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Public health relevant virological features of Influenza A(H7N9) causing human infection in China

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As of 4 April 2013, the China Health and Family Planning Commission has notified WHO of a total number of eleven (11) confirmed cases of human infection with influenza A(H7N9) virus in China. Five of the 11 cases have died (http://www.who.int/csr/don/2013_04_04/en/index.html).

This particular strain of A(H7N9) virus has not previously been detected in human or animal populations. WHO is responding to this event, including dissemination of information about the virus in order to support diagnosis, treatment and vaccine development. This document describes some key virological features of the three A(H7N9) viruses analysed so far. These virological features are based on initial analyses carried out by the WHO Collaborating Centres for Reference and Research on Influenza in Beijing and Tokyo, and the WHO Collaborating Centre for Surveillance, Epidemiology and Control of Influenza, Atlanta.

Gene sequences of four viruses have been deposited for A/Shanghai/1/2013, A/Shanghai/2/2013, A/Anhui/1/2013 and A/Hangzhou/1/2013 in GISAID by the WHO Collaborating Centre for Reference and Research on Influenza in Beijing.

Table. Accession numbers in GISAID of A(H7N9) virus gene sequences.

Gene	A/Shanghai/1/2013	A/Shanghai/2/2013	A/Anhui/1/2013	A/Hangzhou/1/2013
PB2	EPI439488	EPI439495	EPI439504	
PB1	EPI439489	EPI439501	EPI439508	
PA	EPI439490	EPI439498	EPI439503	
HA	EPI439486	EPI439502	EPI439507	EPI440095
NP	EPI439491	EPI439496	EPI439505	
NA	EPI439487	EPI439500	EPI439509	EPI44096
M	EPI439493	EPI439497	EPI439506	EPI440097
NS	EPI439494	EPI439499	EPI439510	

Several features of these influenza A (H7N9) viruses infecting humans are relevant to public health:

Possible origin of the virus

It is considered likely that the new virus stems from a reassortment of three virus strains that infect only birds:

- The 6 genes coding for the internal proteins are similar to recent H9N2 viruses found in China and South Korea. H9N2 viruses are endemic in birds, including poultry, in Asia and elsewhere.
- The gene for the N protein is similar to avian H11N9 viruses found in South Korea in 2011; in Hongze, Jiangsu, in 2010; and in the Czech Republic in 2005.
- The gene for the H protein belongs to a Eurasian group of H7 avian influenza viruses.

However, the reservoir for these viruses infecting humans may or may not be poultry.

Hallmarks of pathogenicity in poultry do not appear to be present

- The HA gene sequences do not encode the hall-mark of a highly pathogenic avian influenza (HPAI) virus, this being a series of basic amino acids at the HA1/HA2 cleavage site; rather they encode a single arginine at this site as found in low pathogenic avian influenza (LPAI) virus.
- This finding suggests that infections in poultry could be mild or silent and thus go unnoticed. Pathogenicity of the virus needs to be confirmed by the intravenous pathogenicity index test in 6-week old chicks (http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.03.04_AI.pdf).

Markers for adaptation to a mammalian host

Three findings suggest that these influenza A(H7N9) viruses have undergone adaptation to mammalian hosts:

- The HA gene sequences of two of the isolates encode leucine at residue 217 of HA1 and another carries isoleucine at this position, the equivalent of residue 226 in HA1 of H3-HA containing viruses, indicative of recognition of sialic acid linked α2-6 to galactose which is present in the upper respiratory tract of humans and other mammals.
- The stalk region of the NA has a deletion of 5 amino acids. Substitutions in the NA stalk are frequently observed on the transfer of viruses from wild fowl to poultry or mammals.
- The PB2 gene of each virus encodes an E627K substitution. This change is associated with improved replication of avian influenza viruses in mammals.

Sensitivity to neuraminidase inhibitors relevant to clinical management of human infection from these viruses and other antiviral drugs

- The NA gene of one of the four genetically characterized viruses encodes a R292K substitution which has been associated with oseltamivir and zanamivir resistance in NAs of other subtypes. However, this is not a universal marker for resistance to neuraminidase inhibitors in influenza A viruses (see PMID 21253602, table 1).
- Phenotypic assessment of the sensitivity of these three influenza A(H7N9) viruses has shown them to be sensitive to oseltamivir and zanamivir.
- The M genes of the viruses encode S31N substitution. An asparagine at residue 31 is consistent with resistance to amantadine and rimantadine. This finding has yet to be confirmed by phenotypic assay.

Antigenic properties of the virus and vaccine development

- Antigenic properties of these A(H7N9) viruses relative to existing potential vaccine candidates, largely dependent on their H7-HA components, have yet to be determined.
- Current H7 candidate vaccine viruses are not expected to be cross-protective and candidate vaccine viruses based on the A(H7N9) virus will be developed.