流感疫苗施打策略

四價三價? 兩劑一劑?

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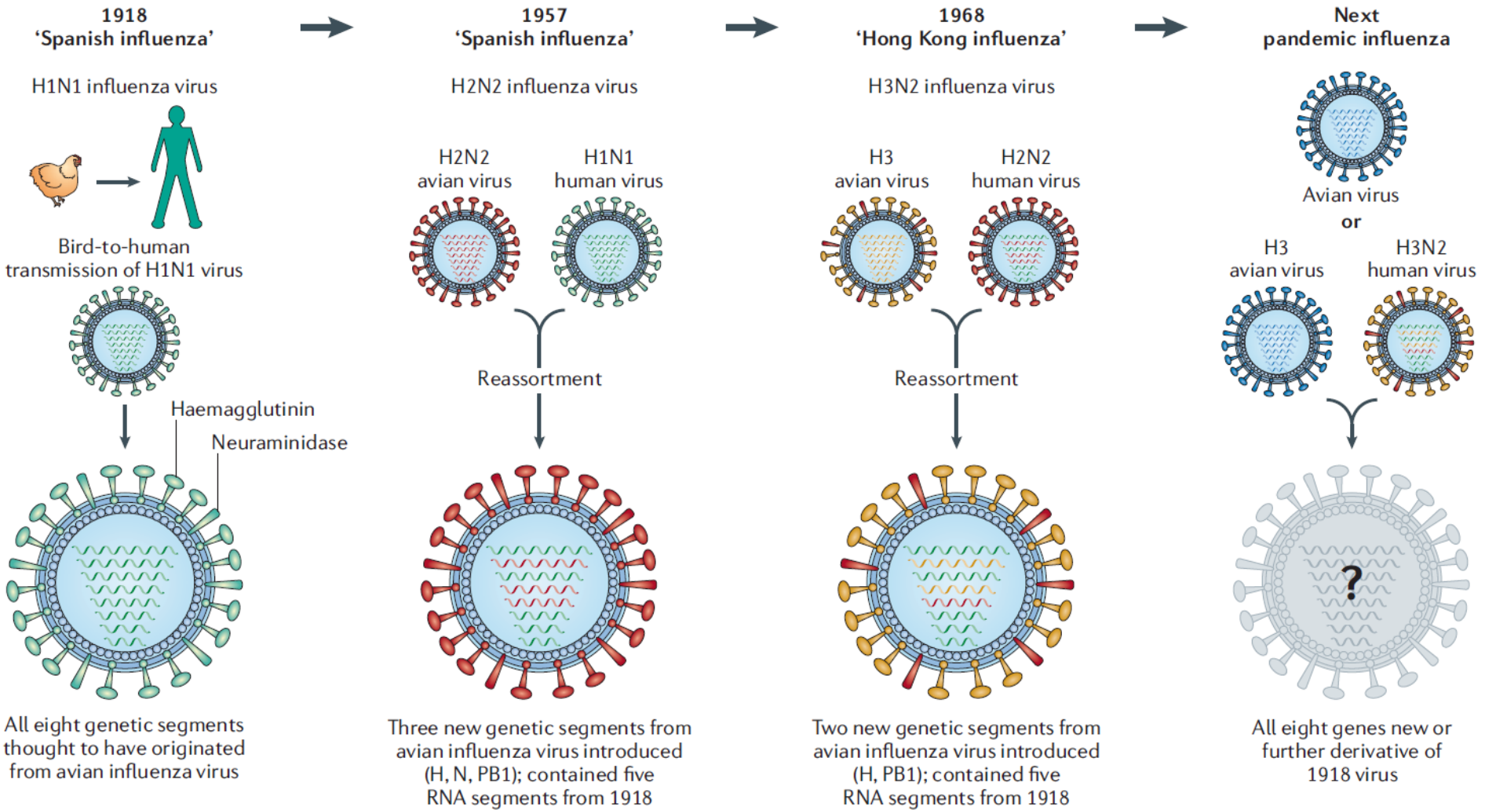
Evolution of influenza virus

Evidence of annual vaccination

Comparison of different type of vaccines

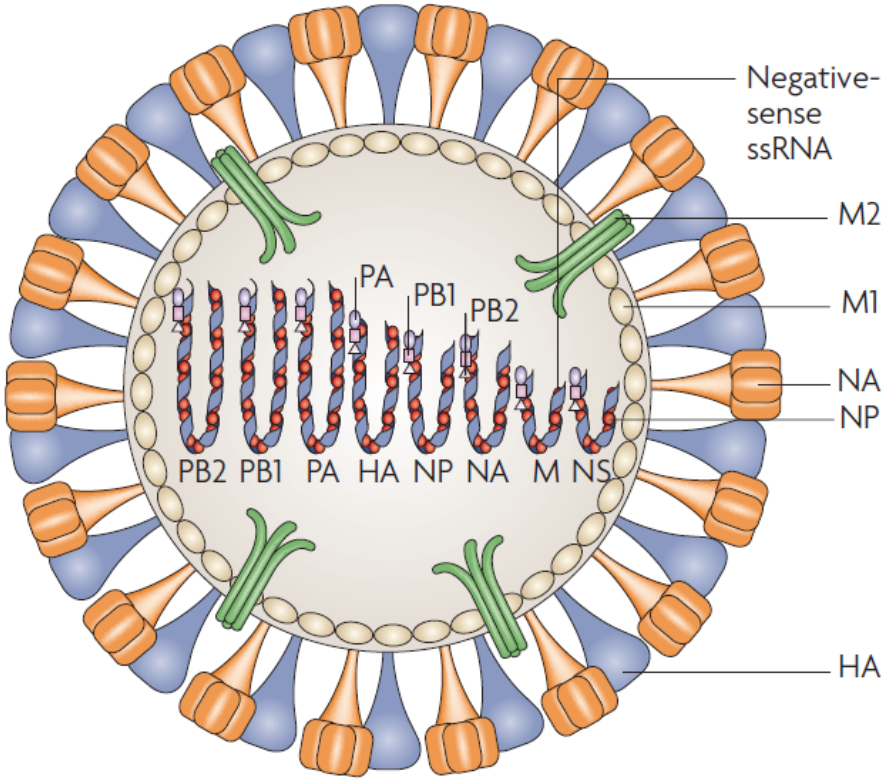
Vaccination strategy in specific group

Model for the evolution of pandemic strains of influenza virus by recombination



~ Nat Rev Drug Discov 2006; 5: 1015-25

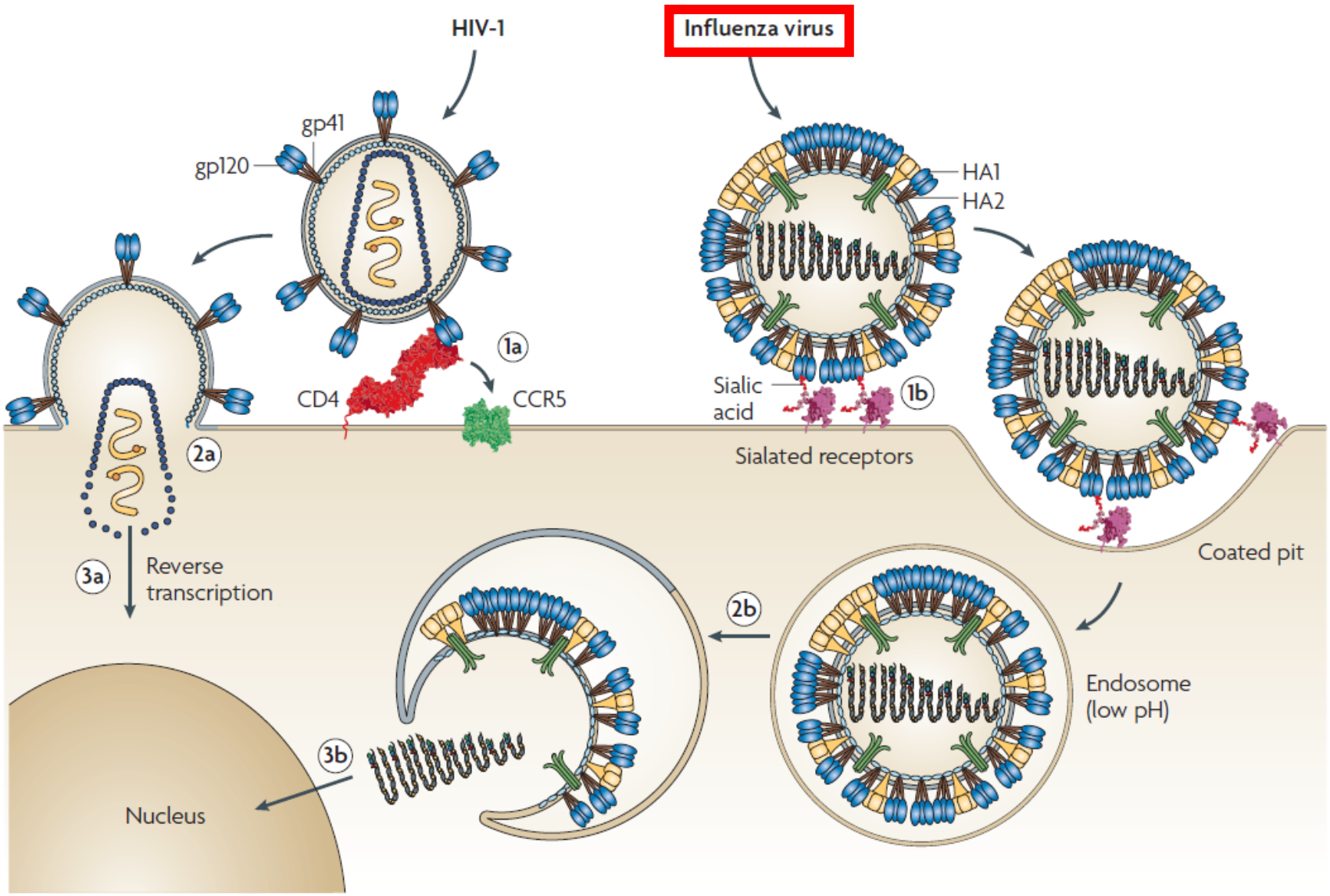
The structure of influenza virus



- Single-stranded, negative sense RNA viruses of the family ***Orthomyxoviridae***
- Type of antigen: **Haemagglutinin** (HA, 16) and **Neuraminidase** (NA, 9)
- The antigenically distinct viral types — **A**, **B** and **C**.
- Virus polymerase complex: PB1, PB2, PA; Surface envelope glycoproteins: HA, NA; Nuclear protein: NP; Nonstructural protein: NS1, NS2; Matrix protein: M1.

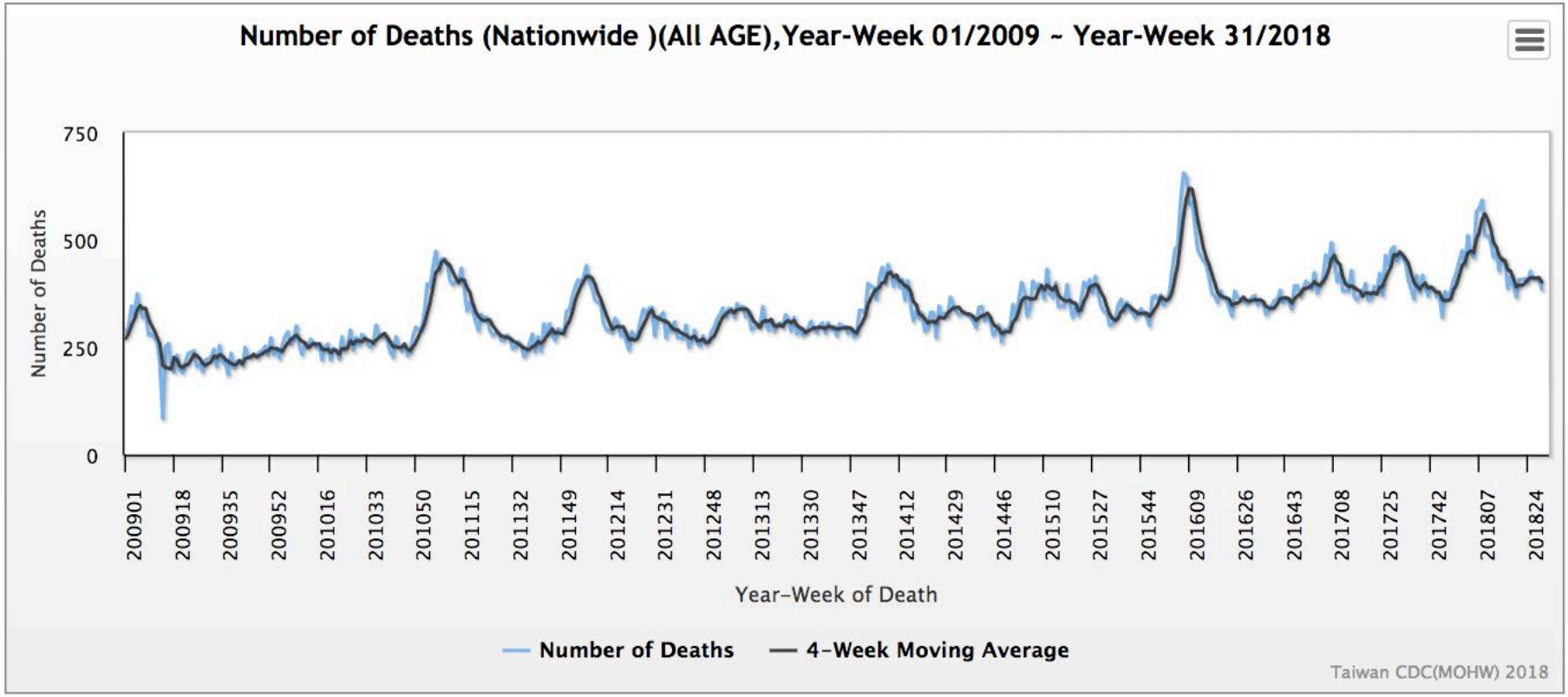
~ Nat Rev Genet 2007; 8: 196-205

The entry of influenza virus in target cells

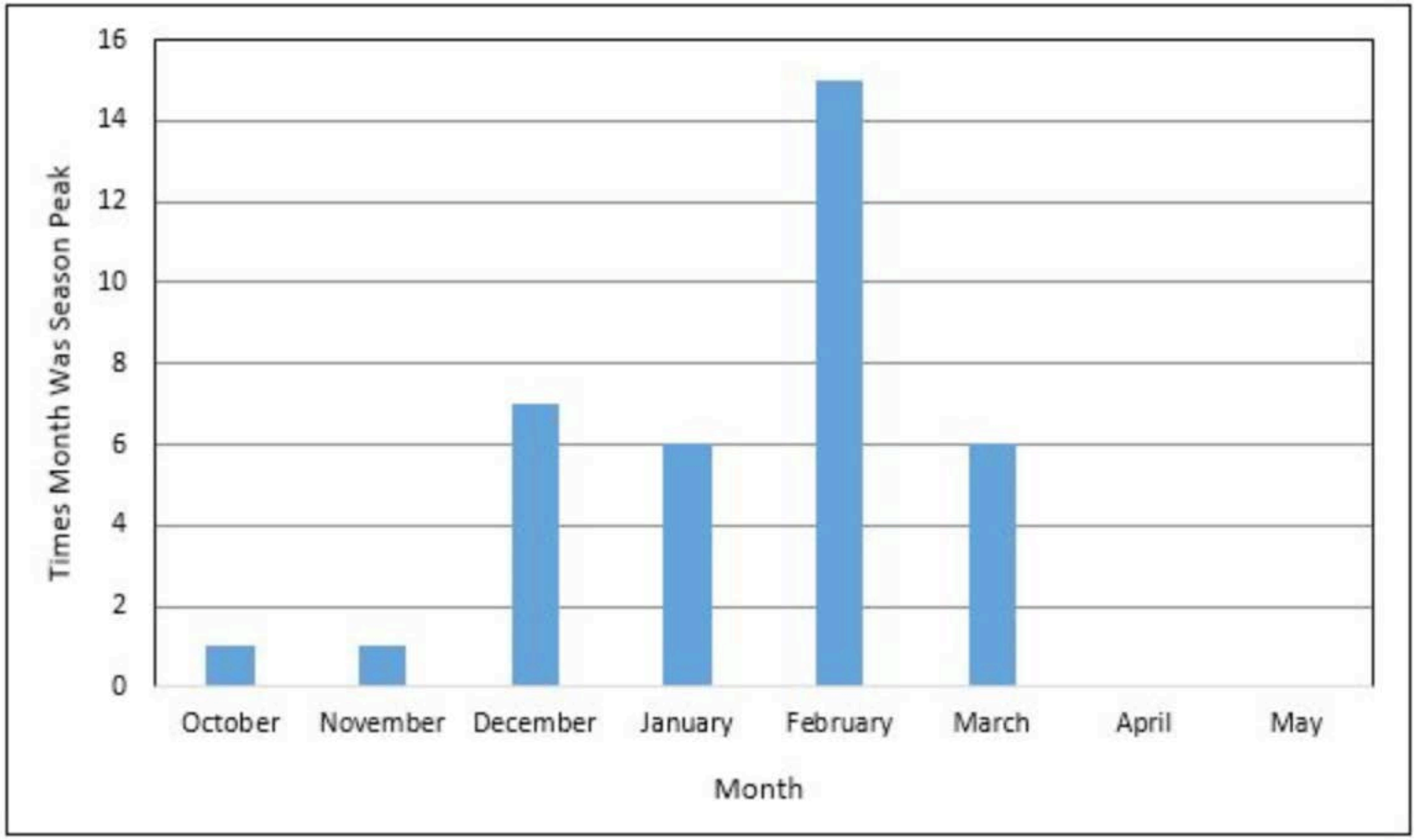


~ Nat Rev Microbiol 2008; 6: 143-55

Mortality caused by Influenza and pneumonia in Taiwan

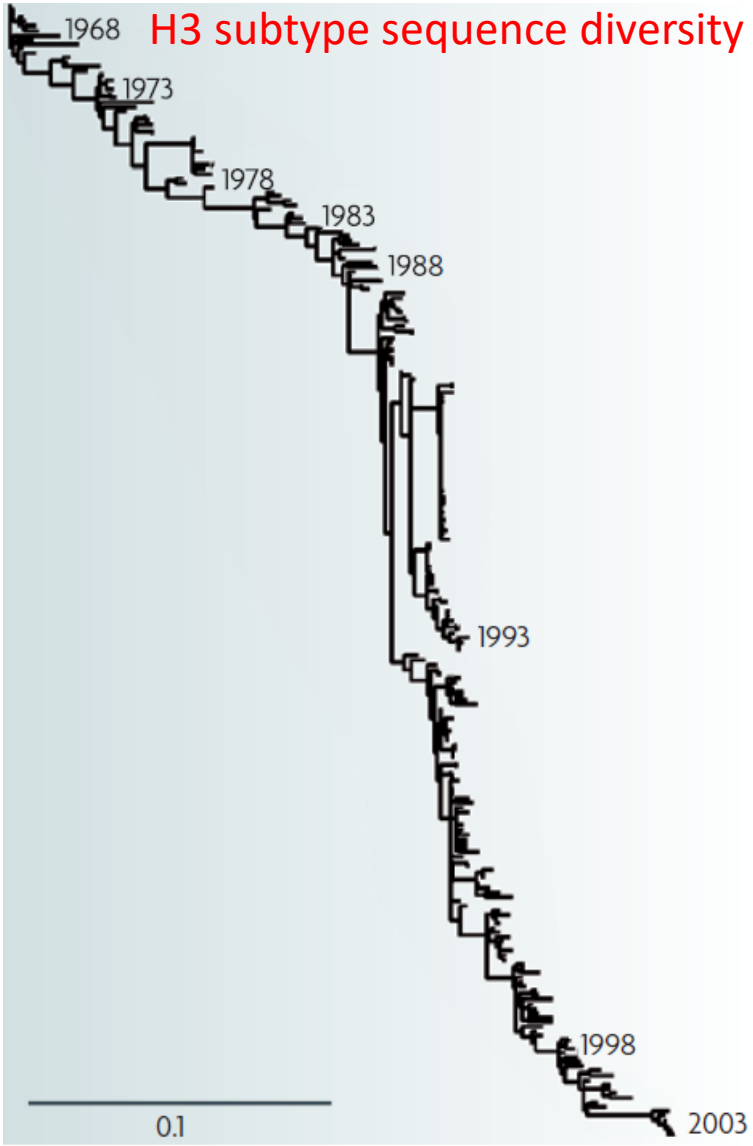


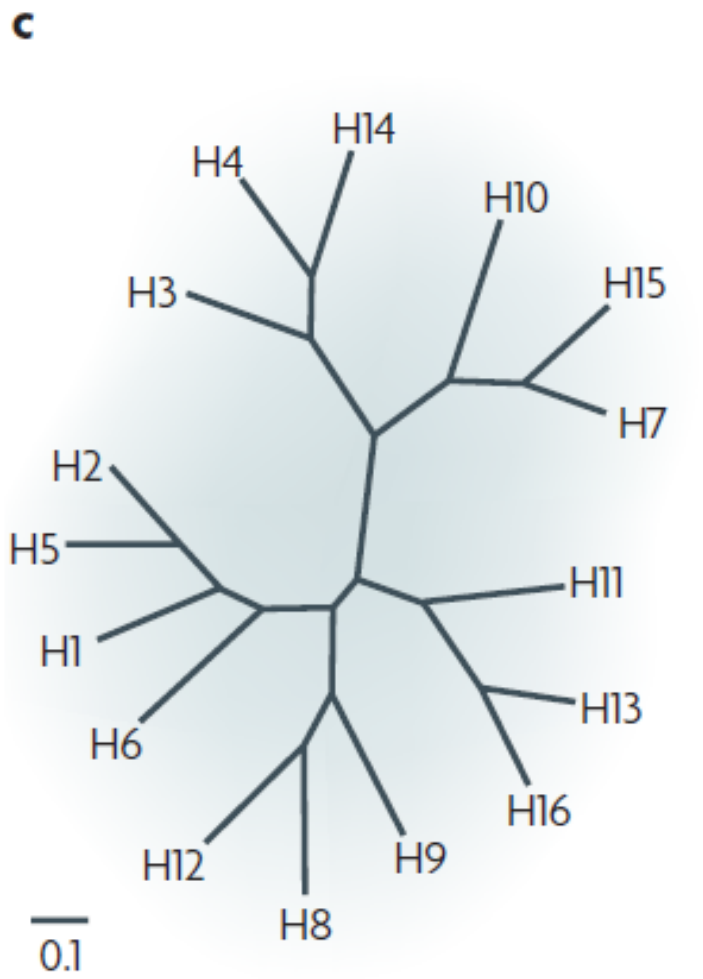
Peak month of flu-activity from 1982-2018 in U.S.



From https://www.cdc.gov/flu/about/season/flu-season.htm

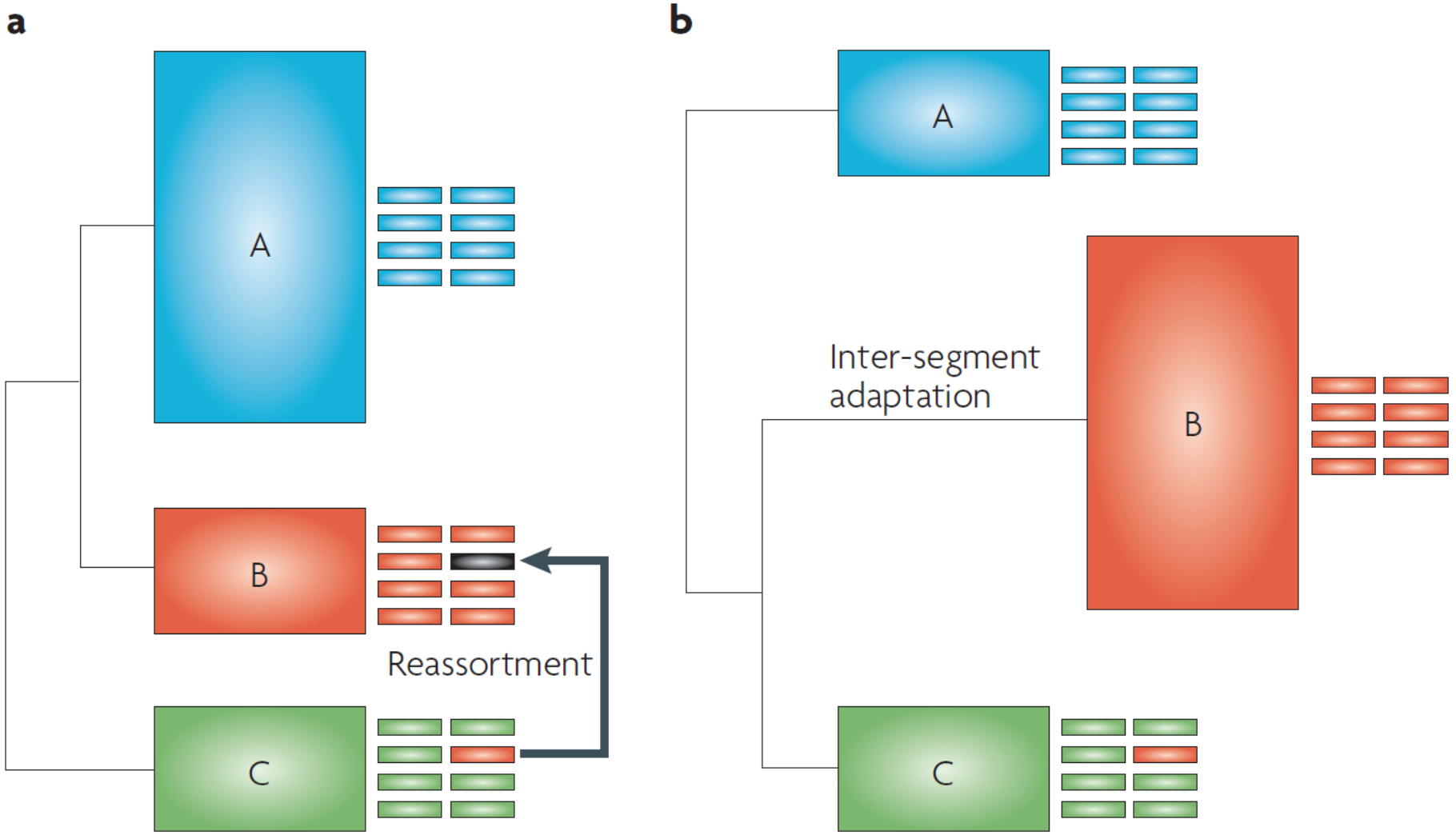
DNA maximum-likelihood trees of influenza virus





Nat Rev Microbiol 2008; 6: 143-55

A model for the genome-wide evolution of human influenza virus



~ Nat Rev Genet 2007; 8: 196-205

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Vaccination strategy in specific group

ACIP Recommended immunization schedule for adults

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza[1]	1 dose annually				

Vaccine	Pregnancy[1-6]	Immuno-compromised (excluding HIV infection)[3-7,11]	HIV infection CD4+ count (cells/μL)[3-7,9-10]		Asplenia, complement deficiencies[7,10,11]	End-stage renal disease, on hemodialysis[7,9]	Heart or lung disease, alcoholism[7]	Chronic liver disease[7-9]	Diabetes[7,9]	Health care personnel[3,4,9]	Men who have sex with men[6,8,9]
			<200	≥200							
Influenza[1]	1 dose annually										

ACIP. Available at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

WHO recommends seasonal influenza vaccines in 2018 to 2019

- **The northern hemisphere (November to April)**
  - A/Michigan/45/2015 (H1N1) pdm09-like virus
  - A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
  - B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
  - B/Phuket/3073/2013-like virus
- **The southern hemisphere (May to October)**
  - A/Michigan/45/2015 (H1N1) pdm09-like virus
  - A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
  - B/Phuket/3073/2013-like virus
  - B/Brisbane/60/2008-like virus

Recommended composition of influenza virus vaccine by WHO

World Health Organization

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Influenza

- Influenza
- 70 years of influenza control
- Surveillance and monitoring
- GISRS and laboratory
- PIP Framework
- Vaccines
  - Vaccine viruses
  - Vaccine use
  - Vaccine in tropics
- Respiratory Syncytial Virus
- Avian and other zoonotic influenza
- Public health preparedness

Recommended composition of influenza virus vaccines for use in the 2018-2019 northern hemisphere influenza season

22 February 2018

It is recommended that quadrivalent vaccines for use in the 2018-2019 northern hemisphere influenza season contain the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that the influenza B virus component of trivalent vaccines for use in the 2018-2019 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.

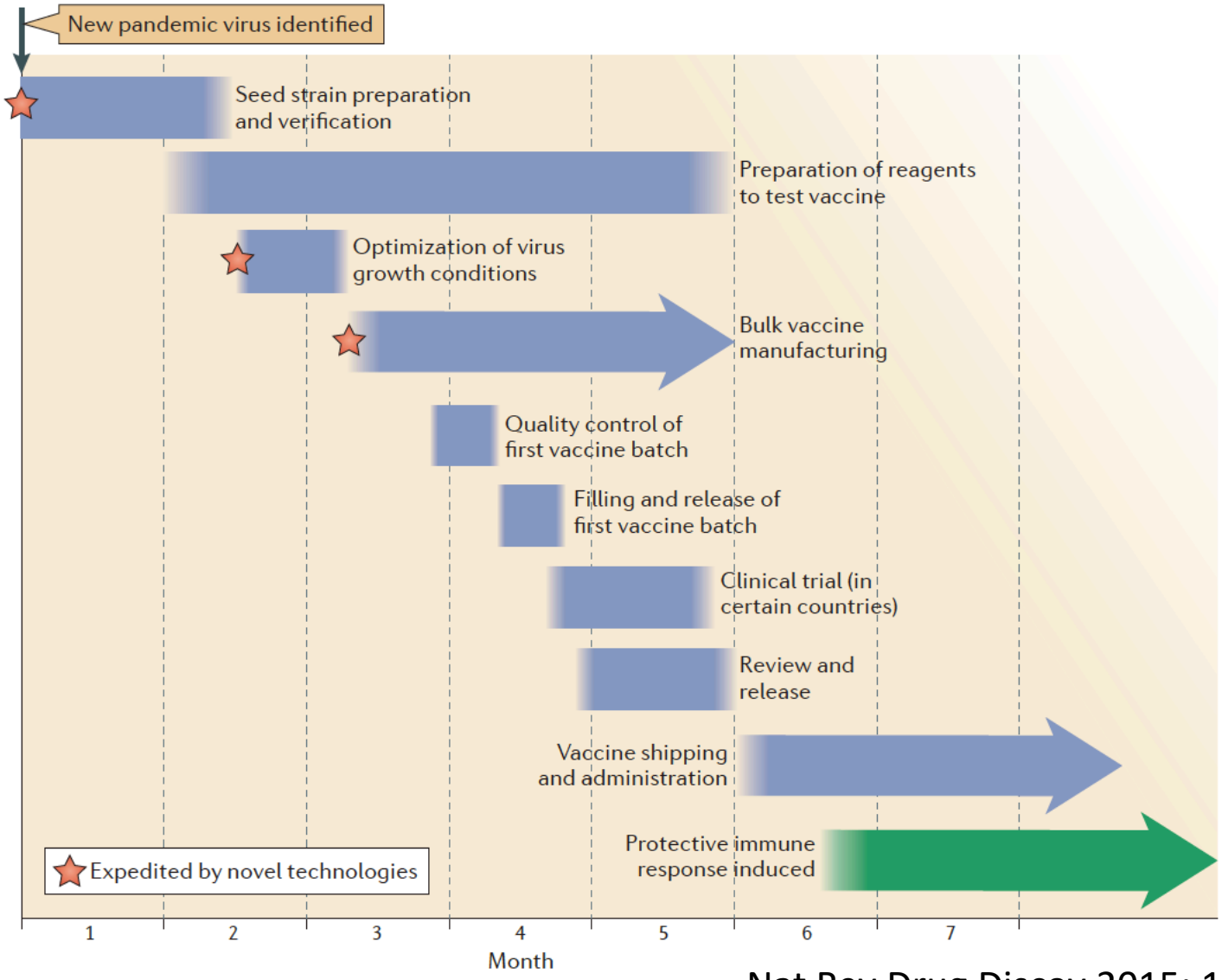
For more information

Recommended composition of influenza virus vaccines for use in the 2018-2019 northern hemisphere influenza season - full report
pdf, 27kb

Questions and answers - Recommended composition of influenza virus vaccines
pdf, 85kb

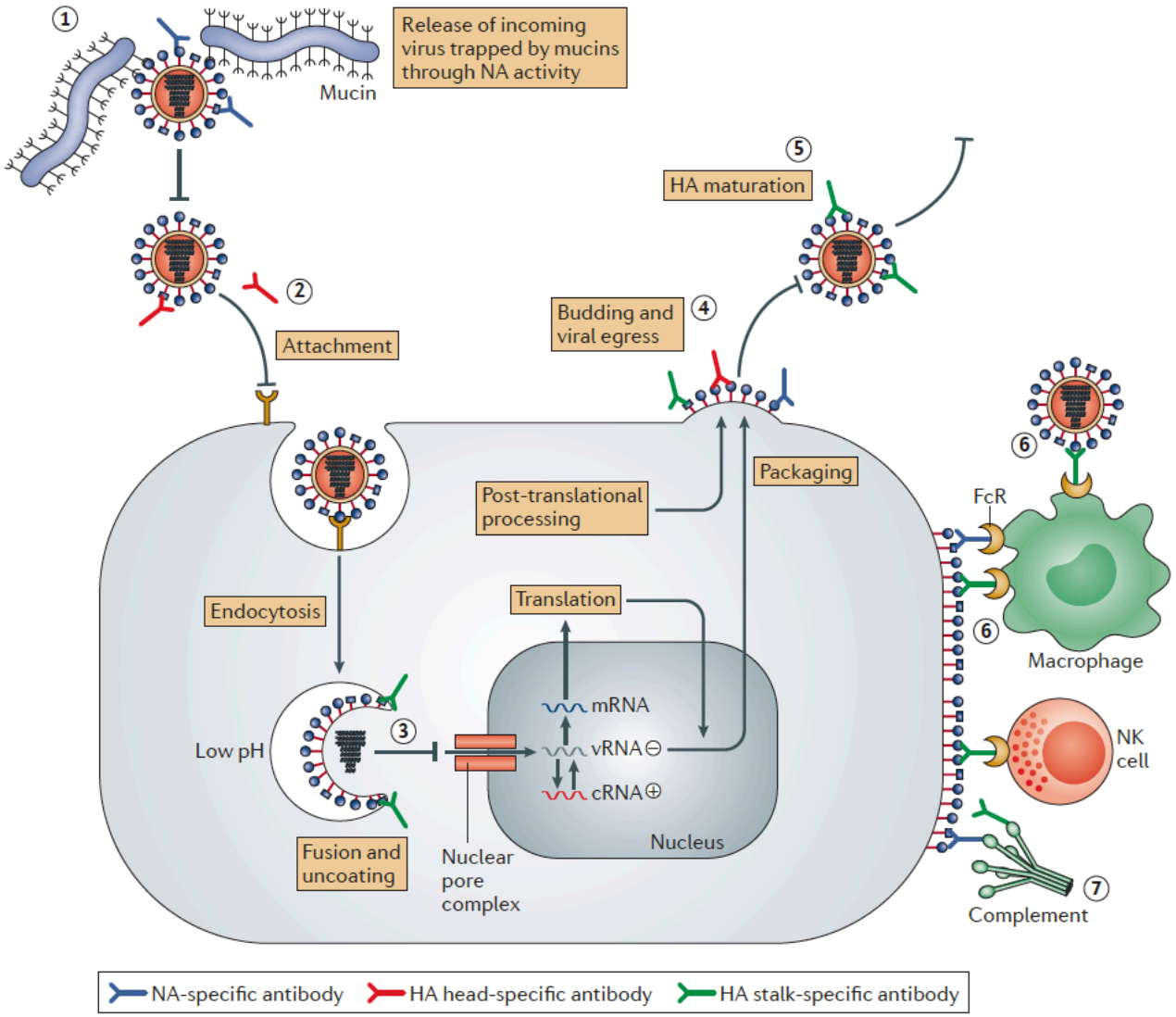
WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for Use in the 2018-2019 Northern Hemisphere Influenza Season

Time course in the influenza virus vaccine production process



Nat Rev Drug Discov 2015; 14: 167-82

Mechanism of haemagglutinin- and neuraminidase-specific antibodies



Nat Rev Drug Discov 2015; 14: 167-82

Benefit of annual vaccination on reduction of mortality risk

Odds ratio*	Odds ratio*	p†	% vaccine efficacy (95% CI)
Previous vaccination only (1985–88)	1·2	0·66	0 (0–47)
First-time vaccination in 1989	0·91	0·83	9 (0–59)
Vaccination in 1989 and previously (1985–88)	0·25	0·008	75 (31–91)

*For certified influenza death. †For likelihood ratio.

Table 4: **Efficacy of influenza vaccine in 1989–90 according to current and previous vaccination status**

Lancet 1995; 346: 591-95

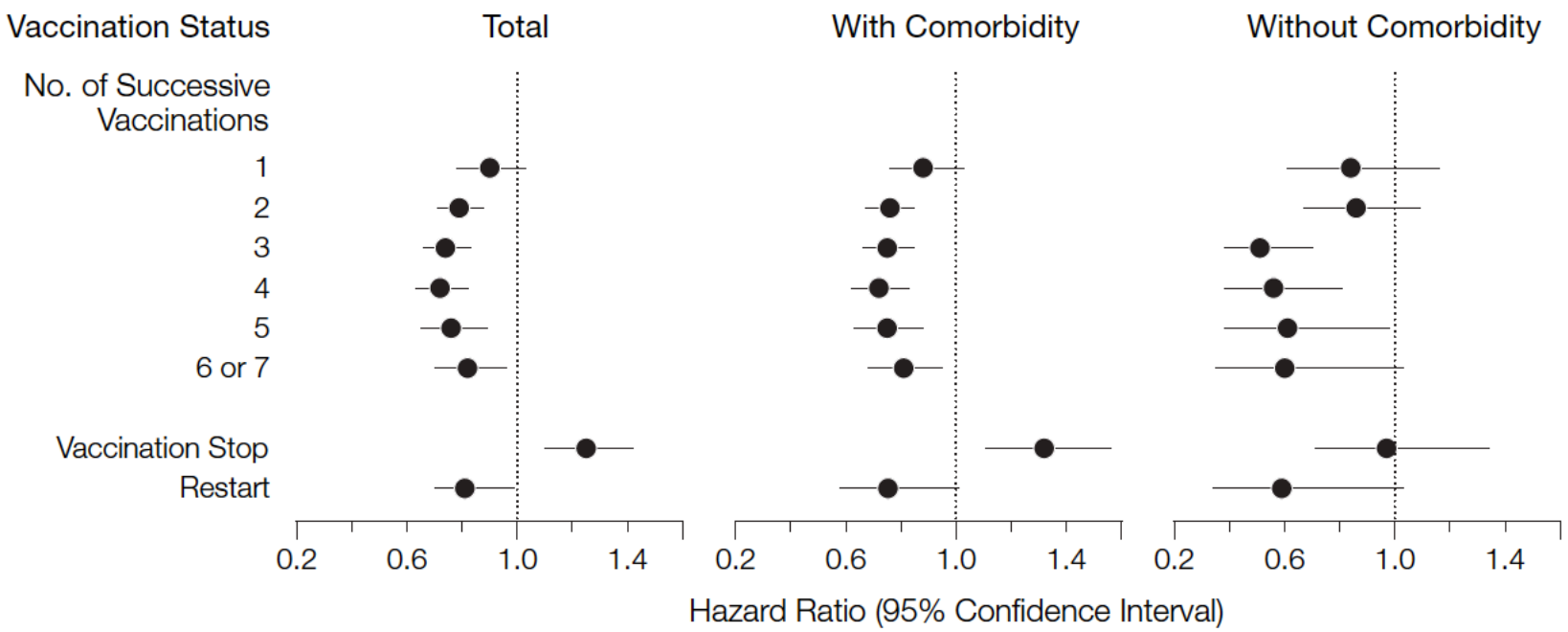
Evidence of annual vaccination on mortality risk reduction

	Death, No. of Cases	Hazard Ratio (95% Confidence Interval)	
		Crude	Adjusted*
Total population			
Any vaccination	2225	0.91 (0.84-0.99)	0.78 (0.72-0.85)
First vaccination	284	0.97 (0.85-1.12)	0.90 (0.78-1.03)
Revaccination	1941	0.90 (0.83-0.98)	0.76 (0.70-0.83)
Vaccination interruption	366	1.43 (1.26-1.62)	1.25 (1.10-1.42)
Vaccination restart	121	0.91 (0.75-1.11)	0.81 (0.67-0.99)
Population without comorbidity†			
First vaccination	47	0.86 (0.62-1.18)	0.84 (0.60-1.16)
Revaccination	217	0.66 (0.54-0.80)	0.66 (0.54-0.80)
Population with comorbidity			
First vaccination	237	0.91 (0.78-1.06)	0.88 (0.76-1.03)
Revaccination	1724	0.82 (0.75-0.90)	0.75 (0.68-0.83)
Age at baseline, y			
65-69			
First vaccination	56	1.20 (0.87-1.66)	1.11 (0.81-1.53)
Revaccination	300	1.25 (1.00-1.56)	0.98 (0.78-1.23)
70-79 y			
First vaccination	109	1.02 (0.81-1.28)	0.93 (0.75-1.17)
Revaccination	803	0.95 (0.83-1.10)	0.78 (0.68-0.91)
≥80 y			
First vaccination	119	0.87 (0.70-1.07)	0.81 (0.66-1.00)
Revaccination	838	0.78 (0.69-0.88)	0.69 (0.61-0.78)

*Adjusted for comorbidity (respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, and malignancy) and sex. Age adjustment by age in days as time axis.
†No recorded predefined comorbidity at baseline or developing at any time during follow-up.

JAMA. 2004;292:2089-2095

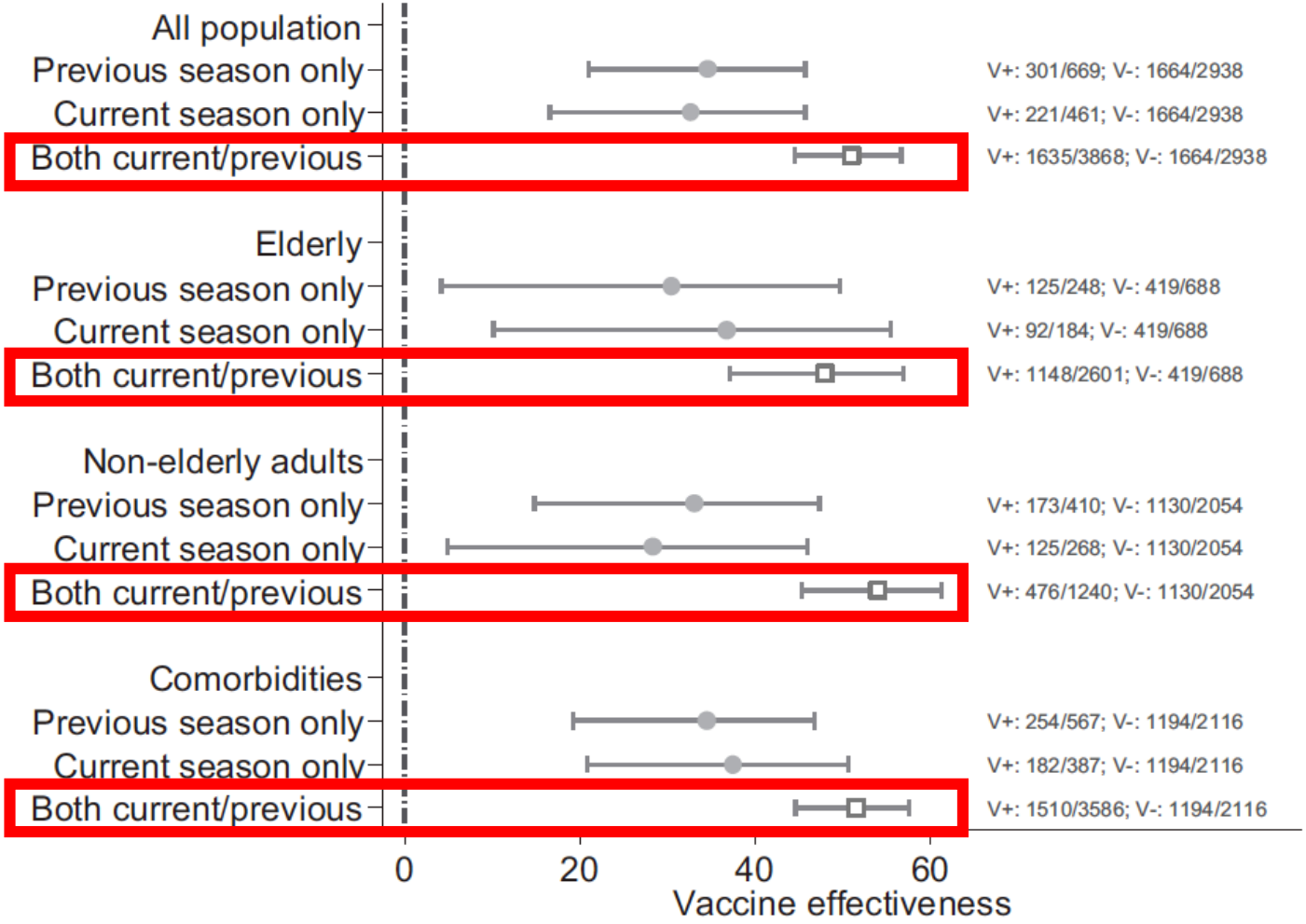
Evidence of annual vaccination on mortality risk reduction



Mortality risk is shown by the number of successive vaccinations, ie, first, second, third, fourth, fifth, more than 6, interruption of vaccination (stop), or restart. The hazard ratio indicates the mortality risk following vaccination vs no previous vaccination.

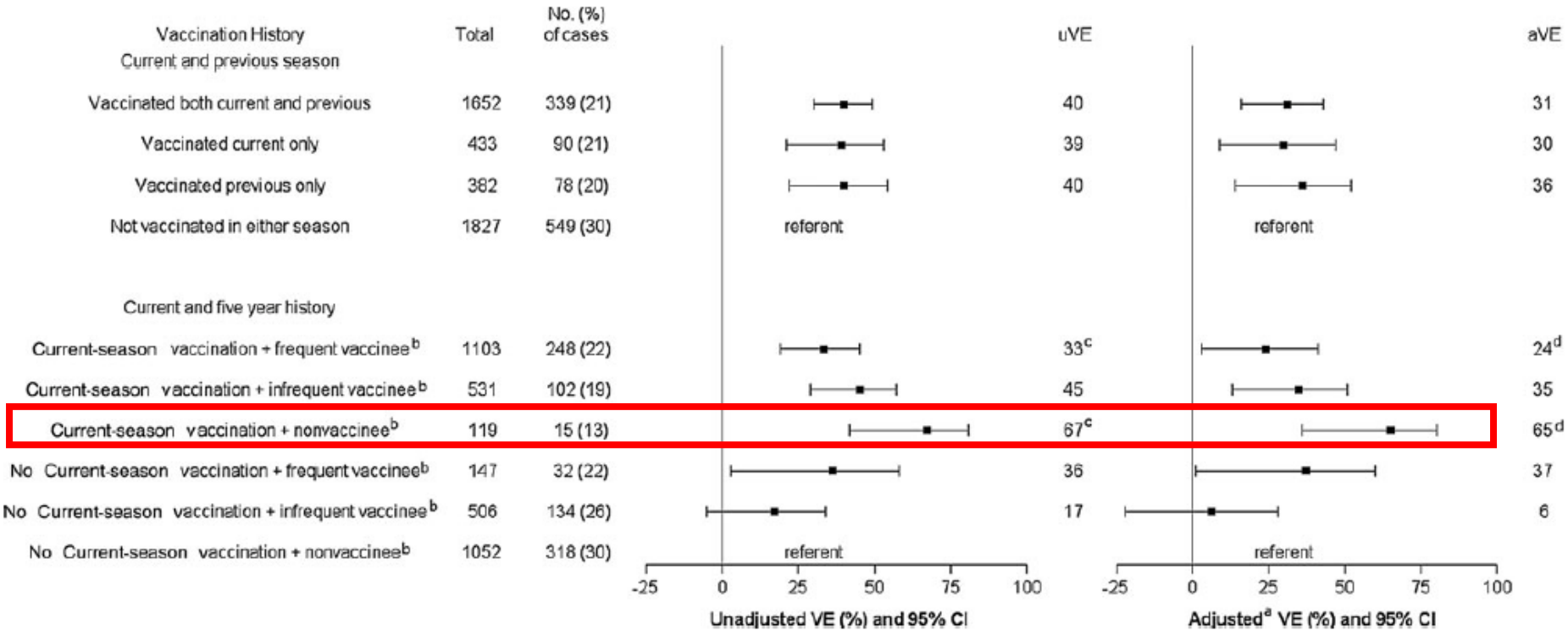
JAMA. 2004;292:2089-2095

Repeated Influenza vaccination against Hospitalization With Confirmed Influenza



Clin Infec Dis 2017; 64: 1564–72

Vaccine effectiveness of vaccination histories against H3N2 virus infection



Clin Infect Dis 2014; 59: 1375-85

Effectiveness of influenza vaccines varied with antigenic match

Season, type or subtype	Vaccine component	Influenza virus isolated from study participants	Isolates, no. (%)
2004–2005			
H1N1	A/New Caledonia/20/99	None	0
H3N2	A/Wyoming/3/2003 (H3N2) [A/Fujian/411/2002–like[a]]	**A/California/7/2004–like**	**59 (95)**
B	B/Jiangsu/10/2003 [B/Shanghai/361/2002–like[a]][b]	B/Shanghai/361/2002–like	3 (5)
2005–2006			
H1N1	A/New Caledonia/20/99(H1N1)	A/New York/55/2004–like	2 (5)
H3N2	A/New York/55/2004(H3N2) [A/California/7/2004–like[a]]	**A/Wisconsin/67/2005–like**	**14 (33)**
B	B/Jiangsu/10/2003/361/2002 [B/Shanghai/361/2002–like[a]][b]	**B/Victoria/2/87–like**	**26 (62)**
2006–2007			
H1N1	A/New Caledonia/20/99(H1N1)	A/New Caledonia/20/99–like **A/Solomon Islands/03/2006–like**	68 (73) **3 (3)**
H3N2	A/Wisconsin/67/2005(H3N2)	A/Wisconsin/67/2005–like	15 (16)
B	B/Ohio/01/2005 [B/Malaysia/2506/2004–like[a]][c]	**B/Florida/07/2004–like** B/Ohio/01/2005–like	**5 (5)** 2 (2)

Antigenic match

J Infect Dis 2009; 199: 159-67

Effectiveness of influenza vaccines varied with antigenic match

Season	Immunized case subjects/total case subjects	Immunized control subjects/total control subjects	Crude VE using test-negative control subjects	Adjusted VE[a] (95% CI)
2004–2005	112/164 (68)	397/598 (66)	−9	10 (−36 to 40)
2005–2006	25/49 (51)	188/297 (63)	40	21 (−52 to 59)
2006–2007	33/100 (33)	435/771 (56)	62	52 (22 to 70)

NOTE. Data are proportion (%) or %. Participants were classified as immunized beginning 14 days after receipt of influenza vaccination. Partially immunized children who had received only 1 of 2 recommended doses were excluded from analyses. CI, confidence interval.

[a] Logistic regression models adjusted for age, week of enrollment, interval from symptom onset to collection of swab sample, and presence of any high-risk medical condition.

J Infect Dis 2009; 199: 159-67

Effect of antigenic drift of H3N2 in 2014-2015 influenza season

Influenza Type/Age Group	Influenza Positive		Influenza Negative		VE		
	No. Vaccinated/ Total	%	No. Vaccinated/ Total	%	Unadjusted % (95% CI)	Adjusted[a] % (95% CI)	VE Fully Adjusted[b] % (95% CI)
Influenza A and B							
Overall	1098/2233	49.2	3866/7078	54.6	20 (12 to 27)	19 (10 to 27)	22 (13 to 30)
6 mo–8 y	186/473	39.3	1013/1946	52.1	40 (27 to 51)	25 (6 to 40)	26 (7 to 41)
9–17 y	137/392	35.0	391/950	41.2	23 (2 to 40)	25 (2 to 42)	26 (3 to 44)
18–49 y	272/642	42.4	996/2206	45.2	11 (–7 to 25)	7 (–12 to 33)	9 (–11 to 26)
50–64 y	229/378	60.6	739/1118	66.1	21 (0 to 38)	20 (–3 to 38)	25 (2 to 42)
≥65 y	274/348	78.7	727/858	84.7	33 (8 to 51)	32 (3 to 52)	33 (3 to 54)
Influenza A/H3N2							
Overall	939/1817	51.7	3866/7078	54.6	11 (2 to 20)	6 (–5 to 17)	11 (–1 to 21)
6 mo–8 y	160/396	40.4	1013/1946	52.1	38 (22 to 50)	20 (–3 to 37)	23 (1 to 40)
9–17 y	119/306	38.9	391/950	41.2	9 (–18 to 30)	7 (–26 to 31)	7 (–26 to 32)
18–49 y	236/531	44.4	996/2206	45.2	3 (–18 to 20)	–6 (–31 to 24)	–3 (–28 to 18)
50–64 y	176/281	62.6	739/1118	66.1	14 (–13 to 34)	12 (–19 to 34)	18 (–13 to 40)
≥65 y	248/303	81.9	727/858	84.7	19 (–15 to 42)	12 (–29 to 40)	15 (–28 to 43)
Influenza B/Yamagata							
Overall	128/340	37.7	3866/7078	54.6	50 (37 to 60)	55 (43 to 65)	54 (41 to 64)
6 mo–8 y	18/60	30.0	1013/1946	52.1	60 (31 to 77)	54 (17 to 74)	50 (9 to 72)
9–17 y	9/60	15.0	391/950	41.2	75 (48 to 88)	77 (51 to 89)	77 (50 to 89)
18–49 y	26/90	28.9	996/2206	45.2	51 (21 to 69)	55 (27 to 73)	53 (22 to 71)
50–64 y	52/90	57.8	739/1118	66.1	30 (–9 to 55)	24 (–20 to 52)	24 (–22 to 52)
≥65 y	23/40	57.5	727/858	84.7	76 (53 to 87)	74 (45 to 87)	74 (43 to 88)

Clin Infect Dis 2016; 63: 1564–73

Variable influenza vaccine effectiveness by influenza subtype

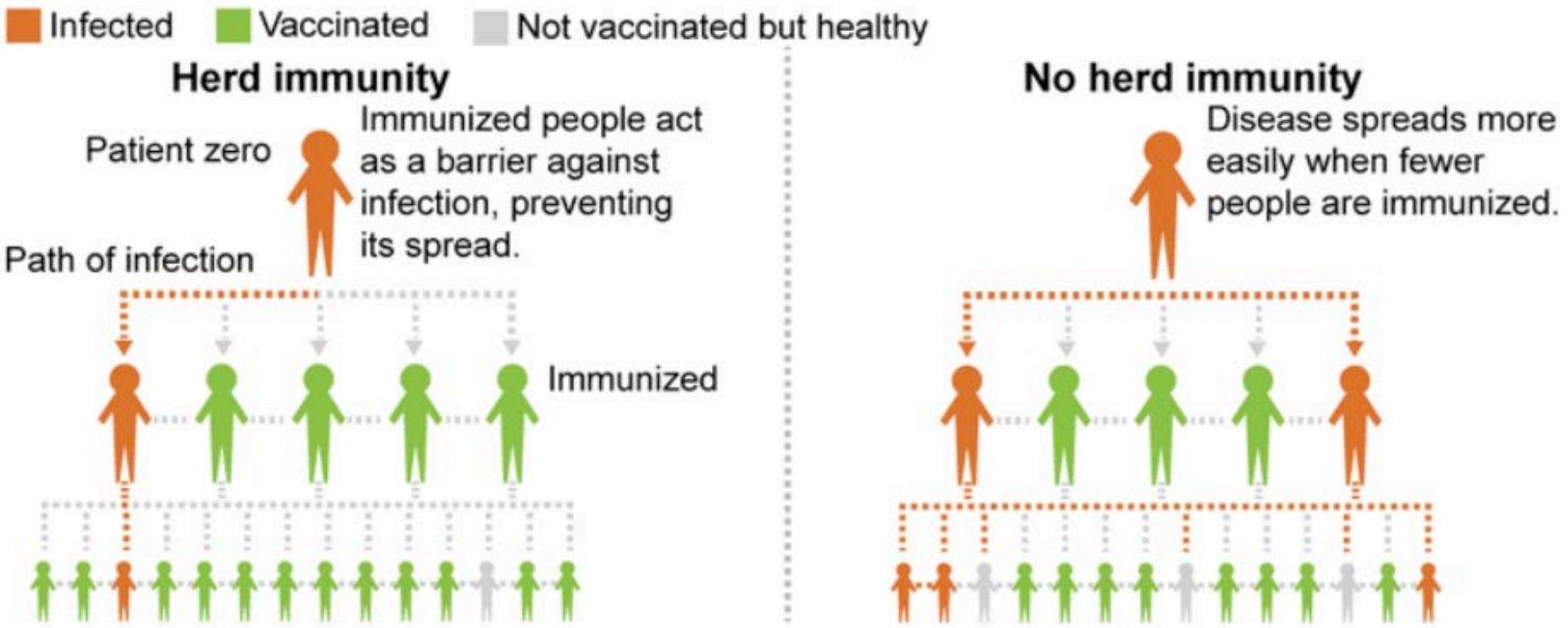
	Vaccine type	Pooled VE (%)	Pooled standard error	VE estimates (n)	p value for heterogeneity	I^2
Type B	Seasonal	54% (46–61)	0·083	36	<0·0001	61·3
H3N2	Seasonal	33% (26–39)	0·050	34	0·005	44·4
H1N1pdm09	Seasonal	61% (57–65)	0·048	29	0·783	0·0
H1N1pdm09	Monovalent	73% (61–81)	0·188	10	0·217	31·4
H1N1 (pre-2009)	Seasonal	67% (29–85)	0·397	5	0·093	57·6

Data in parentheses are 95% CIs. VE=vaccine effectiveness.

Table 2: **Pooled VE by type and subtype in studies without age restriction**

Lancet Infect Dis 2016; 16: 942–51

Influenza vaccination and herd immunity



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Overview of established and novel influenza virus vaccine technologies

Technology	Type of immunity	Breadth of protection	Development stage	Comments	Refs
LAIVs (seasonal or pandemic)	Humoral, cellular and mucosal	Strain-specific but broader than inactivated vaccines	Licensed (seasonal), clinical (pandemic)	Mucosal administration	14–16, 65–74
IIVs (seasonal or pandemic)	Predominantly humoral	Strain-specific	Licensed (seasonal and pandemic)	–	2
Quadrivalent influenza vaccines (seasonal; as IIVs or LAIVs)	Dependent on the platform used	Strain-specific	Licensed (seasonal)	Protects against both influenza B lineages	30–32
Recombinant insect-cell-produced HA vaccines (seasonal as TIVs or pandemic)	Predominantly humoral	Predominantly strain-specific	Licensed (seasonal), clinical (pandemic)	Rapid production, no infectious virus during production process, no antigenic changes during production or passaging, does not rely on egg supply	37
High-dose IIV	Predominantly humoral	Strain-specific	Licensed	Higher dosage used to induce better immune responses in the elderly	25,26
Adjuvanted IIV (seasonal or pandemic)	Predominantly humoral	Strain-specific but broader than inactivated vaccines	Licensed in several countries	Broader and stronger immune responses compared to regular IIVs, dose sparing	27–29
Cell-culture-derived IIVs (seasonal or pandemic)	Predominantly humoral	Strain-specific	Licensed (seasonal), clinical (pandemic)	Rapid production, does not rely on egg supply	36,55, 79,80
Heterologous prime–boost regimens (seasonal or pandemic)	Predominantly humoral	Broad	Clinical	Combinations of LAIV or DNA prime vaccinations with IIV or recombinant protein booster vaccinations	33,34, 76–78
DNA vaccines (seasonal or pandemic)	Predominantly humoral	Strain-specific	Clinical	Highly cost-effective, easy scale-up	103
Insect-cell-derived VLPs (seasonal or pandemic)	Humoral and cellular immunity	Strain-specific	Clinical	Rapid production, no infectious virus during production process, no antigenic changes during production or passaging, does not rely on egg supply	94,101
Plant-derived influenza virus vaccines (seasonal or pandemic)	Predominantly humoral but also cellular immunity (VLPs)	Strain-specific	Clinical	Rapid production, no infectious virus during production process, no antigenic changes during production or passaging, does not rely on egg supply	84,99, 100,102
Bacterial-expressed influenza vaccines (seasonal or pandemic)	Predominantly humoral	Strain-specific	Clinical	Rapid production, no infectious virus during production process, no antigenic changes during production or passaging, does not rely on egg supply, highly cost-effective	85,86,92
MVA-vectored vaccines (pandemic)	Humoral and cellular	Strain-specific	Clinical	Does not rely on egg supply, no antigenic changes during production or passaging, safe vaccine platform	105–109, 111
MVA-vectored vaccines (universal)	Cellular	Broad, universal	Clinical	Strong cellular immune responses, also considered as an additive to seasonal IIVs	209–213
M2e (universal)	Humoral (ADCC)	Broad, universal	Clinical	Tested in different forms of fusion proteins and VLPs	200–205
Epitope or peptide vaccines (universal)	Cellular	Broad, universal	Clinical	Developed as an additive to IIVs	222,223
Headless HA (universal)	Humoral	Broad, universal	Preclinical	Induces broadly reactive antibodies to the HA stalk domain	169–174
Chimeric HA (universal)	Humoral	Broad, universal	Preclinical	Induces broadly neutralizing antibodies to the HA stalk domain, production platform independent	7,62–64, 175–181
Centralized HA (broad seasonal)	Humoral	Broad, seasonal	Preclinical	Production platform independent	182–185, 188
Ferritin nanoparticle-based vaccines (broad, seasonal)	Humoral	Broad, seasonal	Preclinical	–	35

Nat Rev Drug Discov 2015; 14: 167-82

Comparison of efficacies between inactivated and live attenuated influenza vaccine

Table 4. Estimated Absolute and Relative Efficacies of the Inactivated Influenza Vaccine and the Live Attenuated Influenza Vaccine during the 2004–2005 Influenza Season in Michigan.*

Laboratory-Confirmed Symptomatic Influenza	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Relative Reduction (95% CI)		
	Inactivated Vaccine (N=522)	Live Attenuated Vaccine (N=519)	Placebo (N=206)	Inactivated Vaccine vs. Placebo	Live Attenuated Vaccine vs. Placebo	Inactivated vs. Live Attenuated Vaccine	Inactivated Vaccine vs. Placebo	Live Attenuated Vaccine vs. Placebo	Inactivated vs. Live Attenuated Vaccine
	no. of participants (%)								
Culture positive	7 (1.3)	13 (2.5)	12 (5.8)	0.23 (0.08 to 0.63)	0.43 (0.18 to 1.03)	0.54 (0.18 to 1.44)	77 (37 to 92)	57 (–3 to 82)	46 (–44 to 82)
Real-time PCR positive	10 (1.9)	18 (3.5)	15 (7.3)	0.26 (0.11 to 0.63)	0.48 (0.23 to 1.02)	0.55 (0.23 to 1.26)	74 (37 to 89)	52 (–2 to 77)	45 (–26 to 77)
Culture or real-time PCR positive	10 (1.9)	21 (4.0)	16 (7.8)	0.25 (0.10 to 0.58)	0.52 (0.26 to 1.07)	0.47 (0.20 to 1.05)	75 (42 to 90)	48 (–7 to 74)	53 (–5 to 80)
Serologic positive†	6 (1.6)	20 (5.5)	11 (7.5)	0.22 (0.07 to 0.63)	0.72 (0.33 to 1.67)	0.30 (0.10 to 0.77)	78 (37 to 93)	28 (–67 to 67)	70 (23 to 90)
Culture or serologic positive†	10 (2.7)	21 (5.8)	12 (8.2)	0.33 (0.13 to 0.84)	0.70 (0.33 to 1.57)	0.47 (0.20 to 1.04)	67 (16 to 87)	30 (–57 to 67)	53 (–4 to 80)

* Relative reduction in vaccine efficacy was defined as (1 – relative risk) × 100. CI denotes confidence interval, and PCR polymerase chain reaction.

† These cases were reported for the per-protocol population, defined as the participants who provided all three annual blood specimens according to the timing specified in the protocol. In this population, 367 participants received the inactivated vaccine, 363 the live attenuated vaccine, and 146 placebo.

N Engl J Med. 2006; 355: 2513

Comparison of efficacies between inactivated and live attenuated influenza vaccine

Table 2. Estimated Absolute and Relative Efficacies of the Trivalent Inactivated and Live Attenuated Influenza Vaccines.*

Confirmation of Symptomatic Influenza†	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Relative Reduction (95% CI)‡		
	TIV (N=813)	LAIV (N=814)	Placebo (N=325)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV	Absolute Efficacy, TIV vs. Placebo	Absolute Efficacy, LAIV vs. Placebo	Relative Efficacy, TIV vs. LAIV
	no. of participants (%)								
Positive culture	21 (2.6)	38 (4.7)	31 (9.5)	0.27 (0.15–0.49)	0.49 (0.30–0.81)	0.55 (0.31–0.97)	73 (51–85)	51 (19–70)	45 (3–69)
Positive PCR	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)
Positive culture, positive PCR, or both	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)

N Engl J Med. 2009;361(13):1260.

Difference Between the Vaccine and Circulating Strains of Influenza B Viruses

Season	Vaccine B Lineage	Circulating B Lineages	Lineage-Level Vaccine Match, %	Lineage-Level Vaccine Mismatch, %
1999–2000	Yamagata	Yamagata (100%)	100	0
2000–2001	Yamagata	Yamagata (100%)	100	0
2001–2002	Yamagata	Yamagata (100%)	100	0
2002–2003	Victoria	Victoria (90%), Yamagata (10%)	90	10
2003–2004	Victoria	Yamagata (60%), Victoria (40%)	40	60
2004–2005	Yamagata	Yamagata (100%)	100	0
2005–2006	Yamagata	Victoria (95%), Yamagata (5%)	5	95
2006–2007	Victoria	Yamagata (100%)	0	100
2007–2008	Victoria	Yamagata (100%)	0	100
2008–2009	Yamagata	Victoria (100%)	0	100
2010–2011	Victoria	Victoria (90%), Yamagata (10%)	90	10
2011–2012	Victoria	Victoria (100%)	100	0

Clin Infec Dis 2014; 59: 1519–24

Infections Caused by Lineage-Level Mismatched Influenza B Viruses

Season	Total No. of Patients		Lineage-Level Mismatched B Viruses		Proportion of Patients With Mismatched B Viruses Among All Influenza Patients, % (95% CI)
	Any Influenza	Influenza B	Proportion (%)	No. of Patients	
1999–2000	1792	50	0	0	0.0 (.0–.2)
2000–2001	1608	331	0	0	0.0 (.0–.2)
2001–2002	1628	168	0	0	0.0 (.0–.2)
2002–2003	1228	910	10	91	7.4 (6.0–9.0)
2003–2004	2539	40	60	24	0.9 (.6–1.4)
2004–2005	2056	272	0	0	0.0 (.0–.2)
2005–2006	1867	639	95	607	32.5 (30.4–34.7)
2006–2007	2117	127	100	127	6.0 (5.0–7.1)
2007–2008	3669	1821	100	1821	49.6 (48.0–51.3)
2008–2009	4224	722	100	722	17.1 (16.0–18.3)
2010–2011	5811	3564	10	356	6.1 (5.5–6.8)
2011–2012	6249	349	0	0	0.0 (.0–.1)
All Seasons	34788	8993		3748	10.8 (10.4–11.1)

Abbreviation: CI, confidence interval.

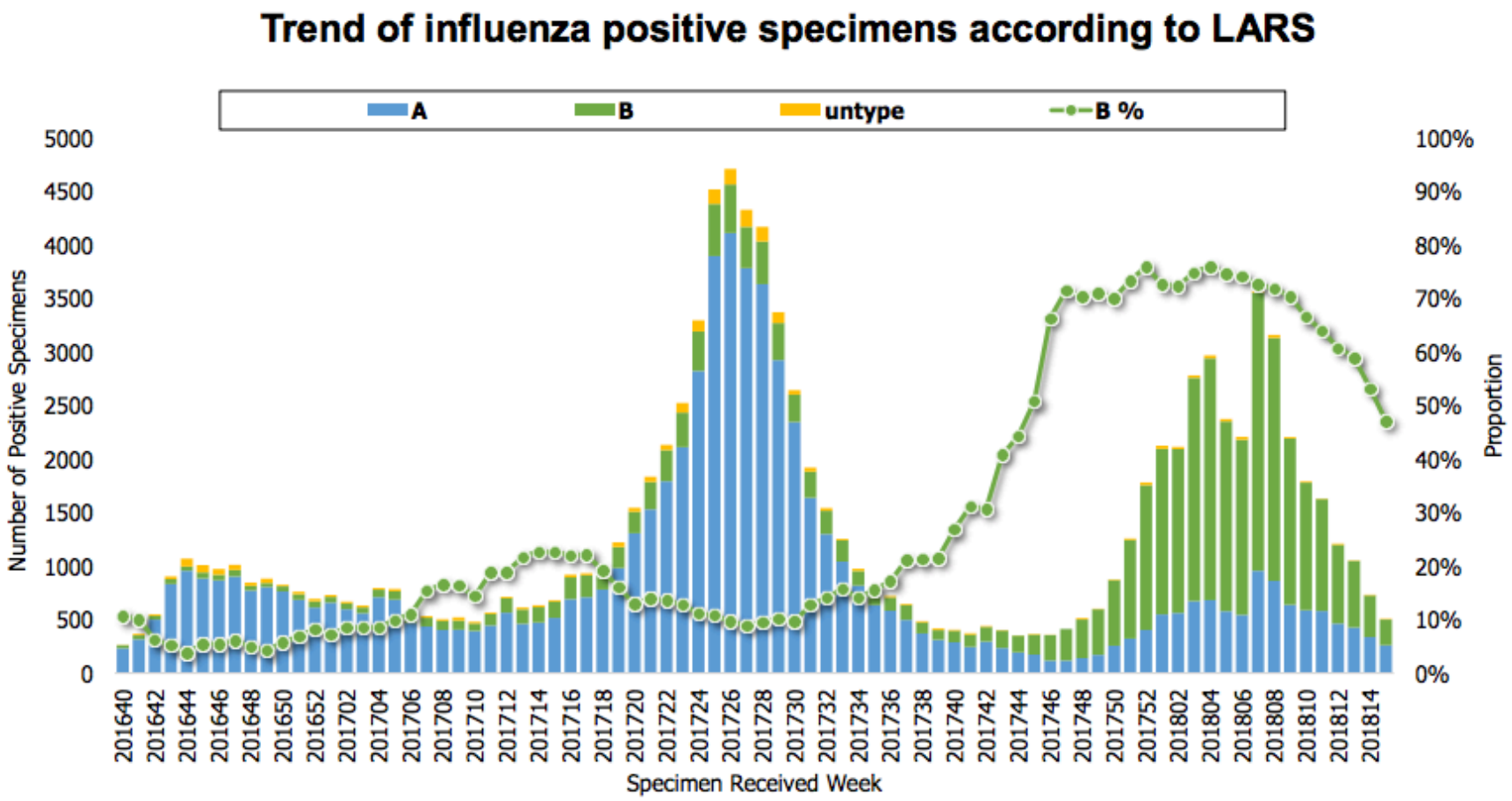
Clin Infec Dis 2014; 59: 1519–24

NEWS

Trivalent flu vaccine won't protect against influenza B strain predominantly circulating

Both influenza A and B are circulating this flu season. Early indications are that viruses related to the B/Yamagata lineage are predominating among laboratory confirmed cases. Out of 25 influenza B viruses analysed by Public Health England's respiratory virus unit, 21 were the B/Yamagata strain. This year's trivalent vaccine does not protect against this strain whereas the quadrivalent vaccine, including the nasal spray given to children, provides protection against both strains of B virus.

Circulating virus strains in Taiwan



Cost-Effectiveness of Quadrivalent versus Trivalent Influenza Vaccine

Table 2 – Health outcomes and costs of replacement of TIV by QIV in the United States over the next 20 y (2014–2034).

Outcomes	TIV	QIV	Difference
Clinical outcomes			
Total number of symptomatic B cases (input from dynamic transmission model)	54,752,913	38,769,820	−15,983,094
Total number of patients with outpatient visit	20,765,647	14,659,055	−6,106,592
To			
To			
Heal			
To			
To			
To			
Cost			
Va			,798
Outpatient visit	5,047,241,705	3,499,717,979	−1,547,523,725
Hospitalized	8,065,030,717	5,538,868,166	−2,526,162,550
Death	2,461,272,640	1,660,860,902	−800,411,738
Productivity losses	2,593,650,999	1,797,327,693	−796,323,306
OTC medications	161,308,724	112,012,536	−49,296,188

OTC, over the counter; QALY, quality-adjusted life-year; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine.
Costs and health effects discounted at 3%.

Incremental cost-effectiveness ratio:
US $27,411/QALY

Value Health 2016; 19: 964-975.

Evolution of influenza virus

Evidence of annual vaccination

Comparison of different type of vaccines

Vaccination strategy in specific group

The benefit of high dose influenza vaccination in the elderly population

Phase IIIb–IV, multicenter RCT, 31,989 participants aged ≥ 65 years

Table 2. Efficacy of High-Dose Vaccine Relative to Standard-Dose Vaccine against Confirmed Influenza Caused by Any Viral Type or Subtype.*

Variable	Laboratory-Confirmed Influenza†			Culture-Confirmed Influenza		
	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)	Relative Efficacy (95% CI)	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)	Relative Efficacy (95% CI)
	no. (%)		%	*no. (%)*		%
Protocol-defined influenza-like illness	228 (1.4)	301 (1.9)	24.2 (9.7 to 36.5)‡	206 (1.3)	268 (1.7)	23.1 (7.5 to 36.2)
Influenza A	190 (1.2)	250 (1.6)	24.0 (7.8 to 37.4)	170 (1.1)	222 (1.4)	23.4 (6.0 to 37.6)
A/H1N1	8 (<0.1)	9 (0.1)	11.1 (–159.6 to 70.2)	7 (<0.1)	9 (0.1)	22.2 (–134.7 to 75.4)
A/H3N2	171 (1.1)	223 (1.4)	23.3 (6.0 to 37.5)	156 (1.0)	199 (1.2)	21.6 (2.8 to 36.8)
Influenza B	38 (0.2)	51 (0.3)	25.5 (–15.7 to 52.4)	36 (0.2)	46 (0.3)	21.7 (–23.8 to 50.8)
Modified CDC-defined influenza-like illness	96 (0.6)	121 (0.8)	20.6 (–4.6 to 39.9)	84 (0.5)	110 (0.7)	23.6 (–2.4 to 43.2)
Influenza A	86 (0.5)	104 (0.7)	17.3 (–11.1 to 38.6)	75 (0.5)	94 (0.6)	20.2 (–9.3 to 41.9)
A/H1N1	3 (<0.1)	2 (<0.1)	–50.0 (–1696.0 to 82.8)	2 (<0.1)	2 (<0.1)	0.0 (–1280.0 to 92.8)
A/H3N2	77 (0.5)	95 (0.6)	18.9 (–10.7 to 40.8)	69 (0.4)	85 (0.5)	18.8 (–12.9 to 41.8)
Influenza B	10 (0.1)	17 (0.1)	41.2 (–36.0 to 75.9)	9 (0.1)	16 (0.1)	43.7 (–35.2 to 78.1)
Respiratory illness	316 (2.0)	387 (2.4)	18.3 (5.0 to 29.8)	277 (1.7)	339 (2.1)	18.3 (3.9 to 30.5)
Influenza A	262 (1.6)	313 (2.0)	16.3 (1.0 to 29.2)	227 (1.4)	272 (1.7)	16.5 (0.1 to 30.3)
A/H1N1	14 (0.1)	10 (0.1)	–40.0 (–252.4 to 42.2)	13 (0.1)	10 (0.1)	–30.0 (–231.3 to 47.33)
A/H3N2	231 (1.4)	281 (1.8)	17.8 (1.8 to 31.2)	205 (1.3)	246 (1.5)	16.6 (–0.7 to 31.1)
Influenza B	54 (0.3)	74 (0.5)	27.0 (–5.1 to 49.6)	50 (0.3)	67 (0.4)	25.4 (–9.3 to 49.3)

N Engl J Med 2014;371:635-45.

Immune response after influenza H1N1 vaccination

Table 2
Immune response after vaccination in dialysis patients and healthy participants, as measured on Hemagglutination-Inhibition (HI) assay.

Immunogenicity end point	Dialysis population			Healthy population		
	All	Adults	Elders	All	Adults	Elder
Including all participants (method A)						
Baseline						
Numbers of subjects	110	47	63	173	120	53
Seroprotection rate % (95%CI)[a]	18.2% (11.5–26.7)[b]	19.2% (9.2–33.3)[c]	17.5% (9.1–29.1)[d]	3.5% (1.3–7.4)[b]	3.3% (0.9–8.3)[c]	3.8% (0.5–13.0)[d]
Geometric mean titer (95% CI)	13.2 (11.0–15.9)[b]	13.2 (9.7–18.0)[c]	13.2 (10.3–16.7) [d]	6.6 (6.0–7.2)[b]	6.3 (5.6–7.0)[c]	7.4 (6.3–8.7)[d]
After 15 μg-dose vaccination						
Seroprotection rate % (95%CI)[a]	40.0% (30.8–49.8)[b]	42.6% (28.3–57.8)[c]	38.1% (26.2–51.2)[d]	88.4% (82.7–92.8)[b]	93.33% (87.29–97.08)[c,e]	77.4%(63.8–87.7)[d,e]
GM titer (95% CI)[a]	23.6 (19.4–28.7)[b]	23.9 (17.2–33.1)[c]	23.3 (18.2–29. 9)[d]	154.3 (125.8–189.4)[b]	206.3 (165.5–257.2)[c,e]	80.0 (53.1–120.4)[d,e]
Fold increase of GM titer(95% CI)[a]	1.8 (1.51–2.1)[b]	1.8 (1.4–2.4)[c]	1.8 (1.4–2.2)[d]	23.4 (18.8–29.2)[b]	32.9 (25.9–41.9)[c,e]	10.8 (7.1–16.5)[d,e]
Seroresponse rate % (95%CI)[a]	32.7% (24.1–42.3)[b]	31.9% (19.1–47.1)[c]	33.3% (22.0–46.3)[d]	90.2% (84.7–94.2)[b]	95.8% (90.5–98.6)[c,e]	77.4% (63.8–87.7)[d,e]
	24.5% (16.8–33.7)[b]					
Seroconversion rate % (95%CI)[a]		23.4% (12.3–38.0)[c]	25.4% (15.3–37.9)[d]	86.7% (80.7–91.4)[b]	92.5% (86.2–96.5)[c,e]	73.6% (59.7–84.7)[d,e]
Exclusion of patients with seroprotection at baseline in both dialysis and healthy population (method B)						
Baseline						
Numbers of subjects	90	38	52	167	116	51
Geometric mean titer (95% CI)	9.0 (8.0–10.1)	8.5 (7.2–10.0)	9.4 (7.9–11.1)	6.1 (5.7–6.5)	5.8 (5.4–6.2)	6.9 (6.0–8.0)
After 15 μg-dose vaccination						
Seroprotection rate % (95%CI)[a]	29.0% (19.8–39.4)[b]	29.0% (15.4–45.9)[c]	28.9% (17.2–43.1)[d]	88.0% (82.1–92.5)[b]	93.1% (86.9–97.0)[c,e]	76.5% (62.5–87.2)[d,e]
GM titer (95% CI) [a]	18.1 (15.1–21.7)[b]	17.3 (12.8–23.3)[c]	18.7 (14.8–23.6)[d]	149.1 (121.0–183.7)[b]	200.8 (160.2–251.6)[c,e]	75.8 (50.1–114.7)[d,e]
Fold increase of GM titer(95% CI)[a]	2.0 (1.7–2.4)[b]	2.0 (1.5–2.8)[c]	2.0 (1.6–2.5)[d]	24.4 (19.5–36.0)[b]	34.8 (27.4–44.2)[c,e]	10.9 (7.0–17.0)[d,e]
Seroresponse rate % (95%CI)[a]	36.7% (26.8–47.5)[b]	36.8% (21.8–54.0)[c]	36.5% (23.6–51.0)[d]	89.8% (84.2–94.0)[b]	95.7% (90.2–98.6)[c,e]	76.5% (62.5–87.2)[d,e]
Seroconversion rate % (95%CI)[a]	26.7% (17.9–37.0)[b]	26.3% (13.4–43.1)[b]	26.9% (15.6–41.0)[d]	86.2% (80.1–91.1)[b]	92.2% (85.8–96.4)[c,e]	72.6% (58.3–84.1)[d,e]

[a] *Abbreviation*: CI, confidence interval; GM, geographic mean; definition of seroprotection, HI titers ≥1:40; seroresponse, ≥4-fold increase in antibody titer after vaccination; seroconversion, ≥4-fold or more increase in HI titer and HI titer ≥1:40 after vaccination.

[b] $p < 0.001$ when comparing the corresponding values between the hemodialysis and healthy groups.

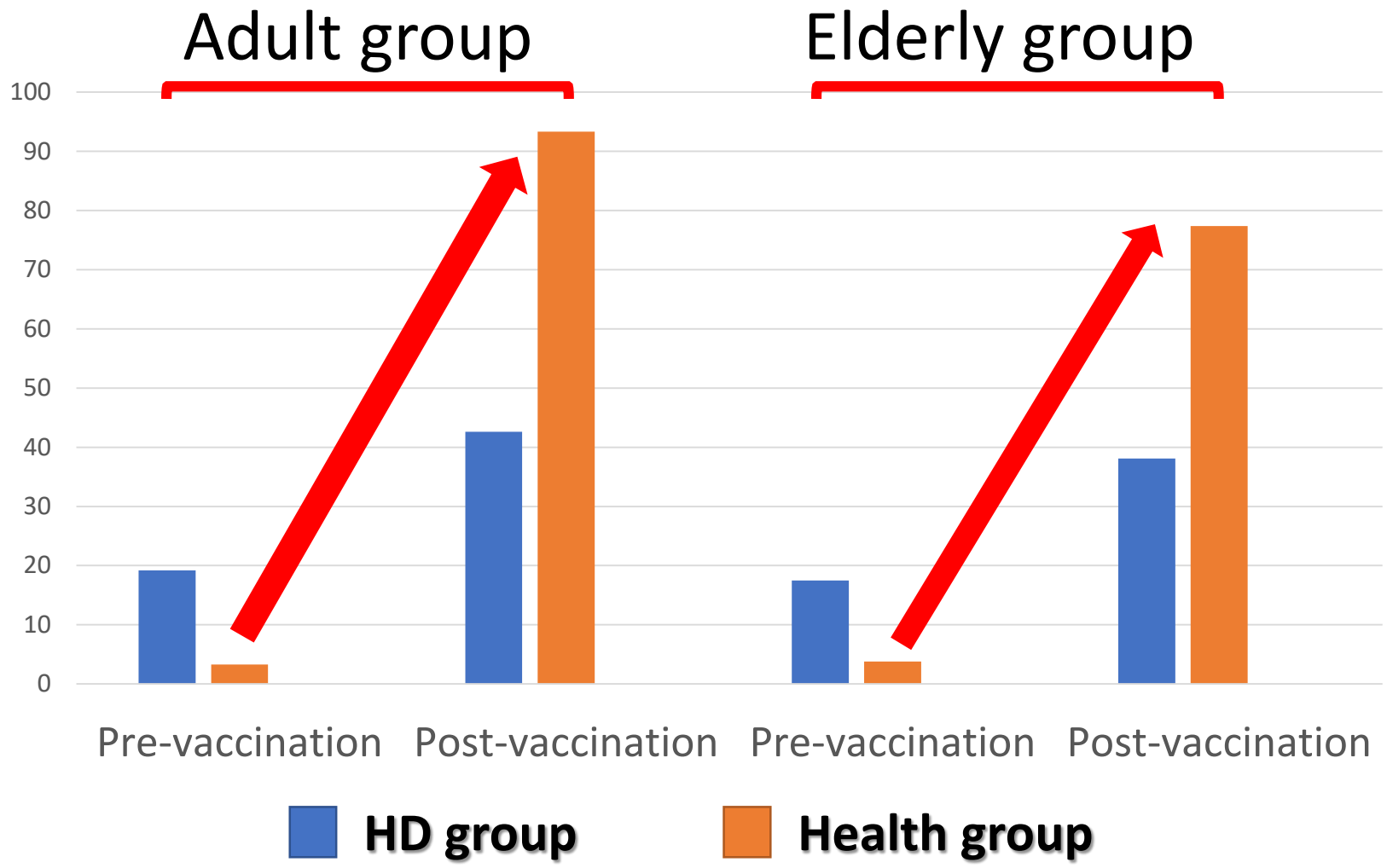
[c] $p < 0.001$ when comparing the corresponding values between the adult hemodialysis and healthy subgroups.

[d] $p < 0.001$ when comparing the corresponding values between the elder hemodialysis and healthy subgroups.

[e] $p \leq 0.01$ when the value of the elder was compared with the corresponding value of adults in the healthy population.

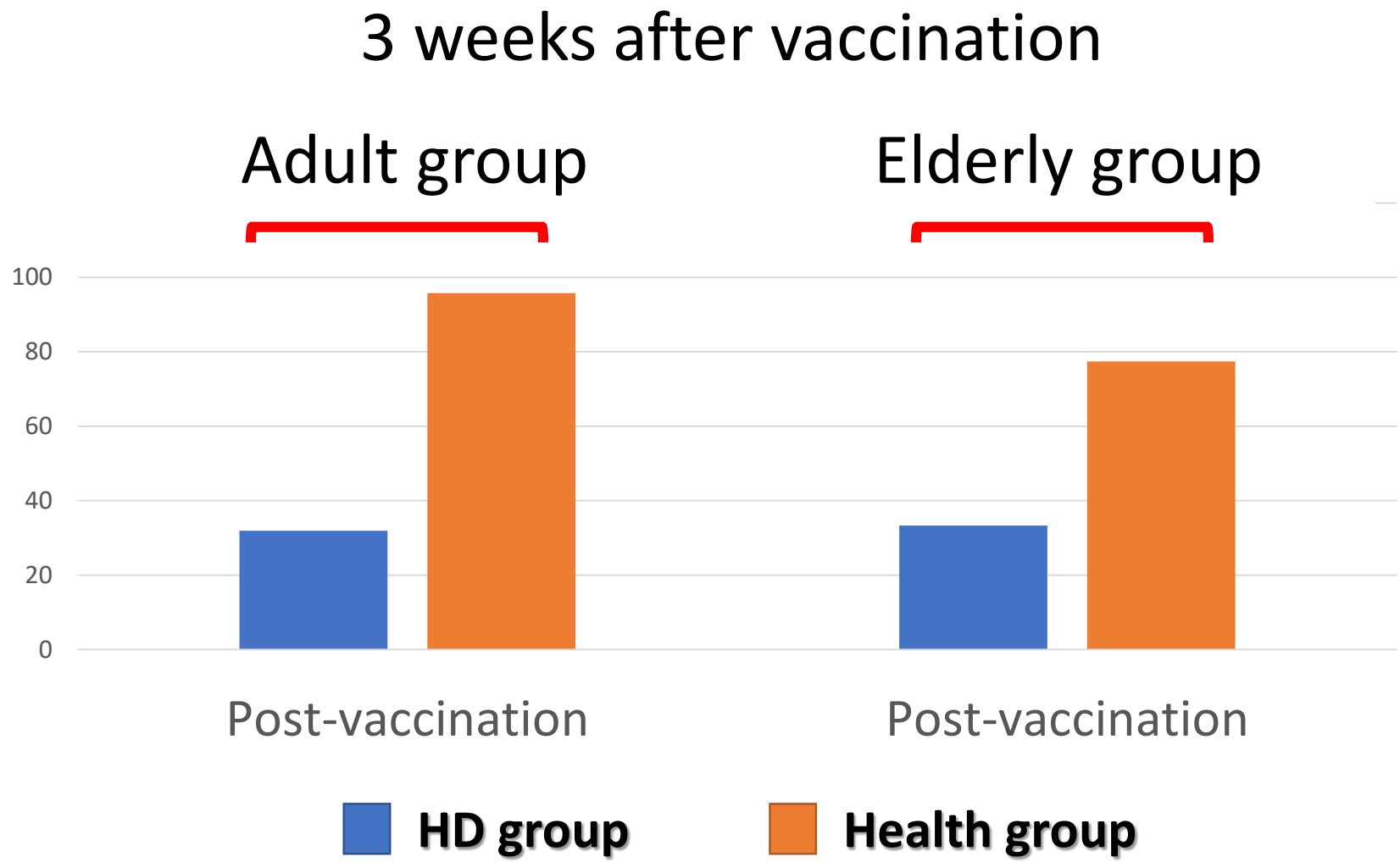
Vaccine 2012; 30: 5009– 5018

Change of seroprotection after vaccination



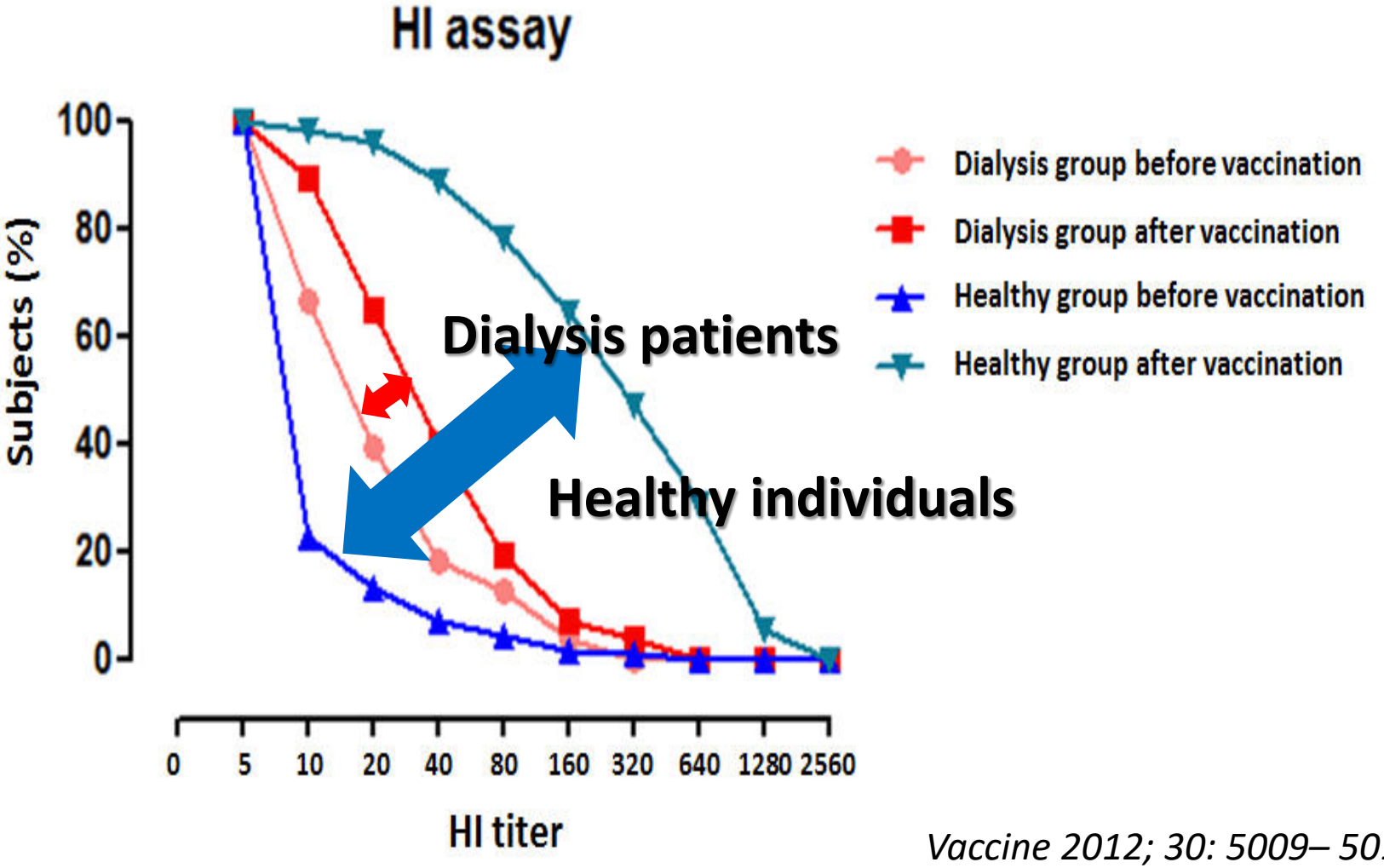
Vaccine 2012; 30: 5009– 5018

Change of seroresponse after vaccination



Vaccine 2012; 30: 5009– 5018

Reverse cumulative distribution curves of antibody titers before and after vaccination



Vaccine 2012; 30: 5009– 5018

Can a booster influenza vaccination improve immune response in ESRD patients?

SCIENTIFIC REPORTS

OPEN

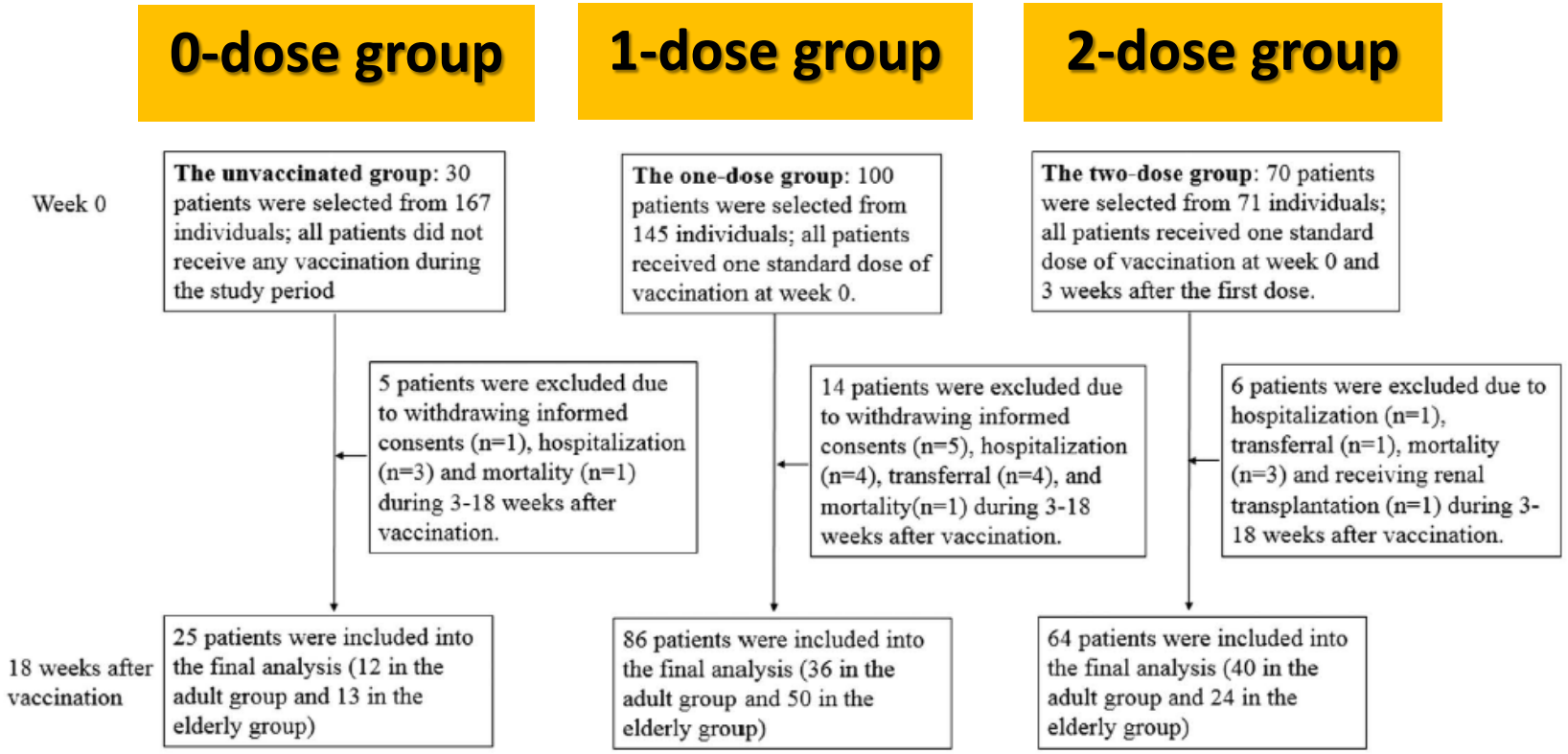
Changes of immunogenic profiles between a single dose and one booster influenza vaccination in hemodialysis patients – an 18-week, open-label trial

Received: 21 July 2015
Accepted: 11 January 2016
Published: 12 February 2016

Yu-Tzu Chang[1,2], Jen-Ren Wang[3,4], Meng-Te Lin[5], Chi-Jung Wu[2,4], Ming-Song Tsai[5], Chiang Lin Wen-Chi[5], Te-En Shih[5], Te-Hui Kuo[2], Eing-Ju Song[6] & Junne-Ming Sung[2,5]

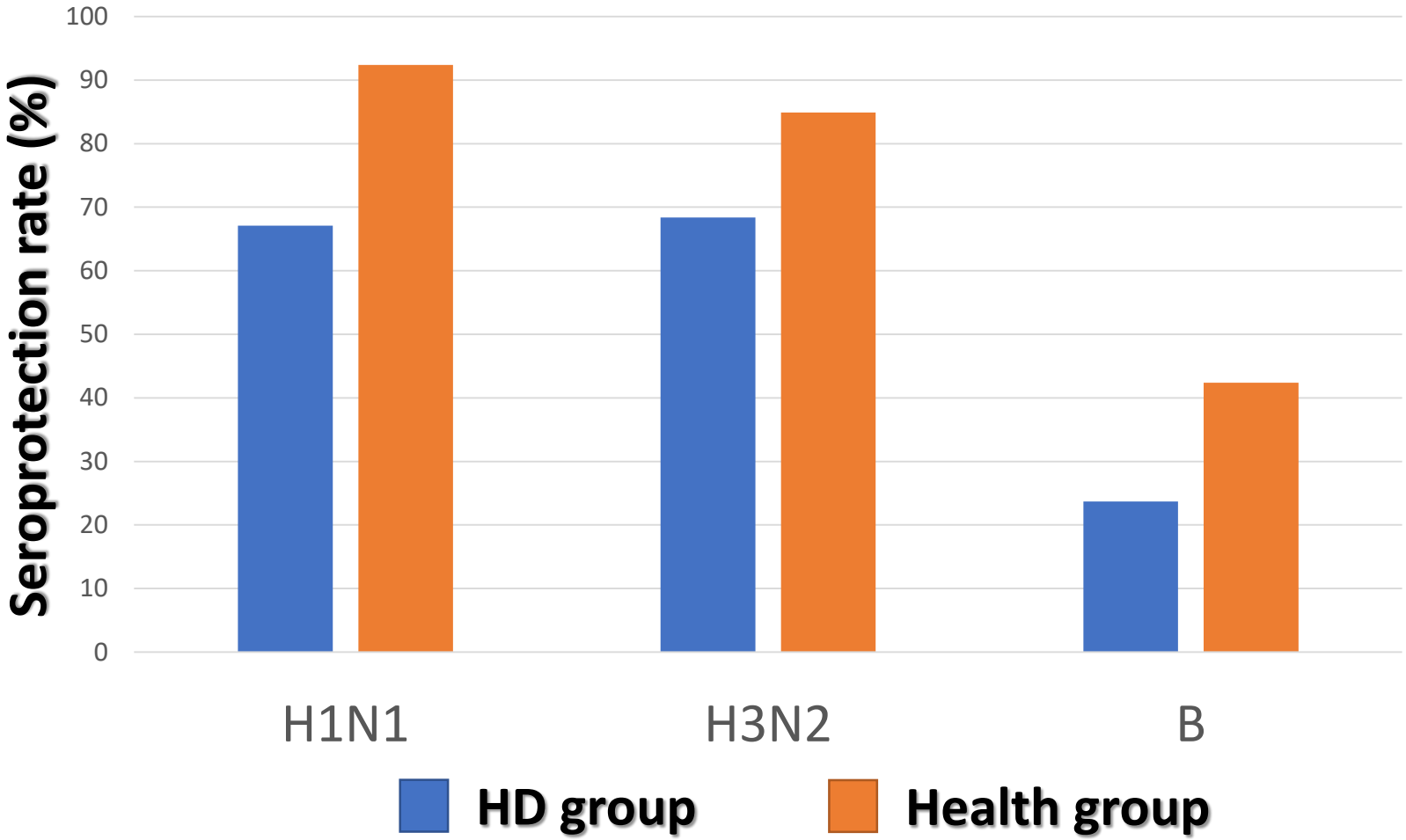
Sci. Rep. 2016; **6**: 20725

The flow chart and the immunization protocol of the study



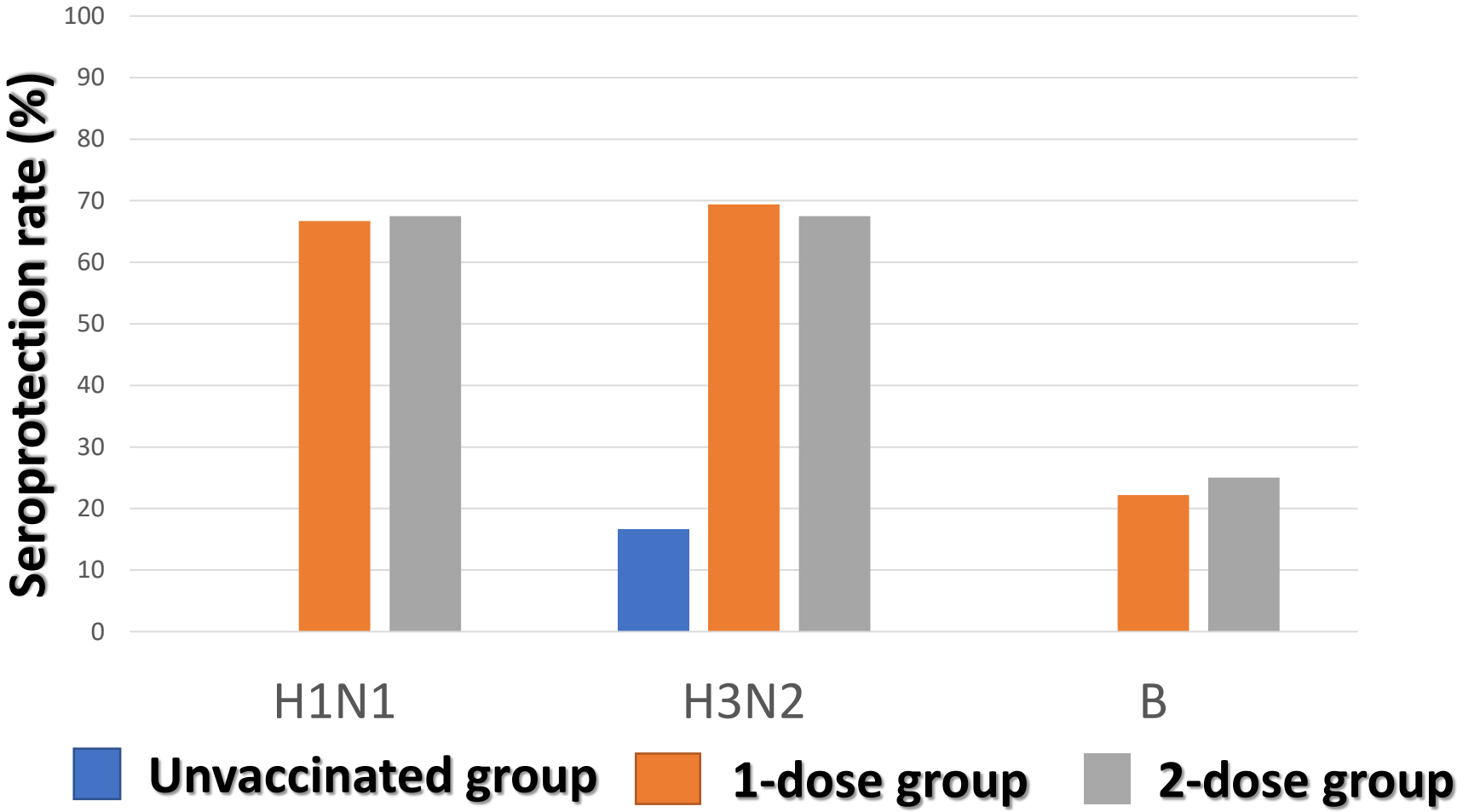
Sci. Rep. 2016; **6**: 20725

Seroprotection at 3 weeks after vaccination in adult group



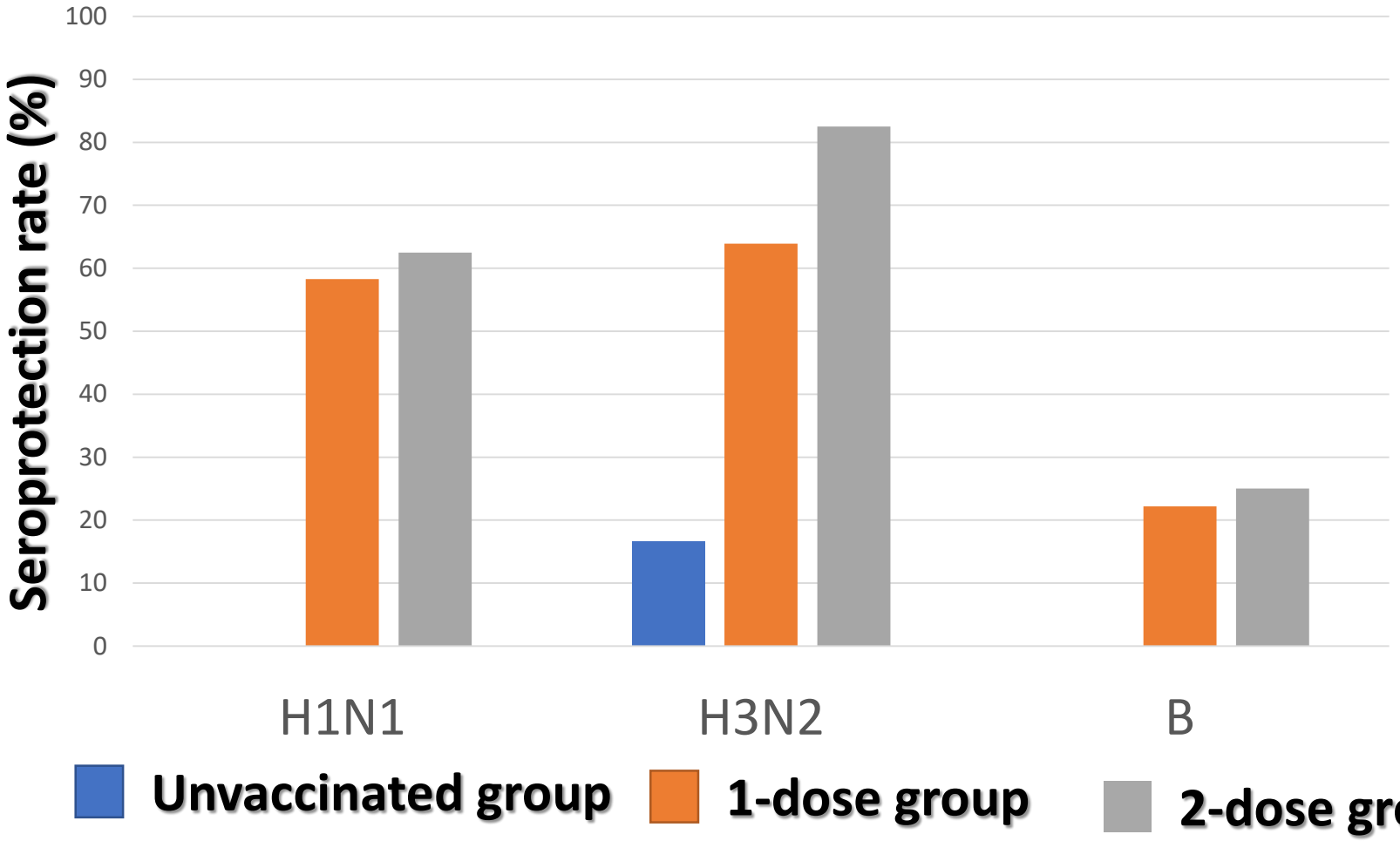
Sci. Rep. 2016; **6**: 20725

Change of seroprotection at 3 weeks after vaccination in adult group



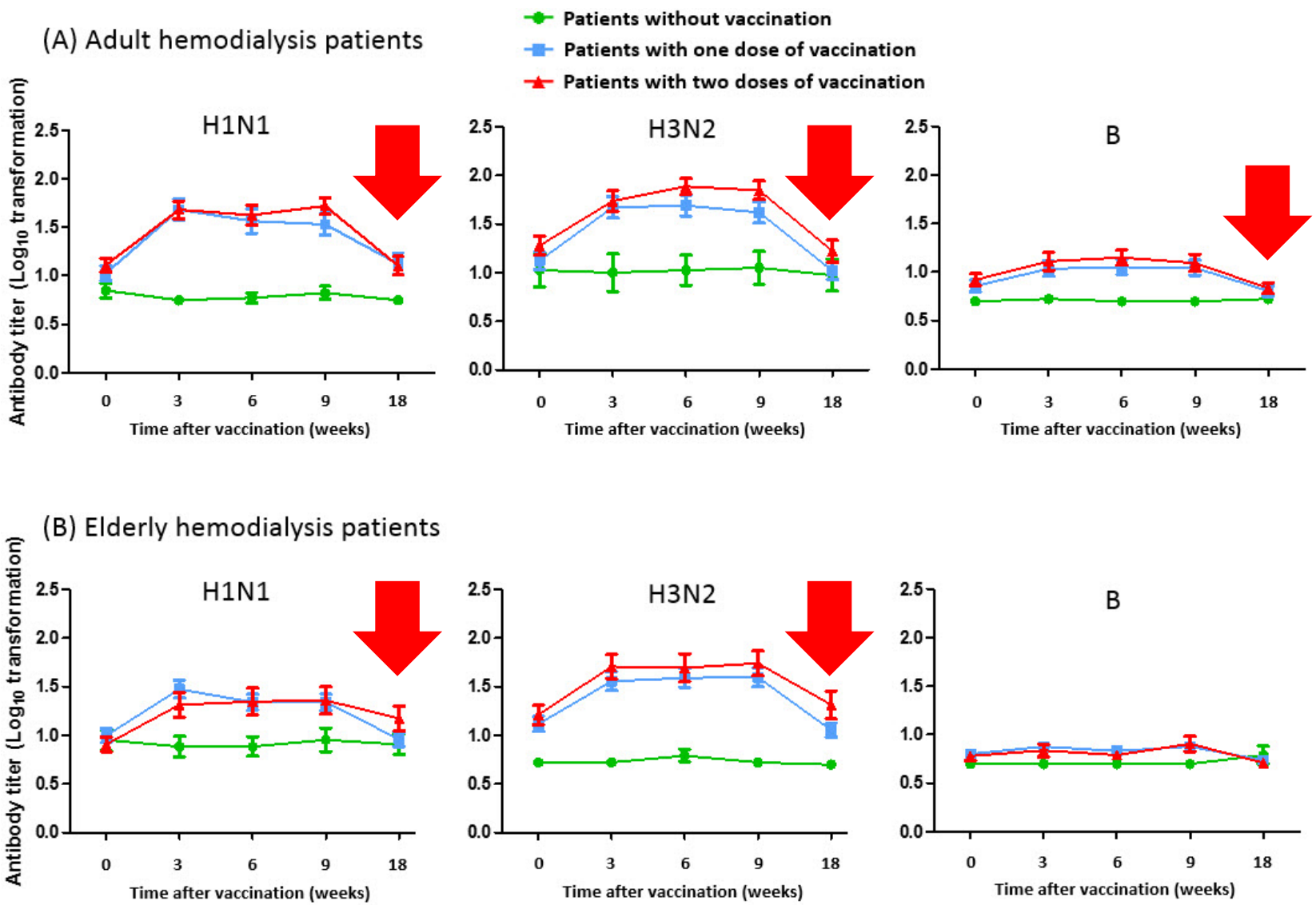
Sci. Rep. 2016; **6**: 20725

Change of seroprotection at 6 weeks after vaccination in adult group



Sci. Rep. 2016; **6**: 20725

Changes of antibody titers after vaccination



Sci. Rep. 2016; **6**: 20725

Determinants of seroprotection and seroresponse by the logistic model with GEE

Variable	H1N1		H3N2		B	
	Seroprotection	Seroresponse	Seroprotection	Seroresponse	Seroprotection	Seroresponse
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Vaccination schedule (2 vs. 1 dose)	1.01 (0.58–1.75)	1.14 (0.65–2.00)	1.30 (0.78–2.17)	1.34 (0.76–2.36)	1.33 (0.58–3.07)	1.36 (0.65–2.82)
Age (year)	0.98 (0.95–1.00)	0.97 (0.95–1.00)	0.99 (0.97–1.01)	0.99 (0.97-1.02)	0.95 (0.92–0.97)	0.96 (0.93–0.98)
Seroprotection before vaccination	5.31 (3.29–8.57)	0.13 (0.04–0.38)	4.57 (2.84–7.37)	0.18 (0.09–0.36)	25.25 (8.01–79.57)	0.13 (0.01–1.17)
Total-cholesterol (mg/dL)	1.00 (0.99–1.01)	1.00 (1.00–1.01)	1.01 (1.00–1.01)	1.00 (1.00–1.01)	1.00 (0.99–1.02)	1.01 (1.00–1.02)
Hematocrit (%)	0.98 (0.93–1.03)	0.96 (0.90–1.01)	1.02 (0.97–1.07)	0.97 (0.91–1.04)	1.01 (0.93–1.10)	1.00 (0.90–1.07)
Ferritin (g/dl)	0.98 (0.94–1.05)	1.03 (0.96–1.10)	1.01 (0.95–1.07)	1.03 (0.97–1.10)	0.94 (0.85–1.03)	0.96 (0.86–1.08)

Sci. Rep. 2016; **6**: 20725

Efficacy of Influenza vaccination in renal transplant recipients

Table 2: Seroprotection and seroresponse rates (%)

Strain		HV	RTR
H1N1	SP0	25.0	78.2[a]
	SP1	70.7	92.7[a]
	SR1	45.0	30.3
H3N2	SP0	62.5	49.7
	SP1	82.9	78.7
	SR1	30.0	29.9
B	SP0	17.5	55.8[a]
	SP1	48.8	82.9[a]
	SR1	27.5	23.2

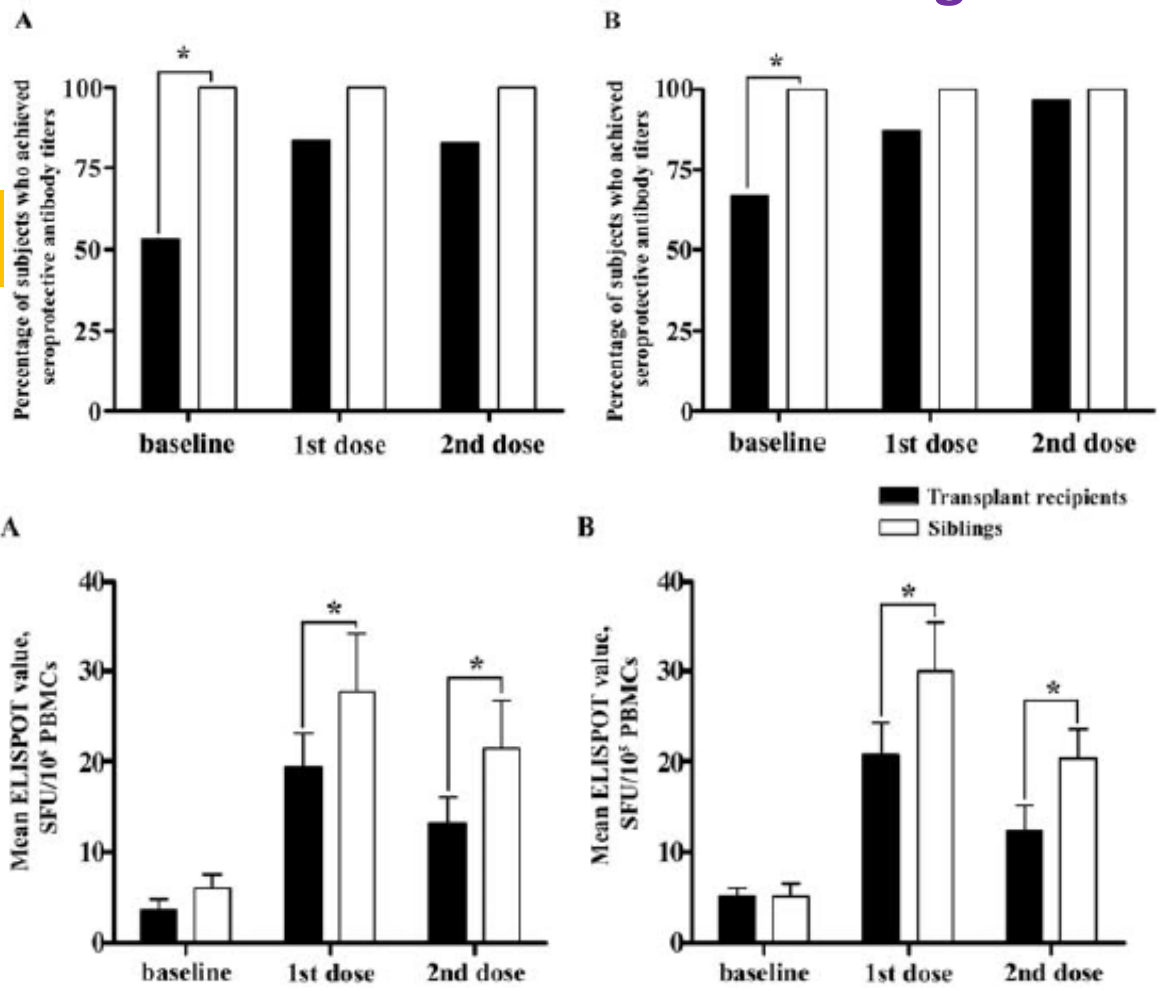
[a]$p < 0.0001$ versus HV (chi-square statistics).
Seroprotection rates at baseline (SP0), after 1 month (SP1) and seroresponse rates after 1 month (SR1) in healthy volunteers (HV) and renal transplant recipients (RTR). Values expressed as percentage of patients.

Am J Transplant 2008; 8: 332-7

Efficacy of Influenza vaccination in pediatric liver transplant recipients

Seroprotection

IFN-γ assay



Clin Infect Dis 2008; 46:712–8

Alternative vaccine strategies in solid organ transplant recipients

Table 1. Comparison of alternative influenza vaccine strategies to intramuscular standard-dose inactivated influenza vaccine

Intervention	Immunogenicity	Allograft rejection risk	Injection site reaction	References
High-dose (unadjuvanted) inactivated influenza vaccine	↑	→	→[a] ↑[b]	Natori *et al.* [12▪▪] GiaQuinta *et al.* [26]
Unadjuvanted inactivated influenza vaccine booster dose in same season	↑	→		Cordero *et al.* [13▪▪] Hojsak *et al.* [27]
MF59 adjuvanted inactivated influenza vaccine	→	→	↑	Kumar *et al.* [11▪▪]
Unadjuvanted intradermal inactivated influenza vaccine	→	→	↑	Baluch *et al.* [23] Morelon *et al.* [24] Manuel *et al.* [25]

[a]Adult solid organ transplant recipients.
[b]Pediatric solid organ transplant recipients.

Curr Opin Infect Dis 2018, 31: 309–315

Take home message

- **Annual one dose of influenza vaccination** is suggested for adults and those comorbid with multiple illnesses.
- The **quadrivalent vaccine** might provide more protection against influenza infection than the trivalent influenza vaccine.
- Alternative strategy to improve vaccine efficacy, including **high dose**, **booster dose** or with the use of **adjuvants**.

張育誌醫師
成大醫院腎臟科

Still a long way to go