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Flu virulence linked to species jump

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The Spanish flu pandemic of 1918 killed more people than died in the First World War - at least 20 million - but why this strain of the disease was so virulent has remained a mystery. Analysis of the crystal structure of viral hemagglutinin (HA) - a major surface antigen that mediates binding to the host cell - shows the 1918 virus antigen is related to the avian antigen, suggesting that the virulence resulted from a recent chicken/human cross-species jump.

Alan Hay, director of the World Health Organization Collaborating Centre for Reference and Research on Influenza at the National Institute for Medical Research (NIMR) and who was not involved in the studies, told us, "All this information helps us to understand what sort of changes may facilitate human infection by an avian virus. The accumulated data that we have on the structural detail helps us to look for changes which might have an impact on the ability of these viruses to spread within the [human] population."

In the first of two papers published in February 5 Science, Steve Gamblin and colleagues, also at the NIMR, determined the structures of HA expressed from DNA recovered from tissues infected with the virus in 1918 together with those of the 1934 human and the 1930 swine HAs in complex with analogs of avian and human receptors. The structures were solved by molecular replacement and crystallographic statistics. The authord found the H1 HAs to be most similar to those of the H5 subtype (as are most avian viruses) (*Science* 2004, DOI:10.1126/science.1093155).

James Stevens and coworkers at the Scripps Institute cloned the ectodomain of the HA gene from the 1918 influenza virus A/South Carolina/1/18 (18HA0) in a baculovirus expression system. Its structure was determined by molecular replacement to 3 Å resolution. By superimposing other published HAs onto the 18HA0 monomer via their HA2 domains, the authors showed that 18HA0 is most closely related to the avian H5 subtype, while the human H3 subtype is the most divergent (*Science* 2004, DOI:10.1126/science.1093373).

"If it [the 1918 subtype] was an avian-like virus, it would have to be adapted to some extent to get into human cells because avian virus receptors are different from the human viral receptors. There seem to be some differences around the [HA precursor] cleavage site that had not appeared on human viruses before and which we think are worth investigating to see whether that might be some reason why this virus was more effective," said Ian Wilson, coauthor of the second paper.

John Skehel, coauthor of the first paper, believes they have the answer. "By comparison with other avian binding sites that we've analyzed, this 1918 binding site has a slightly different shape, and that shape allows particular residues in the site to bind to human receptors."

Hay said the Thailand outbreak is very serious because it is not clear how easy it will be to contain or control it. He believes that the longer it persists and the greater it spreads, the more likely it is that, with more human cases, the virus will acquire some adaptation to the human host.

Carol Cardona, an extension poultry veterinarian in California, told us, "This is a virus that is spreading very easily in chickens. Chickens are kept in very large numbers and flocks in every country. This is an explosive chicken disease, so even if it doesn't spread from human to human, it's a very big

problem. It's out of control in the chickens right now. It's not out of control in other countries, but it is across Asia."

"Influenza is an annual problem that kills millions of people, and the more information we have, particularly with more distant strains that are likely to cause pandemics [the better], and that's really the concern: as to whether we can actually look at these structures and get information that will ultimately be able to help us when a new pandemic arises," said Wilson.

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