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# Flu genome sequenced

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Ishani Ganguli
**Email**: iganguli@the-scientist.com

The genome sequences of over 200 influenza A viruses reveal a much more diverse array of influenza strains—and greater potential for segment exchange between these strains—than was previously realized, researchers report in this week's *Nature*.

While it's long been known that the RNA-based influenza virus survives by rapidly evolving, the paper provides new insights into the degree of its variability and the mechanisms of its success, helping scientists design better ways of protecting against influenza, said Robert Belshe at the St. Louis University Center for Vaccine Development, who did not participate in the studies.

This report, which assessed genetic variations in the strains over a five year period, is one of a trio of papers about the flu virus published this week. The other two recreate and research the particularly virulent strain responsible for the 1918 Spanish flu epidemic, which killed all laboratory mice within 6 days. The findings have since been engulfed in controversy out of fear that the recreated strain might escape, or that the virulent strain's now publicly available genome, deposited in GenBank, might be used by hostile nations as a bioterrorism agent.

The findings raised enough concerns to inspire the US National Science Advisory Board for Biosecurity (NSABB) to call an emergency meeting with the journals' editors, after which officials agreed that the benefits of publication outweighed any risks. Still, the agency asked the authors to include statements in the papers about the safety precautions they took, and the importance of the research for public health.

At a press conference on Wednesday (October 4), Julie Gerberding, director of the US Centers for Disease Control and Prevention, which led the team that reconstructed the 1918 virus, assured that investigators took proper "precautions," and all work was carried out in an enhanced biosafety level-3 laboratory.

The *Nature* paper on the 1918 epidemic reveals the complete genome sequence of the responsible strain, while the *Science* paper reconstructs the virus to test its effects on mice. The third paper, also published in *Nature*, takes a broader look at influenza, studying the dynamic genetic landscape provided by over 200 whole genome sequences.

The results elucidate the mutation events—both during and in between flu seasons—that have helped render vaccines ineffective. These mutation events, in turn, may help researchers predict which strains will be most important to protect against next, according to final author Steven Salzberg at the University of Maryland in College Park.

For example, the researchers were able to show that a minor flu subpopulation, or clade, donated the haemaglutinin (HA) gene—encoding one of the two most immunogenic surface proteins—to what would become the dominant clade, in or before the spring of 2003. The "epidemiologically significant" result of this reassortment event was the Fujian-like strain that frequently eluded vaccination in the 2003-2004 flu season, according to the paper. "The flu was able to draw upon this pool of genetic diversity that it had, pull out a gene that is more adaptive, and go ahead with that," Salzberg told *The Scientist.*

The researchers used large-scale sequencing techniques on a set of 209 predominantly H3N2 influenza isolates collected in New York state over five years, with no preference towards particularly virulent strains. This technique provided a comprehensive, true-to-life picture of the virus's dynamic evolution and transmission patterns in the region, according to Salzberg. The approach reveals three clades even within this limited region, and shows "how quickly strains are moving around, emerging and disappearing," he said.

By studying the complex interplay of genetic material in these sequences, scientists may be better able to identify circulating influenza strains before they become public health threats, and scrutinize potentially important changes in internal genes. Earlier work largely focused only on HA and neuraminidase (NA) gene segments, which both encode surface proteins that make good vaccine targets.

"It's going to make the [vaccine development] process much more sophisticated, [since] we have a much more complete picture of what's happening," Belshe told *The Scientist*.

During the 2003-2004 flu season, for example, first author of the 209 sequences paper Elodie Ghedin at the Institute for Genomic Research said that researchers might have considered "both lineages in the design rather than focus on this dominant one" and then used reverse genetics to design the optimal vaccine.

The researchers also found mutations that may be important for receptor binding affinity and the efficiency of viral replication, suggesting the need for further investigation of their functional significance.

The authors of the *Science* paper found the HA gene in the 1918 strain to be essential for its high virulence.

The report about the 209 sequences is the first analysis of data from the ongoing Influenza Genome Sequencing Project, which is led by US National Institute of Allergy and Infectious Disease; sequenced genomes are publicly available.

According to Belshe, scientists had historically thought that reassortment events were solely responsible for influenza pandemics, as they were in 1957 and 1968. But the complete sequence of the 1918 Spanish influenza strain demonstrates that it most likely evolved directly from the avian flu virus, providing a potential alternate mechanism for this threat that Belshe calls "quite alarming."

Jeffrey Taubenberger at the Armed Forces Institute of Pathology in Rockville, Maryland, first author of the *Nature* paper on the 1918 epidemic, said at Tuesday's press conference that he and his colleagues have established the "theoretical framework of amino acid changes that we think are important, and the next part is to do the careful basic science to try to address the significance of these changes to allow the bird virus to become a human virus, and that's going to take some time."

# References

1. E. Ghedin et al., "Large-scale sequencing of human influenza reveals the dynamic nature of viral genome evolution," *Nature*, October 5, 2005., [http://www.nature.com]

2. P. Hunter, "Outsmarting Influenza's Rapid Evolution," *The Scientist*, June 30, 2003., [http://www.the-scientist.com/2003/6/30/31/1]

3. Robert Belshe, [http://medschool.slu.edu/vaccine/index.phtml?page=belshe&cat=faculty]

4. National Science Advisory Board for Biosecurity, [http://www.biosecurityboard.gov/]

5. Julie Geberding, [http://www.cdc.gov/od/dirbio.htm]

6. J.K. Taubenberger et al., "Characterization of the 1918 influenza virus polymerase genes," *Nature* October 6, 2005., [http://www.nature.com]

7. T. M. Tumpey et al., "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus," *Science* October 7, 2005., [http://www.sciencemag.org]

8. Steven Salzberg, [http://cbcb.umd.edu/~salzberg/]

9. Elodie Ghedin, [http://www.tigr.org/faculty/Elodie_Ghedin.shtml]

10. Jeffrey Taubenberger, [http://www.afip.org/Departments/cell/Molecular_pathology.html]