China—WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus

18 – 24 April 2013

Mission Report

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Annex 4 – Timeline of H7N9 events

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Executive Summary

Introduction

On 31 March 2013, in accordance with the International Health Regulations (2005) [IHR], the Government of China reported the detection of three cases of human infection with a novel influenza A(H7N9) virus (hereafter, H7N9) in Shanghai and the province of Anhui. At the same time, the Chinese Center for Disease Control and Prevention (China CDC) posted full genome sequences of viruses isolated from the first three cases in a publicly accessible database. Over the next two weeks additional cases were confirmed in the municipalities of Shanghai and Beijing, and in the provinces of Anhui, Jiangsu and Zhejiang. Most cases were marked by severe pneumonia and a substantial number of deaths followed. Investigations identified live bird markets as a possible source of human infection.

In response to this situation and at the invitation of the National Health and Family Planning Commission of China, a China–WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus was formed to assess the outbreak and provide guidance on its management (see terms of reference in Annex 3. The Joint Mission was composed of experts from China and WHO and four from Australia, Europe, Hong Kong, Special Administrative Region of China, and the United States of America. The team visited Beijing and Shanghai over 6 days, 19 – 24 April 2013, meeting with senior officials and many experts from the human and animal health sectors involved in the continuing outbreak investigation, following an agreed method of work (see Agenda in Annex 6).

Although the team was unable to visit other affected areas because of time constraints, outcomes of the extensive investigations already undertaken in China were openly shared and vigorously discussed. The team’s findings, assessment and recommendations were formed on the basis of the data available, site visits and discussions. These are presented in this report.

Main Findings

Epidemiology

As of 22 April 2013, 104 confirmed cases, including 21 deaths, have been reported in Zhejiang (40 cases), Jiangsu (24), Henan (3), Anhui (3) provinces, Shanghai (33), and Beijing (1). Patients are predominantly older (median 62 years) and male (69%). Of 77 cases reported nationally for which data are available, 18 (23%) reported no identified contact with poultry; 56 (72%) reported some recent contact with live poultry and live poultry markets.

An additional case in an asymptomatic four-year-old boy was detected by Beijing CDC during enhanced case finding that followed the identification of the first case in Beijing.

Almost all cases have been sporadic but three family clusters have been identified. Evidence thus far is not sufficient to conclude that person-to-person transmission has occurred. Of more than 3000 close contacts, 19 developed respiratory symptoms. None of these symptomatic patients tested positive for H7N9 by reverse-transcriptase polymerase chain reaction (RT-PCR) testing. Results of serology testing are pending.

On 1 April, enhanced surveillance was introduced throughout the country for pneumonia of unknown origin and in sentinel influenza-like illness (ILI) surveillance sites; molecular diagnostic kits were also distributed. Since then, an increase has been observed in the number of ILI consultations in ILI sites. This increase is more likely to be related to concerns among the population than to an increase in H7N9 cases. Enhanced ILI surveillance has identified one ILI case that tested positive for H7N9 by RT-PCR. Although it is too early to confirm the effectiveness of the closure of live bird markets in Shanghai, which took place on 6 April, no new cases have been reported there with dates of onset later than 13 April.

Areas of major uncertainty Some important uncertainties remain, including the following: (1) It is unclear why severe disease has been found predominantly in older male urban residents. This pattern could be associated with behavioural factors or, as for seasonal influenza, H7N9 could be causing a larger number of mild and symptomatic infections that have gone undetected to date; (2) Although surveillance for pneumonia of unknown origin is routine, it is impossible to exclude the possibility that these infections have been occurring for some time; (3) Currently, evidence so far is not strong enough to conclude there is person-to-person transmission; (4) The extent of occurrence of unrecognized mild / asymptomatic infections is unclear and may affect estimates of case-fatality. Persons who have mild or asymptomatic illness may not have been tested in any of the testing algorithms outlined.

Clinical features and management

The most common presenting signs and symptoms were those characteristic of influenza. Encephalopathy and conjunctivitis were uncommon, and nasal congestion and rhinorrhoea were not reported as initial presentations. Common laboratory findings included normal white cell count, leukocytopenia, lymphocytopenia, thrombocytopenia, and mildly elevated liver enzymes. Most cases were severe, and a number of these rapidly deteriorated within 1 to 2 days of hospitalization to acute respiratory failure, leading to refractory hypoxemia and multiple organ failure, the major cause of death. A few mild cases were reported, especially in children. Neuraminidase inhibitors (NAIs) were given to almost all patients but only after a median of 6 days after disease onset. NHFPC developed a risk-based management protocol for areas where confirmed cases are reported so that NAIs could be given earlier to symptomatic cases, even before the confirmatory result of laboratory tests for H7N9 virus. Infection prevention and control measures in fever clinics and designated hospitals complied with national and WHO guidance.

Characteristics of avian influenza A(H7N9) viruses

The novel viruses are reassortants, comprising H7 HA, N9 NA and the six internal genes of H9N2 influenza A viruses. This combination of influenza genes has not previously been identified among viruses obtained from birds, humans or any other species, although individual genes are related to those of recent avian influenza viruses circulating in East Asia. H7N9 viruses obtained from human cases, poultry and environmental samples are closely related and contain a number of genetic signatures previously associated with low pathogenicity in poultry, enhanced capacity for mammalian infection and resistance to the adamantane class of antiviral drugs. Several human H7N9 viruses were shown to be sensitive to the NAIs oseltamivir and zanamivir in vitro. It is important to note that one mammalian adaptation (E627K in the PB2 gene) occurred in many of the human H7N9 viruses but did not occur in any of the non-human viruses. Continuing analyses are essential to improve understanding of these viruses and to detect any future changes affecting their transmissibility between humans and their pathogenicity in birds. Preliminary analyses suggest that many people lack antibodies to this virus and that production of an effective vaccine will require the selection of a new candidate H7 vaccine virus.

Animal health

The detection of H7N9 virus in live poultry markets in the vicinity of human cases in Shanghai, the contact history with live poultry or live poultry markets in a substantial number of cases, and the apparent reduction in human cases after the closure of live poultry markets in Shanghai, suggest exposure to live poultry as a key risk factor for human H7N9 infection. Although the H7N9 virus has not been detected in poultry farms so far, it is likely that they provide the source of infection, with subsequent amplification within live poultry markets leading to human infections. Although data are limited at this early stage of the investigation, it may be that the H7N9 virus is currently sustained through intra- and inter-provincial trading of live poultry. If infection in poultry is not controlled the H7N9 virus may spread to additional provinces in China, leading to an even greater zoonotic threat, and thus increasing its pandemic potential. It may also facilitate the emergence of a virus that is highly pathogenic in poultry. The human and poultry viruses genetically sequenced thus far show that this H7N9 virus has adaptations that allow it to infect humans, although virological information is limited as the animal A(H7N9) test and the test strategy in China remain to be validated.

Response strategies and measures

A joint multi-sectoral prevention and control mechanism (JPCM) has been established at national and local levels to lead and coordinate the emergency response to H7N9 virus. The national JPCM, led by the National Health and Family Planning Commission, consists of 13 governmental ministries and commissions, including the Ministry of Agriculture, the State Forestry Administration, and the Ministry of Science and Technology. An inter-regional

JPCM has also been established to support sharing of information and coordinated response among the affected provinces and municipalities, including Anhui, Jiangsu, Shanghai, and Zhejiang. Significant efforts are being made to ensure that the emergency response to the newly detected H7N9 virus is based on laws and regulations, the principle of transparency, prioritization and international collaboration. An approach based on risk assessment and evidence is being applied to inform coordinated, balanced public health interventions. Coordinated but tailored response strategies and guidance have been provided to the different provinces based on the epidemiological situation and local needs. Early detection, early reporting, early diagnosis and early treatment ("the Four Earlys") have been the general guiding principles for the operational response.

Response measures include close collaboration between public health and animal health sectors, enhanced surveillance in humans and animals, case investigation, field investigation, risk assessment, clinical management, hospital infection prevention and control, public health interventions, risk communication, and research. Reagents for PCR detection of H7N9 viruses in humans have been distributed to more than 400 laboratories throughout China. Several national guidelines have been issued for surveillance and epidemiological investigation, including contact tracing, laboratory testing and patient isolation and treatment.

The priority response measures have been focused on the following:

- Field investigations, including source of infection
- Enhanced surveillance in humans and animals
- Clinical management, infection prevention and control
- Risk communication
- Scientific research.

The current response at national and local levels seen by the Team has been excellent and appears to be effective. The risk assessment and evidence-based response to H7N9 virus could serve as a model of emergency response to similar events.

International collaboration

Any novel influenza A virus that causes human infections is of global interest and, if disease is severe, is a cause for serious concern. After it first identified the H7N9 virus, China recognized its vital role in contributing to global public health through open channels of communication with global influenza partners and the international community. On 31 March 2013 the China National IHR Focal Point notified WHO of the first three cases of human infection with H7N9 virus and has since made regular reports to WHO and its Member States. Regular situation updates and transparent sharing of information have demonstrated the openness of Chinese Government authorities. In addition, China CDC has shared genetic sequence data, diagnostic test protocols and viruses with the global public health and research communities. The National Avian Influenza Reference Laboratory, Harbin, has also shared genome sequences of H7N9 viruses. These actions have contributed greatly to the global risk assessment and response, including the selection and development of candidate human H7N9 vaccine viruses and vaccine potency and diagnostic reagents, as well as a better understanding of antigenicity, pathogenicity and transmissibility of the virus.

The National Health and Family Planning Commission has maintained close technical collaboration with WHO staff through China CDC. As a newly designated WHO Collaborating Centre for Reference and Research on Influenza, the National Influenza Centre in China has maintained regular communication and technical discussions with other WHO Collaborating Centres for influenza. As a member of the Global Outbreak Alert and Response Network (GOARN), China CDC provided a situation update to GOARN partners.

In summary, China’s transparent and timely sharing of technical information, data and viruses is greatly appreciated and has contributed immensely to current global understanding of the H7N9 virus, risk assessment and actions required to manage the shared risk.

Assessment

In March 2013, China identified three human infections by an avian influenza A(H7N9) virus. This virus had never been known to infect people before. China responded quickly including by establishing a joint multi-sectoral coordination mechanism, initiating several investigations, notifying WHO under the International Health Regulations (2005), posting sequences of the virus, sharing viruses with the WHO Influenza Collaborating Centers and other laboratories and mounting effective counter measures such as closure of live poultry markets in some locations. The response has demonstrated that health authorities were well prepared and acted quickly, effectively and professionally.

Since then, this virus has caused over 100 human infections. Most of these infections have led to severe disease, including more than 20 deaths.

Currently, evidence so far is not strong enough to conclude there is person-to-person transmission. The limited available information suggests that many infections caused by this virus may be related to exposure to infected poultry in live poultry markets or to environments contaminated by this virus. However, future studies can strengthen the evidence.

The risk to people posed by the emergence of the H7N9 virus must be considered unusually serious, for several reasons. First, this virus has caused serious disease, including death, in some people. Second, this virus does not appear to cause disease in poultry (although it could change in the future to become highly pathogenic) and therefore could spread silently. Third, this virus has caused more human infections and disease in a shorter period of time than any other known avian influenza virus. Fourth, some H7N9 viruses show genetic changes that suggest they are partially adapted to infect humans more easily than other avian influenza viruses. Taken together, these findings suggest that the possibility of this virus becoming transmissible among people is higher than for any other known avian influenza virus and therefore it must not be ignored.

On the basis of this assessment, the Joint Mission has made seven high-level recommendations to the Government of China, as below.

Recommendations

- Undertake intense and focused investigations to determine the source(s) of human H7N9 infections. Identification of the source will enable urgent action to prevent continuing virus spread, with its potentially severe consequences for human and animal health.

- Maintain a high level of alert, preparedness and response even though human cases might drop in the summer (as they do for many other avian influenza viruses) because of the seriousness of the risk posed by this virus and because much basic information remains unknown.

- Continue to conduct and strengthen both epidemiological and laboratory-based surveillance in human and animals in all provinces of China to identify changes that might indicate the virus is spreading geographically and gaining the ability to infect people more easily or transmit efficiently from person to person.

- Ensure frequent mutual sharing of information, close and timely communication and, when appropriate, coordinated or joint investigations and research among ministries of health, agriculture and forestry because this threat requires the combined efforts of all these sectors.

- Continue high-level scientific collaboration, communication and sharing of sequence data and viruses with WHO and international partners because the threat of H7N9 is also an international shared risk and concern.

- Encourage and foster the scientific and epidemiological studies and research needed to close major gaps in critical knowledge and understanding.

- Continue preparedness planning and other IHR core capacity strengthening work because such investments make a major difference in readiness to address health security risks and emergencies, including H7N9.

Annexes

Annex 1 – Detailed Findings

Epidemiology

Data as of 23 April 2013

The first cases of infection with novel avian influenza A(H7N9) were a father and son pair in Minhang District, Shanghai. They both had disease onset dates of 19 February 2013, initially presenting with influenza-like illness, which rapidly progressed to pneumonia. A second son had previously been hospitalised with pneumonia. Concerned by these three cases, clinicians immediately alerted public health authorities. Four more patients with similar symptoms were admitted to the same hospital in Shanghai in late February and early March.

Specimens from the father and an unrelated case with onset date of 27 February 2013 were positive for influenza A but unsubtypable: hence, specimens were referred to the WHO Influenza Collaborating Centre at the Chinese CDC (see timeline). A third similar influenza A unsubtypable case was reported to the Chinese CDC from neighbouring Anhui Province. The isolates from all three were very similar novel reassortant avian influenza viruses. Therefore, on 31 March the Chinese authorities notified them to WHO under the IHR.

Diagnostic test kits were distributed to laboratories across the country beginning 1 April. As of 22 April 104 confirmed cases have been reported in five adjoining Chinese Provinces, plus Beijing, with 54 counties/district involved. The affected areas include Zhejiang (40 cases), Shanghai (33), Jiangsu (24), Henan (3), Anhui (3) and Beijing (1). An additional case in an asymptomatic 4-year-old boy was also detected by Beijing CDC during enhanced surveillance for those who had the same exposure to potentially infected poultry and the environment.

As of 22 April the virus has not been detected in the other 25 provinces in China despite ongoing routine sentinel ILI surveillance, increasing numbers of persons seeking testing and enhanced surveillance for pneumonia with unknown aetiology. Eighty-three per cent of cases were reported to be urban residents.

Of reported cases, three have been mild, 21 cases (20%) are known to have died and 13 cases are known to have been discharged from hospital. There were more than twice as many males as females (69% vs. 31%), with a median age of 62 (range 2-89 years). Generally, the age pattern was considerably older and far more male dominated than was observed in China for A(H5N1) (Figure 1). Child cases discovered were either mild or asymptomatic. Many more H7N9 cases had been confirmed over four weeks than had been confirmed and reported for A(H5N1) in China over ten years (Figure 1), Examination of risk factors showed the prevalence of chronic ill health that would be expected in such an older population. An association with contact with animals and in particular live poultry was observed. Of 77 cases reported nationally for which data were available, only 18 cases (23%) reported no contact with animals and 56 (72%) reported some recent contact with live poultry. In the 33 Shanghai cases, after detailed questioning only 2 cases reported no exposure of any kind to poultry. However, an unknown factor is the frequency of such exposure in an older population living in urban areas where visits to live bird markets (so-called wet markets) are common. The incubation period is estimated to be approximately 7 days by calculating the median number of days from exposure to poultry or live poultry markets to illness onset, both for confirmed cases with clear multiple exposures and for those with a single exposure.

The cases occurred mainly as sporadic incidents, with only three small clusters of two and three cases. Intensive case finding among 3000 contacts found 19 persons with respiratory symptoms, including 14 health care workers but none of these were positive for H7N9 by the new specific PCR test. Currently, evidence so far is not strong enough to conclude there is person-to-person transmission. The occurrence of asymptomatic and milder cases could not be excluded as serological testing is awaited.

Results of interventions

After declaration of the outbreak by national authorities on 31 March, alerting of populations to seek care and intensified surveillance by a number of regions, sentinel sites for ILI reported a significant rise in the number of consultations. However, virtually no new

H7N9 cases were detected at these sites. For example, in Shanghai Municipality, although some influenza A(H1N1) cases were detected, no new unsubtypable influenza A infections were seen.

Because of the association with exposure to poultry and, in particular, live bird markets, three provinces with the largest number of cases closed large live bird markets in some cities. Closure was followed by a substantial drop in the numbers of new cases reported to authorities, though two incubation periods have yet to be passed (Figure 3).

Areas of major uncertainty

At this time a number of important uncertainties remain. These include the following:

Why severe disease occurs predominantly in older male urban residents is not clear. It could be that behavioural factors and exposure to live birds in wet markets increased the risk of infection. Alternatively, it could be that they represent only a proportion of a much larger number of mild and symptomatic infections and disease progression is mainly observed in the most vulnerable population, as is the case for seasonal influenza (Figure 4). However, a problem with this hypothesis is how to explain the gender imbalance.

Similarly, it remains to be determined whether the predominance of exposure to live poultry in the cases is in fact a risk factor or simply the norm in the older male urban populations where these infections occur.

Although active surveillance for pneumonia of unknown aetiology is routine, the possibility cannot be excluded that these infections have been occurring for some time.

Figure 1. Age comparison between H7N9（n=104）and H5N1 cases（n=43, 2003-2013)

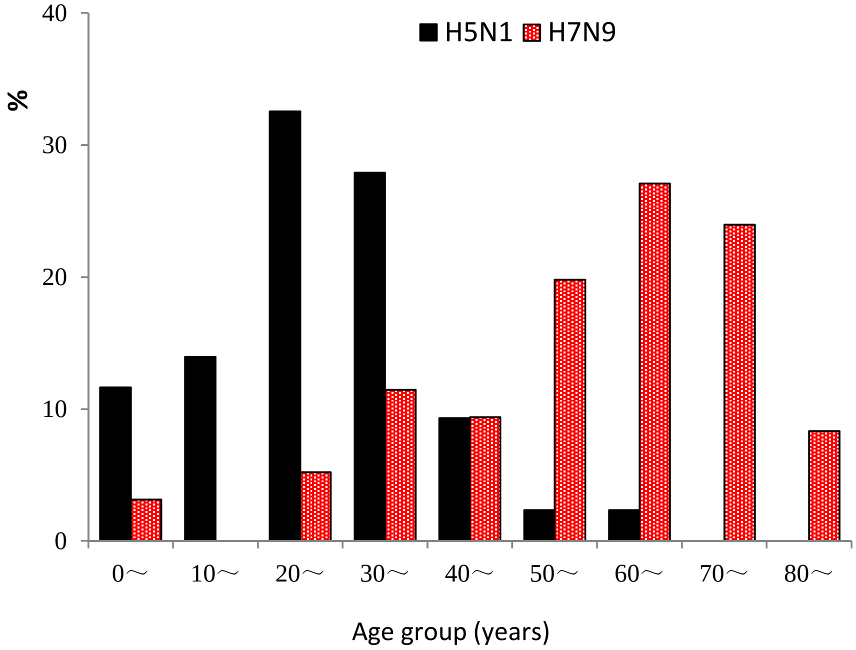


Figure 2.

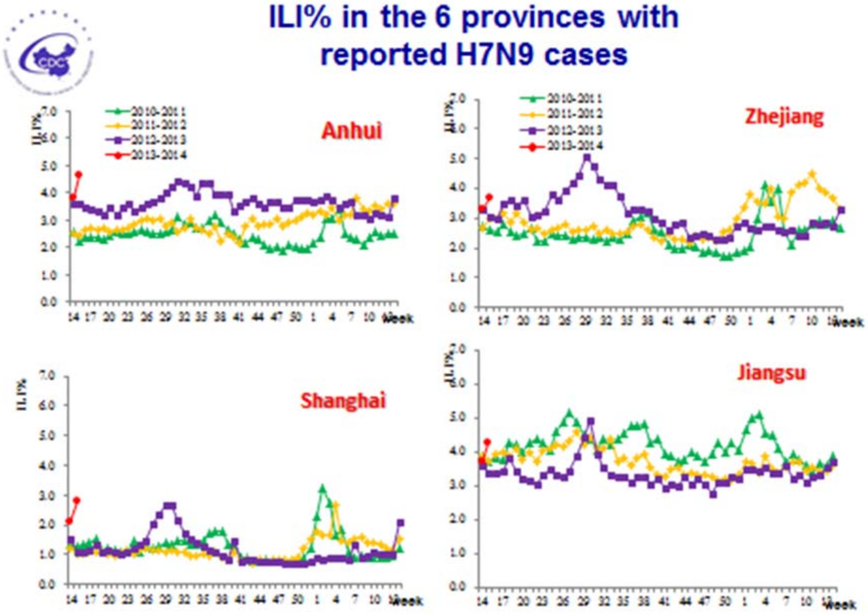


Figure 3. Epi-curve of confirmed H7N9 cases by province by date of onset (as of 22 April 2013, 17:00 Beijing time)

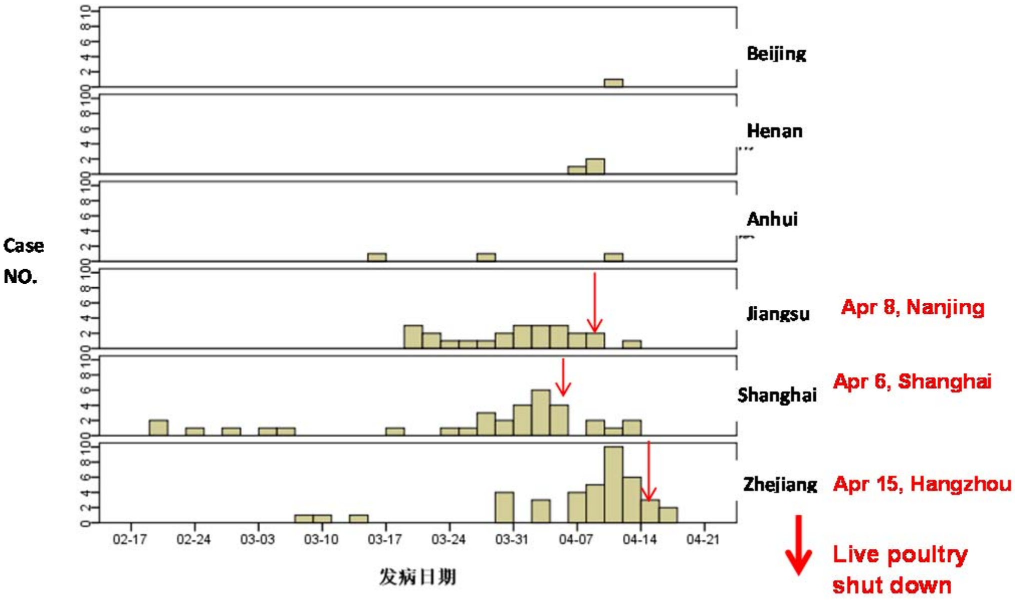
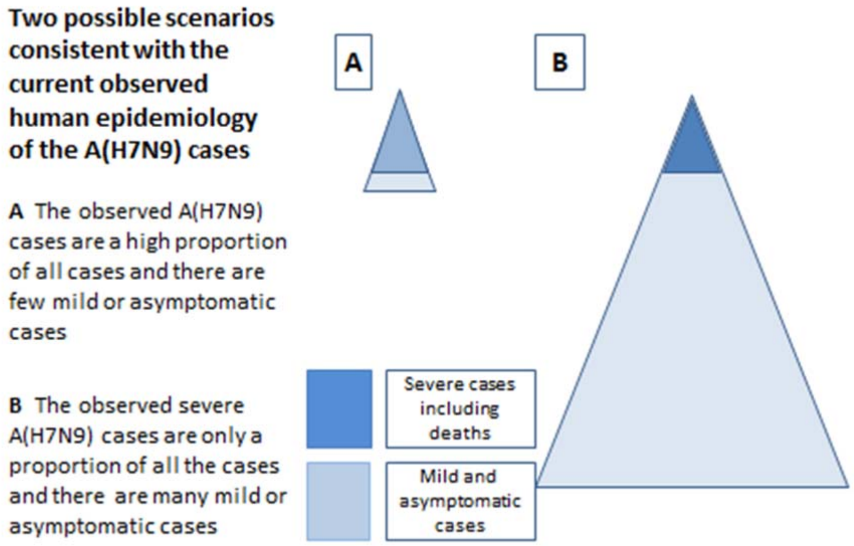


Figure 4. Two Potential Scenarios Underlying Observed Human Epidemiology



Clinical features and management

Clinical features

As of 16 April, a total of 77 confirmed cases were reported in six provinces and municipalities, among whom 67 had sufficient clinical data to analyse. The outcomes of these patients as of 22 April were 14 deaths and 9 discharges; the remaining 44 patients were still hospitalized. In some cases hospitalization was for infection control considerations rather than active treatment.

The median age of the patients was 63 years (range 4 to 87), and two-thirds were male. Comorbidities would be expected in this age and gender group; about 60% of the patients had comorbidities such as coronary heart disease, diabetes, hypertension, and chronic obstructive pulmonary disease.

Presenting symptoms

These included fever, cough, shortness of breath, fatigue, muscle aches, hemoptysis, and gastrointestinal symptoms (Figure 5). Signs such as encephalopathy (n = 2) and conjunctivitis (n = 1) were uncommon. Nasal congestion and rhinorrhoea were not reported as initial symptoms.

Mild cases were described, all in children and often manifested as fever only. In comparison, some adult patients had rapid progression to bilateral pulmonary infiltrates, often leading to severe hypoxemia within 1 to 2 days.

Laboratory findings

These included normal white cell count, leukocytopenia, lymphocytopenia, thrombocytopenia, and mildly elevated liver enzymes.

Initial treatment

A National Practice Guideline for Clinical Management of Avian Influenza A(H7N9) Infection was issued by the NHFPC on 2 April, and revised on 10 April. In most cases, initial treatment complied with the recommendations of these guidelines. Specifically, NAIs were given to almost all patients but only after a median of 6 days (range 0 to 23) after disease onset.

Medical complications and their treatment

About two-thirds of cases developed severe pneumonia and required ventilatory support in intensive care units. Other complications included shock, acute renal failure, and barotrauma. Some patients with severe hypoxemia responded poorly to conventional mechanical ventilation, which necessitated advanced supportive therapy, such as high-frequency oscillation ventilation (HFOV) and ECMO. Refractory hypoxemia and multiple organ failure were the leading causes of death. Lymphocytopenia and organ failure, rather than age, sex, or comorbidities, appeared to be risk factors for mortality in hospital. Patients treated with NAIs within three days appeared to have had better clinical outcomes than other patients. More than 60% of patients received intravenous corticosteroids in an initial daily dose equivalent to 100 mg hydrocortisone (range 25 to 300 mg).

Patient handling and infection control

A risk-based protocol was developed in national practice guidelines to support early antiviral therapy in suspected cases (Table). In addition, training materials for epidemiology, clinical manifestation, diagnostic specimen collection, and diagnosis and treatment were distributed to all hospitals in affected areas. The planned referral system in these areas was such that, for every suspected case, respiratory specimen testing using PCR would be completed at the local Center for Disease Control and Prevention within 6 to 8 hours. All confirmed cases, except those whose severe condition did not permit transportation, were then transferred to designated hospitals. Close contacts were closely monitored under medical observation, with NAIs prescribed only after onset of clinical symptoms. Among the 2033 close contacts, no confirmed cases were reported as of 22 April.

In general, infection prevention and control measures in fever clinics and designated hospitals complied with national and WHO guidance. Apart from hand hygiene, different types of personal protective equipment (PPE) were reported to have been used during the care of suspected and confirmed cases. Intense surveillance was undertaken in healthcare workers exposed to cases, and there were no reported infections among healthcare workers.

Table. Indications for early antiviral therapy*

- Confirmed case with avian influenza A(H7N9) infection
- ILI case testing positive by influenza A rapid antigen test
- ILI case testing negative by influenza A rapid antigen test or without access to influenza A antigen test, who meets any of the following criteria:
    - Close contact (including healthcare workers)
    - One of the cluster cases
    - Recent exposure to poultry (within one week)
    - Significant comorbidities, such as chronic cardiopulmonary diseases, advanced age, or pregnancy
    - Rapid progression that merits antiviral therapy as judged by treating physician
    - Pneumonia of unknown cause

* From *National Practice Guidelines on Clinical Management of Avian Influenza A(H7N9) Infection.* ILI, influenza-like illness

Conclusions

- Severe cases deteriorated rapidly, within 1 to 2 days, leading to refractory hypoxemia and multiple organ failure, which were the major causes of death.
- Mild cases were reported, though there were few
- NHFPC developed a diagnostic and treatment protocol for human infection with avian influenza A(H7N9) virus for areas where confirmed cases were reported such that NAIs could be given earlier, even before confirmation by laboratory testing for H7N9 virus.

Figure 5

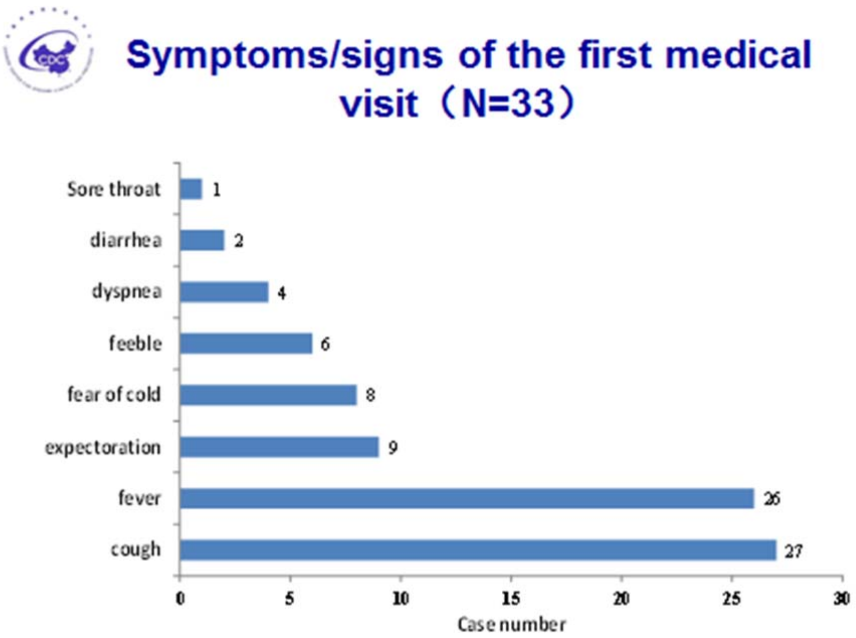
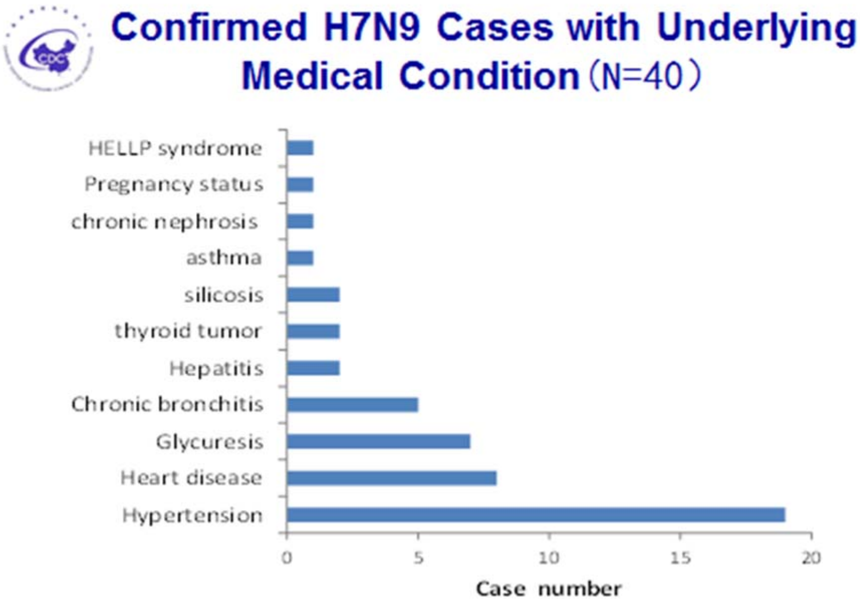

Symptoms/signs of the first medical visit（N=33）

Figure 6


Confirmed H7N9 Cases with Underlying Medical Condition（N=40）

HELLP：hemolysis, elevated liver enzymes, and low platelets

Characteristics of the avian influenza A(H7N9) viruses

The preliminary analysis of the first cases by the Shanghai Public Health Clinical Center and the Shanghai CDC, followed by the isolation and full genome sequencing of three viruses (A/Shanghai/1/2013, A/Shanghai/2/2013 and A/Anhui/1/2013) by China CDC, were critically important steps in the management of the outbreak. Immediate posting of the sequences in the publicly accessible GISAID database and rapid sharing of viruses by China CDC have enabled Chinese and international scientists to begin analysing the viruses at the earliest possible stage.

Analyses of the first three isolates showed that the viruses were reassortants comprising H7 HA, N9 NA and the six internal genes of H9N2 influenza A viruses. This gene constellation had not been identified previously among viruses obtained from birds, humans or any other species. While all three viruses were closely related, A/Shanghai/2/2013 and A/Anhui/1/2013 were more similar to each other across all 8 gene segments than to A/Shanghai/1/2013, which was distinct at multiple sites. Comparisons with other influenza A virus sequences in public databases showed that the most closely related viruses were recent low-pathogenic Eurasian H7N3 viruses (eg, A/duck/Zhejiang/12/2011(H7N3)), Eurasian H7N9 (eg, A/wild bird/Korea/A14/2011(H7N9)) and H9N2 viruses (eg, A/brambling/Beijing/16/2012(H9N2)).

The first three isolates contained a number of genetic signatures previously associated in other subtypes with low pathogenicity in poultry, enhanced capacity for mammalian infection, resistance to the adamantane class of antiviral drugs and sensitivity to the neuraminidase inhibitors oseltamivir and zanamivir. These signatures include the following:

- A single arginine at the HA cleavage site, consistent with low pathogenicity in poultry;
- Deletion of five amino acids in the NA stalk, associated with adaptation to poultry;
- Q226L substitution in the HA, associated with enhanced binding to the α-2,6-linked sialylated receptors found in the mammalian respiratory tract;
- E627K in the PB2 protein, associated with viral replication at the lower temperature of the mammalian respiratory tract;

- S31N in the M2 protein, conferring resistance to adamantanes;
- Absence of the H275Y substitution in the NA, associated with resistance to the oseltamivir in H1N1 viruses;
- R292K in one virus (A/Shanghai/1/2013), associated with markedly reduced sensitivity to oseltamivir and modestly reduced sensitivity to zanamivir.

In vitro analyses confirmed that all three viruses bound both α -2,3- and α -2,6 linked sialic acids, suggesting an ability to bind to both avian and mammalian cells. In functional assays, all three isolates were sensitive to both NAIs. In the case of A/Shanghai/1/2013, this result appears to reflect the presence of a mixture of viruses with R or K at position 292 of the NA.

All three viruses could be propagated readily in embryonated hen's eggs and human, canine and porcine cell lines. Pathogenicity studies in birds or animals have not yet been performed but these and comprehensive antigenic analyses will begin soon. It is expected that production of an effective vaccine against the new H7N9 viruses will require the development of a new candidate vaccine virus.

Further isolates and full or partial genome sequences have since been obtained by several laboratories. These isolates were from other human cases and from poultry and environmental samples taken from live poultry markets or other locations in Shanghai, Jiangsu, Zhejiang and Beijing, including many samples analysed by the National Avian Influenza Reference Laboratory, Harbin. Some of these sequences have been posted in the GISAID database. These viruses have provided important additional information on the diversity of H7N9 viruses currently circulating in eastern China. For example:

- Viruses isolated from humans, avian species and environmental samples are closely related;
- All lack a multi-basic amino acid cleavage site in the HA;
- Most but not all human isolates have 226L in the HA;
- Only some human isolates have 627K in PB2; all tested avian and environmental isolates have 627E in PB2;
- All apart from A/Shanghai/1/2013 have R292 in the NA;
- All those tested to date are susceptible to oseltamivir and zanamivir in vitro.

Development and availability of human diagnostic and serological assays

Between 2 and 13 April (see timeline), real-time PCR primers and probes based on the sequences of the first three virus isolates were distributed by China CDC to more than 400 surveillance and other diagnostic laboratories throughout China. Protocols, along with primer and probe sequences, were posted on the WHO website. All PCR-confirmed human cases have been diagnosed using these reagents.

Preliminary human serological assays have been undertaken using antigens from A/Anhui/1/2013, with early data indicating that sera from children, adults and the elderly lack antibodies to this virus before and after immunization with 2012–2013 seasonal influenza vaccine. This assay was used to detect antibodies in convalescent serum from two patients. Assays of avian serum samples to date have used A(H7N2) antigens and antisera (see section on animal health). Full development of H7N9-specific serological assays for human and animal use awaits the availability of specific post-infection antisera raised against H7N9 viruses in ferrets or chickens.

Animal health

In response to the detection of H7N9 human infections, agricultural authorities have as of 22 April sampled 2582 live bird markets, 8798 poultry farms, 337 poultry slaughter houses, 341 wild bird habitats, 227 pig slaughter houses and 633 environmental sites. A total of 218,344 samples from 22 provinces have been tested. These samples were collected from three surveillance zones. The first zone comprises the four Chinese Provinces Zhejiang, Jiangsu, Henan, and Anhui, plus the municipalities of Shanghai and Beijing, from which 122,344 samples have been tested; the second comprises those provinces adjacent to the affected provinces from which 38,759 samples have been tested; and the third comprises the other provinces, from which 57,039 samples have been tested.

The swab samples (both oro-pharyngeal and cloacal) were tested in provincial laboratories by real-time PCR using H7 Eurasian lineage HA primers; positives were confirmed by virus isolation at the National Avian Influenza Reference Laboratory, Harbin. Blood samples were tested using a low pathogenic H7N2 virus antigen and a corresponding positive control antiserum provided by the National Avian Influenza Reference Laboratory, Harbin.

Preliminary data suggest that this antigen will detect antibody raised against the recent H7N9 virus. Of these, 39 positive swab samples from live bird markets were identified by virus isolation: 20 in Shanghai, 12 in Jiangsu, six in Zhejiang and one in Anhui. One additional specimen from a wild pigeon in Nanjing, Jiangsu Province, was also positive. No positive serum samples were detected.

As a result of targeted investigation of the source of infection for the first confirmed H7N9 case and suspected family cluster in Shanghai, environmental samples from a poultry market frequented by these family members tested positive for H7N9 by PCR. Further, poultry in four other live poultry markets within 1.5 km of the residence of the infected cases were found to be infected with H7N9.

Following the H7N9 outbreak, surveillance in wild birds was also enhanced nationally but no H7N9-positive samples from wild birds or their environments have been detected thus far.

Initial conclusions

- H7N9 viruses were detected in live bird markets in 3 provinces (Anhui, Jiangsu and Zhejiang) and one municipality (Shanghai).
- Environmental samples collected from a poultry market frequented by the members of the family cluster in Shanghai had evidence of extensive contamination by H7 virus RNA.
- It appears that the closure of live poultry markets in Shanghai was associated with a reduction in the number of new human cases, although a causal relationship should not be inferred and a definitive conclusion cannot be drawn at this time (see Epidemiology section and Figure 3).
- Taken together with contact history with live poultry/live poultry markets in a substantial number of cases, these findings support a key role for exposure to live poultry as a risk factor for human H7N9 infection.

Viruses have not been detected in poultry farms thus far. For example, in Shanghai, viruses have not been detected in the local farms that supply Shanghai live bird markets. However, 75% of the Shanghai poultry supply comes from adjacent provinces where the virus source has not been identified (as of 21 April). Although H7N9 viruses have not been detected in poultry farms, it is well recognized that avian influenza is amplified and maintained in live poultry markets. It is possible therefore that a small number of infected farms could explain the level of infection in live bird markets. Given the number and severity of H7N9 human infections it is critical to identify the source(s) of H7N9-infected poultry so that appropriate interventions can take place. The extensive surveillance in farms so far is still likely to be insufficient to detect small numbers of farms that may be infected with H7N9 virus at low prevalence rates.

Eleven human virus isolates and 39 poultry/environmental isolates have been genetically sequenced thus far at the China CDC and the National Avian Influenza Reference Laboratory, Harbin, respectively. The majority of the sequenced isolates from both humans and poultry/environment have the amino acid 226L in the haemagglutinin gene, which is known to confer enhanced binding to the α 2-6- linked sialic acid receptors found in human upper airways. It is notable that none of the 39 viruses isolated from poultry have the mammalian adaptation marker PB2 627K while over half of the human virus isolates do. Adaptation within infected humans may explain this observation; however, other possibilities cannot be excluded at this time.

Although data at this early stage of the investigation are limited, it appears that the H7N9 virus is currently sustained through intra- and inter-provincial trading of live poultry. If infection in poultry is not controlled, the virus may spread to additional provinces in China. Such a situation would lead to an even greater zoonotic threat, and thus increase its pandemic potential. Continued circulation of a low pathogenic H7 virus in poultry also poses the risk of the emergence of a virus that is highly pathogenic in poultry.

Initial conclusions based on combined epidemiological, clinical, virological and animal health information

- The data are most consistent with an avian influenza virus that is considerably more transmissible to humans than any earlier avian influenza virus known to date. This H7N9 influenza virus is also the first reported low pathogenic A(H7) avian influenza virus of any subtype that has caused severe disease in humans.

- Evidence so far is not sufficient to conclude there is person-to-person transmission. Moreover, no sustained person-to-person transmission has been found.

- The reasons for the unusual age and gender distribution of the human cases are unknown and demand deeper investigation. This would include seroepidemiological studies to determine whether there have been larger numbers of mild and asymptomatic infections than have thus far been recognised.
- The virological adaptations to mammalian hosts are particularly concerning but they need to be studied in combination with clinical and epidemiological data rather than in isolation.

Response strategies and measures

Leadership, command and coordination

In line with the national and local pandemic influenza preparedness and response plans, a joint multi-sectoral prevention and control mechanism (JPCM) has been established at national and local levels to lead and coordinate the emergency response to the H7N9 virus. The national JPCM, led by the National Health and Family Planning Commission, consists of 13 governmental ministries and commissions, including the Ministry of Agriculture, the State Forestry Administration, and the Ministry of Science and Technology. An inter-regional JPCM has also been established to support sharing of information and coordinated response among the affected provinces, including Anhui, Jiangsu, Shanghai, and Zhejiang.

Response principles

Significant efforts are being made to ensure that the emergency response to the newly detected H7N9 virus is based on laws and regulations, the principle of transparency, prioritization and international collaboration. An approach based on risk assessment and evidence is being applied to inform coordinated, balanced public health interventions. Different response strategies and guidance have been provided to the different provinces based on the epidemiological situation and local needs. Early detection, early reporting, early diagnosis and early treatment ("the Four Earlys") have been the general guiding principles for the operational response.

Response measures

Response measures include close collaboration between public health and animal health sectors, enhanced surveillance in humans and animals, field investigation, risk assessment, clinical management, hospital infection prevention and control, public health interventions, risk communication, and research. Several technical guidance documents have been issued for surveillance and epidemiological investigation including contact tracing, laboratory testing and patient isolation and treatment.

The priority response measures have been focused on the following:

Field investigations, including source of infection

Field investigations on all confirmed cases, including contact tracing, have been conducted by local CDCs with the support from China CDC. The National Influenza Centre at China CDC, which is also a WHO Collaborating Centre of the Global Influenza Surveillance and Response System (GISRS), isolated and sequenced the full genomes of the first three H7N9 viruses from humans and shared, at the earliest possible moment, the gene sequences through the publicly accessible database GISAID. Genome sequences of three A(H7N9) viruses from birds and environment were also uploaded to GISAID by China Avian Influenza Reference Laboratory in Harbin, China.

Based on the preliminary findings that the virus was an avian virus, the Ministry of Agriculture classified A(H7N9) as first class at interim for animal surveillance and notification, and with other ministries enhanced joint surveillance in poultry farms and live bird markets (so-called wet markets). In some cities where human cases were occurring live bird markets were closed temporarily.

In Shanghai, studies have been developed through collaboration between the Shanghai CDC, Shanghai Animal Institute) the Shanghai Bureau of Industry and Commence and the Forestry Commission under the Joint Investigation Structure to find the source of human infection.

Enhanced surveillance in humans and animals

The national surveillance network was alerted and surveillance was enhanced. In addition to the routine ILI surveillance, emphasis was placed on enhancing surveillance for pneumonia of unknown origin and severe acute respiratory infections. Surveillance data are being reported in a timely manner to provincial authorities and to China CDC for risk assessment and response. As part of the global WHO GISRS, the CNIC, in addition to uploading sequences of the whole genome of the first three novel H7N9 viruses, has contributed significantly to global alert and surveillance activities. These contributions include the PCR protocol for virus detection and virus isolates to enable WHO Collaborating Centres and Essential Regulatory Laboratories to select and develop vaccine viruses, vaccine reagents and diagnostic reagent kits, and to conduct further characterization of the virus, e.g. pathogenicity and transmissibility. China CDC published its findings in the *New England Journal of Medicine* within 15 days.

Diagnostic kits were developed by the CNIC based on PCR technology. Reagent kits were distributed to all provincial CDCs, and to all prefecture/city CDCs in affected provinces within 48 hours. Reagent kits have been sent to all CDC laboratories at provincial, prefecture and city levels, and military and border-control laboratories in China.

Surveillance for H7N9 has been initiated in animals, including poultry, pigeons, and ducks by virus or antibody detection. Where H7N9 viruses were detected in markets, backward source tracing was undertaken to determine the source farms of the poultry, and additional specimens were collected from the source(s) for analysis.

Clinical management, infection prevention and control

Fever clinics were activated in health care facilities for screening of patients and to ensure appropriate infection prevention and control and clinical management. National guidance on H7N9 case management was issued. Hospitals, with infection control recommendations strictly implemented, were designated specifically to manage H7N9 cases. In Shanghai the Municipal Public Health Clinical Centre, which has 500 beds and hosts high-level expertise in clinical management, has hospitalized and managed suspected cases, and accumulated valuable experience in managing and treating patients with a disease associated with a new virus. The Chinese government is providing free clinical care for all H7N9 patients.

At national level, expertise was absorbed into groups for case management, in particular for severe cases, and information was dispatched nationwide whenever there was a need.

The Chinese regulatory agency, the China Food and Drug Administration (CFDA), accelerated the regulatory process and has approved Peramivir, an injectable NAI, for treatment. National stockpiles of Oseltamivir and Zanamivir were also reviewed and renewed. Medical supplies have also been ensured.

Risk communication

Epidemiological and virological findings were shared in a timely and transparent manner with WHO, the Food and Agriculture Organisation of the United Nations (FAO) and the World Organisation for Animal Health (OIE). Continuous information was supplied through the International Health Regulations (IHR) system and was posted on the WHO website; formal notifications were made of outbreaks in poultry through the OIE system.

Updates on surveillance and risk assessment were shared with the public in a timely manner in collaboration with media at national and local levels.

Regular press releases were made to the public by local and national governments, especially by the health authorities, to provide timely updates on the H7N9 situation and to address public concerns.

Health education activities are being implemented to advise about health risks of H7N9 and to promote good hygiene practices, including handwashing, cough etiquette and safe handling of food.

Scientific research

Under the overall coordination of JPCM, a research programme has been developed with the Ministry of Science and Technology as the lead agency to better understand the virus and disease, including the source of infection, antigenicity, pathogenicity and transmissibility of H7N9, and to develop and evaluate interventions, including pharmaceutical and non-pharmaceutical measures.

Conclusions

- Response at national and local levels has been excellent and appears to be effective.
- The risk assessment and evidence-based response to H7N9 virus could serve as a model of emergency response to similar events.

International collaboration

Any human infection with a new subtype of influenza virus, especially one causing severe disease, is of global interest and serious concern. After it first identified the H7N9 virus, China, in addition to fulfilling its obligations in timely notification under the IHR, has recognized its vital role in contributing to global public health work through open channels of communication with global influenza partners and the international community.

Event reporting and information sharing with the international community

The China National IHR Focal Point notified WHO of the first three cases of human infection with H7N9 on 31 March 2013. The outbreak is considered an event that may constitute a potential Public Health Emergency of International Concern. Since then, regular reporting has been made to WHO through the WHO IHR Contact Point for the Western Pacific Region, and updated information has been shared with all WHO Member States through the Event Information Site, which is open to all the National IHR Focal Points.

Other channels of communication include regular updates on the NHFPC website, as well as on WHO websites at Country, Regional, and Headquarters level, including through Disease Outbreak News (DON).

Given strong interest from the public and the media, and to address concerns about this new virus, joint NHFPC-WHO press briefings were convened, including the first such press conference with WHO Country Office on 8 April 2013, to supplement individual press contacts with both offices. These situation updates and transparent sharing of information demonstrated Chinese collaboration with WHO and the openness of Government authorities, and was widely disseminated by more than 75 media representatives.

Sharing of virus and information

The whole genome sequences of the first three human cases were uploaded by the National Influenza Centre, which is also a WHO CC for Reference and Research on Influenza, to the GISAID as quickly as possible for public access. Genome sequences of three H7N9 viruses from birds and the environment were also uploaded to GISAID by the national avian influenza reference laboratory in Harbin in China. This has contributed significantly to global risk assessment and risk response, and promoted the spirit of the Pandemic Influenza Preparedness (PIP) Framework. As the H7N9 viruses are defined as PIP Biological Materials under the PIP Framework, their distribution is covered by the principle of sharing of benefits arising from their use according to public health risk and need.

The WHO CC in Beijing has undertaken timely sharing of virus isolates with other WHO CCs for influenza and WHO Essential Regulatory Laboratories of GISRS. Thus far, all six WHO CCs and four WHO Essential Regulatory Laboratories of GISRS have received H7N9 virus isolates from the WHO CC in Beijing. In addition, the virus has been shared with laboratories in Taiwan and Hong Kong SAR, WHO H5 Reference Laboratories, and other requesters. As of 22 April, 15 shipments have been made to 13 recipients, including GISRS laboratories and other entities such as vaccine manufacturers. This is a significant contribution to the global risk response and will lead to the selection and development of H7N9 candidate vaccine viruses, potency reagents, PCR reagent kits and diagnostic protocols, as well as better understanding of antigenicity, pathogenicity and transmissibility of H7N9.

Technical collaboration

The NHFPC, through the Chinese CDC, quickly established and has maintained very close technical collaboration with WHO staff, with daily discussions at country level, and frequent consultation involving all three levels of WHO: Country Office, Western Pacific Regional Office and WHO Headquarters. As a newly designated WHO Collaborating Center for Reference and Research on Influenza, the National Influenza Center in China has maintained close and regular communication and technical consultation with other WHO Collaborating

Centers for Reference and Research on Influenza. The Chinese CDC, as a member of the Global Alert and Response Network (GOARN), also provided a situation update to the GOARN Steering Committee members. Bi-lateral collaboration is also ongoing, including sharing of information and technical collaboration with US CDC, Canada Public Health Agency, ECDC, NIID and Korean CDC

In the second week of April, the NHFPC formally invited WHO to identify technical experts to join a China-WHO joint mission on human infection with avian influenza A(H7N9) virus. The on-site mission was conducted in Beijing and Shanghai 19-24 April to understand the nature of the outbreak, investigate the prevention and control measures already taken by the Chinese Government, assess the outbreak situation and public health risks, and to provide recommendations on future prevention and control measures, and priority areas for specific research, resulting in this report.

Conclusions

- International collaborative efforts, especially transparent and timely sharing of information and viruses, as well as technical level discussions and consultations convened by China in the response to H7N9 are highly appreciated and well recognized by the international community.

- The collective efforts by China and the international community in line with the IHR and other international and regional frameworks have greatly contributed to our current understanding about the nature of the H7N9 virus, public health risk assessments and actions required to manage the shared risk.

Annex 2 Consolidated recommendations

Epidemiology

- Agreed national protocols, data collection tools, questionnaires and procedures for investigation of cases should be established and followed at provincial and local levels.
- Particular emphasis should be placed on using linked epidemiological, clinical and virological data to monitor changes in the characteristics and behavior of the viruses in order to detect emerging findings such as increasing efficiency of person-to-person transmission.
- Undertake validated and standardized seroepidemiological studies to determine the extent of asymptomatic and mild infections in the contacts of cases (these are underway in some localities) and to determine the true infection fatality ratio.
- A quality assurance program for serological and virological diagnosis within the provincial laboratories should be implemented.
- Other seroepidemiological studies (such as those from the Consortium for the Standardization of Influenza Seroepidemiology [CONSISE] initiative), should be carried out among the general population and among those working with poultry to determine the level of prior infection. Such community studies will also be essential to determine age-specific levels of immunity in the population.
- A national case-control study should be undertaken led by the Chinese CDC to determine risk factors, the strength of the apparent association with direct or indirect contact with poultry and to understand the unusual observed age and gender pattern to date.
- The extension of evidence-based interventions that reduce risk of virus persistence within live-poultry markets, which for example include, a) the introduction of “rest-

days” where the markets remain free from poultry allowing disinfection, b) banning of keeping of live-poultry within these markets overnight, or c) complete closure of live poultry markets in cities (as currently implemented in Shanghai, Nanjing and Hangzhou), should be implemented and utilized if shown to be effective in reducing human cases.

Clinical features and management of cases

- Distribute disease-specific information and training materials to all provinces in China to maintain continued alertness among healthcare workers.
- Encourage postmortem needle biopsy of the lung as a diagnostic alternative if full autopsy is unacceptable.
- Share and evaluate experience in treatment and care of patients with severe disease as a result of H7N9 disease, including the use of different ventilatory strategies, extracorporeal membrane oxygenation (ECMO) and other therapies.
- Conduct research on confirmed cases to determine when patients are likely to be infectious (virus shedding) and optimal sampling strategies for making diagnoses.
- Investigate the effectiveness of early treatment with neuraminidase inhibitors (NAIs) in patients with H7N9 infections.
- Investigate ways in which NAIs can be made available earlier in care for example by having them given to patients with influenza like illness in localities where infection is present before test confirmation is available.
- Ensure that appropriate infection prevention and control practices are applied during the care of suspected and confirmed cases according to national and WHO guidance.

Virological analysis and development and application of diagnostics

- The rapid release of virus sequences and other information and the sharing of additional H7N9 viruses should continue to enable deeper understanding of these novel viruses and aid continuing risk assessment.

- Detailed antigenic analyses of human and other H7N9 virus isolates should be undertaken and reported as soon as possible to monitor antigenic variation and to aid in the selection of suitable candidate vaccine viruses.

- Continuing evaluation of the suitability of molecular diagnostic reagents and of antigen-based rapid tests should be undertaken and reported to assist Chinese and other laboratories in the specific and sensitive detection of new human cases and animal infections.

- H7N9-specific serological assays should be developed as soon as possible to enable seroepidemiological studies (see Epidemiology). Interaction with the CONSISE laboratory network is recommended to take advantage of international experience and standard protocols and reagents as they are developed.

Animal health

- The serological methods currently used are based on an H7N2 virus. The sensitivity of this serological test for experimentally infected poultry should be assessed to evaluate the sensitivity of past serological tests. In parallel, the use of inactivated H7N9 virus for future testing should be encouraged.

- Current molecular diagnostic methods used for screening for H7N9 viruses in poultry are based on generic primers for screening for Eurasian H7 viruses in poultry. It is important to validate the analytical sensitivity of this PCR assay with the current H7N9 virus and to modify primer design if necessary to improve the sensitivity of H7N9 detection.

- Additional sampling of birds and the environment in live poultry markets in affected provinces should continue and be enhanced. Adequate numbers of samples should be taken to ensure that low prevalence (e.g. 1-5%) of H7N9 virus infection would be detected.

- Intensive surveillance efforts should be directed at identifying sources. Until such sources are identified, measures for control are unlikely to be successful in the long term. One suggestion is to conduct a case study to intensively investigate (with adequate sample size) the poultry farms that were used to supply the wholesale markets in Shanghai to identify types of poultry that are carrying this virus.
- The patterns of live poultry movement within and across provincial borders need to be better understood through inter-provincial collaboration.

Public health /emergency response

- Continue to implement coordinated emergency response under the leadership of the Joint Multi-sectoral Prevention and Control Mechanism.
- Adjust future response strategy and measures based on new knowledge, best practices and experiences obtained, taking into consideration local context and other factors.
- Enhance communication and coordination between human health and animal health sectors, including timely sharing of surveillance data and viruses, coordinated or joint field investigations (including tracing of potential sources of infection), joint risk assessments, and research.
- Strengthen surveillance in humans and animals, especially for low pathogenic influenza in animals of public health concern
- Share China’s experiences and best practices with other countries
- Accelerate applied research to generate understanding and knowledge essential to the response to H7N9, including vaccine development.

International collaboration

- Continue to share information and viruses with WHO, WHO Collaborating Centres and other partners to contribute to the continuing risk assessments that are required to support routine capacity development (such as influenza surveillance in humans and animals) and to guide pandemic influenza preparedness and response efforts.

- Support regional and global technical collaboration and assistance among countries, including sharing of country practices, training, collaborative research work, and vaccine development.

Annex 3 Purpose and terms of reference

Proposal for China-WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus

Human infections with avian influenza A(H7N9) occurred in some regions of China since March 2013. Based on the preliminary investigation results, this epidemic is caused by a novel virus with gene resortment and the potential risk of transmission cross species (from animal to human) for this virus is possibly higher than that for H5N1 highly pathogenic avian influenza virus. The outbreak could expand before we discover the source of infection and take control measures. It is so far unable to predict its exact impact on China's social and economic status, let alone its potential global influence.

WHO has been closely following the surveillance, prevention and control of human infection of avian influenza virus and new subgroups of influenza virus, and it has rich experience and evident technical advantage in risk assessment and prevention and control of influenza outbreaks. For the purpose of better response to this epidemic, we propose to invite WHO experts to visit China and establish a "China-WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus" together with Chinese experts, to assess the epidemic and provide suggestions to subsequent prevention and control measures.

1. Composition of the Joint Mission

1) Experts

LIANG Wannian	Director General of Office of Health Emergency, Chinese team leader
YANG Weizhong	Deputy Director General, China CDC
YU Hongjie	Director, Division of infectious disease prevention and control, China CDC

DU Bin	Director, ICU, Peking Union Medical College Hospital
WNAG Dayan	National influenza center, China CDC
ZHOU Lei	Chinese coordinator, Public Health Emergency Center, China CDC.
Keiji Fukuda	ADG, Health Security and Environment Cluster, Foreign team leader（Arrive Shanghai on April 20th）
Michael O'Leary	WHO representative in China（Temporary foreign group leader before April 20th）
Nancy Cox	Director, WHO CC Atlanta
Angus Nicoll	Chief Scientist, European Centers for Disease Control
Malik Peiris	Chairman, Department of Microbiology, University of Hong Kong
Anne Kelso	Director, WHO CC Melbourne
LI Ailan	Director, Health Security and Emergencies, WHO WPRO
ZHANG Wenqing	Acting Coordinator, WHO HQ

WHO is selecting appropriate clinical experts and the selected experts will be included in the joint mission. The Chinese clinical expert, DU Bin from Peking Union Medical College Hospital, will communicate with foreign experts through video conference or email before the initiation of joint mission.

2) Contact persons

REN Minghui	Director General, Department of International Cooperation, NHFPC (Join in the activities in Shanghai)
LI Mingzhu	Deputy Director General, Department of International

	Cooperation, NHFPC (Join in the activities in Beijing)
CONG Ze	Programme Officer, Department of International Cooperation, NHFPC
Sirenda Vong	Medical Officer, WHO China Office
FU Xijuan	Translator, WHO China Office

2. Working scope and expected outcome of Joint Mission

The Joint Mission is responsible for the investigation of epidemic and relevant prevention and control measures taken by the Chinese government, assessing the risk of epidemic, proposing suggestions to field epidemiological investigations and tracing of infection source.

The Joint Mission will collectively draft the “risk assessment report of human infection with avian influenza A(H7N9) virus in China”. The draft report will be completed at the end of this joint mission and the final report agreed both by China and foreign experts will be published during the sixty-sixth session of the World Health Assembly.

Annex 4 - Timeline of avian influenza A(H7N9) events

Date	Event	Source
22 March	Shanghai HFPC reported three patients with pneumonia of unknown cause to the National Health and Family Planning Commission (NHFPC)	NHFPC Notification Report (19 April version)
24 March	1830: Pharyngeal swabs of 2 case-patients in Shanghai were sent to China CDC	China CDC Report
25 March	Pharyngeal swab of one case-patient in Anhui was sent to China CDC	China CDC Report
28 March	H7N9 virus was isolated	China CDC Report
29 March	China CDC completed H7N9 virus sequence analysis and identified it as a novel avian-origin influenza A (H7N9) virus	NHFPC Notification Report (19 April 2013 version) China CDC Report
30 March	Three cases (2 in Shanghai, 1 in Anhui) were diagnosed	NHFPC Notification Report (19 April 2013 version)
31	(1) Chinese NHFPC informed WHO through IHR and officially	NHFPC Notification Report (19 April 2013 version)

March	announced three confirmed cases of infection with H7N9 virus (2) China CDC published the sequences of H7N9 virus isolated from human case on GISAID	Website: http://www.moh.gov.cn/mohwsyjbgs/s3578/201303/44f25bd6bed14cf082512d8b6258fb3d.shtml http://www.gov.cn/gzdt/2013-03/31/content_2366911.htm
1 April	Training in surveillance, epidemiological investigation, laboratory test conducted for 31 Provincial CDCs through video teleconference	China CDC
2 April	(1) NHFPC human infection with avian influenza H7N9 virus work leading group established (2) First batch of primer/probe sets distributed to all the network labs in the provinces with reported cases and to provincial-level labs in other provinces	NHFPC Notification Report (Apr 19th 2013 version) China CDC
3 April	(1) State Council conference on control and prevention for human infection of H7N9 avian influenza held by Vice-Premier (2) National multi-sectoral prevention and control mechanism led by NHFPC with 13 member ministries established (3) Guidance for case clinical diagnosis and treatment issued (4) Guidance for hospital infection prevention and control	NHFPC Website: http://www.moh.gov.cn/mohwsyjbgs/fkzs/list.shtml NHFPC Notification Report (Apr 19th 2013 version)

	issued (5) Guidance for disease prevention and control (including surveillance case definition, field epidemiology investigation, close contact definition and management, etc.) of human infection with avian influenza H7N9 virus released by NHFPC	
4 April	LPAI H7N9 virus isolated from samples collected from pigeons in Huhuai Wholesale Market in Songjiang District in Shanghai	Ministry of Agriculture Website: http://www.gov.cn/gzdt/2013-04/04/content_2370424.htm
5 April	(1) WHO CC Beijing real-time RT PCR Protocol for Detection of A (H7N9) Avian Influenza Virus (Version 1, 2013) published on WHO website: (as at 8 April, http://www.who.int/influenza/gisrs_laboratory/a_h7n9/en/ (2) LPAI H7N9 virus was isolated from poultry and environment samples collected from Huhuai Wholesale Market in Songjiang District, Jingchuan and Fengzhuang markets in Minhang District in Shanghai (3) Live poultry markets in Shanghai began to be closed	China CDC Report Ministry of Agriculture Website: http://www.gov.cn/gzdt/2013-04/05/content_2370880.htm Shanghai Agriculture Commission Report (Appendix 5)
7 April	(1) State Council conference on control and prevention for human infection of H7N9 avian influenza held by Vice-Premier	NHFPC Notification Report (19 April 2013 version)

	(2) Inter-provincial joint mechanism for H7N9 control and provincial among Shanghai, Jiangsu, Zhejiang, Anhui was established (3) The National Avian Influenza Reference Laboratory, Harbin, published the sequence of H7N9 virus isolated from poultry on GISAID	
8 April	(1) Joint Press by NHFPC and WHO (2) Second batch of primer/probe sets distributed to cover all the 409 network labs and other related labs, including seven China National Mega-projects for infectious diseases labs, Certificate and Inspection system labs, etc.	WHO website China CDC
11 April	Publication of first reports of cases and virological data in a peer-reviewed journal	Gao R et al. Human infection with a novel avian-origin influenza A (H7N9) virus. *New England Journal of Medicine* April 11, 2013. DOI: 10.1056/NEJMoa1304459. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1304459
14 April	Asymptomatic child case was identified as positive for H7N9 by viral nucleic acid	Beijing CDC Report
18 April	Arrival of China-WHO Joint Mission	

Annex 5 - Method of Work

The joint mission consisted of 14 technical experts: six from China (one from the Health Emergency Response Office of the National Health and Family Planning Commission (NHFPC), four from China CDC, and one from Peking Union Hospital); four international technical experts in influenza (from Australia, Europe, Hong Kong SAR, and USA), and five WHO staff—one from China Country Office (Beijing), one from the Regional Office for the Western Pacific (Manila), and two from Headquarters (Geneva).

Professor Liang Wannian, Director of the NHFPC Health Emergency Response Office and Dr Keiji Fukuda, Assistant Director-General of WHO Geneva, were named as co-team leaders, representing China and the international expert members, respectively. The WHO Representative in China took the role of team leader on the first two days in Beijing, before the arrival of Dr Fukuda.

The joint mission travelled and visited all facilities together, although Professor Liang was called away on day 3 to attend to an earthquake in Sichuan. He nominated Dr Yang Weizhong as acting team leader for the Chinese delegation.

The team spent days 1, 2, 6, and 7 in Beijing, and 3, 4, and 5 in Shanghai. The working method included (in both cities) internal team discussions, briefings with senior health and municipal officials, visits to health care facilities and laboratories, and detailed technical briefings from field and laboratory investigators in both human and animal health. In Shanghai the team also visited a specialized infectious disease hospital treating patients with H7N9, a community (affected neighbourhood) and facilities (small live poultry market and poultry wholesale market) selling live poultry (currently closed).

The team was accompanied by interpreters and by information or press officers from both NHFPC and WHO as well as liaison and support staff from the Department of International Cooperation of NHFPC.

Some team members joined a press update convened by Shanghai authorities on the last day in Shanghai, and a final joint press briefing in Beijing.

In advance of the mission, the Joint Mission developed a preliminary list of key questions to address during the visits and consultations. Based on the findings during the visit, the team then jointly drafted a mission report on day 6 and presented their findings on day 7 to NHFPC and China CDC at a final debriefing.

Annex 6 – Agenda for the China-WHO Joint Mission

18–25 April2013

Date	**Time**	**Activities**	**Venue/Details**
18 April (Thursday)	AM & PM	WHO China Office is responsible for pick-ups of foreign experts. Check in the same hotel	Beijing Capital Airport Hotel
	PM	Meeting of joint mission	WHO China Office
19 April (Friday)	AM	Meeting between joint mission and avian Influenza team from NHFPC	Room 108, National Health and Family Planning Commission
	PM	Introduction to the epidemic situation by China CDC & Beijing Health Bureau and discussion with China CDC & Beijing experts	Room 316, New office of China CDC
		Visit WHO influenza Collaborating Centre	National institute for viral disease control and prevention, China CDC
20 April (Saturday)	AM	ADG Dr. Keiji Fukuda arrives in Shanghai	Pudong International Airport
		Joint Mission arrives in Shanghai	Hongqiao Airport
		Meeting with Shanghai H7N9 Team, briefing and	Hotel

		confirmation of the visiting program	
	PM	Meeting with the leadership of Shanghai Municipal Joint Mechanism for Prevention and Control of human infection with Influenza A(H7N9)Virus; introduction of prevention and control program in Shanghai; discussion	City Hall
		Visit to Shanghai Public Health Clinical Center	Presentation on H7N9 cases; visit to fever clinic, wards; discussions
	Evening	Working meeting	Hotel
21 April (Sunday)	AM	Visit to Shanghai Center for Disease Control and Prevention	Presentation on prevention and control measures, epidemiological investigations; discussions; visit to microbiological lab
	PM	Visit to community where one family cluster live	
		Visit to Sanguantang Poultry & Egg Wholesale Market	
		Visit to Shanghai Center for Animal Disease Control and Prevention	
	Evening	Preparing for the report	Hotel
22 April	AM	Meeting with the leadership of Shanghai Municipal	City Hall

(Monday)		Joint Mechanism for Prevention and Control: discussion on the findings of the mission	
		Meetings with Mayor YANG Xiong and Vice Mayor SHEN Xiaoming	City Hall
	PM	Join in the fourth press conference of Shanghai Municipal Joint Mechanism for Prevention and Control	Press Hall,5F,Shanghai Urban Planning Exhibition Hall
		Departure for Beijing	Hongqiao Airport
23 April (Tuesday)	AM & PM & EVENING	Report writing	WHO China Office
24 April (Wednesday)	AM	Meeting with Vice Minister Xiaowei MA	NHFPC
		Joint Mission Briefing	NHFPC
	PM	Meeting with Vice Premier Yandong LIU	Zhongnanhai
		Meeting with Minister Bin LI	