Scientists examine bird flu infections to monitor for 'pandemic' mutations

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Scientists funded by the Wellcome Trust are to examine what is preventing the H5N1 avian influenza virus from causing a human pandemic and what mutations are required to realise its deadly potential. The research could hold the key to early identification of a potential influenza pandemic, and to developing drugs and a vaccine.

Since its reappearance in 1997, the H5N1 influenza virus has caused disease and death in millions of birds around the globe. The number of infections in humans is still relatively small, however: from 2003 to the end of June 2008 there had been 385 known cases in humans, 243 of them fatal(1). So far, there appear to have been very few cases of human-to-human transmission.

Professor Ten Feizi at Imperial College London believes one reason why H5N1 has not yet evolved into an effective pathogen capable of widespread transmission between humans lies in how the virus attaches itself to the respiratory tract. She is leading an international research project which has received over £720,000 from the Wellcome Trust to identify the receptor molecules in the human respiratory tract to which viruses attach and to look at how changes in the binding protein on the surface of the virus might increase its ability to attach to the tract and cause infection.

Professor Feizi will work with Professors Menno de Jong and Jeremy Farrar from the Wellcome Trust's South East Asia Programme in Vietnam, Dr Alan Hay and Dr Steve Gamblin at the Medical Research

Council National Institute for Medical Research, London, and Dr Mikhail Matrosovich at the Philipps University of Marburg, Germany.

"Over the last few years particularly in Asia we have seen just how deadly the H5N1 virus can be," says Professor Farrar from the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam, where a number of people have been treated for infection by the virus. "So far, we have been relatively fortunate and there has been only limited evidence of the virus transmitting from human to human. The more we understand about the virus, how it interacts with the body, the better we will be prepared for any serious mutations that may arise."

In humans, influenza infection occurs via the respiratory tract, or airway. In order to cause disease, the virus must enter the body's cells where it can replicate and spread, but it must first find a site to which it can attach, known as a receptor. The virus can only attach to and enter the cells if the receptor fits into the binding proteins, or haemagglutinins (the "H" in H5N1), on the surface of the virus.

Previous research has shown that the haemagglutinin on H5N1 favours a particular form of receptor known as a "2,3 receptor". These are abundant on cells of birds, but in humans are found mostly on cells of the lower respiratory tract (the lungs). Professor Feizi and colleagues have shown that mucus in the upper airway in humans also contains 2,3 receptors, but here the mucus acts as a defence mechanism to which the virus binds, blocking its progress and enabling the body to "sweep out" the virus. Both factors suggest that huge doses of the virus are required in order to infect humans, a theory supported by evidence that those who have become infected have spent large amounts of time in close proximity to infected fowl.

As with all viruses, H5N1 is continually mutating, and it is changes that allow the virus to attach to "2,6 receptors" in the human upper airway

which may enable the virus to become more infectious to humans.

"If the bird flu virus evolves to favour the receptors in our nose and throat like normal flu, the results could be devastating," says Professor Feizi from the Division of Medicine at Imperial College London. "We could have a virus which is not only highly infectious but is easily transmissible by coughing and sneezing."

Dr Hay and Dr Gamblin will isolate haemagglutinin from samples of the virus taken from the patients in Vietnam, and Dr Matrosovich will grow cultures of human airway cells and isolate cell-membrane receptors and secreted mucus. Then, using a technique known as neoglycolipid (NGL) microarray analysis developed by Professor Feizi and her colleagues, the team at Imperial College will identify which of the various receptor structures the haemagglutinins bind most strongly to. Dr Gamblin's team will then use X-ray crystallography to probe, at the molecular level, how mutations might cause the bird virus to change into a human virus.

"If we can find out which mutations of haemagglutinin prefer which receptors, we may be able to identify quickly or even predict which mutations give the virus pandemic potential," says Professor Feizi.

Current antiviral treatments for influenza, such as Tamiflu, target neuraminidase (the "N" in H5N1), which is responsible for allowing the virus to jump off receptors on one cell and bind to those on another cell, and to replicate and spread once inside the body.

"Targeting the virus's ability to bind to the receptors – which until now has proved far more difficult – may provide an alternative, more effective way of preventing infection," says Professor Feizi. "We hope that our work will make this process simpler and faster."

1. Cumulative Number of Confirmed Human Cases of Avian Influenza

A/(H5N1) Reported to WHO, 19 June 2008.
www.who.int/csr/disease/avian_…_06_19/en/index.html

Source: Wellcome Trust