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VIRAL EVOLUTION

Past, present and future of influenza viruses

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> “the modelling of sequencing data has the power to reconstruct the past and predict the future of influenza virus evolution”

Influenza viruses are genetically diverse owing to high mutation rates, frequent reassortment among genomic segments and their tendency to jump between hosts. Three studies describe new modelling approaches to analyse and predict influenza virus evolution and also shed light on the origin and spread of currently circulating viruses.

Influenza A virus has a segmented genome that encodes the two surface proteins haemagglutinin (HA) and neuraminidase (NA) and several internal proteins. HA and NA show particularly high diversity, as they are easily recognized by the host immune system and are therefore under constant selective pressure to evolve. In birds, the internal proteins show comparatively little diversity — a finding that has been difficult to explain so far. Worobey *et al.* now report a host-specific local clock model, in which evolutionary speed differs depending on the host species. The analysis of more than 80,000 full-length influenza virus genomes from humans, birds, horses and pigs showed that all viruses share a common ancestor that branched off into the equine H7N7 subtype and an avian strain from which almost all current avian, human and pig strains have evolved. Interestingly, between the years 1872 and 1873 in North America, an outbreak of severe influenza occurred in horses, which was followed by influenza virus infections in domestic birds. The model suggests that the common ancestor that evolved around this time provided most of the internal genes that are found in current avian influenza viruses, whereas pre-existing HA and NA diversity was retained, which suggests that a global selective sweep replaced pre-existing, less fit internal genes.

The spread of influenza is traditionally tracked by epidemiological data; however, this approach gives little insight into the different viral variants that are circulating. Lemey *et al.* combined empirical data on human movement patterns with viral genetic data to reconstruct the spread of the human endemic subtype H3N2. The authors developed a model based on H3N2 HA sequence data and flight data from 4,092 airports, which revealed that movement of viral lineages was 15 times higher for the connection that had the highest passenger flow compared with the connection that had the lowest passenger flow. Furthermore, this phylogeographic approach confirmed that mainland China and Southeast Asia are a source of seasonal variants.

The seasonal variation of circulating influenza viruses is a challenge for the development of vaccines. Currently, vaccine strains are selected on the basis of pre-existing immunity in humans. Luksza and Lässig report a new model that can predict the spread of viral clades from one season to the next on the basis of the fitness and frequency of circulating clades. The authors analysed 3,944 HA sequences and determined the fitness effects of epitope mutations, which affect host recognition, and non-epitope mutations, which affect HA stability and function. This fitness model led to a new method for the systematic prediction of vaccine strains.

These three studies show that the modelling of sequencing data has the power to reconstruct the past and predict the future of influenza virus evolution, which should aid surveillance measures and the prevention of epidemics.

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ORIGINAL RESEARCH PAPERS Worobey, M., Han, G.-Z. & Rambaut, A. A synchronized global sweep of the internal genes of modern avian influenza virus. *Nature* http://dx.doi.org/10.1038/nature13016 (2014) | Lemey, P. *et al.* Unifying viral genetics and human transportation data to predict the global transmission dynamics of human influenza H3N2. *PLoS Pathog.* **10**, e1003932 (2014) | Luksza, M. & Lässig, M. A predictive fitness model for influenza. *Nature* http://dx.doi.org/10.1038/nature13087 (2014)