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Researchers Model Evolution of Influenza Virus

As health agencies around the world race to pinpoint the cause of severe acute respiratory syndrome (SARS), researchers are reporting success in developing a new theoretical model that shows how the pressure exerted by the immune response of an infected population can drive evolution of influenza virus.

The model does not aim to predict the emergence of new strains of influenza, but it does suggest that a short-lived general immunity to the virus might affect the virus's evolution. If immunologists can understand the basis of such a response by influenza virus, then vaccine designers might use that understanding to develop a vaccine that offers more general immunity to the virus, said the scientists.

The researchers—led by Howard Hughes Medical Institute international research scholar Neil M. Ferguson at Imperial College London—published an article outlining their model in the March 27, 2003, issue of the journal *Nature*. Co-authors are Alison Galvani from the University of California, Berkeley, and Robin Bush from the University of California, Irvine.

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"The principal question we were trying to address with this model is what biological factors determine the particular patterns we see in influenza evolution," said Ferguson. "We wanted to understand the role of immunity in determining the competition between different flu strains."

Strains of flu virus differ from one another largely in the genes that code for surface molecules called glycoproteins, which are the primary targets of the

body's immune system in defending against flu viruses, said Ferguson. Evolutionary changes in immune response against such “antigen” molecules are the reason that new vaccines must be developed against emerging strains of virus.

A central mystery, said Ferguson, was why only a few new flu strains emerge over time, replacing other strains that go extinct. Limitations on genetic variance distinguish influenza from other RNA viruses such as HIV and dengue fever, which exist in a wide range of variants, he said.

“Given basic evolutionary theory, one might expect naïvely that new influenza strains wouldn't necessarily drive the others extinct, and the virus population would get more and more diverse,” he said. “Understanding what stops that happening was the key question posed in this study.”

To explore evolutionary dynamics, Ferguson and his colleagues developed a computer-intensive mathematical model that simulated mutation in individual genetic units, or codons, of the viral coat and the effect of those changes on the transmission of the virus in human populations. They included mutations that affected immune-related properties of the virus, as well as those that did not. The researchers hypothesized that modeling could yield information on the genetic diversity of the virus population that would result from changes induced by mutation.

The researchers ran their model with various assumptions about mechanisms that might determine viral genetic diversity, and compared the resulting simulated viral populations with real-world genetic sequence data on populations of influenza strains.

“If you naively build a model which captures current understanding in the flu research community of how the virus works, then the model predicts increasing diversity through time - exactly what is not seen,” said Ferguson.

“We therefore inferred that there must be some other form of interaction between strains happening in the population,” he said. “The best fit to genetic data was obtained when a secondary, non-specific immune response was included in the model, on top of the normal adaptive immune response which recognizes individual virus strains. This secondary response gives a person complete protection against nearly all variants of the influenza virus, but only for a short period of time.” This kind of protection, said Ferguson, would last only for perhaps weeks after infection, after which it would fade, rendering a person vulnerable to reinfection with a different viral strain.

Virologists had previously postulated that temporary, non-specific immunity might exist “but it hasn't been thought of up until now as being a very significant driver, either of influenza evolution or of epidemiology. However, this work indicates that non-specific responses probably have a critical effect on both influenza transmission and evolution,” said Ferguson.

Since the mechanism of this kind of immunity remains unknown, Ferguson adds that it remains to be seen whether it might provide the basis of a more general influenza vaccine.

“If innate immunity is responsible, then exploiting this for vaccine development might be difficult due to the negative clinical consequences for the individual associated with inflammatory responses,” said Ferguson. “However, if it's due to an adaptive immune response recognizing other non-changing viral antigens, then vaccines that target those antigens might have a longer-term effect than the annual protection afforded by current vaccines,” he said.

More generally, said Ferguson, this type of modeling offers basic insights into the factors that drive influenza evolution that might improve understanding of which dominant variants that are likely to arise. “If we can understand in much more detail the biological relationship between the genome of the virus and its antigenic phenotype, then we'll be able to get to much more predictive mathematical models of the evolution of the virus,” he said. He emphasized that improved understanding will depend upon improved data from more detailed global surveillance of all influenza variants, not just the newly emerging pathogenic variants.

Ferguson said that the general approach to modeling that he and his colleagues employ is also being adapted to understand the evolution of other RNA viruses including HIV.