Computer model uses virus 'appearance' to better predict winter flu strains

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Combining genetic and experimental data into models about the influenza virus can help predict more accurately which strains will be most common during the next winter, says a study published recently in *eLife*.

The models could make the design of flu vaccines more accurate, providing fuller protection against a virus that causes around half a million deaths each year globally.

Vaccines are the best protection we have against the flu. But the virus changes its appearance to our immune system every year, requiring researchers to update the vaccine to match. Since a new vaccine takes almost a year to make, flu researchers must predict which flu viruses look the most like the viruses of the future.

The gold-standard ways of studying influenza involve laboratory experiments looking at a key molecule that coats the virus called haemagglutinin. But these methods are labor-intensive and take a long time. Researchers have focused instead on using computers to predict how the flu virus will evolve from the genetic sequence of haemagglutinin alone, but these data only give part of the picture.

"The influenza research community has long recognized the importance of taking into account physical characteristics of the flu virus, such as how haemagglutinin changes over time, as well as genetic information," explains lead author John Huddleston, a Ph.D. student in the Bedford Lab at Fred Hutchinson Cancer Research Center and Molecular and Cell Biology Program at the University of Washington, Seattle, US. "We wanted to see whether combining genetic sequence-only models of influenza evolution with other high-quality experimental measurements could improve the forecasting of the new strains of flu that will emerge one year down the line."

Huddleston and the team looked at different components of virus 'fitness' - that is, how likely the virus is to thrive and continue to evolve. These included how similar the antigens of the virus are to previously circulating strains (antigens being the components of the virus that trigger an immune response). They also measured how many mutations

the virus has accumulated, and whether they are beneficial or harmful.

Using 25 years of historical flu data, the team made forecasts one year into the future from all available flu seasons. Each forecast predicted what the future virus population would look like using the virus' genetic code, the experimental data, or both. They compared the predicted and real future populations of flu to find out which data types were more helpful for predicting the virus' evolution.

They found that the forecasts that combined experimental measures of the virus' appearance with changes in its genetic code were more accurate than forecasts that used the genetic code alone. Models were most informative if they included experimental data on how flu antigens changed over time, the presence of likely harmful mutations, and how rapidly the flu population had grown in the past six months. "Genetic sequence alone could not accurately predict future flu strains—and therefore should not take the place of traditional experiments that measure the virus' appearance," Huddleston says.

"Our results highlight the importance of experimental measurements to quantify the effects of changes to virus' genetic code and provide a foundation for attempts to forecast evolutionary systems," concludes senior author Trevor Bedford, Principal Investigator at the Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington. "We hope the open-source forecasting tools we have developed can immediately provide better forecasts of flu populations, leading to improved vaccines and ultimately fewer illnesses and deaths from flu."

More information: John Huddleston et al, Integrating genotypes and phenotypes improves long-term forecasts of seasonal influenza A/H3N2 evolution, *eLife* (2020). DOI: 10.7554/eLife.60067

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