Latching On to a Horror

Scientists fear a pandemic if the deadly avian flu virus, which hooks into victims' cells, mutates and spreads between humans.

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On a spring day in 1997, Dutch virologist Jan De Jong received an unusual specimen of influenza from a colleague in Hong Kong. The sample had been harvested from a sick 3-year-old boy and matched no known human flu strain. Tests at a colleague's lab in Rotterdam found that the boy had been sickened by a bird flu virus. It was the first evidence that birds could give influenza directly to people. Two days later, De Jong was on a plane to Hong Kong. "We had to act very, very quickly," recalled De Jong, now a senior investigator at Rotterdam's Erasmus University. "We realized this could be a pandemic situation." Authorities eventually ordered the eradication of every chicken, duck and goose in Hong Kong. All told, six people, including the boy, died before the outbreak of avian flu faded. But the troubling findings in the Dutch lab continue to haunt health authorities worldwide.

The virus — dubbed H5N1 — has now spread throughout Asia. Although it is innocuous in wild waterfowl, it is so unfamiliar to the human immune system that scientists fear it could seed a deadly influenza pandemic. All it needs is to transform itself so it can be transmitted between humans — a possible scenario if enough people are infected. Once inside human cells, it could mutate on its own or merge with pieces of human influenza already adapted to spreading among Homo sapiens. Influenza assails its victims with high fevers and aches that, in the most serious cases, can lead to secondary infections, pneumonia and death. "Past epidemics have been limited to a few million chickens," De Jong said. "But we are now talking about the whole area of Southeast Asia — so we have to multiply the risk by hundreds of thousands."

The discovery in 1997 "was a profound moment," said influenza researcher Kennedy Short- ridge, emeritus professor of the University of Hong Kong. "What really hit me was the sudden realization … that the next pandemic could arise, doing so right on our doorstep." H5N1 resurfaced in 2001, 2002 and 2003. Last year, while the world was focused on the SARS virus, two Hong Kong residents who had visited China were infected with H5N1, and one died. The latest outbreak has engulfed 10 countries throughout Asia. Authorities have exterminated millions of domestic chickens and ducks to contain the bird epidemic. At least 21 people have died in Vietnam and Thailand.

So far, scientists believe nearly all the human victims contracted the disease from birds. In two cases, however, investigators haven't ruled out human-to-human infection. "It's incredibly troubling," said Richard Webby, influenza researcher at St. Jude Children's Research Hospital in Memphis. "The more chance that virus has of interacting with humans and human viruses, the more danger we're in." If the virus succeeds in tweaking its genome to become a far-traveling human scourge, it will join a rogue's gallery of killer influenza viruses that have struck humanity through the millennia.

Influenza's History

The earliest-known reference to flu probably comes from the writings of the ancient Greek physician Hippocrates, who in the 5th century BC described an outbreak of coughs and pneumonia in the city of Perinthus. It was centuries before the illness came to be known as influenza (Italian for "influence" or "visitation"). People believed the disease was caused by inauspicious alignments of the stars.

Pandemics have swept the world 31 times since 1580, the first clearly recorded case. The most infamous was the 1918 Spanish flu outbreak, which claimed the lives of 20 million to 40 million people before it was over. All the pandemics' viruses belonged to a large family known as Influenza type A. The virus looks like a sphere studded with hundreds of tiny spikes. Inside the sphere's core are eight strands of genetic material carrying building instructions for a modest 10 proteins — all the virus needs to infect, replicate and spread. The spikes on the outside, comprised of two proteins known as H (hemagglutinin) and N (neuraminidase) act like hooks to help the virus get into and out of cells. Hs and Ns come in many different forms, and the major subtypes are all assigned numbers.

How Disease Spreads

A cough from an infected person can send a droplet of fluid packed with millions of flu particles through the air to the next victim's nasal passages. The virus attaches to the victim's cells using its hundreds of spikes. Once inside, it diverts the cell's machinery for its own nefarious purpose: the mass production of more viruses. Errors accrue as the virus' genome is copied, causing a gradual "drift" in the structure of its proteins. Especially important are slight changes in H and N. This drift is why people can get flu over and over, and new vaccines are needed each season. Immune systems can't entirely keep up with the changes, but these flus are usually not lethal because our bodies have been exposed to similar viruses.

A more drastic change is needed to spark a pandemic — a viral "shift." A virus abruptly appears possessing H and N proteins that are especially foreign to human immune systems, different enough to warrant a new number in the flu classification system. A pandemic in 1957 was caused by a new combination of H and N known as H2N2. This replaced the

dominant subtype, H1N1, which was behind the 1918 pandemic. But where were the novel Hs and Ns that cause pandemics coming from? It wasn't until the pandemic of 1968 that scientists learned the surprising truth.

Examining the virus, they saw it was of type N2, which was already circulating. But it had a new kind of H. It looked a lot like an H from a virus in a duck. Years of work by Robert Webster at St. Jude Children's Research Hospital in Tennessee and colleagues revealed that ducks and other wild waterfowl harbor a smorgasbord of 15 different H types and nine distinct Ns. All of these exist in relatively unchanging form and are able to mix in every combination. Their conclusion was that all influenza is ultimately bird influenza; every flu virus on the planet today can probably trace its lineage back to the gut of a waterfowl. Perhaps Homo sapiens only met this killer after we domesticated ducks and brought both a valuable food source and a simmering reservoir of sickness forever close to our hearths.

Although chickens can get sick, these wild water birds have lived with the virus for so long that they typically don't fall ill. They just house the virus in their guts and excrete it in their feces. For humans, this reservoir in birds is the ultimate parts warehouse for pandemics, and it can never be eradicated. Luckily, bird influenzas are extremely hard to catch, even when people deliberately try (and in their laboratories, some scientists have). They are not adapted for living in people, in part because they need bird-like receptors to latch onto cells, and a warmer bird-like temperature to multiply in. In fact, scientists had long supposed that creating a new pandemic flu required a third party — the pig — as a mixing vessel to make the bird-human jump. Pigs have human and bird receptors in their respiratory tracts. That's why the 1997 Hong Kong outbreak from flu caught directly from a bird was such a shock.

The notion was so outlandish that scientists first suspected contamination from a nearby lab where Shortridge was working on animal flu. De Jong spent days in the lab of his colleague, Dr. Wilina Lim, making absolutely sure the sample she had sent him was pure. Lim's lab was meticulous, its paperwork perfect. Contamination from a bird seemed out of the question. It was time to sound the alarm. Webster, in Memphis, heard the news and scrawled a note to himself: "H5 in a child!"

Over the next few months, 17 others sickened and five of them died, all from an H5N1 virus that was traced to exposure to poultry. Testing revealed that there was a lot of H5N1 in Hong Kong. About 20% of the chickens in the live bird markets harbored it, and so did some ducks and geese. Some of the H5N1 strains weren't harmful, but some appeared to mutate, becoming lethal to poultry. Soon chickens were dying horribly. Shortridge recalled walking through the markets testing birds when he spotted what looked like a "chicken Ebola" in action. One moment, birds happily pecked their grain; the next, they fell sideways in slow motion, gasping for breath with blood slowly oozing from their guts. "The infection was obviously tearing away at the inside of the birds," he said. "My reaction was: 'This virus must not escape from Hong Kong.' "

Laboratory sleuthing later revealed that the 1997 H5N1 virus that killed people and poultry was an exotic hybrid cobbled together from three separate viruses. The H5 piece came from a virus in a goose. The N1 piece came from a second virus in a quail. The remaining flu genes came from a third virus, also in quail. And quail probably served as the mixing pot where the three came together. "Who would have thought the quail would be involved in all of this?" Shortridge said.

In hindsight, it is likely that people have occasionally contracted flu from birds for eons. Poultry infections would flare, a farmer might sicken, then the outbreak would die out without spreading. But today's crowded world is different. People and their birds are constantly on the move. Unprecedented numbers of domestic flocks provide vast barracks for the propagation of viruses that can be repeatedly introduced from wild birds. Workers toil among the flocks unprotected by masks or gloves.

The three viral building blocks that were used to cobble together Hong Kong's 1997 H5N1 virus never left, Shortridge said. They were found in birds in the Hong Kong markets and in geese in southern China. Such ingredients are probably widespread in the region. There are other parts of the world where threats could be smoldering, and other threats besides H5N1.

Poultry influenzas are not uncommon. A severe outbreak of H5N2 influenza in Pennsylvania chicken farms in 1983 led to the culling of 17 million birds at the cost of close to $65 million. Last year, 31 million poultry were exterminated in the Netherlands to put a stop to an outbreak of another, H7N7 type of flu virus there. A veterinarian died and more than 80 other people contracted eye infections. And a lethal new type of influenza might yet come from a pig, not a bird.

Shortridge said that the message from the Asian bird flu outbreak is that nations need to identify potential viral threats long before they flare up and spread past containment. That means routinely going into farms and markets to take blood samples from pigs and fowl. It means constantly tracking what viruses the animals are harboring — and keeping an eye out for sudden changes. Even if you do all that, influenza is an unpredictable beast that can catch you if your back is turned. "The thing about flu is — expect the unexpected. Be looking all the time," Shortridge said. "Look at the normal first, for that which you might expect. And then look for what you don't."

class assignment #5

Read the article "Latching On to a Horror," and answer the following questions. The assignment is due by 1:30 p.m. on Friday, 1 March. You may e-mail it (subject is 102#5 Your Name) or turn it in word processed at lecture (Thursday) or to my office no later than 1:30 p.m. on that Friday. 12 points.

1. What was so unusual about the flu that the three-year-old boy described in the article had?

2. The first paragraph of the article has the statement, "We realized this could be a pandemic situation." What is a pandemic?

3. Avian viruses are identified with a pair of letters and a pair of numbers, such as N5H1 that was reported on in the article. What do the letters N and H stand for? What do the numbers represent?

4. Which viral subtype was responsible for the 1918 "Spanish Flu:" outbreak? What about the 1957 pandemic? What was the subtype for the more recent swine flu outbreak?

5. What does an Influenza type A virus looks like? Where are the H and N proteins located on the virus? What do these proteins do?

6. How many different H's and how many different N's are there? Given that these proteins may mix in all possible combinations, how many different HN combinations may exist in nature?

7. Why are bird influenzas described as being "...extremely hard to catch?"

8. Why would a swine flu be easier to catch and pass on than an avian flu?

9. Birds of all sorts have lived with the flu virus for millennia. In fact, it is thought that all human flu viruses originated in birds. What is it about conditions today that make the concern about the possibility of a new avian flu virus jumping into the human population so much greater than it might have been just a hundred years ago?