Predicting an H5N1 Influenza Pandemic –A Great Challenge to the Scientific World–

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Now, as the attention of the news media worldwide is focused on the horrifying outbreaks of bird flu, or avian influenza, in Southeast Asia, Mainland China, and Turkey, which are causing apprehension around the globe, the most frequently asked question is, will the avian flu evolve into a person-to-person transmissible influenza disease? The second question to follow is, when will it occur?

In our recordable history, it is estimated by scholars that the world may have experienced twelve great influenza epidemics over the past four hundred years. That being said, though the so-called Spanish Flu devastated the world in 1918, the cause, the influenza virus, was not identified until 1930, and scientists did not figure out the entire gene sequence of the virus until as recently as 2004. It is still not quite certain that bird flu was indeed the villain in the past disastrous human pandemics, which occurred before the 20th century. However, as far as the outbreaks of the 20th century are concerned, there were definitely three flu pandemics appearing in 1918, 1957, and 1968. Modern medical history clearly has convincing evidence that attributes the pandemics to the evolution or conversion of the original avian influenza viruses, H1N1, H2N2, and H3N2, respectively, into forms transmissible between humans. History tends to repeat itself as they say. What we know now is that H5N1 is already capable of causing infection in human beings and the incidents are becoming more and more intensive and widespread. Therefore, almost all influenza experts are convinced that it seems inevitable that H5N1 will become transmissible among

humans sooner or later and then create a major pandemic that will be devastating. The only question is when it will happen. In the meantime, the only correct choice we have is to monitor the situation closely and to do our best to prepare for it.

Both SARS and influenza are viral zoonoses or zoonotic diseases that can be passed from animals, whether wild or domesticated, to humans. Zoonoses will surely be the predominant causes of newly emerging human communicable diseases in the future. The reasoning behind this opinion is that nowadays, various factors such as an ever rapidly changing environment, well-developed transportation networks, and super dense population allow some viruses, formerly hidden in rare animals and remote wooded areas and thus normally residing far away from populated regions, to become the next door neighbors of human beings. Under such circumstances, once certain deviant mutations occur in one of those rare viruses and cause it to become infectious to human beings, chances are we would end up with a newly emerging communicable disease. Even worse, as the infected human has no immunity against the newly evolved virus; after sensing the viral invasion, the T cells of the body's immune system are most likely to become super alarmed and launch an all-out attack, which would result in the release of a large quantity of cytokines, which in turn may cause great harm and even death to the body's tissue cells.

Actually, for a virus infection to cross the original species border involves some complicated interactions between the viral surface (envelope) proteins and cell receptors. Therefore, this does not easily occur normally, but in the case of RNA viruses, including influenza viruses, SARS virus, and AIDS-causing virus (called HIV), they possess a characteristic quick mutating tendency in their replication process. Scientists have performed thorough studies to find out how an animal (civet cat) coronavirus transformed into the ghastly human SARS-CoV

Epidemiology Bulletin

in the years 2002 and 2003. The fact was, that before November 2002 in the Guangdong area, there were a few human SARS infection incidents but no conspicuous human-to-human cases. At that first stage, results of laboratory analyses showed that the virus had already gone through a sequence of mutations in which 29 nucleotides were deleted. That was the time when in eight townships and rural areas near Foshan, Guangdong, sporadic cases of transmission from animals or birds to humans appeared. Having jumped from animal to human, the mutation rate of the virus accelerated even more quickly possibly due to an increase in the differences in species immunity. This led to a second stage with a mutation spree involving as many as 82 nucleotides, and eventually a mutant evolved, which was capable of transmitting from human to human (evidently the start of the mutation was somewhere in late January and February of 2003). During the second stage of mutation, the virus had to adapt to its new host, so the replication rate would generally slow down, and its toxicity (harmfulness) and speed of spread appeared not so alarming. However, during the following third stage (from late February to June 2003) it persisted in a mutation bazaar of even greater magnitude, that affected a total of 415 Since the virus was becoming equipped with increased toxicity nucleotides. and stronger infectiousness, the outcome was the advent of a worldwide pandemic.

After 80 years of research, we can now infer that the 1918 Spanish flu pandemic likewise underwent roughly three stages, i.e. the very first one featuring transmission from animals (ducks) to humans, followed by a limited prevalence through a human-to-human transmission pattern, and the final pandemic. According to the literature, as early as in 1916 and 1917, Guangdong and other areas already had outbreaks of human cases of avian flu, or people contracting flu through contact with birds (the first stage). In early 1918, human-to-human influenza started to spread but remained at a rather limited level of prevalence (the second stage). However, late that year when winter arrived, the horrible pandemic broke out in full force suddenly and unexpectedly (the third stage), spreading all over Europe, America, and Asia, causing tens of millions of deaths around the globe.

So, the experiences of the 1918 Spanish flu and the more recent SARS outbreaks indicated to scientists a very possible evolving track when it comes to predicting the future avian flu trend in the 21st century. Let us take a look at what has happened recently. Back in 1997, through a route from chicken to human being, a number of human H5N1 bird flu cases appeared in Hong Kong. When the news broke out, WHO and influenza experts around the world were caught shockingly unawares, but they made a quick decision to urge the Hong Kong government to eliminate the entire chicken population in Hong Kong-a total of 3 million chickens. It resulted in a strange and unique Chinese New Year in Hong Kong history, with no chicken (a traditional New Year's dish) on However, because of this drastic but appropriate anyone's dining room table. measure, the evolving chain was fortunately broken and no human-to-human incidents took place. It appears that the wave of H5N1 bird flu had been halted before great harm was done. Then the same virus returned and launched another wave of attacks in late 2003 and early 2004. Incidents of people who got infected from sick birds occurred again in Southeast Asia, China, and Turkey. In view of this wave being much greater than the last one in scale, and the death toll reaching well over eighty, we are afraid that if the spread cannot be controlled soon, and the H5N1 virus is allowed to become prevalent and continue mutating, sooner or later the second stage of limited human-to-human mode will arrive, and then a global H5N1 influenza pandemic will become inevitable, maybe in the near future.

Whether this prediction will eventually come true is one of the greatest challenges now facing the scientific community, and it is by no means the first prediction of such a nature. There was a famous failure in flu epidemic prediction in modern history, related to the 1976 outbreaks of human swine influenza (SI) cases in the United States. The richest country on earth then reacted by investing a considerable amount of money and effort in preparing a huge amount of a specific vaccine, enough to immunize the entire American population. However, not only did the SI pandemic not materialize as predicted after all, but the well-intended vaccinations somehow caused the undesirable side effects of polyneuropathy (Guillain-Barre Syndrome). The scientific world learnt an important lesson from that event, i.e. under the circumstances, a vaccine should be prepared, but one should not jump the gun like the Americans did, but rather wait until the limited human-to-human transmission stage has definitely begun. According to the estimation of some experts, it will probably take about half a year for the second stage flu virus to evolve into the third stage, which is capable of causing a pandemic. That means there is enough time to select appropriate prevalent influenza viral isolates and manufacture needed vaccine after the human-to-human version of virus has definitely emerged.

In recent years, through successful R&D efforts, new types of anti-viral medicines that can effectively control the spread of such diseases in their early stage, as well as ameliorate the symptoms of the patient and decrease mortality, have become available on the market. The new drugs are also apparently efficacious against different types of avian influenza viruses, providing useful tools in the arsenal of the medical profession to fight the disease. Whether we are able to win this major historical challenge, or in other words, whether those

Epidemiology Bulletin

drugs will stop this wave of H5N1 invasion in time to avoid a pandemic, remains to be seen. To maximize our preparedness for a possible looming pandemic, one point worth mentioning here is that we should treat it in the same way as purchasing insurance for any unforeseeable risks. In that way we won't have to blame ourselves for an unfortunate outcome, and endure harsh criticisms eventually coming from the government (the Control Yuan and the Legislation Yuan) and society (mainly through the media) in case the reality turns out to be far removed from our prediction. We sincerely believe that if every country involved in this public health concern can properly contain the propagation of the disease in its early stage, there is a good chance that we will be able to annihilate this H5N1 bird flu in the first stage or even the second stage of its development. That is exactly the target aimed for by the WHO at this moment. If successful, it will be the first major victory of human scientific undertaking in the 21st century.