

Editorial

Avian Flu and Influenza Pandemics in Human Populations*

Influenza viruses infect a wide range of species including pigs, horses, ducks, chickens, and seals. In most of these species the virus produces an acute infection. In wild ducks and other aquatic birds the virus primarily infects the gut and the birds do not appear to have physical symptoms. Ducks may remain infected for 2 to 4 weeks and during this time they shed the virus in their faeces which makes them potentially a major reservoir of infection. The pool of virus present in other species is an important genetic reservoir for the generation of new flu viruses that infect humans. In considering strategies for controlling flu pandemics in human populations the presence of an animal reservoir has to be taken into account.

There are three groups of flu viruses, influenza, A, B, and C. Type A viruses are able to infect a wide variety of warm-blooded animals. Analysis of their genomes indicates that all strains of influenza A originated from aquatic birds. By contrast type B and C are mostly confined to humans. At any one time a number of different strains of virus may be circulating in the human population.

The genome of flu viruses consists of negative sense single-stranded RNA which means that it must be first copied to a complementary positive sense strand of RNA before it can be translated into protein. The genome is segmented and consists of seven or eight fragments of RNA encoding approximately 14 proteins.

The viral RNA is enclosed by nucleoproteins to make a ribo-nucleoprotein complex which is contained in the central core of the virus called the capsid. The viral envelope is a lipid bilayer formed from the plasma membrane of the host cell that produced the virus. The viral envelope contains two virus encoded proteins viz. haemagglutinin and neuraminidase. The virus uses haemagglutinin to attach to the cell that it will infect. Haemagglutinin can bind to a sialic acid containing polysaccharide, glycoprotein, which is present on the surface of a variety of cells. Neuraminidase can cleave sialic acid residues from polysaccharides. It has a role in clearing a path in the surface of the target cell prior to infection, and it promotes release of the budding virus from host cell after infection. Inside the host cell new viral genomes are produced from a complementary strand of RNA which is positive sense but structurally slightly different from the parent mRNA.¹

Viruses which contain RNA are flexible and can mutate rapidly. When this property is combined with a segmented genome that allows recombination easily there can be a variety of genetic diversity in nature. Only a few subtypes H1N1, H1N2, and H3N2 circulate in mammalian hosts, but a wide variety of subtypes circulate freely in wild birds mixing and exchanging gene segments though rarely in association with disease.

The structures of influenza B and influenza C are more or less similar to that of Type A, although in influenza C the functions of the haemagglutinin and neuraminidase are combined in a single molecule, haemagglutinin esterase. Influenza C does not normally cause clinical disease or epidemics.

In humans, pigs and horses flu viruses circulate through the population at regular intervals. Flu is endemic in tropical regions and seasonal in winter months in temperate countries. Sporadic epidemics also occur in sea mammals and poultry. In these species high mortality is typical. The influenza virus accumulates a number of genetic mutations during its replication resulting in what is called *antigen drift* which brings about progressive changes in the molecules present on the surface of the virus. This means that the immune response which was effective at recognizing and eliminating the virus from the previous year is less effective against the strain of the current year. More worrisome is major genetic change occurring at irregular intervals called *antigenic shift*. The process occurs in only influenza A virus at intervals of 10 to 30 years, and results in major pandemics. The pandemic strains are designated according to their surface antigens e.g. Spanish flu (H1N1) in 1918, Asian flu (H2N2) in 1957, and Hong Kong flu (H3N2) in 1968. Research on victims of the 1918–19 pandemic which killed 20 million–50 million people around the world showed that in the 1918 virus the haemagglutinin adapted to human sialo-polysaccharide in a different way from adaptation in subsequent pandemics. This suggests that the virus can jump the species barrier from birds to humans in more ways than have been realized. Major human influenza outbreaks since 1918 and the animal species implicated are listed in Table 1.

In 1997 a new strain of influenza A, H5N1, was identified in Hong Kong. The strain was widespread in poultry but a small number of people also became infected with high mortality.^{2,3} The epidemic was contained by a mass cull of poultry. Whether H5N1

* Images available on www.tropej.oupjournals.org.

TABLE 1
Major influenza outbreaks

Year	Strain of influenza	Animal species implicated
1918	H1N1	Pigs
1957	H2N2	-
1968	H3N2	Pigs
1977	H1N1	Pigs
1997	H5N1	Wild geese, poultry
1999	H9N2	Ducks, pigs
2003	H5N1	Poultry
2003	H7N7	Poultry, pigs

strain was an isolated incident of spread from chicken to humans or whether human-to-human spread can occur cannot be known because the epidemic was nipped in the bud. However the high virulence of the strain could be related to the new variant haemagglutinin (H5), and partly due to a different type of polymerase.

In the binding of the haemagglutinin to the host cell the composition of the haemagglutinin determines how strongly the binding will take place since it depends on the shape of the haemagglutinin molecule being the right shape to fit with a host cell surface polysaccharide molecule. For the same reason it determines what range of the polysaccharide (and thus the cell type) the virus can bind to. More virulent strains tend to have haemagglutinins that can bind to a variety of cell types. Birds have different polysaccharides on the cell walls compared to humans, which means that a strain of avian flu finds it difficult to get a grip on human tissues. This means that even if some humans catch it, the chances are that it will not be passed on to others.

Human disease associated with influenza A subtype H5N1 re-emerged in Hong Kong in January 2003, and again in March 2003. There was an outbreak of avian influenza A subtype H7N7 in the Netherlands, and workers involved in the slaughter of infected flocks contracted viral conjunctivitis.⁴ The H7N7 virus isolated from those patients had several disquieting features. Not only could it replicate in the human conjunctiva but also there was evidence of human-to-human spread. Nearby herds of swine also showed serological evidence of exposure.⁵

What is worrying is what might happen if H5N1 also becomes transmissible between humans, rather than merely on occasion. The most likely way for that to occur would be if someone who caught H5N1 from chicken, say a poultry worker, is also incubating ordinary human flu virus. The two strains might exchange genetic material creating a hybrid virus with haemagglutinin that could easily bind to human cells. Since 1997 five avian outbreaks have infected a

few people by direct transmission from birds, but there were no human epidemics. However, in February of this year it was confirmed at a press conference at WHO headquarters that human-to-human transmission has been recorded in a family in Vietnam.

Another way for such transmission to occur is the presence of an intermediate host such as the pig, whose respiratory epithelium shares sialic acid containing polysaccharide molecules with both birds and humans. Since most farming communities in south east Asia raise chickens and ducks as well as pigs conditions exist for such a transmission to occur. Another situation where assortment of genes is possible is the live animal markets in many parts of Asia. Hence the possibility of a pandemic occurring sooner or later must be taken seriously.

The lack of a specific human receptor in both H5N1 and H7N7 may be the reason for lack of human-to-human transmissibility at present. But taking all the above observation into account it appears that adaptation to a human type receptor would not require many mutational events.^{6,7} When influenza A viruses do cross into humans adaptation is rapid.⁸ A key signal of significant adaptation of avian influenza virus to human host would be the acquisition of the ability to transmit from humans to humans. This adaptation might be a result of sequential mutation in an avian virus genome, or by mixing segments from an avian virus with segments from a virus already adapted to human beings.

Reducing the probability of adaptation of H5 to H7 to humans by reducing the potential for recombination with viruses already adapted to humans underlies the current control policies of wide scale culling of the infected poultry population. But the sheer magnitude of the animal reservoir is a major challenge. In the 1997 outbreak in Hong Kong 1.4 million chickens and other poultry were destroyed. The 1999 outbreak there resulted in 1.25 million birds being culled, and culling is currently in progress in both Vietnam and Thailand, and in several other neighbouring countries. Recurrent threats of avian flu may also be a warning about avoiding overcrowding in methods of raising farm animals not only during rearing, but also in transportation and marketing. Suspicion has also been raised about the dangers of the so called wet markets where birds and animals are sold live for the table.

Developing vaccines against H5N1 and H7N7 influenza strains present a number of challenges. Current influenza vaccines are made utilizing chick embryo. The H5 and H7 strains are rapidly lethal to chick embryos so the current methods cannot work. Recombinant genetic technology will need to be employed, but the techniques involved are patented by biotechnology and pharmaceutical companies and would require negotiations. Assuming that all goes well, the vaccines so produced must undergo

field trials to prove their efficacy and safety before being widely used.

G. J. EBRAHIM

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