There *are* reasons to be optimistic about bird 'flu

Roger Kalla

Life has become much safer over the last 100 years due to advances in medical technology, sanitation and food production. These have resulted in an increased life expectancy accompanied by a decrease in growth of the global population. However, people continue to worry about potential risks and hazards posed by 'man-made' disasters and 'un-natural' diseases that are perceived to threaten our health and lifestyles and which are beyond our direct control. But what are the real risks and what actions are being taken to prevent an outbreak of a global influenza pandemic?

DISEASES THAT JUMP SPECIES

'Zoonosis' is any infectious disease that may be transmitted from animals, both wild and domestic, to humans.

Many of the serious epidemic diseases that have affected humans in historic times are ones that are spread from animals to humans. The plague, salmonella, tuberculosis, and influenza all fall into this category. In fact, for many 'human' diseases, the human is actually an accidental victim and a dead-end host, while the disease mainly spends its time replicating in non-human reservoirs perfecting its counter-defence against the host organism's innate immune system.

Zoonotic diseases that spread on the wing, by birds or bats, before they jump species and infect a human are particularly hard to contain and eradicate. Unrestricted by physical borders, these diseases have the potential of spreading globally. The detection of diseased wild birds carrying the highly pathogenic avian influenza strain H5N1 or the 'bird flu' in Asia and, lately, in Eastern Europe is a good example of a disease spread by birds and one that could be poised to jump the species barrier.

> ***Knowledge about the 'flu is the drug that will beat the next pandemic when it arrives.***

Medical technology that has protected us from many of the scourges of Man from earlier centuries is facing an uphill battle because of the ever-changing nature of influenza viruses. This always leaves the vaccine developer on the back foot, second-guessing the molecular make-up of the virus strain that will jump the species barrier and cause the future human pandemic.

Powerful antiviral drugs, such as Relenza and Tamiflu, the first line of defence against a 'flu pandemic, are the culmination of 20 or more years of molecular studies of the virus's life cycles by public and private research institutions in Australia and overseas. These basic curiosity-driven studies of the virus's intricate interaction with the host cells has led to new medical applications for blocking the replication of the influenza type A virus by targeting proteins on the virus's surface. The Australian government has already stockpiled 3.95 million courses of antiviral drugs, including Tamiflu.

But an estimated 20 million doses would be required for health and emergency workers, and the seriously ill alone, during a short-term outbreak. The antiviral drugs only offer relief of the 'flu symptoms and is no long lasting cure against the 'flu.

PUBLIC AND ANIMAL HEALTH POLICY

There are indications that these drugs are already losing their potency because the virus is building up resistance against the drug by mutating and changing its outward appearance and the surface proteins that the drugs are targeting.

The development of a vaccine will, at most, give a partial immunity to any human strain of the bird 'flu that will be the cause of a pandemic. Vaccines are best for controlling slow, stable epidemics such as smallpox, but are not as good for something as rapidly mutating as the influenza virus.

The best immediate solution seems to be to treat cases of human bird 'flu aggressively and to cull do-

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mestic birds that show signs of the disease, while keeping up the monitoring of sick migratory birds.

International co-ordination and open communication links that can give advanced warnings of an outbreak are vital. The World Health Organisation has epidemiologists in place in South East Asia tracking the spread of disease among human populations and who are looking, in particular, for incidences of possible human-to-human transfer of the virus. The South East Asian countries are trying to educate the rural population about the necessity of keeping poultry, pigs, ducks and other farm animals separated from humans, to look out for any sign of disease and to report it.

In response to the recent findings of diseased wild birds carrying the H5N1 strain in Russia, Romania, and Croatia, the British Government is to consider following the example set by authorities in Holland and Germany—they have made their poultry farmers lock their free-range chickens safely away. Likewise, part of the British Government's contingency plan for an outbreak of bird 'flu is that it can order free-range poultry farmers to bring millions of birds inside to prevent an outbreak of bird 'flu in poultry in the UK.

British national farmer groups are supporting these measures, but the free-range and organic poultry producers believe that there is no need now, or in the near future, to lock up roaming hens. According to the Soil Association, the largest organic marketing body in the UK, to do so would be to destroy the rapidly growing free-range and organic sector, a sector which grew out of fears of the 'mad cow disease' epidemic.

TECHNOLOGICAL FIXES TO THE BIRD FLU

All the suggested actions—the treatment of symptoms in humans using antiviral drugs, the increased surveillance and monitoring of migratory birds, the locking up of poultry and the culling of diseased birds—are at best only a holding strategy.

How do we get on the front foot in combating the influenza virus?

We need to break the chain of infection and re-infection between wild aquatic birds and poultry which is assisting the spread of the virus.

We could genetically engineer the domestic chicken to be immune to all major strains of influenza A that are affecting birds.

If chicken populations were to be replaced with transgenic birds that were resistant to 'flu, it would remove a reservoir of the virus and make it much harder for it to spread to humans and trigger a pandemic.

UK researchers in Cambridge and the Roslin Institute in Edinburgh, where Dolly the sheep was created, have already shown that chicken cells can be protected against 'flu by inserting small pieces of genetic material.

Chickens provide a link between the wild bird population, where avian influenza thrives, and humans, where new pandemic strains can emerge. Removing that bridge would dramatically reduce the risk posed by avian viruses.

The research team is following a couple of parallel approaches. One involves inserting a working copy of a gene that makes an antiviral protein called Mx, which is defective in many chicken breeds, and should improve their ability to fight off influenza strains.

The second approach is to harness a technique called RNA interference, in which small fragments of RNA are used to disrupt the replication of the 'flu virus. This is done in advance of the virus attacking the cell and thus in advance of any viral proteins being expressed that can be used to develop a vaccine.

By engineering chicken cells to make small RNA molecules that confuse the 'flu virus, scientists hope to confer resistance to a wide variety of strains.

However, the replacement of whole poultry flocks with GM birds will have to await a battle to win over public opinion and secure regulatory clearance. If these obstacles are overcome and farmers are willing to adopt GM chickens, the entire world stock could be replaced fairly quickly. Once regulatory approval were granted, it is estimated that it would only take between four and five years to breed enough chickens to replace the entire world population. Unfortunately, this might yet be too late for the present bird 'flu outbreak.

The other more indirect route is to dig deeper into the human influenza genes and to study the evolution of the new highly variable influenza genome.

There is a large-scale sequencing effort that will provide a comprehensive analysis of the evolution of influenza viruses and of the sudden antigenic shifts that precede the outbreak of a world-wide pandemic.

The sequencing of 200 isolates of influenza virus has revealed multiple novel mutational events, including point mutations, deletions and segment exchange. In one instance, an epidemiologically significant re-assortment for which the existing vaccine had limited effectiveness has been detected.

The Influenza Genome Sequencing Project is being expanded to include avian influenza strains such as H5N1. It is through these kind of studies that we will obtain an early indication of when the virus has re-assorted itself to become the next pandemic.

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