鳥インフルエンザの疫学について

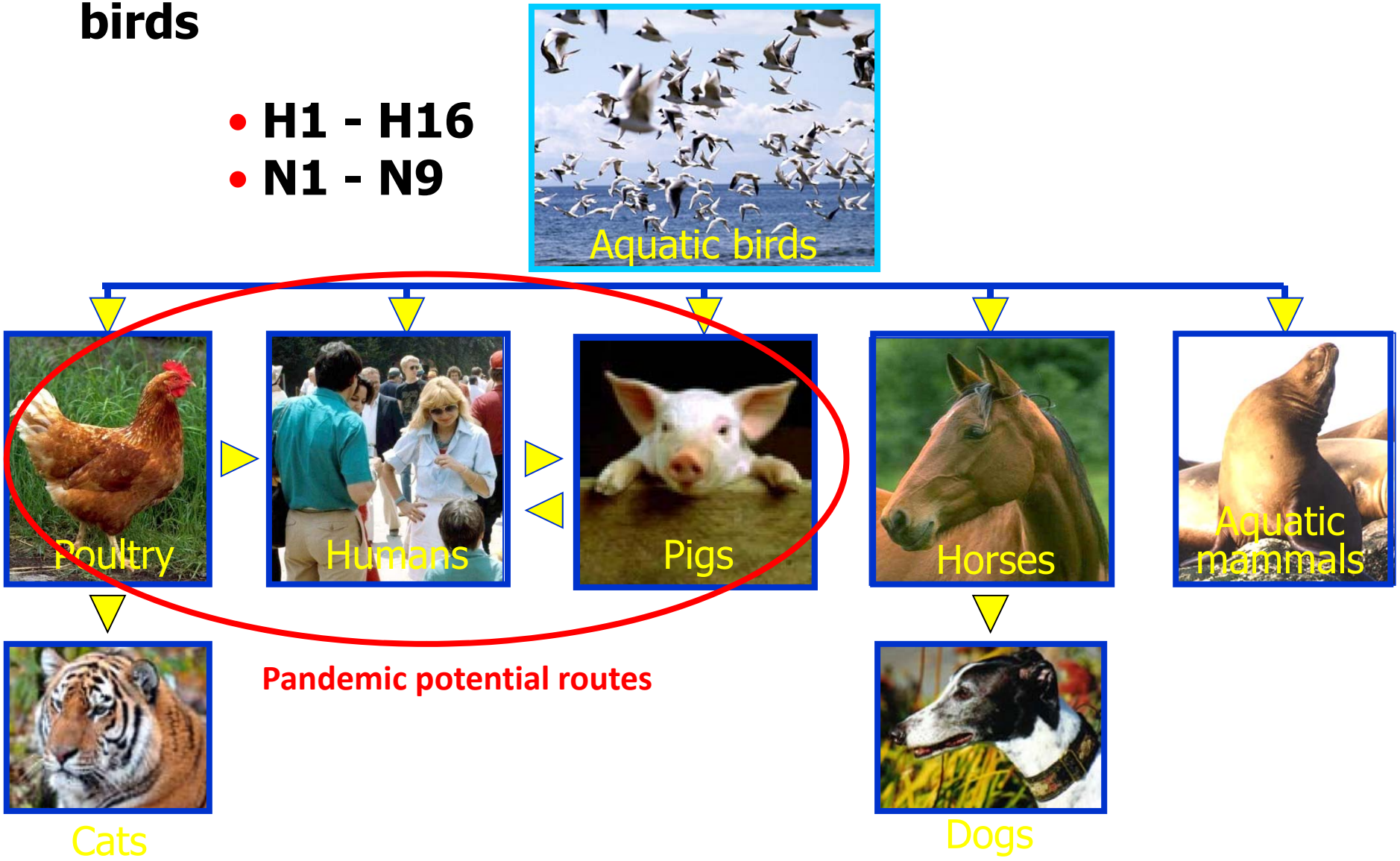
国立感染研インフルエンザウイルス研究センター
WHOインフルエンザ協力センター
センター長　小田切孝人

NIID
NATIONAL INSTITUTE OF INFECTIOUS DISEASES
国立感染症研究所

Influenza A Viruses

All influenza A virus subtypes are detected in aquatic birds

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



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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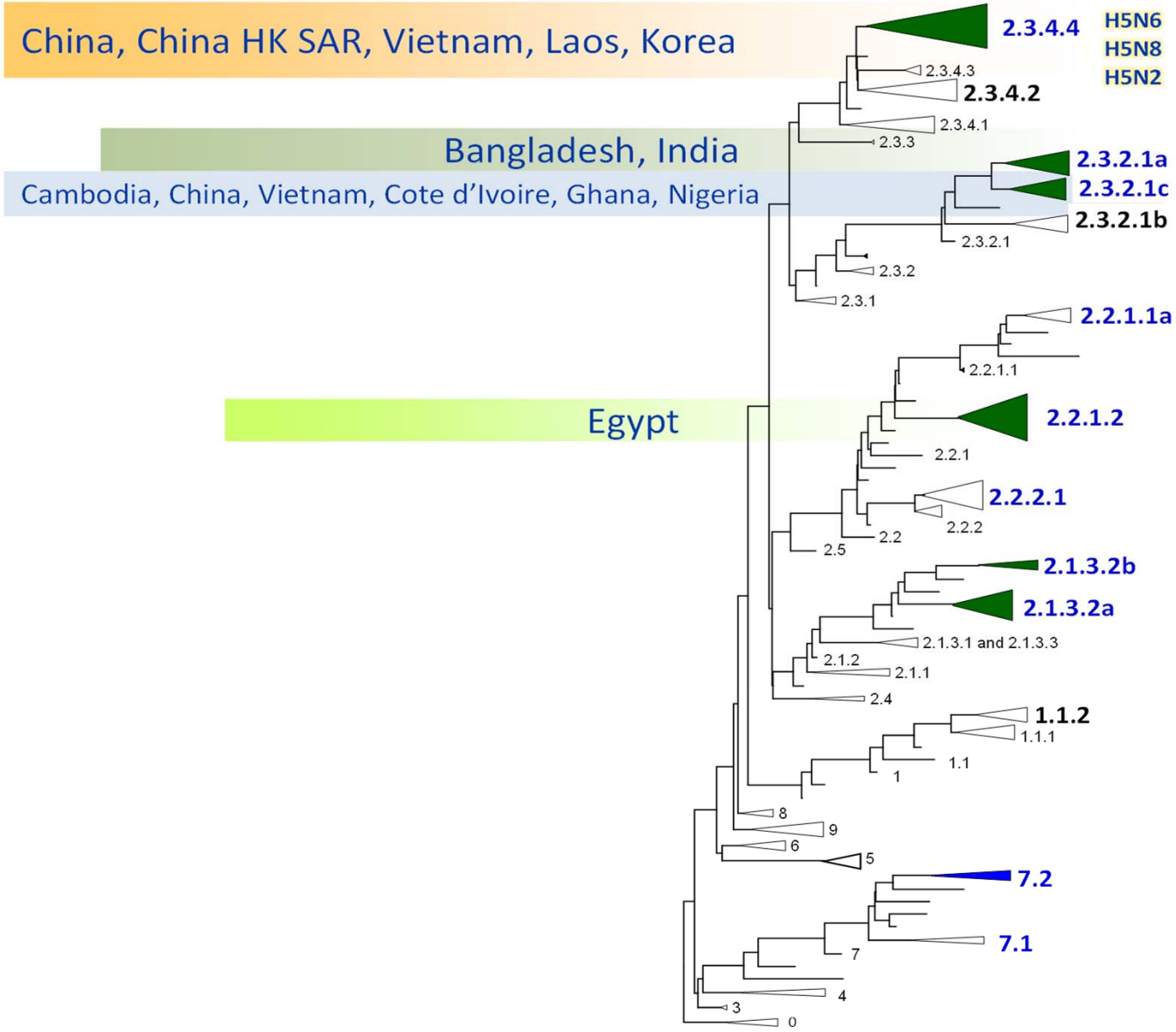
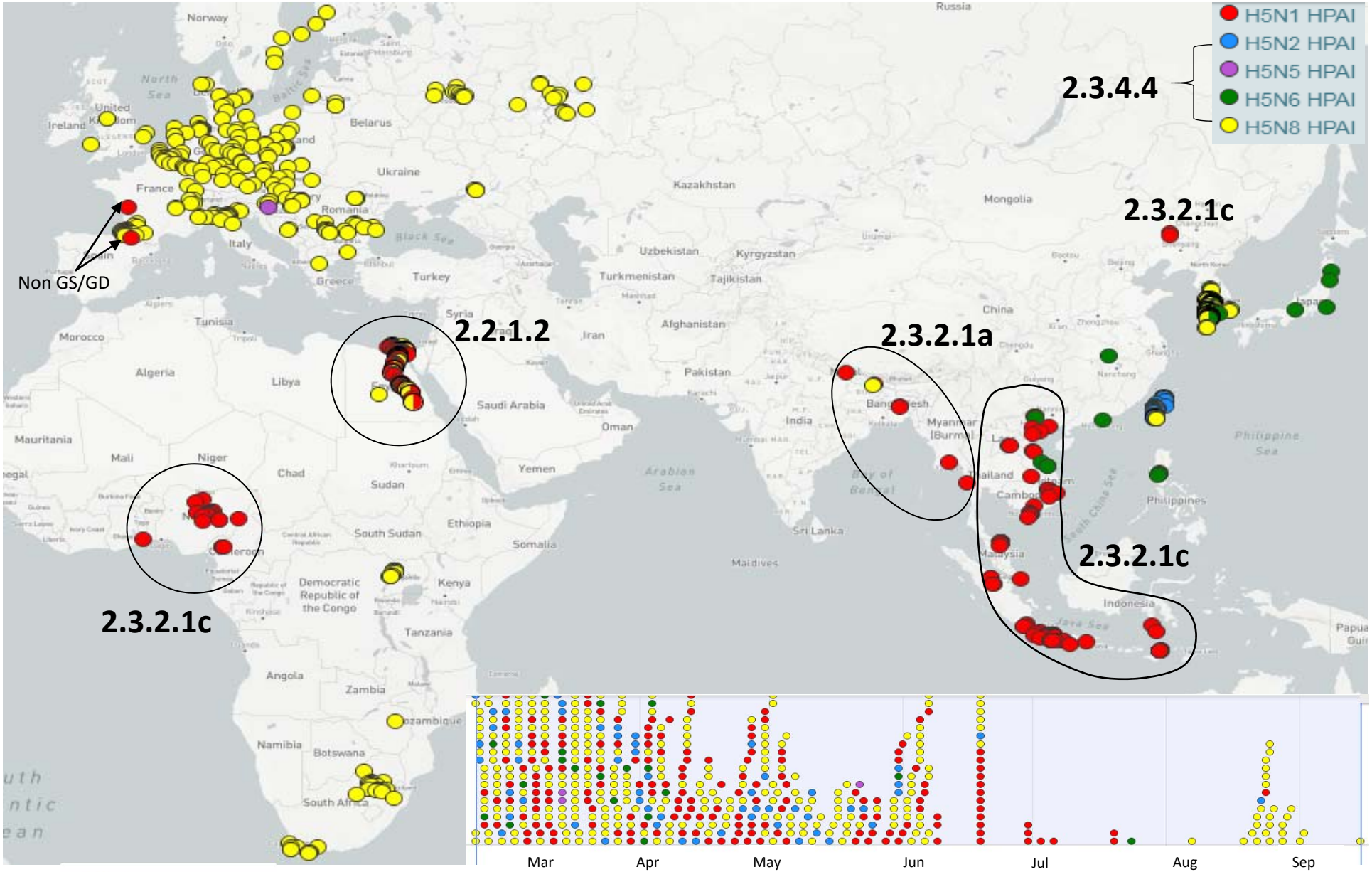
H5N8 (poultry, wild birds)

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

Evolution of A(H5) HA genes



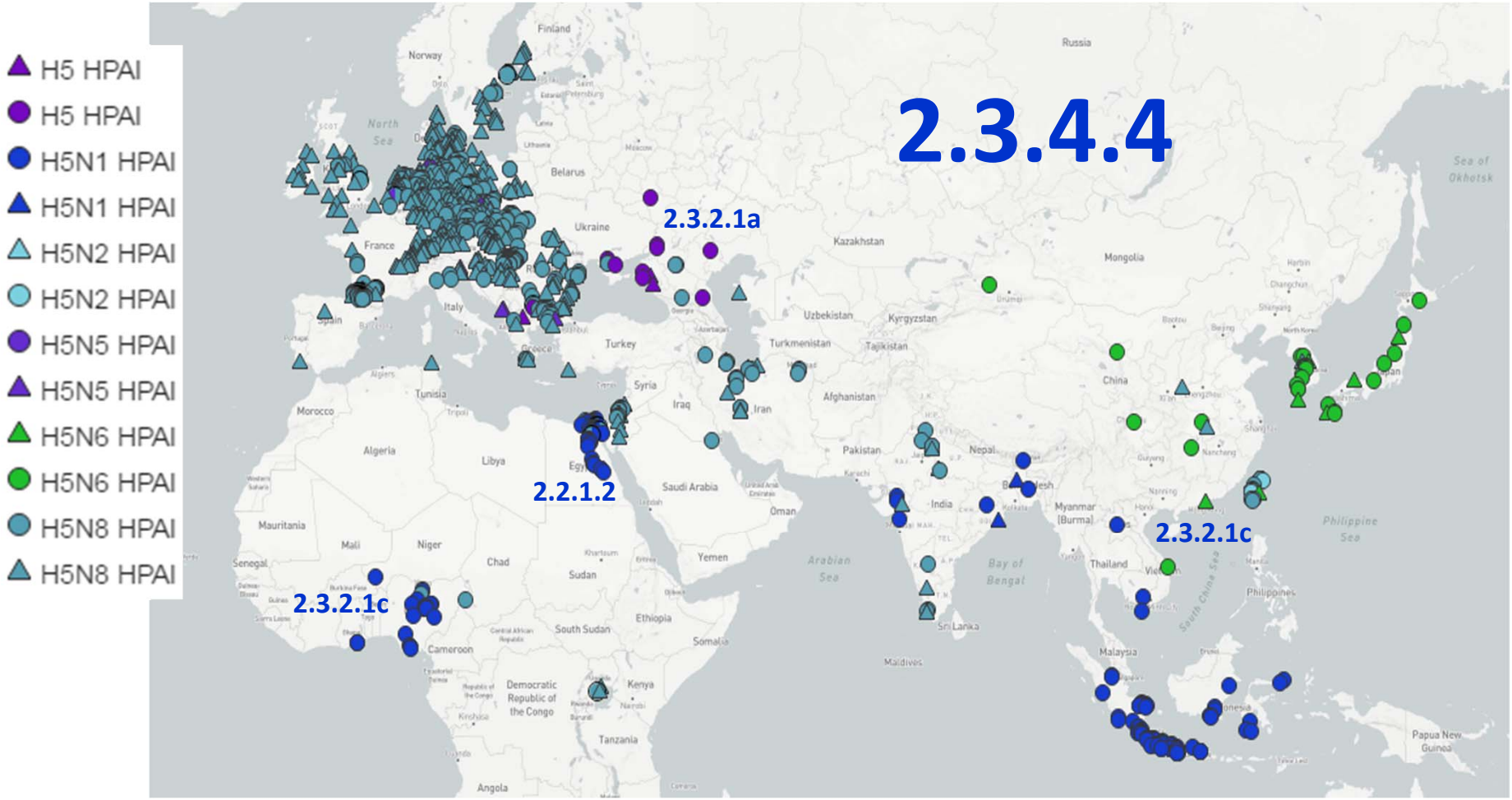
Global distribution of H5Nx virus clades



World Health Organization

WHO VCM for 2018 Southern H, Sept 28 Melbourne

A(H5) activity - birds since 27 September 2016



World Health Organization

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**

Fatality rate = 53%

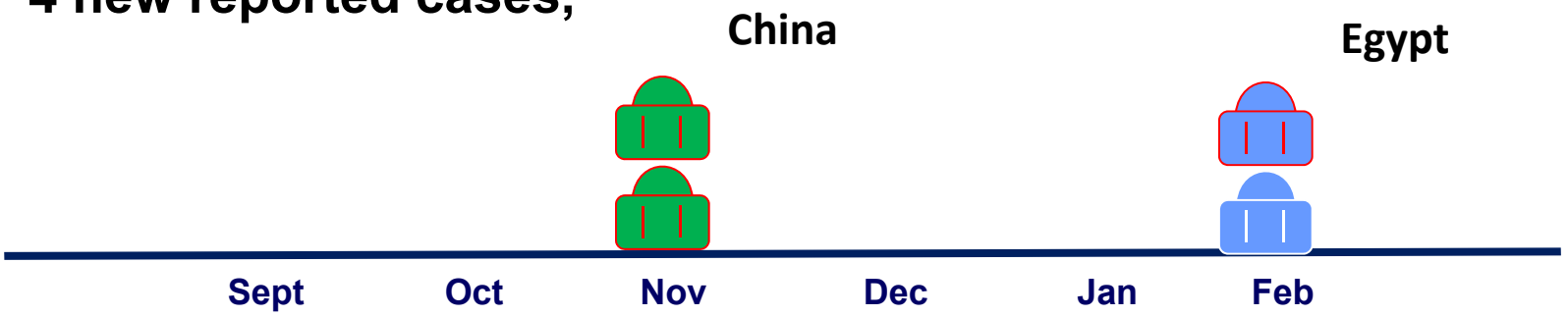
World Health Organization

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

Recent human infection cases with A(H5Nx) viruses

Sept. 2016～Feb. 2017

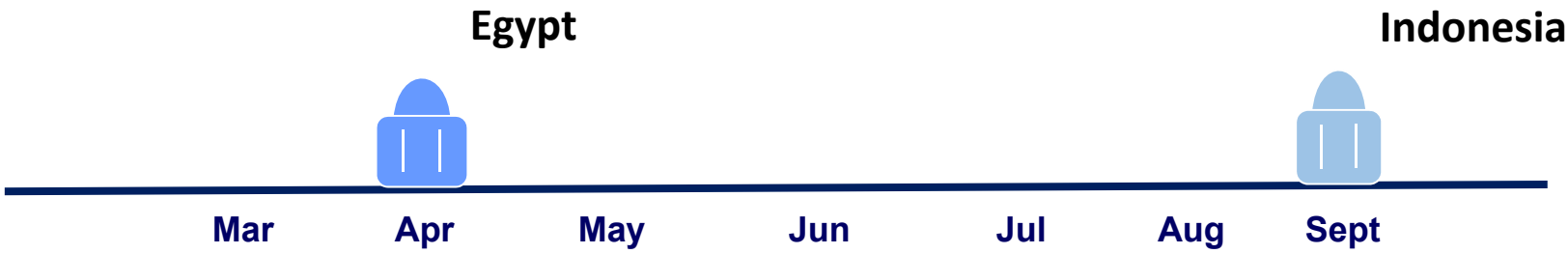
4 new reported cases,



Mar. ～Sept. 2017

2 new A(H5N1) cases

860 A(H5N1) cases/453 fatal
16 A(H5N6) cases/11 fatal



World Health Organization

WHO VCM for 2017-2018 Northern H, Fen Mar 2 Geneva
WHO VCM for 2018 Southern H, Sept 28 Melbourne

World Health Organization

WHO GISRS network

厚労省のインフルエンザウイルス系統保存事業

ワクチン候補野生株の入手

感染研GMP facilityでワクチン製造株の作製

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

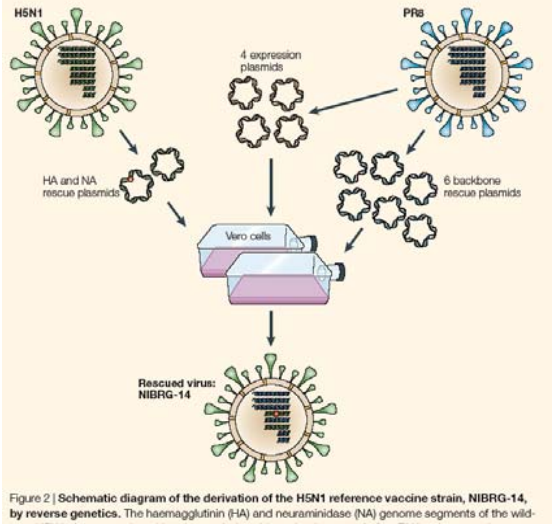


Figure 2 | **Schematic diagram of the derivation of the H5N1 reference vaccine strain, NIBRG-14, by reverse genetics.** The haemagglutinin (HA) and neuraminidase (NA) genome segments of the wild-

国内外のワクチン製造所
研究機関

無償配布

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

New CVV of A/H5N6 (cl 2.3.4.4) from zoonotic virus library in NIID is available for distribution

Candidate vaccine viruses in red

* CVV in preparation

16/17 season isolates in Japan in blue

Bold: HI reference and test viruses

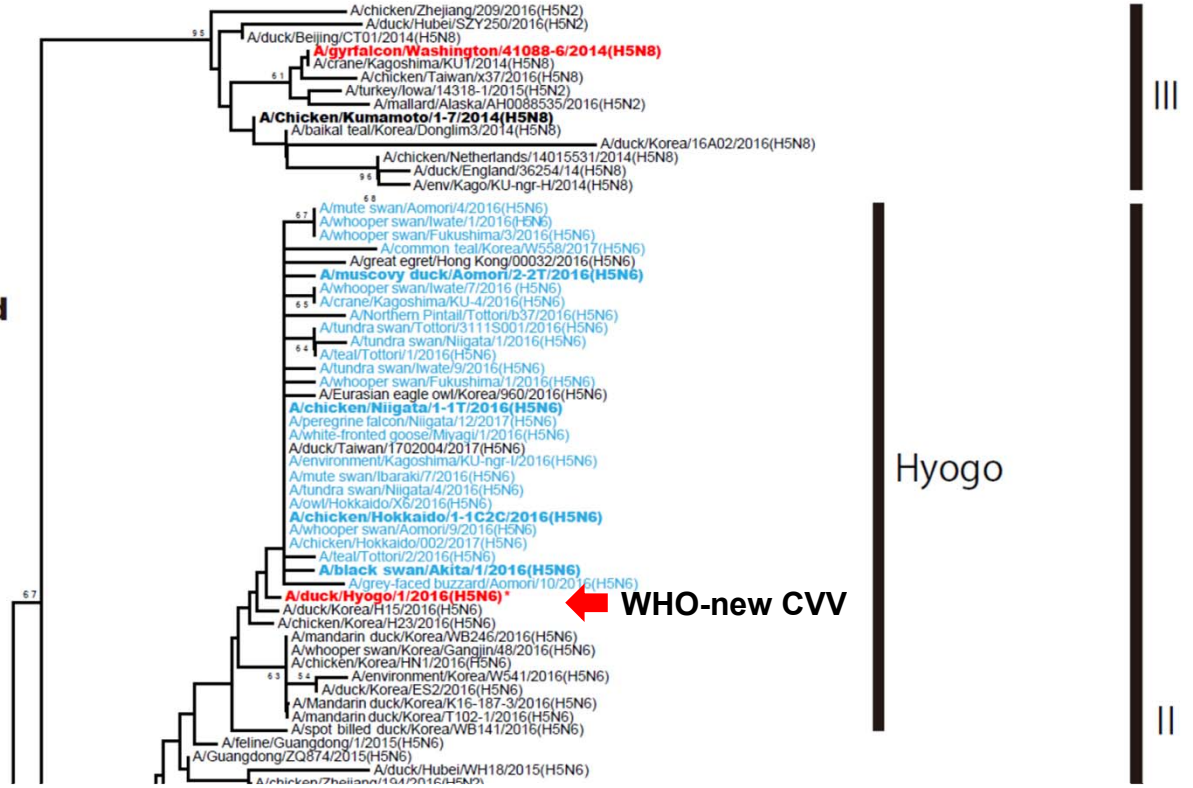


Table 1. Status of influenza A(H5) candidate vaccine virus development

Candidate vaccine viruses	Clade	Institution*	Available
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/duck/Hyogo/1/2016 (NIID-001) (H5N6)	2.3.4.4	NIID	Yes

* Institutions developing and/or distributing the candidate vaccine viruses:

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

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

- **Avian viruses**

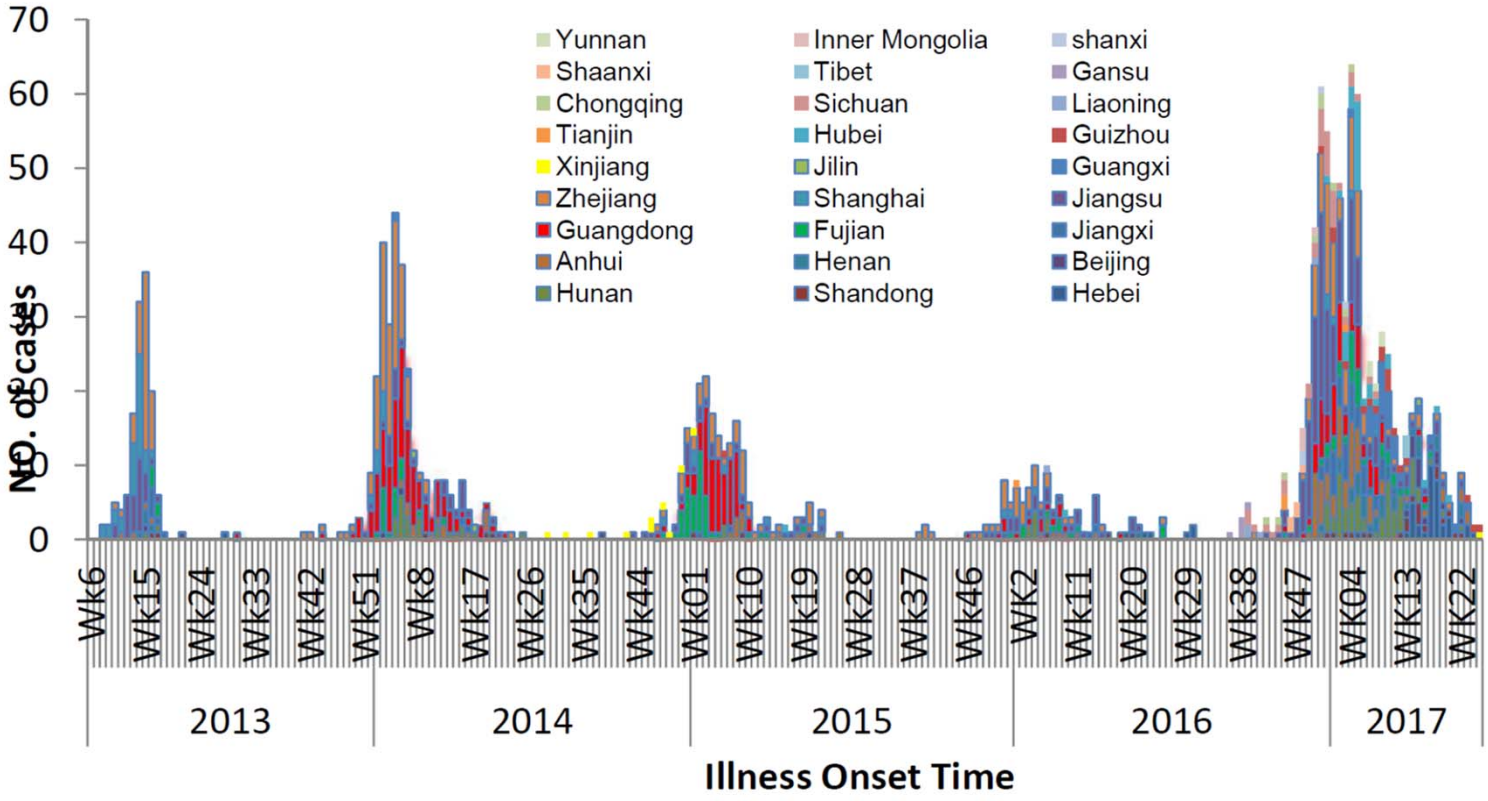
Since 2013,

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

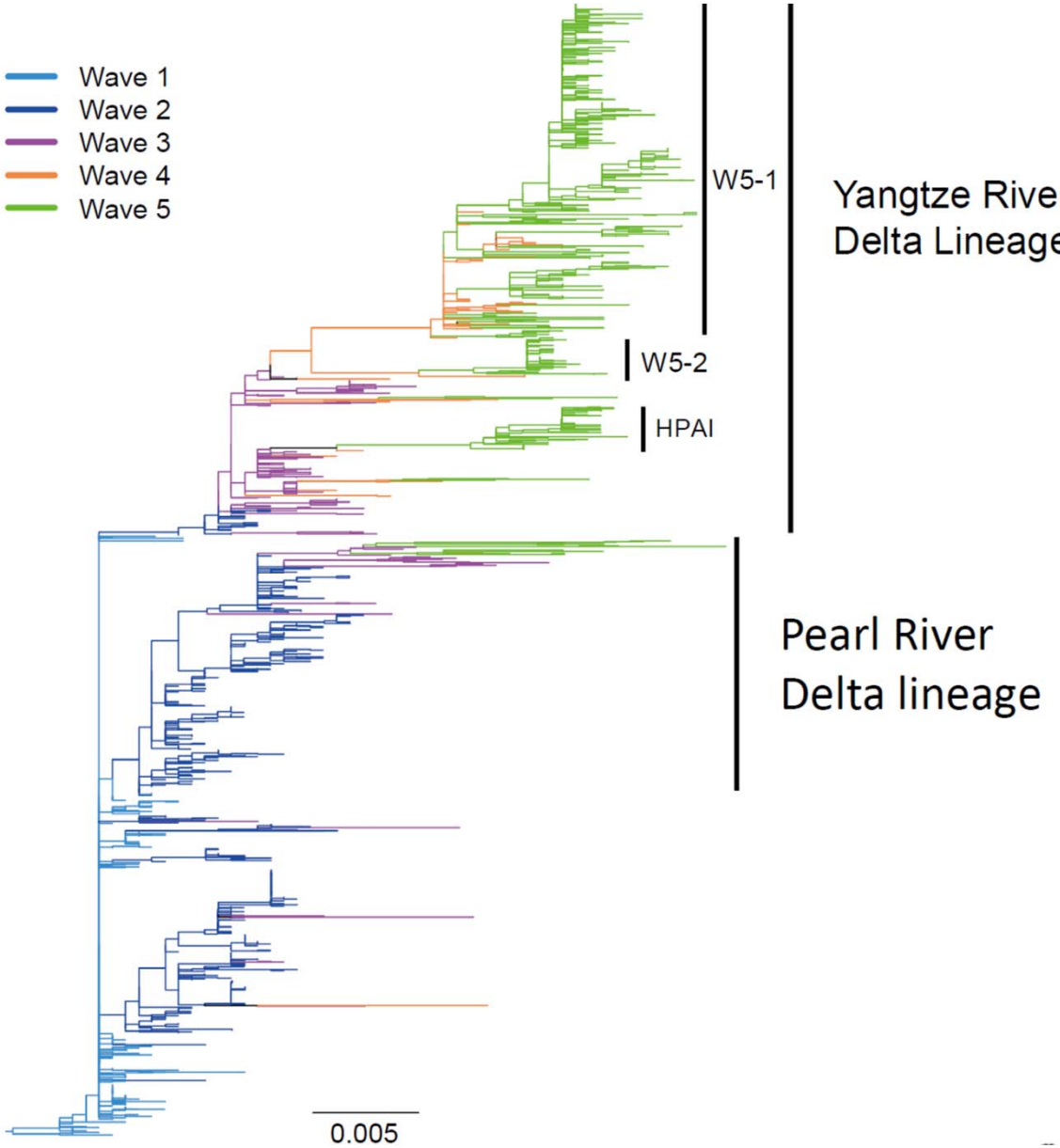
19 Feb, 2013 to 31 Aug, 2017 (N=1531)

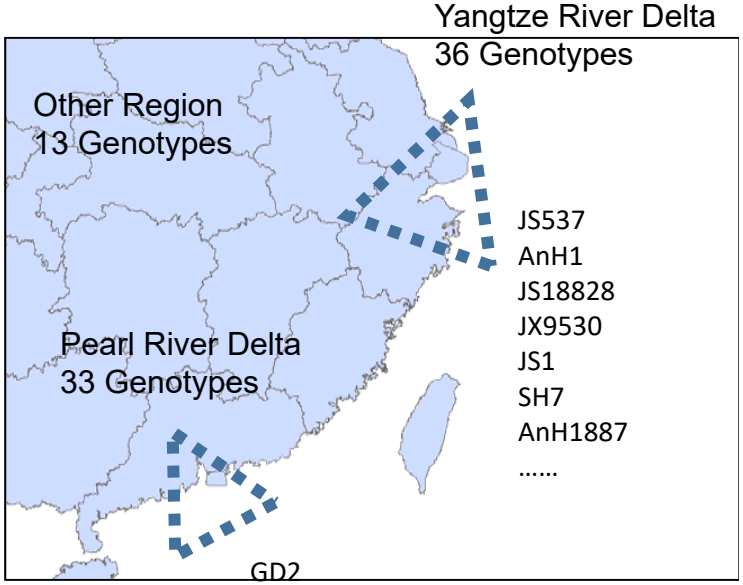


Province	First wave (2013.2~)		Second wave (2013.10~)		Third wave (2014.10~)		Forth wave (2015.10~)		Fifth wave (2016.10~)		Cumulative counts		
	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Number of cases	Deaths	Fatality rate(%)
Total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

Data provided by China CDC

Phylogenetic relationships of H7N9 virus HA genes





Data provided by China CDC

Family clusters of human H7N9 cases

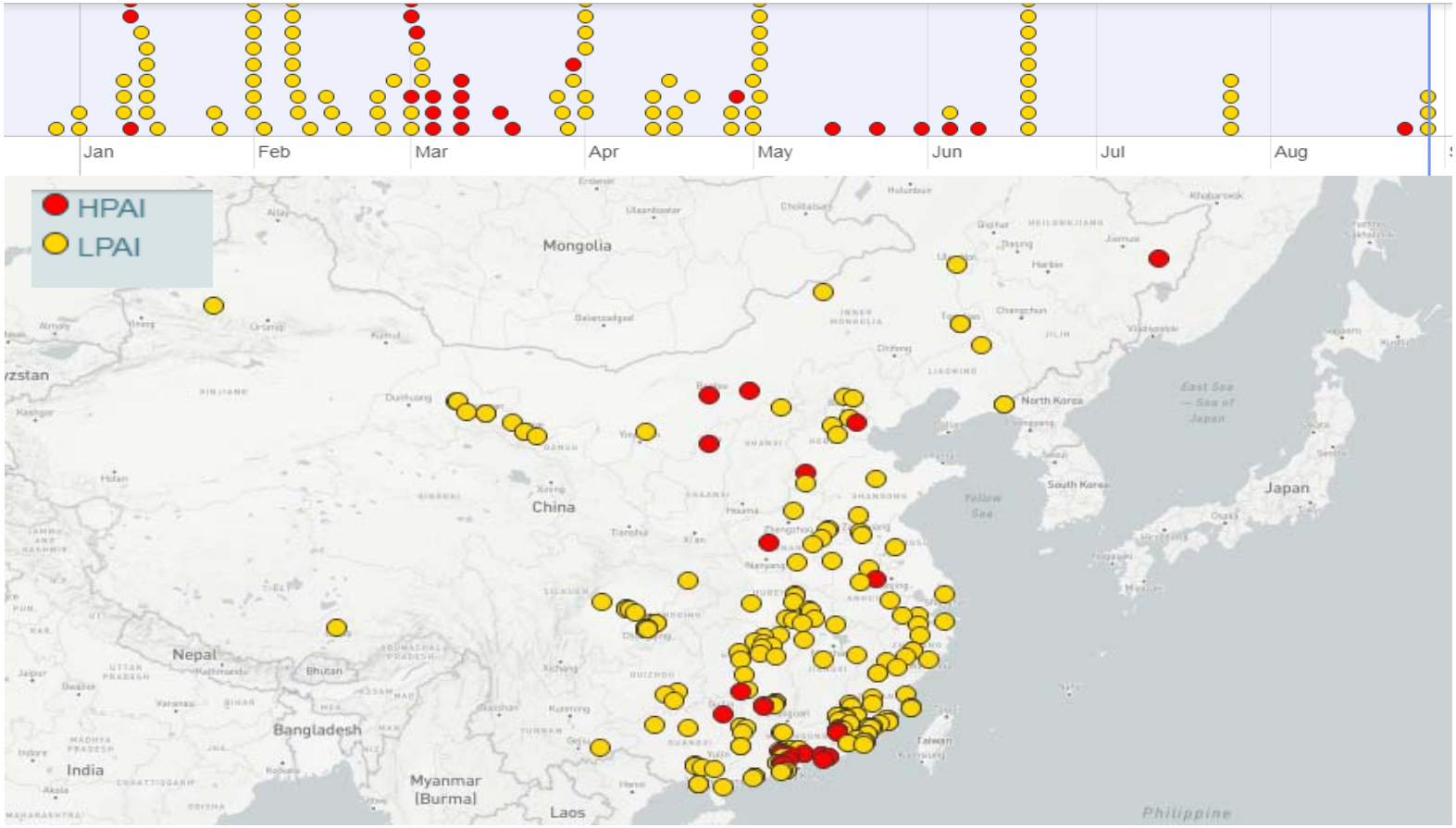
Route of transmission	NO.
Possibility of Human-to-human transmission	19+1
Co-exposure	3+4
Possibility of Human-to-human transmission or Co-exposure	9+4
Total	40

*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**

HPAI-H7N9 viruses emerged in 2017 and cocirculated with LPAI-H7N9 viruses in China



- 758 human cases of A(H7N9) virus infection (288 fatal) in 5th W
- Total cases since 2013 = 1564 with 610 deaths (fatality rate = 39%)
- Since 2017 HPAI-H7N9 viruses were detected in poultry and in 28 human cases (14 fatal)
- Most of LPAI- and HPAI-H7N9 viruses are susceptible to antiviral of NAIs

Cell Host & Microbe
Article

HPAI-H7N9 isolated from humans

A Highly Pathogenic Avian H7N9 Influenza Virus Isolated from A Human Is Lethal in Some Ferrets Infected via Respiratory Droplets

Masaki Imai,[1,8,*] Tokiko Watanabe,[1,8] Maki Kiso,[1,8] Noriko Nakajima,[2,8] Seiya Yamayoshi,[1,8] Kiyoko Iwatsuki-Horimoto,[1,8] Masato Hatta,[3,8] Shinya Yamada,[1] Mutsumi Ito,[1] Yuko Sakai-Tagawa,[1] Masayuki Shirakura,[4] Emi Takashita,[4] Seiichiro Fujisaki,[4] Ryan McBride,[5] Andrew J. Thompson,[5] Kenta Takahashi,[2] Tadashi Maemura,[1] Hiromichi Mitake,[1] Shiho Chiba,[3] Gongxun Zhong,[3] Shufang Fan,[3] Kohei Oishi,[1] Atsuhiro Yasuhara,[1] Kosuke Takada,[1] Tomomi Nakao,[1] Satoshi Fukuyama,[1] Makoto Yamashita,[1] Tiago J.S. Lopes,[1,3] Gabriele Neumann,[3] Takato Odagiri,[4] Shinji Watanabe,[4] Yuelong Shu,[6] James C. Paulson,[5] Hideki Hasegawa,[2] and Yoshihiro Kawaoka[1,3,7,9,*]

HPAI-H7N9 isolated from chickens

Open
ORIGINAL ARTICLE

Cell Research (2017) :1-13.
www.nature.com/cr

H7N9 virulent mutants detected in chickens in China pose an increased threat to humans

Jianzhong Shi[1,*], Guohua Deng[1,*], Huihui Kong[1,*], Chunyang Gu[1,*], Shujie Ma[1,*], Xin Yin[1,*], Xianying Zeng[1], Pengfei Cui[1], Yan Chen[1], Huanliang Yang[1], Xiaopeng Wan[1], Xiurong Wang[1], Liling Liu[1], Pucheng Chen[1], Yongping Jiang[1], Jinxiong Liu[1], Yuntao Guan[1], Yasuo Suzuki[2], Mei Li[1], Zhiyuan Qu[1], Lizheng Guan[1], Jinkai Zang[1], Wenli Gu[1], Shuyu Han[1], Yangming Song[1], Yuzhen Hu[1], Zeng Wang[1], Linlin Gu[1], Wenyu Yang[1], Libin Liang[1], Hongmei Bao[1], Guobin Tian[1], Yanbing Li[1], Chuanling Qiao[1], Li Jiang[1], Chengjun Li[1], Zhigao Bu[1], Hualan Chen[1]

Available H7N9 CVVs provided by WHO CCs/ERLs

Table 2. 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
IDCDC-RG56B (A/Hong Kong/125/2017-like)	Reverse genetics	CDC	Yes
Candidate vaccine viruses in preparation	**Type**	**Institution**	**Availability**
A/Guangdong/17SF003/2016-like	Reverse genetics	CCDC, CDC, FDA, NIBSC	Pending
A/Hunan/2650/2016-like	Reverse genetics	CCDC	Pending

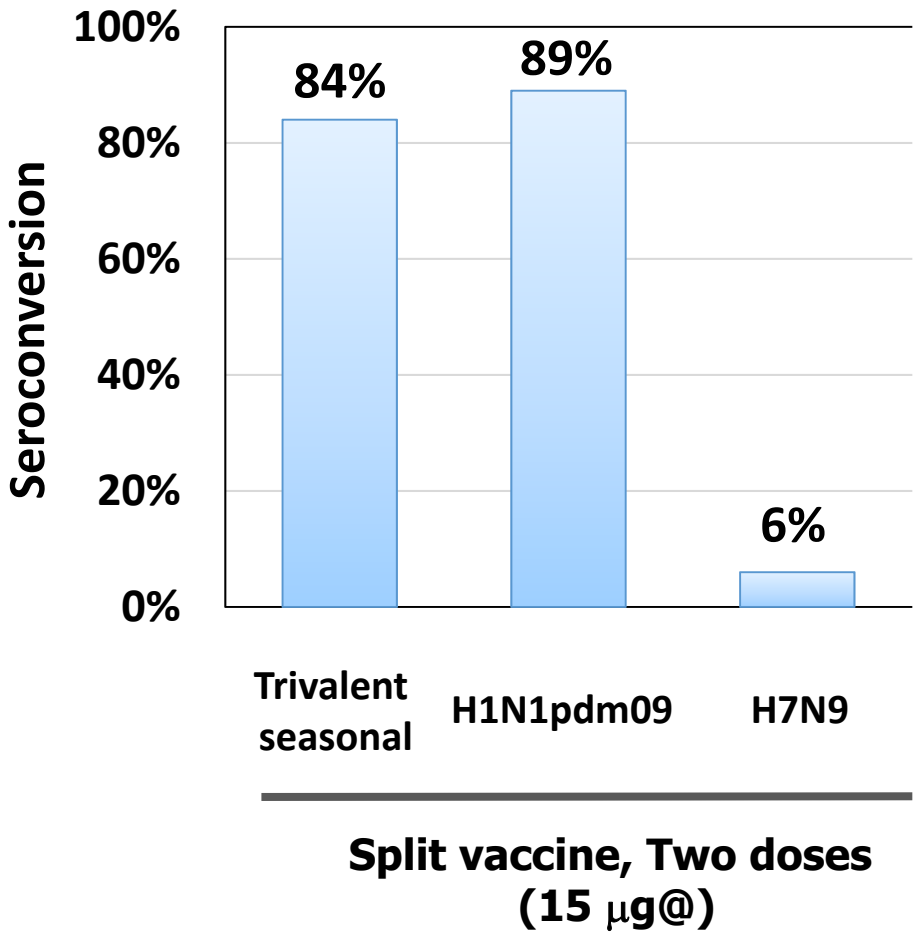
*** Institutions distributing the candidate vaccine viruses:**

Yangtze river delta-lineage viruses (predominant-lineage)

- High-path virus
- Low-path virus

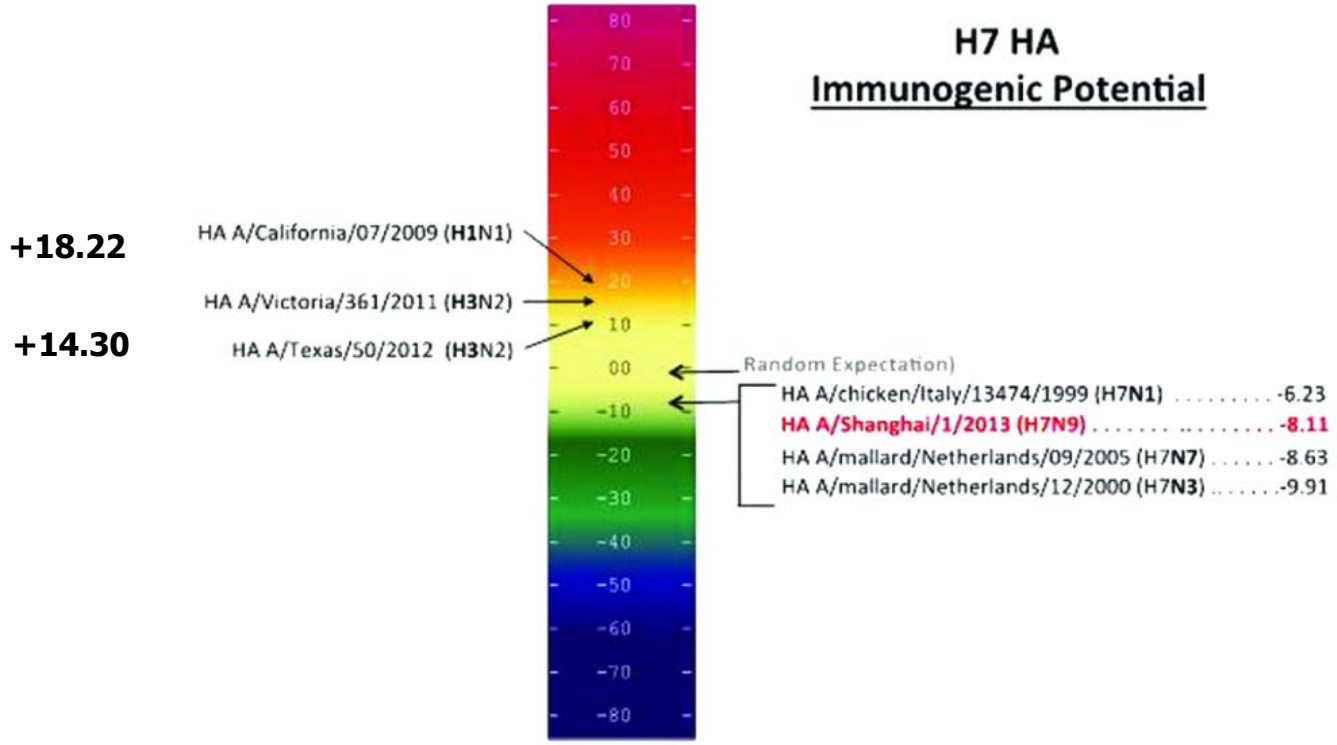
http://www.who.int/influenza/vaccines/virus/201709_zoonotic_vaccinevirusupdate.pdf?ua=1

H7N9 vaccine is low immunogenic in humans



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

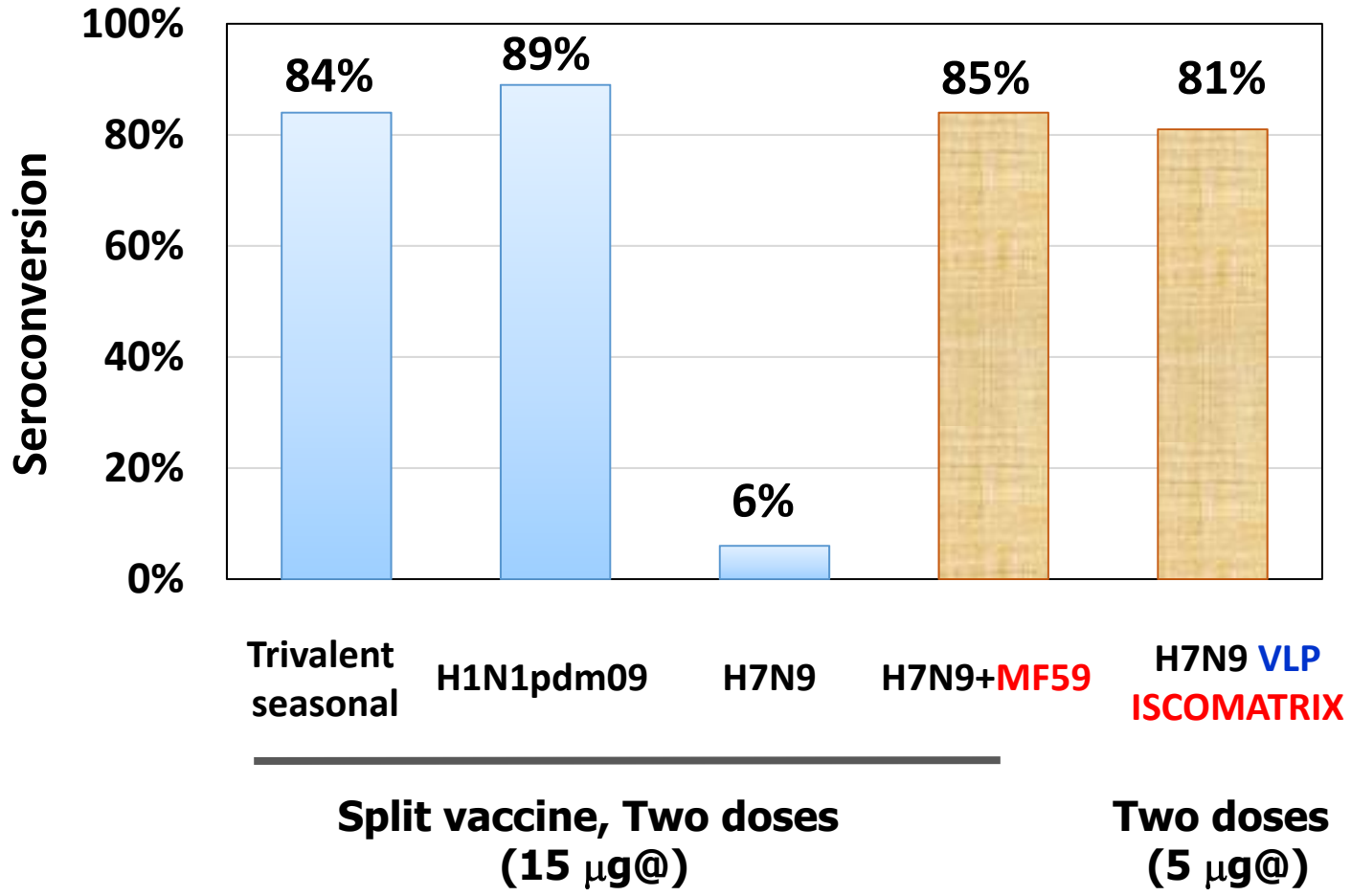


EpiMatrix protein score by immunoinformatic analysis:

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

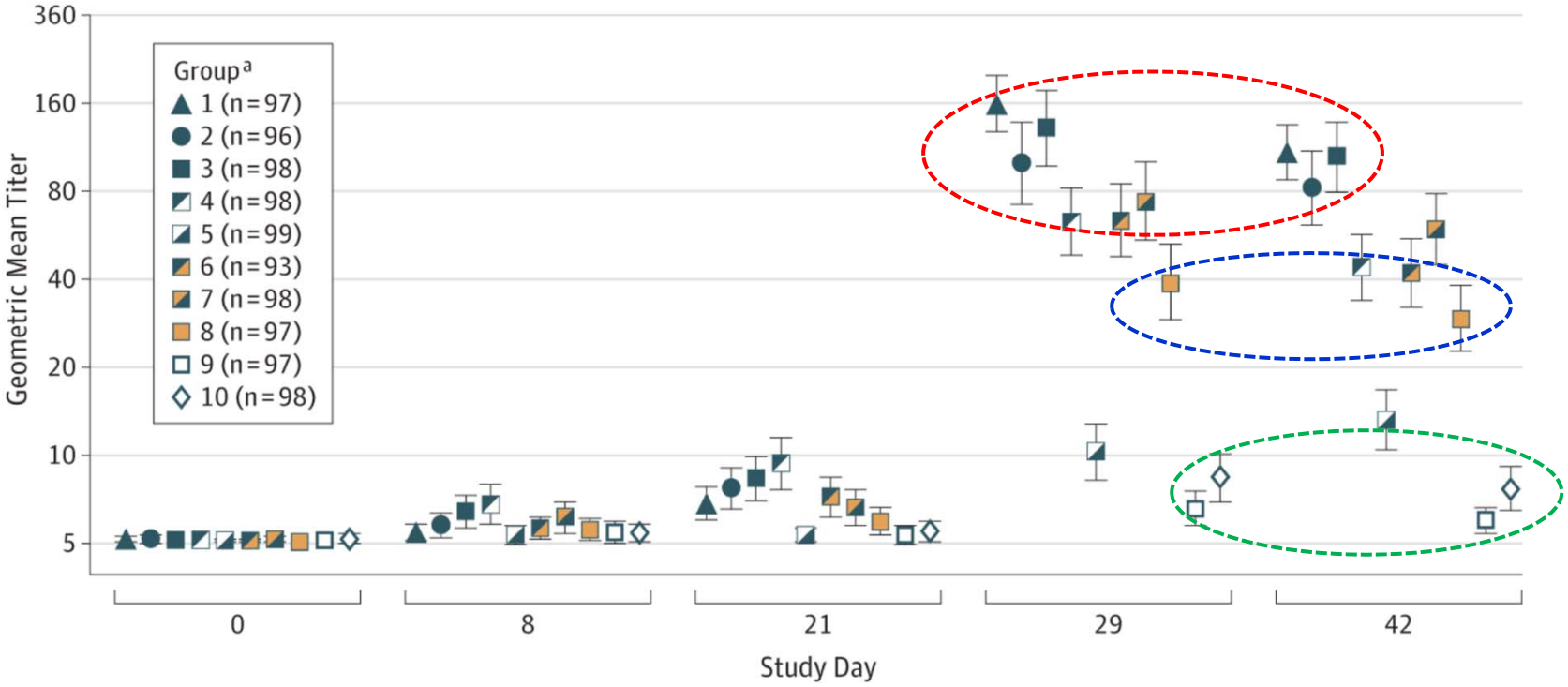
DeGroot AS et al. (2013) Human Vaccines& Immunotherapeutics 9: 5

Immunogenicity of H7N9 vaccine can be improved by adding suitable adjuvants



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



+AS03

+MF59

Without adjuvant

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


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