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The Little Ice Age and the emergence of influenza A ☆

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SUMMARY

Bayesian phylogenetic analysis of the haemagglutinin and neuraminidase proteins of influenza A virus demonstrates that their respective most recent common ancestors (MRCAs) both existed approximately 1000 years ago. Most of the bifurcations within the haemagglutinin and neuraminidase phylogenetic trees occurred within a time window that can be dated with 95% confidence to the years 1411–1932 of the Common Era (AD) for haemagglutinin and 1366–1874 AD for neuraminidase. This subtype diversification episode is temporally congruent with the "Little Ice Age", a period of climatic cooling over the northern hemisphere. Furthermore, Bayesian probability mean ages for the bifurcation points within the haemagglutinin tree indicate two bursts of diversification from 1672 to 1715 AD and from 1825 to 1868 AD. The first of these follows in the wake of the coldest epoch in the Little Ice Age, and the second overlaps a later cooling episode. Since climate change is known to affect migration patterns in the reservoir host of influenza A, the aquatic wildfowl, and allopatric cladogenesis following population disruption is well supported in the evolutionary literature, a mechanism is proposed linking the Little Ice Age to influenza subtype diversification via ecological disruption of the wildfowl annual cycle. The suggestion that past climate change has impacted on influenza evolution implies that current global warming may cause a further burst of influenza subtype diversification with possible serious epidemiological consequences becoming apparent in the 22nd and 23rd centuries.

Introduction

Influenza A is the most medically important member of the family *Orthomyxoviridae*. A single-(negative)-stranded RNA virus with its reservoir host in aquatic wildfowl, influenza A has been the cause of three pandemic outbreaks in humans in the 20th century and one in the 21st century, with the total mortality running into the millions. The severity of pandemic influenza is dependent on the immunological naïveté of human hosts to the *antigenic shift* produced by the arrival of a virus of a novel subtype. After each of the three pandemics of the 20th century, the virus concerned returned as a seasonal form, displaying *antigenic drift* between each annual outbreak. After the second and third pandemics, the descendent viruses of the previous pandemic disappeared from the human population. Thus viruses of subtype H1N1 ("Spanish Flu") were replaced by H2N2 ("Asian Flu") after 1957, which were themselves replaced by H3N2 ("Hong Kong Flu") in 1968. This pattern was broken in 1977 when H1N1 ("Russian Flu") returned in a widespread sub-pandemic outbreak. Since then both H1N1 and H3N2 subtypes have co-circulated seasonally with varying distribution and clinical intensity. The first pandemic of the 21st century was caused in 2009 by the appearance of a further H1N1 strain of porcine origin ("Swine Flu"). At the time of writing it is unclear if the descendents of this new strain will displace either or both of the two current seasonal subtypes.

The subtype nomenclature is derived from the immunological serotypes of haemagglutinin and neuraminidase proteins, to which the major part of a host immune response to influenza A is directed. There are 16 serotypes of haemagglutinin and nine of neuraminidase. Although only haemagglutinin serotypes H1, H2 and H3 have been involved in pandemic and seasonal influenza in humans, serotypes H5, H7 and H9 can cause rare infections of extreme severity, usually by direct transfer from an avian source without subsequent human-to-human transmission. The H1N1 pandemic of 2009 was the first time that porcine H1 haemagglutinin, previously only found in humans through rare direct transmission from pigs, acquired the capacity to spread between humans. This change in host specificity was a result of a reassortment event occurring in a mixed infection between Eurasian and North American swine influenza strains [1]. The genetic structure of influenza virus, with eight non-recombining genome fragments, makes mixed infection reassortment the main source of novel subtypes which would present antigenic shift on entering a human population. This raises the prospect that mixed infections of avian influenza and human seasonal influenza may create a reassorted virus

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with pandemic potential containing one of the virulent H5, H7 and H9 haemagglutinins. Such a scenario is therefore regarded as a major global public health risk for the coming decades. Reassortment also means that any individual influenza virus is the product of eight separate evolutionary lineages. It is therefore not appropriate to refer to the ancestry of, say, Spanish Flu, but rather only to the ancestries of its eight constituent genome fragments.

This paper describes the evolutionary history of two of those eight fragments, those coding for haemagglutinin and neuraminidase, as elucidated using the latest Bayesian phylogenetic methods. The timescale of that history is then compared with climate change events over the last millennium and a correspondence is identified with the major global cooling phenomenon known as the "Little Ice Age". Known ecological and evolutionary mechanisms are then evoked to postulate how an event as macroscopic as climate change can have effects at the molecular level on a virus within aquatic wildfowl. The implications of the hypothesis for future pandemics in humans are then discussed.

Methods

Influenza haemagglutinin and neuraminidase proteins were downloaded from the NCBI Influenza Resource (http://www.ncbi.nlm.nih.gov/genomes/FLU/). Only avian influenza proteins were selected as this is the natural reservoir host in which all serotypes of haemagglutinin and neuraminidase are found. It is therefore reasonable to expect that all the important evolutionary events in the history of the two proteins should take place in avian influenza. Structure-assisted protein sequence alignment was performed in MOE v.2008.10 (http://www.chemcomp.com). Bayesian phylogenetic analysis was carried out in BEAST v.1.4.8 [2,3] (http://beast.bio.ed.ac.uk). A fuller description of the methods is given elsewhere [4]. Climate data was taken from Moberg et al. [5].

The hypothesis

The hypothesis is built on four foundations: three empirical and one theoretical.

Empirical:

(1) Bayesian phylogenetic analysis provides a timescale for haemagglutinin and neuraminidase subtype diversification from their respective most recent common ancestors (MRCAs).
(2) Climate change data indicate contemporaneous global cooling events.
(3) Ecological data indicate that climate change has an important impact on the migration patterns of the aquatic wildfowl, influenza's reservoir host.

Theoretical: evolutionary theory has a well developed and widely accepted mechanism, that of *allopatric cladogenesis*, capable of cementing the three empirical foundations.

Haemagglutinin and neuraminidase evolution

Bayesian phylogenetic analysis on avian influenza haemagglutinin proteins was previously carried out by Gatherer [4]. For the present paper, this procedure was repeated on avian influenza neuraminidase proteins. The resulting phylogenetic trees are shown in Figs. 1 and 2. Tables 1 and 2 show the dates of the nodes in calendar years of the Common Era (AD) and give their Bayesian upper and lower 95% confidence limits.

Both haemagglutinin (Table 1) and neuraminidase (Table 2) have MRCAs around 1000 years ago. It is therefore possible that these ancestral proteins were present in the same strain of virus. However, the independent nature of the evolutionary histories of influenza genome fragments, caused by reassortment and the absence of recombination, does not require this to be the case. Although approximately contemporary, it is entirely possible that the ancestral haemagglutinin and neuraminidase proteins were component parts of different influenza viruses. It should also not be inferred that there was only a single serotype of either of the

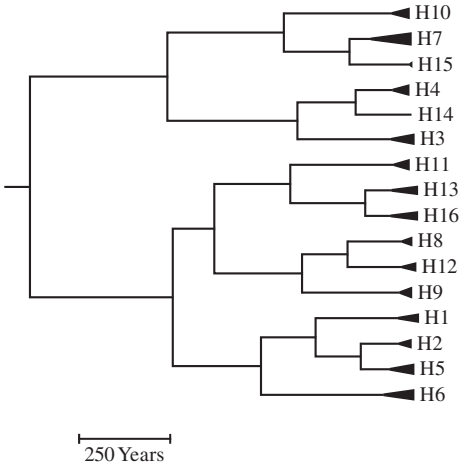

Fig. 1. Phylogenetic tree for haemagglutinin proteins of avian influenza. The dense terminal branches are collapsed into triangles. Serotypes are numbered H1–H16.

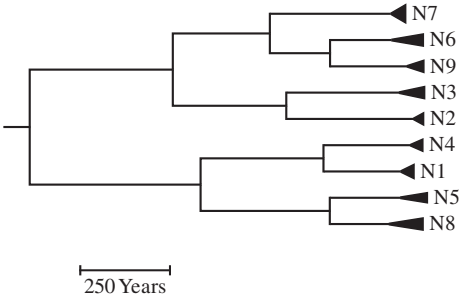

Fig. 2. Phylogenetic tree for neuraminindase proteins. The dense terminal branches are collapsed into triangles. Serotypes are numbered N1–N9.

Table 1
Dates in the Common Era (AD) for the nodes on the Bayesian phylogenetic tree of avian influenza haemagglutinin proteins. The mean represents the centre of the Bayesian probability distribution for the age of that node and the upper and lower limits of the 95% confidence range are given.

Node	Mean	Upper	Lower
Root (MRCA)	1056	517	1497
Top half	1389	996	1781
Lower half	1402	1090	1657
H8/9/12 & H11/13/16	1503	1196	1730
H6 & H1/2/5	1616	1341	1786
H10 & H7/15	1672	1411	1827
H11 & H13/16	1687	1467	1861
H3 & H4/14	1704	1489	1890
H9 & H8/12	1715	1521	1883
H1 & H2/5	1748	1587	1869
H8 & H12	1825	1705	1921
H7 & H15	1831	1760	1885
H4 & H14	1846	1748	1921
H2 & H5	1858	1779	1919
H13 & H16	1868	1786	1932