The dangers of a global bird flu pandemic

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Health authorities around the world are warning that humanity could face the first global influenza pandemic of the twenty-first century. The spread of the H5N1 strain of avian influenza through poultry stocks in Asia and recently into Europe raises the prospect that the virus will mutate so that it can be transmitted from person to person, resulting in millions of deaths. In spite of the constant warning from scientists, governments in wealthier countries have responded in an uncoordinated and belated manner, largely leaving poorer countries to their own devices.

So far the H5N1 avian influenza has mostly affected poultry stocks in Asian countries and has resulted in the culling of over 120 million birds within three months. This has been a huge blow to poor rural communities that depend on their flocks of chickens and ducks as a major source of protein.

According to the World Health Organisation (WHO), so far there have been 117 confirmed cases of human infection and 60 deaths, with Vietnam the worst affected with 91 cases and 41 deaths. Most of the cases have been in previously healthy children and young adults. Although the infection rate among humans is relatively low, scientists fear that the large populations living in close proximity to infected poultry creates the conditions for the virus to mutate and become highly infectious to humans.

Scientists estimate that sometime prior to 1997 the H5N1 strain began to establish itself in Asian poultry populations. The virus at first seemed to pose little threat as it only produced mild symptoms such as ruffled feathers and reduced egg production. However, it mutated into the current highly pathogenic form capable of killing birds within 48 hours and with a mortality rate close to 100 per cent. The first outbreak of this new potent virus was in 1997 in Hong Kong where 18 people were hospitalised and six died. Authorities destroyed 1.5 million birds to remove the source of infection.

The next outbreak was in South Korea in 2003 where a number of commercial flocks were devastated. Health authorities began to raise concerns that a global pandemic was in the making. In January 2004, the H5N1 virus was found in poultry in the southern provinces of Vietnam and was also responsible for the death of several children in the capital Hanoi. Some 400 poultry outbreaks in Vietnam have affected at least 3 million birds. At the same time, the virus was found on a single farm in Japan.

This January a WHO report entitled "Avian influenza: assessing the pandemic threat" concluded that "all prerequisites for the start of a pandemic had been met save one, namely the onset of efficient human-to-human transmission. Should the virus improve its transmissibility, everyone in the world would be vulnerable to infection by pathogen—passed along by a cough or a sneeze—entirely foreign to the human immune system." According to WHO estimates, the virus is now endemic in bird populations in parts of Asia and is becoming more pathogenic in mammals.

The H5N1 virus has continued to spread to central Asia and Europe. Recent assessments published in the science journals *Nature* and *Science* speculate that the virus is being transmitted by an unknown species of wild migratory bird. Scientists first suspected that the poultry trade and other human activities were responsible for the spread of the virus but two months ago 100 wild fowl killed by H5N1 were found at a remote lake in Mongolia.

US Department of Agriculture scientist David Suarez concluded that "there is much stronger evidence that wild birds are spreading the virus" and that "it will be difficult or impossible to control the spread from country to country". In April the virus killed about 6,000 migratory water birds at Lake Qinghai in northwestern China.

In the next few weeks, migratory birds, including possible influenza carriers, could hit the sub-Saharan wetlands. On October 19, UN Food and Agriculture Organisation (FAO) veterinary officer Joseph Domenech said that if the virus becomes endemic in Africa, the chances of it mutating to spread between humans, potentially triggering a pandemic, will increase. The possible consequences are serious, as many African countries are not equipped to even monitor the virus, so it could go undetected for some time. The WHO report also raised the possibility of the avian flu interacting in some unknown and potentially deadly way with a population already devastated by HIV.

It is not clear how or even if the H5N1 virus could become more transmissible in human populations. The WHO report stated that a possible mechanism could involve stepwise changes that occur as the virus mutates during infection of humans or other mammals that gradually would allow the virus to improve its transmissibility to humans.

Viruses are very simple parasitic microorganisms consisting of a protein case containing a piece of genetic material—either Ribonucleic acid (RNA) or Deoxyribonucleic acid (DNA). Viruses have no life functions of their own and have to infect a host cell in order to reproduce, ultimately killing the infected cell and producing symptoms of the infection.

There are three types of influenza virus known as types A, B and C. Only type A influenzas cause pandemics and can infect birds, pigs, horses, seals and whales as well as humans. Type A viruses are further classified according to two proteins on their surface called hemagglutinin (HA) and neuraminidase (NA). Many variations of the two proteins are known to exist, which are designated according to their surface protein subtype.

Type A viruses are notorious for their ability to change. They mutate by two processes. One is known as "antigenic drift"—small changes to the genetic makeup which alter the influenza virus in minimal ways. In this case, humans have some resistance to the altered virus. The second is "antigenic shift"—a major change in the viruses' genetic structure to which victims have little or no resistance. If the antigenic

shift produces a virus that is easily transmissible to humans then a pandemic can occur.

The WHO report stated that viruses of the H5 subtype have probably never infected humans previously or not within the lifetime of the current generation. This means that "vulnerability to an H5N1-like pandemic virus would be universal". Pandemics are always global events and in the past have spread around the world in less than a year.

There were three pandemics during the twentieth century. The worst was the 1918-1919 Spanish influenza that killed between 20 million to 50 million people worldwide. This was many times the total casualties during World War I. During the pandemic an estimated 30 percent of the world's population fell ill. In the US, 28 percent were affected and the average life span fell by 12 years in 1918. Medical authorities were unable to cope and were not even aware of the cause of death, as viruses were not isolated and identified until 1933.

By the time of the 1957-1958 pandemic, which started in Hong Kong, medical authorities had access to vaccines and antibiotic treatments that could be used to relieve secondary complications such as bacterial pneumonia. It took six months for the virus to circle the globe. The total death toll was about 2 million. The 1968-1969 pandemic broke out in south-eastern China and killed about 1 million globally.

In 1976 another pandemic was expected and a mass immunisation campaign was instigated in the US. The pandemic did not occur and the immunisation program sparked extensive litigation.

Genetic studies have shown that the influenza virus is made up of eight genes. If two viruses, such as the avian H5N1 and the human H3N2, infect the same cell they can swap genes resulting is a highly transmissible influenza strain. The 1957 pandemic was caused by the mixture of three genes from the avian virus with five genes from the circulating human strain. With the 1968 influenza virus, a similar reassortment of genes occurred. It is suspected that the reassortment first occurred in a pig and was then passed on to humans in a new more lethal form.

A recent study published in the October 6 issue of *Nature* detailed the final three genes of the 1918 influenza virus. The other five gene sequences had already been published. The viral material was obtained from the frozen lung tissue of victims of the 1918 pandemic who had been buried in the permafrost of Alaska, thus preserving the virus. The first attempt to resurrect the virus from frozen victims was made in 1951 but scientists were not able to culture any viable material.

In the latest study, scientists found that mice infected with the 1918 virus died more quickly than with any other known human influenza virus. The work to sequence the genome of the 1918 influenza virus began 10 years ago. The full sequence provides strong evidence that the 1918 flu virus is derived wholly from one that originally infected birds. Jeffery Taubenberger, a scientist at the Armed Forces Institute of Pathology in Maryland, recently commented that the virus was "the most bird-like of all mammalian flu viruses".

Pennsylvania State University virologist Eddie Holmes said the research was a "landmark": "Not only is this the first time this has been done for any ancient pathogen, but it deals with the agent of the most important disease pandemic in human history." Scientists are attempting to identify the mutations in the 1918 virus that allowed it to become infectious in humans. Such work may offer some strategies to prevent a reoccurrence of a human pandemic.

It is difficult to predict how the H5N1 virus will evolve, if a pandemic will emerge at all or how virulent it will be. The general consensus among scientists, however, is that a pandemic is long overdue. On June 30, WHO officials revealed that they had been considering raising the threat level for a global pandemic, from the current 3 (human infections have occurred, but there is little evidence of sustained human-to-human transmission) to 4 (small localised clusters of human infection) or even 5 (large clusters of infection and just short of a pandemic). The scale has six points.

The trigger was a report in Vietnam that many people had mild cases of influenza. Those in contact with them were testing positive for the H5N1 strain, indicating the virus was being transmitted from human to human. The situation in Vietnam remains uncertain but the cases were not confirmed by subsequent analysis. WHO's Western Pacific director Shigeru Omi warned that H5N1 remained at a "tipping point". The National Institute of Allergy and Infectious Diseases (NIAID) stated that "the last influenza pandemic swept the globe in 1968; many public health officials believe the world is overdue for another one".

An editorial in the May 26 issue of *Nature* concluded: "National governments' performance is half-hearted, incomplete and far too slow. International organisations are working with their hands tied behind their backs, for bureaucratic and diplomatic reasons. In short, the level of current efforts is not commensurate with the threat we face."

The WHO report considered mainland China as the "epicentre of influenza virus activity and the birthplace of pandemics". But little is being done to prevent an outbreak in southern China, where people of economic necessity live side by side with poultry and pigs, providing the perfect breeding ground for a new highly transmissible virus. Although scientists now have the capacity to track the genetic changes taking place in the H5N1 virus, there is no funding to help affected countries build effective surveillance programs.

In wealthy countries, the response of governments to the pandemic danger has concentrated on stockpiling the anti-viral drug Tamiflu (oseltamivir). But the stockpile of drugs is only sufficient to protect a small percentage of people, leaving the remaining population, particularly the poorest layers, highly vulnerable. In the rest of the world, the impact of a deadly bird flu would be even more devastating.