

## Flu pills for a pandemic threat

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In recent months governments of at least 21 countries have begun ordering stockpiles of the antiviral drug Tamiflu to protect their populations against a possible bird flu pandemic.

Bird flu is an infection caused by avian influenza viruses. The Asian bird flu outbreaks that occurred during late 2003 and early 2004 were due to the H5N1 strain. At that time, over 120 millions birds died or were destroyed within three months.

### Deadly evolution

The H5N1 strain belongs to the group of Influenza A viruses, which mutate much more rapidly than influenza B viruses. Indeed, the virus uses its genetic instability as a survival strategy: the speed at which the mutations occur allows it to escape host defence mechanisms.

Prior to 1997, according to the World Health Organization (WHO), the H5N1 strain of avian influenza virus began circulating in poultry in parts of Asia. Back then the virus caused only a mild disease with symptoms that escaped detection. In 1997 however, the virus mutated to a highly pathogenic form that could kill chickens within two days. The first documented human infections with H5N1 occurred also in 1997 in Hong Kong. The virus caused severe respiratory disease in 18 humans, six of whom died.

In 2004, H5N1 evolved: it found a new ecological niche in poultry in parts of Asia. The virus is now more deadly in poultry and in the mammalian mouse model. New animals like cats and tigers are becoming infected for the first time, suggesting the virus is expanding its host range. Viruses in 2004 survive longer in the environment than previously. By mid April 2005, the cumulative number of laboratory-confirmed human cases of avian influenza was 88, 51 of which were fatal. 'We think that the number of human cases is underestimated', says Maria Cheng, spokesperson at WHO. 'It is still a rare disease and cases are often misdiagnosed'.

### Prerequisites for a pandemic

WHO has identified three steps that are prerequisites for the start of a pandemic. First the emergence of a new viral strain to which the general population will have no or little immunity, then the confirmation that humans can be infected and can become seriously ill and finally the proof that the virus is efficiently transmitted from human-to-human, expressed as sustained chains of transmission causing community-wide outbreaks.

So far, two of the three prerequisites have been fulfilled. 'There have been no confirmed human-to-human cases of avian influenza', says Cheng. 'This is extremely difficult to prove, though there have been several incidences where WHO and other health authorities have concluded that this was a possible transmission route. These incidences have occurred in Hong Kong in 1997, and in Vietnam and Thailand last year'.

In the face of a possible threat, antiviral drugs play a role both in terms of prophylaxis and treatment in the management of influenza. Of the two classes of antiviral drugs specific for influenza, the 'M2 inhibitors' amantadine and rimantadine are the oldest and the most affordable. However, these drugs have various drawbacks: their safety in some groups of individuals is questionable and drug resistance can develop.

Drugs in the second and newer class, the neuraminidase inhibitors oseltamivir (Tamiflu of Roche) and zanamivir (Relenza of GSK) are safer and less subject to drug resistance. They are more expensive though. When neuraminidase is inhibited, the virus cannot spread to and infect other cells in the body. Tamiflu is designed to be active against all clinically relevant influenza viruses. Tamiflu can be taken orally, while Relenza comes as a powder to inhale. To date, 11,000 patients aged 1–97 years old have received Tamiflu in a clinical trial programme. In these clinical studies, the drug has been shown to be highly effective in reducing the severity of symptoms and the secondary complications such as bronchitis, pneumonia and sinusitis. It was also shown to be well tolerated and has demonstrated a good safety profile.

### Stockpiling to protect

'Tamiflu's production is quite complex. It takes around 12 months to produce,' said Martina Rupp, spokesperson at Roche. 'In 1999, WHO issued a pandemic preparedness plan. They want to assist the governments to plan ahead for the next pandemic'.

Many governments have ordered large quantities of Tamiflu already, but not all. The UK government has ordered 14.6 million doses of the drug, France 13 million and New Zealand around 800,000 doses. 'Governments are stockpiling in order to protect 20% to 25% of their populations', says David Reddy, Influenza Pandemic Taskforce leader at Roche. Roche has scaled up the drug production to satisfy the demand. 'We doubled the output production of Tamiflu and we will double it again soon. We did this thinking stockpiling will be important'. The US however has only bought 2.4 million doses, which represents <1% of the population. 'We are in close discussion with the US at this point' added Reddy.

Tamiflu sales already have had a big impact in Roche's earnings. On the 19<sup>th</sup> April 2005, the company has announced that its sales rose by 17% in local currencies in the first quarter. Tamiflu sales quadrupled to USD\$357 million in the quarter.

Other important elements in the fight against a pandemic threat are vaccines. 'Companies in the US and in Japan are working on the development of a pandemic vaccine', says Cheng. During past pandemics however, vaccines have never been available early enough and have not been produced in quantities allowing a positive impact on morbidity and mortality.

