

# Pandemic Threat of Avian Influenza

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Apart from human immunodeficiency virus, influenza virus is probably the most studied virus. Despite so much being known about the virus, up to date, the world is still facing the usual problem of annual influenza epidemics and the constant fear of its impending pandemic that has every potential to devastate the world similar to the one that caused the pandemic in 1918-1919 which resulted in more than 40 deaths. The current geographical expansion of avian influenza H5N1 virus in wild and domestic bird populations with more than 115 human infections and 60 deaths has heightened global fear of the impending influenza pandemic. A good understanding of the unique feature of the virus, the relationship of its reservoir hosts with the domestic bird population (forces driving the emergence), and current actions taken by global, regional and national authorities (forces preventing the emergence) will give a better insight whether the impending influenza pandemic resulting from the current avian influenza virus H5N1 will ever materialise.

The influenza viruses belong to the genus *Orthomyxovirus* in the family *Orthomyxoviridae*. They are enveloped, negative sense single-stranded segmented RNA viruses ranging in size from 120 nm to 250 nm in diameter. The influenza viruses are classified into three antigenic types (A, B, C) based on the antigenic structure of their nucleocapsid and matrix proteins. The influenza A viruses are further divided into many subtypes based on the antigenic properties and a various combination of their two types of external glycoproteins; haemagglutinin (HA) and neuraminidase (NA)<sup>1,2</sup>. Up-to-date, there are distinct 16 HA and 9 NA antigenic serotypes known to exist in nature among the feral aquatic birds (such as terns, gulls, wild ducks, geese, shearwaters, etc) as reservoir hosts. Each of these external glycoproteins is encoded by a separate gene segment. Besides the two gene segments that encode

HA and NA, there are six other gene segments which encode other viral internal structural and non-structural proteins. Co-infection of a host with two different subtypes of influenza A viruses can result in genetic reassortment of their various gene segments and lead to the emergence of new subtypes of influenza A virus. This process of genetic re-assortment resulting in a total new subtype of influenza A virus is known as antigenic shift. In addition, due to the inherent error-prone nature of their RNA polymerases during viral replication, new antigenic variant of known circulating subtype (known as antigenic drift) with partial escape of previous existing herd immunity regularly arises in nature resulting in seasonal epidemics<sup>2,3</sup>.

Influenza is a highly contagious acute respiratory illness. Although occasionally occurring as sporadic infection, influenza is more commonly and dramatically seen as local outbreak or widespread regional epidemic. Epidemics can occur at any time, but are usually more prominent during the winter season in the temperate countries and in the months of high humidity in other regions<sup>4</sup>. Though influenza is short-lived and relatively mild in healthy adults, the large number of patients involved in an epidemic can result in a significant number of deaths especially in those in the extremes of age<sup>4-15</sup>. An influenza pandemic occurs with the appearance of a new subtype against which the global population has no prior immunity. This may result in several, simultaneous epidemics worldwide associated with high morbidity and mortality. The increase in global travel and communications, as well as urbanisation with high population density, further increase the risk of rapid global spread of a pandemic should a novel subtype of influenza A virus with high human to human transmission arise. The resultant health and socio-economic impact for each community or country will depend very much on the virulence of the pandemic strain of influenza A virus, population age

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structure and density, socio-economic status and in-place preparedness plan to handle the eventuality. Based on mathematical modeling, Meltzer et. al. estimated 89,000 to 207,000 deaths; 314,000 to 734,000 hospitalisations; 18 to 42 million outpatient visits; and US\$71.3 to US\$166.5 billion economic impact (excluding disruptions to commerce and society) for USA should the next pandemic hit the country<sup>14</sup>.

Though antigenic shift via genetic re-assortment due to co-infection of a host (such as swine, horse or human) by two different subtypes of influenza virus occurring in nature was often attributed as the process that led to the emergent of a novel pandemic influenza A subtype, the potential pandemic new subtype of influenza viruses against which human population has no immunity could arise by other means.

Namely:

1. An avian or another mammalian influenza virus that has accumulated sufficient mutations to jump species barrier and infect humans with high efficiency of human to human transmission;
2. Re-emergence after long period of dormancy in which the human population has lost the prior immunity; or
3. Intentional release by bioterrorist of a new bio-engineered subtype.

Previous studies based on epidemiological features and clinical presentations of influenza showed that the world had experienced a number of influenza pandemics since its first description of epidemic illness by Hippocrates in 412 B.C. Seroarcheological and virological studies confirmed such influenza pandemics occurred in 1889-1890, 1900, 1918-1919, 1957, 1968, and 1977 due to the emergent of new subtypes. Detailed virological studies using powerful molecular techniques (reverse transcriptase-polymerase chain reaction, nucleic acids sequencing and reverse genetic) shed more light even as to the origin of the past pandemic strain of influenza viruses<sup>15-17</sup>. The H1N1 subtype of influenza A virus that caused the 1918-1919 pandemic was shown to derive directly from an avian origin which had accumulated sufficient mutations for efficient human to human transmission. The origin of influenza viruses responsible for the 1957 and 1968 pandemics was by genetic re-assortment of the last circulating human influenza virus with the avian influenza A virus contributing at least 3 (PB1, HA2, and NA2) and 2 (Pb1, and HA3) gene segments respectively. The pandemic strain of H1N1 subtype in 1977 was due to the re-emergent of the long

dormant last circulating strain of influenza A virus H1N1 (speculated to be remained frozen in the Siberian lake till its re-emergence) prior to the appearance of H2N2 in 1957.

The spillover of avian influenza virus from wild birds to domesticated ducks and poultry in nature is not new, but the recent spillover of highly pathogenic avian influenza virus H5N1 into poultry population associated with high mortality in affected poultry and the involvement of humans with fatalities (Hong Kong in 1997, East and Southeast Asia in 2004 and 2005) has triggered substantial concern and fear that the threat of the next pandemic is imminent and often said to be long overdue. This concern is heightened with the geographical expansion of this avian influenza A virus H5N1 in migrating bird population and spillover into domestic birds in Romania and Turkey. Based on the unique genetic characteristics and promiscuous nature of influenza A viruses for different hosts together with past supportive evidences of their emergent, the present highly pathogenic avian influenza H5N1 has every eventual opportunity to evolve into future pandemic strain by either accumulating sufficient mutations or re-assort with current circulating human influenza A viruses (H3N2 and H1N1) (or even other mammalian influenza A viruses) should no drastic measures be concretely and rapidly taken to stamp out its current circulation in domestic bird population and prevent its further re-introduction from wild bird population.

Concerted global, regional, sub-regional and national efforts and activities were pro-actively taken by appropriate authorities and technical staff to contain, control and eliminate the avian influenza virus H5N1 in infected poultry population. Simultaneously, similar efforts were taken to prevent its spread to uninfected poultry and human to minimise the risk of its evolution into the pandemic strain. So far, the outcome and effectiveness appeared to vary with each country with reasons which may due to a combination of factors, such as, political will, financial support, technical expertise and co-operation at all levels to carry out the activities. Thus far, World Health Organisation has in-placed system and logistic of world-wide surveillance for influenza virus since 1950s, policy of vaccine development, guidelines for influenza outbreak investigations, control and pandemic preparedness plan to meet the challenges and threat of pandemic influenza. Unfortunately, all these in-placed WHO measures and activities, as well as, other initiatives carried out by affected countries in the region may not be adequate to

reduce the threat of the next impending influenza pandemic from occurring.

A strategic preparedness plan is good to reduce the health and socio-economic impact should the influenza pandemic occurs. In my opinion, the money and resources could be better utilised to avert or abort an impending pandemic than otherwise. World Health Organisation and/or other international organisations should act urgently and more pro-actively in mobilising the resource-rich countries to assist the affected resource-poor countries to eradicate the current

circulating avian H5N1 virus in the existing poultry population rather than waiting for the pandemic strain to emerge and then kick-in all the so-call preparedness plans. Prioritizing research is also urgently needed to gain better understanding on the ecology of reservoir hosts of avian influenza virus in relationship to the existing pattern of domestic bird farming so that active measures should be taken to re-structure future global poultry farming and marketing to mitigate or at least minimizing the future risk of virus spillover from their reservoir hosts into domestic birds and protect the world against the recurring pandemic threat.

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