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A Virologist's Perspective on Influenza A(H1N1)

Soon after scientists first isolated influenza A type viruses from pigs in 1931 and humans in 1933, they watched it break evolutionary barriers with alarming ease—infecting not only humans, but also aquatic birds, poultry, pigs, horses, dogs, and other species. Now, with an intensifying outbreak driven by the emergence of a new strain of influenza A(H1N1), scientists once again have a unique opportunity to study viral evolution in action.

Howard Hughes Medical Institute investigator Robert Lamb, a virologist and influenza expert at Northwestern University, has followed the current outbreak closely. From his office just outside Chicago, Lamb has been conferring with scientific colleagues worldwide and poring over available data from the Centers for Disease Control and Prevention (CDC) and World Health Organization web sites.

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— Robert A. Lamb

He credits the CDC and other public health officials for moving quickly to assemble – and make publicly available -- a vast amount of information about samples of the virus obtained from Mexico, the United States, and elsewhere. Such information, he says, can tell researchers a lot about the genetic and structural makeup of the virus.

What he's learned so far about influenza A(H1N1) concerns Lamb, but he acknowledges that things are moving fast, and there are many open questions. "It is too early to know what will happen next," he said. From a genetic point of view, Lamb describes the virus as a "complicated reassortant, containing a mixture of genes from influenza viruses that infect Eurasian swine, American swine, birds and humans."

Strains of flu virus differ from one another largely in the genes that code for surface molecules called glycoproteins, which are the primary targets of the

body's immune system in defending against flu viruses. H1N1 belongs to the H1 influenza A virus family, just 1 of 16 subtypes. Labeled H1 to H16, each subtype is named for the distinct structural biology of one of the key influenza surface proteins, hemagglutinin (HA). All H1 viruses, for instance, share a similarly shaped HA protein. Influenza viruses are further distinguished by the shapes of their neuraminidase (NA) proteins, of which there are nine subtypes.

Like a coat of armor, the HA and NA surface proteins stud the tiny influenza virus particle. When the virus mutates, it essentially "changes coats," altering the shape of its exterior surface and becoming unrecognizable to the human (or animal) immune system. This is the essence of immune evasion, a hallmark of influenza.

The virus can undergo two types of structural changes that help it dodge the immune system. Small changes in the virus's coat proteins happen continually and result in new strains. This is a main reason why people can get the flu more than once and why they need to get a new flu vaccine every year. The virus coat can also change abruptly into a new subtype that has an HA protein or an HA-NA protein combination that has not been seen in humans, at least not for many years. Most people would have little or no innate protection against this new virus. And if the virus can spread easily from person to person, a pandemic may occur.

If influenza viruses rarely changed shape, immune evasion wouldn't keep researchers up at night. But influenza viruses evolve constantly, and their physical structure is again the reason. Inside its spherical shell, the virus particle houses eight separate RNA segments—which encode genes for 11 proteins—and this kind of segmented genome is ripe for recombination. If two different influenza viruses infect the same cell, for instance, they can easily exchange gene segments—generating theoretically up to 256 different offspring. Scientists call this phenomenon a genetic "reassortment," and the hybrid viruses are "reassortants."

Flu pandemics in 1918, 1957, and 1968 caused millions of deaths. Both strain H2N2 (the cause of the 1957 pandemic) and strain H3N2 (the 1968 pathogen) are believed to have arisen by the exchange of genes between avian and human flu viruses, possibly following dual infection in humans. The deadliest pandemic, in 1918, was different. It was the result of strain H1N1, thought to be derived wholly from an ancestor that originally infected birds.

Swine influenza, which is at the center of the 2009 outbreak, is a respiratory disease of pigs caused by type A influenza viruses that causes regular outbreaks in pigs. People do not normally get swine flu, but human infections can and do happen. Swine flu viruses have been reported to spread from person-to-person, but in the past, this transmission was limited and not sustained beyond three people.

Lamb and others are keenly interested in the molecular mechanics that permit viruses, such as influenza A(H1N1), to jump between species. The specific cause of the jump from one species to another remains something of a

mystery, but many researchers believe it has to do with changes in the HA protein, which is responsible for recognizing receptors on the cells the virus infects.

Lamb looks at the present circumstances in light of historical influenza outbreaks, such as 1918 and the more recent outbreak of swine flu in the United States in 1976. He notes that there was particular concern about the 1976 strain because at the time scientists thought the devastating 1918 virus was also of swine origin. That was proven to be incorrect later, but Lamb says that the perceived similarity between the two viruses drove the decision to vaccinate approximately 40 million people in the United States. Within several months of receiving the vaccine, more than 30 people had died from complications related to Guillain-Barré syndrome, a paralyzing nerve disease. “In retrospect, if a mistake was made, it was the decision to vaccinate the U.S. population,” Lamb said.

It is too early to know how similar the 2009 strain is to the 1976 strain, influenza A/New Jersey/1976(H1N1). “The 2009 A(H1N1) virus has made the jump already,” Lamb said. “It is basically a zoonotic that has adapted to infect humans.” He says pigs are a likely crucible in which various influenza viruses commingled to produce influenza A(H1N1). “Pigs,” he notes, “have often been considered a potential halfway house for these viruses because they have receptors for both avian and human influenza.”

Although many have described the current influenza A(H1N1) as a “novel virus,” Lamb isn’t so sure how new it is. “We do know the genetic changes that led to influenza A(H1N1) did not all occur at once. The cross between parts of swine genes, avian genes and human genes was already in existing ‘triple reassortant’ viruses. By the looks of this strain of influenza A(H1N1), we’re seeing a switch between swine influenza and this pre-existing triple reassortant.”

One question nagging at Lamb and other scientists is whether the most recent flu vaccine administered in the United States might confer some small amount of protection against influenza A(H1N1), even though it was produced to tamp down other strains of flu virus. “One of the components in that vaccine was against the ‘seasonal’ H1N1 virus that was already out there,” Lamb said. “We want to know how much cross-reactivity there is between the seasonal H1N1 and influenza A(H1N1).” Cross-reactivity is the reaction against an antigen and an antibody that was directed against a similar but different antigen. “It may be that there’s a small amount of cross-reactivity that’s hard to measure, but that nonetheless gives you some protective effect and makes the difference between being very sick or mildly sick,” he said.