

Avian Influenza Pandemic: Fight or Flight?



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Lately, the buzzing about Avian Influenza in the media has been getting louder. Striking images of dead poultry and ducks fill not only our televisions, but our minds. With all this commotion, we cannot help but look down at the chicken on our dinner plates and wonder if we are really safe. What is being done to protect us from another deadly influenza pandemic?

The key weapon against any viral pathogen is a vaccine. Unfortunately, there is currently no human vaccine available against the Avian Flu, and the task of developing one remains daunting (WHO, 2005). The flu virus has the capacity to mutate at high rates, and it takes at least four months to grow and mature vaccines (Park, 2005). By the time one is developed and produced, the virus may have already mutated to another virulent form. Several countries are currently preparing a prototype H5N1 vaccine. However, until the exact strain of H5N1 emerges and a pandemic is declared, the final vaccines will not be available (CBC News Online, 2005).

That is not to say there is no hope against the Avian Flu – several drugs exist to combat the disease. Tamiflu (oseltamivir) and Relenza (zanamivir) are two such drugs under the class of neuraminidase inhibitors (WHO, 2005). They are designed to inhibit the active site of neuraminidase, an enzyme that protrudes from the surface of the influenza virus. These drugs ultimately stop viral replication, inhibiting exchange of newly formed viral particles between cells (Moscona, 2005). They show great potential for

preventing influenza infections and reducing the severity and duration of flu symptoms. In the event of a pandemic, they will play an important role in limiting sickness and death. Trials are desperately needed in order to assess whether these drugs work better alone or in conjunction with one another (CBC News Online, 2005). For maximum effectiveness, Tamiflu and Relenza should be administered within 48 hours of infection. They may also improve prospects of survival in human infections if administered early, but clinical data for this is limited (WHO, 2005).



Figure 1: With the rise in cases human infections and deaths, these Vietnamese women protect themselves from the Avian Flu (US Department of State, 2005).

M2 inhibitors, such as amantadine and rimantadine, are an older class of antiviral drugs also available for use (WHO, 2005). Located in the viral envelope, M2 proteins play a crucial role in uncoating

the virus and exposing its contents to the host cell's cytoplasm. Inhibitors sterically block this process by binding to transmembrane proteins of the host cell (National Institute of Allergy and Infectious Diseases, 2004). Unfortunately, the M2 gene is susceptible to frequent mutations and drug resistance develops rapidly, limiting their effectiveness in a pandemic. The M2 inhibitor, amantadine, also sometimes has rare but disturbing side effects such as psychotic episodes (Abbott, 2005).

DRUG RESISTANCE IN HUMANS

The development of drug resistance is a realistic concern, especially since only a handful of medications exist to treat Avian Flu.

A recent case in Vietnam retrieved ten viral clones from a patient sample. When tested with Tamiflu, six clones were highly resistant ($IC_{50} > 763 \text{ nM}$), three clones were slightly resistant ($7.1 \text{ nM} < IC_{50} < 12.5 \text{ nM}$) and one clone was highly sensitive to the drug ($IC_{50} = 0.6 \text{ nM}$). IC_{50} is the concentration of a drug needed to inhibit viral replication by 50% (Mai Le et al., 2005). More drugs are required to inhibit resistant viruses, and thus IC_{50} values increase with resistance. Tamiflu-sensitive viruses generally have an IC_{50} between 0.1–10 nM (Mai Le et al., 2005). Furthermore, the patient in Vietnam had been taking care of her 21-year old brother, who had also been infected with the H5N1 strain of the Avian Flu. The brother's viral samples contained a neuraminidase gene that was identical to the patient's clone 7 virus. The patient's lack of interaction with poultry, and the timing between infections of the two siblings raised the possibility of viral transmission from human-to-human (Mai Le et al., 2005).

DRUG DILEMMAS

Knowing that this biological concern is no longer limited to avian populations, many developed countries are beginning to stockpile medications (WHO, 2005). Online pharmacies have been receiving a flood of orders – a ten-fold increase in the past month – with each company now receiving 20 orders a day (CBC News Online, 2005). Present levels of global drug production fall short of the quantities required

to manage a pandemic. Roche Pharmaceuticals is currently the sole producer of Tamiflu. They have recently quadrupled production and licensed several generic drug companies to produce the drug (Abbott, 2005). Roche has also made a donation of 3 million doses to the World Health Organization (WHO, 2005). However, a supply bottleneck persists with Roche's monopoly. At current rates of production, it would require over a decade to produce enough Tamiflu to treat 20% of the world's population. Tamiflu production is a complex and time-consuming process and is difficult to transfer to other facilities. The option of overriding the Roche patent to produce a generic version of the drug may be exercised if there was ever a shortage during a pandemic (CBC News Online, 2005). Recent studies using mathematical models suggest that drugs may prevent a pandemic if extensively used around main outbreak centers with strict quarantine and other non-medical measures (Weir, 2005).



Figure 2: Avian Flu vaccine development is a pressing issue (Tribune, 2005).

The prices of drugs are too expensive for many countries, particularly developing countries, which tend to suffer a lack of resources during pandemics (Marshall, 2005). One pill is needed to protect against the virus for one day, and based on past influenza pandemics, the first wave in a given area is believed to last up to 100 days. Knowing this, an individual

would need to stockpile 100 pills and start taking them the moment the virus circulated within the relevant region – a burdensome cost to many third-world countries (CBC News Online, 2005).

How Is Canada Doing?

The WHO has also been urging all countries to develop plans in preparation for a possible outbreak. Currently, only 50 countries have devised a protocol, among which Britain and Canada have obtained legal status for their plans (Abbott, 2005). It has always been difficult to even persuade developed and wealthy countries to stockpile on medications, especially when the drugs may not be used during the term of the current government (Abbott, 2005). The drugs also have a short five-year shelf life, and widespread use could make situations worse by creating resistant strains (CBC News Online, 2005). However, with the 2004 Avian Flu crisis in British Columbia, where an H7 influenza virus was detected on a farm, Canada is beginning to see the urgency of the situation (Public Health Agency of Canada, 2005). That crisis clearly demonstrated how novel strains of influenza, albeit not H5N1, could emerge in Canada.

Canada was one of the first countries to order Tamiflu. It has purchased 23 million doses to protect essential workers and treat those who were already infected (CBC News Online, 2005). Through the Canadian Pandemic Influenza Plan developed in 1988, guidelines are outlined for coordinated efforts between all levels of government, public healthcare officials, and emergency workers, and describes their roles and responsibilities in surveillance and responding to a pandemic (Public Health Agency of Canada, 2005). Health Canada's National Microbiology Laboratory in Winnipeg also works with laboratories across the country to identify and monitor emerging influenza strains (CTV News Online, 2005). According to the WHO, Canada is on the right track. With the measures it has taken through its Pandemic Influenza Plan, it should be well-prepared in the event an Avian Flu pandemic occurs (CBC News Online, 2005).

In addition, Canada is one of the few countries to have obtained the genetically-modified seed strain of H5N1 for vaccine development (CBC News Online, 2005). The contract to produce the vaccine has been

awarded to ID Biomedical Corporation (Quebec City), and they are hoping to begin testing on people next year (CTV News Online, 2005). The goal is to develop a virus seed bank so that a vaccine can quickly be created in the event that a human strain of the virus emerges. Influenza vaccines are traditionally grown in fertilized chicken eggs (WHO, 2005). This cost-effective method uses approximately one or two eggs to produce one dose of vaccine. However, this production method may be problematic as the H5N1 strain is lethal to the embryo, killing it before the virus can be harvested. The promising use of reverse transcriptase to produce a version of the virus that is non-lethal to the embryo is currently being investigated (WHO, 2005). This process involves using reverse transcriptase to convert viral RNA into DNA (Neumann et al., 2005). Naturally, the influenza virus does not encode reverse transcriptase nor does it go through a DNA intermediate. Mutations can then be introduced into the cloned DNA and when this DNA is reconverted back into the RNA state, the mutations pass on and occur in the genome of the viral RNA. In the future, there will likely be an increasing preference to generate influenza vaccine strains through reverse genetics as it is less cumbersome than traditional methods (Neumann et al., 2005).

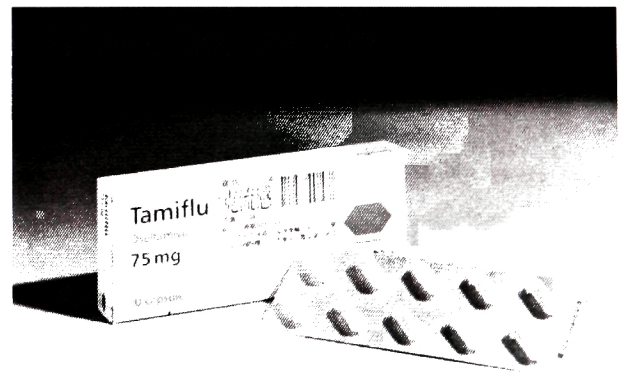


Figure 3: The shortage of Tamiflu and other antiviral medications arouses global anxiety (<http://www.roche.com.tw/medicine/Tamiflu.gif>).

Although we have yet to see the global effects of Avian Flu, the pandemic virus still poses a great threat. The numerous unprepared countries, limited supply of vaccines, and drug production difficulties may limit our ability to contain H5N1 should a pandemic arise. Adequately addressing these issues should be a priority for international health policy. **M**