Présentation sur le futur des vaccins influenza a partir de la synthèse présentée par Arnold Monto

The Future of Influenza Vaccines

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Where Are We Now: The Positives

- Recommendations for annual influenza use in place in many resourced countries. Some universal.
- Attempts underway to expand recommendations to young children through burden studies and to increase use in healthcare workers.
- Programs underway to use herd immunity to enhance protection.
- Quadrivalent vaccines replacing trivalent vaccine in many countries.
- New vaccine approaches being developed for high risk and other populations. In the US, 9 different influenza vaccines licensed, including:
  - high dose egg based,
  - cell-culture,
  - adjuvanted,
  - recombinant,
  - Live attenuated

Where Are We Now: The Negatives

- Recommendation used to claim 70-90% protection against symptomatic seasonal influenza.
- Influenza-like illness in a vaccinated individual was said not to be influenza.
- PCR and the development of observational studies changed this.
- In same year, VE approached the null,
- Repeated reports of identification of variants of pandemic potential,
- In some countries, continuation of pandemic fatigue and reduction in uptake of seasonal vaccine.

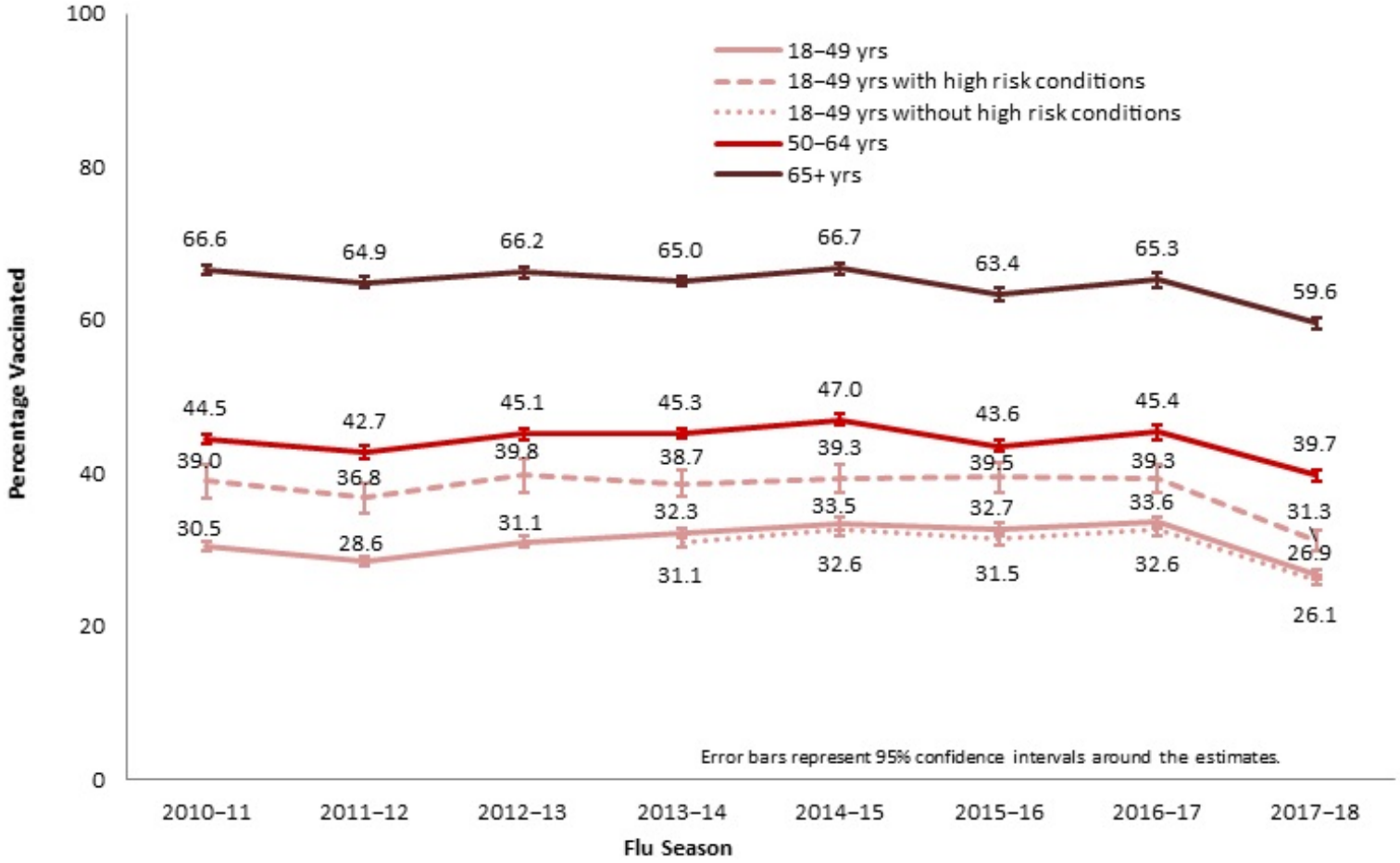
Call to Action: The Universal Vaccine Strategic Plan

- Development as a way to respond to current needs.
- Began as a response to pandemic vaccine needs, but also included type A seasonal influenza in goal for “durable protection against multiple influenza strains.”
- The long term goal is a single vaccine for both seasonal and pandemic protection
- “Precisely characterize influenza immunity and correlates of immune protection” while supporting rational design of influenza.
- Recent developments have emphasized urgent needs for short and midterm improvements, especially in seasonal vaccine.

The Urgent Need

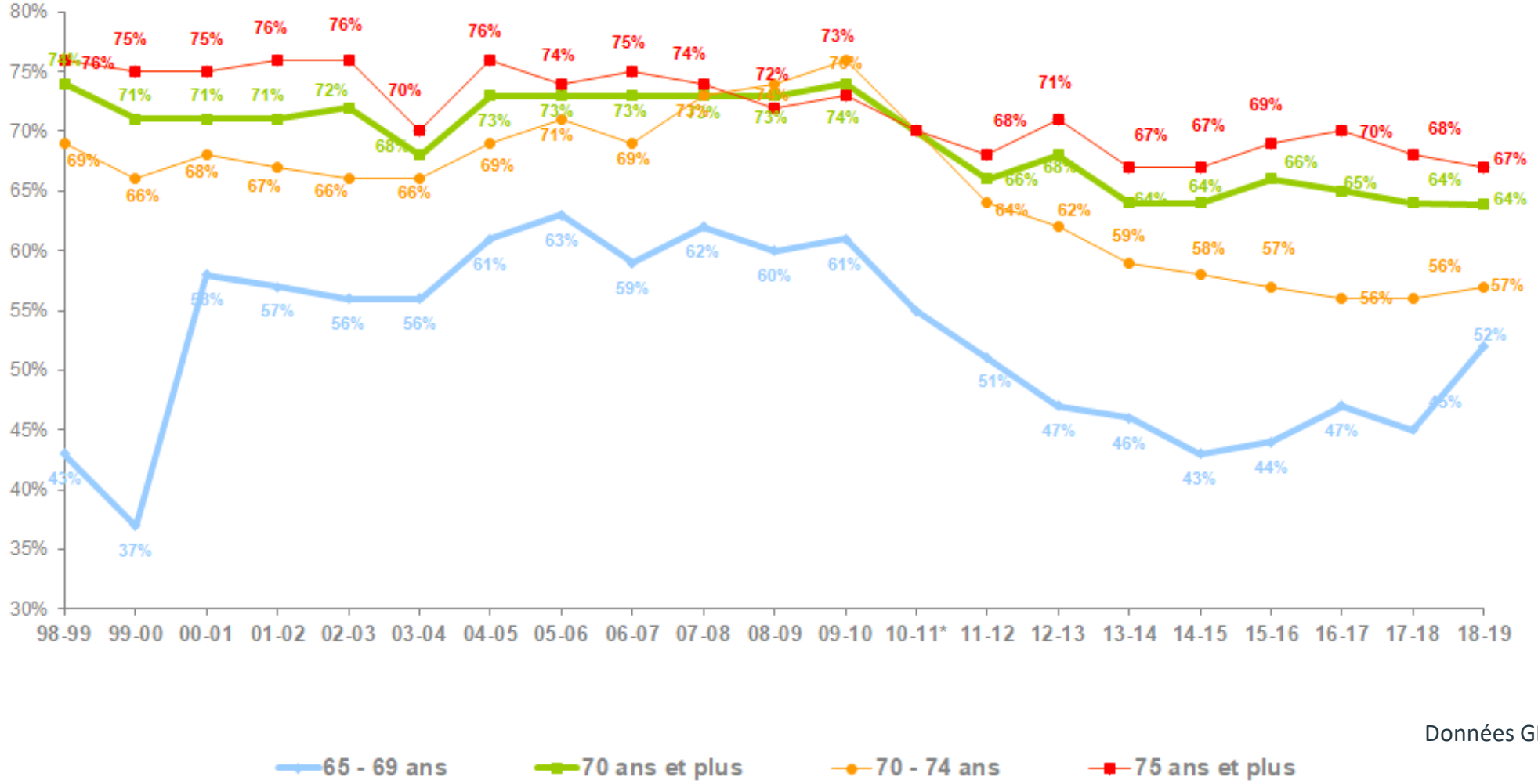
- Rare to see VE goal over 50% at any time with any type or subtype.
- Type B lineages and type A (H1N1) have consistently higher VE than A (H3N2), even when strains apparently well matched.
- Little or no VE of A (H3N2) in at least two years.
- Public notice that there are still high levels of health care utilization in influenza outbreaks, especially in the elderly, in spite of good uptake of vaccine.

Flu Vaccination Coverage Among Adults, by Age Group and Season, US 2010-18



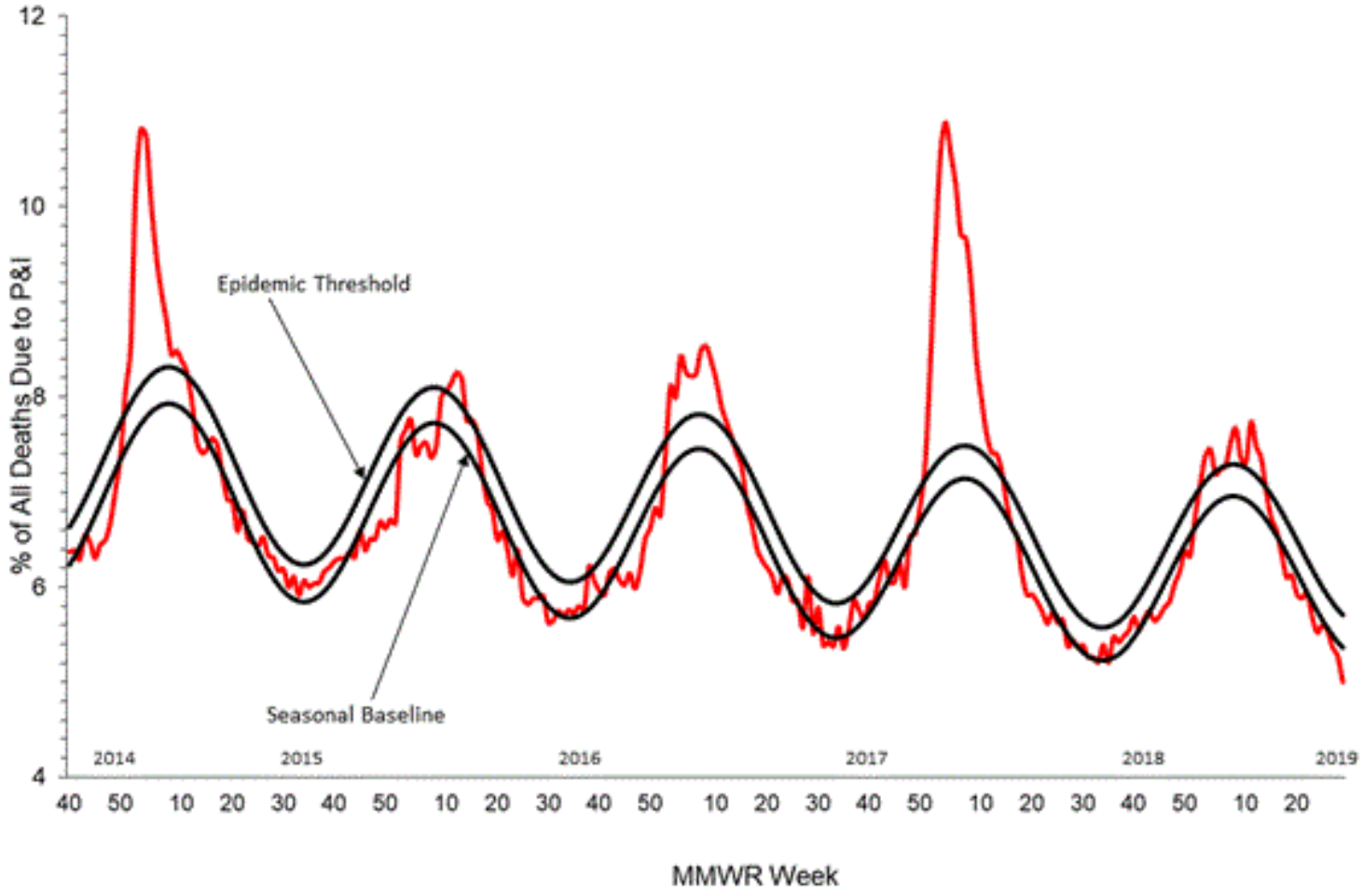
https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates.htm

Flu Vaccination Coverage Among Elederly, by Age Group and Season, France 2010-18



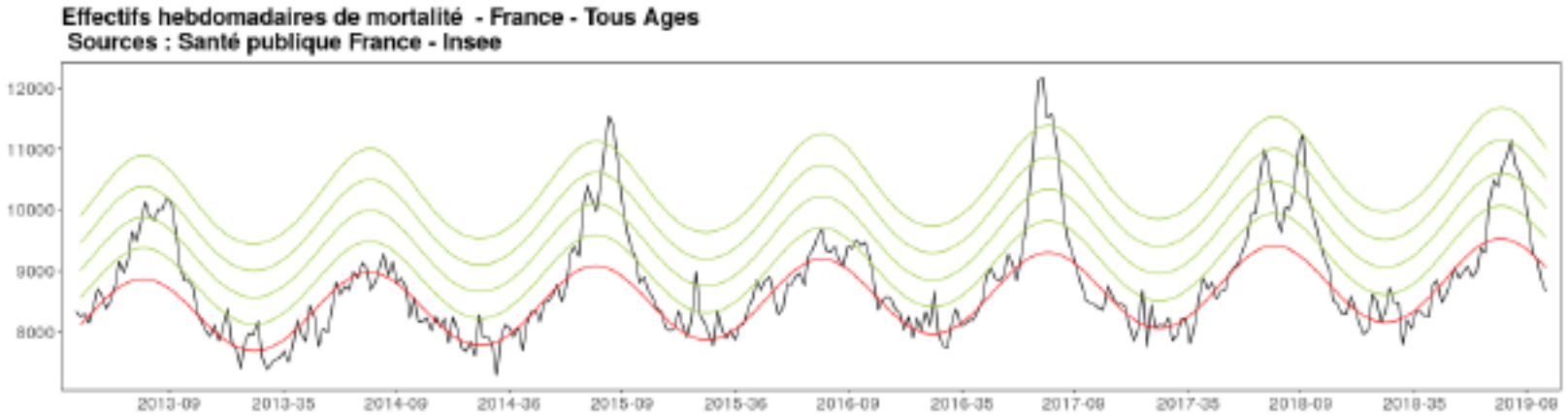
Données GEIG – SFM 2019

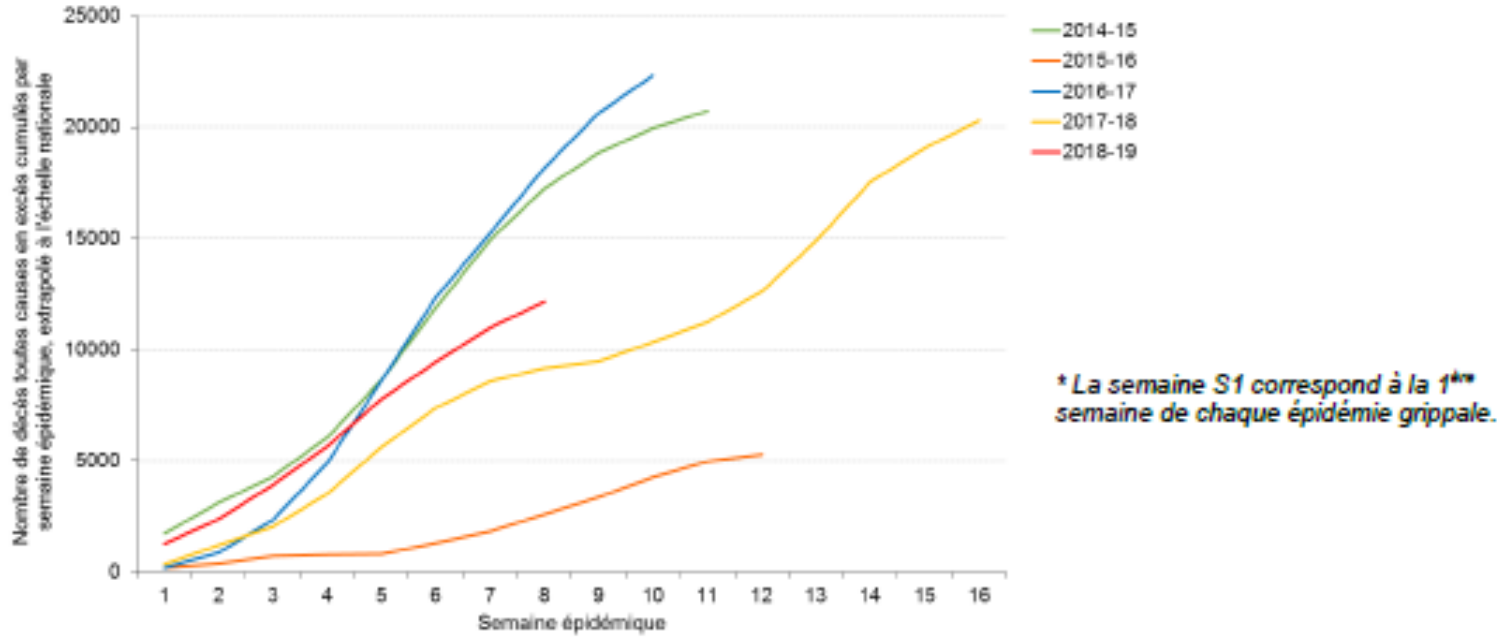
Pneumonia and Influenza Mortality in the USA



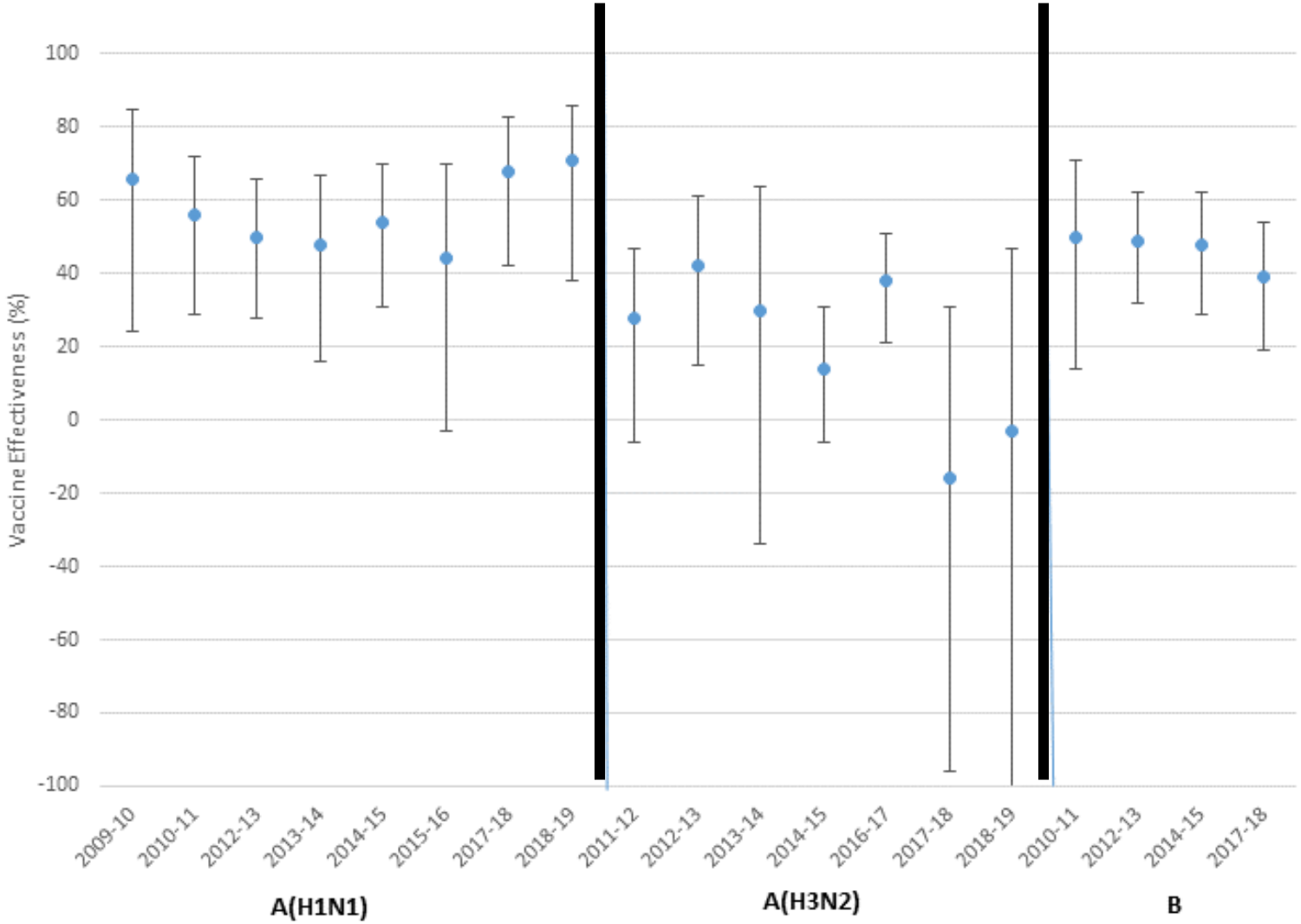
https://www.cdc.gov/flu/weekly/index.htm

Mortality in France





Influenza VE in Preventing Ambulatory Care Visits, I-MOVE 2009-19



Issues with Type A Vaccines

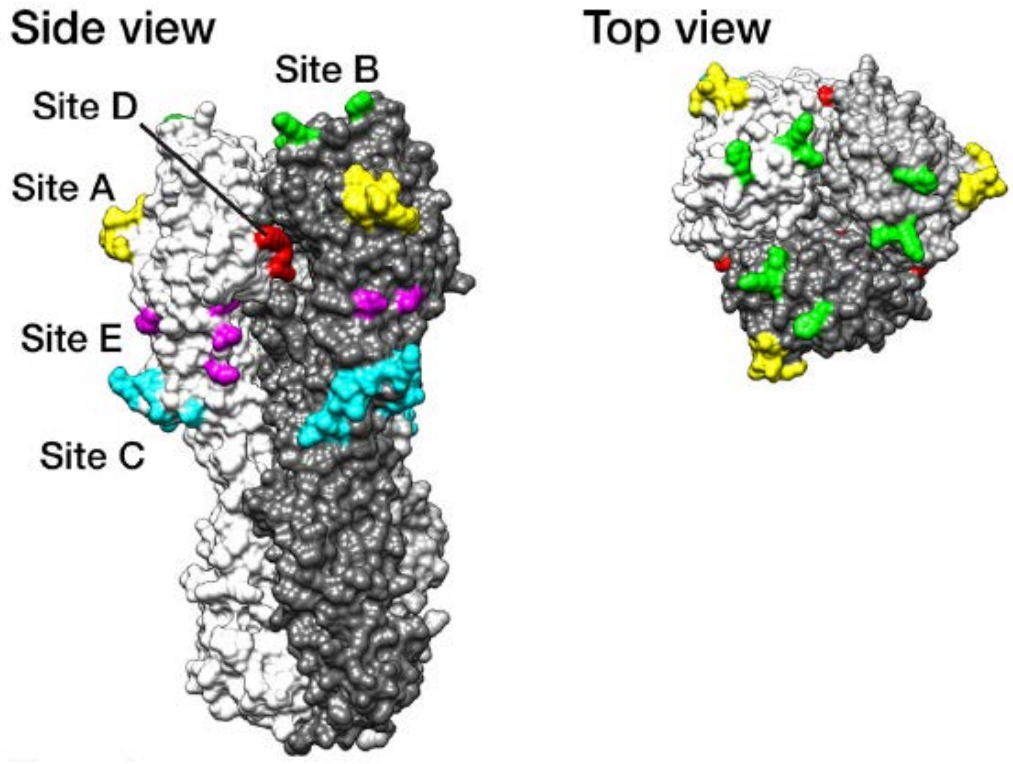
- **HA immunogenicity**
- Egg adaptation
- Hemagglutinin mismatch
- Ignoring neuraminidase
- Imprinting
- Repeat vaccination
- Waning

High Dose Systematic review and Meta-analysis

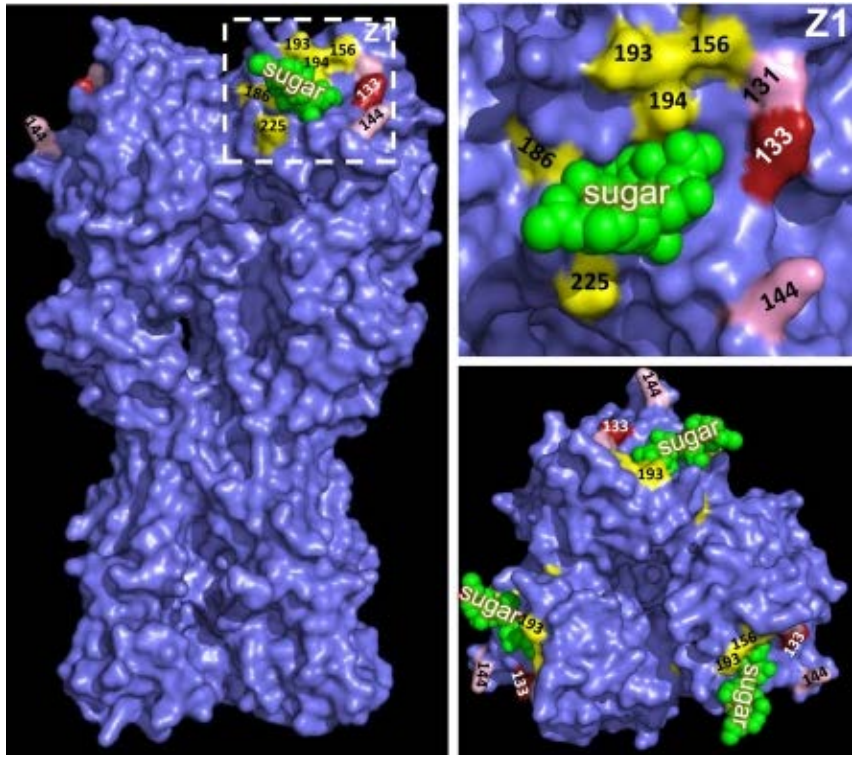
Outcome	All Seasons	
	rVE[a] (95%CI[b])	p-value
Influenza-like Illness[c]	15.9% (4.1% - 26.3%)	0.01
Influenza Hospitalization	12.6% (7.1% - 17.9%)	<0.001
Pneumonia Hospitalization	27.3% (15.3% - 37.6%)	<0.001
Pneumonia/Influenza Hospitalization	13.4% (7.3% - 19.2%)	<0.001
Cardiorespiratory Hospitalization	17.9% (15.0% - 20.8%)	<0.001
All-cause Hospitalization	8.4% (5.7% - 11.0%)	<0.001

Lee J et al, Options X, Singapore

H3 glycosylation can alter immunogenicity of H3N2 HAs



Broecker F et al, J Virol 2018



Das SR et al, PNAS 2011

Issues with Type A Vaccines

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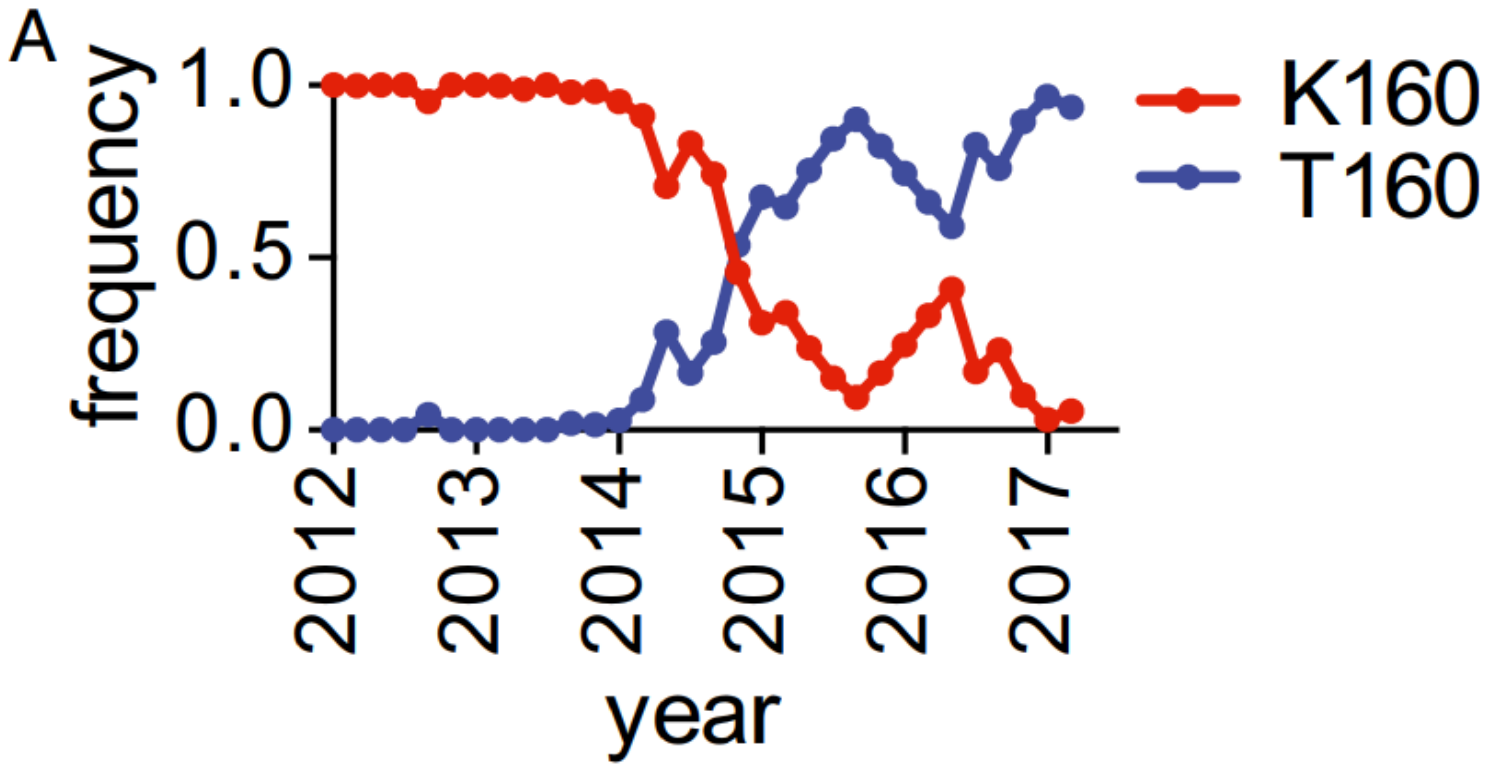
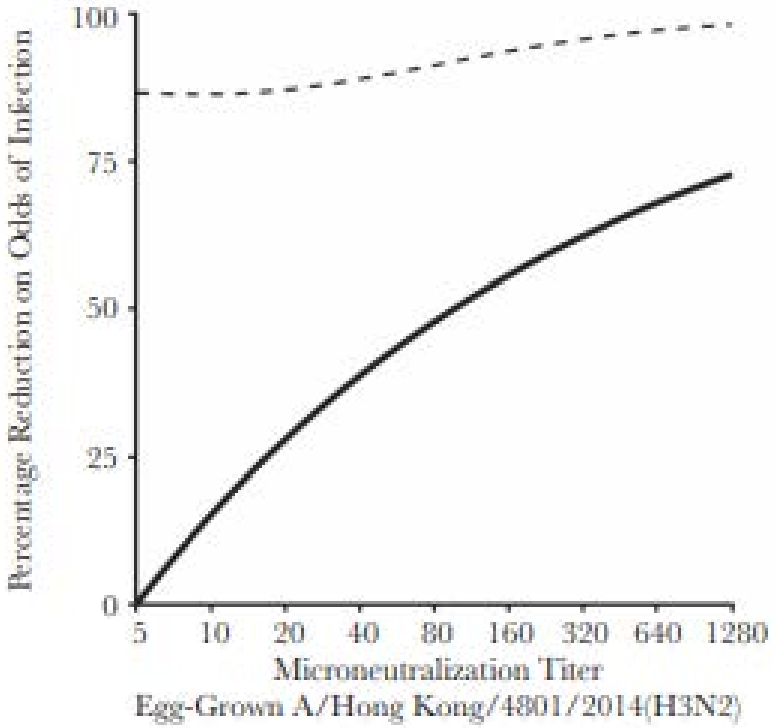
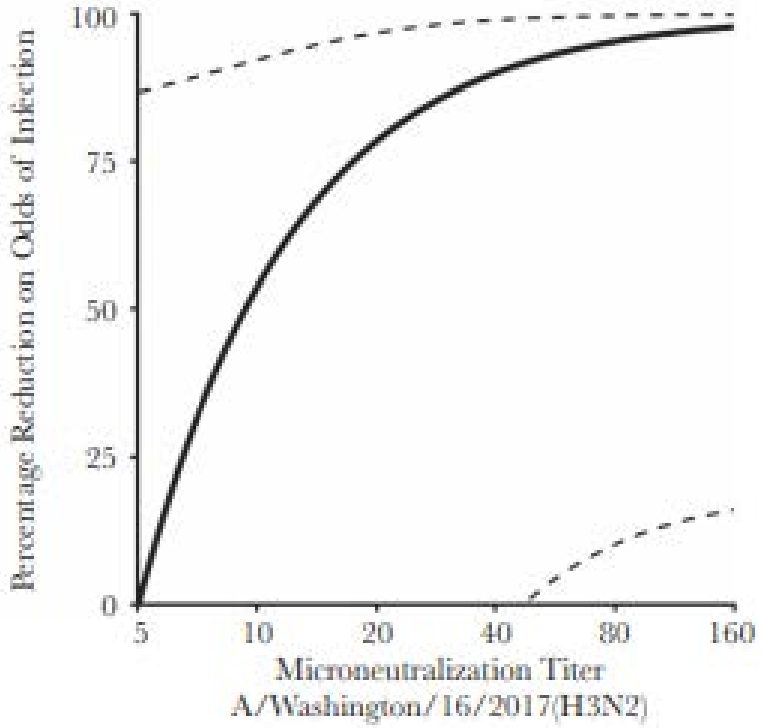
H3N2 Glycosylation Site Alters Binding of Antibodies Elicited by Egg-Adapted Vaccine



Zost SJ et al. Proc Natl Acad Sci 2017;114:12578–83.

Reduction in Influenza Virus Infection against Egg and Cell Grown H3N2 Viruses





Levine et al. J Infect Dis 2019;219:1904-1912.

Issues with Type A Vaccines

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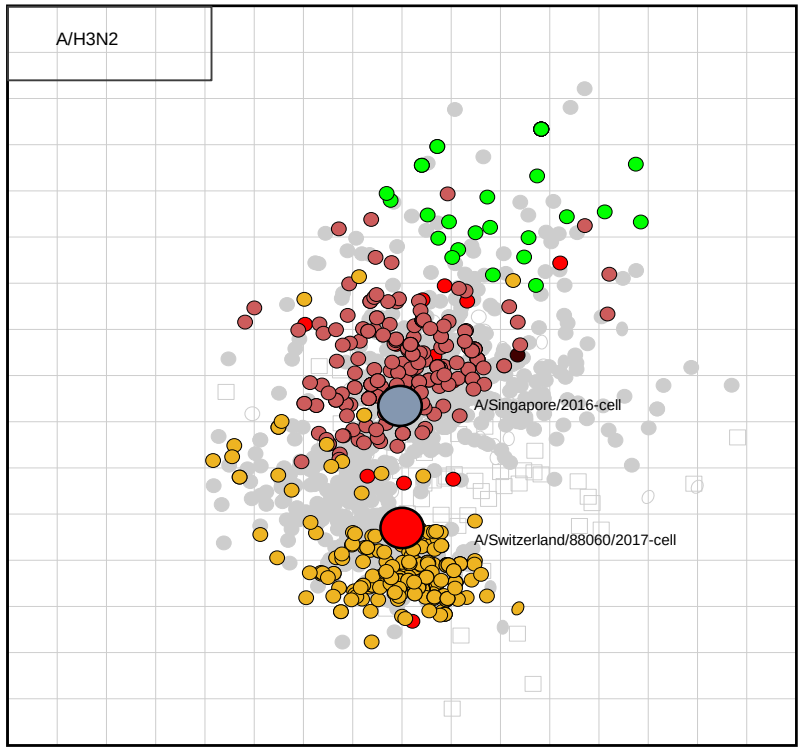
Diversity of H3N2 Viruses at Strain Selection

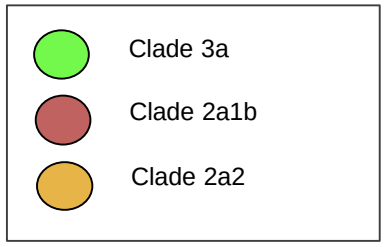
		REFERENCE FERRET ANTISERA								
		2a1	2a1b		2a2	3C.3a				
	REFERENCE VIRUSES	EGG SN/X307A	EGG UE/240	EGG NL/10260	EGG SZ/8060	SIAT KS/14	EGG KS/14	3C Clade	DATE COLLECTED	PASSAGE
1	A/Singapore/INFIMH-16-0019/2016 X-307A	**2560**	320	160	160	80	80	2a1	REASS	E5E2E9/E1
2	A/Abu Dhabi/240/2018	640	**10240**	5120	160	80	40	2a1b	2018/01/01	E6
3	A/Netherlands/10260/2018	1280	10240	**5120**	160	160	80	2a1b	2018/02/15	E4/E2
4	A/Hong Kong/681/2018	2560	5120	5120	320	640	640	2a1b	2018/04/09	E6/E2
5	A Switzerland/8060/17	640	80	80	**2560**	40	40	2a2	2017/12/21	E5/E2
6	A/Kansas/14/2017	80	80	80	80	**160**	80	3a	2017/12/14	S3
7	A/Kansas/14/2017	160	160	320	40	640	**1280**	3a	2017/12/14	E7
TEST VIRUSES										
8	A/Florida/15/2019	80	160	160	80	160	20	2a1b	2019/02/04	S2
9	A/Hawaii/09/2019	80	320	40	40	80	<20	2a1b	2019/02/09	S1
10	A/California/127/2018	160	320	160	40	80	<20	2a1b	2018/12/31	S1
11	A/Hawaii/08/2019	160	320	80	80	160	<20	2a1b	2019/02/01	S1
12	A/New Mexico/09/2019	160	160	160	80	160	<20	2a1b	2019/02/05	S1
13	A/New Mexico/10/2019	160	160	160	80	160	<20	2a1b	2019/02/10	S1
14	A/Delaware/12/2019	40	80	80	20	80	<20	2a1b	2019/02/04	S1
15	A/Vermont/06/2019	40	80	80	40	160	<20	2a1b	2019/02/06	S1
16	A/Vermont/09/2019	80	160	160	80	80	<20	2a1b	2019/02/11	S2
17	A/Brisbane/34/2018	40	40	160	40	320	320	3a	2018/03/17	E2/E1
18	A/Lousiana/14/2019	40	40	20	20	320	160	3a	2019/02/06	S1
19	A/Maine/08/2019	40	80	40	20	320	160	3a	2019/02/06	S1
20	A/New Hampshire/13/2019	40	40	40	20	320	160	3a	2019/02/15	S1
21	A/North Dakota/12/2019	80	80	80	40	320	160	3a	2019/02/10	S1
22	A/South Dakota/10/2019	40	40	40	20	320	160	3a	2019/02/18	S1
23	A/Tennessee/09/2019	20	20	40	20	320	160	3a	2019/02/04	S1
24	A/Texas/45/2019	40	40	20	20	320	160	3a	2019/02/07	S1
25	A/Iowa/11/2019	40	40	40	40	640	320	3a	2019/02/07	S1
26	A/Wyoming/06/2019	80	80	160	40	2560	640	3a	2019/02/04	S1

World Health Organization (2019)

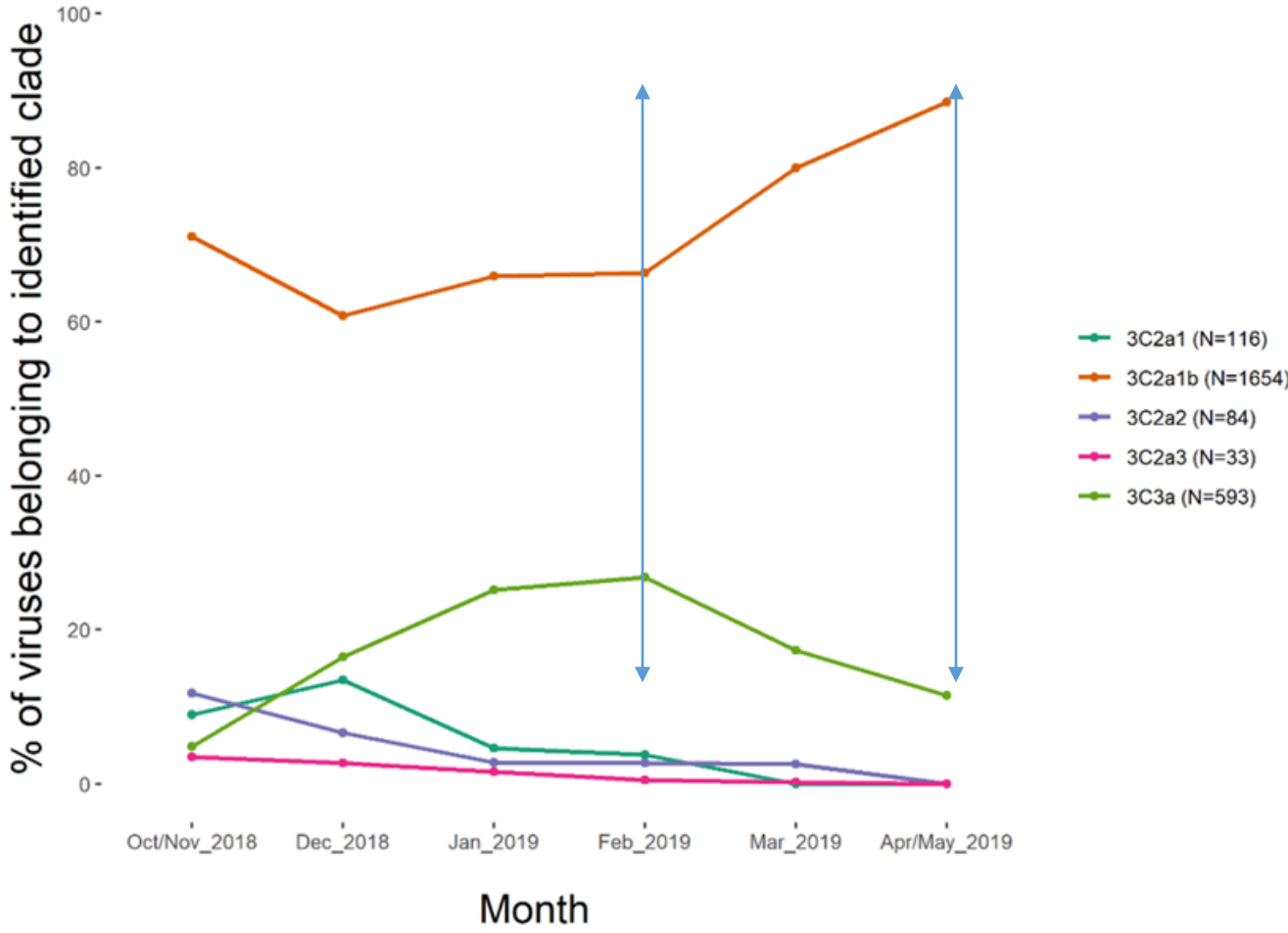
Co-circulation of H3N2 Viruses at Strain Selection



Three distinct antigenic groups



Antigenic cartography provided by Prof Derek Smith and Dr Sarah James, Cambridge University (UK)

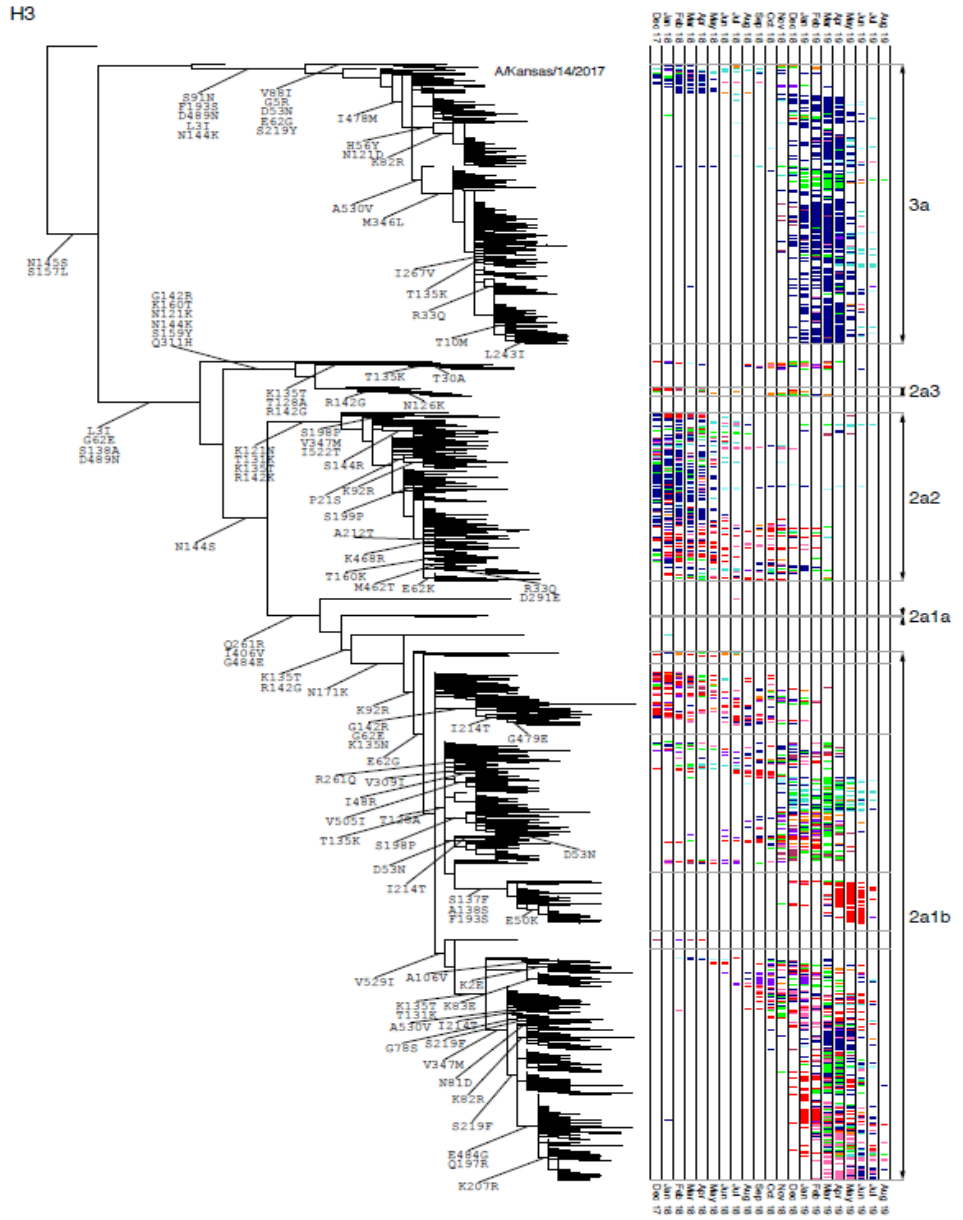


World Health Organization (2019)

Sustained co circulation of H3N2 Viruses

North America
South America
Europe
Africa
Middle East
Russia
E SE Asia
Oceania

Courtesy of Derek Smith
University of Cambridge



Kansas 2018

Singapore 2016

South Australia 2019

Switzerland 2017

World Health Organization (2019)

Vaccine Effectiveness by Genetic clades 2014-15

Genetic Group, Age	Influenza A(H3N2)–Positive Cases, Proportion (%) Vaccinated	Influenza Virus–Negative Controls, Proportion (%) Vaccinated	VE, % (95% CI)[a]
Overall[b]			
All ages	939/1817 (51.7)	3866/7078 (54.6)	7 (–5 to 17)
Genetic group 3C.3b			
All ages	56/156 (35.9)	3866/7078 (54.6)	44 (16 to 63)
Genetic group 3C.2a			
All ages	597/1101 (54.2)	3866/7078 (54.6)	1 (–14 to 14)
Genetic group 3C.3a			
All ages	31/55 (56.4)	3866/7078 (54.6)	–48 (–169 to 19)
Genetic group 3C.3			
All ages	27/47 (57.5)	3866/7078 (54.6)	1 (–87 to 48)

Flannery et al. J Infect Dis. 2016;214(7):1010-1019.

Issues with Type A Vaccines

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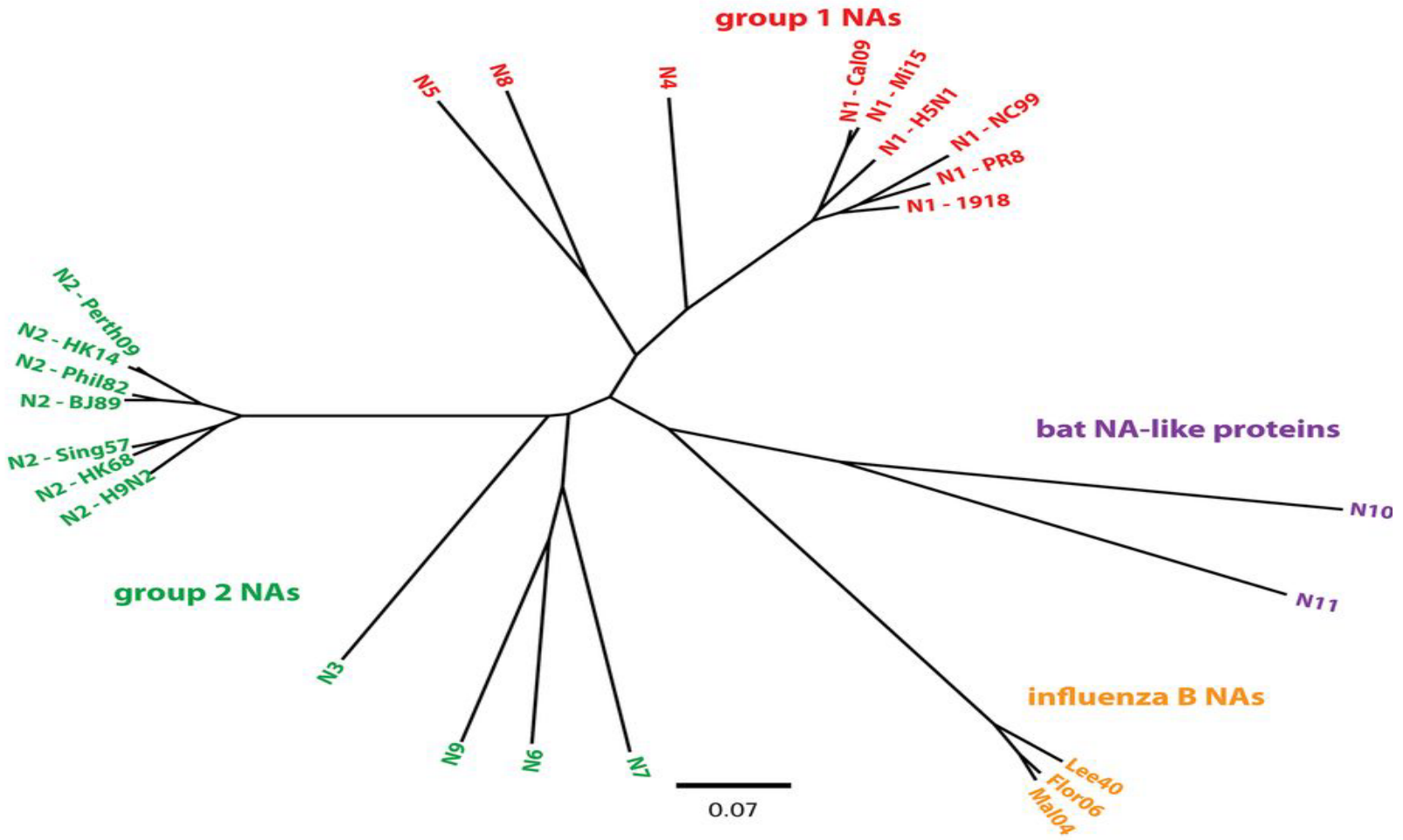
Influenza Virus Neuraminidase Phylogeny



Krammer et al. mBio 2018; doi:10.1128/mBio.02332-17.

Frequency of Neuraminidase Antibody Responses, 2008-09 Influenza Vaccines

Vaccine	A/Brisbane/59/07 (N1)	A/Brisbane/10/07 (N2)
Afluria	17 (57)	14 (47)
Fluarix	7 (23)	22 (73)
Flulaval	8 (27)	18 (60)
Fluzone	12 (40)	14 (47)
Fluvirin	11 (37)	17 (57)
Flumist	5 (17)	0 (0)

Couch et al. Vaccine 2012; 31: 190-195.

Correlation of HAI, Microneutralization and NAI Titers by Intervention Groups

Placebo

	Pre-Vaccination			Post-Vaccination			Post-Season		
	HAI	MN	NAI	HAI	MN	NAI	HAI	MN	NAI
HAI	1.00	0.87	0.47	1.00	0.87	0.55	1.00	0.84	0.53
MN		1.00	0.41		1.00	0.51		1.00	0.56
NAI			1.00			1.00			1.00

Inactivated Influenza Vaccine

	HAI	MN	NAI	HAI	MN	NAI	HAI	MN	NAI
HAI	1.00	0.87	0.40	1.00	0.78	0.37	1.00	0.78	0.31
MN		1.00	0.46		1.00	0.38		1.00	0.40
NAI			1.00			1.00			1.00

Live-Attenuated Influenza Vaccine

	HAI	MN	NAI	HAI	MN	NAI	HAI	MN	NAI
HAI	1.00	0.81	0.42	1.00	0.88	0.37	1.00	0.87	0.45
MN		1.00	0.61		1.00	0.52		1.00	0.41
NAI			1.00			1.00			1.00

Correlation
>0.75
0.50-0.75
<0.50

Monto et al. J Infect Dis. 2015;212:1191-1199.

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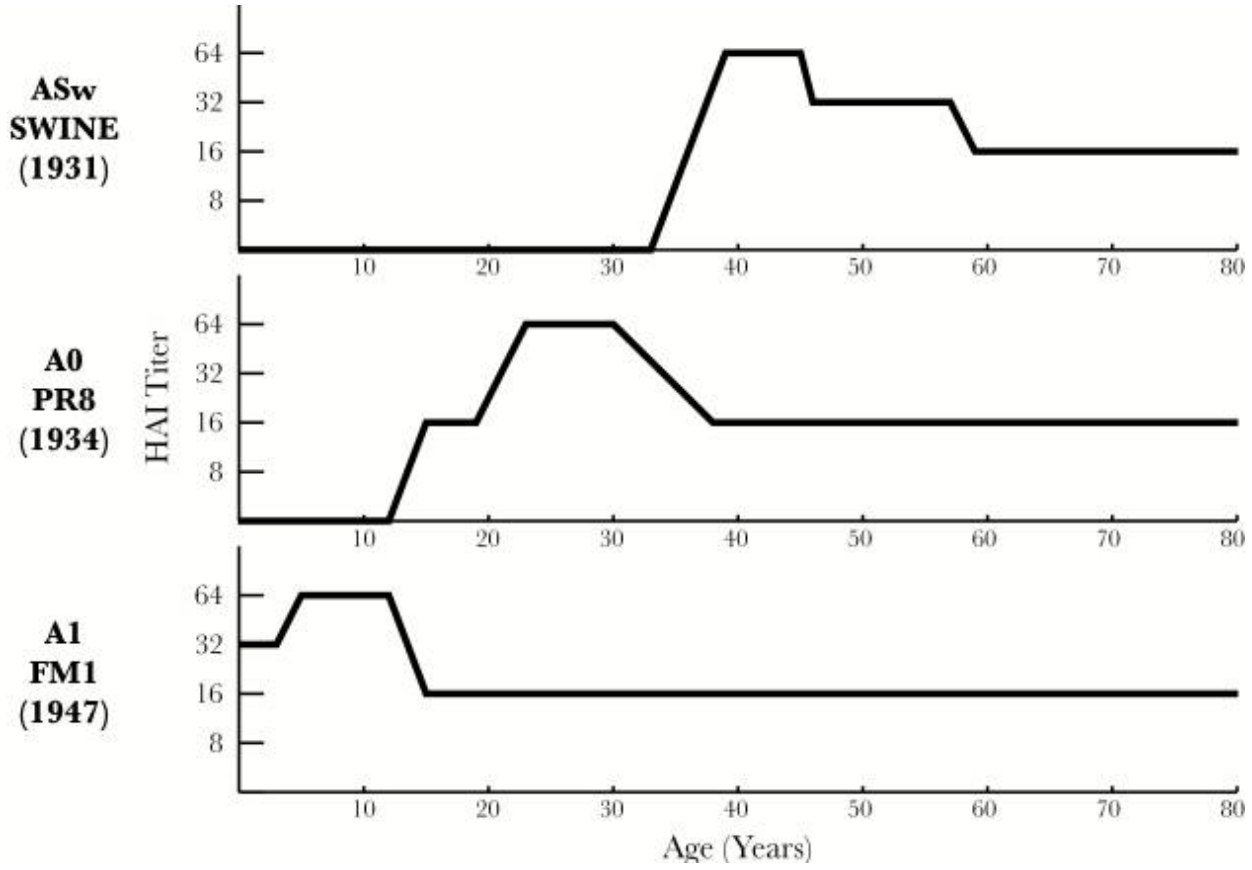
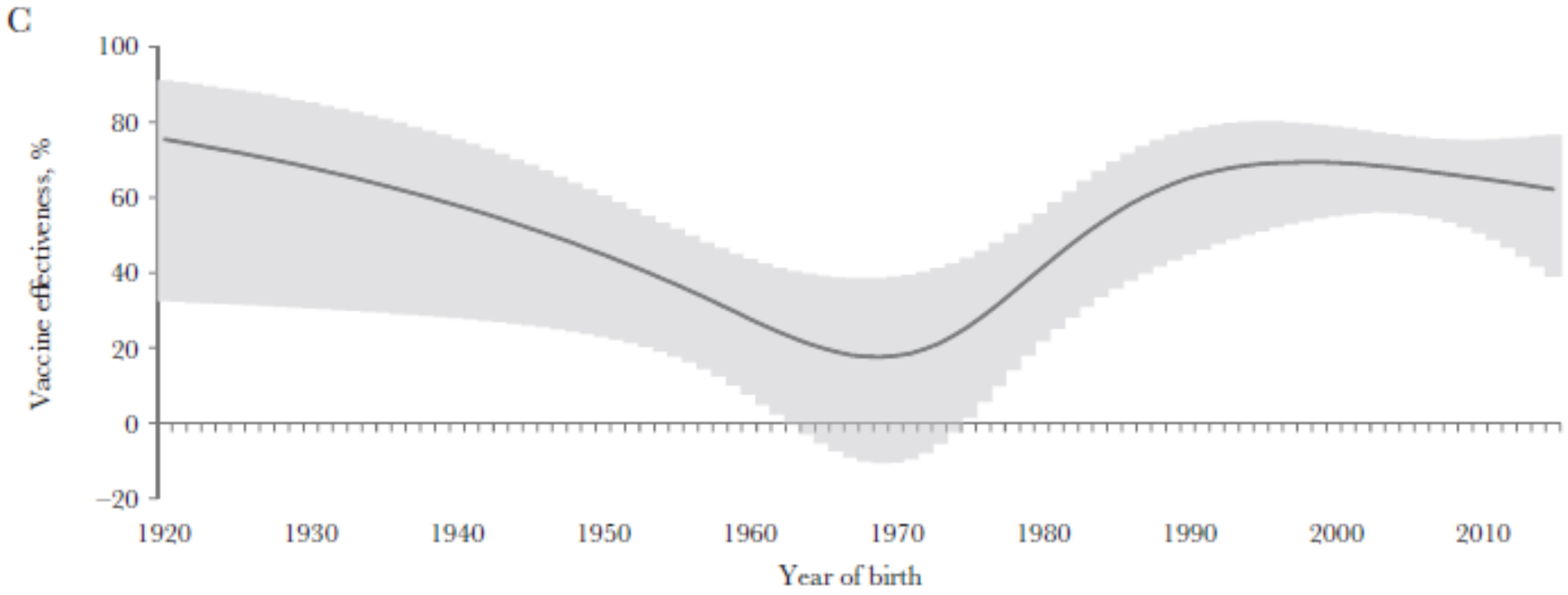
Absence of Antibody in Younger Individuals - Persistence of Antibody in Older



Francis T. Proc Am Philos Soc. 1960; 104:572-578.

Influence of Birth Cohort on H1N1 VE against Medically Attended Illnesses, 2015-16



Flannery B., et al. J Infect Dis 2018; 218:189-196.

How to Counter Original Antigenic Sin

Children represent the most susceptible members of the population and probably the most important material for the building of epidemics. The gaps in their immunity should be eliminated by providing early in life the antigenic stimuli to meet the known or anticipated recurrent strains. Natural exposures would then serve to enhance the broad immunity laid down by vaccination. It is our hope that such vaccines can be made from pools of chemically purified antigens –or even with strains experimentally devised. In this manner the original sin of infection could be replaced by an initial blessing of induced immunity.

Francis, T. Proc Amer Phil Soc 1960;104: 572- 578

Issues with Type A Vaccines

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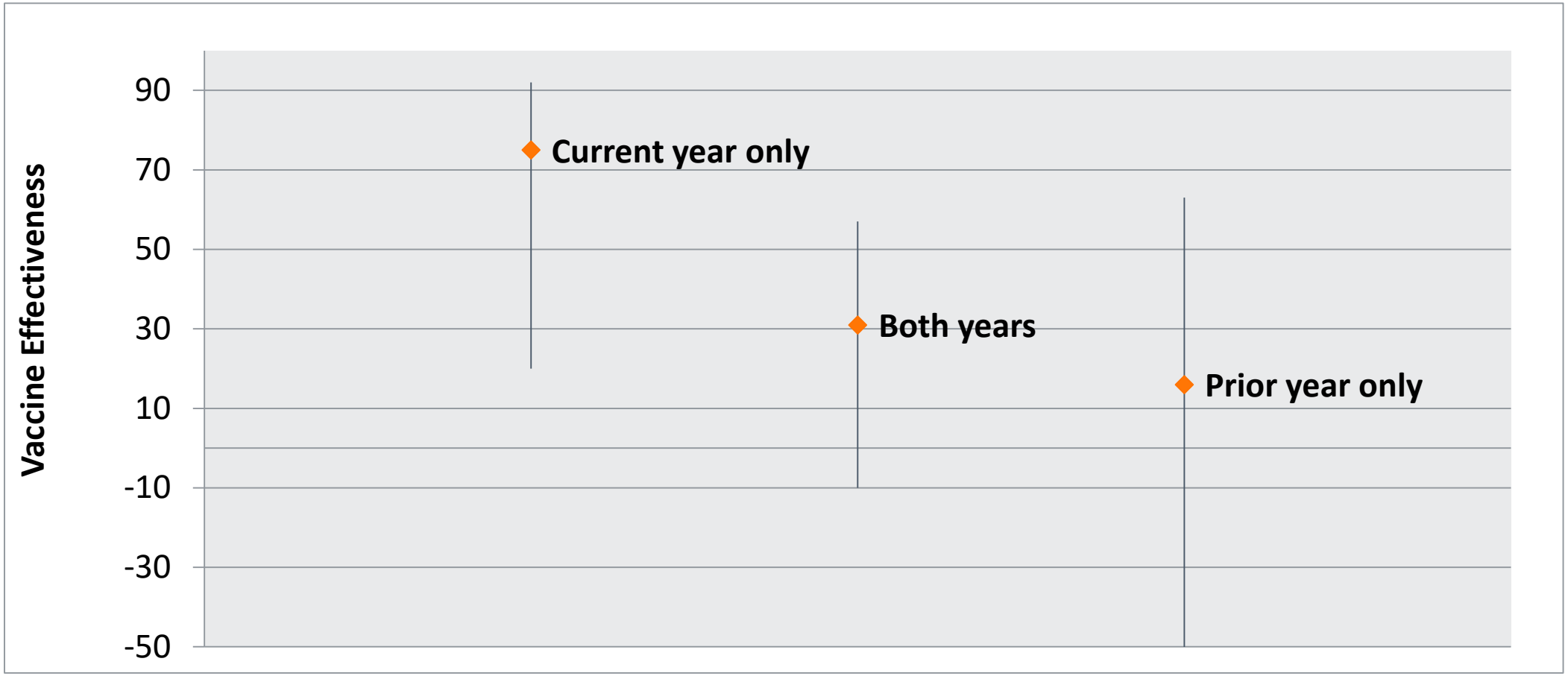
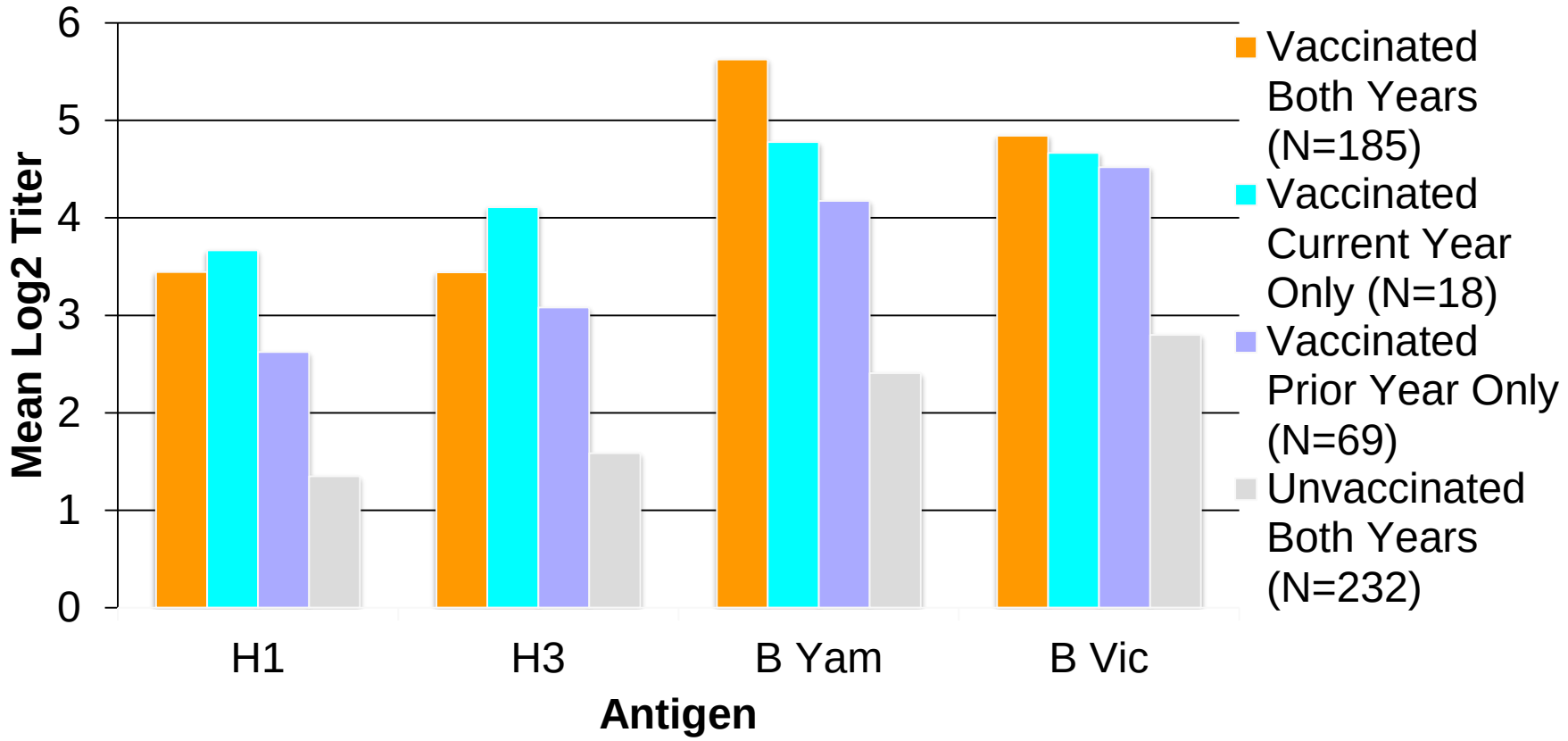
- Imprinting
- **Repeat vaccination**
- Waning

H3N2 VE by Two-Year Vaccination Status 2012-13 (Compared to Those Vaccinated Neither Year): Michigan Households



Ohmit et al J Infect Dis. 2015; 211:1519-1528.

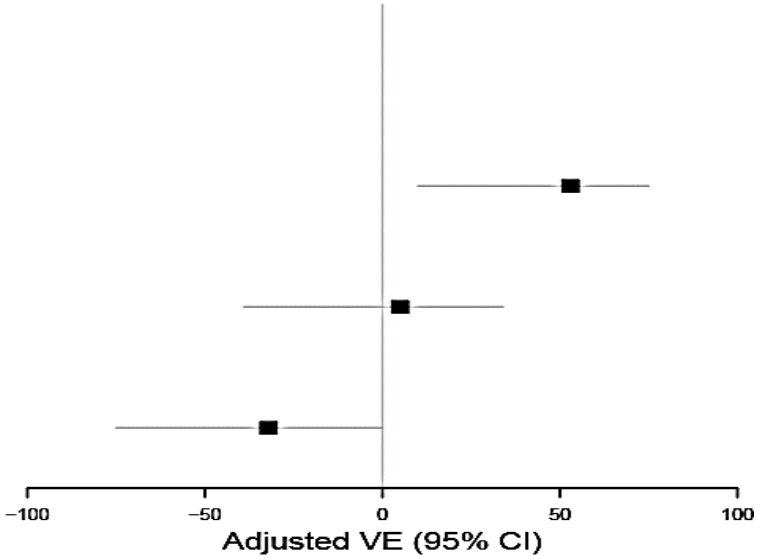
HAI Titers by Vaccination Status in the 2011-12 and 2012-13 Seasons: Michigan Households



Ohmit et al J Infect Dis. 2015;211:1519-28.

Effect of 2013-14 Season Influenza Vaccine on 2014-15 H3N2 Vaccine Effectiveness

Vaccination History (2013–2014 and 2014–2015)	Case n (%)	Control n (%)	Adjsted VE (95% CI)
Unvaccinated both season (Reference)	263 (48)	527 (52)	Ref
Current (2014–2015) but not prior (2013–2014)	13 (2)	67 (7)	53% (10%, 75%)
Prior (2013–2014) but not current (2014–2015)	61 (11)	118 (12)	5% (−39%,34%)
Both 2013–2014 and 2014–2015 vaccines	206 (38)	310 (30)	−32% (−75%, 0%)



Skowronski et al. Clin Infect Dis. 2016; 63:21–32.

VE Against A(H3N2) and B Viruses According to Prior Season (2015-16) and Current Season (2016-17) Vaccination

	Influenza-positive Cases		Influenza-negative Controls		Unadjusted		Adjusted[a]	
	No. Cases/Row Total	(%)	No. Controls/Row Total	(%)	VE %	(95% CI)	VE %	(95% CI)
Influenza A(H3N2)[b]								
Vaccinated current 2016–2017 only	130/708	18.4	578/708	81.6	35%	(19 to 48)	35%	(18 to 48)
Vaccinated current 2016–2017 and prior 2015–2016	399/1804	22.1	1405/1804	77.9	18%	(4 to 29)	26%	(12 to 38)
Vaccinated prior 2015–2016 only	106/444	23.9	338/444	76.1	9%	(−16 to 29)	14%	(−10 to 33)
Not vaccinated either 2015–2016 or 2016–2017	467/1820	25.7	1353/1820	74.3	REF		REF	
Influenza B[c]								
Vaccinated current 2016–2017 only	49/627	7.8	578/627	92.2	53%	(35 to 66)	54%	(35 to 68)
Vaccinated current 2016–2017 and prior 2015–2016	151/1556	9.7	1405/1556	90.3	40%	(26 to 52)	42%	(26 to 55)
Vaccinated prior 2015–2016 only	47/385	12.2	338/385	87.8	23%	(−8 to 45)	22%	(−12 to 46)
Not vaccinated either 2015–2016 or 2016–2017	243/1596	15.2	1353/1596	84.8	REF		REF	

Flannery B et al. Clin Infect Dis 2019;68:1798–806.

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Rate of A(H1N1) Waning Increases with Number of Prior Vaccinations: Michigan Households

Number of Previous Vaccinations	HAI Antibody Half-life months (95% CI)
1	32 (22, 61)
2	23 (17, 38)
3	17 (12, 23)
4	14 (11, 21)
5	12 (9, 18)
6	10 (7, 15)
7	9 (7, 15)

Zelner et al. J Infect Dis 2019; 220:12-19.

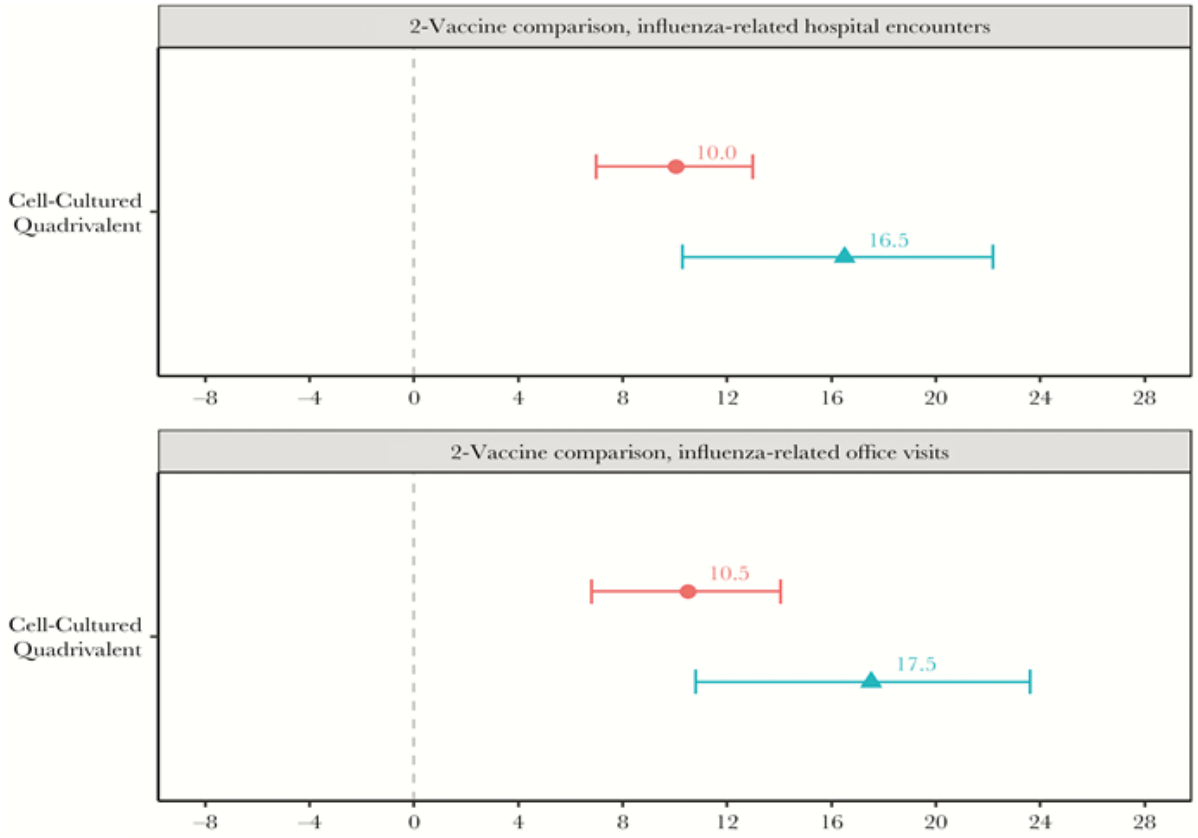
Reality Check - Barriers to Changes in Current Vaccines

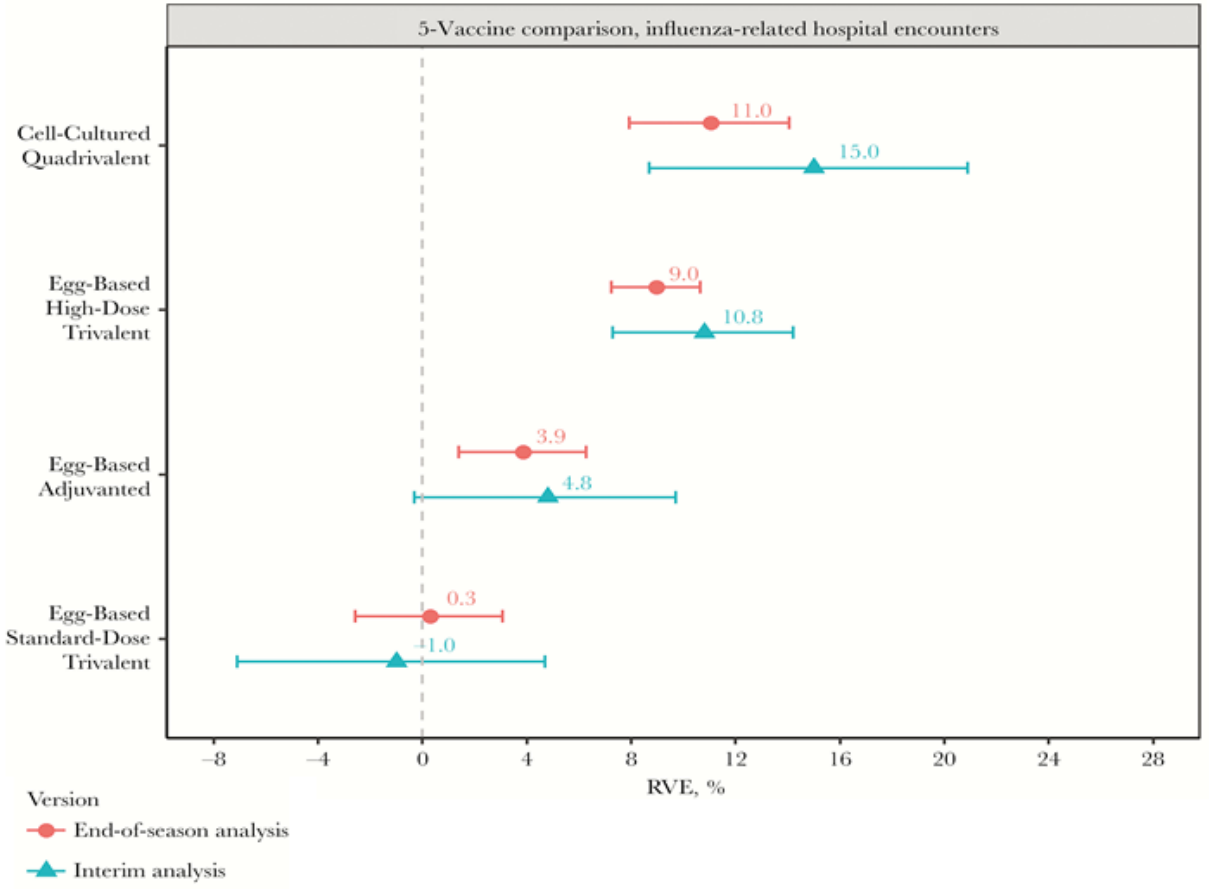
- Need to demonstrate greater breadth and duration of protection
- How to show improvement is worth it
- Safety issues
- Acceptance by the public

Improvements to the Demonstrated Problems for H3N2 ?

- Increased immunogenicity (HD) and use of adjuvants (MF59)
- Replacement of egg adapted H3N2 in vaccines by non-adapted virus (+/- retaining other egg grown components - a hybrid vaccine) (Cell-based)

Improvement in Relative VE with new Vaccines?





Izurieta HS et al. J Infect Dis, jiy716

Improvements to the Demonstrated Problems for H3N2 ?

- Increased immunogenicity (HD) and use of adjuvants (MF59)
- Replacement of egg adapted H3N2 in vaccines by non-adapted virus (+/- retaining other egg grown components - a hybrid vaccine) (Cell-based)

- Specific attention to NA in strain selection while efforts to better NA antibody response continue
- Having 2 H3N2 strains in the vaccine

Ultimate Goal: One or More Universal Vaccines

- NIAID plan calls for 75% protection against symptomatic influenza infection-Necessary for seasonal influenza
- Other goals for pandemic influenza Prevention of severe morbidity and mortality the goals
- Should be able to stockpile the pandemic product and be able to switch from seasonal
- Don’t forget type B
- Don’t forget most of the world which doesn’t currently get vaccinated

Universal Vaccines for Universal Vaccine Use

- Possible with longer duration of protection
- No population will be denied vaccine
- Not something which can be achieved in anything but the very long term
- Acknowledging such a goal also acknowledge that our current improvements will be incremental
- Also acknowledges that we need non-vaccine approaches while we work to this goal

Universal Vaccines

Universal Use