Avian Influenza Viruses with Pandemic Potential

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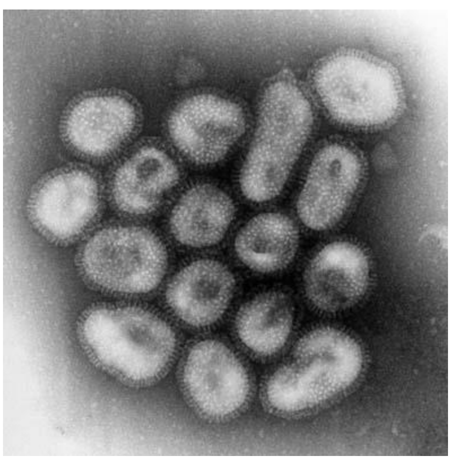
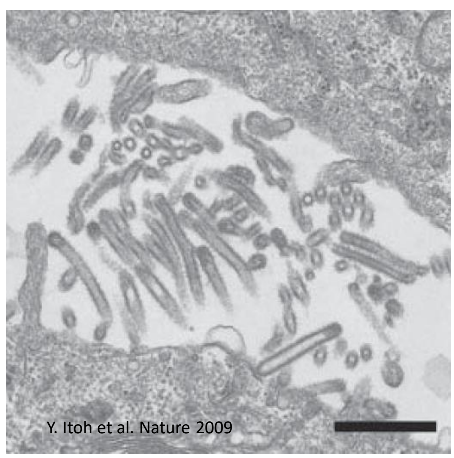
Influenza Viruses



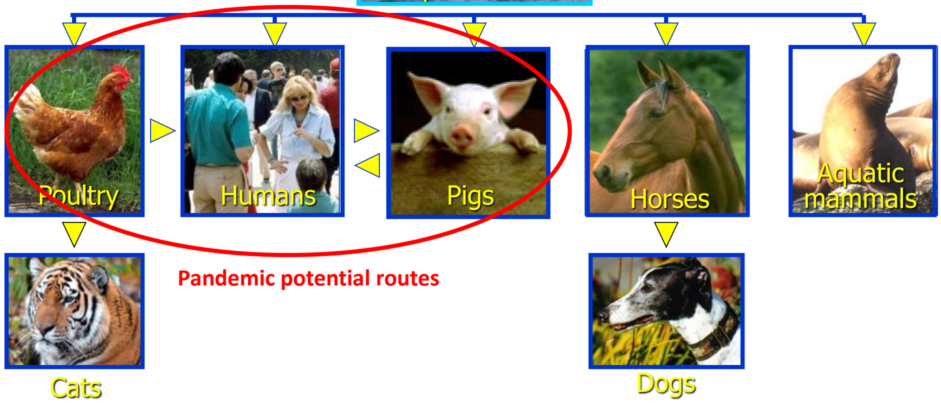


Y. Itoh et al. Nature 2009

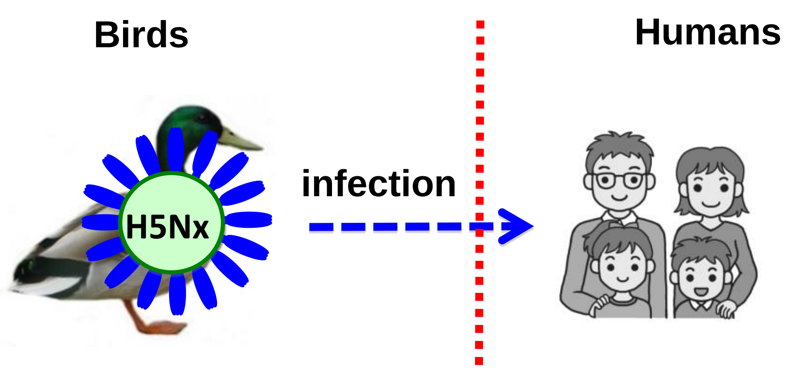
Influenza A Viruses

All influenza A virus subtypes are detected in aquatic birds

- **H1 - H16**
- **N1 - N9**

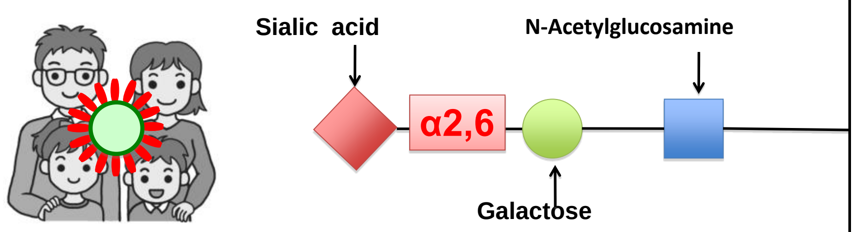


Species barrier

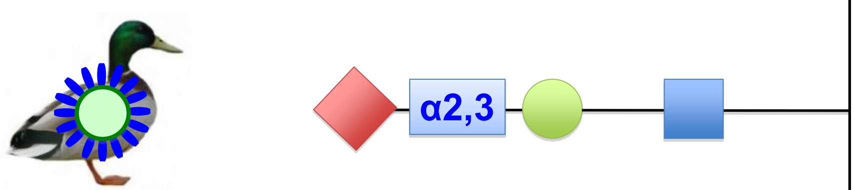


Different receptor specificity

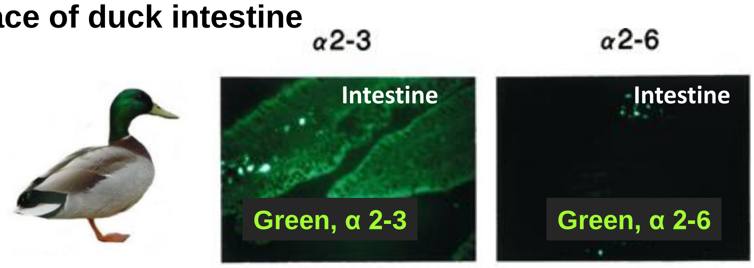
Seasonal flu viruses preferentially bind SAα2,6Gal receptors in human upper respiratory tracts



Avian flu viruses preferentially bind SAα2,3Gal receptors in avian intestinal tracts and in human lungs

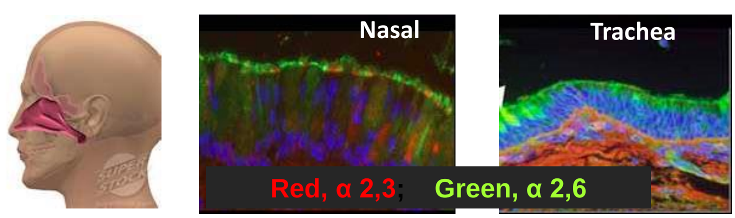


SAα2,3Gal receptors predominantly detected in the surface of duck intestine



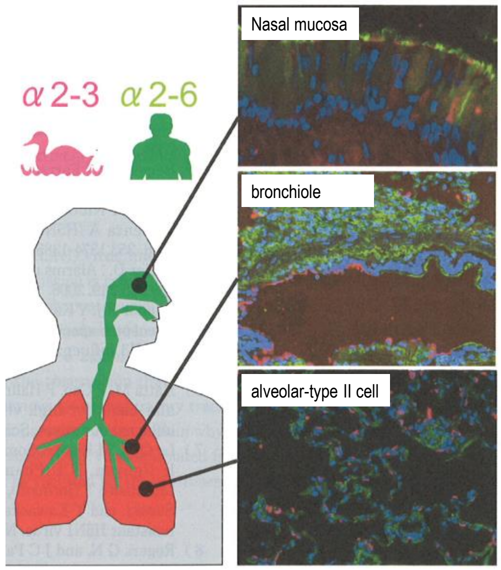
Ito et al., J Virol 1998

SAα2,6Gal receptors predominantly detected in upper respiratory tract cells



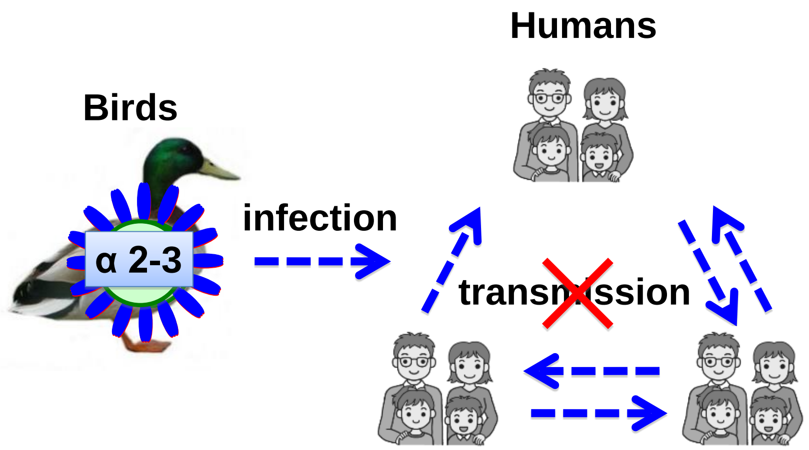
Shinya et al., Nature 2006

Receptor distribution in human respiratory tracts

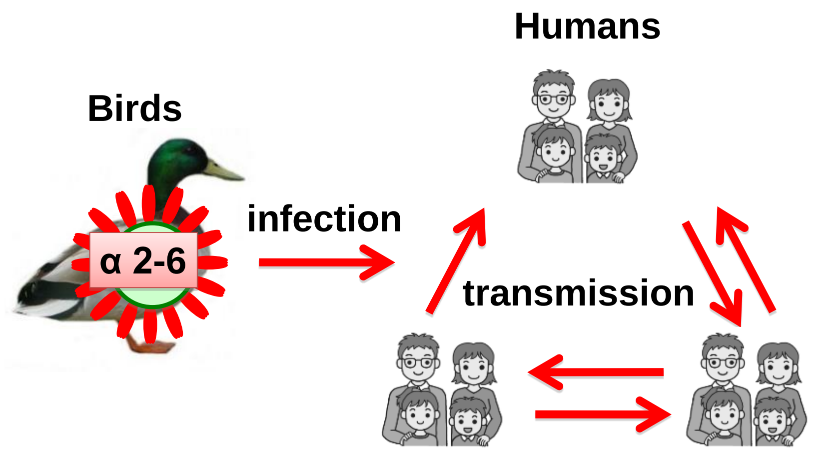


Shinya: Virus, 56 (2006)

Avian flu viruses cannot sustainably transmit among humans



When avian flu viruses acquired mutation(s) to preferentially recognize human type receptors, pandemic potential by the virus increases



Zoonotic Influenza A viruses currently detected in Animals and Humans in the World (since Sept 2016)

- **Avian viruses**

H5Nx :

Since 2003,

- H5N1 (poultry, wild birds, human（6）)(860)
- H5N2 (poultry, wild birds)
- H5N5 (wild birds)
- H5N6 (poultry, wild birds, human（16）)
- H5N8 (poultry, wild birds)

Since 2013,

H7N9 : (poultry, human（758）, environment) (1564)
H7N2 : (poultry)
H9N2 : (environment, human(4))

- **Swine viruses**

H1N1v (pig)
H1N2v (human(2), pig)
H3N2v (human(31), pig)

http://www.who.int/influenza/vaccines/virus/201709_zoonotic_vaccinevirusupdate.pdf?ua=1

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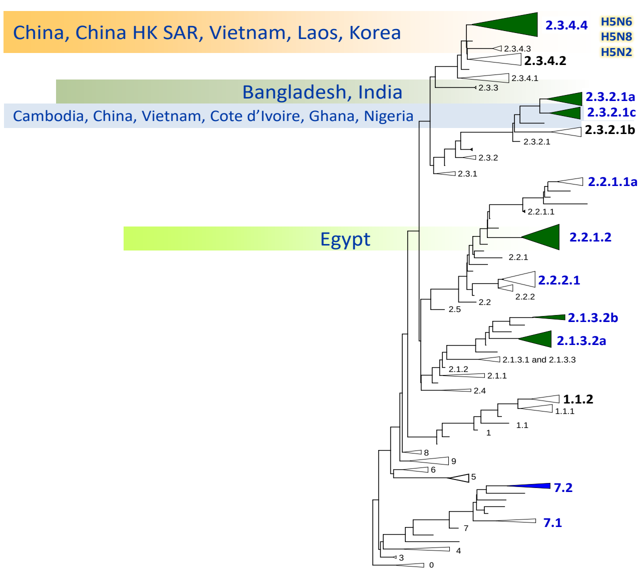
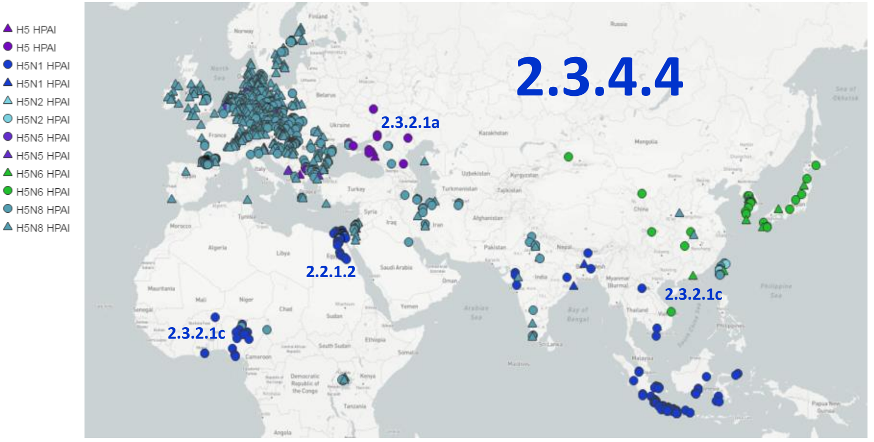
H5N8 (poultry, wild birds)

http://www.who.int/influenza/vaccines/virus/201709_zoonotic_vaccinevirusupdate.pdf?ua=1

Evolution of A(H5) HA genes



A(H5) activity - birds since 27 September 2016



Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2017

Country	2003-2009*		2010-2014**		2015		2016		2017		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	120	50	136	39	10	3	3	1	359	120
Indonesia	162	134	35	31	2	2	0	0	0	0	199	167
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	0	0	127	64
Total	**468**	**282**	**233**	**125**	**145**	**42**	**10**	**3**	**3**	**1**	**859**	**453**

World Health Organization

http://www.who.int/influenza/human_animal_interface/2017_07_25_tableH5N1.pdf?ua=1

Available H5Nx CVVs provided by WHO CCs/ERLs

Table 2. Status of influenza A(H5) candidate vaccine virus development

Candidate vaccine viruses	Clade	Institution*	Available
A/Viet Nam/1203/2004 (CDC-RG; SJRG-161052)	1	CDC and SJCRH	Yes
A/Viet Nam/1194/2004 (NIBRG-14)	1	NIBSC	Yes
A/Cambodia/R0405050/2007 (NIBRG-88)	1.1	NIBSC	Yes
A/Cambodia/X0810301/2013 (IDCDC-RG34B)	1.1.2	CDC	Yes
A/duck/Hunan/795/2002 (SJRG-166614)	2.1.1	SJCRH/HKU	Yes
A/Indonesia/5/2005 (CDC-RG2)	2.1.3.2	CDC	Yes
A/Indonesia/NIHRD11771/2011 (NIIDRG-9)	2.1.3.2a	NIID	Yes
A/bar-headed goose/Qinghai/1A/2005 (SJRG-163222)	2.2	SJCRH/HKU	Yes
A/chicken/India/NIV33487/2006 (IBCDC-RG7)	2.2	CDC/NIV	Yes
A/whooper swan/Mongolia/244/2005 (SJRG-163243)	2.2	SJCRH	Yes
A/Egypt/2321-NAMRU3/2007 (IDCDC-RG11)	2.2.1	CDC	Yes
A/turkey/Turkey/1/2005 (NIBRG-23)	2.2.1	NIBSC	Yes
A/Egypt/N03072/2010 (IDCDC-RG29)	2.2.1	CDC	Yes
A/Egypt/3300-NAMRU3/2008 (IDCDC-RG13)	2.2.1.1	CDC	Yes
A/Egypt/N04915/2014 (NIBRG-306)	2.2.1.2	NIBSC	Yes
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	SJCRH/HKU	Yes
A/Hubei/1/2010 (IDCDC-RG30)	2.3.2.1a	CDC	Yes
A/duck/Bangladesh/19097/2013 (SJ007)	2.3.2.1a	SJCRH	Yes
A/barn swallow/Hong Kong/D10-1161/2010 (SJ003)	2.3.2.1b	SJCRH/HKU	Yes
A/duck/Viet Nam/NCVD-1584/2012 (NIBRG-301)	2.3.2.1c	NIBSC	Yes
A/chicken/Hong Kong/AP156/2008 (SJ002)	2.3.4	SJCRH/HKU	Yes
A/Anhui/1/2005 (IBCDC-RG6)	2.3.4	CDC	Yes
A/duck/Laos/3295/2006 (CBER-RG1)	2.3.4	FDA	Yes
A/Japanese white eye/Hong Kong/1038/2006 (SJRG-164281)	2.3.4	SJCRH/HKU	Yes
A/chicken/Bangladesh/11rs1984-30/2011 (IDCDC-RG36)	2.3.4.2	CDC	Yes
A/Guizhou/1/2013 (IDCDC-RG35)	2.3.4.2	CDC/CCDC	Yes
A/Sichuan/26221/2014 (IDCDC-RG42A) (H5N6)	2.3.4.4	CDC/CCDC	Yes
A/gyrfalcon/Washington/41088-6/2014 (IDCDC-RG43A) (H5N8)	2.3.4.4	CDC	Yes
A/goose/Guiyang/337/2006 (SJRG-165396)	4	SJCRH/HKU	Yes
A/chicken/Viet Nam/NCVD-016/2008 (IDCDC-RG12)	7.1	CDC	Yes
A/chicken/Viet Nam/NCDV-03/2008 (IDCDC-RG25A)	7.1	CDC	Yes
A/environment/Hubei/950/2013	7.2	CDC/CCDC	Yes
Candidate vaccine viruses in preparation	**Clade**	**Institution**	**Availability**
A/chicken/Guiyang/1153/2016-like	2.3.2.1c	SJCRH/HKU	Pending
A/chicken/Ghana/20/2015-like	2.3.2.1c	CDC	Pending
A/chicken/Viet Nam/NCVD-15A59/2015-like (H5N6)	2.3.4.4	SJCRH	Pending
A/Hubei/29578/2016-like (H5N6)	2.3.4.4	CCDC	Pending
A/duck/Hyogo/1/2016-like (H5N6)	2.3.4.4	NIID	Pending

http://www.who.int/influenza/vaccines/virus/201703_zoonotic_vaccinevirusupdate.pdf?ua=1

World Health Organization

WHO GISRS network

ワクチン候補野生株の分与 →

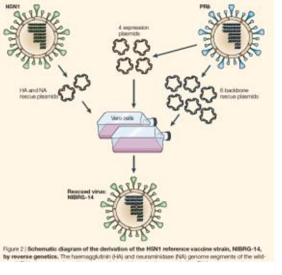
感染研GMP facilityでワクチン製造株の作製

国内外のワクチン製造所
研究機関

← 無償配布

動物への感染等で安全性試験
品質試験確認試験

RG法で弱毒化したワクチン
高増殖株の開発



現在新型インフルエンザワクチン製造株を作製・提供している海外施設

英国・国立生物製剤品質管理研究所（NIBSC） BSL4実験施設

米国・セントジュード小児研究病院 BSL3適合GMP施設

米国・疾病予防対策センター（CDC） BSL3実験施設

感染研インフルエンザウイルス研究センター

Zoonotic Influenza A viruses currently detected in Animals and Humans in the World (since Sept 2016)

- **Avian viruses**

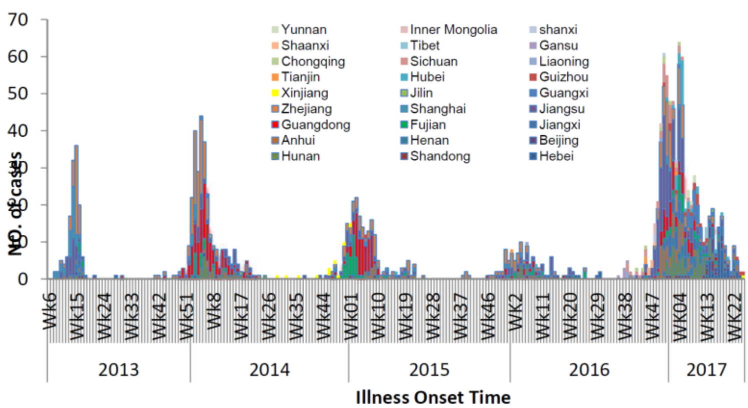
Since 2013,

H7N9 : (poultry, human（758）, environment) (1564)

http://www.who.int/influenza/vaccines/virus/201709_zoonotic_vaccinevirusupdate.pdf?ua=1

Epi-curve of human H7N9 cases by date of illness onset

19 Feb, 2013 to 31 Aug, 2017 (N=1531)



Province	First wave (2013.2~)		Second wave (2013.10~)		Third wave (2014.10~)		Forth wave (2015.10~)		Fifth wave (2016.10~)		Cumulative counts		
	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Fatality rate(%)
Total	134	44	306	128	219	100	116	47	756	285	1531	604	39.5

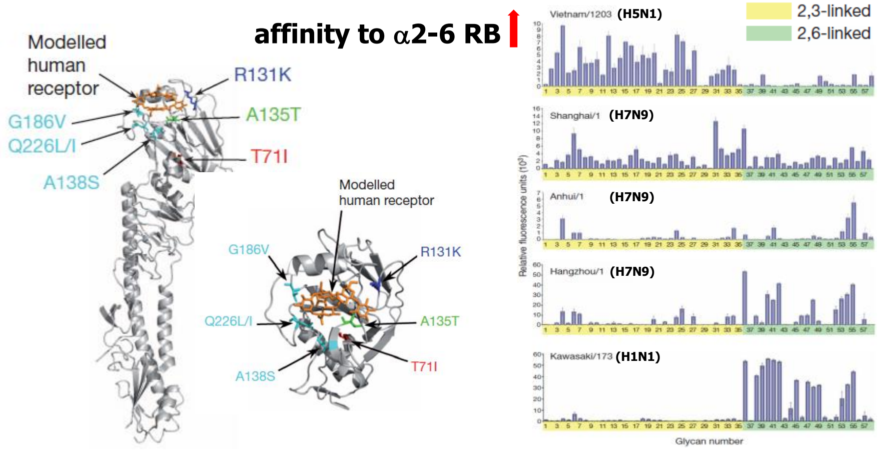
Data provided by China CDC

LETTER

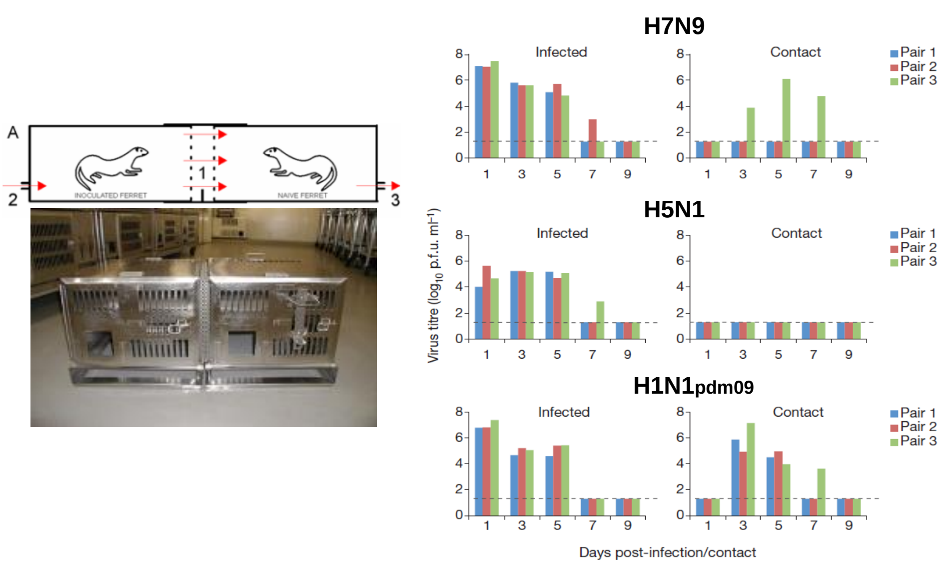
doi:10.1038/nature12392

Characterization of H7N9 influenza A viruses isolated from humans

Tokiko Watanabe[1]*, Maki Kiso[2]*, Satoshi Fukuyama[1]*, Noriko Nakajima[3]*, Masaki Imai[4]*, Shinya Yamada[2], Shin Murakami[5], Seiya Yamayoshi[2], Kiyoko Iwatsuki-Horimoto[2], Yoshihiro Sakoda[6], Emi Takashita[4], Ryan McBride[7], Takeshi Noda[2], Masato Hatta[8], Hirotaka Imai[8], Dongming Zhao[1], Noriko Kishida[4], Masayuki Shirakura[4], Robert P. de Vries[7], Shintaro Shichinohe[6], Masatoshi Okamatsu[6], Tomokazu Tamura[6], Yuriko Tomita[1], Naomi Fujimoto[1], Kazue Goto[1], Hiroaki Katsura[2], Eiryo Kawakami[1], Izumi Ishikawa[1], Shinji Watanabe[1,9], Mutsumi Ito[2], Yuko Sakai-Tagawa[2], Yukihiko Sugita[2], Ryuta Uraki[2], Reina Yamaji[2], Amie J. Eisfeld[8], Gongxun Zhong[8], Shufang Fan[8], Jihui Ping[8], Eileen A. Maher[8], Anthony Hanson[8], Yuko Uchida[10], Takehiko Saito[10], Makoto Ozawa[11,12], Gabriele Neumann[8], Hiroshi Kida[6,13], Takato Odagiri[4], James C. Paulson[7], Hideki Hasegawa[3], Masato Tashiro[4] & Yoshihiro Kawaoka[1,2,5,8,14]



H7N9 virus can partially transmit mammalian (Ferret) by droplets



Family clusters of human H7N9 cases

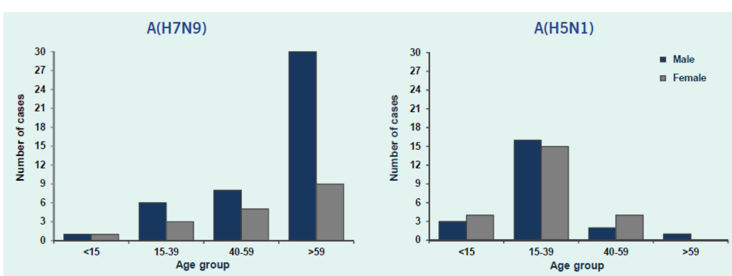
Route of transmission	NO.
Possibility of Human-to-human transmission	19+1
Co-exposure	3+4
Possibility of Human-to-human transmission or Co-exposure	9+4
Total	40

*New family clusters since Sep,2016 in red.

Data provided by China CDC

- **Pandemic potential with H7N9 viruses is not low**
- **Sustained H-to-H transmission is limited so far**

Age distribution of infected cases with A(H7N9) and A(H5N1) viruses

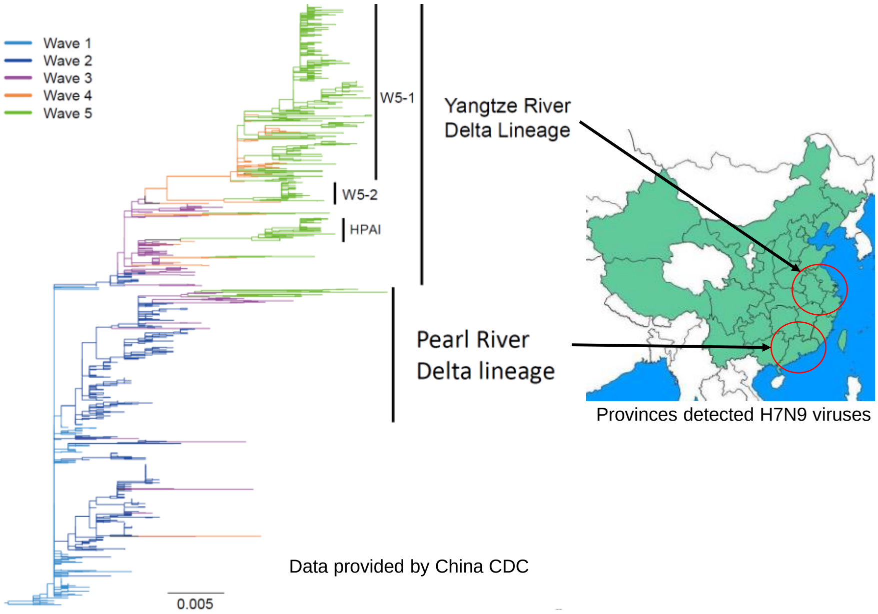


>45 years old: **75% of cases**
<20 **years old: 7% of cases**

<20 **years old: 50% of cases**

WPSAR Vol 4, No 2, 2013 | doi: 10.5365/wpsar.2013.4.2.005

Phylogenetic relationships of H7N9 virus HA genes



Data provided by China CDC

Summary of A(H7N9) human cases reported to WHO since 27 September 2016

- 758 human cases of A(H7N9) virus infection (288 fatal) in 5th W
  - Total cases since 2013 = 1564 with 610 deaths
  - Chinese Taipei, Hong Kong Special Administrative Region and Macau Special Administrative Region reported travel-associated cases
  - CFR in reported cases = 39%
  - 68% exposed to live poultry or contaminated environments
  - 40 clusters confirmed, but not sustained human-to-human transmission

- The majority of A(H7N9) viruses detected in poultry and in humans are low pathogenic
- Since 2016 high pathogenic A(H7N9) viruses were detected in poultry and in human (28 cases)
- Most of H7N9 viruses recovered from patients were susceptible to antivirals of NA inhibitors

Available H7N9 CVVs provided by WHO CCs/ERLs

Table 5. Status of influenza A(H7N9) candidate vaccine virus development

Candidate vaccine virus	Type	Institution*	Available
A/Anhui/1/2013 (IDCDC-RG33A)	Reverse genetics	CDC	Yes
A/Anhui/1/2013 (NIBRG-268)	Reverse genetics	NIBSC	Yes
A/Anhui/1/2013 (NIIDRG-10.1)	Reverse genetics	NIID	Yes
A/Anhui/1/2013 (SJ005)	Reverse genetics	SJCRH	Yes
A/Shanghai/2/2013 (NIBRG-267)	Reverse genetics	NIBSC	Yes
A/Shanghai/2/2013 (CBER-RG4A)	Reverse genetics	FDA	Yes
A/Shanghai/2/2013 (IDCDC-RG32A)	Reverse genetics	CDC	Yes
A/Shanghai/2/2013 (IDCDC-RG32A.3)	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
✸ ● A/Guangdong/17SF003/2016-like	Reverse genetics	CCDC and NIBSC	Pending
✸ ● A/Hunan/2650/2016-like	Reverse genetics	CCDC	Pending
✸ ● A/Hong Kong/125/2017 (A/Hunan/2650/2016-like)	Reverse genetics	CDC and FDA	Pending

✸ Yangtze river delta-lineage viruses (predominant-lineage)

- ● (red) High-path virus
- ● (blue) Low-path virus

http://www.who.int/influenza/vaccines/virus/201703_zoonotic_vaccinevirusupdate.pdf?ua=1

To obtain CVVs and to use CVV for research and vaccine/diagnostic production, member states, industries, and stakeholders are required compliance of pandemic influenza preparedness (PIP)-FW

WHO | Pandemic Influenza | WHO: PIP Framework - Part | WHO | Pandemic Influe

http://www.who.int/influenza/pip/en/

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Pandemic Influenza Preparedness (PIP) Framework

What is the PIP Framework?

The PIP Framework brings together Member States, industry, other stakeholders and WHO to implement a global approach to pandemic influenza preparedness and response. Its key goals include: to improve and strengthen the sharing of influenza viruses with human pandemic potential; and to increase the access of developing countries to vaccines and other pandemic related supplies. The Framework was developed by Member States. It came into effect on 24 May 2011 when it was unanimously adopted by the Sixty-fourth World Health Assembly.

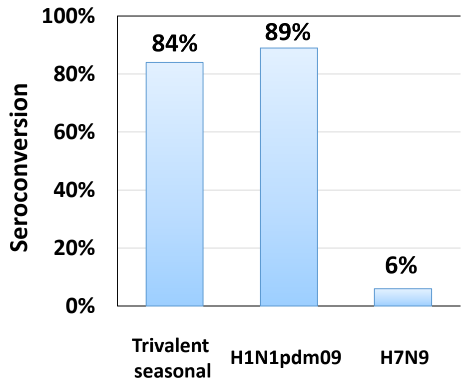
WHO PIP-Framework is for;

Virus sharing

Equally access to vaccines and other benefits

- **To get PIP-CVVs and reference viruses, members and stakeholders need to contract with WHO by S･MTA2**
  (https://youtu.be/RMsR9ZbYN7I)
- **Under the S･MTA2, members and stakeholders are required to response partnership contribution**
- **Partnership contribution is used for equal access of pandemic vaccine and for strengthen of pandemic preparedness**
  (https://youtu.be/7M031gg1AnQ)

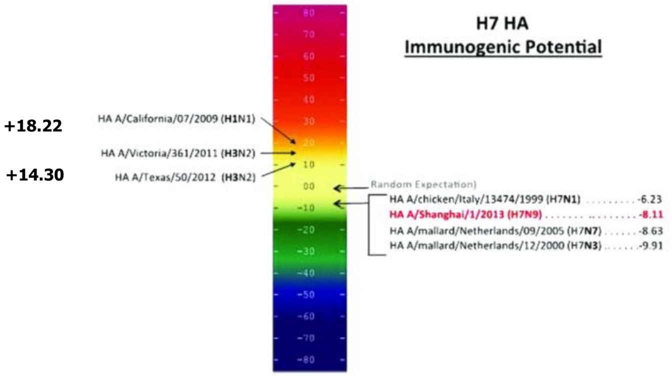
H7N9 vaccine is low immunogenic in humans



Split vaccine, Two doses (15 μg@)

Griffin MR et al. PLosOne (2011)
Goodwin et al. MMWR (2013)
http://www.Novartis.com
NEJM (2014)

Comparison of T cell epitope score among influenza vaccines

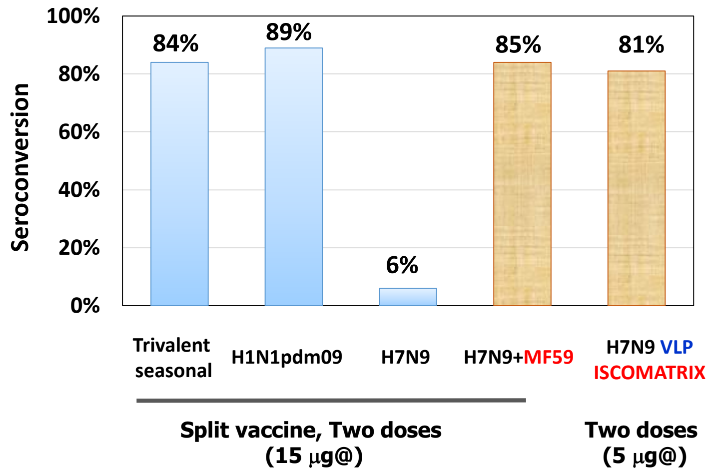


EpiMatrix protein score by immunoinformatic analysis:

Above zero: higher potential for immunogenicity
Blow zero: lower potential for immunogenicity

DeGroot AS et al. (2013) Human Vaccines& Immunotherapeutics 9: 5

Immunogenicity of H7N9 vaccine can be improved by adding suitable adjuvants



Griffin MR et al. PLosOne (2011)
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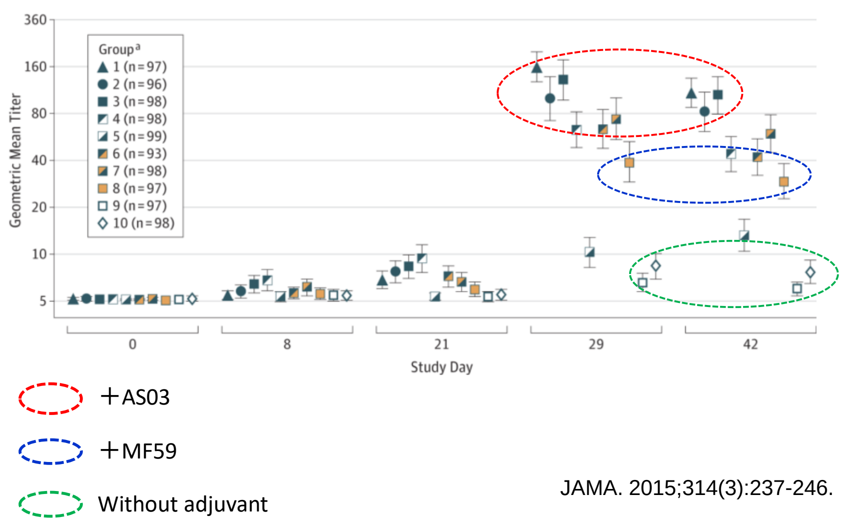
NEJM (2014)

Effect of Varying Doses of a Monovalent H7N9 Influenza Vaccine With and Without AS03 and MF59 Adjuvants on Immune Response in Randomized Clinical Trial



JAMA. 2015;314(3):237-246.


Thank you
Mt. Fuji from
Murayama-campus,
NIID, Tokyo