Inst. of Evolutionary Biology
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January 9, 2012

Dear Editor,

Please find, attached, our manuscript entitled "Canalization of the evolutionary trajectory of the human influenza virus," which we would be grateful for your consideration for publication in *Proceedings of the Royal Society B*. We believe that *Proc Roy Soc B* is an appropriate venue for this work, as it addresses long-standing controversies about the evolution and the epidemiology of the human influenza virus, with important implications for public health.

Despite recent advances in the new field of phylodynamics, our understanding of the coupled dynamics of the seasonal human influenza virus, including *both* evolution and population dynamics, remains limited. Rather than diversification through time, influenza shows serial replacement of antigenic types. This pattern has remained puzzling from an epidemiological standpoint, and previous work has sought explanations in mechanisms such as short-lived strain-transcending immunity and limited antigenic repertoires. No previous model, has incorporated, however, the recent empirical description of antigenic space (Smith et al. 2004 *Science*, Russell et al. 2008 *Science*). Here, we find that doing so allows the development of a simple geometric model of antigenic space that simultaneously explains observed genetic and antigenic data. We harness a large-scale individual-based simulation to show that evolution under such a model appears *canalized*; rather than moving in multiple antigenic directions, the virus population is shunted down a narrow path, constrained by the actions of natural selection. Thus, the myopic perspective of natural selection sacrifices long-term gains in antigenic diversification in exchange for short-term advantages.

This work is the first to simultaneously explain detailed epidemiological, genealogical, antigenic and spatial patterns in the human influenza virus. In uniting data sources, we provide the foundations for a *predictive* modeling effort. We show that on shorter timescales of 1–2 years, the evolution of the influenza virus appears exceptionally repeatable. Building on this approach, it should be possible to better assess the likelihood that an observed antigenic variant will take-off, and warrant a matching vaccine update. Furthermore, our novel computational approach allows us to directly track the genealogical history of the simulated epidemic, rather than relying on the substantially slower and less accurate phylogenetic methods previously in widespread use. We are confident that the results and methodology described in the manuscript will shape future study of the evolution and epidemiology of influenza, but also impact the general study of the phylodynamics of evolving human pathogens.

Sincerely,

Trevor Bedford