroprevalencia elaboradas a partir de los resultados de las pruebas de IH en sueros obtenidos antes de 1968 relacionan la pandemia de 1889-1891 con un virus de tipo H3, no H2, como se ha venido diciendo. Al igual que el virus porcino (H1), el virus H3 de 1889-1891 dejó una huella inmunológica de por vida en la mayoría de las personas que tenían por entonces $\leqslant$ 21 años. Un dato adicional para relacionar la pandemia de 1889-1891 con un virus H3 fue la rápida disminución del exceso de mortalidad previsto entre las personas de edad durante la pandemia de 1968-1969 por H3, observación indicativa de un alto grado de protección entre las personas nacidas antes de 1893.

No hay pruebas similares del origen independiente de anticuerpos preexistentes contra H2 en personas de edad avanzada. Tres de seis laboratorios no hallaron ninguna tendencia de los títulos de anticuerpos anti-H2 a asociarse preferentemente a un determinado grupo de edad. Un laboratorio de Europa y otro de los Estados Unidos fueron las fuentes principales de datos sobre la seroprevalencia de H2; sus resultados difirieron en casi 8 años. Es difícil determinar el origen independiente o la importancia de los títulos preexistentes de anticuerpos anti-H2 entre las personas nacidas en los últimos años del pasado siglo. Sin embargo, está claro que, en la segunda mitad del siglo XIX, ningún virus de tipo H2 se asoció a una pandemia de gripe en medida comparable a la asociación de H3 a la de 1889-1891, o de H1 a la de 1918-1920.

De la estricta consideración de la distribución del exceso de mortalidad por edades se infiere que el virus H3 ha circulado dos veces en los últimos 200 años, entre 1889-1891 y un momento indeterminado antes de 1918, y entre 1968 y el presente; H2 lo ha hecho una vez en los últimos 130 años, entre 1957 y 1967; y H1 lo ha hecho en dos ocasiones en los últimos 170 años, durante el periodo 1918-1956, y entre 1977 y nuestros días. Sin embargo, puede que la aparición de 1977 no fuese un fenómeno natural, sino más bien el resultado de la reintroducción del virus en la especie humana a partir de una forma congelada del mismo.

Aunque no hay ninguna razón para predecir la reintroducción secuencial del virus H2 según la hipótesis de la recirculación, sería prudente incluirlo entre los candidatos potenciales a la hora de prever futuras pandemias. Variantes de H2 siguen circulando profusamente entre aves acuáticas, y es posible que el número de subtipos que puedan transmitirse al hombre sea limitado. No sabemos cuál de los 15 (o más) subtipos definidos por la hemaglutinina será el responsable de la próxima pandemia. Una vigilancia mundial eficaz sigue siendo la clave para estar preparados contra la gripe.

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