Vaccine Options for Seasonal Influenza

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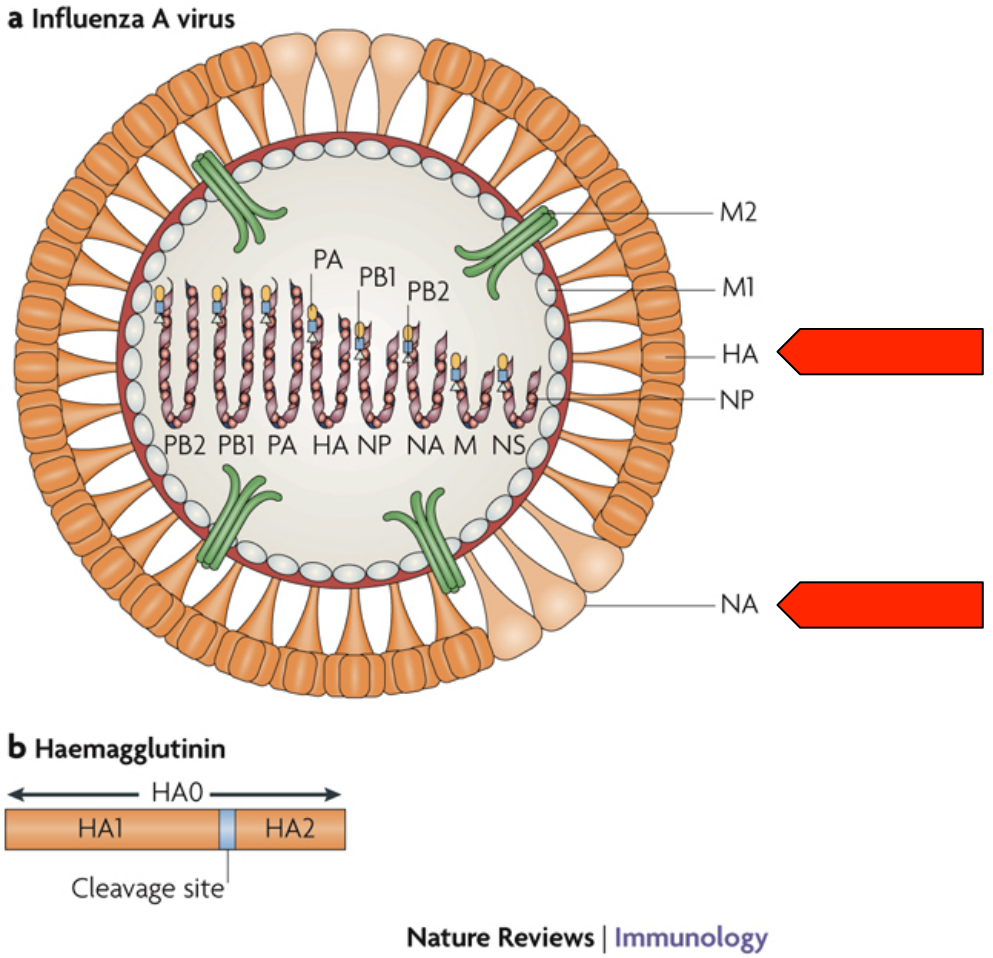
The burden of influenza

Global seasonal influenza-associated respiratory mortality

- Previous estimates were 250,000 to 500,000 deaths globally/year
- New estimates from 47 countries (1995-2015)
  - 291,243 to 645,832 deaths annually ~ 4.0 to 8.8/100,000 persons
  - Highest in sub-Saharan Africa, southeast Asia and persons older than 75 years (17.9-223.5/100,000 persons)
  - In children <5 years: 9,243-105,690 deaths annually
- 36,000 deaths and >200,000 hospitalisations/year in the US
- Ever present threat of pandemic influenza

Iuliano et al Lancet 2018

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



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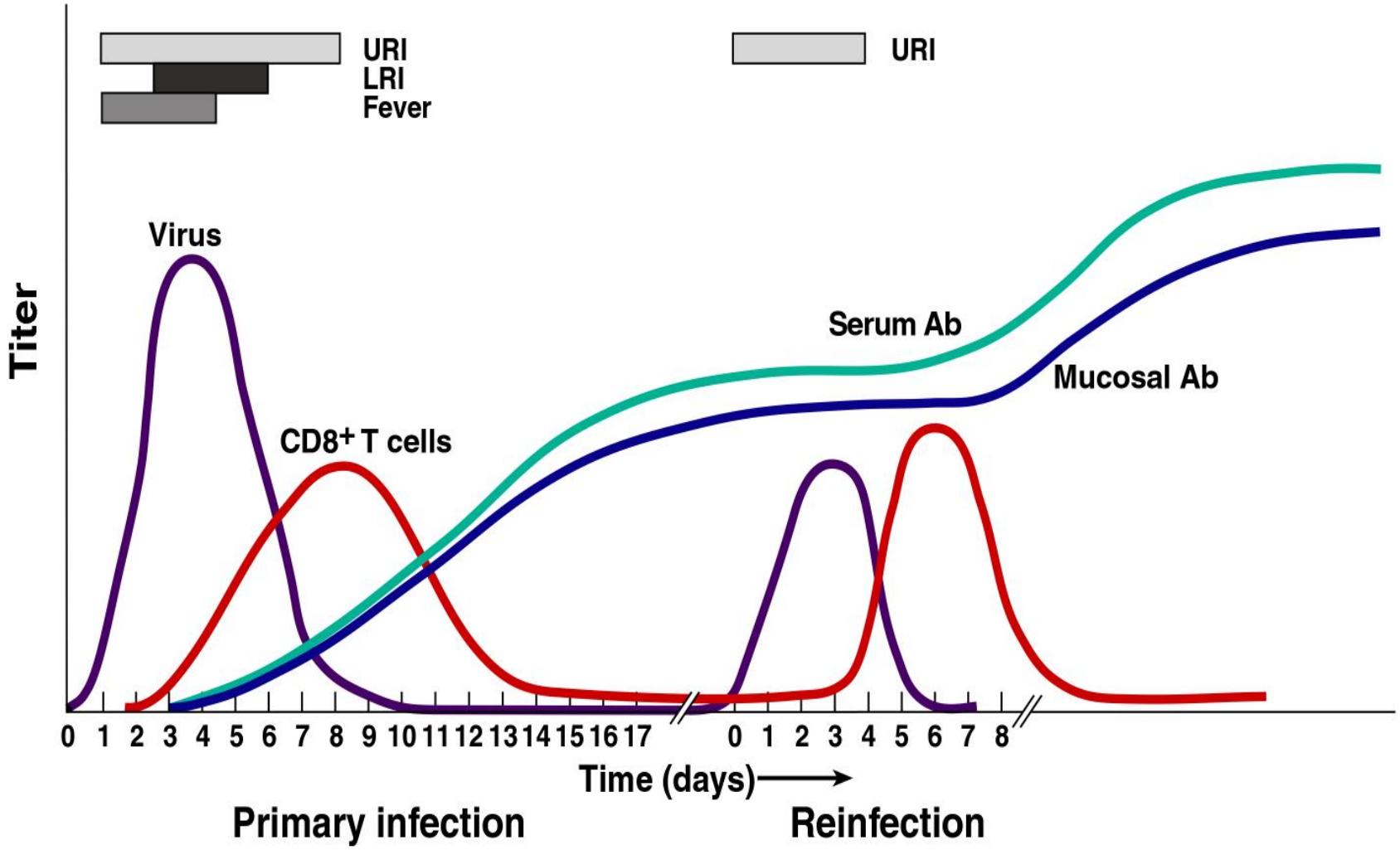
Course of Immune Response During Influenza Infection



Source: Subbarao et al. *Immunity* 24, 5-9 (2006)

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.

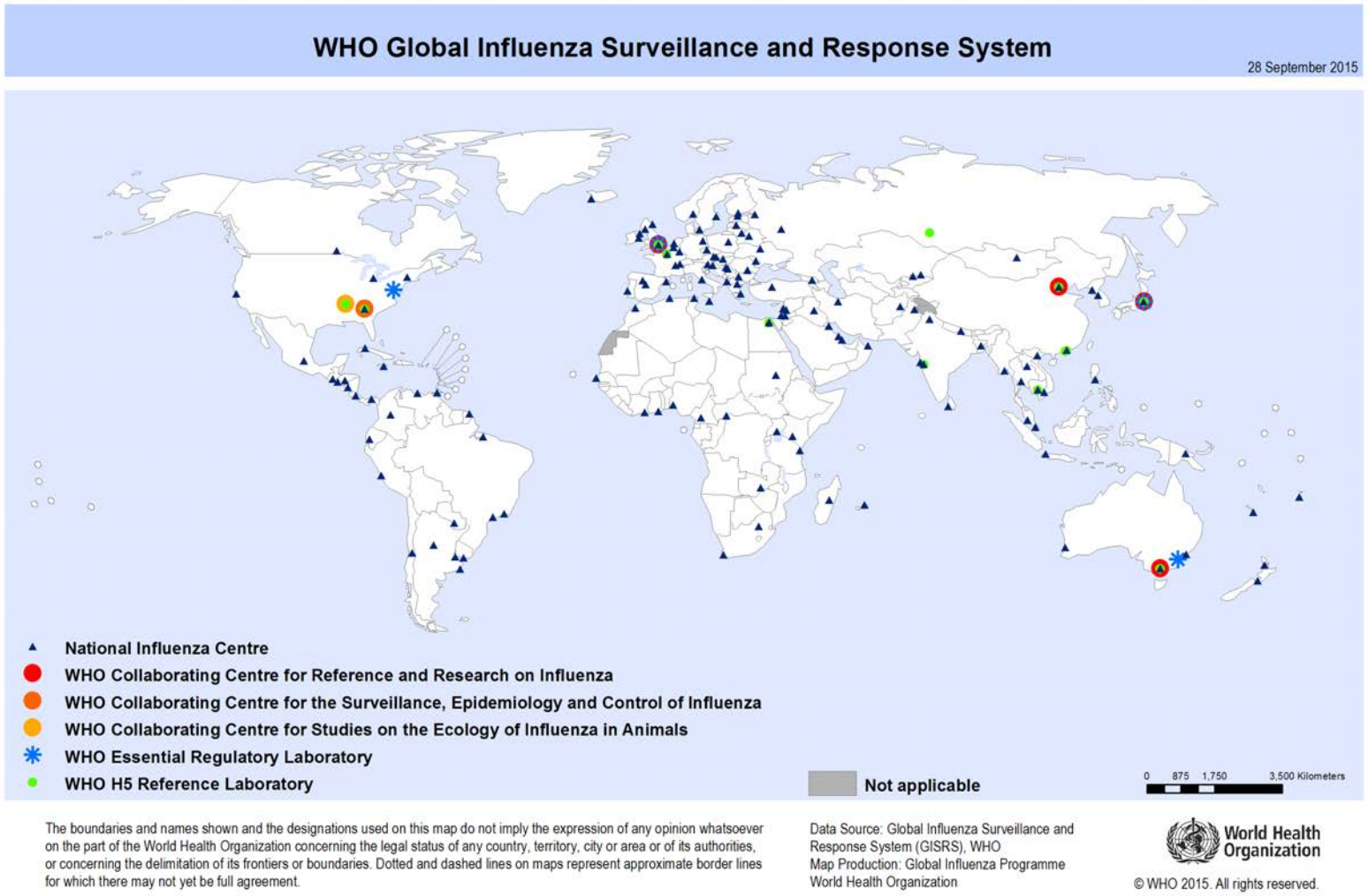
Inactivated influenza vaccine

- The inactivated influenza vaccine (IIV) contains 15μg of each HA antigen and is administered by intramuscular injection
- Virus infectivity is inactivated with formalin or betapropriolactone.
- The virions are detergent-disrupted and the preparation is enriched for glycoproteins (HA and NA) by centrifugation.
- In 2018, trivalent 'enhanced' vaccines were available in Australia for use in people >65 years of age
  - high dose IIV containing 60μg of each HA antigen
  - adjuvanted IIV with an oil in water adjuvant

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



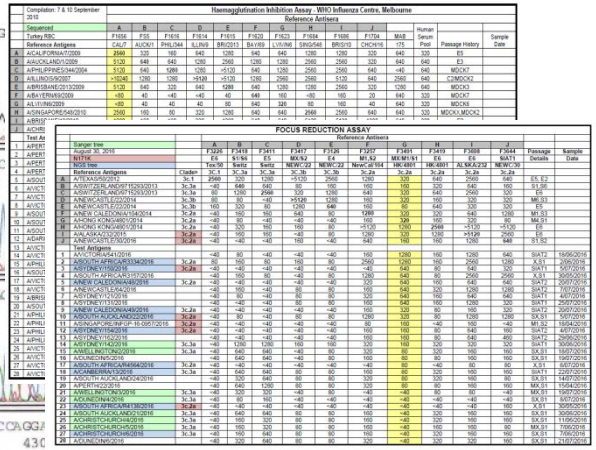
Oldest network in WHO: begun in 1952, 144 NIC's in 114 countries, 5 WHO CC's for human influenza + 1 for animal influenza + 4 essential regulatory labs,

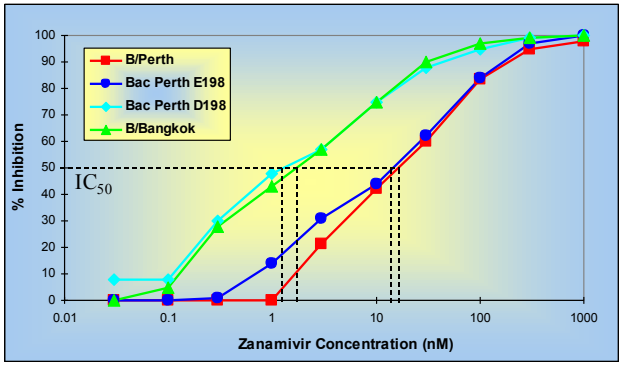
A variety of information is used to select influenza vaccine viruses

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

Vaccine composition recommended for 2018/2019 seasons

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

2019 Southern hemisphere

- H1N1pdm09: A/Michigan/45/2015-like
- H3N2: A/Switzerland/8060/2017-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 2018 recommendations

**** AIVC recommended B/Yam instead of B/Vic in the trivalent vaccine**

Key challenges with seasonal influenza vaccines-1

Antigenic drift necessitates an update in the vaccine composition

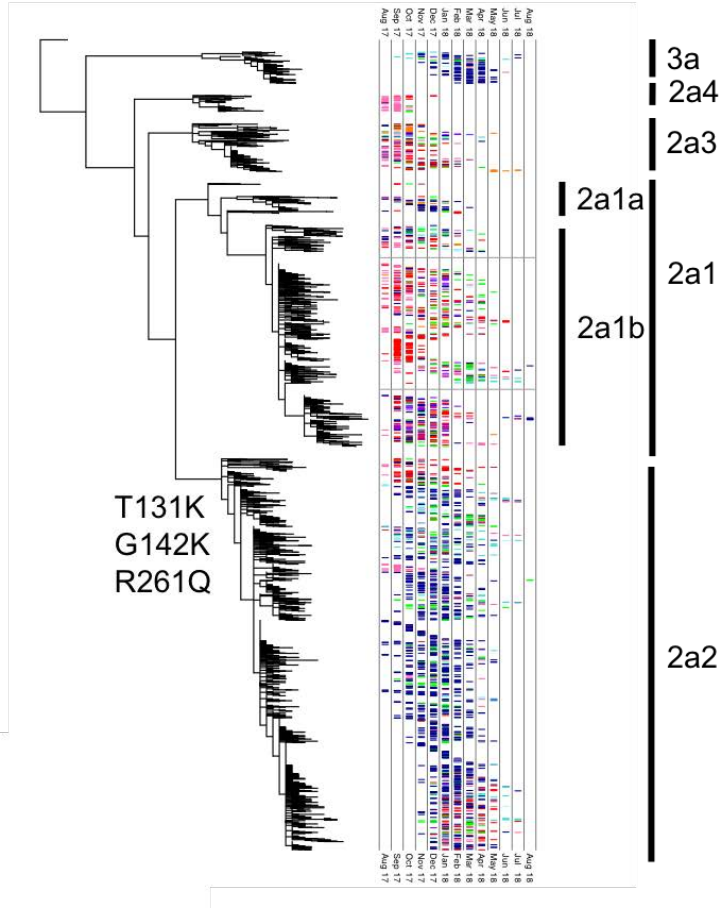
- *Challenge: About 50% of A/H3N2 viruses cannot be isolated or characterised in HAI tests*
- *Potential solution: A focus reduction assay (FRA) as an alternative to the HAI assay - but it is not high throughput*

Genetic drift

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

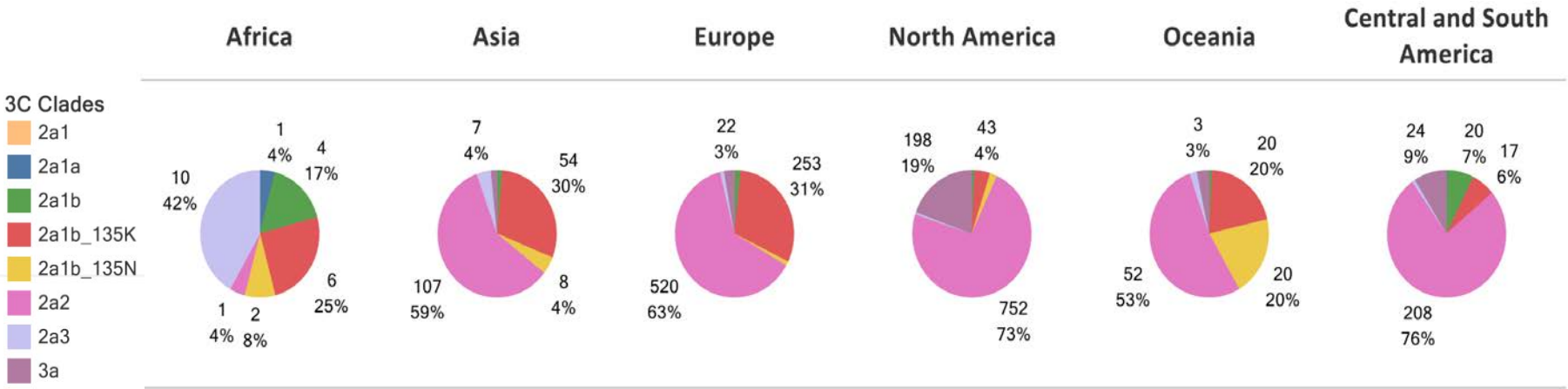
A/H3N2 phylogenetic tree

Phylogenetic analysis from Univ. Cambridge



Slide from WHO GIP

Global A(H3N2) HA 3C clade diversity February-Sept 2018 based on HA sequence availability



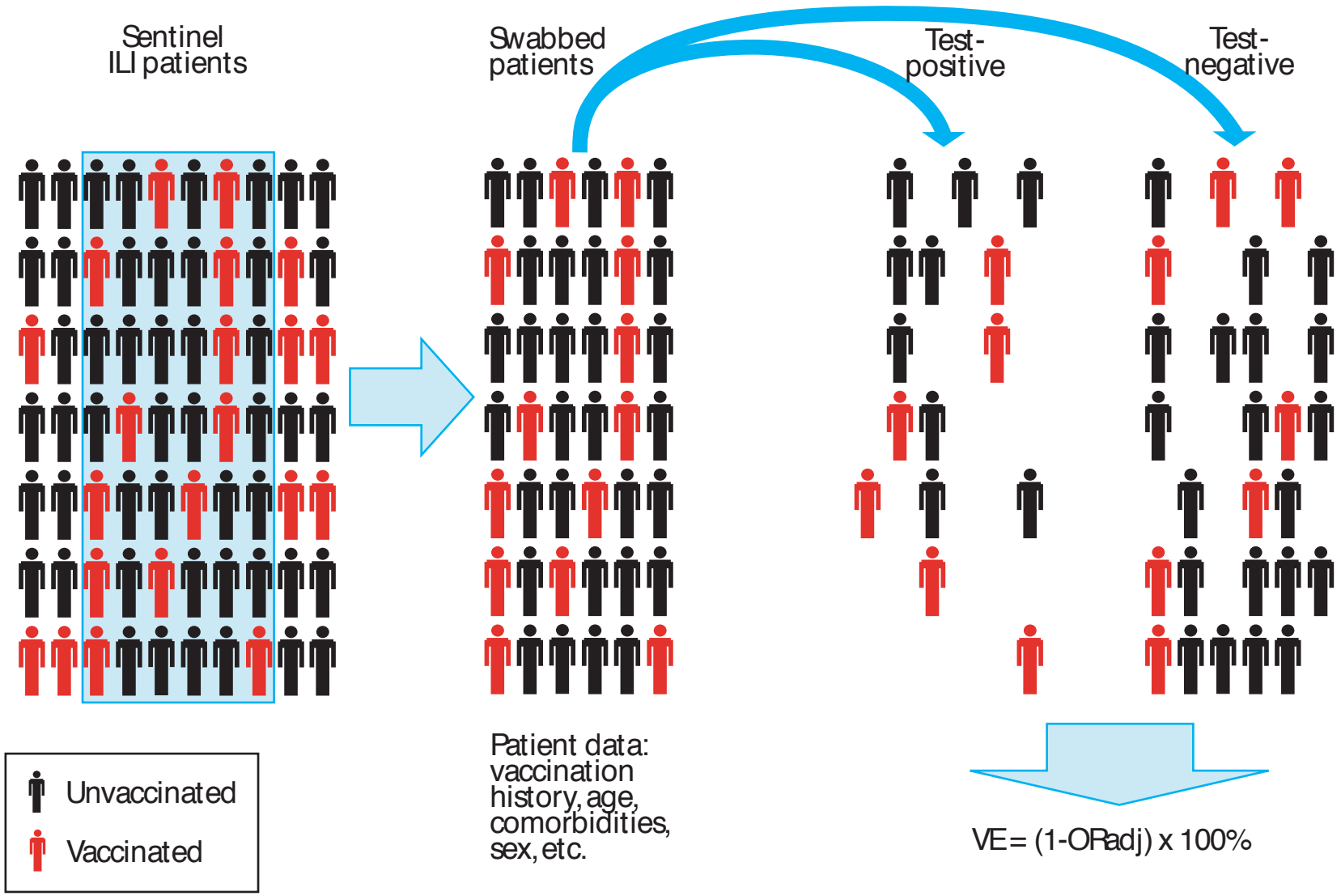
Slide from WHO GIP

Key challenges with seasonal influenza vaccines-2

Manufacture in embryonated eggs

- *Challenge: Adaptation to growth in eggs induces mutations in the HA.*
- *Antibody responses induced by egg-grown vaccines react well with other egg-grown viruses but not with cell-grown viruses.*
  - *The sequence of cell-grown viruses resembles that of virus present in clinical samples.*
- *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*

Assessment of Vaccine Effectiveness: The test negative design



Sullivan SG et al. *Expert Rev Vaccines* 2014;13:1571-91.

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

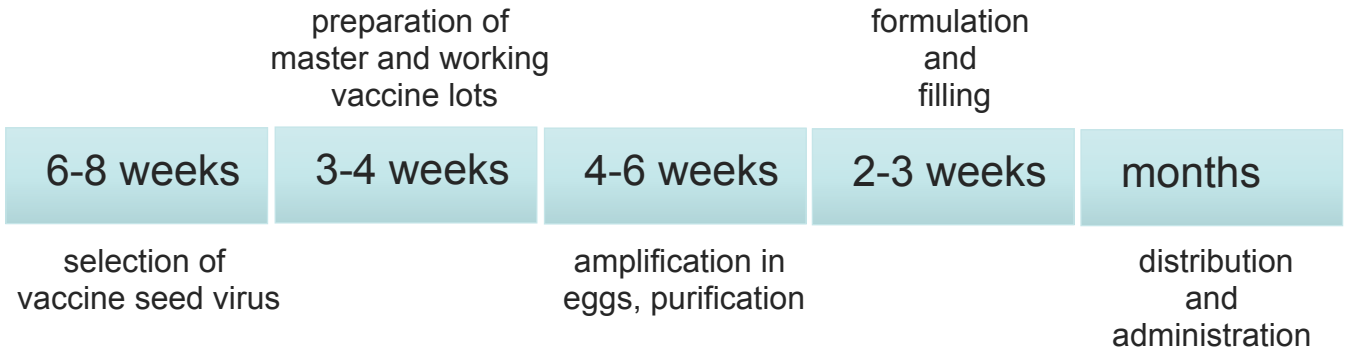
Sullivan et al *Eurosurveillance* 2017: 22(43): pii=17-00707

Challenges with current A/H3N2 influenza viruses- Summary

- Difficult to isolate viruses (only ~50% of viruses can be isolated in culture) due to changes in HA
- Difficult to complete antigenic characterisation using the hemagglutination inhibition (HI) assay due to molecular changes in HA and NA
  - Relying on neutralisation assays instead but they are not high-throughput assays
- Molecular data indicates significant genetic heterogeneity: viruses fall into different clades and subclades
- Ferret antisera do not distinguish among the clades; therefore, there is no antigenic signature for viruses in the different clades

Limitations of current influenza vaccines

- Vaccines require months to manufacture
- Reduced effectiveness when vaccine and epidemic strains are antigenically mismatched
- Suboptimal efficacy in the elderly
- Short duration of protection
  - Antigenic drift results in need for annual reformulation
  - Antigenic shift requires a new vaccine component
- Most of the currently licensed influenza vaccines are generated in embryonated eggs



Research efforts to improve seasonal influenza vaccines

- Increase the immunogenicity of existing vaccines
  - Adjuvants
  - High dose
- Increase the breadth of immunity
  - Adjuvants
  - Neuraminidase
- Change the substrate to avoid effects of egg-adaptation mutations
  - Cell-grown vaccines
  - Recombinant HA vaccines

Influenza Vaccines available in the US

Inactivated

Killed virus

- grown in eggs or cells
- Trivalent or quadrivalent
- injected

Recombinant

Expressed protein

Live

Live, weakened virus

- grown in eggs
- Trivalent or quadrivalent
- given intranasally
- for healthy individuals aged 2-49 years

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

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