Serial Passage Renders H5N1 Influenza More Readily Contagious

News that an H5N1 influenza virus was rendered into a phenotype that spreads readily between mammals startled microbiologists and infectious disease experts attending the 2011 European Scientific Working Group on Influenza (ESWI) conference in Malta last September. By configuring a virus that could attach to respiratory tract cells and passaging the infectious material in ferrets, Ron A. M. Fouchier of Erasmus Medical Center in the Netherlands learned that H5N1 could become increasingly transmittable. These findings challenge a long-held belief that extensive changes are needed before “bird flu” is able to jump from one human to another.

A highly infective version of the H5N1 virus that readily attaches directly to cells in the mammalian upper respiratory tract is so worrying that the National Science Advisory Board for Biosecurity (NSABB) quickly began a review of Fouchier’s findings. Changes that occur to a virus in a laboratory can also happen in nature, according to Albert Osterhaus, who also is at the Erasmus Medical Center and chairs ESWI. “The mutations are out there, they just haven’t come together yet,” he says. However, Paul Offit of the Children’s Hospital of Philadelphia (CHOP) in Pennsylvania wonders why, if such mutations are naturally occurring, “we haven’t as yet had an H5N1 pandemic.”

There is more than one route for H5N1 to become more readily transmissible among ferrets, according to Ruben O. Donis and colleagues at the Centers for Disease Control and Prevention in Atlanta, Ga. Focusing on viral receptor specificity, the group selected for variant viruses that bind α-2–6 sialosides in vitro. Then they combined a variant with two pandemic H5N1 viruses, yielding a mutant that could be transmitted by direct contact in ferrets. From here the researchers configured a reassortant virus that could be partially transmitted via respiratory droplets. Because several changes were needed to make an airborne virus, their findings suggest that H5N1 is unlikely to ever become as easily transmissible as seasonal influenza. Details appear in the 4 November 2011 *Virology* (doi: 10.1016/j.virol.2011.10.006).

It would be a relief for the H5N1 flu virus to remain poorly transmissible. Since it was isolated in 1997, this virus has devastated bird populations, while infecting more than 250 humans and killing 150. Moreover, a variant of H5N1 in Vietnam and China apparently can “sidestep” vaccines, Osterhaus says.

“There is no question that there will be an [H5N1] influenza pandemic someday,” cautions Robert G. Webster at St. Jude Children’s Research Hospital in Memphis, Tenn. Given the deadliness of H5N1, “it would be prudent to develop robust plans for dealing with such a pandemic now.”

“Another pandemic influenza is on the horizon,” agrees Michael Osterholm from the University of Minnesota in Minneapolis. “This is not just a maybe. I know this will happen.”

Paul S. Keim, acting chair of the
Antibodies that bind the polysaccharide capsule of *Streptococcus pneumoniae* can enhance transformation, the uptake by such cells of unadorned genetic material, according to Liise-anne Pirofski of Albert Einstein College of Medicine and Montefiore Medical Center in Bronx, N.Y.—who calls their findings “novel”—and her collaborators. Additionally, these antibodies boost expression of genes that govern fratricide, the ability of certain bacteria to kill sibling cells. Their report appears in the September/October 2011 *mBio*.

In the presence of competence-stimulating peptide, some antibodies to the pneumococcal capsule enhance transformation and quorum sensing. In the case of one such antibody, designated 1E2, expression of genes that induce transformed cells to kill siblings also increases. Thus, transformation-stimulating antibodies induce the pneumococcus cells to clump, triggering quorum sensing, a process by which cells communicate but only when they are in close proximity to one another, Pirofski says. Quorum sensing induces more transformation. Meanwhile, however, capsule-binding antibodies that promote phagocytosis do not induce clumping, or enhance transformation.

Although antibodies were thought to bind polysaccharide capsules of pneumococci and that was the “end of the story,” these findings from Pirofski and her collaborators show things are not so simple, says microbiologist Jorge L. Benach of Stony Brook University in Stony Brook, N.Y.

If transformed cells kill their nontransformed counterparts, that could “allow the host to clear the infection faster,” Benach points out. However, the opposite might be what happens, he adds, describing a scenario in which the pathogen outmaneuvers its infected host:

“It could be argued that enhancing fratricide, particularly if directed to cells that cannot accept new genetic information, may also work in favor of preserving the competent [transformed] cells by the acquisition of resistance factors,” Benach notes. “If conditions are such that the majority of cells in an *S. pneumoniae* culture can accept DNA more readily than before, those cells could well acquire new resistance factors. In this scenario, the random acquisition of new genes could result in the expression of new antigens not recognized by the antibodies, new exogenous proteases that can cleave immunoglobulins, or a number of other possible factors that would enhance the establishment and continuation of an infection.”