2013-04-13-023 PRO/AH/EDR> Avian influenza, human (41): China H7N9 update

To: (06) Virology, general; (07) Zoonoses, general; (09) Resistance of microorganisms;

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AVIAN INFLUENZA, HUMAN (41): CHINA H7N9 UPDATE

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A ProMED-mail post <http://www.promedmail.org>
ProMED-mail is a program of the International Society for Infectious Diseases <http://www.isid.org>
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[1] Global concerns - NEJM
Date: Thu 11 Apr 2013
Source: The New England Journal of Medicine, Perspective [edited]
<http://www.nejm.org/doi/full/10.1056/NEJMp1304661?query=featured_home>

[Ref: Uyeki TM, Cox NJ: Global Concerns Regarding Novel Influenza A (H7N9) Virus Infections. N Engl J Med 2013. DOI: 10.1056/NEJMp1304661]

Severe disease in humans caused by a novel influenza A virus that is distinct from circulating human influenza A viruses is a seminal event. It might herald sporadic human infections from an animal source
-- such as, highly pathogenic avian influenza (HPAI) A (H5N1) virus; or it might signal the start of an influenza pandemic -- such as, influenza A(H1N1)pdm09 virus. Therefore, the discovery of novel influenza A (H7N9) virus infections in 3 critically ill patients is of major public health significance. Chinese scientists are to be congratulated for the apparent speed with which the H7N9 virus was identified, and whole viral genome sequences were made publicly available in relatively short order. Because this H7N9 virus has not been detected in humans or animals previously, the situation raises many urgent questions and global public health concerns.

The key question for pandemic risk assessment is whether there is evidence of either limited or, more important, sustained human-to-human transmission -- the latter being indicative of an emerging pandemic. If human-to-human transmission occurs, transmission dynamics, modes of transmission, basic reproductive number, and incubation period must all be determined. It is possible that these severely ill patients represent the tip of the iceberg and that there are many more as-yet-undetected mild and asymptomatic infections.
Determining the spectrum of illness will help us understand the scope of the problem and assess severity. Enhanced surveillance for H7N9 virus infection is therefore urgently needed among hospitalized patients and outpatients of all ages with less severe respiratory illness. Other useful information can be derived from monitoring close contacts of patients with confirmed H7N9 cases to assess whether family members or health care personnel who provided care for patients with H7N9 virus infection have respiratory illness and laboratory-confirmed H7N9 virus infection. Such investigations will clarify whether H7N9 virus transmission in people appears efficient, or whether limited, nonsustained human-to-human transmission is occurring in persons with prolonged unprotected exposures, such as in clusters of HPAI H5N1 cases in blood-related family members. So far, the information provided by Chinese health officials provides reassurance that sustained human-to-human transmission is not occurring.

In addition to causing severe illness and deaths, the novel H7N9 viruses reported by Gao and colleagues have genetic characteristics that are of concern for public health. The hemagglutinin (HA) sequence data suggest that these H7N9 viruses are a low-pathogenic avian influenza A virus and that infection of wild birds and domestic poultry would therefore result in asymptomatic or mild avian disease, potentially leading to a "silent" widespread epizootic in China and neighboring countries. If H7N9 virus infection is primarily zoonotic, as reports currently suggest, transmission is expected to

occur through exposure to clinically normal but infected poultry, in contrast to HPAI H5N1 virus infection, which typically causes rapid death in infected chickens.

The gene sequences also indicate that these viruses may be better adapted than other avian influenza viruses to infecting mammals. For example, the presence of Q226L in the HA protein has been associated with reduced binding to avian-like receptors bearing sialic acids linked to galactose by alpha-2,3 linkages found in the human lower respiratory tract, and potentially an enhanced ability to bind to mammalian-like receptors bearing sialic acids linked to galactose by alpha-2,6 linkages located in the human upper airway. Equally troubling is that Q226L in HA has been shown to be associated with transmission of HPAI H5N1 viruses by respiratory droplets in ferrets, one of the animal models for assessing pathogenicity and transmissibility of influenza viruses. These H7N9 viruses also possess the E627K substitution in the PB2 protein, which has also been associated with mammalian adaptation and respiratory-droplet transmission of HPAI H5N1 virus in ferrets. This H7N9 virus is a novel reassortant with HA and neuraminidase (NA) genes from an ancestral avian H7N9 virus and the 6 other genes from an avian H9N2 virus. The animal reservoir now appears to be birds, but many experts are asking whether these viruses might also be able to infect pigs, another common reservoir for zoonotic infections. The viral sequence data indicate antiviral resistance to the adamantanes and susceptibility to neuraminidase inhibitors, except for a 292K mutation in the NA protein of the A/Shanghai/1/2012 virus. Because this mutation has been associated with in vitro resistance to neuraminidase inhibitors in another N9 NA subtype virus, additional analyses must be undertaken to understand its significance. It is not known whether this mutation arose de novo in the host or is associated with oseltamivir treatment.
Ongoing surveillance is crucial to assessing the emergence and prevalence of H7N9 viruses resistant to available antivirals.

Since available diagnostic assays used in clinical care (such as, rapid influenza diagnostic tests) may lack sensitivity to identify
H7N9 virus and since existing molecular assays will identify H7N9 virus as a nonsubtypeable influenza A virus, a critical public health issue is the rapid development, validation, and deployment of molecular diagnostic assays that can specifically detect H7N9 viral RNA. Such assays have been developed in China and are in development in many countries including the United States, and they will be deployed as they were for the 2009 H1N1 pandemic. Having available H7-specific assays will facilitate surveillance of H7N9 virus infections and help address key questions such as the duration of viral shedding, the infectious period, the optimal clinical specimens for laboratory confirmation, and the spectrum of clinical illness.

The clinical features described in the 3 patients with H7N9 virus infection, including fulminant pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, multiorgan failure, rhabdomyolysis, and encephalopathy, are very troubling.
Clinical care of severely ill patients should be focused on evidence-based supportive management of complications such as ARDS.
Adherence to recommended infection-control measures in clinical settings to reduce the risk of nosocomial transmission cannot be overemphasised.

All 3 patients with H7N9 virus infection reported by Gao and colleagues received late treatment with oseltamivir starting on day 7 or 8 of illness while critically ill. Data related to human infections with seasonal, pandemic, and HPAI H5N1 viruses indicate that the earlier antiviral treatment is initiated, the greater the clinical benefit. Therefore, oral oseltamivir or inhaled zanamivir should be administered to patients with suspected or confirmed H7N9 virus infection as soon as possible. Secondary invasive bacterial infections associated with influenza can cause severe and fatal complications, and appropriate empirical antibiotic treatment for community-acquired bacterial infections may be indicated for initial management of severe
H7N9 pneumonia. Caution should be exercised regarding the use of glucocorticoids, which are not indicated for routine treatment of influenza. Clinical research, including randomized, controlled trials and observational studies, is urgently needed on new antiviral agents, including parenteral neuraminidase inhibitors and drugs with different mechanisms of action, combination antiviral treatment, and immunotherapy. To inform clinical management, rapid clinical data collection, data sharing, analysis, and timely feedback are needed worldwide.

Because H7N9 virus infections have not occurred in humans before, it is expected that persons of all ages might be susceptible worldwide.
Serologic assays must be developed so that studies can be conducted to determine whether some people have cross-reactive antibodies to these viruses from prior influenza A virus infections. Existing H7-vaccine viruses are not well matched to this novel H7N9 virus, and extensive efforts are under way to develop potential H7N9 vaccines as quickly as possible. These efforts have started worldwide using the H7N9 sequence data obtained from these early cases, and sharing of H7N9 viruses will further facilitate vaccine development. There are many challenges to making H7N9 vaccines available. Previously studied H7 vaccines were poorly immunogenic in humans, and clinical trials to assess the safety and immunogenicity of H7N9 vaccine candidates will be needed. But even if new vaccine manufacturing technologies, such as tissue-cell-culture-derived vaccine antigens, are utilized, the process from vaccine development to availability will probably take many months.

The 2009 H1N1 pandemic taught us many lessons, including that a pandemic virus can emerge from an animal reservoir in an unexpected location and be spread rapidly through air travel. The focus on critically ill adults early in the pandemic led to elevated public concern about pandemic severity. Clear communication of key messages to the public and the clinical community is critical in implementing successful prevention and control activities. The detection of human
H7N9 virus infections is yet another reminder that we must continue to prepare for the next influenza pandemic. The coming weeks will reveal whether the epidemiology reflects only a widespread zoonosis, whether an H7N9 pandemic is beginning, or something in between. The key is intensified surveillance for H7N9 virus in humans and animals to help answer important questions. We cannot rest our guard.
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[2] European implications - Eurosurveillance
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Source: Eurosurveillance Edition 2013, 18(15) [summ., edited]
<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20452>

A novel reassortant avian influenza A(H7N9) virus in China -- what are the implications for Europe
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[Authors: A Nicoll, N Danielsson (Date of submission: 10 Apr 2013) European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden]

What are the possible implications of the current situation for Europe and European citizens and which actions should the EU take and which ones have been taken already? The European Centre for Disease Prevention and Control (ECDC) published its 1st risk assessment on 3 Apr 2013 and is providing updated assessments and short reports on the epidemiology as new information emerges. Several guidance documents on prevention of infections, infection control and case management developed earlier for influenza A(H1N5) by ECDC, WHO and Member States are, with some modifications, applicable to the current situation].
Visitors to China and other countries where avian influenzas have caused severe human disease of late, should avoid visiting bird markets and follow basic hygienic measures. Persons returning from China who develop severe respiratory infection within 10 days should be evaluated and tested for the new virus to rule out such infection [17], though most likely another infection will be detected. Case management and infection control guidelines for A(H5N1) apply in the short term. This will include antiviral treatment given that the Chinese CDC promptly established that the A(H7N9)viruses are susceptible to neuraminidase inhibitors [4,5].

There is a standing procedure in place in Europe to send all non-subtypeable influenza A viruses isolated from humans promptly to the WHO Collaborating Center in London for further analysis. Notwithstanding this, ECDC, the WHO Regional Office for Europe, the WHO Influenza Collaborating Centre, the University of Bonn, and the Community Network Reference Laboratories are working in together to make testing for A(H7N9) possible in all National Influenza Centres in Europe as soon as possible.

Some candidate H7 and H9 vaccines viruses already exist under WHO's strain selection system for the eventuality of an emerging virus [19].
They may not be effective against the new influenza A(H7N9) virus and once the regulatory laboratories have obtained the novel virus, WHO and presumably EU authorities will now need to consider if they wish to proceed with the very early stages of vaccine development as has been done for the candidate H7 and H9 viruses.

Overall, how concerned Europe should be cannot yet be determined. The new virus is a reassortant virus based on an haemaglutinin antigen
A(H7) to which most humans will not have been exposed. Therefore, if human-to-human transmission starts, and that is only an 'if', population immunity cannot be presumed. It would have to be assessed now by determining age-specific sero-reactivity of human sera to this influenza A(H7N9) virus as a priority. Immunity, or lack of it, in the human population are key data required for assessing pandemic risk. As stated above, they needed to come from field investigations in China as well as seroepidemiological studies in Europe based on protocols developed precisely for such situations [20].

At this very moment it cannot be ruled out that there are some human-to-human transmissions causing mild or asymptomatic infections as happened in the Netherlands in 2003. It also remains unclear to what extent the predominance of severe disease may represent a bias because mainly people with severe disease are tested. Investigations of patients' contacts including serological studies, will clarify this point. Such investigations orchestrated by the Chinese CDC are underway.

There will be many other calls for research and it will be important and difficult to prioritise. Fortunately a framework exists for making decisions on priorities. The Influenza Risk Assessment Tool (IRAT) has been developed since 2011 for this purpose by the United States (US) Centers for Disease Control and Prevention with some international partners [21,22]. It looks at 10 parameters bundled into three families: properties of the virus, attributes of the population, ecology and epidemiology. It has already been deployed to inform US decisions on the A(H3N2)v vaccines. It does not predict pandemic risk or make decisions but it informs decisions. Though the IRAT is still being evaluated as a tool it will certainly indicate what should be some of the most important public health research priorities for A(H7N9).

It is also important that the sequence and virological analyses are considered in combination with the epidemiological findings. Despite the virological markers described in the recent report from the WHO Collaborating Centres [5] it should not be seen as inevitable on the longer term that this reassortant A(H7N9) will develop efficient human-to-human transmissibility or become established in Europe, though both should be kept in mind as possibilities. Neither has happened for the highly pathogenic influenza A(H5N1) virus in the decade and a half since its emergence in China in 1996 [23]. Despite multiple detections of the A(H5N1)virus in wild birds and some outbreaks in domestic poultry flocks in Europe, the high levels of biosafety in the EU have not permitted A(H5N1) viruses to become established in European domestic poultry. It is fortunate that the European Commission and the Member States have since 2007 established surveillance for low pathogenicity avian influenza in domestic and wild birds in Europe [14]. The recent events have underlined the importance of this system.

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[The full article and references are available at the source URL above. - Sr.Tech.Ed.MJ]

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[3] WHO update - 12 Apr 2013
Date: Fri 12 Apr 2013
Source: WHO Global Alert and Response (GAR), Disease Outbreak News [edited]
<http://www.who.int/csr/don/2013_04_12/en/index.html>

Human infection with influenza A(H7N9) virus in China -- update

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As of 12 Apr 2013 (17:30 CET), the National Health and Family Planning Commission notified WHO of an additional 5 laboratory-confirmed cases of human infection with influenza A(H7N9) virus. Of the latest laboratory-confirmed cases, 3 are from Zhejiang and 2 from Shanghai.

The 1st patient is a 66-year-old man from Zhejiang who became ill on 8 Apr 2013; the 2nd patient is a 74-year-old man from Zhejiang who became ill on 6 Apr 2013; the 3rd patient is a 54-year-old woman from Zhejiang who became ill on 6 Apr 2013; the 4th patient is a 53-year-old man from Shanghai who became ill on 3 Apr 2013; and the 5th patient is an 86-year-old man from Shanghai who became ill on 3 Apr 2013.

In addition, a patient earlier reported from Shanghai has died. To date, a total of 43 patients have been laboratory confirmed with influenza A(H7N9) virus in China; including 11 deaths. More than 1000 close contacts of the confirmed cases are being closely monitored.

The Chinese government is actively investigating this event and has heightened disease surveillance. Retrospective testing of recently reported cases with severe respiratory infection may uncover additional cases that were previously unrecognized. An inter-government task force has been formally established, with the National Health and Family Planning Commission leading the coordination along with the Ministry of Agriculture and other key ministries. The animal health sector has intensified investigations into the possible sources and reservoirs of the virus.

WHO is in contact with national authorities and is following the event closely. The WHO-coordinated international response is also focusing on work with WHO Collaborating Centres for Reference and Research on Influenza and other partners to ensure that information is available and that materials are developed for diagnosis and treatment and vaccine development. No vaccine is currently available for this subtype of the influenza virus. Preliminary test results provided by the WHO Collaborating Centre in China suggest that the virus is susceptible to the neuraminidase inhibitors (oseltamivir and zanamivir).

At this time there is no evidence of ongoing human-to-human transmission. WHO does not advise special screening at points of entry with regard to this event, nor does it recommend that any travel or trade restrictions be applied.

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Communicated by:
ProMED-mail Rapporteur Marianne Hopp

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[4] UK: travel advice - Public Health England
Date: Fri 12 Apr 2013
Source: Public Health England, Health Protection Report 7(15), Travel Health [edited]
<http://www.hpa.org.uk/hpr/infections/travel.htm#nthnch7n9>

H7N9 avian influenza in China -- travel advice

The National Travel Health Network and Centre (NaTHNaC) has published updated information for travellers and health professionals on H7N9 avian influenza human infections in China.

As of 11 Apr 2013, 38 human cases [now 43], including 10 [now 11] deaths, had been reported from 4 different provinces, with no evidence of ongoing human-to-human transmission.

The risk of disease spread to Europe remains low, although individual cases arriving from China cannot be ruled out. NaTHNaC recommends that basic hygiene practices and food safety precautions are taken by all travellers. In addition, travellers should avoid visiting live bird markets and, in particular, should avoid any direct contact with bird and animal faeces and untreated bird feathers. Travellers who become ill with respiratory symptoms within 7 days of a trip to China should seek medical advice from their GP or NHS 111.

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[5] Case update - newswire
Date: Fri 12 Apr 2013
Source: Shanghai Daily, Agency reports [edited]
<http://www.shanghaidaily.com/nsp/National/2013/04/12/Concern%2Bat%2Bspread%2Bacross%2Bborders/>

Three new H7N9 cases were reported in Shanghai yesterday [11 Apr 2013], with one of the patients dying from the bird flu infection. 6 of the city's 18 patients have now died. 11 are still undergoing treatment in isolation, while a boy, 3 years and 7 months old, had recovered, the Shanghai Health and Family Planning Commission said.

There were also 2 new cases reported in Jiangsu Province yesterday [11 Apr 2013], bringing the country's total to 38, with 10 fatalities.

The Shanghai cases were all elderly Shanghainese. The patient who died was a 74-year-old man who complained of dizziness and fatigue on 31 Mar 2013. Last Friday [5 Apr 2013], at Putuo District Central Hospital, he was diagnosed with pneumonia. His condition had become severe by Tuesday [9 Apr 2013] and he tested positive for the H7N9 virus on Wednesday night. He died yesterday afternoon.

An 83-year-old woman developed a fever and a cough on 2 Apr 2013 and went to Shidong Hospital in Yangpu District for treatment. When she failed to get better, she went to Changhai Hospital on Sunday [7 Apr 2013], where she was admitted. She also tested positive for H7N9 on Wednesday [10 Apr 2013].

The 3rd new case was a 68-year-old man who started to have a fever and an aching body on 4 Apr 2013. He took cold medicine, but when he failed to get better he went to Jiading District Central Hospital last Saturday [6 Apr 2013] for treatment. On Tuesday [9 Apr 2013] he went to Ruijin Hospital's north branch in Jiading District and was diagnosed with pneumonia. He tested positive for H7N9 virus on Wednesday. None of the Shanghai patients' close contacts have developed flu-like symptoms.

The Jiangsu cases were a 31-year-old chef in Yangzhou and a 56-year-old teacher in Suzhou. Both men were in a critical condition, but none of their close contacts had exhibited any abnormal symptoms, Xinhua news agency reported.

A total of 12 H7N9 cases have now been confirmed in Jiangsu, including one fatality.

Other cases have been reported in Anhui Province, which confirmed 2 cases, including one death, and Zhejiang Province, which confirmed 6 cases, including 2 deaths.

Shanghai officials said that more than half of the city's cases had been in contact with live poultry recently, whether in the business or by buying live chickens at market.

By yesterday [11 Apr 2013], local industrial and commercial administrative bureaus had shut 23 unlicensed poultry sales stalls and
119 roadside live poultry stands, netting 1649 live waterfowl and 9 wild birds. Authorities also ordered 162 bird sales stalls at 34 flower and bird markets to cease trading and sealed off 16 812 birds inside stores.

Dr Zhang Wenhong, director of the infectious diseases unit of Shanghai's Huashan Hospital, said yesterday that avoiding contact with live poultry and birds should be effective in preventing infection. At a lecture at the Shanghai Science and Technology Museum on H7N9 prevention and control, he said: "After studying the current cases, I found the infection is related with wet markets and fowl." Apart from avoiding contact with fowl and maintaining good hygiene, Zhang said that going to hospital at an early stage was important.

"Concerning all the deaths, there are only 13 days from [the onset of] symptoms to death. Many patients don't go to hospital until the symptoms have become serious," Zhang said. "People should go to hospital whenever they have a fever of feel their muscles ache for diagnosis and screening. The 1st 4 to 5 days are crucial," Zhang added.
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ProMED-mail Rapporteur Kunihiko Iizuka
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[6] Shanghai - newswire
Date: Fri 12 Apr 2013
Source: Xinhua News Agency [edited]
<http://news.xinhuanet.com/english/health/2013-04/12/c_132304742.htm>

Shanghai reported one more death from H7N9 bird flu on Friday [12 Apr 2013], while 2 new cases were confirmed, local health authorities said in a statement.

A 74-year-old man who tested positive for the virus on 6 Apr 2013, died on Thursday night [11 Apr 2013] after treatment failed, according to the Shanghai Municipal Health and Family Planning Commission. The death has brought the country's total fatalities to the disease to 11, including 7 in Shanghai, while infections totalled 40 [now 43] nationwide.

A 53-year-old man began showing symptoms of fever on 5 Apr 2013 and was diagnosed with pneumonia and tested positive for H7N9 on Thursday
[11 Apr 2013]. Another man, 86, also tested positive for the H7N9 virus on Thursday after being diagnosed with pneumonia on 6 Apr 2013.
Both patients are receiving medical treatment. 16 people who had close contact with them have not exhibited abnormal symptoms, according to the statement.

So far, Shanghai alone has confirmed 20 cases of infection, accounting for half of the national total.

[Editor: Mu Xuequan]
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[Overall the number of cases has risen to 43 with 11 fatalities, with about half of the cases occurring in the Shanghai area. The victims have predominantly been middle-aged or elderly, with severe illness. No confirmed transmission of infection from human-to-human has been reported up to the present. Enhanced surveillance for H7N9 virus infection is therefore urgently needed among hospitalized patients and outpatients of all ages with less severe respiratory illness.

An immediate priority will be the design of H7-specific assays to facilitate surveillance of H7N9 virus infections and help address key questions such as the duration of viral shedding, the infectious period, the optimal clinical specimens for laboratory confirmation, and the spectrum of clinical illness. The development and production of an appropriate vaccine may be many months away, therefore WHO and possibly EU authorities will now need to consider if they wish to proceed with the very early stages of vaccine development.

According to the most recent WHO assessment there have now been at 43 cases and 11 deaths, about half of the cases occurring in the Shanghai area and the remainder in adjacent provinces. Significantly Shanghai officials have said that more than half of the city's cases had been in contact with live poultry recently, whether in business or by buying live chickens at market. - Mod.CP]

[For a map of China showing provinces, see <http://www.sacu.org/maps/provmap.png>. - Mod.MPP]

[see also:
Avian influenza, human (40): China H7N9 update 20130411.1638767 Avian influenza, human (39): China (SH, JS, ZH) H7N9 update

20130410.1636073
Avian influenza, human (38): China (SH, JS) H7N9 update
20130409.1633860
Avian influenza, human (35): China (SH, JS) H7N9 update
20130408.1630825
Avian influenza, human (34): China (SH, AH) H7N9, RFI
20130407.1628848
Avian influenza, human (33): vaccine development 20130407.1628472 Avian influenza, human (32): China (SH, AH) H7N9 20130407.1628294 Avian influenza, human (31): China (Shanghai) H7N9 20130406.1626812 Avian influenza, human (30): China (Hong Kong, Taiwan) H7N9, NOT
20130406.1626565
Avian influenza, human (29): China (ZH) H7N9, market quail
20130406.16264
Avian influenza, human (28): China H7N9, WHO 20130406.1626360 Avian influenza (28): China (SH) H7N9, OIE, update 20130405.1624901 Avian influenza, human (27): H7N9 update, more fatalities
20130405.1624260
Avian influenza, human (26): China H7N9 case list & map
20130404.1623110
Avian influenza, human (25): China (SH) H7N9, update 20130404.1622647 Avian influenza (27): China (SH) H7N9, avian case 20130404.1621938 Avian influenza (26): China, H7N9, RFI 20130403.0666 Avian influenza, human (24): China (ZJ) H7N9 update 20130404.1621801 Avian influenza, human (22): China (SH) H7N9, fatal: correction
20130404.1621799
Avian influenza, human (22): China (SH) H7N9 fatal 20130404.1621700 Avian influenza, human (20): China (JS) H7N9 patient details
20130403.1617279
Avian influenza, human (16): China (SH, AH) H7N9 WHO 20130401.1614707]
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