



2013-04-12-022 Avian influenza, human (40): China H7N9 update

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

AVIAN INFLUENZA, HUMAN (40): CHINA H7N9 UPDATE

A ProMED-mail post

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International Society for Infectious Diseases <<http://www.isid.org>>

[1] Nature journal

[2] New Scientist news report

[3] WHO GAR update

[4] WHO report

[5] Shanghai: 3 new cases

[6] 5 new cases (Shanghai 3, Jiangsu 2), 1 death (Shanghai)

[1] Nature journal

Date: Tue 9 Apr 2013

Source: Nature [edited]

<http://www.nature.com/news/urgent-search-for-flu-source-1.12762?WT.ec_id=NATURE-20130411>

[Ref: Butler D: Urgent search for Flu Source. Nature 496, 145-6 (11 Apr 2013)

doi:10.1038/496145a]

Virologists know its name: H7N9. What they don't yet know is whether this novel avian influenza virus -- first reported in humans in China less than 2 weeks ago -- will rapidly fizzle out, become established in animal hosts to fuel future human outbreaks, or morph into a virus that can spread easily between people and spark a deadly pandemic.

In a frantic effort to find answers, scientists are bearing down on H7N9 on multiple fronts. They are testing wild birds and thousands of domestic fowl; analysing the viruses they find; and trying to trace people who have been exposed to infected patients. Chinese health authorities say that they have 400 laboratories looking for genetic changes in the virus.

"We are going to be sitting with bated breath over the next month to find out what happens," says Michael Osterholm, who heads the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis. As Nature went to press, 24 [now 33] human cases, including 8 [now 9] deaths, had been reported in 11 cities, some a few hundred kilometres apart, in eastern China (see map at <<http://tinyurl.com/bu8gcdl>>). So many cases in such a short time over such a wide area -- up from 3 cases in 2 cities a week ago -- is "a very concerning situation", says Osterholm.

Scientists urgently want to find out which sources are stoking the human infections that result in flu-like symptoms and, in most reported cases, severe pneumonia. So far, investigations of the cases remain largely inconclusive: some patients had contact with poultry or other animals just before falling ill, whereas others had not. Late last week, the H7N9 virus was found in chickens, pigeons and ducks in live bird markets in Shanghai and Hangzhou -- making markets the leading suspected source. Authorities have since culled tens of thousands of birds and closed down markets in Shanghai, Nanjing and Hangzhou.



The genetic sequences of the H7N9 viruses found in the birds are highly similar to those isolated from human patients, says Chao-Tan Guo, a virologist at the Zhejiang Academy of Medical Sciences in Hangzhou. Although the virus might have come from other sources, including mammals, the pattern of many human cases over a wide area in a short time could be explained by live markets alone, because birds from one or a few sources would be transported to multiple markets, says Malik Peiris, a flu virologist at the University of Hong Kong.

But the various bird species found to be infected may not be the original source, because much cross-infection can occur in live markets. Investigators must now trace which farms and wholesalers the birds came from, Peiris says, and test birds up through the supply chain.

Researchers know that H7 flu viruses mainly infect wild birds such as ducks, geese, waders, and gulls, and that they occasionally jump into poultry flocks. Kwok-Yung Yuen, an infectious-disease expert at the University of Hong Kong, notes the proximity of the reported human cases to the Yangtze River delta, home to many wild birds, and to Chongming Island near Shanghai, a renowned site for watching migratory birds. "It's likely wild ducks and geese that are carrying it," he suggests.

But this H7N9 virus has not yet been detected in wild birds in the area. "There is very little specific information on the source of this particular virus strain, its ecology or reservoir, and it is premature to be hypothesizing on the vectors," says Taej Mundkur, who is flyways programme manager for conservation group Wetlands International in the Netherlands. He also co-convenes the Asia-Pacific Working Group on Migratory Waterbirds and Avian Influenza with the Food and Agriculture Organization of the United Nations (FAO).

Wherever the virus originated, a crucial question is whether it could become established in poultry, creating a reservoir that might lead to continued, sporadic human infections. Health authorities in China are trying to learn to what extent that has happened already. Unlike its cousin H5N1 -- which has killed millions of birds and several hundred people in Asia and elsewhere since 2003 -- H7N9 does not cause serious bird disease, greatly complicating efforts to control it, says Vincent Martin, interim head of the FAO's Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases (EMPRES) in Rome. It would be next to impossible to detect H7N9 through routine surveillance for sick poultry among China's 6 billion domestic birds.

"This means stopping animal-to-human transmission is impossible," says Masato Tashiro, a virologist at the Influenza Virus Research Center in Tokyo, the World Health Organization's influenza reference and research centre in Japan.

Each time the virus encounters new human hosts, it has fresh opportunities to mutate and to acquire the ability to spread between people. That does not seem to have occurred yet. But experts say that it will be crucial to identify and track new cases of suspicious severe pneumonia and their close contacts, and to isolate people if necessary. Researchers working on the molecular biology of the virus say that it seems to derive from a reassortment of genetic material from at least 3 known bird-flu groups (see Nature <<http://doi.org/k4j>>). A key component -- the haemagglutinin (H) protein on the surface of the virus -- already contains mutations known to shift its binding preference from bird cells to those of mammals. Scientists are watching for telltale changes that could signal a shift towards a form that is more transmissible between humans.

Because flu viruses evolve rapidly, comparing viral sequences from each of the human cases might reveal whether person-to-person transmission is occurring, says Andrew



Rambaut, an expert in the evolution of human viral pathogens at the University of Edinburgh, UK.

If many patients have very similar viral sequences, then that would imply human spread; if viral sequences are more diverse, it would imply that each person had separately picked up infections from birds.

Only 4 sequences from 4 human cases are so far available, but virologists are sequencing more and posting them on the GISAID [Global Initiative on Sharing All Influenza Data] flu database.

If human-to-human transmission does start to occur, "further spread may be inevitable", warns Tashiro. Humanity has never been widely exposed to H7 or N9 flu viruses, and so lacks resistance to these subtypes. If a pandemic were to occur, it would probably have a severe toll. But it is too early to predict how events will unfold; experts in emerging infectious disease are only just becoming acquainted with the latest villain in their roster.

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Communicated by:
ProMED-mail
<promed@promedmail.org>

[2] New Scientist news report

Date: Wed 10 Apr 2013

Source: New Scientist, Health [edited

<<http://www.newscientist.com/article/dn23368-china-bird-flu-may-be-two-mutations-from-a-pandemic.html>>

China bird flu may be 2 mutations from a pandemic

In China, 9 people have died and more than 20 are seriously ill in the latest outbreak of bird flu, H7N9. And there are fears that the death toll could rise much higher because the virus already has 3 of the 5 mutations that we know could allow another bird flu, H5N1, to spread between mammals. No one knows for sure if the 5 mutations discovered last year [2012] by Ron Fouchier and colleagues at the Erasmus Medical Center in Rotterdam, the Netherlands [<<http://www.newscientist.com/article/dn21958-publication-of-flu-study-reveals-full-nature-of-threat.html>>],

will do the same thing in H7N9. But we do know that some of the mutations helped viruses from 3 other flu families go pandemic. For the moment, Chinese authorities tracing contacts of known cases say there is no evidence yet

[<http://news.xinhuanet.com/english/health/2013-04/08/c_132292088.htm>

that the infection has spread between humans.

Most recent pandemic viruses have been hybrids of bird and mammalian flu, and therefore relatively mild because mammalian flu tends to be less severe in people than bird flu. Pure bird flu viruses, like H5N1 and H7N9, are potentially more dangerous. The most lethal pandemic we know of, which spread across the world in 1918, was a pure bird flu that acquired mutations [<<http://www.newscientist.com/article/mg18825204.000-reconstruction-of-1918-flu-virus-prompts-warnings.html>>]

that allowed it to spread in humans. Virologists fear H7N9 could be doing that.

H7N9 might be unusually severe: it carries a mutation thought to promote deep lung infection, which is also in H5N1, the 1918 flu, and severe cases of the 2009 pandemic [<<http://pesquisa.bvsalud.org/portal/resource/en/mdl-20844044>>]. But 2 known cases of H7N9 only show mild symptoms, so the Chinese authorities are trying to establish how often



it makes people seriously ill, in order to estimate the number of unreported mild cases, and therefore the total number of human cases there have already been.

As for H5N1, despite spreading widely in birds in recent years, it has not evolved the ability to spread readily between mammals. Fouchier's work which came under fire because of fears that it would allow bioterrorists to engineer an H5N1 pandemic shows that, in principle, it can spread between ferrets, and with no obvious loss of virulence [<http://www.newscientist.com/blogs/shortsharpscience/2012/03/mutant-bird-flu-virus-still-as.html>].

To get transmissible H5N1, Fouchier first had to prime the virus with 3 mutations known to adapt bird flu to mammals, then allow the virus to evolve the other requisite mutations while infecting the ferrets: as few as 2 more appeared to be needed. 2 of the 3 deliberately added mutations allow the HA surface protein from bird flu in the H5, H2, and H3 families to bind to cells in mammals' noses. This is what allowed flu viruses carrying HA proteins from H2 and H3 bird flu to cause pandemics in 1957 and 1968. The pandemic virus that broke out in 1918 -- from the H1 family -- had similar mutations with the same effect.

Such binding mutations have never been seen in wild H5N1 -- but H7N9 already has one of the 2. If H7N9 can bind to mammalian cells, it could adapt even further to mammals, just as Fouchier's primed H5N1 did in his ferret experiments. We do not yet know for certain that the mutation has the same effect in H7 as in the other flu families, but researchers are gearing up to do the experiments. "If what we know about these mutations in other flu subtypes is also the case for this virus, then it's already part way there," says Derek Smith at the University of Cambridge. "That's why everybody is concerned about this."

The H7N9 virus has another mutation that Fouchier deliberately gave H5N1 in the ferret experiment -- a change in a gene coding for a polymerase protein. The polymerase enzyme, which replicates the virus, is extra-powerful in bird flu, part of what makes these viruses so virulent in mammals -- and this mutation allows it to work at mammalian temperatures. It has been present in all pandemic viruses.

H7N9 also has another of Fouchier's mutations, one that arose as the virus infected ferrets. It removes a sugar group from HA. That leaves only 2 more mutations, both in HA, before this H7N9 has all of Fouchier's 5. The virus's passage through humans parallels the ferret experiment -- in which only 4 sequential infections of ferrets made H5N1 fully transmissible. "All pandemic viruses have acquired this [mammalian cell] binding and polymerase activity," says Fouchier. "The H7N9 has these characteristics. So the question is, what else does it need -- if anything?"

[Byline: Debora Mackenzie]

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Communicated by:
ProMED-mail Rapporteur Mary Marshall

[3] WHO Global Alert and Response (GAR) update
Date: Thu 11 Apr 2013
Source: WHO Global Alert and Response (GAR) update
<http://www.who.int/csr/don/2013_04_11/en/index.html>

Human infection with influenza A(H7N9) virus in China - update 11 Apr



2013

As of [11 Apr 2013] (17:00 CET), the National Health and Family Planning Commission notified WHO of an additional 10 laboratory-confirmed cases of human infection with influenza A(H7N9) virus.

The patients include:

- 70-year-old man from Jiangsu who became ill on 29 March 2013;
- 74-year-old man from Jiangsu who became ill on 2 April 2013;
- 65-year-old man from Zhejiang who became ill on 3 April 2013;
- 76-year-old woman from Shanghai who became ill on 1 April 2013;
- 81-year-old woman from Shanghai who became ill on 4 April 2013;
- 74-year-old man from Shanghai who became ill on 31 March 2013 and died on 11 April 2013;
- 83-year-old woman from Shanghai who became ill on 2 April 2013;
- 68-year-old man from Shanghai who became ill on 4 April 2013;
- 31-year-old man from Jiangsu who became ill on 31 March 2013; and
- 56-year-old man from Jiangsu who became ill on 3 April 2013.

To date, a total of 38 patients have been laboratory confirmed with influenza A(H7N9) virus in China; including 10 deaths, 19 severe cases and 9 mild cases.

More than 760 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.

About this Disease Outbreak News

1. WHO is currently publishing information on laboratory confirmed cases received through the official notification from the Chinese National International Health Regulations (IHR) Focal Point once a day. This formal notification and publication follows verification of the information, and may therefore come after, or not include, some cases reported through public media and other sources.



2. To date, there is limited information to determine whether the reported number of cases represents some or all of the cases actually occurring. As some relatively mild cases of illness have now been reported, it is possible that there are other such cases that have not been identified and reported.

3. If the current pattern of sporadic infections continues, WHO will cease frequent reporting of case numbers, and focus its Disease Outbreak News on new developments or changes in the pattern or presentation of infections.

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ProMED-mail
<promed@promedmail.org>

[4] WHO report
Date: Wed 10 Apr 2013
Source: WHO, Influenza, human and animal interface, influenza H7N9 [edited]
<http://www.who.int/influenza/human_animal_interface/influenza_h7n9/01_ReportWebH7N9Number.pdf>

Number of confirmed human cases for influenza A(H7N9) reported to WHO as of 10 Apr 2013

Country / Month / Cases / Deaths

China / February / 2 / 2
China / March / 23 / 6
China / April / 3 / 1
China / Total / 28 / 9

[This table will be updated weekly. The data are also displayed by geographic location and as an epidemic curve. - Mod.CP]

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Communicated by:
ProMED-mail
<promed@promedmail.org>

[5] Shanghai: 3 new cases
Date: Thu 11 Apr 2013
Source: Weibo [in Chinese, trans., edited] <<http://www.weibo.com/shanghaicity>>

Shanghai confirmed 3 new cases of human infection of influenza A(H7N9): a 74-year-old male retiree; an 83-year-old female retiree; and a 68-year-old male retiree. Among these patients one died despite the rescue efforts. This brings the total confirmed cases of influenza A(H7N9) in Shanghai to 18 with 6 deaths. 11 of these cases are under treatment, and a child has recovered and been discharged.

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<promed@promedmail.org>

[6] 5 new cases (Shanghai, Jiangsu), 1 death (Shanghai)

Date: Thu 11 Apr 2013

Source: Shanghai Daily, Xinhua News Agency report [edited]

<http://www.shanghaidaily.com/article/article_xinhua.asp?id=136163>

During the 24-hour period ending 5 pm on Thu 10 Apr 2013, China confirmed 5 new cases of H7N9 avian influenza, with 3, including one death, in east China's Shanghai and 2 in neighboring Jiangsu Province, authorities said. The National Health and Family Planning Commission said in a daily update on H7N9 cases that so far the country has reported a total of 38 H7N9 cases, including 10 that ended in fatalities.

A total of 18 cases, including 6 ending in fatalities, have been reported in Shanghai. 12 cases, including one death, have been reported in Jiangsu; and 2 cases, including one death, in the eastern province of Anhui. 6 have been reported in the eastern province of Zhejiang, with 2 deaths.

No epidemiological link between those cases has been identified to date, the commission said. Those who have had close contact with people infected by H7N9 have been placed under medical observation and have exhibited no abnormal symptoms, it added.

According to the commission, China's confirmed H7N9 cases are isolated and there has been no sign of human-to-human transmission.

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Communicated by:

ProMED-mail Rapporteur Kunihiko Iizuka

[Overall the pattern remains unchanged, the victims are mainly elderly males. Infection in children is rare and mild. Despite the speculation there is no evidence so far of evolution of human-to-human transmissible virus. The case numbers are rising dramatically but this may in part be a consequence of greater availability of diagnostic agents. - Mod.CP]

[see also:

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



CENTAUR GLOBAL NETWORK

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]
