

H5N1: Real Potential for Influenza Pandemic

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June 21, 2012 — Bruce Alberts, MD, the editor-in-chief of *Science*, announced in a press teleconference that in the June 22 issue, "*Science* will be openly publishing complete details of 2 research articles that reveal that there's a real potential for the H5N1 virus to directly evolve to a form that could cause a pandemic."

"To help guide further progress, *Science* will also publish...6 thoughtful commentary pieces, plus 2 news articles, along with the research papers," Dr. Alberts said.

The first research paper is the long-awaited article by Ron Fouchier, MD, a virologist from the Erasmus Medical Center in Rotterdam, the Netherlands, and colleagues, titled, "Modified H5N1 Virus Transmitted by Aerosols in Ferrets." Publication of this study, and another similar study by Yoshihiro Kawaoka, MD, and colleagues were initially delayed because of concerns that the research could be used by others to cause harm. The Kawaoka article was published in *Nature* in May.

The Threat Is Real

"[I]f you put both [Kawaoka's and Fouchier's]...papers together, they very nicely showed some very important things: That you can get a transmissible virus both by mutation alone, as Ron showed, and by a combination of mutation and reassortment, as Yoshi showed," said Anthony S. Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

Dr. Alberts noted that the second study published in *Science* ("The Potential for Respiratory Droplet-Transmissible A/H5N1 Influenza Virus to Evolve in a Mammalian Host") assesses the potential of the virus to evolve the ability to cause a pandemic.

Dr. Fouchier explained that his study shows the H5N1 virus can develop the ability of aerosol transmission between mammals in as few as 5 mutations, but definitely fewer than 10. "In addition to the well-known mutations that change receptor specificity of the hemagglutinin gene of the virus and the activity of the PB2 polymerase gene, we identified previously unknown mutations that can now be associated with aerosol transmission. These mutations that so far remain unknown will form the basis of much more fundamental research on how influenza viruses become airborne," Dr. Fouchier said.

"What we show in the paper is that within the first 3 or 4 passages, we already see the strong adaptation of the virus based on the phenotypes, so it better replicates an upper respiratory tract. And so only a limited chain of transmissions in ferrets is sufficient to make the virus adapt, and we assume that also in humans it would only take a relatively low number of transmission events for these mutations or similar mutations to accumulate," said Dr. Fouchier.

"But when we look at this virus, it has a changed receptor specificity. So rather than preferring the receptors that are present in the lower airways...this airborne virus now prefers to bind to virus receptors present in upper airways, and that's why it can be transmitted. But it's also likely that the virus that binds more efficiently to the upper airways would have less virulence because it cannot really attach very strongly to these lower airways anymore, and so it's less likely to cause pneumonia," Dr. Fouchier added. Caution is needed, he noted, because there is still some possibility that the virus could cause pneumonia.

Derek J. Smith, PhD, a professor of infectious disease informatics at the University of Cambridge in the United Kingdom, and a research scientist in the Department of Virology at Erasmus Medical Center, was also at the press conference. He is one of the authors of the second study published in this issue of *Science*. He said it is difficult to predict for sure how likely it is that the virus would mutate in this way.

"Right now, we know that it's possible that this can happen, and we know that accumulating, let's say, 3 mutations within a single host is within the realm of possibility. But we can't yet say, because of some of these unknowns, exactly what that risk is. And it makes a big difference whether that risk is 1 in 1000 or whether it's 1 in 100 million," said Dr. Smith.

"Fortunately, for the case of figuring out the situation with these viruses, the path is now clear for what needs to happen next in terms of the steps that have to happen in order to more accurately assess the risks of these viruses emerging in nature," Dr. Smith said.

"As we know, seasonal influenza is a continual threat to the public health in the United States and worldwide. Furthermore, when these viruses undergo extensive genetic changes and/or jump species, the result can be a virus to which humans have little to no immunity, leading to an influenza pandemic," said Dr. Fauci.

"I think the benefit that will come out of the Fouchier paper, in stimulating thoughts and stimulating pursuing ways to understand better transmissibility, adaptability, pathogenesis, in my mind, far outweighs the risk of nefarious use of this information," Dr. Fauci said.

Also at the media briefing was Rino Rappuoli, PhD, Global Head of Vaccines Research for Novartis Vaccines and Diagnostics in Siena, Italy. He spoke about improving pandemic preparation.

In the 2009 pandemic, "we responded very well to the pandemic, making vaccines available, but the vaccines became available in large quantities shortly after the peak of the virus had happened. The other problem was that in developing countries there was [not enough vaccine]," said Dr. Rappuoli.

"We're in a much, much better position than we were when we had vaccine available after the peak of the 2009 H1N1 2 years ago," said Dr. Fauci.

Some Research Still on Hold

In January 2012, Dr. Fouchier, Dr. Kawaoka, and 37 other researchers involved with similar work voluntarily agreed to suspend this type of research for 60 days so that governments and others could work out a solution to the publication issue. That moratorium is still in place. Dr. Fauci explained, "I can't tell you when it's going to be voluntarily lifted, but we are working very hard right now to get processes in place where we could have some broad general criteria of the kinds of experiments that could be done. Because, remember, the moratorium is a very, very restrict[ed], confined moratorium. It's for gain of function experiments that increase the transmissibility and/or the pathogenesis of H5N1. That's the only thing that the moratorium is on."

Both studies received support from Nederlandse Organisatie voor Wetenschappelijk Onderzoek VICI, European Union FP7 program EMPERI and/or ANTIGONE, and Human Frontier Science Program. The study by Dr. Fouchier and colleagues was supported by the National Institute of Allergy and Infectious Diseases. Two researchers received support from a National Institutes of Health Director's

Pioneer Award. The authors have various relationships with companies that conduct influenza research and produce vaccines. Complete information can be found on the Science Web site. Two researchers are holders of certificates of shares in ViroClinics Biosciences BV. To avoid any possible conflict of interests, Erasmus MC policy dictates that the shares as such are held by the Stichting Administratiekantoor Erasmus Personeelsparticipaties. The board of this foundation is appointed by the Board of Governors of the Erasmus MC and exercises all voting rights with regard to these shares. The study by Dr. Smith and colleagues received funding from Wellcome, the Bill and Melinda Gates Foundation, and a National Institutes of Health Director's Pioneer Award. The researchers in Dr. Smith's study have various relationships with companies that conduct influenza research and produce vaccines. Complete information can be found on the Science Web site.

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