Control of avian influenza and preparedness for pandemic influenza

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For control of avian influenza and preparedness for pandemic influenza

1. Is influenza eradicable?

2. Why have the H5N1 HPAIVs persisted in poultry for 18 years and antigenic variants been selected in poultry birds?

3. Will the HPAIVs returned to migratory birds persist in nature?

4. How should HPAI be controlled?

5. Does AI vaccine confer complete protective immunity in birds?

6. Will H5N1 HPAIV and H7N9 LPAIV cause pandemic influenza?

7. Are the measures for the control of seasonal influenza satisfactory?
Acquisition of pathogenicity of avian influenza virus in chicken and return of the HPAIV from domestic poultry to migratory water birds.
HPAI viruses isolated from wild birds in Mongolia

A/whooper swan/Mongolia/3/05 (H5N1)
A/bar-headed goose/Mongolia/1/05 (H5N1)
A/common goldeneye/Mongolia/12/06 (H5N1)
A/whooper swan/Mongolia/2/06 (H5N1)
A/whooper swan/Mongolia/2/09 (H5N1)
A/whooper swan/Mongolia/9/09 (H5N1)
A/bar-headed goose/Mongolia/X53/09 (H5N1)
A/rubby sholduck/Mongolia/X42/2009 (H5N1)
A/common goldeneye/Mongolia/X60/09 (H5N1)
A/whooper swan/Mongolia/1/10 (H5N1)
A/whooper swan/Mongolia/7/10 (H5N1)
62 Countries where H5N1 HPAIV infections were reported in wild birds, poultry, and both
Japan, Republic of Korea, China, Mongolia, Myanmar, Lao PDR, Thailand, Cambodia, Viet Nam, Malaysia, Indonesia, Bangladesh, India, Pakistan; Afghanistan, Iran, Azerbaijan, Georgia, Iraq, Kuwait, Saudi Arabia, Turkey, Israel; Russian Federation, Kazakhstan, Ukraine, Romania, Bulgaria, Albania, Serbia, Hungary, Slovakia, Czech Republic, Croatia, Poland, Slovenia, Bosnia & Herzegovina; Greece, Switzerland, Austria, France, Italy, Germany, Netherlands, Denmark, Sweden, Spain, England, Ireland; Djibouti, Gaza Strip, Egypt, Sudan, Nigeria, Niger, Cameroon, Burkina Faso, Cote d'Ivoire
### Confirmed human cases of H5N1 HPAIV infection

<table>
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<tr>
<th>Country</th>
<th>Deaths/Cases</th>
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<td>China</td>
<td>30 / 45</td>
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<tr>
<td>Viet Nam</td>
<td>62 / 125</td>
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<tr>
<td>Indonesia</td>
<td>163 / 195</td>
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<td>Egypt</td>
<td>63 / 173</td>
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<td>Cambodia</td>
<td>33 / 47</td>
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<td>Lao PDR</td>
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<td>Thailand</td>
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<td>Iraq</td>
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<td>Azerbaijan</td>
<td>5 / 8</td>
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<td>Turkey</td>
<td>4 / 12</td>
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<td>Djibouti</td>
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<td>Nigeria</td>
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<td>Myanmar</td>
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<td>Pakistan</td>
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<td>Bangladesh</td>
<td>1 / 7</td>
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<td>Canada</td>
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<td><strong>Total</strong></td>
<td><strong>386 / 650</strong></td>
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*As of 24 Jan. 2014*

*WHO (2014), Kuribayashi*
Bird flu vaccines

**Vietnam:**
H5N2 and H5N1
(Adjuvant inactivated vaccines)

**China:**
H5N1 and recombinant NDV
(Reverse genetics inactivated vaccines)

**Indonesia:**
H5N1, H5N2, H5N9 and recombinant H5N1
(inactivated vaccines)

**Egypt:** since 2006

**Thailand:**
Officially prohibited vaccination in 2006

**As stockpiles**

**Singapore:**
H5N2
(Inactivated, adjuvanted vaccine)

**Japan:**
H5N1 and H7N7
(Oil-adjuvanted inactivated vaccines)

**Pakistan:**
H5N1, H5N2, H5N9, and H5N3
(Water based with alum hydroxide and oil based with mineral oil)
Influenza vaccine for avian influenza

- may prevent manifestation of disease signs and decrease the amount of virus shed, but does not confer protective immunity from infection.

- “Stamping-out policy” is recommended for the control of avian influenza.

- Vaccination was not recommended but later approved as one of the options applied only under DIVA based strategy.

- Country where vaccine is used is not designated as HPAI-free.

→ leads silent spread of virus.
It is considered that:

- H5N1 HPAIV strains have persisted in domestic poultry for 14 years and antigenic variants have been selected due to the misuse of vaccine.
- HPAI has been put under control in several countries.
- Stamping out policy has been the most effective measures for the control HPAI.
- Vaccine is used in 4 countries where HPAI has not been controlled yet.
- Vaccine is used instead of stamping out in 2 countries and in the other 2 countries, basically in addition to stamping out.
- Sentinel bids are put in the vaccinated poultry population in Viet Nam and not in the other 3 countries where vaccine is used.
- Compensation for livestock owners is done in most countries in case of stamping out.

It is recommended that:

1. Since stamping out is the best and ultimate measure for the control of HPAI, vaccine should be used in addition to, not instead of stamping out.
2. The OIE should continue and develop standards on animal influenza surveillance, prevention and control.
3. For the preparedness for pandemic influenza, surveillance of swine flu is crucial in the countries where avian flu has not been controlled.

795 isolates from 22,744 samples

**Mongolia (324)**
- H1N1 (5)
- H2N3 (1)
- H3N6 (34)
- H4N2 (2)
- H4N6 (72)
- H4N8 (4)
- H5N3 (4)
- H7N6 (1)
- H7N9 (3)
- H9N2 (1)
- H10N5 (2)
- H12N5 (1)

**Australia (6)**
- H2N5 (6)

**China (2)**
- H3N8 (1)
- H4N6 (1)

**Hokkaido (296)**
- H1N1 (12)
- H2N5 (1)
- H3N8 (37)
- H4N6 (33)
- H5N3 (11)
- H6N5 (2)
- H7N1 (18)
- H9N2 (7)
- H9N9 (1)
- H10N5 (7)
- H10N8 (1)
- H11N9 (21)
- H13N6 (2)

**Russia (56)**
- H3N8 (17)
- H4N9 (2)
- H5N2 (1)
- H5N3 (11)
- H6N1 (17)
- H6N8 (7)
- H7N7 (1)
- H8N4 (1)
- H9N2 (7)
- H10N2 (1)
- H10N7 (1)

**USA (111)**
- H2N3 (1)
- H3N8 (39)
- H4N6 (57)
- H7N7 (1)
- H10N7 (11)

**H12N5 (1)**
Surveillance of avian influenza in autumn 2010

- Mongolia (36 isolates)
  - H1N1 (1)
  - H3N3 (1)
  - H3N6 (7)
  - H3N8 (14)
  - H4N6 (8)
  - H7N9 (1)
  - H10N8 (4)

- Hokkaido (15 isolates)
  - H3N8 (3)
  - H5N2 (1)
  - H6N2 (2)
  - H7N7 (9)
  - H5N1 (2)

- Hong Kong (3 isolates)
  - H3N2 (1)
  - H5N1 (2)

- Vietnam (1 isolate)
  - H9N6 (1)

- Laos (none)

Number of samples: 4,515
Influenza virus isolates: 55
As of 25 October 2010
Outbreaks of HPAI caused by H5N1 viruses in Japan in 2010-2011 winter

- Wild birds (63)
- Chicken farms (24)

Okamatsu (2011)
Global surveillance of avian influenza in 2012

**Mongolia (23 isolates /300+838+353+1000+900)**
- H2N9 (1)  
- H3N6 (1)  
- H3N8 (16)  
- H4N6 (2)  
- H4N8 (1)  
- HxN2 (1)  
- H8N4 (1)

**Vietnam (114 isolates/706+600+601+600)**
- H3N2 (11)  
- H3N6 (9)  
- H3N8 (10)  
- H4N6 (7)  
- H5N1 (30)  
- H5N2 (1)  
- H6N2 (5)  
- H6N6 (6)  
- H7N1 (2)  
- H9N2 (23)  
- H9N8 (1)  
- H10N7 (3)  
- H11N3 (2)  
- H11N9 (4)

**Hokkaido (20 isolates/198+714+4)**
- H2N2 (1)  
- H3N8 (1)  
- H4N2 (2)  
- H4N6 (1)  
- H6N1 (8)  
- H6N2 (2)  
- H10N5 (1)  
- H11N3 (2)  
- H11N9 (4)  
- H13N2 (1)

**West Siberia (25 isolates /1594+300)**
- H1N1 (1)  
- H2Nx (1)  
- H3N8 (7)  
- H4N6 (8)  
- H4Nx (4)  
- HxN2 (1)  
- H8N4 (1)  
- HxNx (2)

**East Siberia (5 isolates /112)**
- H3N8 (5)

**Russian Far East (3 isolates /200)**
- H3Nx (3)

**Russian Far East (3 isolates /200)**
- H3Nx (3)

**As of July. 9, 2013**

**Number of sample**: 9,020  
**Influenza A virus positive**: 190
Global surveillance of avian influenza in 2013

Mongolia (59 isolates/813)
- H1N1 (5)
- H1N3 (2)
- H3N1 (5)
- H3N5 (1)
- H3N8 (25)
- H4N1 (3)
- H4N5 (1)
- H4N6 (9)
- H6N1 (4)
- H6N2 (1)
- H6N5 (1)
- H10N3 (1)
- H12N5 (1)

Hokkaido (18 isolates/466+150+5)
- H3N8 (1)
- H4N2 (1)
- H4N6 (6)
- H6N5 (2)
- H7N2 (5)
- H12N2 (2)
- H16N3 (1)

Number of sample: 1,434
Influenza A virus positive: 77

As of Nov. 11, 2013
45 deaths of 137 cases as of 25 Oct 2013
64 deaths of 333 cases as of 12 Feb 2014
Number of Confirmed Human H7N9 Cases
by week as of 2014-04-08
H5N8 HPAI outbreaks

**Phase I**
- During 1.16-1.22
- Poultry farms (12 cases) & wild birds (9 cases) around Donglim reservoir in JB province

**The first wild bird report case, in Donglim Reservoir, 1.17.**

**The first poultry report case in Gochang, 1.16.**

Wild birds (9 cases) and poultry (12 cases) during 1.17-1.22

Lee, Youn-Jeong (2014); Avian Influenza Lab. Animal and Plant Quarantine Agency, Korea
Phylogenetic tree of the HA genes of H5N1, H5N2 and H5N8 influenza viruses

Okamatsu (2014)
Human pandemic influenza

- **Spanish flu**
  - 1918
  - H3N8
  - H1N1

- **Asian flu**
  - 1957
  - H2N2
  - H3N2

- **Hong Kong flu**
  - 1968
  - H1N1
  - H1N1 (Russian type)

- **Swine-origin H1N1 influenza virus**
  - 2009
  - A/2009 (H1N1) pdm

- **Outbreaks of HPAI caused by H5N1 viruses in Japan**
  - 2004
  - 2007
  - 2010

- **Human cases of H5N1 HPAI virus infection in Hong Kong**
  - 2007
  - 2010-2011

- **Highly pathogenic avian influenza viruses (H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N3, H7N4, H7N7)**
  - 1925
  - 1925

- **First isolation of influenza virus from human**
  - 1925

- **Outbreak of HPAI caused by H7N7 virus in Japan**
  - 1977

- **Outbreaks of HPAI caused by H5N1 viruses in Japan**
  - 1997
  - 1997
1957 Asian virus (H2N2), 2009 pdm H1N1 strain and even 1918 Spanish flu virus (H1N1) must have appeared similarly.

Gene derivation of the swine-origin influenza A (H1N1) virus

At least 18,366 deaths in 214 countries as of 18 July 2010

PB2 - North American avian
PB1 - Human H3N2
PA - North American avian
H1 - Classical swine
NP - Classical swine
N1 - Eurasian avian-like swine
M - Eurasian avian-like swine
NS - Classical swine

- Each of the pandemic strains has been generated in pigs.
- Genetic reassortment often occurs in birds and pigs.

The H1N1 strain is a genuine swine influenza virus.

Modified from Novel Swine-Origin Influenza A (H1N1) Virus investigation Team, N Eng J Med, 2009
HPAI virus and human pandemic virus strains

- Goose
- Turkey
- Quail
- Duck
- Pig
- Humans

Low Pathogenic AIV

Apathogenic AIV

>6 months in chickens

HPAIV

Genetic reassortant virus

HPAI virus and human pandemic virus strains
Thus, 1,900 avian influenza viruses of 144 combinations of HA and NA subtypes have been stocked as vaccine strain candidates. Their pathogenicity, antigenicity, genetic information and yield in chicken embryo have been analyzed, data-based, and opened for Web site (http://virusdb.czc.hokudai.ac.jp/vdbportal/view/index.jsp).

### Library of vaccine strain candidates

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- ★ Virus isolated from a waterfowl (74 combinations)
- ★ Virus generated in the laboratory (70 combinations)

Influenza viruses of 74 combinations of the HA and NA sub-types have been isolated from fecal samples of ducks in Alaska, Siberia, Mongolia, Taiwan, China, and Japan. (black)

70 other combinations have been generated by genetic reassortment procedure in the laboratory. (red)

Dec 9, 2013
How should we control HPAI and prepare for pandemic influenza?

1. Is influenza eradicable?  
   No, influenza is a typical zoonosis.

2. Why have the H5N1 HPAIVs persisted in poultry for 17 years and been antigenic variants selected?  
   Misuse of Vaccine.

3. Will the HPAIVs returned to migratory birds persist in nature?  
   Started contamination of HPAIVs in the nesting lakes of migratory ducks. Eradication of the H5N1 HPAIVs from poultry throughout the world, therefore, is urgently needed.

4. How should avian influenza be controlled in poultry?  
   Enhanced surveillance, early detection, culling the flock, movement restriction, and strengthening hygiene without misuse of vaccine to contain the infection just in birds.

5. What are the advantage and disadvantage of the use of vaccines?  
   Vaccine should be carefully used in addition to, not instead of stamping out.

6. Will H5N1 HPAIV and H7N9 LPAIV cause pandemic influenza?  
   It is unlikely, but may occur via pigs. H5N1 or H7N9 AIVs are not only candidates of pandemic strain.

7. Are the measures for the control of seasonal flu satisfactory?  
   How to control pandemic influenza should be based on the measures for the control of seasonal influenza. Especially seasonal flu vaccine should be much more improved.

★ Global surveillance of avian, swine and human influenza, and drastic improvement of seasonal flu control measures by international collaboration under the One Health concept are of crucial importance.
Control of avian influenza and preparedness for pandemic influenza

1. For control of highly pathogenic avian influenza, Stamping-out policy that contains enhanced surveillance, early detection, culling, restriction of movement, and improved hygiene practices without too much reliance on vaccination should be applied to restrict infection to domestic birds.

2. The genes of all influenza viruses in birds and mammals including humans have originated from those circulating among the natural host reservoir, water fowls.

3. All of the 4 pandemic influenza virus strains that have emerged in the last 100 years must have been transmitted from pigs as genetic reassortants between avian and human strains. The HA genes of these strains are closely related to those of viruses circulating in the natural host, migratory ducks.

4. Pigs are susceptible to infection with avian influenza virus strains with each of the HA subtypes generating reassortants. This indicates that none of the 16 HA subtype viruses can be ruled out as candidates for future pandemic strains.

5. Methods for control of pandemic influenza should be based on the same measures for the control of seasonal influenza. For this reason, seasonal flu vaccines should be greatly improved.