Avian influenza

In a flap

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Alarm over bird flu has focused attention on preparing for a human version

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HOWEVER much fear there is over bird flu spreading in Asia and Europe, at present the disease tends to make birds sick and not humans. This may change, and some countries are preparing for a pandemic of human influenza. This is wise, given the huge costs of having a significant fraction of the workforce off sick or nursing relatives. But the best way of preventing a human pandemic might be to monitor and limit the spread of bird flu.

The particular strain of bird flu currently circulating began in South Korea in 2003. It is the largest and most severe outbreak on record. Millions of birds have caught the disease and 150m poultry have been culled. Despite this action, the virus is now endemic in many parts of Indonesia and Vietnam, some parts of Cambodia, China and Thailand, and possibly Laos. Yet only 117 people have caught the virus because it is difficult to catch. In the unlikely event it is caught, it is highly lethal. More than half those infected, 60 people, have died. Those most at risk are poultry workers in these countries, their families and those working with wild birds.

The broader problem, and the reason for worldwide alarm, is that animal diseases often become human ones. This strain of bird flu—the highly pathogenic H5N1—could well

become something particularly nasty to humans. The virus can infect and kill a range of other mammals, including those which were previously considered resistant to infection by avian influenza. With H5N1 endemic in some countries, there is a continual possibility that the virus could mutate into a full-blown human disease.

Should the virus turn into something easily transmitted between humans, it would be likely to infect a large proportion of the world's population, as few people would be immune to such a novel strain. There is no way of predicting how dangerous it would be. But because a large proportion of the population would be vulnerable, even a low fatality rate could mean millions of deaths. And there is historical evidence that just this sort of thing happens three or four times a century.

If a new influenza virus were to cause only a mild disease, projections from the 1957 pandemic suggest it would cause between 2m and 7.4m deaths. Recent evidence suggests that the less severe pandemics in the second half of the last century, in 1957 and 1968, were caused by a human flu virus that had swapped genes with a bird flu virus. The more serious 1918 pandemic was caused when a bird flu virus adapted on its own to become transmissible between humans. The mortality rate was about 2.5% and 40m-50m died.

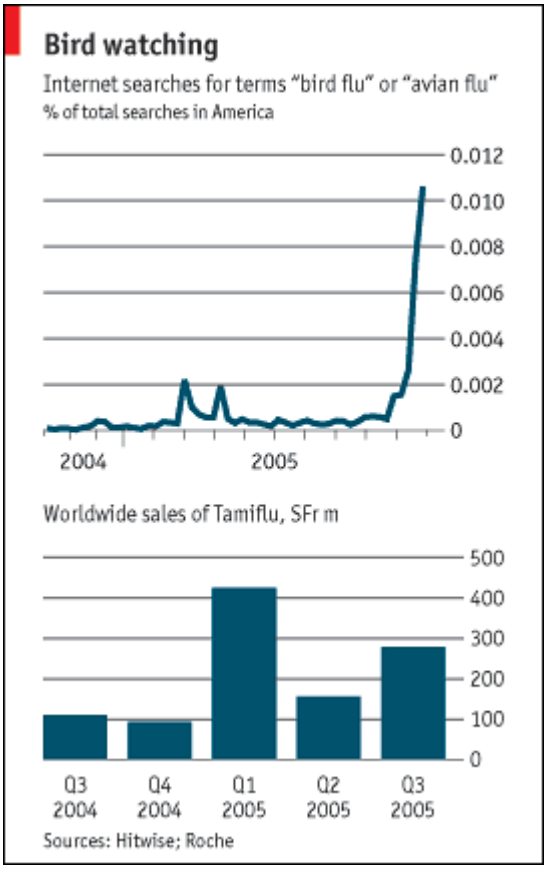
While neither the severity nor the timing of the next pandemic can be predicted, the spread of bird flu increases the probability it will happen. Many people—including Rajeev Venkayya, the senior director for biodefence at the White House—give warning that a major pandemic is overdue. If one happened this year, the world's ability to respond would be limited. Thus, the sprint to prepare for a pandemic is under way.

When human influenza begins to spread internationally, it is considered unstoppable. The disease spreads rapidly by coughing and sneezing and through direct contact, so regular hand washing is important to prevent infection. However, because infected people can spread the virus before they show symptoms, it will not be possible to use quarantine to halt its spread. Past pandemics, in less globally connected eras, have taken six to nine months to complete their global passage. There was nowhere to hide.

Although the 1918 mortality rate was low, lots of people died because so many people caught the virus. During pandemics, there are large surges in the number of people needing medical treatment, and health services quickly become overwhelmed. Many stay at home, either because they are ill or because they need to look after dependants who are ill, so disruptions can occur to essential services such as the police, transport and communications. Furthermore, many countries are likely to experience emergency conditions simultaneously, so international assistance could be limited.

The best preparation against an existing pandemic would be to produce a vaccine quickly and in sufficient quantities to protect people soon after the pandemic strain of virus emerged. Unfortunately, this is not yet possible. If an outbreak were to happen tomorrow, it would take four to six months to produce a vaccine. Even then, there would only be enough for those at greatest risk, such as health-care workers, pregnant women and asthmatics. Without a way of stretching vaccines, they will also be restricted to a small number of rich countries. Work is under way to change this, but it will take time.

Another option is to use anti-viral drugs in the event of an outbreak. They can be taken continuously to prevent infection, or given to the infected to reduce the severity of their symptoms and associated complications, perhaps saving their lives. Anti-viral drugs such as Tamiflu (oseltamivir) and Relenza (zanamivir) reduce the duration of illness caused by seasonal influenza if taken within 48 hours of symptoms appearing. It is thought likely they would do the same for pandemic influenza. But it is Tamiflu that is the drug of the moment, because it is a convenient tablet while Relenza is a dry powder that must be inhaled—and inhaled correctly. There are other, older, anti-viral drugs available—amantadine and rimantadine—but any emerging influenza is more likely to develop resistance to these drugs.



As countries have started to plan for a pandemic, many have begun stockpiling Tamiflu. It is expensive. But a study by Ran Balicer and colleagues at the Israeli Ministry of Health, published in August in *Emerging Infectious Diseases*, concluded that in Israel it was worthwhile at 2004 prices to stockpile Tamiflu not just for essential workers, but for all patients. What makes the study's conclusions more plausible is that the authors used very conservative assumptions, only counting the direct costs to the health system and lost workdays of a pandemic. They omitted wider indirect costs of disruptions to the economy and the value of lives saved—other work shows this is 83% of the benefits of fighting a pandemic. Dr Balicer argues that sizeable Tamiflu stockpiles are worthwhile even if a pandemic comes only once every 80 years. Most scientists believe that the next pandemic will come far sooner than that.

Yet, at current rates of production, some reports suggest it would take Roche, the Swiss drug firm that makes Tamiflu, a decade to produce enough to treat 20% of the world's population. Such is the demand for this drug that there is now a worldwide shortage and Roche appears to be bowing to pressure to allow other companies to produce it. There are signs of impatience everywhere. Researchers in Taiwan have just announced they have been trying to replicate the drug for the past few months. Cipla, a manufacturer of off-patent drugs in India, says that it plans to supply the drug cheaply next year. Thailand and Argentina, too, have warned they will bypass Roche's patent and make their own versions of the drug.

The shortage of the drug is particularly acute in America. It has Tamiflu for less than 1% of its population, while France has enough for 24%. Earlier this year, the Infectious Diseases Society of America said the nation's stock of anti-viral medicine was “totally inadequate and unlikely to provide any meaningful benefit”. Today, with Katrina-tinted spectacles, America wants to prepare but must wait at the end of a long line for its supplies. Countries that have disclosed orders for Tamiflu include Britain, the Czech Republic, Hong Kong, Singapore, South Korea and Thailand.

The World Health Organisation (WHO), which has been trying for years to attract attention to the threat posed by influenza pandemics, has called on governments to update their pandemic plans to minimise the health consequences. So far, only a small number of countries have done so. National plans cover topics such as who will be first in line for treatment, how to keep essential services running and when it might be a good idea to prevent public gatherings and close schools to slow the pandemic's spread.

Some of the countries with well-developed plans, such as Canada and Australia, were in the front line of the effort to stop the spread of severe acute respiratory syndrome from Asia in 2003. SARS—which was not as infectious or virulent as influenza—was limited to 8,000 infections; one in ten died. But it still cost an estimated $60 billion in lost output to South and East Asia because people cut back on travelling and shopping.

Again, notably, America has not published a plan, and there is confusion over when one might be produced. Earlier estimates suggested a pandemic could cause 89,000-207,000 deaths in America, but a draft plan leaked recently suggested 1.9m. The challenges are great, given that the country lacks a co-ordinated public-health system and 40m people have no medical insurance. The links between federal, state and local government are also weak.

Widespread alarm over bird flu is now focusing minds. Robert Shapiro, formerly Bill Clinton's economic adviser and now chairman of Sonecon, an economic advisory firm in Washington, DC, has been looking at the economic consequences of epidemics. He found that epidemics only have a big economic effect if they are pervasive and protracted.

So a pandemic that will make a lot of people sick over a long period of time is something to worry about. Mr Shapiro also warns that physically small and less well-developed countries, such as South Korea and Vietnam, are more vulnerable because the effects of a pandemic will be more pervasive there. But big countries have plenty to worry about, too. One study suggests that, if 15% of the American population were to fall ill, the economic

cost might amount to $93 billion. If 35% were to succumb, the cost would rise to $217 billion. These figures include health-care costs, lost workdays and the lost earning potential of the dead.

No wonder businesses are fretting about disruptions to travel and trade. Furthermore with the use of more overseas suppliers and “just-in-time” supply chains, some firms worry that their operations could be brought to a standstill even if enough of their own employees make it to work. As for the costs, companies themselves would have to shoulder them. Aon, an American insurance broker and risk consultant states, “broadly speaking, a pandemic will be an uninsured event.” Employee shortages are likely and Aon suggests that companies should assume 25% of workers could fall ill.

The top priority for everyone from scientists such as Klaus Stohr, who leads the WHO's global influenza programme, to economists such as Paul Gertler, at the World Bank, is better surveillance and prevention. Mr Shapiro, too, adds that “with sufficient resources, which are frankly trivial for an international effort, we could spend $250m-500m on an effective system of monitoring and rapid response to an outbreak in Asia.”

Computer models suggest that the WHO's global stockpile of Tamiflu (about 3m doses) could be deployed to the site of first emergence of a pandemic strain and used to eliminate it at source. However, the outbreak has to be detected within 21 days to have a chance of working. Close surveillance is vital to check that bird flu is not mutating into a human form.

The problem with surveillance is that some countries, such as Cambodia and Vietnam, lack the infrastructure needed to do it effectively. Even in countries that should be able to monitor the virus, such as China and Russia, the extent to which they are doing so, or are disclosing how far bird flu has spread, is open to doubt.

Reuters

Stalking horse

China's handling of bird flu has been characteristically secretive. It has not provided virus samples in spite of repeated requests from WHO officials. It has reported four outbreaks of bird flu this year (Qinghai in May, two in Xinjiang in June and Tibet in August) but no human cases, which has aroused some scepticism. It was sluggish about giving WHO officials access to affected areas. Part of the problem could be bureaucratic: the Ministry of Agriculture rather than the Ministry of Health is responsible for animal monitoring.

During a tour of South-East Asia last week, Mike Leavitt, America's health secretary, pledged support for an international surveillance network to quickly determine when the current strain of bird flu evolves into a virus that could spread rapidly between humans. More international co-operation and planning of this sort will be high on the agenda at a meeting of health ministers in Canada later this month. But if countries with avian influenza are to be persuaded to open up to surveillance and co-operation, they will want rich countries to loosen the purse strings for better diagnostics, anti-viral drugs and aid for veterinary and health facilities.

The most effective way to prevent a human pandemic would be to control any outbreak in domestic birds (the disease cannot be stopped in wild birds). Containing this disease would also make economic sense for the poultry industry and the many farmers in poor countries with smallholdings of ducks, geese and chicken that are a crucial part of the food supply but vulnerable to the H5N1 virus.

The United Nations Food and Agriculture Organisation (FAO) has called on countries on the flight paths of wild birds to set up warning and surveillance systems. These include northern Africa, the Middle East, Central Europe, India and Bangladesh. In such places, people live more closely with poultry, and the arrival of bird flu is cause for concern because it could lead to many new human cases.

In Europe, surveillance and veterinary health care are good, so the opportunities for infection of poultry workers (and subsequent mutation of the virus) are limited. Similarly, outbreaks of H5N1 in Japan, North Korea and Malaysia were quickly brought under control and are now believed to have been eradicated.

In an outbreak of H5N1 in Hong Kong in 1997, the territory acted quickly to destroy 1.5m chickens, virtually its entire stock. This action undoubtedly prevented an expensive regional outbreak until H5N1 emerged again in 2003. It may also have prevented a human pandemic. If the world is to keep the threat at bay, more painful sacrifices like this will be vital.

For that, some kind of global fund would be helpful to encourage culling, monitoring and the correct use of animal vaccines. The FAO estimates that $175m is needed to begin tackling the problem of avian flu at source by setting up control programmes. To date, $30m has been pledged but the World Bank and the European Commission are expected to invest much more in the control of flu through vaccination and better monitoring.

In the longer term, technological advances, if they are pursued, could reduce the threat of a pandemic, and the cost of containing and responding to one. The ability to stretch vaccines further might not be far away, increasing their supply once they are available. It

is possible, too, that some other cheap drug will be found that reduces the chances of fatal complications. Some recent research has indicated that statins, of which there are plenty, may be able to do this. And in five years (possibly much less, with effort) it is possible that the technology for producing flu vaccines will be transformed. Two companies, PowerMed and Vical, are working on flu vaccines that can be cooked up quickly in vats instead of being grown laboriously on eggs. Hundreds of millions of doses could be made in as little as three months by cheap automated factories. There are other possibilities and drugs on the horizon, too. Maybe one day, influenza will be a horror of the past and not of the future.