Incorporating virologic data into seasonal and pandemic influenza vaccines

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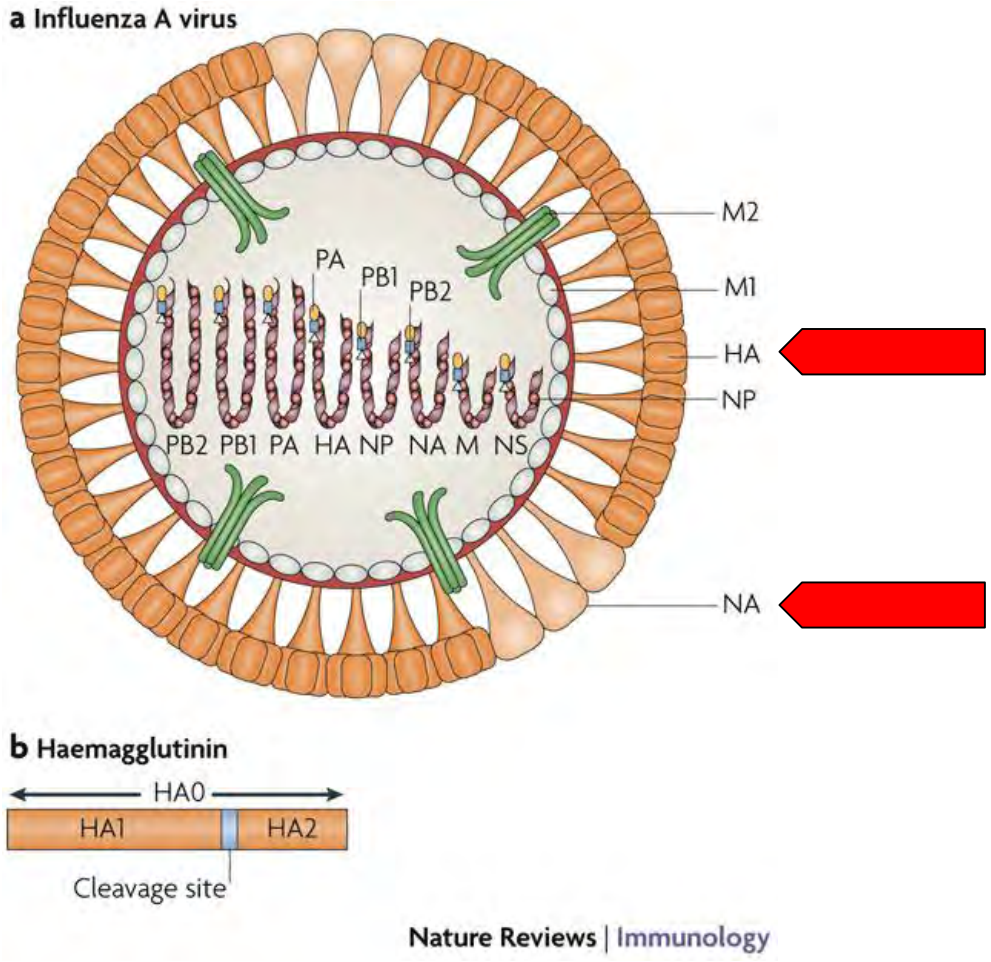
The haemagglutinin and neuraminidase are the main targets of the protective antibody response



nature REVIEWS IMMUNOLOGY

Currently licensed influenza vaccines

Principle: Induction of a protective immune response against the haemagglutinin protein

- Based on serum antibody response to the hemagglutinin (HA) protein
- Offered as trivalent or quadrivalent formulations to cover epidemic influenza A and B viruses
  - Trivalent vaccines contain A/H1N1, A/H3N2 and one B strain
  - Quadrivalent vaccines contain A/H1N1, A/H3N2, B Yamagata-lineage and B Victoria-lineage viruses.

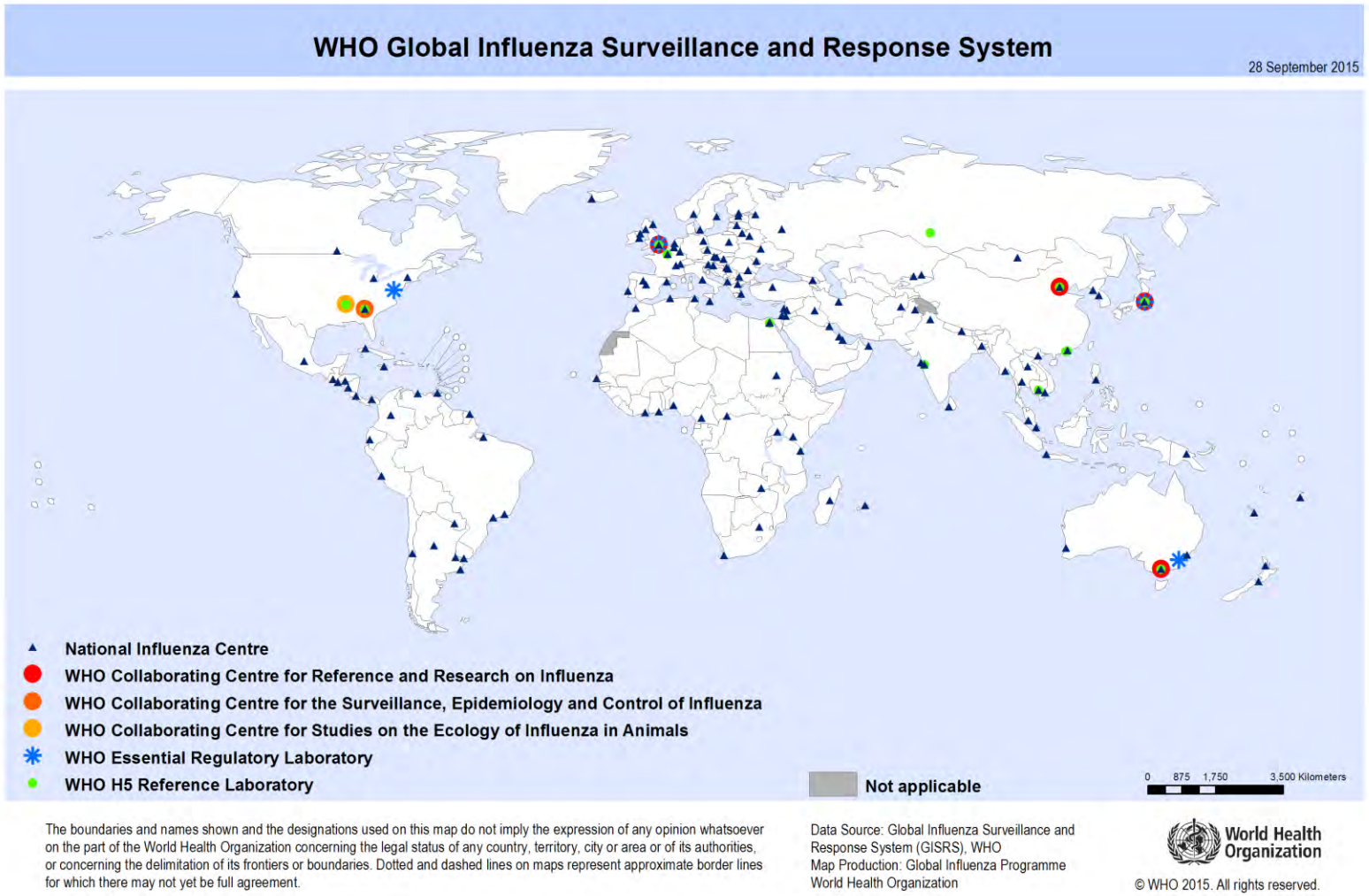
Antigenic Drift

- Gradual alteration of the influenza surface proteins (mainly HA) within a subtype, resulting in the inability of antibody to previous strains to neutralize new viruses.
- Antigenic drift results from point mutations in the HA and NA genes.
- The composition of the influenza vaccine has to be updated annually as a consequence of antigenic drift.

Key principles underlying licensed influenza vaccines

- Influenza vaccines mediate protection through antibody directed at the haemagglutinin (HA). Therefore, antigenic drift often necessitates an update in the vaccine composition.
- Antigenic changes are the result of genetic drift, which can be monitored by sequencing the HA but genetic drift doesn't always lead to antigenic change.
- >95% of the global vaccine supply is manufactured in embryonated eggs

WHO GISRS network



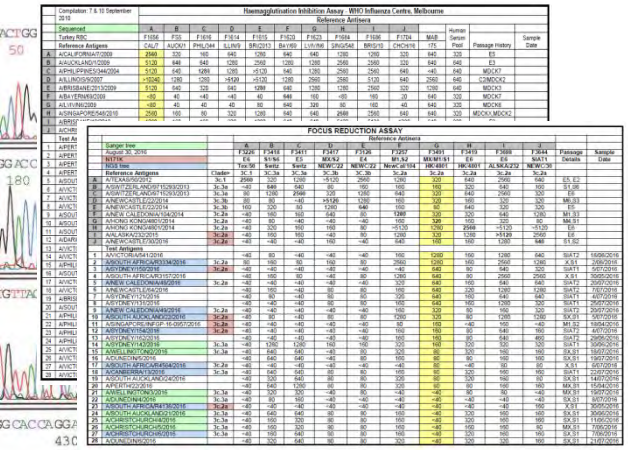
Oldest network in WHO: begun in 1952, 144 NIC's in 114 countries, 5 WHO CC's for human influenza + 1 for animal influenza + 4 essential regulatory labs,

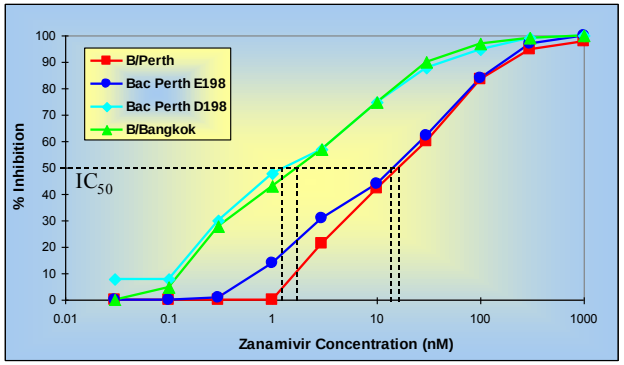
A variety of information is used to select influenza vaccine viruses

Comparative titres by haemagglutination inhibition & VN assays

Sequence data
- HA & NA
- Some full genome

Antiviral drug resistance
- Oseltamivir
- Zanamivir
- Other compounds





Also used
- Epi data
- **Vaccine effectiveness data**
- Human Serology
- Structural data
- Modellers predictions

Candidate vaccine viruses (CVV's)

Other information

Growth in eggs/qualified cells

WHO vaccine strain recommendation process

A WHO committee meets twice a year to recommend suitable strains to be included in the vaccine for the upcoming influenza season:

- northern hemisphere winter (decided in February)
- southern hemisphere winter (decided in September)

Surveillance and vaccine candidate data are compiled and shared between WHO Collaborating Centres.

A vaccine strain change is recommended only if the following are widely observed amongst circulating viruses:

Antigenic changes
Marked changes in the antigenic profile in 2-way HI assays compared with previous vaccine strains

+

Sequence changes
Changes in HA gene sequences, especially at known antigenic and receptor-binding sites

+

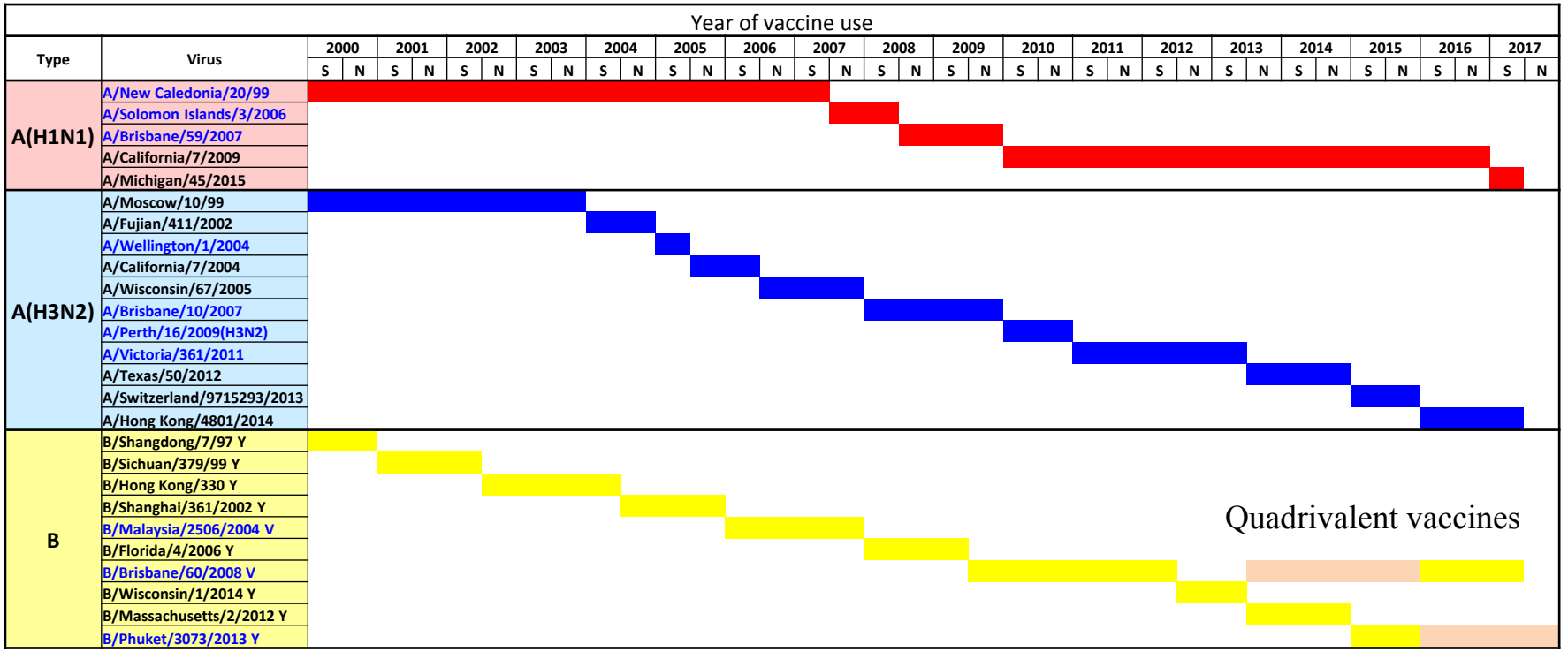
Serology changes
Poor recognition by serum panels from human recipients of the previous vaccine

+

Availability of suitable candidate vaccine strains

National authorities make the final decision for their country.
Vaccine production takes about 6 months

WHO prototype vaccine viruses 2000-2017 (egg isolates)



Viruses in blue font=Prototype vaccine viruses isolated at Melbourne CC

Vaccine composition recommended for 2018/2019 seasons

2018 Southern hemisphere

- H1N1pdm09: A/Michigan/45/2015-like
- H3N2: A/Singapore/INFIMH 16-0019/2016-like*

Quadrivalent vaccine:
B/Yam: B/Phuket/3073/2013-like
B/Vic: B/Brisbane/60/2008-like

Trivalent vaccine:
B/Yam: B/Phuket/3073/2013-like*

* Changed from 2017 recommendations

2018/19 Northern hemisphere

- H1N1pdm09: A/Michigan/45/2015-like
- H3N2: A/Singapore/INFIMH 16-0019/2016-like*

Quadrivalent vaccine:
B/Yam: B/Phuket/3073/2013-like
B/Vic: B/Colorado/06/2017-like*

Trivalent vaccine:
B/Vic: B/Colorado/06/2017-like*

* Changed from 2017/2018 recommendations

Key challenges with seasonal influenza vaccines

Antigenic drift necessitates an update in the vaccine composition

- *Challenge: About 50% of A/H3N2 viruses cannot be isolated or characterised in HAI tests*
- *Potential solution: A focus reduction assay (FRA) as an alternative to the HAI assay - but it is not high throughput*

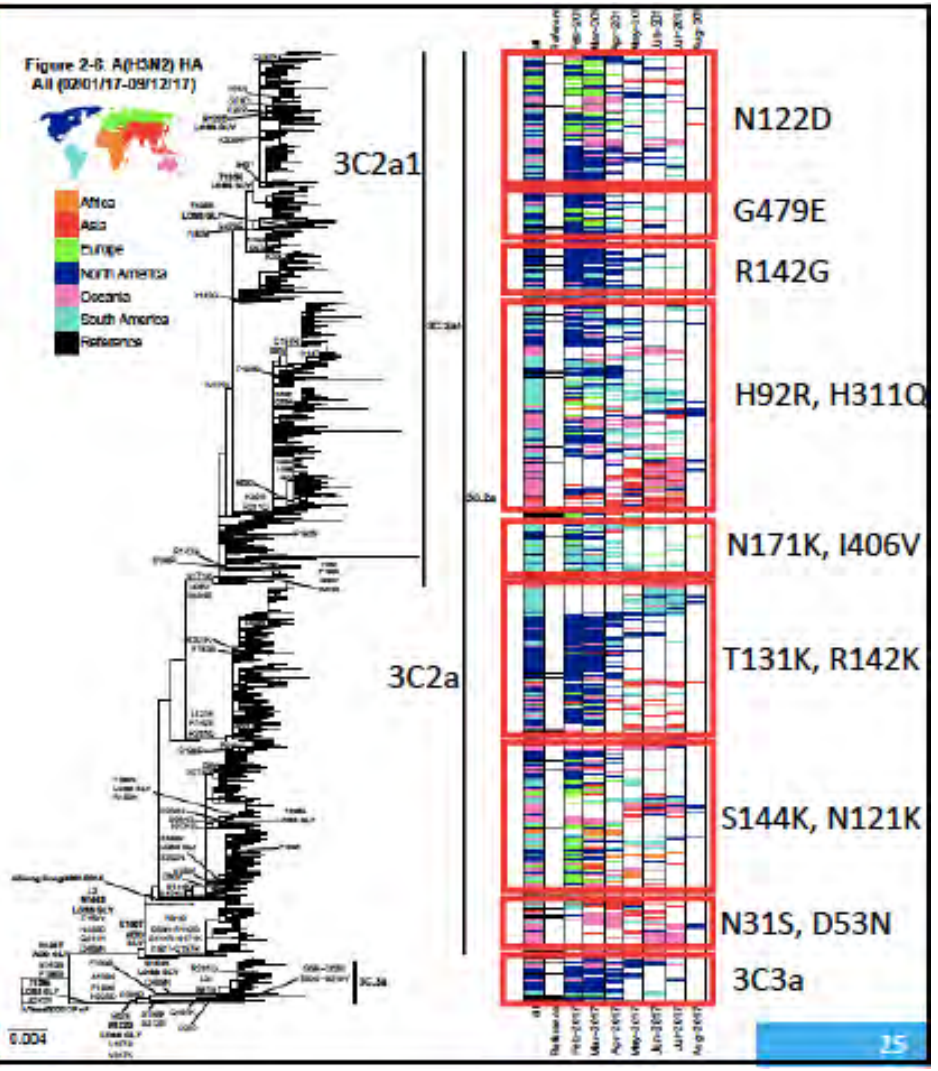
Genetic drift

- *Challenge: Enormous genetic diversity with several clades and subclades co-circulating but few clades are associated with antigenic difference in HAI assays*

World Health Organization

H3N2 HA - globally

- **Currently circulating H3N2 viruses are genetically very diverse and several clades are circulating in varying proportions around the world**
- 3C2a1 have a least 5 clades co-circulating
- 3C2a viruses outside this group have at least 3 clades currently circulating



Key challenges with seasonal influenza vaccines

Manufacture in embryonated eggs

- *Challenge: Adaptation to growth in eggs induces mutations in the HA. Part of the antibody response to egg-grown vaccines can be directed against egg-adaptation changes that are not present in cell-grown viruses*
- *Potential solutions:*
  - *Isolate and characterise more egg isolates in order to select viruses without signature egg-adaptation changes for vaccine development*
  - *Cell grown vaccine*
  - *Recombinant HA vaccine*

Antigenic analysis of virus isolates: Australia May-Sept 2017

Influenza strain	Assay	Number of viruses	Cell propagated reference strain	
			Like	Low-reacting
A/H1N1pdm09	HAI	46	46	0
A/H3N2	HAI	90	60	7
	FRA		31	0
A/H3N2: Insufficient titer for HAI	FRA	98	44	0
B/Victoria lineage	HAI	6	3	1
B/Yamagata lineage	HAI	90	52	0

Sullivan et al *Eurosurveillance* 2017: 22(43): pii=17-00707

Antigenic analysis of virus isolates: Australia May-Sept 2017

Influenza strain	Assay	Number of viruses	Cell propagated reference strain		Egg propagated reference strain	
			Like	Low-reacting	Like	Low-reacting
A/H1N1pdm09	HAI	46	46	0	46	0
A/H3N2	HAI	90	60	7	45	22
	FRA		31	0	28	0
A/H3N2: Insufficient titer for HAI	FRA	98	44	0	32	12
B/Victoria lineage	HAI	6	3	1	0	4
B/Yamagata lineage	HAI	90	52	0	50	2

Sullivan et al *Eurosurveillance* 2017: 22(43): pii=17-00707

Interim vaccine effectiveness: Australia May-Sept 2017

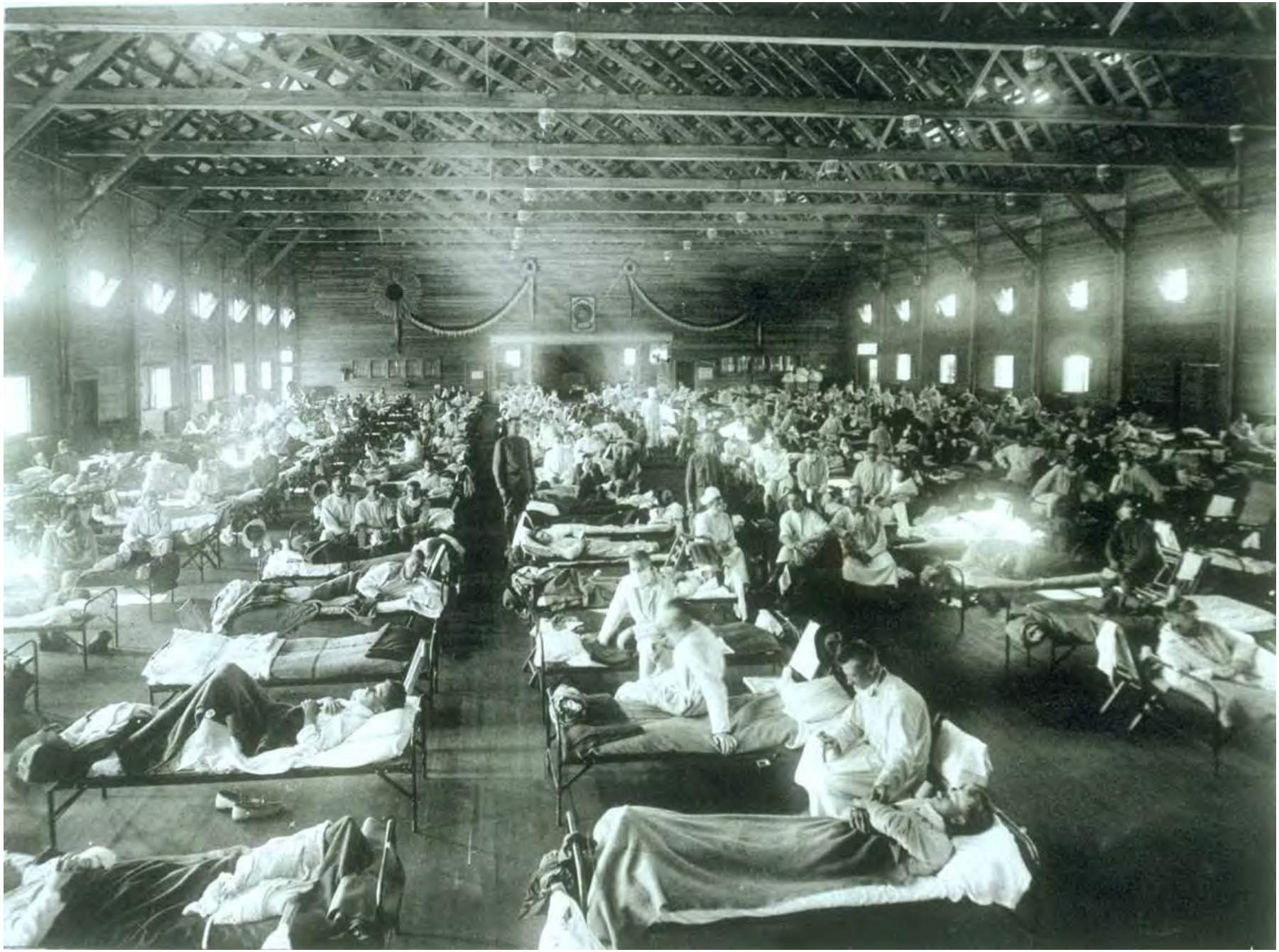
Type/ subtype	Cases (test positive)		Controls (test negative)		Adjusted VE	95% CI
	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated		
A or B	772 (73%)	288 (27%)	802 (63%)	477 (37%)	33%	17 to 46
A/H1N1 pdm09	74 (84 %)	14 (16%)	802 (63%)	477 (37%)	50%	8 to 74
A/H3N2	347 (66%)	175 (34%)	802 (63%)	477 (37%)	10%	-16 to 31
B/Vic	11 (100%)	0 (0%)	802 (63%)	477 (37%)	Not estimated	
B/Yam	206 (80%)	53 (20%)	802 (63%)	477 (37%)	45%	22 to 62

Sullivan et al *Eurosurveillance* 2017: 22(43): pii=17-00707

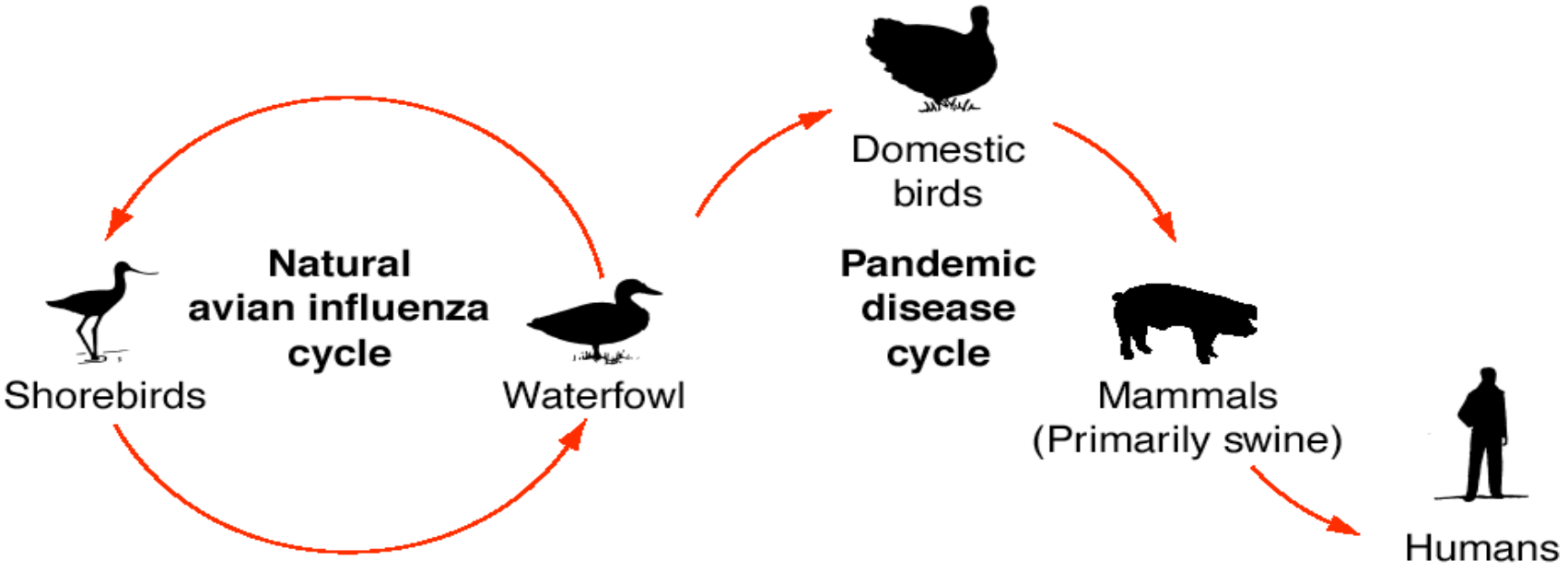
The 1918 ‘Spanish Flu’ Pandemic

I saw hundreds of young stalwart men in uniform coming into the wards of the hospital. Every bed was full, yet others crowded in. The faces wore a bluish cast; a cough brought up the blood-stained sputum. In the morning, the dead bodies are stacked about the morgue like cordwood.

Victor Vaughn, US Surgeon General, 1918

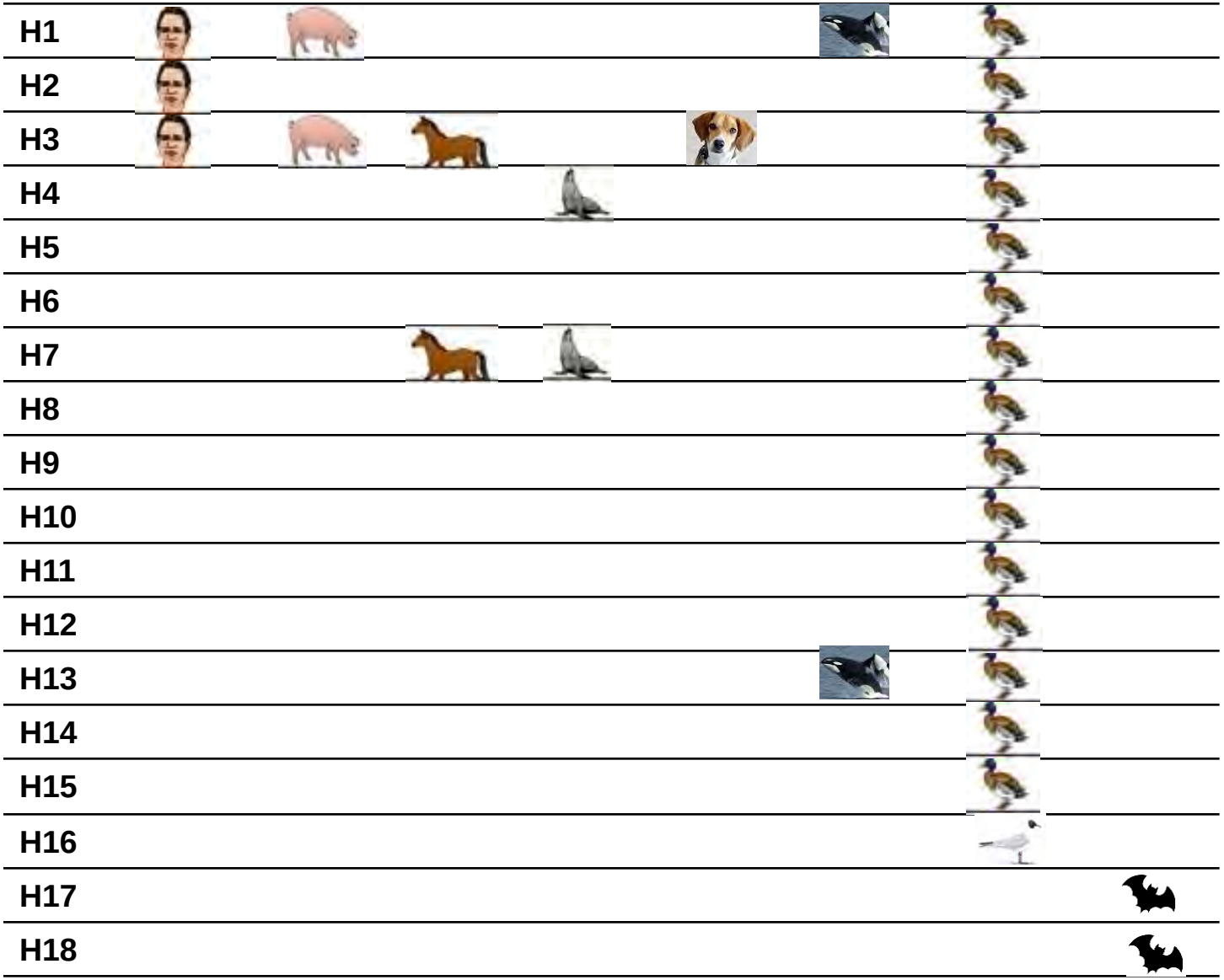


Cycle of Influenza A viruses

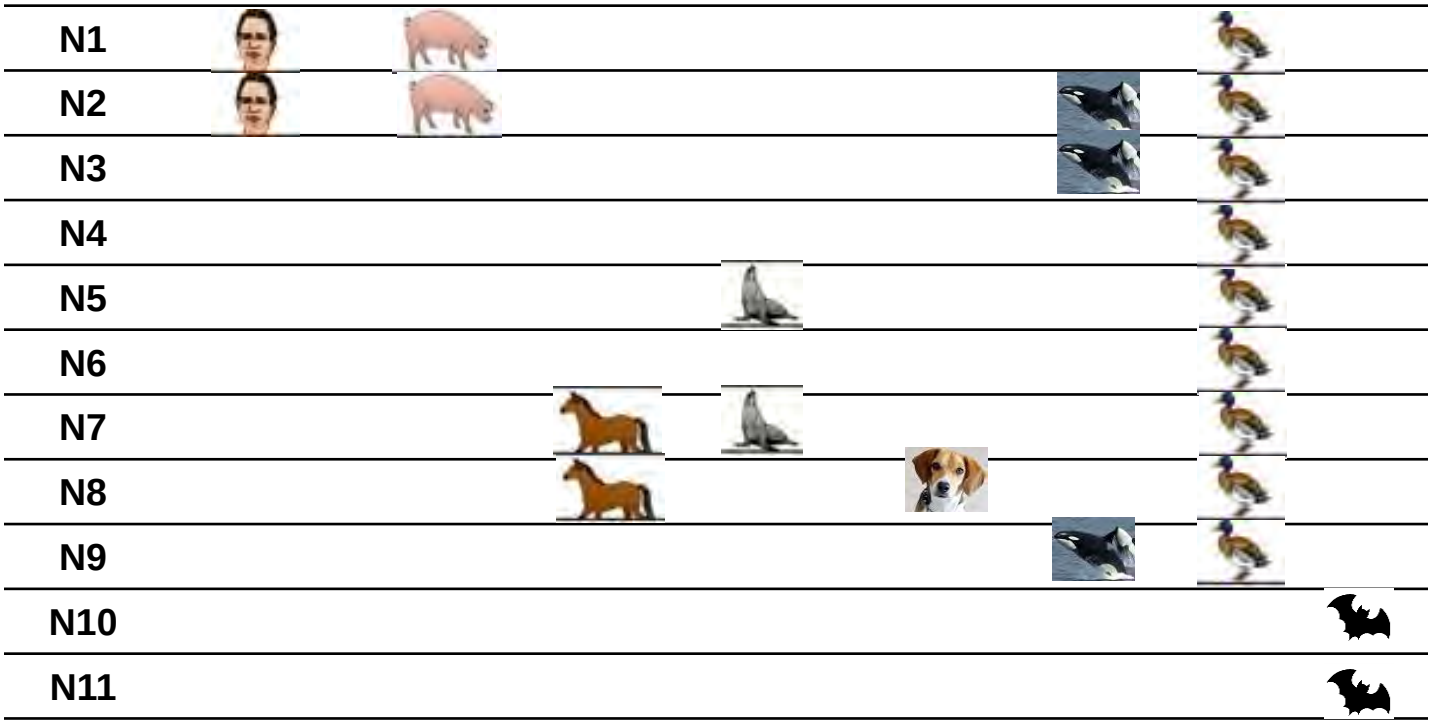


Source: Excerpt from ‘Field Manual of Wildlife Diseases’ (http://www.pandemicflu.gov)

Distribution of influenza A haemagglutinin subtypes in nature



Distribution of influenza A neuraminidase subtypes in nature



Direct Infection of Humans with Avian Influenza Viruses

Year	Country	Subtype/pathotype	Cases	Fatalities
1959	US	H7N7 HPAI	1	0
1978-79	US	H7N7 LPAI	?	0
1996	England	H7N7 LPAI	1	0
1997	Hong Kong	H5N1 HPAI	18	6
1999	China	H9N2 LPAI	5	0
1999, 2003	Hong Kong	H9N2 LPAI	3	0
2002-03	US	H7N2 LPAI	2	0
2003	Hong Kong	H5N1 HPAI	5	2
2003	Netherlands	H7N7 HPAI	89	1
2004	Canada	H7N3 HPAI	2	0
2004	Egypt	H10N7 LPAI	2	0
2003-2017	16 countries	H5N1 HPAI	860	454
2013-2017	China	H7N9 LPAI	1625	623
2014	Taiwan	H6N1 LPAI	1	0
2014	China	H10N8 LPAI	3	2
2014-2017	China	H5N6 HPAI	16	6

Sources: Perdue & Swayne (2005) Avian Dis 49:317 and EID Weekly Updates (2004) 2(18), 2, WHO, FAO

Goal of a Pandemic Influenza Vaccine

To prevent severe illness and death from pandemic influenza and it's complications.

An ideal influenza vaccine will

- induce a systemic and mucosal immune response directed at the HA, NA and conserved internal proteins of the virus
- protect against a broad range of influenza viruses, within a subtype and across subtypes

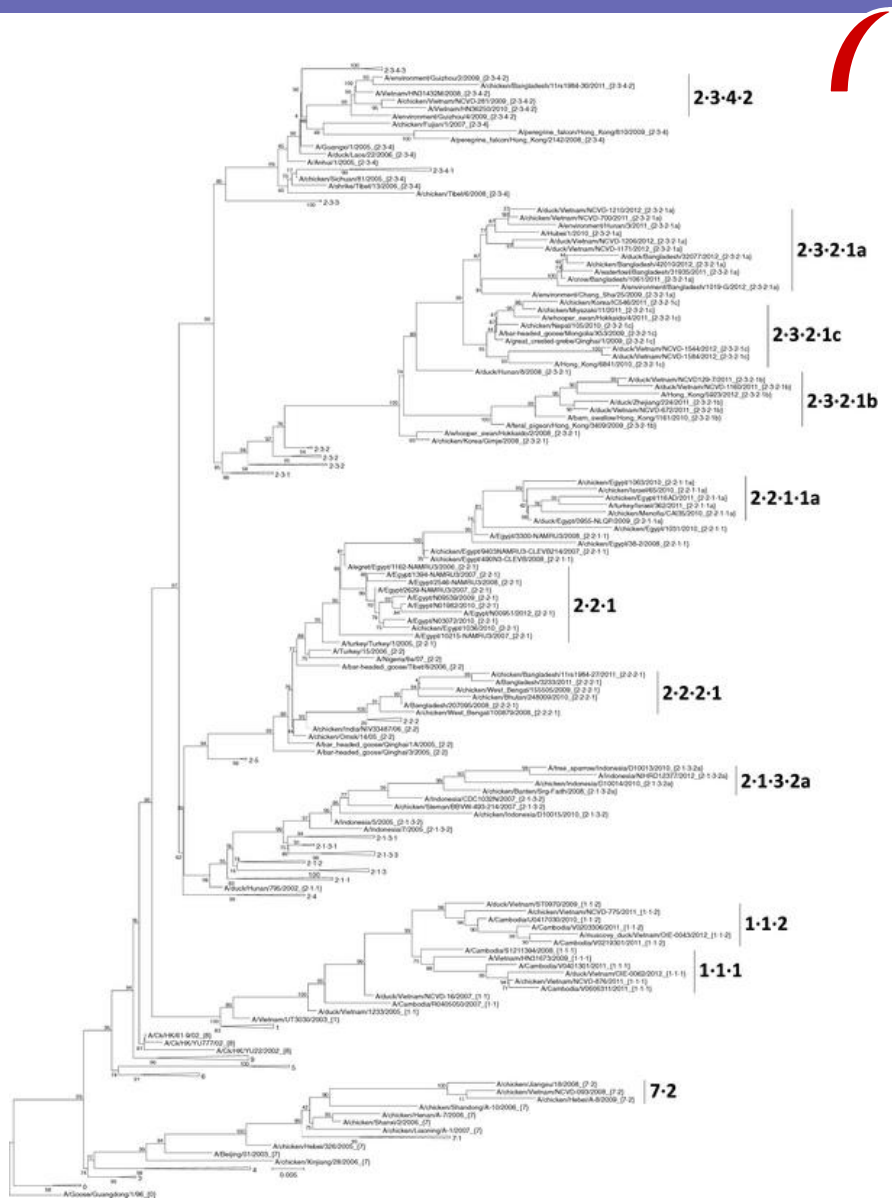
3 Options for Pandemic Influenza Vaccines

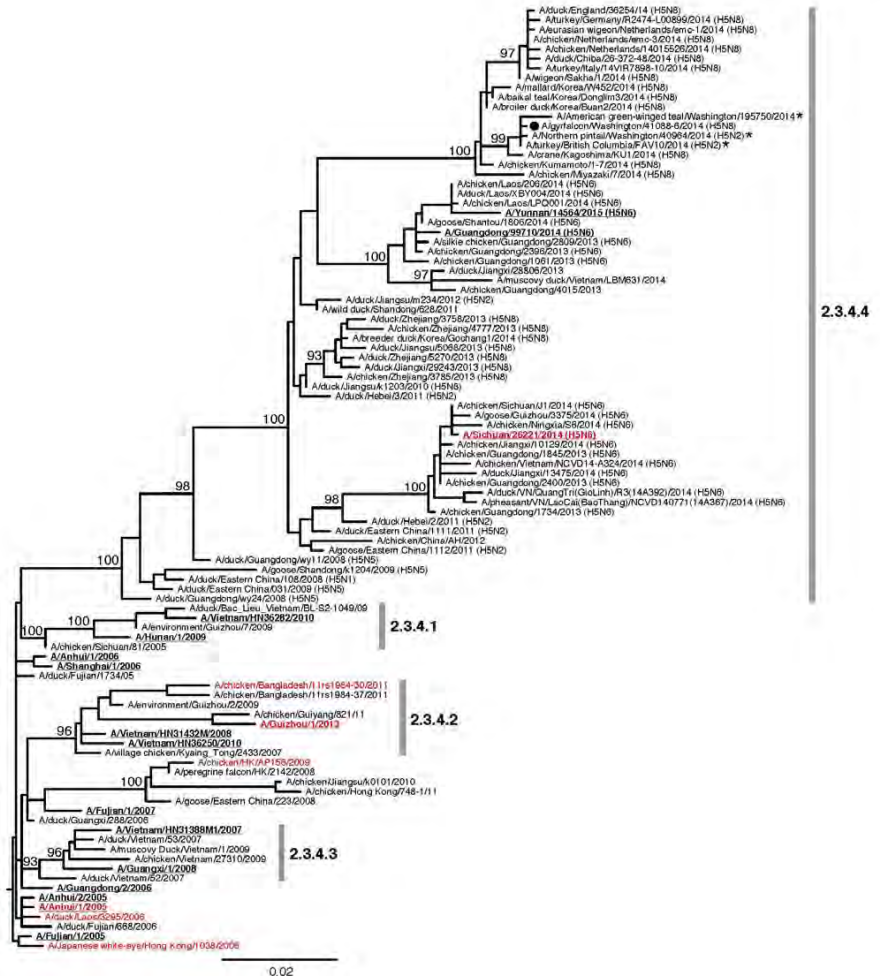
Option A	Option B	Option C
Conventional Approach	Enhance the breadth of cross reactivity	The 'game changer' Approach
Strain Specific Vaccines	Subtype Specific Vaccines	Universal Vaccine

The Conventional Approach:
Strain-specific vaccines

- **Principle**: Elicit strain-specific immunity
- **Goal**:
  - Prepare a library of Candidate Vaccine Viruses (CVVs)
  - Encourage vaccine manufacturers to develop experience working with CVVs
- **Process**:
  - Monitor genetic and antigenic drift in nature through surveillance
  - Determine when antibody elicited against previous CVVs fail to cross-react with drift variants
  - Prepare a new CVV
- **Caveat:**
  - Clinical trials are largely supported by the US government

The Diversity of H5N1 viruses





http://www.who.int/influenza/vaccines/virus/201502_zoonotic_vaccinevirusupdate.pdf?ua=1

Influenza and Other Respiratory Viruses 8: 384-388; 2014

Alternative Approaches

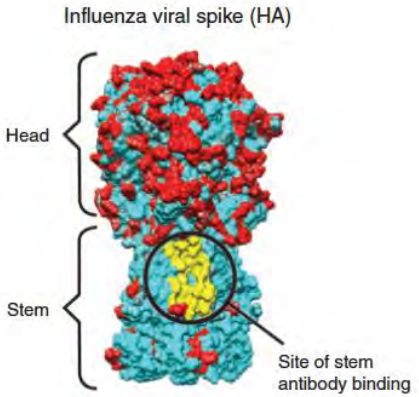
- **Principle**: Elicit broadly cross-reactive subtype-specific immunity
- **Goal**:
  - Enhance the cross-reactivity of the Ab response
- **Processes**:
  - Oil-in-water adjuvants
  - Whole virion vaccines
  - Combine vaccine platforms
  - Select different viruses for development of CVVs
    - Select among existing influenza viruses
    - Select antigenically advanced variants
    - An ancestral/computationally optimized broadly reactive HA
  - Multivalent vaccine e.g. VLPs expressing different HAs
  - Combinations of antigens e.g. NP + M1 ± HA or T cell epitope vaccine + HA

Universal influenza vaccines: a game-changer approach

Option C

Targets

- Hemagglutinin
  - Head
  - Stem
- Neuraminidase
- M2
- NP + M1
- T cell based protection



HA stem vaccines

Option C

- Sequential immunization with chimeric HAs with novel heads on a conserved stem
- A stable trimeric HA stem
- HA stem nanoparticles
- Bacterially expressed re-folded stem peptide

The challenges of universal influenza vaccine development

Option C

Technical challenges:

- Identify targets that are conserved across a wide range of influenza viruses
- Develop a vaccine strategy to induce an immune response that is
  - Sufficiently robust to confer protection
  - Elicited at the appropriate site (serum/mucosal antibody, pulmonary T cells)
  - Without adverse effects e.g. immunopathology

Regulatory challenges:

- Immune correlates of protection and assays to measure them

Implementation:

- Who should be vaccinated, when and how often?

What does the future hold?

- Continued vigilance to identify antigenic drift and antigenic shift events
- More cell based influenza vaccine components and vaccines
- Adjuvants to increase the immunogenicity of influenza vaccines
- High dose vaccines for the elderly
- New platforms e.g. virus like particles
- Universal influenza vaccines that elicit broad immunity against a range of influenza viruses and subtypes

The WHO Collaborating Centre for Reference and Research on Influenza in Melbourne is supported by the Australian Government Department of Health