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# Clonal interference in the evolution of influenza.

Strelkowa N, Lässig M.
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Evidence for the role of clonal interference in driving recurrent selective sweeps in a seasonal influenza virus.

Human influenza viruses are known to undergo antigenic drift, a process by which structural changes to the virus's hemagglutinin surface protein result in escape from humoral immunity. Along with this rapid antigenic evolution, the seasonal flu virus called A/H3N2 shows a pattern of genetic evolution with rapid lineage turnover and low levels of genetic diversity. This pattern of genetic evolution is best visualized through the hemagglutinin protein's 'ladderlike' phylogeny. Over the past decade, many epidemiological models have sought to reproduce this pattern of influenza's genetic evolution under a variety of different assumptions about the tempo and mode of viral evolution. In this paper, the authors additionally develop and apply statistics based on frequencies of single nucleotide polymorphisms ('frequency propagators') to effectively argue that this virus's evolutionary dynamics result from a process of clonal interference, by which viral strains with beneficial mutations evolve frequently enough to compete with one another. The implications of these findings are highly interesting: as elaborated on by the authors, evolution by clonal interference through selection on epitope as well as on non-epitope sites would lead to a hemagglutinin that is particularly brittle and would necessitate us to consider influenza evolution in the context of factors other than antigenicity alone.

**Disclosures**
None declared

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## Abstract:

ABSTRACT

The seasonal influenza A virus undergoes rapid evolution to escape human immune response. Adaptive changes occur primarily in antigenic epitopes, the antibody-binding domains of the viral hemagglutinin. This process involves recurrent selective sweeps, in which clusters of simultaneous nucleotide fixations in the hemagglutinin coding sequence are observed about every 4 years. Here, we show that influenza A (H3N2) evolves by strong clonal interference. This mode of evolution is a red queen race between viral strains with different beneficial... more »
mutations. Clonal interference explains and quantifies the observed sweep pattern: we find an average of at least one strongly beneficial amino acid substitution per year, and a given selective sweep has three to four driving mutations on average. The inference of selection and clonal interference is based on frequency time series of single-nucleotide polymorphisms, which are obtained from a sample of influenza genome sequences over 39 years. Our results imply that mode and speed of influenza evolution are governed not only by positive selection within, but also by background selection outside antigenic epitopes: immune adaptation and conservation of other viral functions interfere with each other. Hence, adapting viral proteins are predicted to be particularly brittle. We conclude that a quantitative understanding of influenza's evolutionary and epidemiological dynamics must be based on all genomic domains and functions coupled by clonal interference.

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