

China's Antiviral Treatment for Potential Avian Flu Outbreak

By Li Yang, 10th Feb, 2004

I analyzed the current situation and proposed the conclusion that the use of Tamiflu as an alternative treatment during the time gap between the possible human bird flu outbreak in China and outcome of a vaccine was unaffordable and unreachable

As the avian flu outbreak swept through the Asia region. Experts had called for the stockpile of the antiviral drugs in case of emerge of new flu strain which could hit the human population badly as the vaccine won't be ready in a short term of time([news](#),[news](#)). Oseltamivir, also known as it's commercial name 'Tamiflu', was in the center of people's eyes again since its embarrassing imagine in the last year SARS outbreak in China (see my previous report). Last March, the Roche China was blamed for its 'unusual' sales strategy as they claimed the mysterious disease spread in Guangdong was bird flu and 'Tamiflu' was capable to cure birdflu. But this year, things are much different. The announcement made by WHO ([Avian Flu fact sheet](#)) and the Hongkong research team gave out a clear message that the neuraminidase inhibitors (Tamiflu or Relenza) could be the 'only choice' for human during an emergency avian flu outbreak, based on two main reasons: **A.** the avian flu virus seemed to be resistant (further testing is underway) to the conventional M2 inhibitors (amantadine and rimantadine); **B.** Research showed the neuraminidase inhibitors were effective against the H5N1 strains.

Let's first ignore the driven forces behind these research and take a look at the current situation in China. Unlike the SARS, Bird Flu hasn't affected much of the people's life in China as it's mainly a poultry disease. Though continue reports of human deaths connected with H5N1 infection came out from south-east Asia. China has cleared any human infection of bird flu so far ([news](#)), though [Mingpao](#), a Hongkong based news agency announced a suspected human case in Shanghai at the beginning of Feb ([news](#)). As the only licensed neuraminidase inhibitor in China, the need for Tamiflu won't rise unless there have a dramatic raise of human infection

cases in mainland (which would hardly be the case as I pointed out at the ‘communication strategy’ part). We did a market research this week and found out several facts:

- A. The sales of Tamiflu did NOT raise much though the massive media coverage of bird flu outbreak national wide;
- B. The production date of Tamiflu sold by the major distributor in Feb 2004 in Guangdong of Roche China were Jan, 2003.
- C. Nearly two thirds of the 14 hospitals we interviewed in Guangdong and Zhejiang don’t have Tamiflu on stock.

With the interview of the drug representatives (sales man), we concluded the possible reasons contributed to the above facts:

- A. **The price.** The two 75mg capsules/box Tamiflu would cost as high as RMB 59.00/box. Together with the instruction in the box said one need to take 2x75mg/day for 5 days for the treatment of flu, one could end up with RMB 300.00 for a single treatment. Compared with the more common drugs cost as low as RMB 1.00/box, few people could afford the use of Tamiflu;
- B. **Major part of people couldn’t tell the difference of cold and flu** (see my previous report ‘Is it a cold or flu?’), and seldom realized the serious complication the flu could have. Besides that, most people believed the conventional treatment for cold works for flu too. The advertisements of some manufactures also contributed to the confusion. People tended to take cheaper ‘cold drugs’ even in a flu outbreak;
- C. **The use of Tamiflu largely depended on the rapid diagnostic of flu** as the drug should be taken within the 48 hours of the onset of flu symptoms. In our previous report of the flu surveillance system, we found out that the conventional rapid diagnostic methods were not available even in major hospitals in major cities. A BD Directigen Flu test was supplied by the MOH to the local CDC for trials. Most rapid diagnostic of flu was conducted using RT-PCR in key labs (see English abstracts of Chinese flu research journals) and most hospitals used serum tests and viral isolation which couldn’t provide

a timely result. Without a rapid diagnostic of flu, there won't be need for 'Tamiflu', we concluded. Again, the price of rapid diagnostic method was also the obstacle as the QuickVue Influenza Test (produced by a US based company, haven't formally registered in China) had a price of RMB 128.00/test for bulk order in China. I have to say not 'many' people can afford the price. The major order of the QuickVue Influenza Test in 2003 was from an antiviral drug manufacture in Jiangsu Province who ordered several thousand tests for their drug research in the lab as the QuickVue test was a CLIA Waived test (the above information was obtained from telephone interviews with two major distributors of QuiDel Co. in Shanghai);

- D. **The control from the authority** During the SARS outbreak, the supply of Tamiflu was regulated by the government. This might due to the embarrassing sales strategy of the Roche China. The sell the Tamiflu in Guangdong wasn't so good since then and the distributor was still busy trying to clean out their stock of last year drugs.

The above are the basic imagine we formed about the antiviral treatment of flu in China. From which we proposed our conclusion: The expensive neuraminidase inhibitor won't have a dramatic raise of need unless China declares bird flu infections among humans. And the current stock of Tamiflu will quickly run out of supply once the outbreak occurs. We concluded that not matter how the international organizations find about the effectiveness of neuraminidase inhibitor against current H5N1 strains, the use of Tamiflu as an alternative treatment during the time gap between the possible human bird flu outbreak in China and outcome of a vaccine was unaffordable and unreachable. We hope this could be taken into consideration by the policy makers when they assess risks proposed by the potential bird flu outbreak in humans.

You can find my previous report below

The continue story of disease outbreak in China: Roche (China) is suspicious for releasing incorrect information of the epidemic situation thus to boost the sales of their new anti-flu drug --- Tamiflu.

By Li Yang Feb, 2003

As the chaos caused by the disease outbreak in Guangdong is about to quiet down, the national authorities and media are started to look back the whole incident. They find people were misled by some deliberately released information. That information at some degree caused the scare buying for drugs and worsened the situation. Today's cover story of Nanfang Daily questioned the credibility of Roche as the world 6th largest pharmaceutical company as evidence showed that Roche (China) released incorrect information about the epidemic situation and Tamiflu during the disease outbreak.

The timetable of 'Tamiflu incident' (from Nanfang Daily)

- **9th, Feb.** The Shanghai Roche Pharmaceutical Company invited some media, including Nanfang Daily, Guangzhou Daily, and Guangzhou's major TV stations to Guangzhou Holiday Inn and told them 'based on the symptoms, the disease outbreak in Guangzhou are very similar to the bird-flu outbreak in Hong Kong in 1997.' The company also announced their new anti-flu drug 'Tamiflu' was out of stock in Guangzhou.

During the outbreak, drug representatives of Tamiflu promoted the drug in most hospital in Guangzhou and clearly told the hospitals that Tamiflu was effective to bird-flu.

Since that day, a message about ‘ the atypical pneumonia in Guangdong was caused by bird-flu virus and Tamiflu can treat the bird-flu’ spread rapidly among people by Internet and SMS and reached the climax on 11th, Feb.

- **8th, Feb to 13th, Feb.** Tamiflu’s shipment in Guangdong reached 105,000 boxes, 100 times to the stock amount in Guangdong before 20th, Jan.
- **10th, Feb.** the market manager Chenqi told the reporter ‘according to the national authorities and experts in Beijing, the most likely cause of disease outbreak in Guangdong is bird-flu’
- **13th, Feb.** Roche (China) denied any fraud during the promotion of Tamiflu during the disease outbreak.
- **14th, Feb.** Nanfang Daily gave all the information they found about Roche (China)’s conduct during the disease outbreak to the Guangdong Provincial Bureau of Public Security. The government told the press they would launch an investigation on Roche (China) and would timely announce any news of the investigation.

The argument of this incident is mainly about 3 key questions. Had the caused of atypical pneumonia been identified as the Influenza B viruses which caused bird-flu? Is Tamiflu effective against bird-flu? Did the release of incorrect information help the boost of sales of Tamiflu?

Things are not clear right now as no official announcement has been made. But two facts we knew were that the Roche (China)'s drug representatives did tell the hospital Tamiflu is effective against bird-flu and the sales of Tamiflu boosted dramatically during the disease outbreak.

During the earlier stage of disease outbreak, I did suspect the bird-flu but I soon ruled out it. To my knowledge, H5N1 and H9N2 influenza viruses caused the bird-flu. The viruses used to exist in birds and domestic poultry. But during the 'bird-flu' incident in Hong Kong the viruses escaped the species barrier and transmitted directly from domestic poultry to human being. The incident shocked the international world and much attention had been paid to these highly pathogenic avian influenza viruses since then. Fortunately, the bird-flu viruses can only transmit through 'poultry to human' pattern, they can't transmit from human to human. By slaughter the domestic poultry, Hong Kong government soon controlled the situation. Though we still heard about the bird-flu in Hong Kong occasionally, the outbreaks remain in minor scale. Professor K.F.Shortridge in the University of Hong Kong had proposed a global-accepted theory that H5N1 viruses might acquire their interspecies transmission ability from the 'mix-vessel' of avian and human influenza viruses---pigs. And Professor Shortridge pointed out that mainland's mix-raise pattern of pigs and poultry might provide a perfect breeding ground for the new virus and could be the original source for bird-flu viruses. This January, the official of Health, Welfare and Food Bureau in Hong Kong admitted to the public that bird-flu had become an endemic disease in Hong Kong. Though many countries including US announced bird-flu cases, China's authorities never officially admit the presence of bird. But the close connection between Guangdong Province and Hong Kong made the people here be more aware of bird-flu news than any others. So, you could imagine

people's reaction when they heard the atypical pneumonia might be caused by bird-flu viruses.

Scare, panic, and they all rushed to drugstores.

The question is, do we have an effective treatment to bird-flu? Do we have the magic drug?

Though the international society had studied the H5N1 and H9N2 influenza viruses for years, we

are still not clear about mechanism for the unusual severity of the disease. The recently research

progress was made by Professor J.S.M. Peiris's team in the University of Hong Kong. They argued

that the induction of proinflammatory cytokines in human macrophages by influenza A (H5N1)

viruses might be the key factor for the high severity of the disease. Even though, our knowledge to

bird-flu viruses remains insufficient. Without sufficient information of the mechanism of the

disease, it's very difficult to find a proper treatment. Interestingly, I studied the neuraminidase of

influenza viruses during my M.Phil project in Birmingham and I was pretty familiar with

neuraminidase inhibitor. The clinical used neuraminidase inhibitor including Roche's Tamiflu®,

Glaxo-Wellcome's Relenza® and *etc., al.* The inhibitor won't affect the numbers of the infected

cells and, in addition, act late in the infection cycle to inhibit virus yields. As the viruses' yields

reach the peak during the earlier stage of disease, it's important to take the Tamiflu or Relenza as

soon as flu symptoms appear. No research has been taken on neuraminidase of H5N1 and H9N2

viruses so far (in fact, my PhD research proposal is about the study of neuraminidase activity of

H5N1 and H9N2 viruses). Even during the bird-flu outbreak in Hong Kong in 1997, doctors

mainly used Amantadine, a traditional anti-viral drug for the treatment. **We can conclude from**

the above information that Roche (China)'s announcement, 'Tamiflu is effective against

bird-flu', is not based on any hard evidence.

As the government has already launched the investigation, further inside information will come out of the surface. Roche (China) will face criminal charge if the authorities prove 'they deliberately release false information to boost their sales of drug and thus worsen the chaos'. No matter what happens in the end, Roche's bright imagine as the 6th largest pharmaceutical company in the world has already been damaged and it will take a long long time for them to overcome it.

Is it a cold or the flu?

By Li Yang 22nd Mar, 2002

Both a cold and the flu are viral infections that cause similar symptoms such as coughing and sore throat. But if you suffered a characteristic high fever and prominent headache, you might have got the flu rather than a cold. A cold is only a minor viral infection of the nose and throat, while the flu, on the other hand, is usually more severe. The flu, or influenza, is a respiratory infection caused by type A and type B influenza viruses that occurs mostly in fall and winter. The highly contagious virus usually enters the body through mucous membranes in the mouth, nose or eyes after an infected person coughs or sneezes. As the airborne virus can be inhaled by anyone nearby, no one can escape the risk of catching it.

It's already difficult for the ordinary people to tell the difference between a cold and the flu, but, to the Chinese and Japanese, things are even more confusing. In English, the word 'cold' and 'flu'

don't share any similarities, while in Chinese and Japanese, the word for 'flu' actually means 'epidemical cold'. One thing is right for this word is that it shows an important character of the flu---epidemical; but it also made a huge mistake---this word mislead people to think that flu is actually a kind of cold. We don't know how did this word come out of. What we do know is this word has already caused serious consequences in the prevention and treatment of the flu.

As we mentioned before, a cold and the flu share symptoms like coughing and sore throat. If people mistaken the epidemical flu with a cold, they will probably take some OTC medicine by themselves instead of going to see a MD. Cause from their interpretation, the 'epidemical cold' should be a kind of cold and medicine works for cold will also work for the flu. This could lead to some serious problems as the complications caused by the flu can sometimes be life-threatening. Based on same misunderstanding, people also blamed that the vaccination of flu was useless when they got a common cold. As they thought the vaccination of 'epidemical cold' should prevent them from getting any kinds of 'cold'. There are many other examples of the incidents caused by this misinterpretation.

As the word 'epidemical cold' has been used for more than half century, it's impossible to eliminate the bad impact by simply introducing a new word. An official regulation and guidance for using this word in public media can be a good solution. Besides that, we should put efforts to let the people know more about a cold and the flu. By doing so, people will understand the difference of these two diseases and won't be misled by 'epidemical cold' any more.