

MAY 27, 2010

## Seasonal Influenza: Made in the USA



**Image Title:** Global migration patterns of influenza A (H3N2) estimated from sequence data between 2002–2008. Arrows represent movement of influenza from one region to another, with arrow width proportional to the rate of migration of a single lineage of influenza. - Trevor Bedford

Every autumn, the seasonal flu arrives in the United States, causing tens of thousands of deaths and many more hospitalizations. Now, a new genetic analysis suggests that the strains of influenza circulating in the United States can migrate to the rest of the world. Such an event happened in 1999, when a strain of seasonal influenza virus evolved in the United States and later spread to China, Southeast Asia, Australia, and South America.

The finding may change the way researchers think about how seasonal influenza and one of its instigators, the H3N2 influenza virus, travel from the United States to the rest of the world, says Mercedes Pascual, the Howard Hughes Medical Institute investigator who led the work. Understanding how the virus migrates is an important goal of scientists hoping to develop new ways to monitor and control flu infection. The study is published in the May 27, 2010, issue of *PLoS Pathogens*.

“The predominant view has been that China and Southeast Asia always served as the source for new variants of seasonal influenza, and the rest of the world always served as a sink for those strains,” says Pascual, who is also a professor of ecology and evolutionary biology at the University of Michigan in Ann Arbor. “That view is sometimes accurate, but our analysis shows that the pattern is much more nuanced and can change from year to year. We’ve found that temperate regions, and in particular the United States, can be a place where novel variants of the flu sometimes arise and then spread to the

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The analysis, largely conducted by Trevor Bedford, a postdoctoral fellow in Pascual's laboratory, drew on publicly available genetic sequences of 2,165 different influenza viruses collected around the world between 1998 and 2007. To study the H3N2 flu, public health officials and infectious disease researchers often determine the DNA sequence of the virus's gene for hemagglutinin (the "H" in "H3N2") and deposit those sequences in GenBank, a public database. Hemagglutinin coats the surface of influenza particles and latches onto human cells; variations in the protein determine the infectivity of each strain. Importantly, hemagglutinin can evolve rapidly in response to antiviral drugs or simply by hopping from person to person.

Bedford applied a computer algorithm that analyzed the hemagglutinin sequences from all 2,165 strains and reconstructed how all of the viruses are genetically related to each other. Because the GenBank entries list the collection date and location of each strain, the algorithm could then trace how each variant had moved around the globe. The statistical method iteratively reconstructed the genetic relationships of all the strains, with each iteration moving closer to the true chain of events. Bedford ran several billion iterations of the algorithm, a computationally-intensive operation that tied up the HHMI-funded computing cluster at the University of Michigan for several weeks.

The analysis found that in 1999, a strain of influenza arrived in the United States, most likely from Asia, then evolved within the United States and spread back to China and Southeast Asia. From there, it spread to the rest of the world. The variant was so successful that "all seasonal flu that exists today is descended from that strain that existed in the United States in 1999," Bedford says.

During the 10 years analyzed, widely successful influenza strains originated in China 34 percent of the time, in Southeast Asia 32 percent of the time, and in the United States 24 percent of the time. Bedford says that these historical averages offer researchers a strong foundation on which to predict where important new strains will arise.

Passengers on airplanes presumably serve as the main vector for the rapid spread of influenza each year. "Seasonal influenza moves very quickly across

the world, washing north and south every six months,” says Bedford. “This kind of speed is probably only possible with air travel.”

Pascual says the findings offer important lessons for global influenza control efforts. “Our analysis has relevance for questions of vaccine development and for questions of surveillance,” she says. For instance, because the analysis found that the influenza that circulates in South America during the southern winter almost always originate in North America the previous season, vaccines for South American influenza should be tuned to North American strains. Likewise, she says that public health officials should carefully monitor influenza strains in the United States because they could contribute to the evolution of the virus globally.

Bedford makes a similar point. “If the strains we see in the United States always died out, we wouldn't have to worry about what we were doing in terms of fighting the flu,” he says. “We could throw as many antiviral medications at it as we wanted and any drug resistance that evolved would die out. But because the United States does sometimes seed the global influenza population, what we do here matters. We could inadvertently spur antiviral resistance that could spread around the world.”