# Measles-flu comparison yields insights for vaccine design

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Credit: National Cancer Institute

By comparing flu viruses to the virus that causes measles, researchers fine-tuned a tool that may enable faster vaccine design, according to a study led by Mount Sinai researchers and published online this week in the journal *Cell Reports*.

The study results revolve around viruses, which are designed perfectly by

evolution to invade human cells, inject viral genes and use human genetic machinery to make copies of them. In an endless back and forth, human immune cells have evolved to recognize and attack viral surface proteins, and viruses to constantly change their surface proteins to avoid being recognized. Called antigenic drift, these viral genetic changes proceed at different speeds in different viruses, with implications for vaccine design. While one childhood vaccination provides lifetime protection against measles, for instance, people need a different flu shot every year. The field has long known that flu viruses are much "tolerant" of constant change in certain genes than measles, but not why.

The answer may advance the design of vaccines that target parts of flu viruses they cannot afford to change, the so-called "universal" flu vaccines that would provide permanent immunity. Beyond flu, the new study validates a method that may help the field more quickly design vaccines that provide permanent protection when new and deadly viruses emerge.

"Our team used the measles virus to test a tool that offers a new way to measure the resistance of key viral genes, and related proteins, to change," said lead study author Nicholas Heaton, PhD, a post-doctoral fellow in the Department of Microbiology at the Icahn School of Medicine at Mount Sinai. "It's vital to quickly determine the parts of a virus so vital to its survival that it can't randomly change them because they often make the best vaccine components."

The field has long understood that key parts of the gene code for the measles virus remain unchanged over time, while similar genes in flu viruses constantly change, despite the two both being RNA viruses that infect the lungs. Specifically, the new study found that measles is much less able than the flu to survive genetic changes to the viral surface protein hemagglutinin or H. This protein is central to this story because it both enables viruses to latch onto cells and is well known to human

immune cells that seek to destroy anything attached to it.

From past analysis, the team knew going that analogous H protein in influenza viruses is very tolerant of mutations, but the new study confirmed that the measles virus is not. Comparing two related viruses, one rigid and one flexible, in terms of evolutionary speed of surface proteins confirmed that influenza H is more open to change. The researchers reached this conclusion using a high-speed experimental technique, insertional mutagenesis, which changes all of the genes in a virus in one experiment—a useful tool to understand the future of viral evolution. They inserted mutations across the measles genome and found measles cannot survive too much change to the gene for its HA protein especially.

All a flu virus HA needs to attach to a target cell is to find one of the simple sugar structures that cover human cell surfaces. According to a theory supported by the current study results, this simple sugar may be better suited to binding a wider variety of viral HA structures, which may account for the ability of flu H genes to constantly change without consequence. Measles HA and related proteins require a specifically shaped protein receptor to attach to, which may explain why the genes for that protein, and related protein shapes, cannot change and still work.

"In theory, how different viruses evolved to attach to target cells may be a major factor driving their genetic rigidity, or flexibility, which influences the ability to tolerate the random genetic changes that are happening all the time," said Dr. Heaton. "Both the flu and measles have historically been very successful invaders of human cells, so both rigidity and constant change genetic change have conferred value. Exactly why tradeoffs are made in viral evolution is very interesting, and the subject of ongoing studies."

**More information:** *Cell Reports*, Fulton et al.: "Mutational analysis of

measles virus suggests constraints on antigenic variation of the glycoproteins" dx.doi.org/10.1016/j.celrep.2015.04.054

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