Review

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Changes in and shortcomings of control strategies, drug stockpiles, and vaccine development during outbreaks of avian influenza A H5N1, H1N1, and H7N9 among humans

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Summary **The purpose of this review is to provide a reference for the future prevention and control of emerging infectious diseases by summarizing the control strategies, the status of drugs and vaccines, and shortcomings during three major outbreaks of avian influenza among humans (H5N1 in 2003, H1N1 in 2009, and H7N9 in 2013). Data on and documents regarding the three influenza outbreaks have been reviewed. Results indicated that the response to pandemic influenza outbreaks has improved markedly in terms of control strategies, stockpiles of antivirals, and vaccine development. These improvements also suggest advances in disease surveillance, transparency in reporting, and regional collaboration and cooperation. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases. However, there are shortcomings since strategies failed to focus on high-risk groups, quantitative and measurable results (both direct and indirect) were unclear, and quantitative assessment is still lacking.**

Keywords: Direct and indirect results, rapid-response stockpile, guidelines, timetable

1. Introduction

The experience of the 2003 SARS outbreak in Asia emphasized the need to enhance the capacity to fight emerging infectious diseases include disease surveillance, transparency in reporting, and regional collaboration and cooperation. Increasing available information, enhancing awareness, and introducing policies have dramatically increased the capacity to prevent and control emerging infectious diseases. However, defects in existing prevention and control systems are consistently noted during the fight against a new disease, and such systems must never stop improving. This paper seeks to provide a reference for the future prevention and control of emerging infectious diseases by summarizing the control strategies, the status of drugs and vaccines, and shortcomings during two major outbreaks of pandemic influenza (H5N1 in 2003, H1N1 in 2009) and human infection with influenza A (H7N9) virus in China recently.

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2. Pandemic influenza A (H5N1) in 2003

2.1. *The epidemiology of pandemic influenza A (H5N1) in humans*

According to the latest data from the World Health Organization (WHO) (*1*), 15 countries reported a total of 622 laboratory-confirmed human cases and 371 deaths of H5N1 avian influenza, with a total case-fatality rate of 0.597, from February 1, 2003 to March 12, 2013 (Table 1, Figure 1). As Table 1 shows, the two countries with the most cases and deaths were Indonesia and Egypt. However, the highest case-fatality rate was in Cambodia (the Lao People's Democratic Republic and Nigeria are excluded since cases were so rare).

Table 1. Cumulative number of confirmed human cases of avian influenza A (H5N1) reported to the WHO, 2003-2013

Country	Cases/deaths (Case-fatality rate[b])											
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
Azerbaijan				8/5 (62.5)								8/5 (62.5)
Bangladesh						1/0 (0.0)			2/0 (0.0)	3/0 (0.0)		6/0 (0.0)
Cambodia			4/4 (100.0)	2/2 (100.0)	1/1 (100.0)	1/0 (0.0)	1/0 (0.0)	1/1 (100.0)	8/8 (100.0)	3/3 (100.0)	9/8 (88.9)	30/27 (90.0)
China	1/1 (100.0)		8/5 (62.5)	13/8 (61.5)	5/3 (60.0)	4/4 (100.0)	7/4 (57.1)	2/1 (50.0)	1/1 (100.0)	2/1 (50.0)	2/2 (100.0)	45/30 (66.7)
Djibouti				1/0 (0.0)								1/0 (0.0)
Egypt				18/10 (55. 6)	25/9 (36.0)	8/4 (50.0)	39/4 (10.3)	29/13 (44.8)	39/15 (38.5)	11/5 (45.5)	1/1 (100.0)	170/61 (35.9)
Indonesia			20/13 (65.0)	55/45 (81.8)	42/37 (88.1)	24/20 (83.3)	21/19 (90.5)	9/7 (77.8)	12/10 (83.3)	9/9 (100.0)		192/160 (83.3)
Iraq				3/2 (66. 7)								3/2 (66.7)
LPDR[a]					2/2 (100.0)							2/2 (100.0)
Myanmar					1/0 (0.0)							1/0 (0.0)
Nigeria					1/1 (100.0)							1/1 (100.0)
Pakistan					3/1 (33.3)							3/1 (33.3)
Thailand		17/12 (70.6)	5/2 (40.0)	3/3 (100.0)								25/17 (68.0)
Turkey				12/4 (33.3)								12/4 (33.3)
Viet Nam	3/3 (100.0)	29/20 (69.0)	61/19 (31.2)		8/5 (62.5)	6/5 (83.3)	5/5 (100.0)	7/2 (28.6)		4/2 (50.0)		123/61 (49.6)
Total	4/4 (100.0)	46/32 (69.0)	98/43 (43.9)	115/79 (68.7)	88/59 (67.1)	44/33 (75.0)	73/32 (43.8)	48/24 (50.0)	62/34 (54.8)	32/20 (62.5)	12/11 (91.7)	622/371 (59.7)

[a]LPDR: Lao People's Democratic Republic; [b]Case-fatality rates are given as percentages (number of deaths/number of cases).

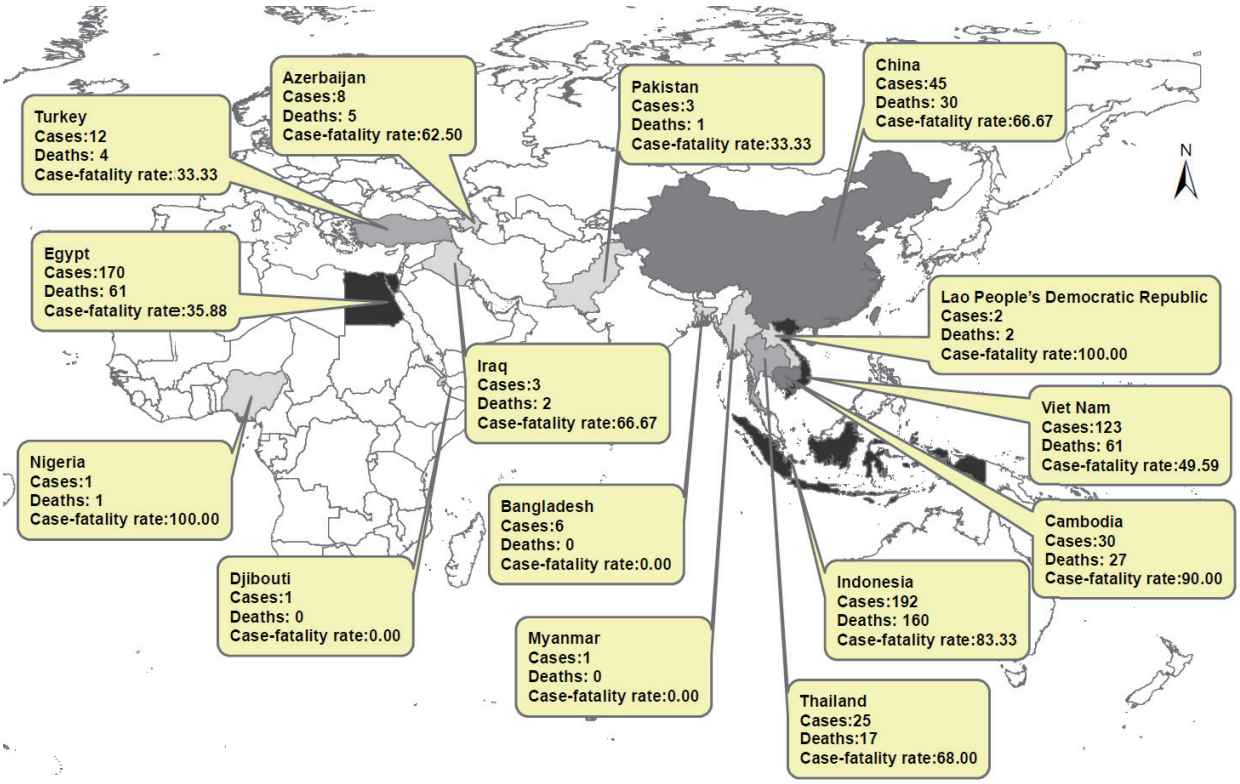

Figure 1. Areas with confirmed human cases of avian influenza A (H5N1) reported to the WHO, 2003-2013.

According to WHO reports (*1-5*), more than 50% of the infected people were under 20 years of age, and 90% were under 40 years of age. The overall case-fatality rate was 59.7% (Table 1). The highest fatality rate among all age groups was for people ages 10 to 39 years. The fatality rate of pandemic influenza A (H5N1) among different age groups differed from the fatality rate of seasonal influenza (the elderly had the highest fatality rate). The case-fatality rate (2004-2006) was highest in 2004 (69%), dropping in 2005 (43.9%) and then increasing again in 2006 (68.7%). The evaluation of mortality and time intervals between cases of infection and hospitalization and between cases of infection and death indicated that the disease pattern had not changed much from 2004 to 2006. Cases appeared all year long. The peak in cases of human infection occurred in the winter and spring in mostly the Northern hemisphere during all three years.

2.2. *The response to pandemic influenza A (H5N1)*

2.2.1. *Strategies to control pandemic influenza A (H5N1)*

The world paid great attention to the outbreak of H5N1 infection among humans and worked hard to respond to the threat. To begin with, there were plenty of general control strategies. After the outbreak of SARS and pandemic influenza A (H5N1), the WHO issued a series of guidelines to control H5N1, as shown in Table 2 (*6-16*).

In addition to those guidelines, other strategies were also implemented, such as the WHO global influenza preparedness plan in May 2005 (*17*) and collection, preservation, and shipping to specimens to diagnose avian influenza A (H5N1) virus infection in October 2006 (*18*). Two of these strategies are the most important. The WHO adopted International Health Regulations (2005) in May 2005 (*19*) "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade". In November 2005, the Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE), and WHO jointly published a Global Strategy for the Progressive Control of Highly Pathogenic Avian Influenza (HPAI) (*20*). This strategy was a worldwide H5N1 control strategy emphasizing the capacity to handle pandemic influenza, cooperation, and the exchange of information.

The effect of these general strategies was significantly. The number of cases reflects the direct result of control strategies. Based on WHO data on disease outbreaks (*1,21*), the number of cases decreased after 2006. However, the overall case-fatality rate did not decrease with the number of cases according to the data shown in Table 1.

Moreover, many strategies were implemented in different countries at the same time. In India, for instance, the most important strategy to prevent pandemic influenza A (H5N1) was the ban on importing live chickens and other poultry products from countries affected by 'bird flu'. Other strategies were also implemented, such as requiring persons handling poultry to wear masks and gloves, cleaning kitchen surfaces and utensils before and after use, cooking chicken until its boiling temperature was reached, and controlling human traffic in poultry farms (*22,23*). As a result of India's strategies, no human cases of H5N1 infection were detected in the country (*24*) despite the fact that it is one of the world's most populous and has an extremely high population density. The Thai government developed a public health response to the emerging disease. First, response strategies included active case surveillance, prompt outbreak investigation and control, proper case management with hospital infection control, and improved public communication; the response was backed up by the stockpiling and distribution of essential medical supplies. These strategies were continuously maintained and improved (*25*). The response strategies adopted and maintained in Thailand resulted in a continuous decline in human infections. The number of human cases dropped from 17 in 2004 to 5 in 2005 and 3 in 2006. The year 2007 passed without detection of a human case in the presence of well-maintained surveillance (*1*). The Chinese government formulated a national emergency plan to deal with highly pathogenic avian influenza in 2004 (*26*), a program for diagnosis and treatment of human avian influenza in 2005 (*27*), and an emergency plan to deal with people infected with highly pathogenic avian influenza in 2006 (*28*) during the fight against H5N1. The number of cases of human H5N1 infection in China decreased after 2006 (*1*).

Furthermore, developed countries such as the United States and members of the European Union also adopted strategies to fight H5N1 infection in humans. The US Homeland Security Council published a National Strategy for Pandemic Influenza in December 2005 (*29*). The US Department of Health and Human Services published a Pandemic Influenza Plan the same month (*30*). Members of the European Union cast a vote for a council directive on community measures for the control of avian influenza (*31*).

There were also specific strategies that focused more on the characteristics of the spread of H5N1. Transmission of the H5N1 virus from a patient to a health care worker (*32*) was reported after prolonged, close, and unprotected contact with a severely ill patient, and serological evidence of patient-to-health care worker transmission was reported (*33*). The WHO recommended use of personal protective equipment (gown, gloves, goggles, and a surgical mask) and implementation of standard, contact, and droplet

Table 2. WHO guidance documents on pandemic influenza A (H5N1), pandemic influenza A (H1N1), and influenza A (H7N9)

Publication date	No.	Guidelines
		Pandemic influenza A (H5N1)
2004	1	Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection.
	2	WHO guidelines for global surveillance of influenza A (H5N1).
2005	1	WHO guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection.
	2	WHO laboratory bio-safety guidelines for handling specimens suspected of containing avian influenza A virus.
	3	WHO guidance on public health measures in countries experiencing their first outbreaks of H5N1 avian influenza.
2006	1	WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus.
	2	WHO case definitions for human infections with influenza A (H5N1) virus.
2007	1	WHO guidelines for investigation of human cases of avian influenza A (H5N1).
	2	Clinical management of human infection with avian influenza A (H5N1) virus.
2008	1	Protection of individuals with high poultry contact in areas affected by avian influenza H5N1: consolidation of pre-existing guidance.
2009	1	WHO guidelines for the storage and transport of human and animal specimens for laboratory diagnosis of suspected avian influenza A infection.
		Pandemic influenza A (H1N1)
June,2007	1	Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care.
May,2008	1	Pandemic influenza preparedness and mitigation in refugee and displaced populations. WHO guidelines for humanitarian agencies.
June,2008	1	Reducing excess mortality from common illnesses during an influenza pandemic.
April,2009	1	Viral gene sequences to assist update diagnostics for influenza A (H1N1) - GenBank accession numbers.
	2	Viral gene sequences to assist update diagnostics for influenza A (H1N1).
	3	Global surveillance during an influenza pandemic.
May,2009	1	Case management of influenza A (H1N1) in air transport.
	2	Clean hands protect against infection.
	3	Considerations of influenza A (H1N1) and HIV infection.
	4	Advice on the use of masks in the community setting in influenza A (H1N1) outbreaks.
	5	Pandemic influenza prevention and mitigation in low resource communities.
	6	Update of WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines.
	7	Characteristics of the emergent influenza A (H1N1) viruses and recommendations for vaccine development.
	8	Protocol for antiviral susceptibility testing by pyrosequencing.
	9	Sequencing primers and protocol.
	10	Status of candidate vaccine virus development for the current influenza A (H1N1) virus.
	11	Countries able to perform PCR to diagnose influenza A (H1N1) virus infection in humans.
	12	Instruction on how to obtain CDC realtime RT-PCR kits for detection of influenza A (H1N1).
	13	Summary report of a High-Level Consultation: new influenza A (H1N1).
	14	Recommendations of the Strategic Advisory Group of Experts (SAGE) on influenza A (H1N1) vaccines.
	15	WHO Technical Consultation on the Severity of Disease Caused by the new influenza A (H1N1) virus infections.
	16	WHO *ad hoc* scientific teleconference on the current influenza A (H1N1) situation.
June,2009	1	Consultation on potential risks of pandemic (H1N1) 2009 influenza virus at the human-animal interface.
	2	Influenza A (H1N1) patient care checklist.
	3	Behavioural interventions for reducing the transmission and impact of influenza A (H1N1) virus: a framework for communication strategies.
	4	WHO Consultation on suspension of classes and restriction of mass gatherings to mitigate the impact of epidemics caused by the new influenza A (H1N1).
July,2009	1	WHO recommendations on pandemic (H1N1) 2009 vaccines.
September,2009	1	Reducing transmission of pandemic (H1N1) 2009 in school settings.
October,2009	1	CDC protocol of realtime RT-PCR for influenza A (H1N1).
November,2009	1	Pandemic influenza A (H1N1) 2009: considerations for tuberculosis care services.
	2	Clinical management of human infection with pandemic (H1N1) 2009: revised guidance.
	3	Summary of available potency testing reagents for pandemic (H1N1) 2009 virus vaccines.
	4	WHO interim technical advice for case management of pandemic (H1N1) 2009 on ships.
	5	Interim planning considerations for mass gatherings in the context of pandemic (H1N1) 2009 influenza.
December,2009	1	Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses.
	2	Preliminary review of D222G amino acid substitution in the haemagglutinin of pandemic influenza A (H1N1) 2009 viruses.
	3	Statement from WHO Global Advisory Committee on vaccine safety about the safety profile of pandemic influenza A (H1N1) 2009 vaccines.
February,2010	1	WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses.
April,2010	1	Laboratory biorisk management for laboratories handling pandemic influenza A (H1N1) 2009 virus.
May,2010	1	Clinical management of adult patients with complications of pandemic influenza A (H1N1) 2009 influenza: emergency guidelines for the management of patients with severe respiratory distress and shock in district hospitals in limited-resource settings.
July,2010	1	Pregnancy and pandemic influenza A (H1N1) 2009: information for programme managers and clinicians.
August,2010	1	Surveillance recommendations for Member States in the post-pandemic period.
		Influenza A (H7N9)
April 2013	1	WHO suggested that the infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care is still effectively.
	2	Real-time RT-PCR protocol for the detection of A (H7N9) influenza virus.

precautions for routine care of patients with H5N1 virus infection (*34,35*).

Public knowledge of avian influenza is an important component of a control strategy. However, this knowledge was insufficient. Studies (*36-39*) indicated a relatively low level of public knowledge of avian influenza, suggesting that control strategies needed to improve health education.

2.2.2. *Drugs and vaccines to treat pandemic influenza A (H5N1)*

Table 3 shows the timetable of drug stockpiling and development of vaccines against H5N1. After the outbreak of pandemic influenza A (H5N1) in February 2003, the WHO tried to stockpile enough treatment courses of oseltamivir as an effective drug against H5N1 infection among humans in the beginning of 2006. In January 2006, Roche (a major manufacturer of oseltamivir) announced that it would donate 2 million treatment courses of oseltamivir to the WHO (*40*). In April 2006, Roche announced that another 3 million treatment courses were ready to be shipped to sites of pandemic influenza outbreaks (*41*). As this information shows, amassing effective drug stockpiles took three years.

In April 2004, the WHO obtained the wild-type H5N1 virus and provided it to the National Institute of Allergy and Infectious Diseases (NIAID) for research and development of a vaccine (*42*). In August 2005, NIAID declared that the vaccine had proven effective during the first phase of adult experiments (*43,44*). Although there were several H5N1 vaccines for several of the avian H5N1 varieties, the continual mutation of H5N1 rendered them of limited use to date: while vaccines can sometimes provide cross-protection against related flu strains, the best protection would be from a vaccine specifically produced for any future pandemic flu virus strain (*45*). However, "pre-pandemic vaccines" had been created, were being refined and tested, and did have some promise both in furthering research and preparedness for the next pandemic (*46,47*). Therefore, candidate vaccines to prevent H5N1 infection had been developed, but they were not ready for widespread use because of the continual mutation of H5N1 (*48*).

2.3. *Shortcomings during the outbreak of pandemic influenza A (H5N1)*

The outbreak of pandemic influenza A (H5N1) in 2003 was the first serious pandemic influenza outbreak the world faced after SARS. Much work had done during the fight against the outbreak of H5N1, and huge successes had been achieved. However, the response had shortcomings that should be discussed. First of all, the strategies did not focus on the younger population as a high-risk group. According to data from the WHO, the younger population had the highest proportion of cases and the highest case fatality rate. However, there is no evidence of a specific strategy focusing on the younger population. Therefore, prevention strategies should put more emphasis on high-risk groups to better control the spread of H5N1. Second, an evaluation process was missing. Although avian influenza H5N1 is not currently a substantial threat (phase 3 pandemic alert for avian influenza H5N1 according to the WHO) (*49*), an evaluation of pandemic influenza A (H5N1) still needs to be performed. Third, the stockpiling of effective drugs and vaccine development was relatively slow. As mentioned above, amassing an effective drug stockpile took more than three years, and no effective vaccine had been developed. Therefore, more attention should be paid to drug stockpiles and the development of vaccines. Lastly, the results of strategies were unclear, especially with regard to indirect results. Further research should be conducted.

Table 3. The timetable of drug stockpile and vaccine development of H5N1 and H1N1

Time	Event
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.
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.

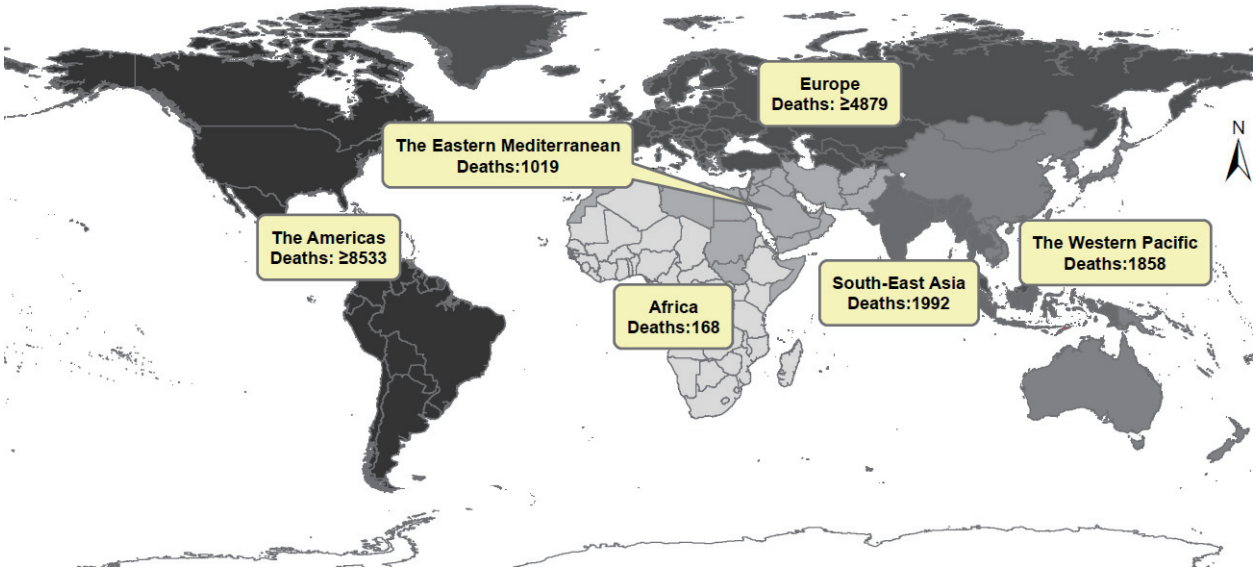

Figure 2. Areas with confirmed human deaths due to avian influenza A (H1N1) reported to the WHO, April 2009 - August 2010.

3. Pandemic influenza A (H1N1) in 2009

3.1. *The epidemiology of human pandemic influenza A (H1N1) 2009*

The emergence of a new H1N1 virus in early 2009 was the cause of the first influenza pandemic of the 21st century (*50,51*). In early April 2009, a new influenza A (H1N1) 2009 virus emerged among humans in California and Mexico, quickly spreading worldwide through human-to-human transmission. By August 2010, when the transition from a pandemic to post-pandemic period was announced, 18,449 laboratory-confirmed deaths from pandemic influenza A (H1N1) 2009 had been recorded (*52*) (Figure 2). However, the actual number of influenza A (H1N1) cases worldwide remains unknown, as most cases were diagnosed clinically and were not confirmed in the laboratory. In most countries, the capacity for laboratory diagnosis was so stressed that diagnosis was limited to hospitalized patients (*53*). However, the total number of cases of pandemic H1N1 influenza worldwide was probably on the order of several tens of millions (*54,55*). Modeling estimates of the global burden of pandemic influenza A (H1N1) 2009 ranged from several tens of millions to 2 billion (*56*). The official number of deaths from laboratory-confirmed pandemic influenza A (H1N1) 2009 infection worldwide reported to the WHO as of May 7, 2010 was at least 18,449 (*52*). This number appears to be much lower than the estimated annual global mortality associated with seasonal influenza. However, the actual fatality of the A (H1N1) 2009 pandemic cannot be accurately ascertained at this time. Given the relatively high mortality rates for at-risk groups and hospitalized patients (*57,58*), the annual mortality due to A (H1N1) 2009 is presumed to be higher.

Geographically, pandemic influenza A (H1N1) transmission remains most active in parts of South Asia and in limited areas of tropical South and Central America. After the first two cases emerged in California, 208 countries, overseas territories, and communities had reported laboratory-confirmed A (H1N1) 2009 cases in humans on December 30, 2009 and more than 214 reported such cases on April 18, 2010. Most countries in the Southern hemisphere reported more cases of pandemic H1N1 in 2009 than any of the seasonal subtypes.

One characteristic feature of the H1N1 2009 pandemic is that it disproportionately affected young children. Studies and data show that the virus was spreading rapidly around the world and appeared to primarily affect children and young adults (*59,60*), and the same was true of the outbreak of H5N1 in 2003.

3.2. *The response to pandemic influenza A (H1N1) 2009*

3.2.1. *Strategies to control pandemic influenza A (H1N1) 2009*

With experience fighting the outbreak of SARS and H5N1 in 2003, the world responded rapidly after the H1N1 outbreak. After the outbreak of H1N1 in February and early March 2009 in Mexico, the WHO issued a series of guidelines for control of H1N1, as shown in Table 2 (*61-66*).

As usual, those guidelines were accompanied by control strategies, such as WHO recommendations for the post-pandemic period (*67*) in August 2010. During the fight against the outbreak of H1N1, school closure was a policy option considered in some countries, such as Argentina and Japan. Argentina and Japan had closed all schools early in their epidemic by extension of or

overlap with school holidays, while other countries closed only certain schools (*68*). Studies (*69,70*) and data showed that these general strategies had significant results. Based on the disease outbreak data from the WHO (*71-73*), the number of cases decreased after November 2009. However, according to outbreak data (*71,72*) the overall case-fatality rate remained steady.

Each country also had different control strategies. Since the breakout of H1N1, vigorous responses to influenza A H1N1 were implemented by the Chinese government, which included aggressive case identification, vaccine development, and mass vaccination at a speed and scale unparalleled elsewhere (*73*). One study used a counterfactual to evaluate the results of these responses (*74*) and found that China would have had 139,693 cases of infection and 2,266 deaths. In fact, there were only 5,542 cases of infection and 6 deaths, suggesting that these responses were effective. The Italian government also implemented several control strategies, including containment measures, surveillance, communication of data, and mitigation measures. After these strategies were implemented, the incidence of influenza-like illness in Italy decreased from a peak of almost 20% to almost 6% (*75*).

However, some strategies were also ineffective. Egypt, which had no cases of H1N1, implemented a policy in March 2009 to prohibit raising pigs and by ordering the "killing of all pigs in the country and compensating the farmers for the loss." In fact, the virus is not transmitted by pigs, so the pig slaughter did nothing to stop the spread of H1N1 (*76*).

Because of the experience with H5N1, health care workers tended to use personal protective equipment and vaccination (*77,78*), limited their infection. Because of this trend, few cases of patient-to-health care worker transmission were reported during the outbreak of pandemic influenza A (H1N1) 2009.

The level of public knowledge of H1N1 increased in comparison to the outbreak of H5N1. Studies (*79,80*) showed an average level of public knowledge of H1N1 (had knowledge about general influenza and preventive measures but lacked an adequate understanding of H1N1), suggesting that control strategies had improved in comparison to the outbreak of H5N1 but that health education still needed to be improved.

3.2.2. *Drugs and vaccines to treat pandemic influenza A (H1N1) 2009*

Table 3 presents the major timeline for drug stockpiling and vaccine development during the outbreak of pandemic influenza A (H1N1) 2009. After the outbreak of H5N1, the WHO began to store emergency stocks of oseltamivir. Like the H5N1 virus, the H1N1 virus was susceptible to the drugs oseltamivir and zanamivir, so the WHO started deploying 3 million doses of the drug to Mexico and to 71 pre-identified low-income countries immediately after the declaration of pandemic alert Phase 5 on April 29, 2009 (*81,82*). Within a month, this rapid-response stockpile had been delivered and the WHO was to provide additional shipments as required during the course of the pandemic. Some higher-income countries subsequently donated antivirals to the global response.

In May 2009, the WHO sent the wild-type H1N1 virus to vaccine manufacturers that requested it (*83*). 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, vaccination against pandemic H1N1 influenza was first implemented in China (*84*), followed by a large number of other countries. The safety of the A (H1N1) 2009 vaccines had been thoroughly monitored during various clinical trials. Current data show that the pandemic influenza vaccines are well-tolerated and behave like corresponding seasonal vaccines in terms of safety and absence of severe adverse events. Compared to the development of vaccines against H5N1, there was a significant improvement in both timeliness and results.

3.3. *Shortcomings during the outbreak of pandemic influenza A (H1N1) 2009*

Compared to the fight against pandemic influenza A (H5N1) in 2003, the fight in 2009 was a marked improvement. Both direct results and indirect results of control strategies improved. A rapid-response stockpile of antivirals had been prepared in advance, and the stockpile was quickly delivered. Vaccines were also developed faster. The WHO also evaluated pandemic influenza (H1N1) 2009 after the pandemic. Therefore, the response to pandemic influenza improved significantly.

However, there were shortcomings during response to the outbreak of pandemic influenza (H1N1) 2009. First of all, just like the strategies against pandemic influenza A (H5N1) in 2003, strategies against H1N1 also failed to pay enough attention to the younger population as a high-risk group. There is no evidence of a specific strategy focusing on the younger population beside the school closure mentioned above. Second, the evaluation needed to go further. The evaluation of H1N1 was a qualitative evaluation, lacking convincing quantitative evidence.

4. The outbreak of influenza A (H7N9)

4.1. *The epidemiology of human cases 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) (February 19th, February 27th, and March 15th) (*85*). Prior to April 11, 2013, a total of 38 patients in China were confirmed to be infected with the influenza A (H7N9) virus; of these patients, 10 died, 19 had a severe infection, and 9 had a mild infection (*86*). Cases also appeared in the 4 provinces of Shanghai (18 cases, 6 deaths), Jiangsu (12 cases, 1 death), Anhui (2 cases, 1 death), and Zhejiang (6 cases, 2 deaths) and in 23 cities (*87*) (Table 4 and Figure 3). To date, no epidemiological link between confirmed cases has been reported. More than 760 close contacts of the confirmed cases are being closely monitored. Sporadic distribution was observed in cases where no person-to-person transmission was noted.

Table 4. Cumulative number of confirmed human cases of avian influenza A (H7N9) reported to the WHO, February 1 - April 11, 2013

Region	Cases	Deaths	Case-fatality rate[a]
Shanghai	18	6	33.3
Jiangsu	12	1	8.3
Anhui	2	1	50.0
Zhejiang	6	2	33.3
Total	38	10	26.3

[a] Case-fatality rates are given as percentages (number of deaths/ number of cases).

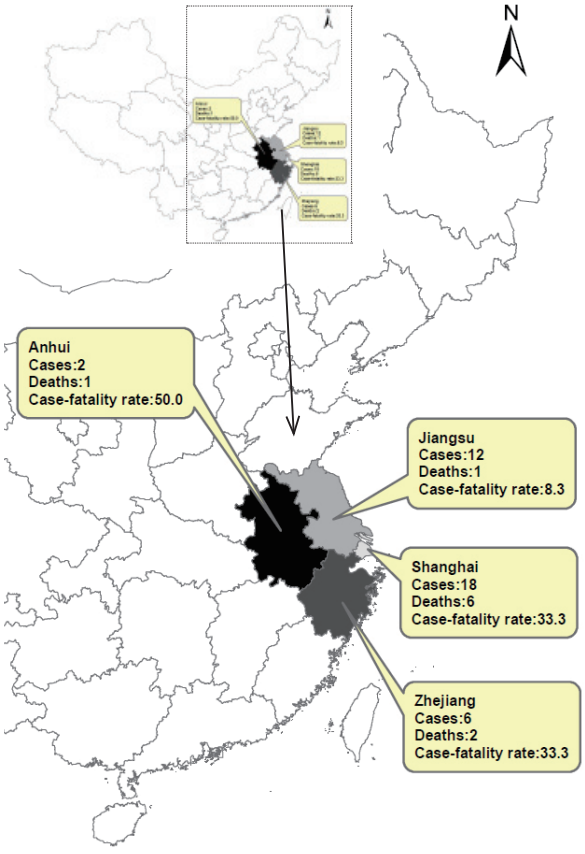

Figure 3. Areas with confirmed human cases of avian influenza A (H7N9) in China reported to the WHO, March 31 - April 11, 2013.

The source of infection and the mode of transmission are currently unknown. No association with outbreaks of disease among animals or clear exposure to animals has been established. Some of the confirmed cases involved individuals who had contact with animals or with environments in which animals were located. The virus has been found in a pigeon in a market in Shanghai. The possibility of animal-to-human transmission is being investigated, as is the possibility of human-to-human transmission (*88*).

4.2. *The response to influenza A (H7N9)*

4.2.1. *Strategies to control influenza A (H7N9)*

Since detection of the first case, many actions have been taken by the WHO, national authorities, and technical partners. On April 5, 2013, the WHO suggested that infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care is still effective at preventing and controlling the infection in health care settings (*88*). A Real-time RT-PCR Protocol for the Detection of A (H7N9) Influenza Virus was published on April 8, 2013 (*89*). As more information becomes available, the WHO will revise its guidance and actions accordingly as they did in the past pandemic cases (Table 2).

In addition to the WHO, individual countries also took action. Table 5 shows control strategies adopted by China and the United States. China's NHFPC issued a notice on enhancing efforts to prevent and control human infection with H7N9 avian influenza (*90*), a scheme for diagnosis and treatment of human infection with H7N9 avian influenza (Version 1, 2013) (*91*), and a guideline on prevention and control of human infection with H7N9 avian influenza in hospitals (2013) (*92*) on April 3, 2013. The scheme for diagnosis and treatment of human infection with H7N9 avian influenza (Version 2, 2013) was improved (*93*), and procedures to diagnose cases of human infection with H7N9 avian influenza (*94*) were established on April 10, 2013. On April 9, 2013 the Centers for Disease Control and Prevention (CDC) of the United States activated its Emergency Operations Center (EOC) in Atlanta. Activation was prompted because the novel H7N9 avian influenza virus has never been seen before in humans and because reports from China have linked it to severe human disease (*95*). In addition, the CDC issued guidance to US clinicians and public health departments (*96*) on how to test for this virus on April 5, 2013, and the CDC issued interim guidance on case definitions for possible H7N9 cases in the United States (*97*) (April 5, 2013) and interim infection control guidance for U.S. health care workers (*98*) (April 11, 2013).

However, the results of these control strategies cannot be quantitatively assessed based on existing information. As mentioned above, however, these strategies were timely.

Table 5. Strategies to control influenza A (H7N9) adopted in China and the United States

Date issued	Issued by	Control strategy
April 3, 2013	NHFPC of China	Notice on enhancing efforts to prevent and control human infection with H7N9 avian influenza. Scheme for diagnosis and treatment of human infection with H7N9 avian influenza (Version 1, 2013). Guideline on prevention and control of human infection with H7N9 avian influenza in hospitals (2013).
April 5, 2013	US CDC	Human Infections with Novel Influenza A (H7N9) Viruses. Interim Guidance on Case Definitions to be Used for Novel Influenza A (H7N9) Case Investigations in the United States.
April 10, 2013	NHFPC of China	Scheme for diagnosis and treatment of human infection with H7N9 avian influenza (Version 2, 2013). Procedures to diagnose cases of human infection with H7N9 avian influenza.
April 11, 2013	US CDC	Interim Guidance for Infection Control Within Healthcare Settings When Caring for Patients with Confirmed, Probable, or Cases Under Investigation of Avian Influenza A (H7N9) Virus Infection.

4.2.2. *Drugs and vaccines to treat influenza A (H7N9)*

Laboratory testing conducted in China has shown that the influenza A (H7N9) viruses are sensitive to the anti-influenza drugs known as neuraminidase inhibitors (oseltamivir and zanamivir). Because of the small number of cases and the rapid-response stockpile of drug stockpiled after outbreak of H5N1, there are no reports of drug shortages. These drugs have yet to be used to treat H7N9 infection. On April 5, 2013, about one month after the outbreak of H7N9, China's Food and Drug Administration (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 (*99*).

No vaccine for the prevention of influenza A (H7N9) infections is currently available. However, viruses have already been isolated and characterized from the initial cases. The NHFPC of China indicated that vaccine development is underway. Generally, 6 to 8 months are needed to develop an effective vaccine, yet more time may be needed to develop the 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 (*100*) on April 10, 2013, and the development of vaccine should be completed within seven months.

Because of the experience with H5N1 and H1N1, the response to influenza A (H7N9) was timely in terms of both drug stores and vaccine development.

4.3. *Suggestions regarding the fight against influenza A (H7N9) based on previous experience*

As mentioned above, there have been marked strides in preventing pandemic influenza. Control strategies are faster and more effective, a rapid-response stockpile of antivirals is ready, and vaccines are developed more efficiently. These improvements also suggest advances in disease surveillance, transparency in reporting, and regional collaboration and cooperation. A faster response comes only with good disease surveillance, the spread of influenza can be controlled only with transparency in reporting, and international strategies will be effective only with constructive regional collaboration and cooperation. As these trends continue, they offer prospects of a faster response, better disease surveillance, more open reporting, and closer international cooperation.

However, there are still some concerns. To begin with, more attention should be given to high-risk groups. Experience shows that control strategies consistently focused on the general level and placed less emphasis on high-risk groups. Groups that are at risk for influenza A (H7N9) infection have not been identified, and control strategies should be targeted more toward possible high-risk groups.

Moreover, quantitative and measurable results (both direct and indirect) should be evident. Although reducing the number of cases is important, indirect results, such as improvement of health professionals (capacity, awareness, *etc*.) and improvement of vaccine manufacturers, should be evident.

Finally, quantitative assessment should be performed. Overwhelming evidence is vitally needed to better identify shortcomings and forecast future influenza outbreaks. Therefore, quantitative assessment should be performed during an outbreak.

5. Conclusion

The response to influenza outbreaks has improved markedly. The response was faster and more effective in terms of control strategies, stockpiling of antivirals, and vaccine development. These improvements also suggest advances in disease surveillance, transparency in reporting, and regional collaboration and cooperation. These trends also foreshadow better prospects for prevention and control of emerging infectious diseases.

However, there are shortcomings since strategies failed to focus on high-risk groups, quantitative and measurable results (both direct and indirect) were unclear, and quantitative assessment is still lacking.

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