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Emerging Problems in Infectious Diseases

H7N9 Incident, immune status, the elderly and a warning of an influenza pandemic

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Abstract
The novel re-assortment A influenza H7N9 (nrH7N9) emerged in humans in the Shanghai and surrounding provinces of China in late February and early March. Three infected index patients developed severe viral pneumonia with acute respiratory distress syndrome (ARDS) and resulted in fatal outcome. As of 15 April 2013 there were reported 60 confirmed nrH7N9 infections with 13 fatalities. Human-to-human transmission has not been observed, but zoonotic infections of nrH7N9 from birds to humans appear to be associated with live poultry markets. Elderly patients greater than 60 years of age accounted for 61% of the cases, indicating that the elderly may be at high risk for severe disease.

Key words: H7N9; influenza; immunology; elderly; severe disease

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Background

On Sunday, 31 March 2013, the Chinese National Health and Family Planning Commission issued a statement that described the infection of three individuals, two in Shanghai and one in Anhui province, with a novel reassortant H7N9 avian influenza virus [1]. Worldwide avian infections of H7 subtype of viruses are commonly seen, however, server human infections are very rare. Previously sporadic cases of subtypes H7N2, H7N3 and H7N7 were observed but they were limited to conjunctivitis and mild illness [2-5] except in 2003, in the Netherlands, when a localized H7N7 outbreak claimed one human life [6].

Transmission

The details of the three Chinese cases were reported in a recent publication by Gao *et al*. [7]. Clinically the three individuals developed symptoms consistent with influenza, developing high fever and cough and, after one week or more, a chest X-ray positive bi-lateral pneumonia with the opaque appearance of ground glass. All three patients developed ARDS-like disease and had fatal outcomes. Septic shock and multi-organ failure developed in one of the patients. In all three patients a novel reassortment H7N9 (nrH7N9) subtype virus was isolated and sequenced [7]. The viral sequences were released to GIVAID prior to publication and several groups analyzed the viral sequence [8] looking for possible mutations that could account for infection in humans and severity of illness. The nrH7N9 virus appears to be a reassortant of earlier H7N9, H7N3 and H9N2 viruses [7,8]. The virus might have incorporated genes from three different avian viruses; its hemagglutinin (H7-HA) was closely related to A/duck/Zhejiang/12/2011-like (H7N3) viruses, so the neuraminidase (N9-NA) might have been obtained from migratory birds along the eastern Asia migratory flyway (A/wild bird/Korea/A14/2011-like, H7N9), whereas the internal gene segments were derived from H9N2 virus (A/brambling/ Beijing/16/2012-like), which has been endemic in poultry in China since 1994.

Since the initial 31 March statement, accumulating information from multiple sources [9-16] indicates that at least 60 confirmed nrH7N9 human infections have been identified (supplemental Table 1). Interestingly, of the 52 cases with known clinical status, the vast majority (83%; 43/52, unknown status in 8 patients)

Figure 2: Typical wet market in China showing staked cages of chickens, ducks and pigeons

Figure 3: Typical wet market in China showing close proximity of multiple species including rabbits

Figure 4: Typical wet market in China showing open air butchering and client traffic

Figure 1: Number of severe cases, mild cases, and fatal outcomes in nrH7N9 human infections in China as of April 15

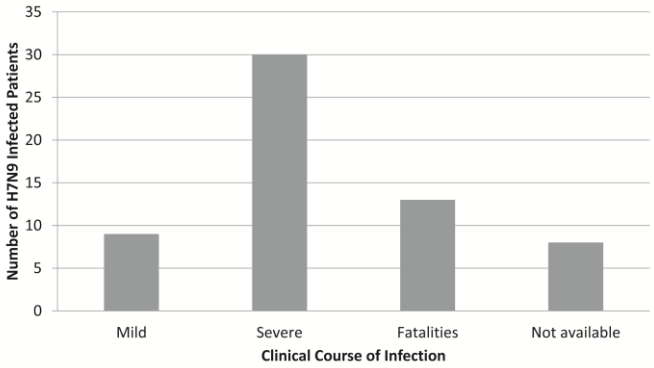
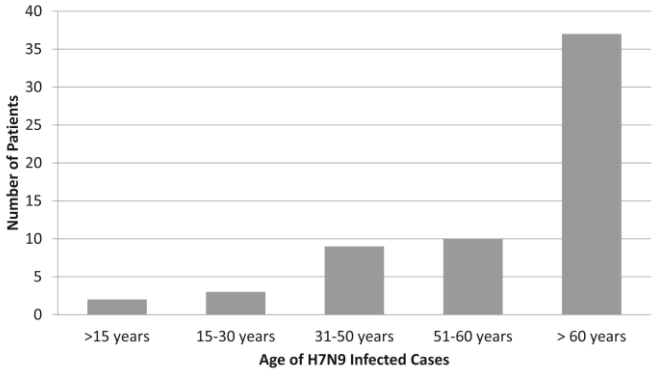


Figure 5: Number of nrH7N9 human cases per age group in China as of April 15



developed severe disease. There are now 13 deaths associated with this outbreak and many patients remain hospitalized patients and are in ICU (Figure 1). Contact tracing of nrH7N9 infected individuals indicates there is no clear evidence to support sustained human-to-human transmission of nrH7N9; however, transmission by close contact cannot be ruled out [17]. Two family clusters of nrH7N9 infection, where multiple members showed severe respiratory illness and one or more members were confirmed nrH7N9, suggest monitoring is necessary to determine if human-to-human transmission is possible [17]. This type of transmission might have also occurred in 2003 during the H7N7outbreak in the Netherlands [6].

While efficiently sustained human-to-human transmission is not observed at the present time, zoonotic introduction from avian species to humans appears to be quite obvious. Several of the confirmed nrH7N9 cases reported having had close contact with birds at wet markets or consumed poultry from wet markets. Surveillance on live-poultry markets indicated that pigeons, chickens and ducks were all positive for the nvH7N9 but did not display any disease symptoms or obviously increasing mortality. The mixing of multiple species of poultry along with mammals at live markets in China creates a dynamic mirco-environment that favour interspecies transmission, even from animals to humans. In Figures 2 and 3, stacked cages of pigeons, chickens and ducks and rabbits at a typical wet market in China illustrate how close contact and exposure to biological secretions and feces from different animal species could facilitate zoonotic transmission and consequential reassortment between different subtypes of influenza virus. Furthermore, the butchering of birds or other animals in an open environment could expose wet market workers and consumers to additional infected material (Figure 4).

Are the elderly at risk for nrH7N9 severe disease?

On closer examination, the age distribution for severe nvH7N9 patients (Figure 5) reveals that over 61% of severe patients are over the age of 60. Similarly, there are very few children who have confirmed severe nrH7N9 illness. In cases of H5N1 a very high proportion of severe cases and deaths occur in children [18]. The high proportion of elderly patients with severe nvH7N9 disease may be due to unbalanced exposure of the elderly to nrH7N9 or may be due to physiological factors related to ageing, such as decreased immune function. One of the common features among severe human H5N1, severe pandemic H1N1, and severe human SARS coronavirus infections is the robust hypercytokinemia associated with the development of ARDS. Will we find hypercytokinemia in nvH7N9 severe human infections? Or does a decreased immune function in the elderly allow unabated viral infection? Co-morbidities must also be considered as a factor in nvH7N9 infection and severe outcome. The detailed patient data from Gao *et al*. indicates that all three patients in their study had co-morbidities, including two who were infected with Hepatitis B. Is it possible that Hepatitis B co-infection prevents activation of critical host responses needed to overcome nvH7N9 infection and aid in clearance of the virus? The extremely high number of hepatitis infections in China and other Asian countries may be problematic if nvH7N9 expands circulation to other regions and is a factor in severe disease outcome.

China has responded in an unprecedented fashion to the current nrH7N9 outbreak. Now increased research and surveillance are badly needed to understand nrH7N9 pathogenesis, the epidemiological factors that contribute to severe disease, to aid in the identification of the reservoir of nvH7N9. On the therapeutic front the creation of a new generation of anti-viral drugs that work in both the early and late stages of nvH7N9 disease is essential for controlling sporadic human nrH7N9 infections, while the generation of nrH7N9 vaccines can be available for the possible emergence of a highly transmissible nrH7N9 virus.

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Supplemental table 1: Demographic presentation of human H7N9 infected cases

No	Location	Age	Sex	Occupation/ History of animal contact	Reported on	Date of			Symptoms	Clinical Course of infection	Outcome	Date of death
						Onset of symptoms	Hospitalization	Symptom severity/ ICU admission				
1	Shanghai	55	M	Farmer	Mar 31	Feb 14	NA	NA	Pneumonia	Severe	Dead??	Feb 28
2	Shanghai	87	M	Farmer	Mar 31	Feb 19	Feb 19	NA	Fever, cough, Pneumonia, difficulty in breathing	Severe	Dead	Mar 4
3	Anhui	27	M	Pork Dealer	Mar 31	Feb 27	Mar 3	NA	Pneumonia	Severe	Dead	Mar 10
4	Anhui	35	F	Purchased live chicken	Apr1	Mar 9	Mar 19	Mar 20	Pneumonia	Severe	Critical	Apr 10
5	Jiangsu	48	F	Poultry Culler	Apr1	Mar 20	Mar 30	Mar 30	Fever, dizziness, pneumonia	Severe	critical	
6	Jiangsu	83	M		Apr 1	Mar 20	Mar 29	Mar 29	Fever, cough, sputum	Severe	Dead	Apr 9
7	Jiangsu	32	F	Backyard poultry	Apr 2	Mar 21	Mar 28	Mar 28	NA	Severe	Critical	
8	Zeijiang	38	M	Cook	Apr 3	Mar 7	Mar 18	Mar 18	NA	Severe	Dead	Apr 1
9	Zeijiang	67	M	retired	Apr 4	Mar 25	Apr 2	Apr 2	NA	Severe	Critical	-
10	Zeijiang	64	M	Peasant farmer	Apr 3	Mar 29	NA	Mar 31	NA	Severe	Dead	Apr 4
11	Shanghai	48	M	Chicken Transporter	Apr 4	Mar 28	Apr 1	Apr 3	Cough, sputum, fever	Severe	Dead	Apr 3
12	Shanghai	52	F	NA	Apr 4	Mar 27	NA	NA	NA	Severe	Dead	Apr 3
13	Shanghai	4	M	NA	Apr 4	Mar 31	-	-	NA	Mild	Recovered	-
14	Shanghai	67	F	NA	Apr 4	Mar 22	NA	NA	NA	Severe	Dead	Apr 14
15	Jiangsu	61	F	NA	Apr 5	Mar 20	NA	NA	NA	Severe	Critical	-
16	Jiangsu	79	M	NA	Apr 5	Mar 21	NA	NA	NA	Severe	Critical	-
17	Shanghai	74	M	NA	Apr 6	Mar 28	NA	NA	NA	Severe	Dead	Apr 12
18	Shanghai	66	M	NA	Apr 6	Mar 29	NA	-	-	Mild	Recovering	-
19	Shanghai	67	M	NA	Apr 7	Late March	NA	NA	NA	Severe	Critical	-
20	Shanghai	59	M	NA	Apr 7	Late March	NA	NA	NA	Severe	Critical	-
21	Anhui	55	M	Work with live birds	Apr 7	Mar 28	Apr 1	NA		Severe	Critical	-
22	Jiangsu	85	M	Retired	Apr 8	Mar 28	Apr 1	NA	NA	Severe	Critical	-
23	Zeijiang	25	F	Unemployed	Apr 8	Mar 30	NA	NA	NA	Severe	Critical	-
24	Shanghai	64	M	NA	Apr 8	Apr 1	Apr 7	Apr 7	No severe symptoms first 2 days, later developed mild pneumonia, Shortness of breath 12 hrs before death	Mild-Severe (with rapid progression)	Dead	Apr 7
25	Shanghai	62	M	NA	Apr 9	Apr 1	NA	NA	Fever, pneumonia	Severe	Stable	-
26	Shanghai	77	M	NA	Apr 9	Apr 3	NA	NA	Fever, Pneumonia	Severe	Dead	Apr 14
27	Zeijiang	51	F	NA	Apr 9	NA	NA	NA	NA	NA	Stable	-
28	Zeijiang	79	M	NA	Apr 9	NA	NA	NA	NA	Severe	Critical	-
29	Shanghai	76	F	Retired	Apr 10	Apr 1	Apr 2	Apr 5		Mild	Stable	-
30	Shanghai	81	F	Farmer	Apr 10	Apr 4	NA	NA	Cough, Sore throat, Fever, weakness	NA		-
31	Jiangsu	70	M	NA	Apr 10	Mar 29	NA	NA	Diarrhea, Fever, Acute enteritis, pneumonia	NA		-
32	Jiangsu	74	M	NA	Apr 10	Apr 2	NA	NA		NA		-
33	Zeijiang	65	M	NA	Apr 10	Apr 3	NA	NA		NA		-
34	Shanghai	74	M	NA	Apr 11	Mar 31	NA	NA	Pneumonia	Severe	Dead	Apr 11
35	Shanghai	83	F	NA	Apr 11	Apr 2	NA	NA	Fever, Cough	Mild	Stable	-

Supplemental table 1 (continued): Demographic presentation of human H7N9 infected cases

36	Shanghai	68	M	NA	Apr 11	Apr 4	NA	NA	Fever, Muscle pain, Pneumonia	Mild	Stable	-
37	Jiangsu	31	M	Chef	Apr 11	Mar 31	NA	NA	NA	Severe	Critical	-
38	Jiangsu	56	M	Teacher	Apr 11	Apr 3	NA	NA	NA	Severe	Critical	-
39	Shanghai	53	M	NA	Apr 12	Apr 5	Apr11	NA	Pneumonia	Severe	Critical	-
40	Shanghai	86	M	NA	Apr 12	Apr 6		NA	NA	NA	NA	-
41	Zheijiang	66	M	NA	Apr 12	Apr 8	NA	NA	NA	Severe	Critical	-
42	Zheijiang	74	M	NA	Apr 12	Apr 6	NA	NA	NA	Severe	Critical	-
43	Zheijiang	54	F	NA	Apr 12	Apr 6	NA	NA	NA	Severe	Critical	-
44	Beijing	7	F	Parent are poultry dealers	Apr 13	Apr 11	Apr 11	Apr 11	Fever, Cough, Lung infection, Sore throat, Headache	Severe	Recovering	-
45	Jiangsu	77	F	NA	Apr 13	NA	NA	NA	NA	Severe	Critical	-
46	Jiangsu	74	M	NA	Apr 13	NA	NA	NA	NA	Severe	Critical	-
47	Zheijiang	38	M	NA	Apr 13	NA	NA	NA	NA	Severe	Critical	-
48	Zheijiang	65	M	NA	Apr 13	NA	NA	NA	NA	Severe	Critical	-
49	Shanghai	54	M	Husband of H7N9 confirmed case	Apr 13	NA	NA	NA	NA	NA	NA	-
50	Henan	34	M	Chef	Apr 14	Apr 6	NA	NA	NA	Severe	Critical	-
51	Henan	65	M	Farmer	Apr 14		NA	NA	NA	Severe	Stable	-
52	Zheijiang	64	F	Farmer	Apr 14	Apr 6	NA	NA	NA	Severe	Critical	-
53	Zheijiang	62	F	Retired	Apr 14	Mar 29	NA	NA	NA	Severe	Critical	-
54	Zheijiang	75	M	Retired	Apr 14	Apr 9	NA	NA	NA	Severe	Critical	-
55	Zheijiang	79	M	Retired	Apr 14	Apr 9	NA	NA	NA	Severe	Critical	-
56	Shanghai	73	M	NA	Apr 14	NA	NA	NA	NA	NA	NA	-
57	Shanghai	54	M	NA	Apr 14	NA	NA	NA	NA	NA	NA	-
58	Shanghai	78	M	NA	Apr 14	NA	NA	NA	NA	NA	NA	-
59	Jiangsu	50	M	NA	Apr 14	NA	NA	NA	NA	NA	NA	-
60	Jiangsu	26	M	NA	Apr 14	NA	NA	NA	NA	NA	NA	-