6 The Risk and Prevention and Control of Influenza

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Influenza is a contagious respiratory illness caused by influenza viruses that infect the nose, throat, and sometimes the lungs. It can cause mild-to-severe illness, and at times, deaths. According to core proteins and matrix proteins, the influenza viruses can be divided into four types: A, B, C, and D. Human influenza A and B viruses cause a seasonal epidemic of disease around the world every year. A pandemic can occur when a new and very different influenza A virus that can infect people and spread fast between people emerges. Influenza type C infections generally cause mild illness and are not thought to cause human flu epidemics. Influenza D viruses primarily affect cattle, and it is not sure whether they can infect or cause illness in people.

Influenza A viruses are divided into subtypes based on two proteins on the surface of the virus: hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1 to H18 and N1 to N11, respectively). Therefore, there are potentially 198 different influenza A subtype combinations. Influenza A (H1N1 and H3N2) viruses cause seasonal epidemics in humans every year. In the spring of 2009, a new type of influenza A (H1N1) virus emerged and caused the first influenza pandemic in the twenty-first century, more than 40 years after the Hong Kong influenza pandemic in 1968. This new type of virus subsequently replaced the seasonal influenza A (H1N1) virus circulated before 2009. Influenza B viruses are not divided into subtypes, but instead, further classified into two lineages: B/Yamagata and B/Victoria.

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Influenza A viruses with low genetic stability and prone to mutation and reassortment are found in many different animals, such as ducks, chickens, pigs, horses, cats, and dogs. Genetic mutation is the cause of changes in the subtype and strains of the human seasonal influenza viruses, and also the biological basis for cross-species transmission of zoonotic influenza viruses. The spread of influenza A virus among animals, especially chickens, frequently causes substantial losses to the poultry industry. Zoonotic influenza A virus can occasionally spread across species, infecting people or causing illness in them. For example, there has been human infection with avian influenza H5N1, H7N9, H5N6, and H10N8 viruses since 2003 in China, and the case fatality rate of H5N1 and H5N6 has reached 60%. Fortunately, these avian influenza viruses cannot spread easily among humans. Influenza A viruses from different species could infect the same person or animal, mix existing genetic information (reassortment), and produce a new influenza A virus. If this virus with genetic reassortment could infect people easily and spread from person to person in an efficient and sustained way, it is likely to cause a new influenza pandemic that spread quickly across the world. Further, the number of patients, hospitalizations, and deaths can be significantly higher in an influenza pandemic than in seasonal influenza, and social and economic activities were seriously impacted, hence huge damages to human health and the economy. In 1918–1919, the number of deaths in the Spanish pandemic caused by an H1N1 virus with genes of avian origin was estimated to be at least 50 million worldwide. It was the most serious disaster of medical science in the twentieth century.

6.1 Overview of the Influenza/Avian Influenza Epidemic in "Belt and Road" ("B&R") Countries

Influenza was the first disease to be monitored globally. Global influenza surveillance has been conducted through WHO's Global Influenza Surveillance and Response System (GISRS) since 1952. The mission of GISRS is to protect people from the threat of influenza by constantly recommending vaccine strains for annual seasonal influenza vaccine production, vaccine prototype strains with potential pandemic risk in response to influenza pandemics. Another mission of GISRS is continuously updating influenza virus detection and surveillance reagents based on global surveillance data, providing the scientific basis for clinical antiviral treatment through monitoring drug resistance, ongoing risk assessment for influenza epidemic and pandemic.

6.1.1 Seasonal Influenza

The influenza intensity and dominant strains vary with climates and areas (Fig. 6.1 [1]). In the temperate zone, seasonal epidemics occur mainly in winter and spring each year. In tropical regions, influenza activity shows a highly diverse

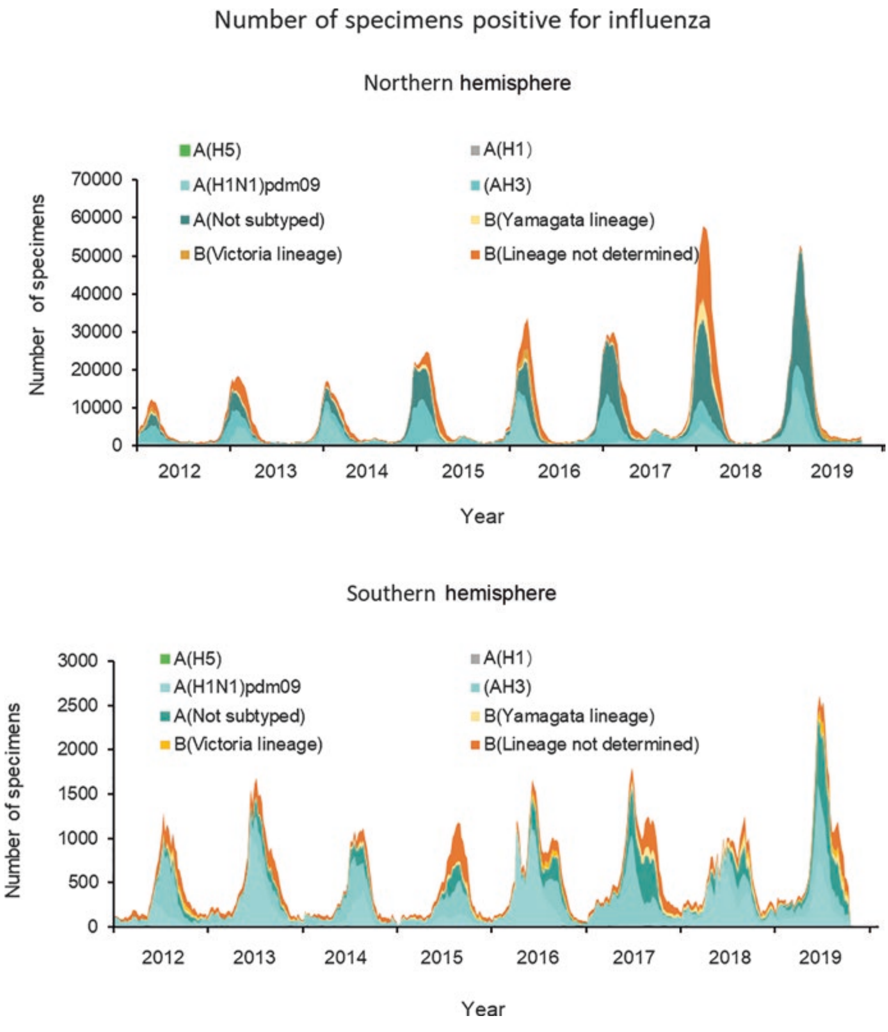

Fig. 6.1 Number of specimens positive for influenza by subtype in the Northern and Southern hemisphere from the 1st week of 2012 to the 40th week of 2019

seasonal pattern, which can be cyclically endemic for 6 months (summer peak) or throughout the whole year, causing outbreaks more irregularly. Take influenza surveillance data as of October 25, 2019 as example, in the northern "B&R" including China, Mongolia, Russia, and several countries in Central Asia, the dominant strain was influenza A(H3N2) and the influenza activity was extremely low or inactive while there were influenza A (H3N2), influenza A (H1N1), and dominant influenza B viruses co-circulated with much higher positive rate of influenza virus in the southern "B&R".

6.1.2 Avian Influenza

Avian influenza refers to the disease caused by infection with avian influenza type A viruses. These viruses exist naturally among wild aquatic birds worldwide and can infect domestic poultry and other bird and animal species. Sporadic human infections with avian flu viruses have occurred. Avian influenza viruses cannot spread easily from person to person. Avian influenza can cause mild-to-severe illness, including death. An outbreak of highly pathogenic avian influenza A (H5N1) caused 18 infections and 6 deaths in Hong Kong in 1997. Since 2003, H5N1 and other avian influenza viruses have spread from Asia to Europe and Africa. In 2013, China reported the first case of human infection with avian influenza A (H7N9) virus. It experienced several waves of the epidemic and the cases totaled over one thousand, among which only three were reported abroad and all of them were epidemiologically related to China. As of September 2019, a total of 861 cases of A (H5N1), including 455 deaths, had been identified in 17 countries around the world, most of which were in "B&R" countries in South Asia, Southeast Asia, and Egypt (Table 6.1 [2]). Since the first case of avian influenza A (H5N6) reported in Sichuan province in April 2014, a total of 24 cases of H5N6 avian influenza have been reported in China Mainland, with 16 deaths, or fatality rate, 66.7%.

With current scientific knowledge and technology, it is impossible to predict when and where such a pandemic will occur, the virus strain that causes it, and how serious it will be (as mild as the pandemic A (H1N1) 2009, or as catastrophic as the 1918 Spanish pandemic), but it will definitely happen in the future. Due to economic globalization, urbanization, and increasing mobility, not only "B&R" countries but also various regions of the world will be affected severely within 1 or 2 months if influenza pandemic occurs.

Table 6.1 Cumulative number of confirmed human case for avian influenza A (H5N1) reported to WHO, 2003–2019

Country	2003-2009*		2010-2014*		2015		2016		2017		2018		2019		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	0	0	0	0	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	120	50	136	39	10	3	3	1	0	0	0	0	359	120
Indonesia	162	134	35	31	2	2	0	0	1	1	0	0	0	0	200	168
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nepal	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	0	0	0	0	0	0	127	64
Total	**468**	**282**	**233**	**125**	**145**	**42**	**10**	**3**	**4**	**2**	**0**	**0**	**1**	**1**	**861**	**455**

* 2003-2009 total figures. Breakdowns by year available on subsequent tables.
** 2010-2014 total figures. Breakdowns by year available on subsequent tables.
Total nuber of cases includes number of dearhs
WHO reports only laboratory cases.
All dated refer to onset of illness.
Source: WHO/GIP, data in HQ as of 27 September 2019

World Health Organization

6.2 The Risk and Principles for the Prevention and Control of Influenza

6.2.1 The Risk of Epidemic

Annual influenza vaccination is the most cost-effective way to prevent seasonal influenza. However, influenza vaccines can only provide moderate protection if the circulating influenza viruses are well-matched to the flu vaccine. Although the national influenza vaccination rate in the United States is close to 50% [3], influenza still causes a large number of illnesses, hospitalizations and deaths every year. Depending on its intensity and severity, it can affect tens of millions of people and causes tens of thousands or even 60,000 deaths in US [4]. “B&R” countries will inevitably have influenza epidemics in winter, spring, and summer or throughout the year, as may vary to their climatic zones.

The US CDC uses the Influenza Risk Assessment Tool (IRAT) to assess 16 new subtypes of influenza A viruses, including H7N9. The H7N9 virus was found to have the highest risk score and was characterized as having a medium to high risk of a potential pandemic [5]. Surveillance data in China found that despite the highly pathogenic H7N9 virus in poultry outbreaks and human infections, there were no significant changes in its etiology, main infection routes, and patterns of cases. The H7N9 virus is still of bird origin, and its route of infection is still from bird to human. Contact with infected birds or exposure to live poultry markets are still important risk factors for human infection. In view of the wide distribution of H7, H5, and H9 viruses in poultry and the environment, and the basically unchanged pattern of poultry farming, transportation, and consumption, human infection with existing avian influenza viruses will continue in the future. There is also the possibility of cases of infection with new subtype influenza viruses. However, the scale of poultry and human epidemics will remain within controllable range. China has implemented a lot of stringent live poultry market management measures, stressed cross-regional transport management of live poultry, and provided (by the Ministry of Agriculture) compulsory immunization of poultry throughout the country in recent years. As the family poultry production patterns and consumption habits of live poultry in some “B&R” countries are similar to those in China, the possibility of local cases infected with the avian influenza virus cannot be ruled out. As long as the infection of humans with animal-derived influenza continues, a pandemic influenza virus may appear at any time.

6.2.2 Prevention and Control Principles

6.2.2.1 Seasonal Influenza

In summary, China has been persistent in “enhancing surveillance and early warning, immunizing high-risk populations, regulating epidemic management, implementing medical treatment, and conducting extensive publicity and mobilization.”

Surveillance is the foundation of prevention and control for all diseases. Influenza vaccination is the most effective way to prevent influenza. People above 6 months of age and without contraindications can be vaccinated. Children aged 6 months through 4 years (59 months), the elderly, people with underlying conditions, pregnant women, and medical staff are the priority population to be recommended for vaccination. Clusters and outbreaks of influenza are unavoidable, and they need to be controlled timely to curb the spread of the epidemic once detected. Scientific diagnosis and treatment of influenza cases can not only prevent the emergence of resistant strains but also shorten the course of the disease and reduce the occurrence of severe cases and deaths. Through publicity and mobilization, comprehensive prevention and control of influenza could be carried out by improving people's awareness of influenza and vaccines, advocating healthy lifestyles, developing good hygiene practices, and adopting nonpharmaceutic interventions (NPIs). NPIs usually include avoiding close contact, staying at home when being sick, covering your mouth and nose with a tissue when coughing or sneezing, cleaning hands, avoiding touching your eyes, nose or mouth, etc.

6.2.2.2 Avian Influenza

After assessing China's response to the avian influenza H7N9 epidemic in 2013, WHO stated that "China's response to the H7N9 avian influenza epidemic is a global model."

A series of scientific research carried out after the outbreak has timely identified the key epidemiological characteristics of the disease, and has provided scientific evidence for H7N9 epidemic prevention strategies and measures, which, with the involving understanding of the disease and judgment of the epidemic situation, were timely adjusted at different stages of the epidemic. This was of great significance for stabilizing society, avoiding panic, and ensuring national security while reducing economic losses. The specific measures were as following:

- Disease surveillance and risk assessment: carry out surveillance on cases, the environment, and live poultry and conduct epidemic detection, risk assessment, early warning, etc.
- Reduce the risk of human exposure and infection: suspend live poultry trading, close live poultry markets, etc.
- Control outbreaks in poultry: vaccinate poultry, cull infected poultry, manage the cross-regional transport of live poultry, etc.
- Patients' clinical treatment and medical management: timely release and update case diagnosis and treatment plan of human avian influenza A (H7N9) cases and adopt "four concentration" and "four early" principles, that is, "concentration of patients, experts, resources, and treatment" and "early detection, reporting, diagnosis, and treatment."
- Communicate risks and public opinion guidance: disseminate authoritative and scientific epidemic information to the public in a targeted manner, publicize knowledge of prevention and control, and respond to social concerns in a timely manner.

6.3 Cases of Influenza Prevention and Control

The Response to Pandemic A (H1N1) 2009 in China

1. Overview

Since the twentieth century, there have been four pandemics worldwide, the most serious of which was the Spanish flu of 1918, which killed about 20–50 million people worldwide [6]. Almost a century after it, the pandemic H1N1 2009 influenza virus began to spread from Mexico and the United States to the whole world. As of August 1, 2010, laboratory-confirmed influenza A (H1N1) cases had been reported in more than 214 countries and regions, including at least 18,449 deaths [7]. It was estimated that the number of respiratory and cardiovascular deaths due to influenza A (H1N1) infection was more than 15 times the number reported [8].

The first human case of H1N1 in China was an imported case from the United States, discovered by the Chengdu Center for Disease Control (Chengdu CDC), and then confirmed by Sichuan Center for Disease Control (Sichuan CDC) and the Chinese Center for Disease Control and Prevention (China CDC). Within a short period, local cases also appeared one after another, and the epidemic spread rapidly to all provinces and cities nationwide. According to a nationwide cross-sectional seroprevalence study [9], an estimated number of 200 million individuals (16%) were infected with H1N1 in China.

2. Strategies and Measures of Prevention and Control

When WHO announced that A (HINI) outbreak was an "international public health concern" on April 25, 2009, the emergency response actions were triggered immediately in China. Under the leadership of the State Council, a joint emergency response mechanism was timely established. In order to protect the public from security threats and to guarantee normal economic activities and social stability, all ministries were involved in a coordinated manner to fight against the A (HINI) pandemic.

2.1 Develop a Scientific-Based Strategy with a Timely Update to Different Epidemic Situations

After the SARS outbreak in 2003 and H5N1 human infection reported in 2005, China developed a pandemic response plan that covered surveillance, laboratory capacity building, vaccine development, and stockpiling.

To strictly prevent the imported case before the first confirmed human case was reported, it strengthened the exit–entry inspection and quarantine, enhanced surveillance, conducted communication and education campaigns, and carried out research on diagnostic reagents, antiviral drugs, and vaccines. After reporting the first case of human infection, the surveillance network was expanded and specific hospitals were designated to treat patients. After the pandemic was announced on June 11, 2009, the strategy was adjusted to strengthen prevention and control in schools and communities and to speed up clinical trials of vaccines. As the epidemic spread further, the strategy was adjusted again to improve clinical treatment and, in particular, to promote vaccination of severe cases and high-risk populations and strengthen risk communication and health promotion to reduce the impact of the epidemic and minimize its morbidity and mortality.

2.2 Develop Test Kit and Build Laboratory Surveillance Capacity

Chinese National Influenza Center (CNIC) developed the test kits successfully within 72 h after the US CDC provided the pandemic H1N1 virus and sequences. The test kits were distributed to all national influenza surveillance networks, quarantine and inspection laboratories, and other 13 countries, including Cuba and Mongolia. The influenza surveillance network was expanded from 63 laboratories to 411 laboratories in order to strengthen the diagnostic capacity in China.

2.3 Promote Vaccine Development and Vaccination Campaign

The pandemic influenza virus antigenicity is significantly different from seasonal H1N1, and the original trivalent seasonal influenza vaccines could not provide cross-protection. Therefore, relevant national ministries and ten influenza vaccine manufacturers have actively participated in vaccine development trials only 1 month after the pandemic was announced [10]. Eventually, the vaccine was approved for use in early September, making China the first country in the world to successfully complete vaccine development and registration.

2.4 Improve the Treatment of Patients

Clinical treatment in the healthcare system, with enhanced surgical capacity, is one of the most important components to mitigate the pandemic's impact. Clinical case management and treatment guidelines were rapidly developed and timely updated in China, and all confirmed patients received antiviral treatment in designated hospitals. Antivirals were also provided to close contacts at high risk for severe influenza. High-risk populations included pregnant women, those with chronic illnesses, children aged under 5 years, elders aged 65 and above, and healthcare workers. In addition, the Chinese government strengthened the treatment capacity of low-income provinces through additional investments in medical facilities and stockpiles.

2.5 Use Traditional Chinese Medicine

During the A (H1N1) pandemic, traditional Chinese medicine and antiserum therapy were also introduced. A prospective randomized and controlled clinical trial was conducted in four provinces in China. The results showed that oseltamivir and maxingshigan-yinqiaosan, alone and in combination, reduced the time to bring down a fever in patients with H1N1 influenza virus infection. These data suggested that maxingshigan-yinqiaosan might be used as an alternative treatment to H1N1 influenza virus infection [11].

2.6 Strengthen Risk Communication and Health Education

China considered active communication with media as one of the most important measures for pandemic response. Public information and risk communication messages were disseminated through a variety of media, including television, radio, and extensively distributed printed materials.

China has set up a regular mechanism to timely release epidemic information and prevention and control progress and established a 24/7 hotline 12320 to reply to inquiries. More importantly, it was very useful to monitor public opinions, make real-time analysis, and adjust media policy in time. These measures played an important role in maintaining public social harmony and stability.

3. Experience and Lessons Learned

3.1 An Influenza Pandemic Can Occur Anywhere in the World and in Any Season

Before the 2009 pandemic occurred, people assumed that Southeast Asia might be the epicenter of influenza pandemics. This hypothesis was supported by the 1957 Asian H2N2 and the 1968 Hong Kong H3N2 pandemics. However, the pandemic H1N1 2009 originating from Mexico indicates that it can emerge anywhere in the world. Therefore, global influenza surveillance and preparedness for influenza pandemics need to continue.

3.2 A Functional and High-Quality Surveillance System Is the Foundation for Epidemic Response

By 2005, the influenza surveillance system, established in China in 2000, had expanded to 63 network laboratories and 197 sentinel hospitals in 31 provinces. In 2009, in order to respond to the pandemic, the system further expanded to more than 400 network laboratories and 556 sentinel hospitals, thus covering all prefectures/cities and priority counties throughout the country. The surveillance system could perform real-time PCR and virus isolation, and the isolated viruses were sent to CNIC for further identification, via genetic sequencing, antigen analysis, etc. to provide timely evidence for risk assessment.

3.3 Joint Emergency Response Mechanism and Hierarchical Prevention Strategy Are the Keys to the Scientific and Efficient Response

A joint prevention and control working mechanism led by the Ministry of Health and joined by 33 departments is the core of overall responses to the H1N1 pandemic 2009, especially in terms of the vaccine development and related trials. This mechanism ensured the establishment of a strong leadership before the pandemic virus spread to China, the development of an integrated approach to coordinate actions taken by different departments, and the management of information sharing and risk communication in a timely and accurate manner. With the progress of the pandemic, China adopted a hierarchical prevention strategy under the "joint prevention and control" mechanism to stringently prevent the imported cases in the early stage and focus on severe cases in the later stage.

Pandemic H1N1 2009 was the first pandemic in the twenty-first century but will definitely not be the last one. One of the most important legacies from the 2009 pandemic response is the expanded national influenza surveillance network, which is critical for quick detection of any pandemic potential influenza virus in China. There is a need to continually refine and improve influenza identification, prevention, and treatment options to prepare for the next pandemic.

Prevention and Control of Human Infection with H7N9 Avian Influenza in China

1. Overview

On March 31, 2013, China reported the first case of human infection with H7N9 avian influenza in the world. After that, the National Health and Family Planning Commission announced that it would include H7N9 in China's notifiable category B infectious diseases for management. As of October 2019, China mainland had reported a total of 1537 cases and 612 deaths of avian influenza A (H7N9), with a fatality rate of 39.8%. The avian influenza H7N9 virus has been clarified as a new gene reassortant virus that could infect humans across species barriers and cause morbidity and death. It was a strong warning for China and global prevention and control of emerging infectious disease and influenza pandemic preparedness. Although the H7N9 avian influenza was only endemic in China and effectively controlled, the H7N9 avian influenza virus and relevant epidemic have attracted widespread attention from domestic and international experts.

1.1 Etiology

The avian influenza A (H7N9) virus is a new gene reassortant virus. Its genome is derived from wild bird and poultry influenza gene fragments. H7N9 virus can bind to α-2,3 and α-2,6 sialic acid receptors. As α-2,3 receptors are mainly distributed in the avian digestive tract and human lower respiratory tract, and α-2,6 receptors are mainly distributed in the human upper respiratory tract, it indicates that the H7N9 virus has the ability to bind avian and mammalian cells and its ability to bind α-2,3 receptors is stronger [12, 13]. From March 2013 to October 2016 (the first four epidemic seasons), the H7N9 virus showed low or no pathogenicity to poultry, but most of the human infection presented severe pneumonia. The highly pathogenic H7N9 virus was first detected in H7N9 cases and poultry in late 2016 [14, 15].

1.2 Clinical Features

Human infection with the H7N9 virus causes acute respiratory infections with high severity and mortality. The H7N9 severe cases generally develop rapidly with severe pneumonia occurring most often within 3–7 days of onset. Most of the body temperature remains above 39 °C and often progresses rapidly to acute respiratory distress syndrome (ARDS). The average interval from onset to ARDS in severe cases is 7 days (1–19 days), from onset to shock, 8 days (3–55 days), and from onset to death, 14 days (8–24 days). Most severe cases require admission to the intensive care unit (ICU).

1.3 Epidemiological Characteristics

The new H7N9 virus that causes the human infection is highly homologous to that detected in the live poultry market at the same time. About 60–70% of patients had a clear history of poultry contact. The most likely site of infection was the live poultry retail and wholesale market, a site that provided an ideal place for virus mixing, amplification, and spread of the virus. Exposure to infected chickens is the primary source of human cases. H7N9 virus could be transmitted to individuals through the respiratory tract or close contact with the secretions or excreta of infected poultry and exposure to an environment contaminated by the H7N9 virus. Few cluster cases have been reported, which indicated that the H7N9 virus cannot easily spread from person to person.

Human beings are generally not susceptible to infections by avian influenza viruses. Although a large number of people visit the live poultry market each day, contact or raise live poultry, or engage in poultry-related work, the number of them infected with H7N9 virus or even get sick is still a minority. Therefore, there might be some host factors (such as differences in innate immunity or susceptibility genes) that lead to differences in susceptibility to the H7N9 virus in different individuals. Patients, especially adults or the elderly, get more severe after being infected with H7N9, possibly due to their exposure opportunities, underlying diseases, and autoimmunity.

1.4 Epidemic Overview

Overall, the incidence of the H7N9 epidemic is obviously high in winter and spring. When winter comes, the H7N9 virus becomes active, hence a gradual increase and the first peak of incidence. With the implementation of prevention and control measures such as closing the live-poultry market and restricting cross-regional transport of live poultry, the epidemic level began to decline. As the Spring Festival approached, residents' consumption of live poultry increased, so did the risk of exposure and infection. This led to the second peak of the epidemic, and with the routine market closure in the Spring Festival holiday, the epidemic fell again rapidly. In the winter and spring of 2016 and 2017, the peak of incidence was significantly higher than the historical level. The subsequent epidemic season appeared to be sporadic, which was the lowest level in history.

2. Strategies and Measures of Prevention and Control

After the outbreak of human H7N9 avian influenza in 2013, facing the serious and complex situation of prevention and control, China promptly put forward the overall prevention and control principles, that was, "to attach great importance, be proactive in response, adopt joint prevention and control mechanism, and insist on scientific prevention and control," and formulated a specific prevention and control strategy. Since then, as the epidemic went on and the understanding of the disease deepened, the strategies were adjusted and improved accordingly.

The prevention and control of the H7N9 epidemic in China could be divided into three stages:

First, early emergency response (March 2013 to August 2014), mainly in Eastern China and Southern China. Most of the people infected were from urban areas. The prevention and control work was aimed at the rapid containment of the epidemic. Key measures included establishing and improving joint prevention and control mechanisms at all levels, conducting surveillance, handling outbreak, strengthening the measure of "concentrating experts and resources for concentrated admission of patients," and "early detection, reporting, diagnosis, and treatment." Additional measures, such as the closure of a large number of live poultry markets or the ban on live poultry trading, were adopted in various places.

Second, intensive response (September 2014 to August 2016), when the epidemic was still mainly concentrated in areas of Eastern and Central China. The previous scientific research on the etiology and epidemiology carried out in the first stage helped deepen the understanding of the disease and accumulate some response experience. Further, combined with the epidemic judgment and risk assessment conducted by disease control departments, the control strategies were shifted to reducing the risk of human exposure and infection. The key was to continuously improve the management measures for live poultry, to shift gradually from emergency response to regular and routine control, and to form a live poultry management model suitable for local control. At the same time, local authorities stepped up their efforts on environment surveillance related to poultry and applied the monitoring results to risk assessment, which played an increasingly important role in prevention and control.

Third, continuous strengthening of the exposure control (September 2016 to present). At this stage, the H7N9 virus has shown highly pathogenic mutations in poultry and the epidemic in poultry increased. The epidemic among humans peaked and spread to more than 20 provinces across the country. The number of cases in rural areas has increased significantly. The epidemic rapidly spread to more areas and infect more people. The low-pathogenic and high-pathogenic avian influenza A (H7N9) virus co-circulated in poultry. Thus, the previous control measures could not meet the needs of prevention and control. The agriculture and health departments have reached an agreement on the importance of controlling the H7N9 epidemic in poultry. While further strengthening the management of live poultry sales and wholesale, more and more places have implemented live poultry transport control measures. In addition, poultry vaccination to block the spread of the virus has been carried out to further reduce the risk of human infection from the source.

3. Experience and Lessons Learned

The prevention and control of human infection with H7N9 avian influenza in China has been so far relatively successful. The experience can be summarized as follows:

- Joint prevention and control mechanism, multiple-department cooperation, and scientific decision-making are the cornerstones of a successful response.
- Improved emergency capabilities facilitate the success in early response.
- Technical support is a powerful guarantee for a successful response.
- The control of the epidemic in poultry and the risk of human exposure to the virus is the core of avian influenza epidemic prevention and control.
- Clinical diagnosis and treatment, especially of severe cases, are critical to reducing the harm and impact of the H7N9 epidemic.

There are still many challenges, including inadequate management and control of live poultry transport, poultry vaccination coverage and sustainability, and strong consumer demand for poultry.

In the future, China will continue to carry out successful control measures mentioned above, such as controlling the epidemic in poultry, promoting the transformation and upgrade of the poultry industry, and managing live poultry transport. Influenza virus detection in medical institutions will be promoted for early diagnosis. The development and application of new antiviral drugs should also be on the agenda for avian influenza control.

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