Cell-based human influenza vaccines may provide greater protection against A(H3N2) influenza viruses

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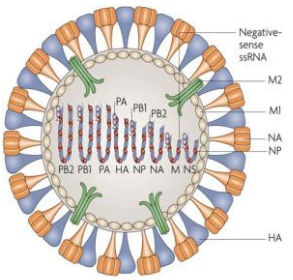
WHO Collaborating Centre for Reference and Research on Influenza VIDRL

Seqirus A CSL Company

Doherty Institute — A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Influenza virus structure

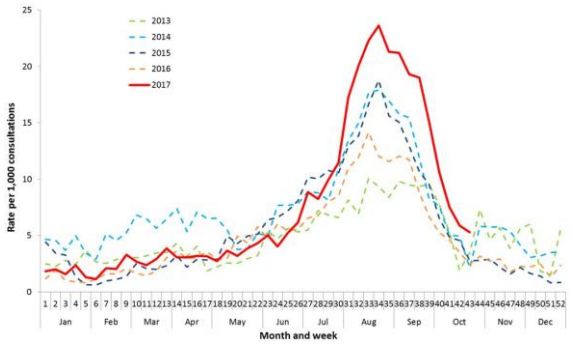
- Have eight separate segments of negative-sense RNA
- Two major surface glycoproteins: **Haemagglutinin (HA)** and **Neuraminidase (NA)**
- HA protein is the target of seasonal influenza vaccines:
  - Responsible for binding virus to sialic acid-containing cell-surface receptors
  - Is the principal target for neutralising antibodies
- No proof-reading during virus replication
  - Leads to antigenic drift
  - Positive selection under immune pressure



Nature Reviews | Genetics

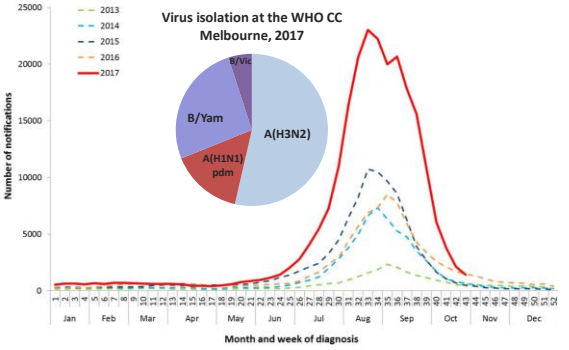
Australia's 2017 Influenza season

Rate of ILI reported from sentinel GP surveillance systems, Australia, 1 January 2013 to 29 October 2017) ASPREN data



Australia's 2017 Influenza season

Notifications of laboratory confirmed influenza, Australia, 1 January 2013 to 27 October 2017



Low interim vaccine effectiveness (VE) in Australia

Interim A(H3N2) vaccine effectiveness estimates, Australia, 1 May 2017-24 September 2017

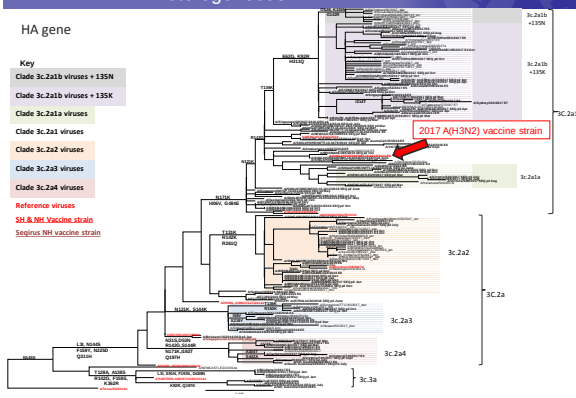
Type/subtype	Age group	Cases				Controls				Adjusted[a] VE (95% CI)
		Unvaccinated		Vaccinated		Unvaccinated		Vaccinated		
A or B	All ages	772	73%	288	27%	802	63%	477	37%	33% (17 to 46)
	Children <15y	235	94%	14	6%	179	94%	12	6%	16% (-95 to 63)
	Adults 15–64y	512	74%	181	26%	587	65%	322	35%	39% (24 to 51)
	Adults ≥ 65y	25	21%	93	79%	36	20%	143	80%	-3% (-92 to 44)
A(H3)	All ages	347	66%	175	34%	802	63%	477	37%	10% (-16 to 31)
	Children <15y	100	94%	6	6%	179	94%	12	6%	17% (-132 to 73)
	Adults 15–64y	233	68%	110	32%	587	65%	322	35%	16% (-11 to 36)
	Adults≥ 65y	14	19%	59	81%	36	20%	143	80%	-20% (-160 to 42)

- VE estimated using case-control test-negative design
- All ages VE for A(H3N2) was estimated to be 10% (CIs however include negative numbers and cross the null)
- Other VE studies from the Northern Hemisphere indicate low VE for the A(H3N2) component of the vaccine
  - Canada 17% (95% CI -14-40) Skowronski et al Euro Surveill.2018: 23(5)
  - US 25%(95% CI 13-36) Flannery et al MMWR 2018; 67:180-185

Sullivan et al , Euro Surveill. 2017;22(43)

A(H3N2) viruses in 2017 were quite heterogeneous

HA gene



Why was the A(H3N2) vaccine component VE so low?

- Virus evolution
- Egg adaptations
- Demography
  - A(H3N2) affects all age groups
  - >65 year age group respond poorly to the A(H3N2) component of the influenza vaccine

Isolation of influenza viruses in a qualified cell line

- **CRADA (Co-operative Research and Development Agreement) between Seqirus Pty Ltd (formerly Novartis vaccines and diagnostics) and WHO CCs in Melbourne (VIDRL) and Atlanta (CDC)**
  - Initiated May 2007 (CDC) and April 2008 (Melbourne)
  - Use of Seqirus proprietary MDCK suspension cell-line for vaccine production

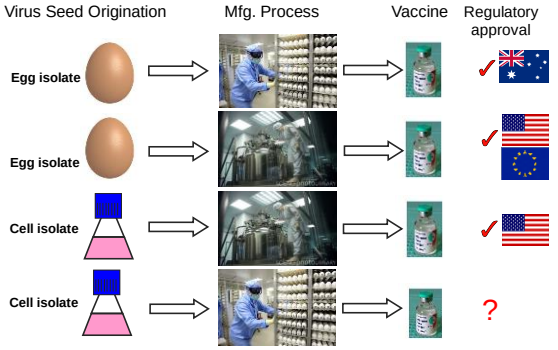
Aims:

- To compare isolation rates, characteristics and growth properties of influenza viruses isolated from MDCK33016PF with respect to eggs

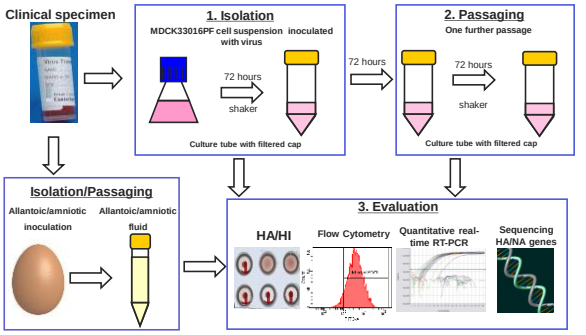
Rationale:

- Influenza seeds for vaccine production in cell culture could originate from MDCK33016PF derived seeds as well as from eggs
- Cell derived isolates may better represent viruses circulating in humans than egg isolates and may result in improved influenza vaccine efficacy

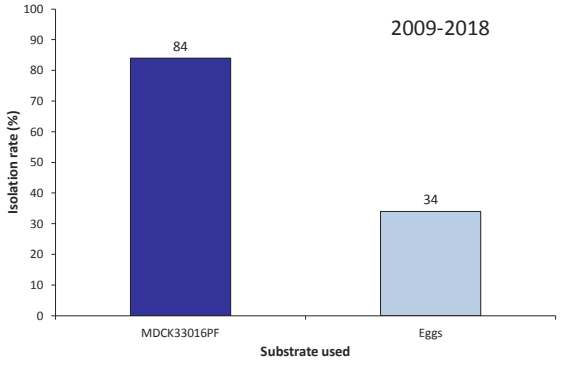
Seed viruses for vaccine manufacture



Virus isolation: methods



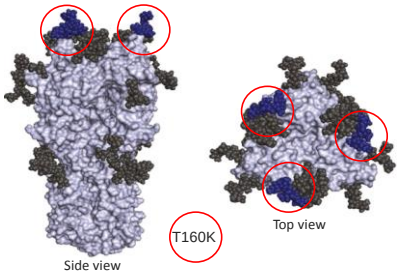
Isolation rates for A(H3N2) viruses are higher in the qualified MDCK33016PF cell-line



Egg-isolated A(H3N2) viruses are more likely to acquire mutations in the HA gene

Virus	Passage history	HA position in MDCK33016PF sequence									
		96	138	156	160	186	190	194	203	219	225
		N	A	H	T/R	G	D	L	T	S	D
A/Tasmania/37/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E7	.	S	.	K	X	X	.	.	.	G
A/South Australia/209/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	X	.	.	I	.	.	P	.	.	X
A/Victoria/624/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	.	.	.	K	.	.	P	X	.	.
A/Victoria/653/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E5	.	.	.	K	.	.	P	I	.	.
A/Brisbane/185/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E5	.	.	Q	K	V	.	.	.	F	G
A/Brisbane/190/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	.	.	.	.	.	.	P	.	.	.
A/Brisbane/192/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	.	.	.	K	.	.	P	.	.	.
A/Christchurch/516/2017	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	.	.	.	K	.	.	P	.	.	.
A/Brisbane/01/2018	MDCK33016PF p2	.	.	.	.	.	.	.	.	.	.
	E4	.	.	.	K	.	.	P	.	.	.

Putative glycosylation sites

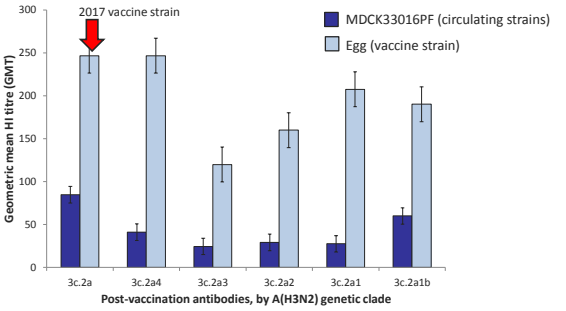


A/Victoria/361/2011 HA trimer

- Recent A(H3N2) isolates possess a glycosylation site in antigenic site B of the HA: **K160T**
  - Introduces an N-linked glycosylation site
- A(H3N2) viruses with a K160T mutation grow poorly in eggs
  - the 2017 egg-based A(H3N2) vaccine component possesses a **T160K** reversion mutation

Zost et al, PNAS 2017

Antibody responses to egg-based vaccines provide protection against egg-derived influenza viruses; but not circulating influenza viruses



- This means that egg-based vaccines will not protect as well as expected against circulating A(H3N2) viruses

Seqirus (ex-Novartis) Holly Springs (NC, USA)
Cell Culture Plant for Influenza Vaccine production

SEQIRUS FLUCELVAX QUADRIVALENT 2017-18 FOR THE USA

15 mcg HA of each of the following four influenza strains:

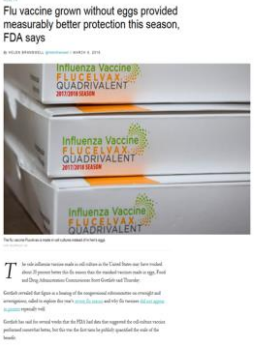
- A/Singapore/GP1908/2015* IVR-180 (H1N1) EGG
- **A/Singapore/GP2050/2015 (H3N2) CELL***
- B/Utah/9/2014; (B/Yam) EGG
- B/Hong Kong/259/2010 (B/Vic) EGG

In formulation for the 2018-19 USA season:

- A/Singapore/GP1908/2015* IVR-180 (H1N1) EGG
- A/North Carolina/04/2016 (H3N2) CELL
- **A/Singapore/INFTT-16-0610/2016 (B/Yam) CELL***
- B/Iowa/06/2017 (B/Vic) CELL

*Isolated at the WHO CC Melbourne

Did the new cell vaccine perform better in the US?


Flu vaccine grown without eggs provided measurably better protection this season, FDA says

https://www.statnews.com/2018/03/09/cell-culture-flu-vaccine-flucelvax/ STAT is produced by Boston Globe Media

Medicare study in the US

- Study sponsored by CDC
- 16 million people aged 65 and older
- Comparing rates of people who were hospitalised for influenza based on which kind of flu vaccine they received
- Data obtained from medical records
- FDA commissioner Scott Gottlieb stated the cell-based vaccine may have 'worked about 20 % better' compared to vaccines produced in eggs
- Data currently under review

US Military study

- US military used a large amount of cell-based vaccine in the 2017-18 season
- Department of Defence health services are working on VE studies in this population

Conclusions and future directions

- MDCK33016PF cells were superior in isolating influenza A(H3N2) viruses when compared to eggs
  - Also maintained the same HA sequence as the virus present in the original clinical sample
  - Important for antigenic characterisation, as egg-adapted genetic changes alter the antigenicity of a virus
- Interim results of Flucelvax Quad® use with an A(H3N2) cell component suggest a possible improved vaccine efficacy in the elderly of around 20% for the 2017-18 US influenza season (relative to the current egg-based quadrivalent vaccine)
- Final data analysis for US studies are currently underway (elderly and military cohorts) will provide updated VE estimates
- Upcoming influenza season in the US (2018-19) will contain 3 cell-derived components (of a possible 4); more studies are needed to assess VE to determine if there are further improvements

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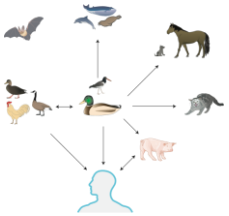
Influenza Ecology

Type A



Type B

- Genetically and structurally similar
- Estimated influenza A and B diverged about 4000 years ago
- **Strikingly different host range**

Influenza is an ongoing global problem

Recent Article Iuliano et al Lancet 2017

Estimated the number of global annual influenza-associated respiratory deaths using country-specific influenza associated excess respiratory mortality estimates from 1999–2015 based on 33 countries data (57% of the global population)

0·1 to 6·4 deaths per 100 000 for <65y
2·9 to 44·0 d. per 100 000 for 65-74y
17·9 to 223·5 d. per 100 000 for >75y

Total of 291,243 to 645,832 deaths/y

9,243–105,690 deaths/y in <5y

Highest mortality rates were estimated in sub-Saharan Africa