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Changes in and shortcomings of drug stockpiling, vaccine development and related policies during outbreaks of avian influenza A H5N1, H1N1, and H7N9 among humans

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ABSTRACT: The purpose of this paper is to provide a reference for the future stockpiling of drugs and developing vaccines for treatment of emerging infectious diseases by summarizing the status of drug stockpiling, vaccine development, and related policies during three major outbreaks of avian influenza among humans (H5N1 in 2003, H1N1 in 2009, and H7N9 in 2013). Documents regarding drug stockpiling and vaccine development during three influenza outbreaks have been reviewed. Results indicated that the response to pandemic influenza outbreaks has improved markedly in terms of stockpiles of antivirals and vaccine development. These improvements also suggest advances in related policy planning. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases. However, the rationality of drug stockpiling and international cooperation still needs to be enhanced.

Keywords: Rapid-response stockpile, guidelines, timetable

1. Introduction

The experience of the 2003 SARS outbreak in Asia emphasized the need to enhance the capacity of stockpiling drugs and developing vaccines. This paper seeks to provide a reference for the process of stockpiling drugs, developing vaccines, and the related policies of emerging infectious diseases by summarizing the status and shortcomings of drug stockpiling, vaccine development, and related policies during three major outbreaks of avian influenza among humans (H5N1 in 2003, H1N1 in 2009, and H7N9 in 2013).

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2. Drug stockpiling, vaccine development and related policies during outbreaks of influenza A (H5N1)

Outbreaks of the highly pathogenic H5N1 avian influenza in humans are now known to have begun in parts of South-east Asia in 2003. So far, 15 countries reported a total of 622 laboratory-confirmed human cases and 371 deaths due to H5N1 avian influenza *(1)*.

2.1. *Drug stockpiling during outbreaks of influenza A (H5N1)*

Many researchers believed that oseltamivir, an antiviral drug, combined with draconian measures can stop the virus from further developing *(2)*. Soon after the outbreak, antiviral drugs had been stocked worldwide. Until August 2009, United states had stocked 50 million courses, United Kingdom had stocked 30 million courses, South Korea had stocked more than 21 million courses, and Canada had stocked 1.4 million courses of antiviral medications *(3)*.World Health Organization (WHO) had stocked 2 million treatment courses of oseltamivir in January 2006 *(4)*. In addition, Roche announced that another 3 million treatment courses were ready to be shipped to sites of pandemic influenza outbreaks in April 2006. Table 1 shows the timetable of the antiviral stockpile against H5N1 of the World Health Organization (WHO). As this information shows, amassing effective drug stockpiles took three years.

2.2. *Vaccine development during outbreaks of influenza A (H5N1)*

Table 1 also presents the timetable of development of vaccines against H5N1. WHO obtained the wild-type

Table 1. Timetable of drug stockpiling and vaccine development of human infection with H5N1, H1N1 and H7N9

Time	Event
H5N1	
February 2003	First outbreak of H5N1 in Hong Kong, China.
April 2004 (14 months after first outbreak)	Isolation of wild type viruses of H5N1.
August 2005 (30 months after first outbreak)	Valid result during the first stage of vaccine's adults experiment.
April 2006 (38 months after first outbreak)	Rapid response stockpile of oseltamivir gets ready.
H1N1	
April 2009	First outbreak of H1N1 in Mexico.
April 2009 (same month of first outbreak)	Deploying rapid-response stockpile of drug.
May 2009 (1 month after first outbreak)	Isolation of wild type viruses of H1N1.
July 2009 (3 months after first outbreak)	Vaccination against pandemic H1N1 influenza first implemented in China.
H7N9	
March 2013	First outbreak of H7N9 in China.
April 2013 (1 month after first outbreak)	Isolation of wild type viruses of H7N9.
April 2013 (1 month after first outbreak)	CFDA approved the production of a new anti-influenza drug which is effective in fighting influenza H7N9

H5N1 virus and provided the virus to the National Institute of Allergy and Infectious Diseases (NIAID) for developing a vaccine against H5N1 infection among humans in April 2004 *(5)*. In August 2005, NIAID declared that the vaccine had proven effective during the first phase of adult experiments. The US Department of Health and Human Services (HHS) announced that the U.S. government had stockpiled enough vaccine (against former avian Influenza virus) to treat more than 3 million patients in 2006. U.S. Food and Drug Administration (FDA) approved the first U.S. vaccine for humans against the avian Influenza virus H5N1 in April 2007 *(6)*. China food and drug administration (CFDA) also approved China's first vaccine for humans against H5N1 in April 2008 *(7)*. However, the continual mutation of H5N1 limited the practicability of existing vaccines. Therefore, candidate vaccines to prevent H5N1 infection had been developed, but they were not ready for widespread use.

2.3. *Related policies of drug stockpiling and vaccine development during outbreaks of influenza A (H5N1)*

Researchers raised the idea of stockpiling oseltamivir for better controlling H5N1 in 2005 for the first time. WHO also proposed the idea of an oseltamivir stockpile and added oseltamivir as an essential medicine to treat H5N1 *(8)*. This idea had supportfrom many countries.

However, vaccine, as a more effective prevention and control measure, gained more attention. WHO came up with the idea to develop a global plan to increase the supply of pandemic influenza vaccine in 2006 *(9)*. This global plan focused on the poor resource countries which considered the H5N1 virus to be a national security and public health threat. As Table 2 shows, WHO also issued a series of guidelines, containing information about production, control and use of vaccines, related to the development of human H5N1 vaccines.

2.4. *Shortcomings of drug stockpiling, vaccine development, and related policies during outbreaks of influenza A (H5N1)*

Drug stockpiling and vaccine development had played a positive role during the process of controlling the outbreak of H5N1 among humans as the number of human infections was reduced and the influenza controlled. However, there were still some shortcomings that should be noted.

First, the policy's focus on drug stockpiling and vaccine development had not been issued on time. As the information mentioned above, the majority of related policies had been published in 2005, which indicated a two year delay. Second, the stockpiling of effective drugs was still relatively slow. As mentioned above, amassing an effective drug stockpile by WHO took more than three years. Finally, the process of vaccine development was unfavorable. According to the recent research mentioned above, no vaccine was available to civilian populations, nor produced in quantities sufficient to protect more than a tiny fraction of the Earth's population in the event of an H5N1 pandemic.

3. Drugstockpiling, vaccinedevelopment and related policies during outbreaks of influenza A (H1N1) 2009

The emergence of H1N1 virus in 2009 caused the first influenza pandemic of the 21st century *(10)*. By

Table 2. Guidelines related to antiviral stockpiling and vaccinedevelopment against pandemic influenza A (H5N1) published by WHO

Publication date	NO.	Guidelines
2004	1	Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection.
	2	WHO Guidelines on the use of vaccines and antivirals during Influenza Pandemics.
2005	1	Strengthening pandemic influenza preparedness and response.
	2	WHO guidance on development of influenza vaccine reference viruses by reverse genetics.
	3	Recommendations for the production and control of influenza vaccine (inactivated).
	4	WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines.
2006	1	WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus.

Table 3. Guidelines related to antiviral stockpiling and vaccinedevelopment against pandemic influenza A (H1N1) 2009 published by WHO

Publication date	NO.	Guidelines
2009	1	Recommendations of the Strategic Advisory Group of Experts (SAGE) on Influenza A (H1N1) vaccines.
	2	Characteristics of the emergent influenza A (H1N1) viruses and recommendations for vaccine development.
	3	Update of WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines.
	4	WHO recommendations on pandemic (H1N1) 2009 vaccines.
	5	Summary of available potency testing reagents for Pandemic (H1N1) 2009 virus vaccines.
	6	Statement from WHO Global Advisory Committee on Vaccine Safety about the safety profile of pandemic influenza A (H1N1) 2009 vaccines.
2010	1	WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses.

August 2010, 18,449 laboratory-confirmed deaths from pandemic influenza A (H1N1) 2009 had been recorded *(11)*. However, the actual number of influenza A (H1N1) cases worldwide remains unknown, as most cases were diagnosed clinically and not confirmed in the laboratory.

3.1. *Drug stockpiling during outbreaks of pandemic influenza A (H1N1) 2009*

Table 1 also presents the major timeline for drug stockpiling during the outbreak of pandemic influenza A (H1N1) 2009. As mentioned above, after the outbreak of H5N1, the WHO began to store emergency stocks of antivirals. As the H1N1 virus was susceptible to the drugs oseltamivir and zanamivir just like the H5N1 virus, the WHO started deploying 3 million doses of the drug, stored after 2003, to Mexico and to 71 pre-identified low-income countries immediately after the declaration of pandemic alert Phase 5 on April 29, 2009 *(12)*. Within a month, this rapid-response stockpile had been delivered. Governments also took steps to stockpile antiviral drugs. U.K. government estimated that the UK had enough antiviral drugs for 50% of the population as of 13 June 2009 and over 30 million doses of antiviral treatments available in April 2009 *(13)*. CFDA announced that the China government stored enough antiviral drugs against the outbreak of H1N1 *(14)*. However, even though there was no evidence suggesting an antiviral drug deficiency during the outbreak of H1N1 virus, the specific numbers of each country's emergency stocks of antivirals remained unknown.

3.2. *Vaccine development during outbreaks of pandemic influenza A (H1N1) 2009*

In contrast with the H5N1 virus, vaccines against H1N1 virus for humans are effective. As Table 1 presented, in May 2009, the WHO isolated and sent the wild-type H1N1 virus to vaccine manufacturers that requested it. At the same time, WHO Collaborating Centers for Influenza (WHO CCs), Essential Regulatory Laboratories (ERLs), and other institutions were developing candidate vaccines with coordination by the WHO. In July 2009, the China government announced that vaccination against pandemic H1N1 influenza was first implemented in China *(15)*. U.S. government launched the national influenza 2009 H1N1 vaccination campaign in October 2009. Between September and October 2009, European Union (EU) had approved some vaccines for human use *(16)*.

3.3. *Related policies of drug stockpiling and vaccine development during outbreaks of pandemic influenza A (H1N1) 2009*

After the outbreak of H5N1, many countries have chosen to stockpile antiviral medications in advance against pandemic influenza. Table 3 presents the guidelines for using and stockpiling antivirals against H1N1, proposed by WHO.

WHO also issued some guidelines for using and developing vaccines, as Table 3 shows. Besides the WHO, governments also took some steps. United States Center for Disease Control (USCDC) issued a series of statements including general information and safety information about 2009 H1N1 vaccines soon after the outbreak of H1N1 *(17)*. The China government issued guidelines for development process of vaccine as well *(18)*.

3.4. *Shortcomings of drug stockpiling, vaccine development, and related policies during outbreak of pandemic influenza A (H1N1) 2009*

Compared to drugstockpiling against H5N1, there was a significant improvement. A rapid-response stockpile of antivirals had been prepared in advance, and the stockpile was quickly delivered. As for the development of vaccines, the improvement in both timeliness and results were remarkable. However, some shortcomings should be noted.

Because of the lack of information about the amount of emergency stocks of antivirals, it is hard for people to stock antivirals rationally. A study concluded that approximately half of the prescriptions of Tamiflu during the 2009-10 influenza pandemic went unused in England *(19)* which was a huge waste and an unreasonable disposition of medical resources. Therefore, more attention should be paid to enhance the rationality of drug stockpiling.

4. Drug stockpiling, vaccine development and related policies during outbreaks of influenza A (H7N9)

On March 31, 2013, the National Health and Family Planning Commission (NHFPC) of China (formerly the Ministry of Health) announced three confirmed human cases of influenza A (H7N9). Prior to May 7, 2013, a total of 130 patients in China were confirmed to be infected with the influenza A (H7N9) virus; of these patients, 31 died and 42 recovered *(20)*.

4.1. *Drug stockpiling during outbreaks of influenza A (H7N9)*

Laboratory testing conducted in China have shown that the influenza A (H7N9) viruses are sensitive to anti-influenza drugs. Until now, there is no report of drug shortages. Hong Kong government announced HK well stocked with antiviral drugs with a stock of 18 million doses of Tamiflu and other medicines *(21)*. On April 5, 2013, about one month after the outbreak of H7N9, CFDA approved the production of a new anti-influenza drug (a Peramivir sodium chloride injection) that has proven effective in fighting influenza H7N9 according to existing clinical trials *(22)*, as presented in Table 1.

4.2. *Vaccine development during outbreaks of influenza A (H7N9)*

One month after the outbreak of H7N9, Greffex scientists had created the first comprehensive vaccine for H7N9 avian influenza *(23)*. However, no vaccine for the prevention of influenza A (H7N9) infections has been created by China's scientists. However, as Table 1 shows, viruses have already been isolated and shared with WHO by China government. The NHFPC of China indicated that 6 to 8 months are needed to develop an effective vaccine generally, yet more time may be needed to develop an effective vaccine against a new virus like H7N9. The Ministry of Science and Technology of the People's Republic of China launched research on the H7N9 avian influenza virus *(24)* on April 10, 2013, and the development of vaccine should be completed within seven months.

4.3. *Related policies of drug stockpiling and vaccine development during outbreaks of influenza A (H7N9)*

A statement about vaccine response had been made by WHO on May 2, 2013 *(25)*. USCDC and European centre for disease prevention and control (ECDC) also issued guidelines of using antivirals. However, since the outbreak of H7N9 has been in a relatively short period of time, the existing policies about drugstockpiling and vaccine development to treat influenza A (H7N9) are still limited.

4.4. *Suggestions regarding the drug stockpiling, vaccine development, and related policies against influenza A (H7N9) based on previous experience*

Based on the above information, it is easy to see the response improvement to influenza on both drug stores and vaccine development. From a more than 3 year period to stock enough drugs for H5N1, to deploying a rapid-response stockpile just after the outbreak of H1N1, the world has made huge progress on the drug stockpile. The same kind of progress can be seen in the aspect of vaccine development as an effective vaccine against H5N1 virus is still missing, and the vaccine against H1N1 virus had already been accepted by many countries as an effective control strategy. The aspects of related policies have also taken a huge step. As Table 2 and Table 3 show, the policy document of drugs and vaccines about H5N1 showed up about one year after the outbreak, and the majority of policy documents about H1N1's drugs and vaccines were published in the same year as the outbreak.

Because of the experience handling H5N1 and H1N1, the response to influenza A (H7N9) was timely in terms of both drug stores and vaccine development. The effective new drugs and the isolation of wild type viruses had been accomplished relatively soon after the first outbreak. However, according to the existing experience, people should pay more attention to the rationality of drug stockpiling. Maybe start with disclosing the actual number of antivirals stockpiled to the public. Second, as the influenza occurs in China, the China government should put more emphasis on promoting international cooperation in many aspects such as developing an effective vaccine.

5. Conclusion

Drug stockpiling, vaccine development, and related policies to treat influenza outbreaks have improved markedly. The response was faster and more effective in terms of stockpiling of antivirals and vaccine development. These improvements also suggest advances in related policy planning. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases. However, the rationality of drug stockpiling and international cooperation still need to be enhanced.

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References

1. WHO. Cumulative number of confirmed human cases for avian influenza A (H5N1) reported to WHO, 2003-2013. *http://www.who.int/influenza/human_animal_interface/EN_GIP_20130312CumulativeNumberH5N1cases.pdf* (accessed May 6, 2013).
2. WHO. Donation of three million treatments of oseltamivir to WHO will help early response to an emerging influenza pandemic. *http://www.who.int/mediacentre/news/releases/2005/pr36/en/index.html* (accessed May 6, 2013).
3. Wikipedia. Stockpiling antiviral medications for pandemic influenza. *http://en.wikipedia.org/wiki/Stockpiling_antiviral_medications_for_pandemic_influenza* (assessed June5, 2013).
4. WHO. Donation of three million treatments of oseltamivir to WHO will help early response to an emerging influenza pandemic. *http://www.who.int/mediacentre/news/releases/2005/pr36/en/index.html* (accessed May 6, 2013).
5. NIAID. NIAID announces contracts to develop vaccine against H5N1 avian influenza. *http://www.niaid.nih.gov/news/newsreleases/2004/pages/flucontracts.aspx* (assessed May 6, 2013).
6. FDA. FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1. *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108892.htm* (assessed May 6, 2013).
7. CFDA. CFDA approves vaccine against the avian influenza. *http://www.sda.gov.cn/WS01/CL0051/28996.html* (assessed May 6, 2013) (in Chinese).
8. WHO. The selection and use of essential medicine. *http://www.who.int/medicines/publications/TRS958June2010.pdf* (assessed May 6, 2013).
9. WHO. Global pandemic influenza action plan to increase vaccine supply. *http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.13_eng.pdf* (assessed May 6, 2013).
10. Scalera NM, Mossad SB. The first pandemic of the 21st century: A review of the 2009 pandemic variant influenza A (H1N1) virus. Postgrad Med. 2009; 121:43-47.
11. WHO. Disease outbreak news: Pandemic (H1N1) 2009 – update 112. 6 Aug 2010. *http://www.who.int/csr/don/2010_08_06/en/index.html* (assessed May 7, 2013).
12. WHO. Influenza A (H1N1). *http://www.who.int/mediacentre/news/statements/2009/h1n1_20090429/en/index.html* (assessed May 7, 2013).
13. BBC News. Swine flu: How serious a threat? *http://news.bbc.co.uk/2/hi/health/8022102.stm* (assessed May 7, 2013).
14. CFDA. CFDA launch the prevention and control work against pandemic influenza A (H1N1) 2009 legally and scientifically. *http://www.sda.gov.cn/WS01/CL0051/37736.html* (assessed May 7, 2013) (in Chinese).
15. Stone R. Swine flu outbreak. China first to vaccinate against novel H1N1 virus. Science. 2009; 325:1482-1483.
16. Baxter. Baxter receives European commission approval for CELVAPAN H1N1 pandemic influenza vaccine. *http://www.baxter.com/press_room/press_releases/2009/10_07_09-celvapan.html* (assessed May 7, 2013).
17. USCDC. 2009 H1N1 Flu Vaccine. *http://www.cdc.gov/h1n1flu/vaccination/* (assessed June5, 2013).
18. Liang XF, Li L, Liu DW, et al. Safety of influenza A (H1N1) vaccine in postmarketing surveillance in China. N Engl J Med. 2011; 364(7):638-647.
19. Singer AC, Järhult JD, Grabic R, Khan GA, Fedorova G, Fick J, Lindberg RH, Bowes MJ, Olsen B, Söderström H. Compliance to oseltamivir among two populations in Oxfordshire, United Kingdom affected by influenza A (H1N1) pdm09, November 2009 - a waste water epidemiology study. PLoS One. 2013;8(4):e60221.
20. NHFPC of China. New case of human infection of H7N9 avian influenza confirmed cases in Jiangxi Province, May 7. *http://www.moh.gov.cn/mohwsyjbgs/yqxx/20130 5/0b7c2806859b46b885af21a0bedfc54f.shtml* (assessed May 8, 2013) (in Chinese).
21. News.gov.hk. HK well stocked with antiviral drugs. *http://www.news.gov.hk/en/categories/health/html/2013/04/20130412_144223.shtml* (assessed June5, 2013).
22. CFDA. Anti-influenza drug peramivir sodium chloride injection approved. *http://www.sfda.gov.cn/WS01/CL0051/79543.html* (assessed May 8, 2013) (in Chinese).
23. The wall street journal. H7N9: Greffex "Beats the Clock" to Build the First Comprehensive H7N9 Vaccine. *http://online.wsj.com/article/PR-CO-20130501-905066.*

html?mod=googlenews_wsj (assessed June5, 2013).
24. NHFPC of China. Ministry of science and technology of the People's Republic of China launch a science and technology research for H7N9 avian influenza virus. *http://www.moh.gov.cn/mohbgt/wzbd/201304/6489ef372b8a445690d69a5c023cd8a4.shtml* (assessed May 8, 2013) (in Chinese).
25. WHO. Vaccine response to the avian influenza A (H7N9) outbreak. *http://www.who.int/influenza/vaccines/virus/CandidateVaccineVirusesH7N9_02May13.pdf* (assessed May 8, 2013).

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