

Study uncovers cause of flu epidemics

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The exchange of genetic material between two closely related strains of the influenza A virus may have caused the 1947 and 1951 human flu epidemics, according to biologists. The findings could help explain why some strains cause major pandemics and others lead to seasonal epidemics.

Until now, it was believed that while reassortment – when human influenza viruses swap genes with influenza viruses that infect birds – causes severe pandemics, such as the ‘Spanish’ flu of 1918, the ‘Asian’ flu of 1957, and the ‘Hong Kong’ flu of 1968, while viral mutation leads to regular influenza epidemics. But it has been a mystery why there are sometimes very severe epidemics – like the ones in 1947 and 1951 – that look and act like pandemics, even though no human-bird viral reassortment event occurred.

“There was a total vaccine failure in 1947. Researchers initially thought there was a problem in manufacturing the vaccine, but they later realized that the virus had undergone a tremendous evolutionary change,” said Martha Nelson, lead author and a graduate student in Penn State’s Department of Biology. “We now think that the 1947 virus did not just mutate a lot, but that this unusual virus was made through a reassortment event involving two human viruses.

“So we have found that the bipolar way of looking at influenza evolution is incorrect, and that reassortment can be an important driver of epidemic influenza as well as pandemic influenza,” said Nelson, whose team’s findings appear in the current issue of *PLoS Pathogens*. “We have

discovered that you can also have reassortment between viruses that are much more similar, that human viruses can reassort with each other and not just with bird viruses. ”

Nelson and her colleagues analyzed the evolutionary patterns in the H1N1 strain of the influenza A viruses by looking at 71 whole-genome sequences sampled between 1918 and 2006 and representing 17 different countries on five continents.

Using the genome data, the researchers constructed phylogenetic trees representing evolutionary relationships across all eight genome segments of the virus.

Big differences in the shapes of these eight trees signified that reassortment events had occurred.

The swapping of genes between two closely related strains of the influenza A virus through reassortment may also have caused the 1951 epidemic, which looked and acted in many ways like a pandemic as well. Deaths in the United Kingdom and Canada from this epidemic exceeded those from the 1957 and 1968 pandemics.

Currently, there are many types of influenza virus that circulate only in birds, which are natural viral reservoirs. Though the viruses do not seem to cause severe disease symptoms in birds, so far three of these viral types have infected humans – H1N1, H2N2, and H3N2.

Understanding how each strain evolves over time is crucial. H3N2 is the dominant strain and evolves much more rapidly than H1N1. So the H1N1 component of each year’s flu vaccine has to be updated less often. In comparison, the H3N2 component of the vaccine has been changed four times over the past seven years.

“Last year the infections were dominated by H1N1 but we had no way of predicting it,” said Nelson. “This year the vaccine failure is due to the H3N2 mismatch because researchers picked the wrong strain.”

The H1N1 virus is particularly unusual because it disappeared completely in 1957, only to mysteriously re-emerge in humans in 1977 in exactly the same form in which it had left. It is still not certain what happened to the virus during its disappearance. But since it did not evolve at all over these twenty years, “the only plausible explanation is that it was some kind of a lab escape,” says Nelson, who is also affiliated with Penn State’s Center for Infectious Disease Dynamics (CIDDD).

In recent decades, flu infections in the United States have been dominated by yet another reassorted viral strain known as H3N2. This strain caused the Hong Kong flu pandemic of 1968, which killed nearly a million people.

The Penn State researcher says the study shows that the evolution of a virus is not limited to the mutation of single lineage, and that there are multiple strains co-circulating and exchanging genetic material. The H1N1 and H3N2 strains, for instance, are occasionally generating hybrid H1N2 viruses.

“If we really want effective vaccines each year, our surveillance has to be much broader than simply looking at one lineage and its evolution, and trying to figure out how it is going to evolve by mutation,” said Nelson. “You have to look at a much bigger picture.”

Source: Penn State

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