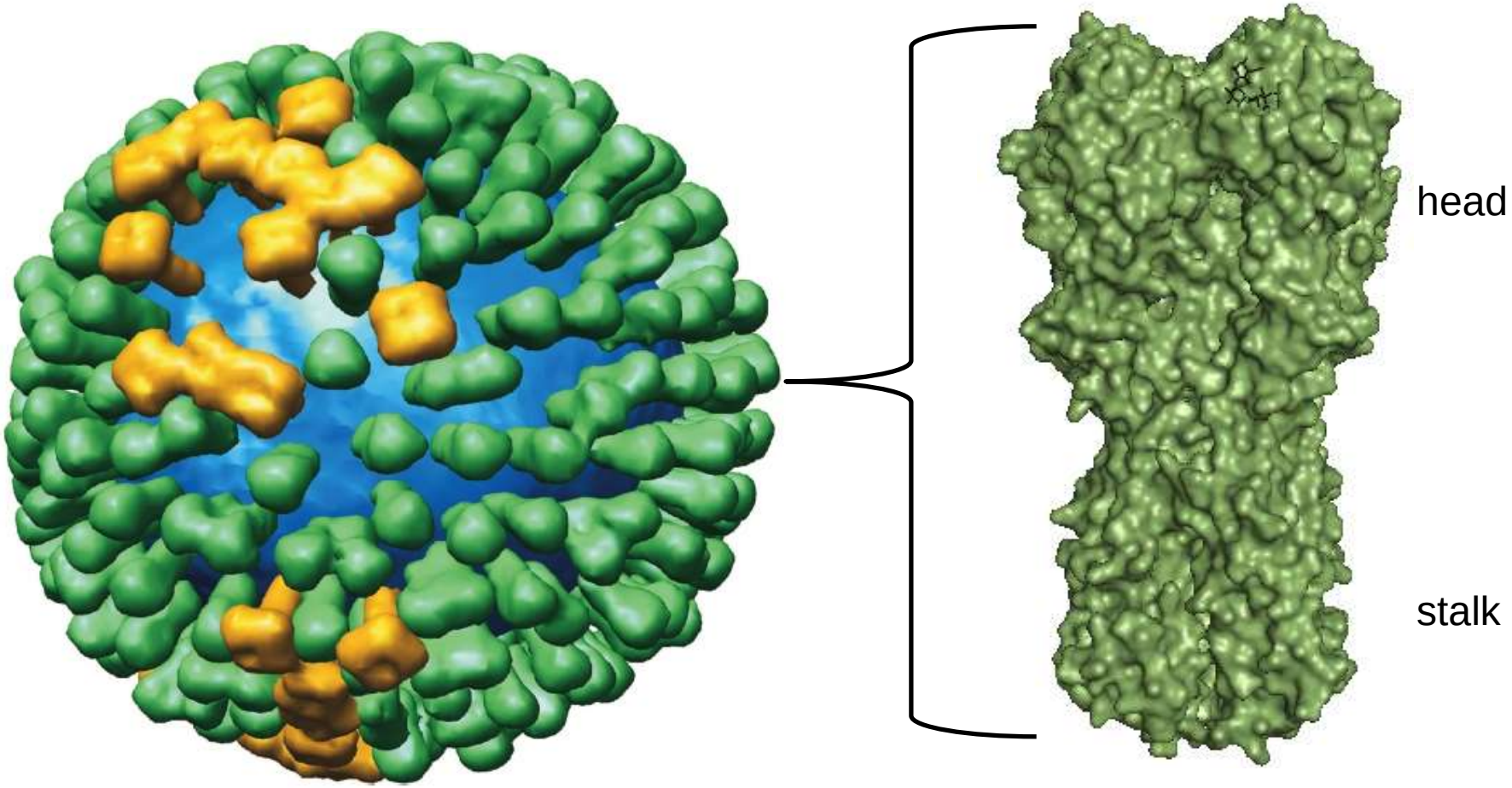
Immune history and seasonal influenza virus susceptibility

Scott E. Hensley

Penn Medicine

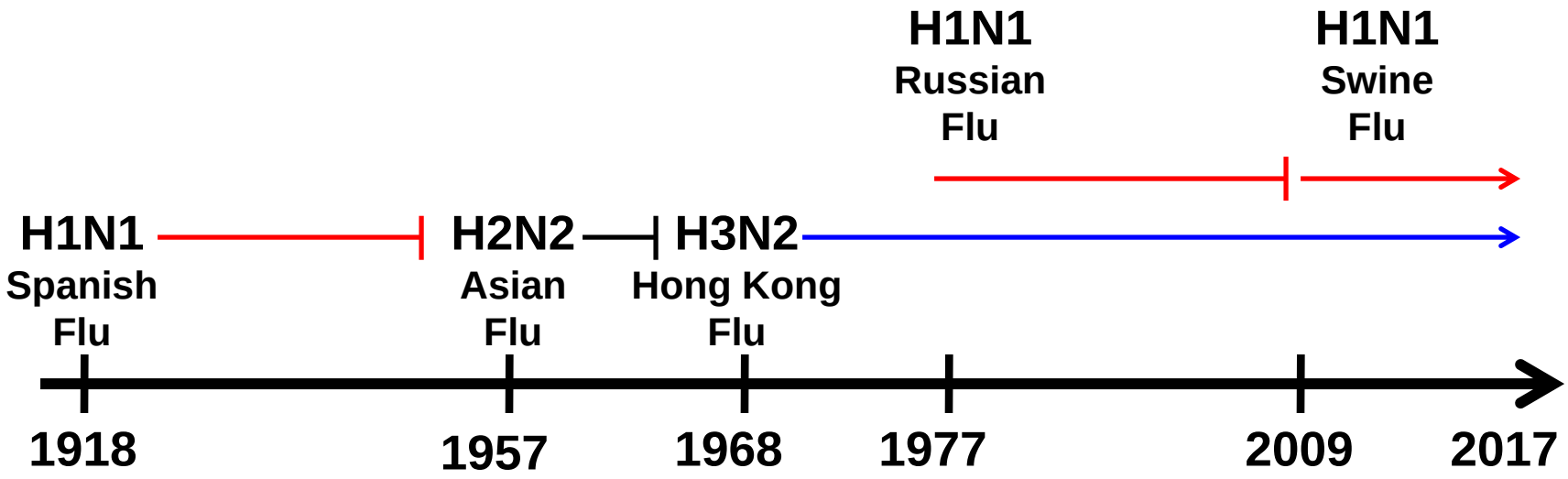
Influenza virus

Hemagglutinin

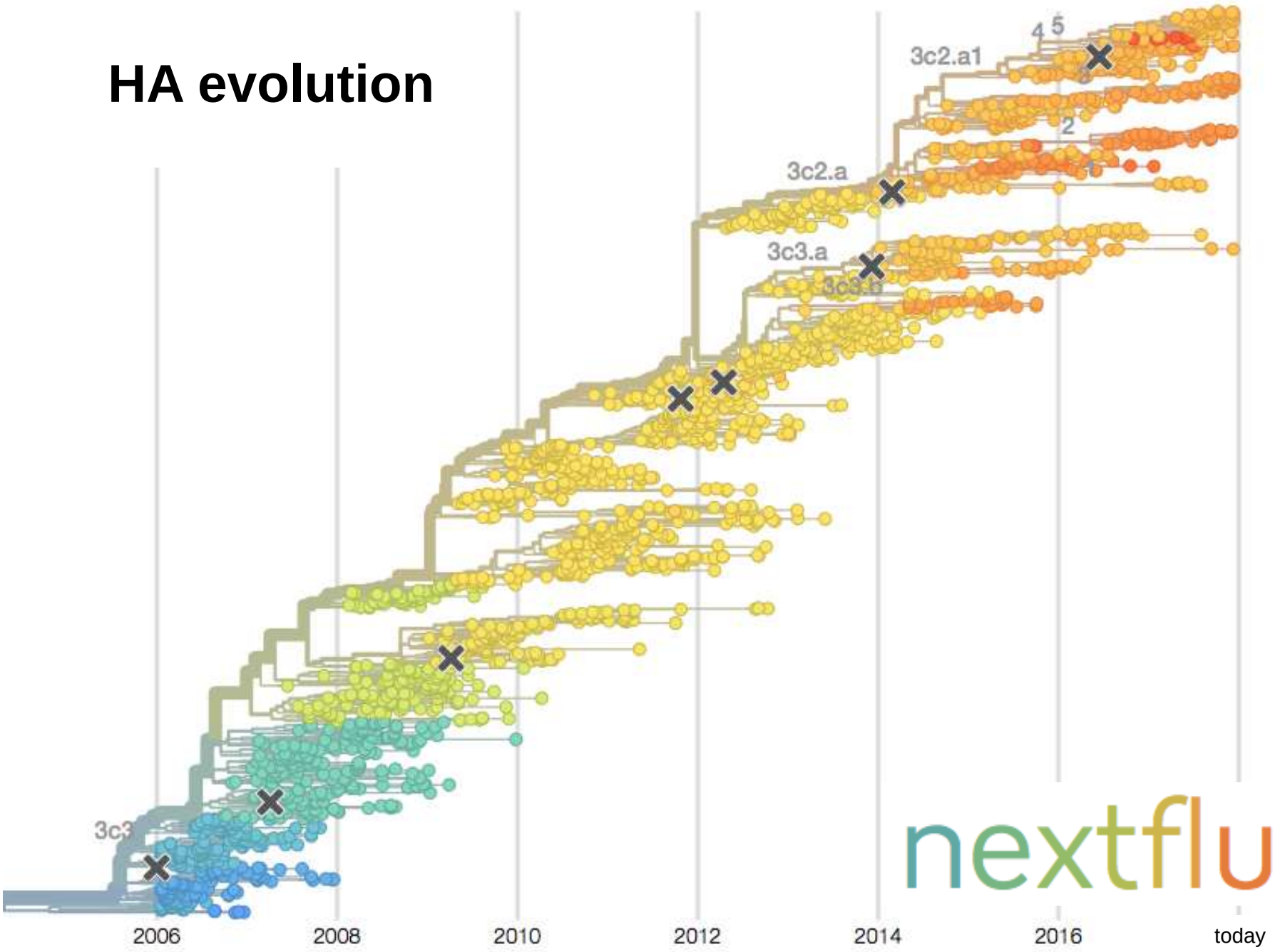


Harris et. al. PNAS (2006) 50:19123

Humans are constantly exposed to new flu strains



HA evolution



It takes a long time to make influenza vaccines and they are not very effective

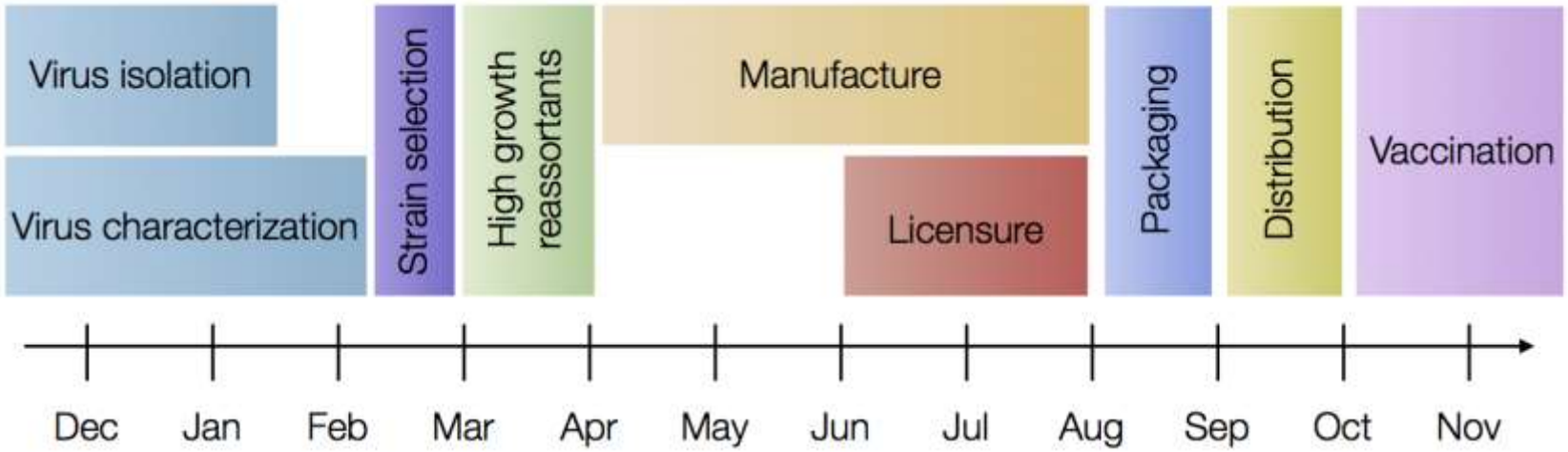
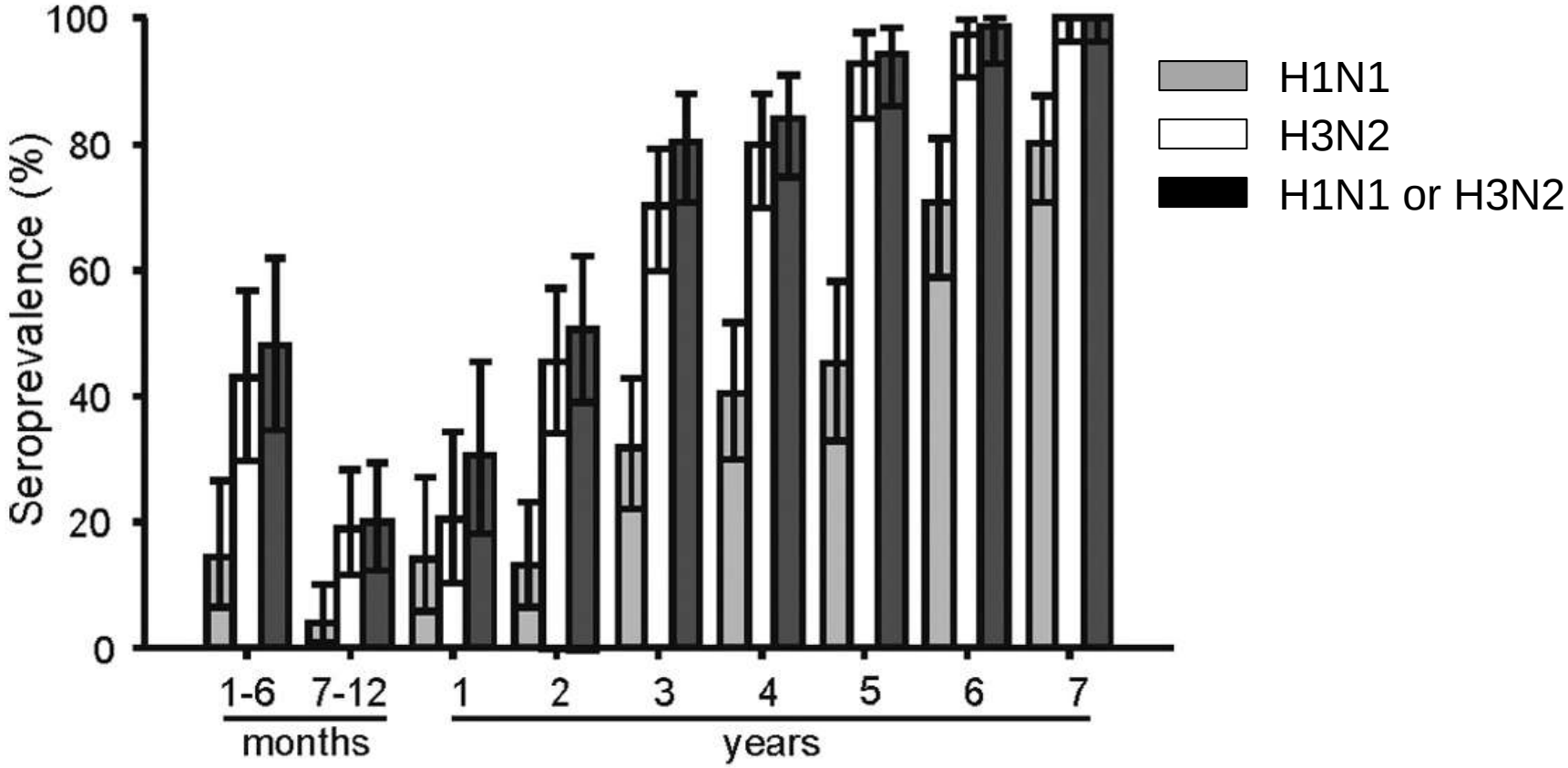


image from:
Trevor Bedford
http://bedford.io

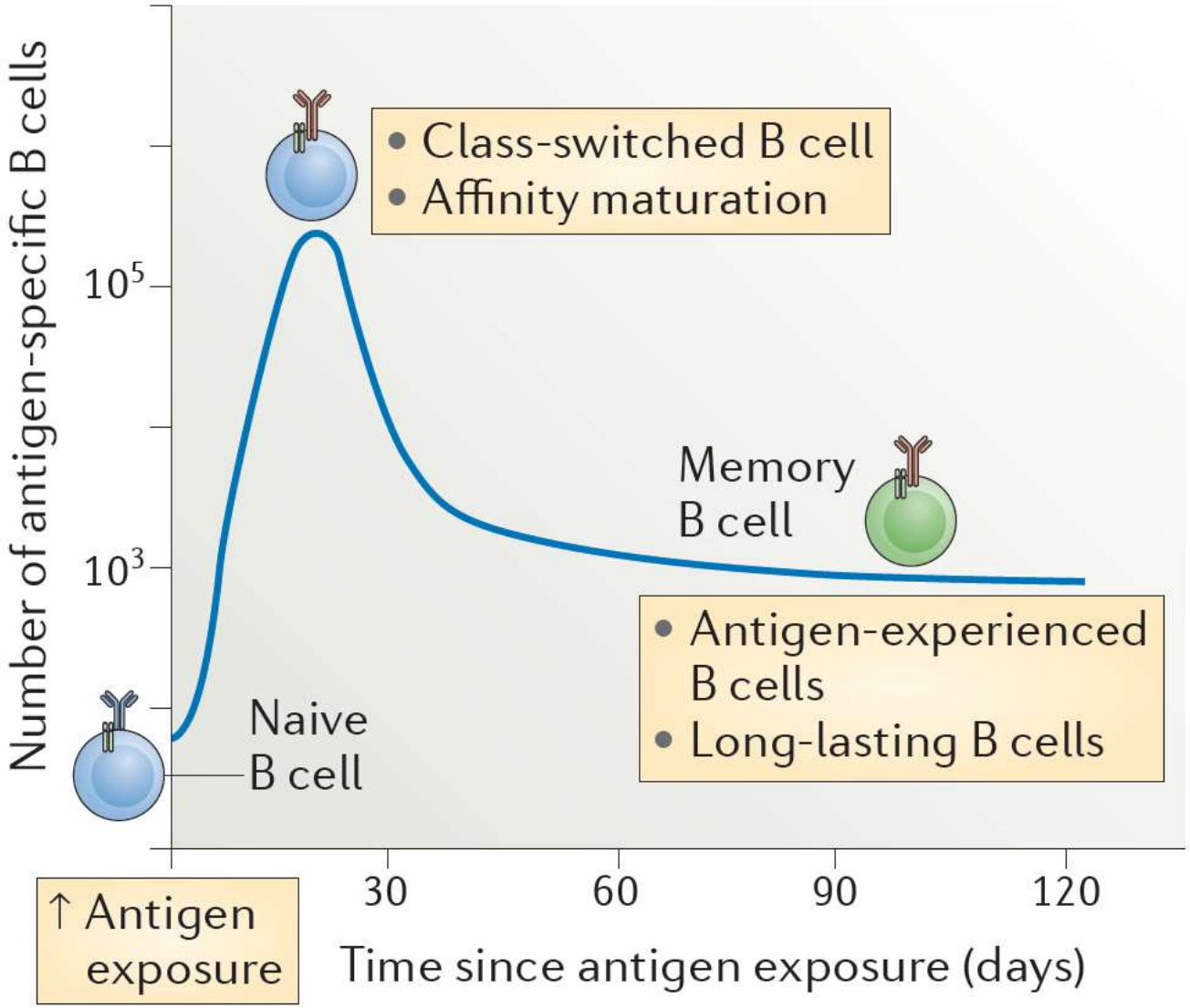

There is something magical about childhood

We are all exposed to flu during childhood



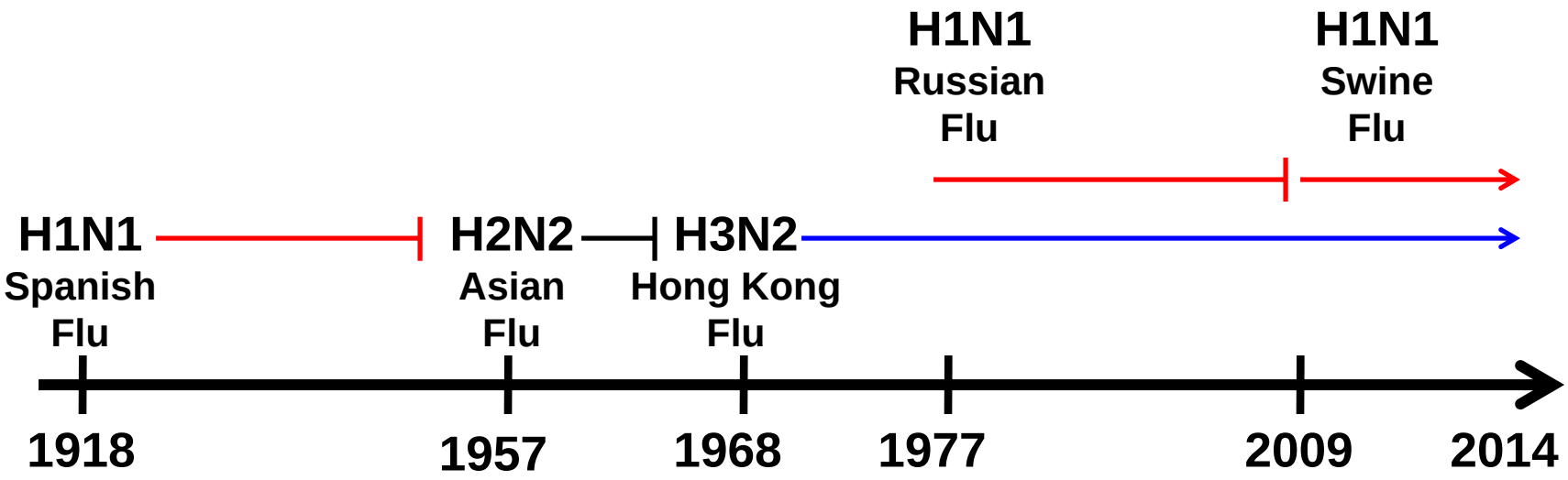
Bodewes et al. *CVI* 2011

Early childhood flu exposures leave lifelong immunological imprints

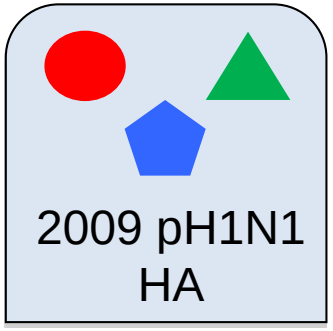


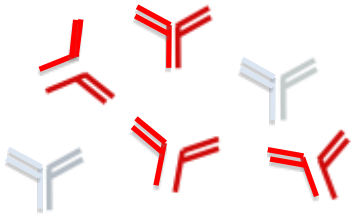
Kurosaki et al, *NRI* 2015

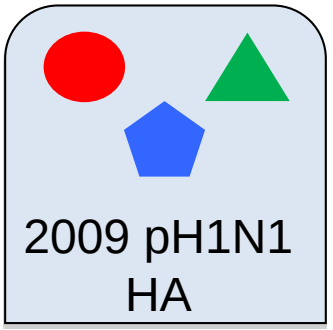
Depending on our year of birth, we all have different immunological imprints!

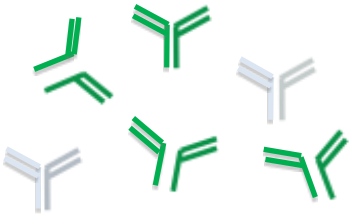


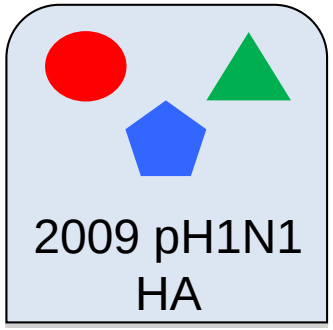
Childhood imprinting shapes specificity of influenza virus antibody responses

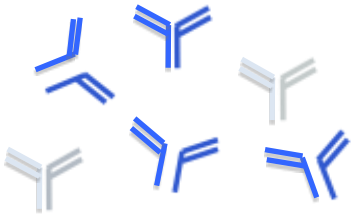








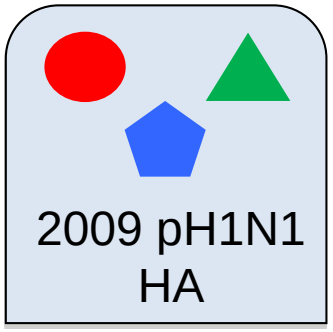


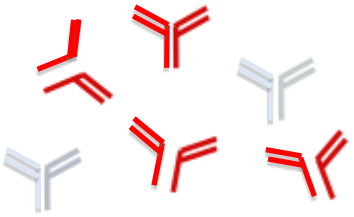


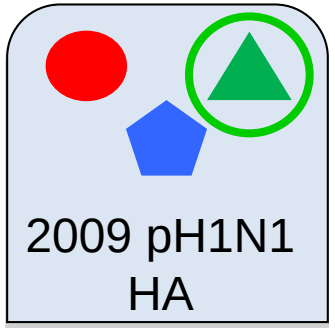
Childhood imprinting shapes specificity of influenza virus antibody responses

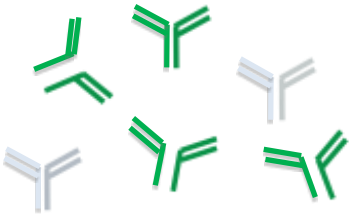
Previous HA

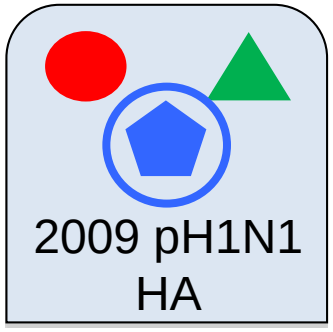
X

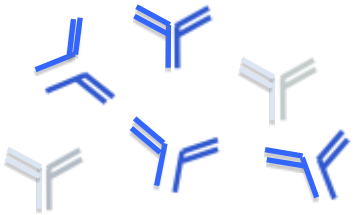




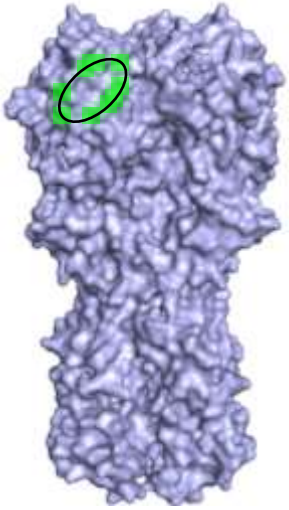








An example of immune-focusing on a viral epitope encountered in childhood



1983

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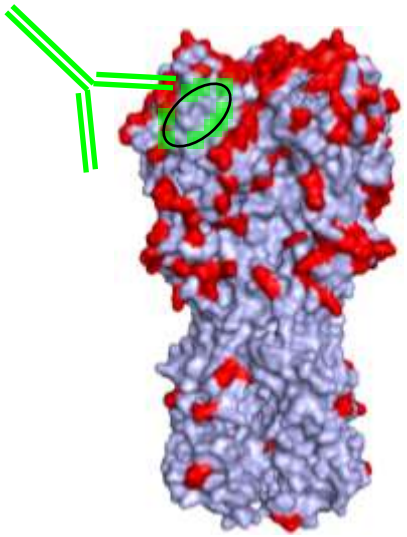
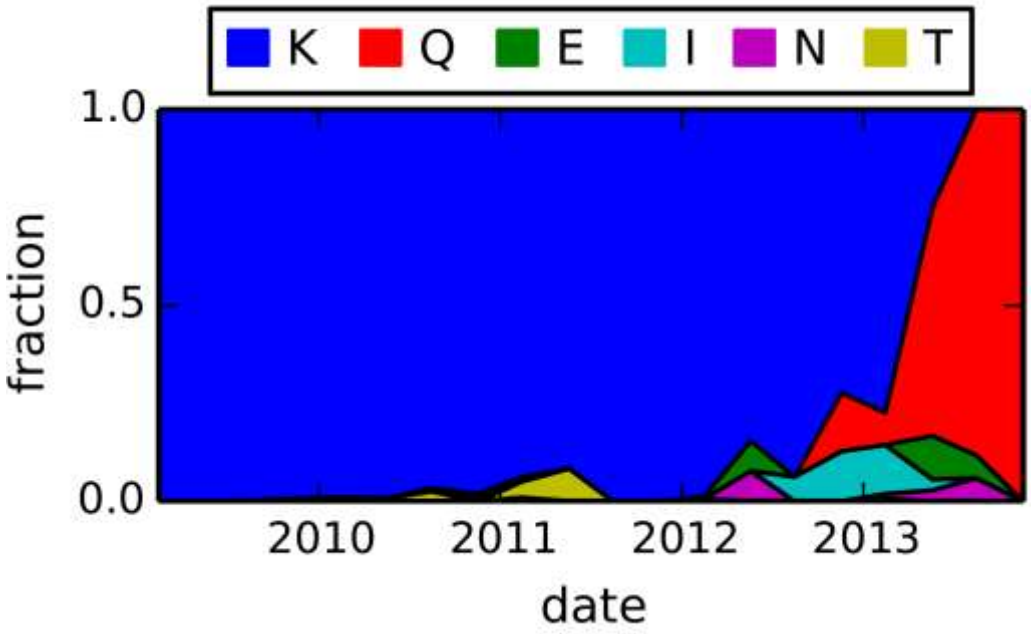
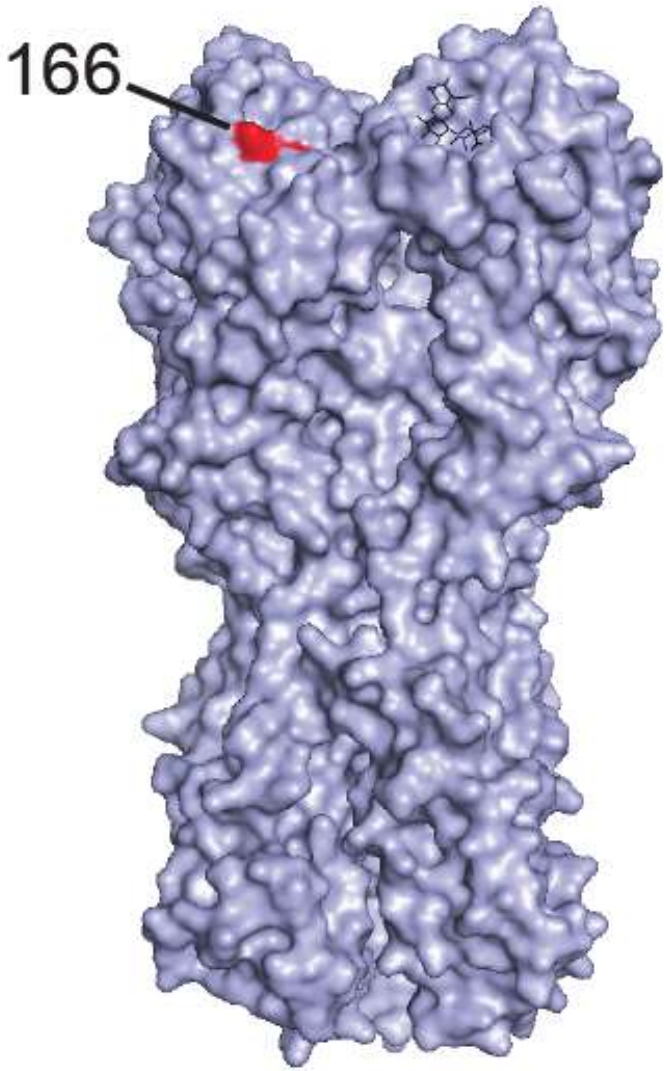


focused Ab response

Li et al. *JEM* 2013
Linderman et al. *PNAS* 2014
Petrie et al. *JID* 2016

The 2009 H1N1 virus acquired a mutation in an epitope recognized by ‘middle-aged’ individuals





Linderman et al., *PNAS* 2014

Many ‘middle-aged’ individuals were susceptible to drifted H1N1 strain in 2013-14 season

- 382 humans bled prior to 2013-2014 season
- 20 of these individuals were naturally infected with H1N1 (PCR-confirmed)
- Did these 20 people have pre-season antibody titers against vaccine strain, but not the circulating strain?

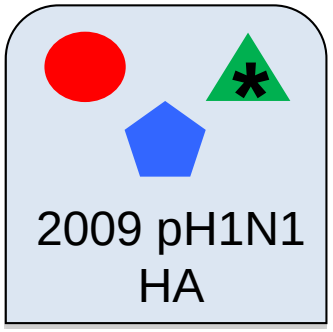
A/Cal/7/09-WT	**-**	**+**	**+**
A/Cal/7/09-K166Q	**-**	**+**	**-**

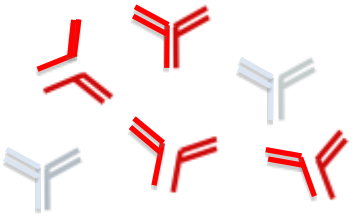
Petrie et al. *Journal of Infectious Disease* (2016)

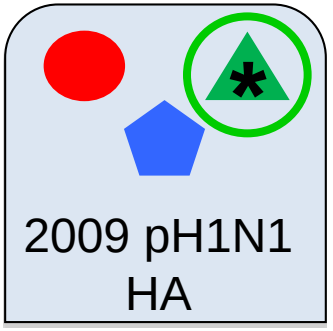
Childhood imprinting affects seasonal influenza virus susceptibility

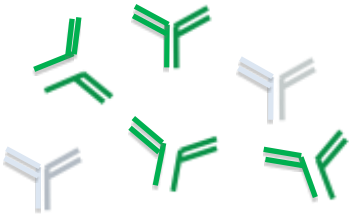
Previous HA

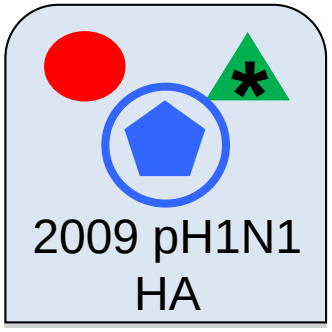
X

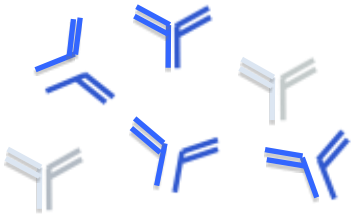




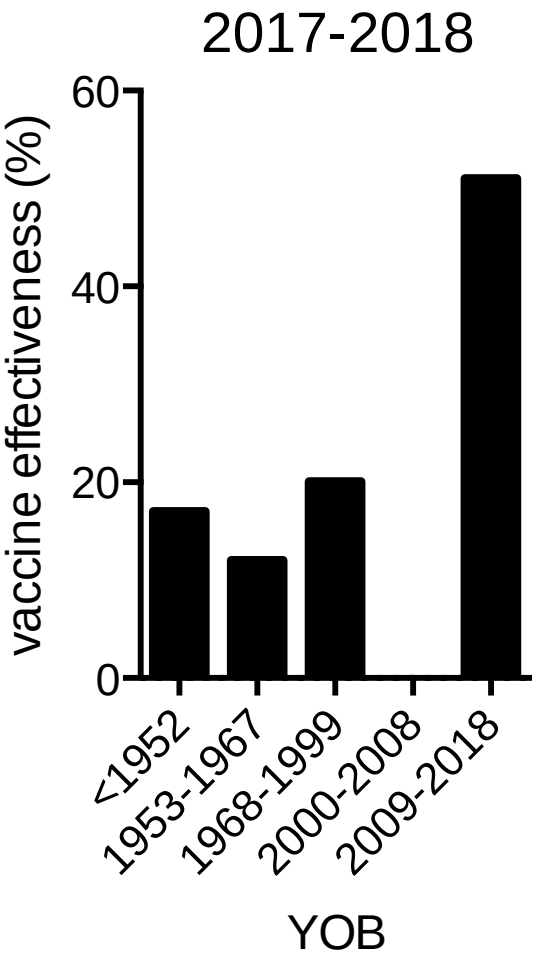








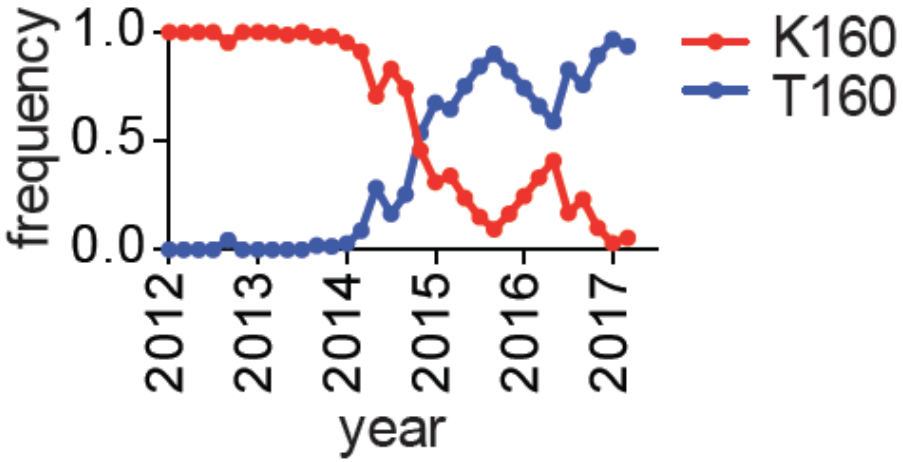
The H3N2 vaccine has only been effective in very young individuals over the past 2 years

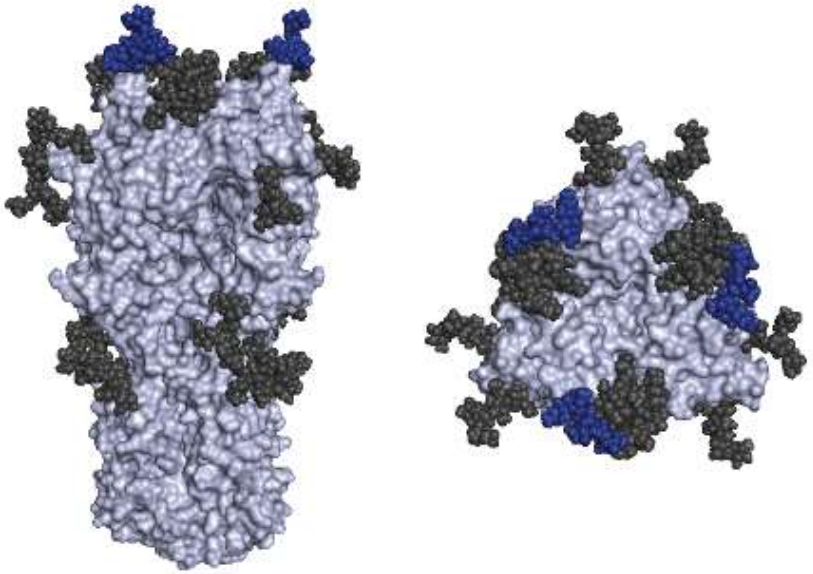


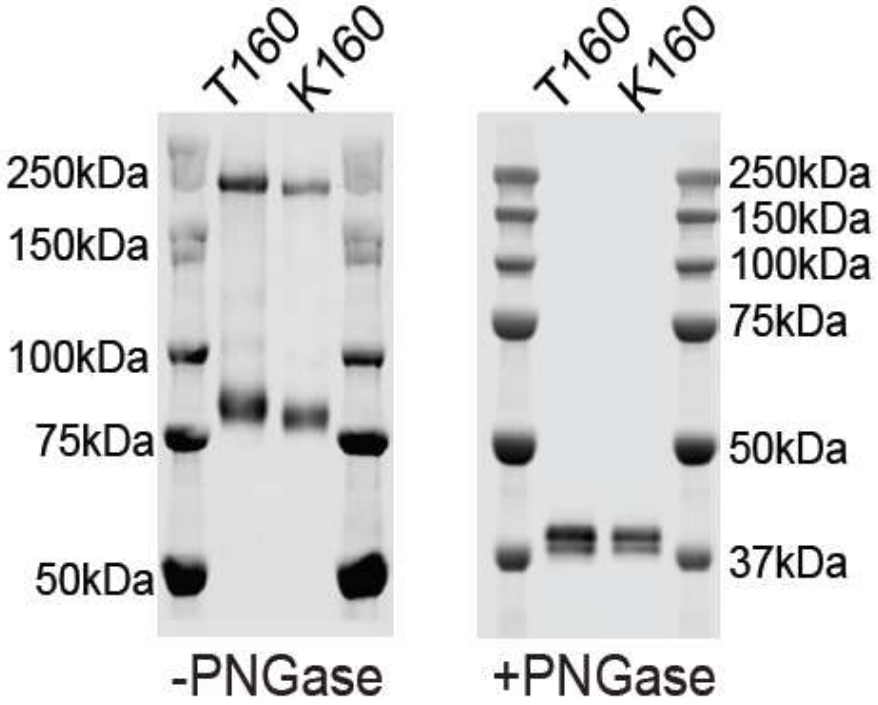
Is childhood imprinting involved?

www.cdc.gov/vaccines/acip/meetings

Contemporary H3N2 strains possess new glycosylation site in HA



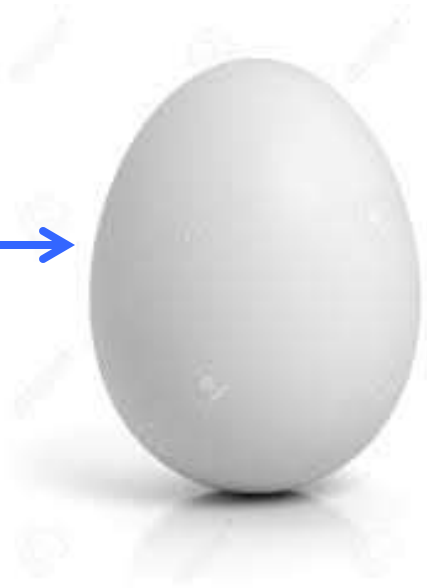




Zost et al. *PNAS* (2017)

The problem of egg adaptation

A/Hong Kong/4801/2014



A/Hong Kong/4801/2014
#X263

T160 HA

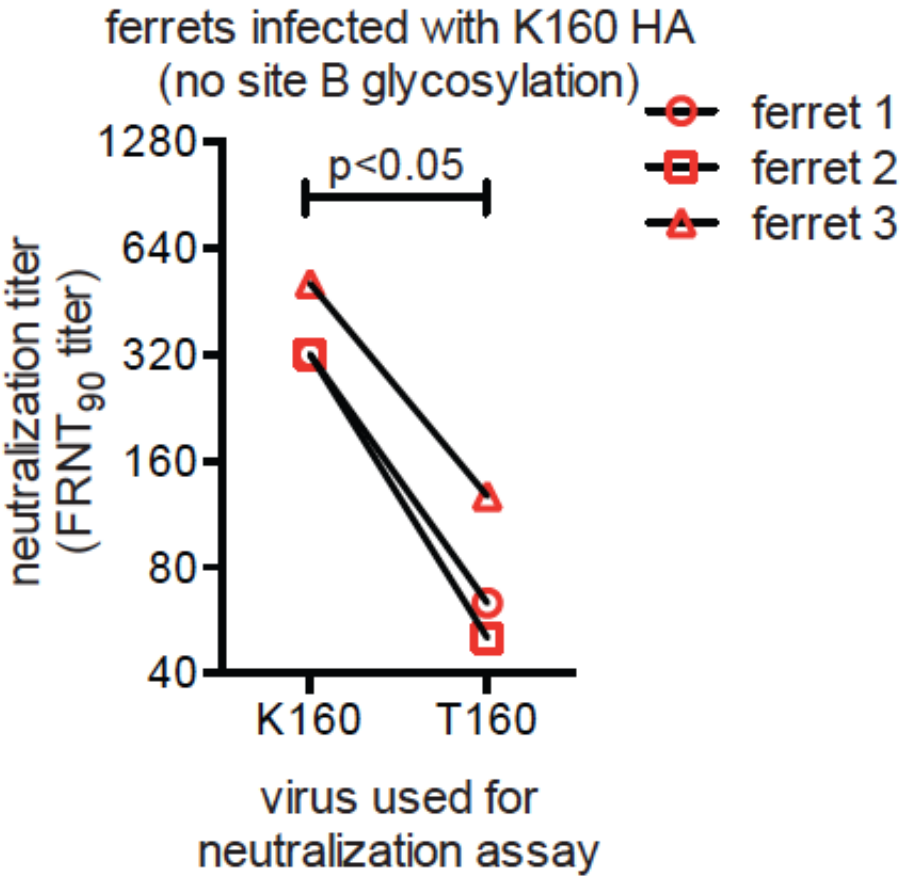
K160 HA

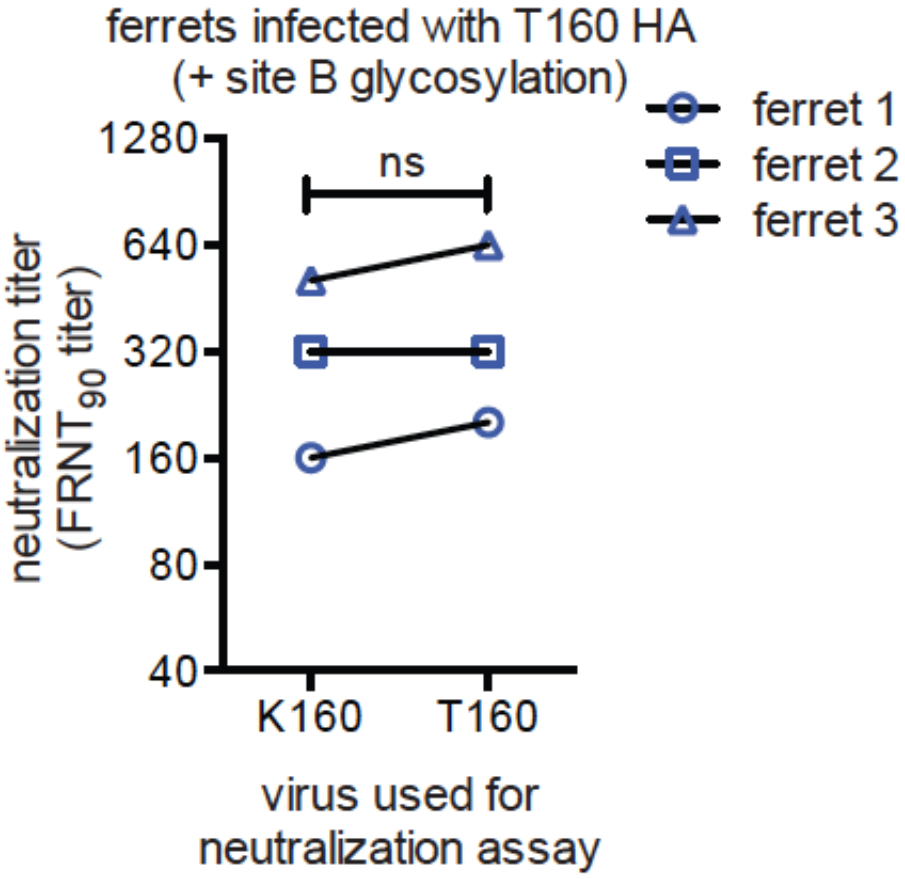
Glycosylation matches circulating strains

No antigenic site B glycosylation

Zost et al. *PNAS* (2017)

Abs from ferrets infected with current H3N2 vaccine strain poorly recognize circulating H3N2





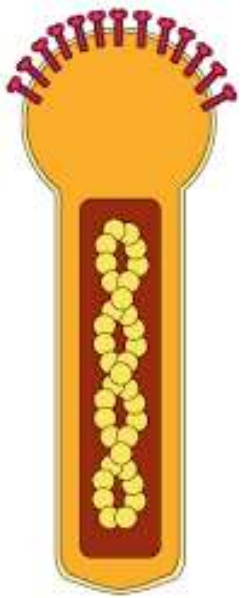
Zost et al. *PNAS* (2017)

What about humans?

Human influenza vaccine antigens are prepared in eggs, cell culture, and via baculovirus system

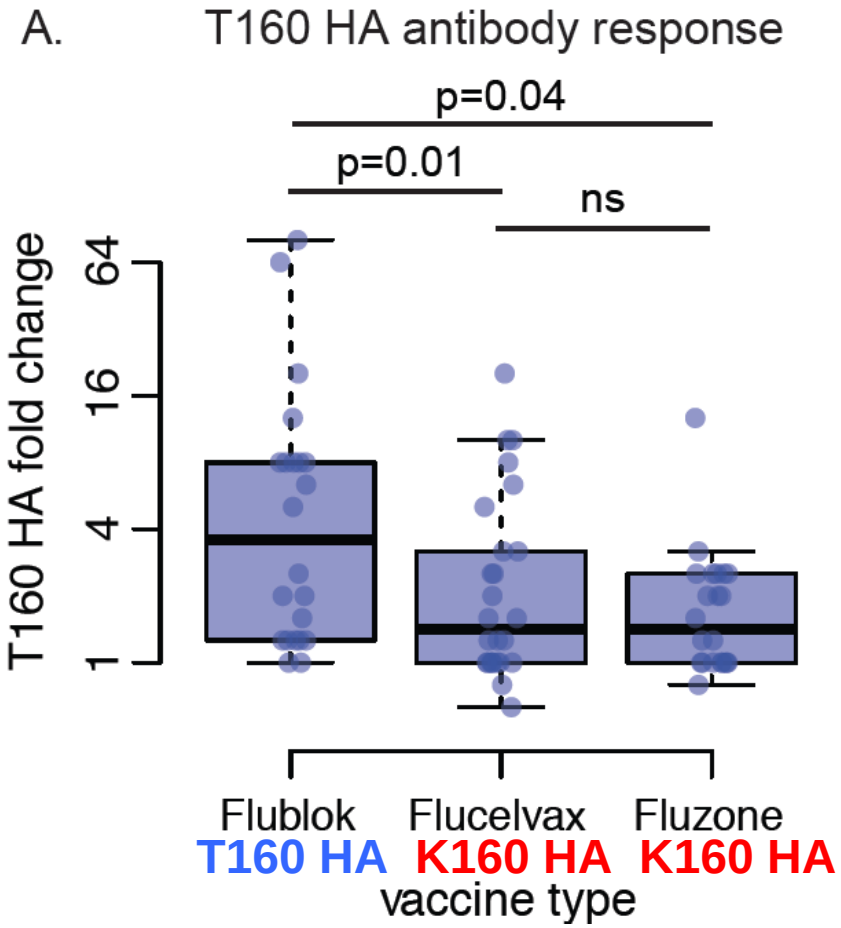
K160 HA

K160 HA



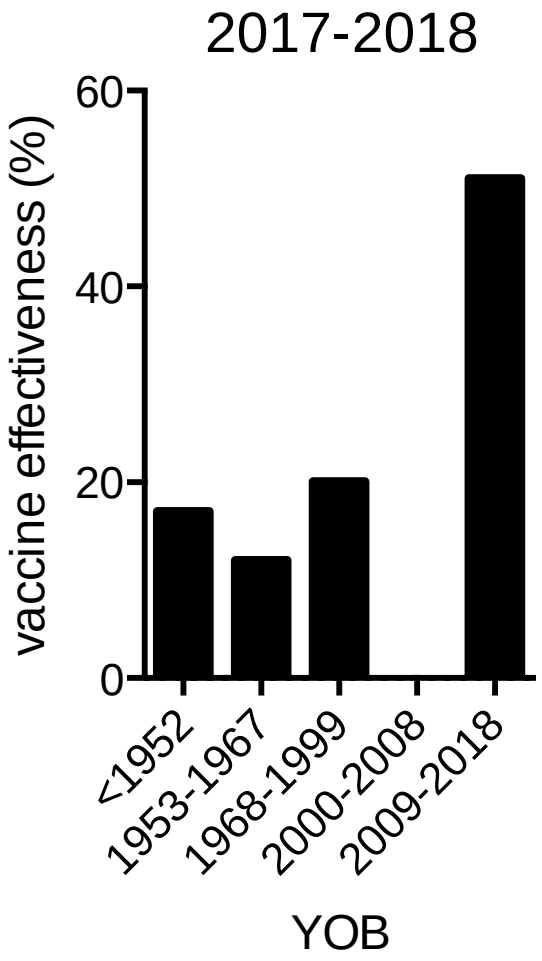
T160 HA

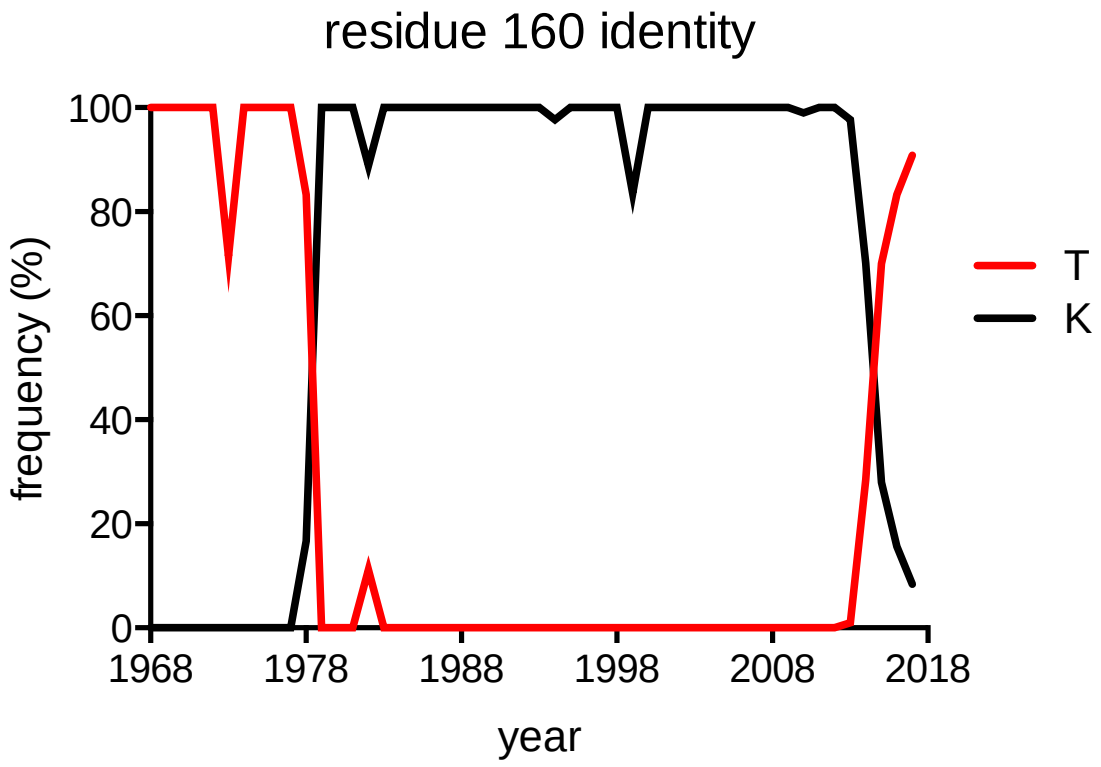
Abs elicited by Flublok (baculovirus antigen) neutralize current circulating H3N2 strain



Zost et al. *PNAS* (2017)

But why does the current H3N2 vaccine have such low VE in everyone except very young kids?



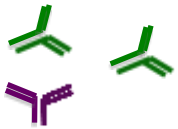


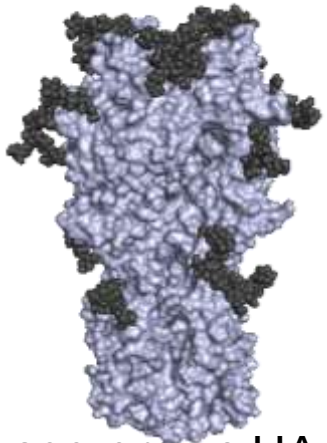
Hypothesis: egg-adapted H3 strain (that has K160 HA) recalled memory B cells in older children that were primed by H3N2 viruses that had K160 HA

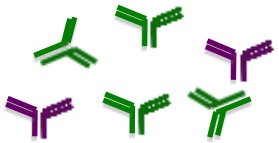
Summary of the past two H3N2 seasons

Prevax Ab repertoire

Individual 1

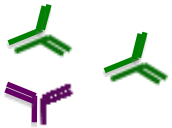


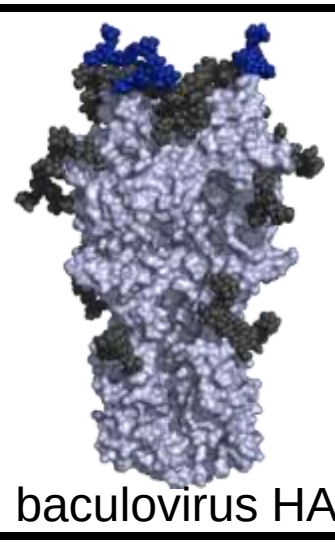


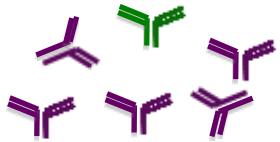


Low neutralizing Ab titer against glycosylated strain

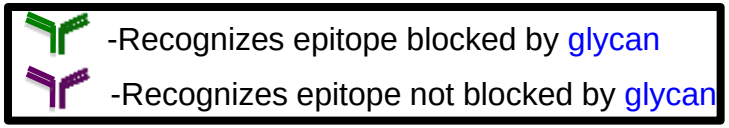
Individual 2







Higher neutralizing Ab titer against glycosylated strain

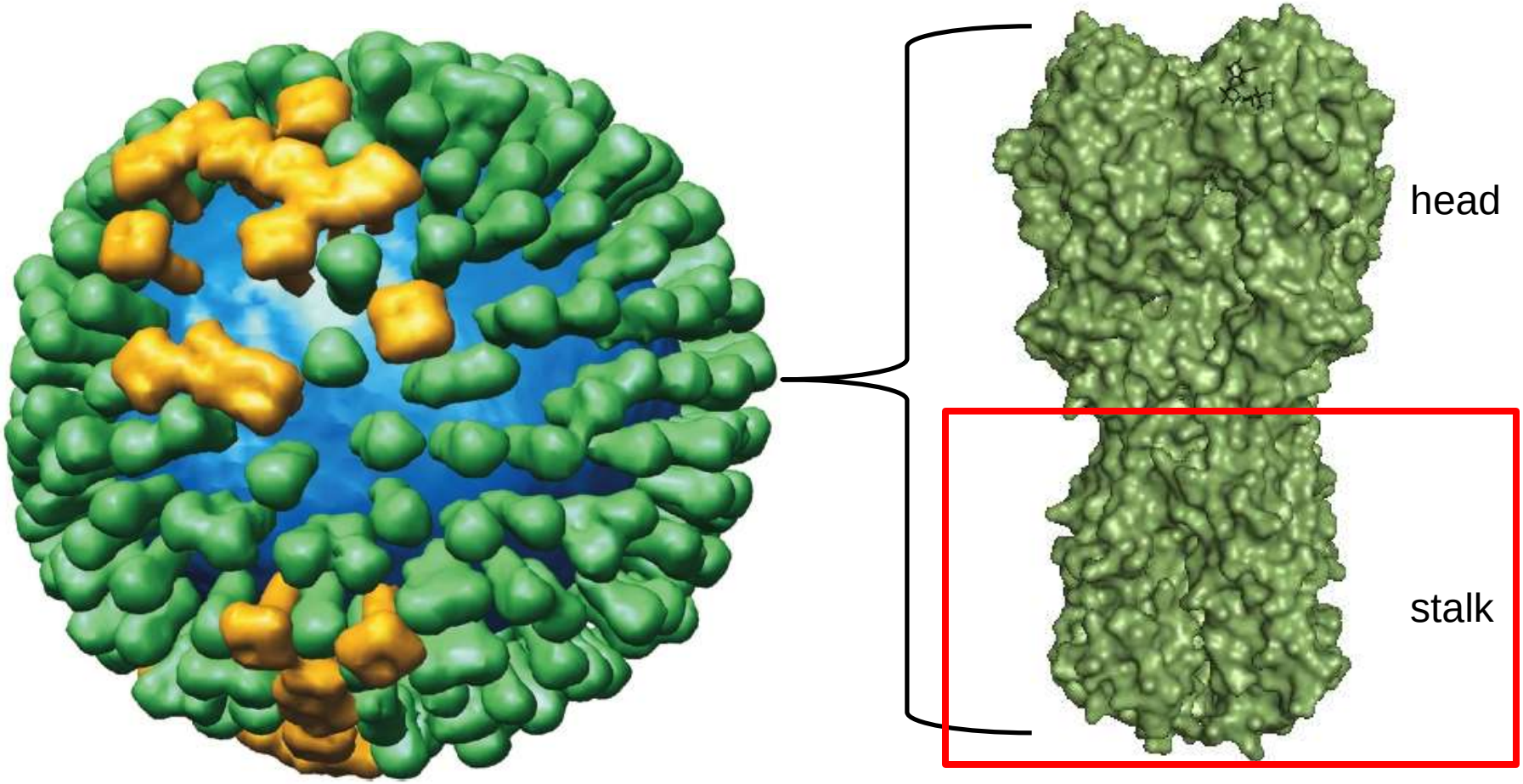


Can we make better influenza vaccines?

- Universal influenza vaccines based on HA stalk immunity
- mRNA-based influenza vaccines

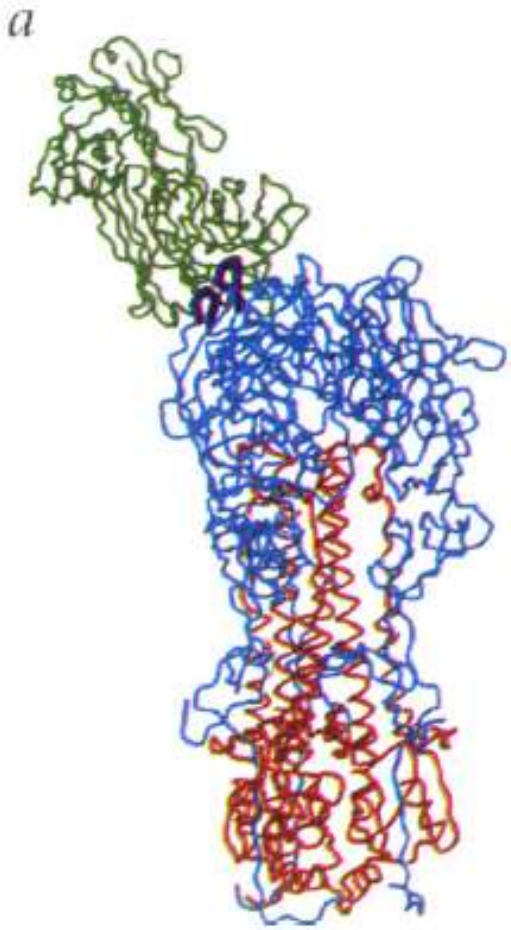
Influenza virus

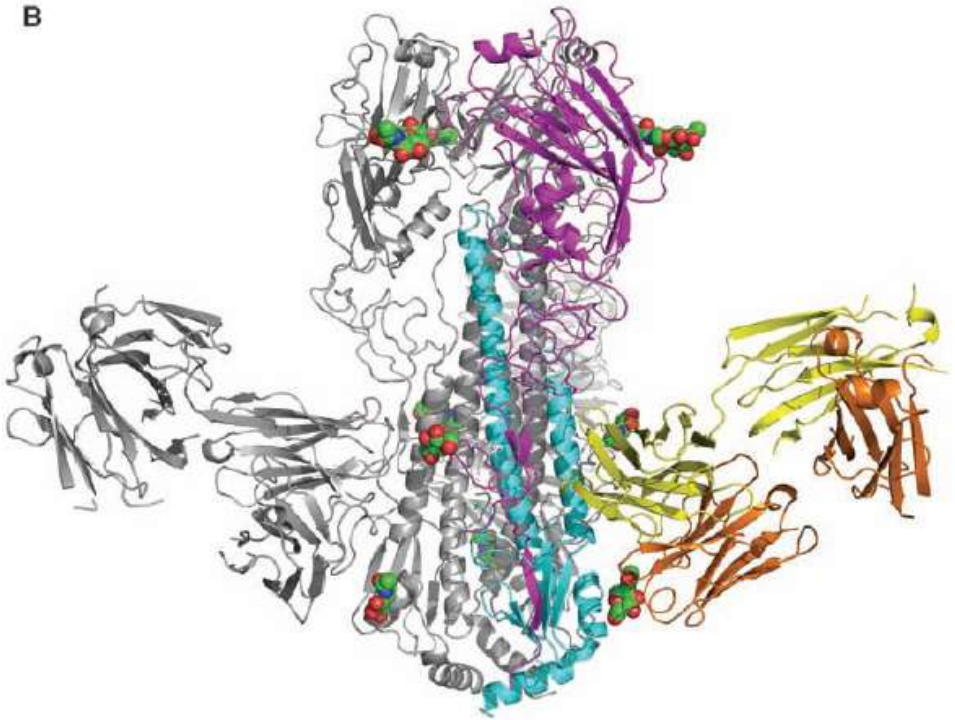
Hemagglutinin



Harris et. al. PNAS (2006) 50:19123

HA head versus HA stalk Abs

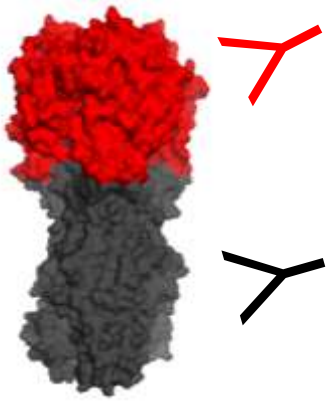


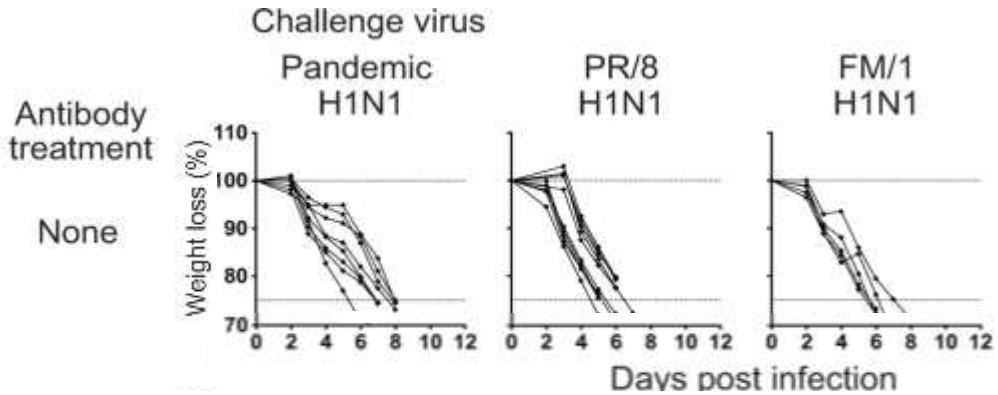


nature structural biology • volume 5 number 2 • february 1998

www.sciencemag.org SCIENCE VOL 324 10 APRIL 2009

HA stalk Abs are not as great as HA head Abs (but they protect against many viral strains)





Wrammert *et. al, JEM* 2011

Are HA stalk Abs associated with protection in humans?

	Household Cohort	Hospitalization Cohort
Donors	373 healthy individuals enrolled prior to the flu season (both 2013-14 & 2015-16)	184 patients hospitalized with severe respiratory illness symptoms were enrolled upon admission
Infection	Naturally acquired pH1N1 infection	Hospitalization with naturally acquired pH1N1 infection
Sera	Sera obtained prior to the season	Sera obtained upon hospital admission
Monitoring	Influenza infection confirmed via PCR	Influenza infection confirmed via PCR

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HA head Abs <u>are</u> associated with protection in the 2015-16 ‘household’ study

st

Barbour et al. *manuscript in prep*

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Barbour et al. *manuscript in prep*

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Sera	Sera obtained prior to the season	Sera obtained upon hospital admission
Monitoring	Influenza infection confirmed via PCR	Influenza infection confirmed via PCR

HA head Abs are associated with protection in the 2015-16 ‘hospitalization’ study

Barbour et al. *manuscript in prep*

HA stalk Abs are not associated with protection in the 2015-16 ‘hospitalization’ study

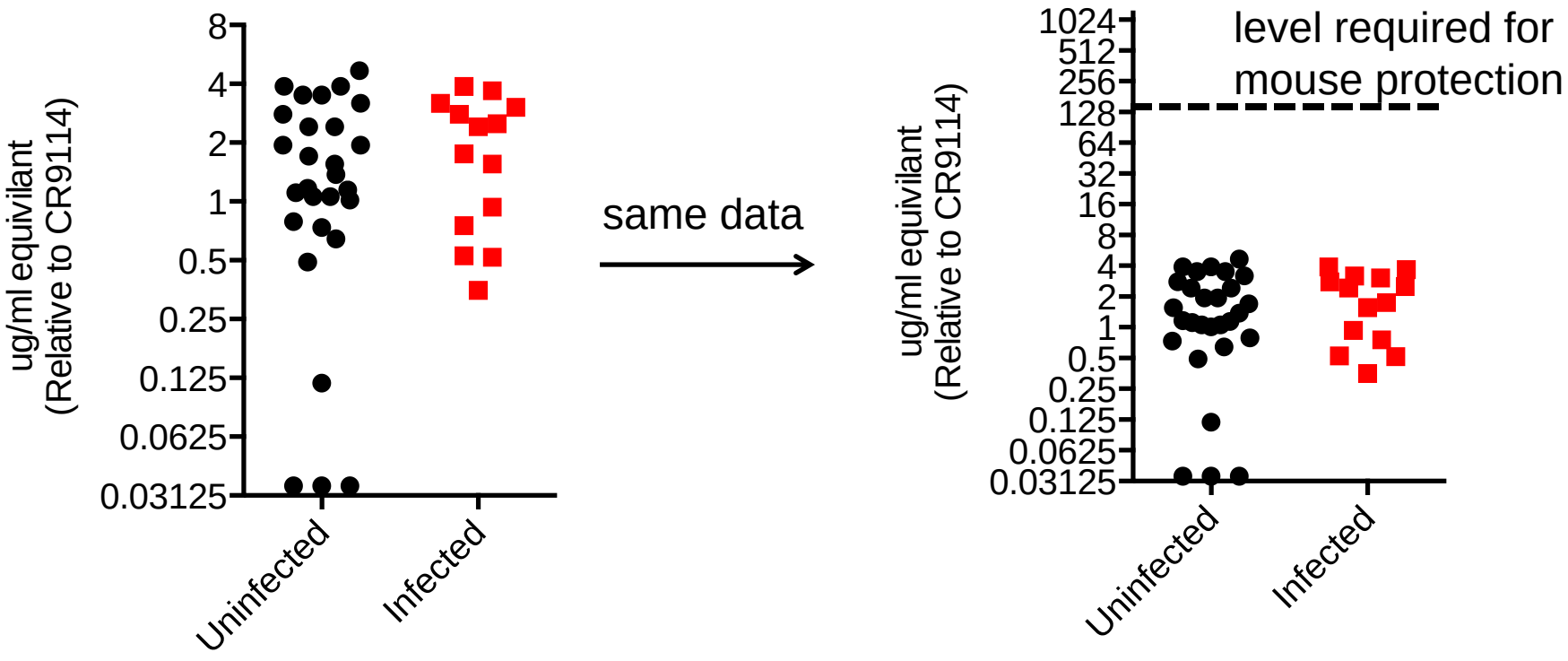
Barbour et al. *manuscript in prep*

HA stalk Abs are not independently associated with protection in the 2015-16 'hospitalization' study

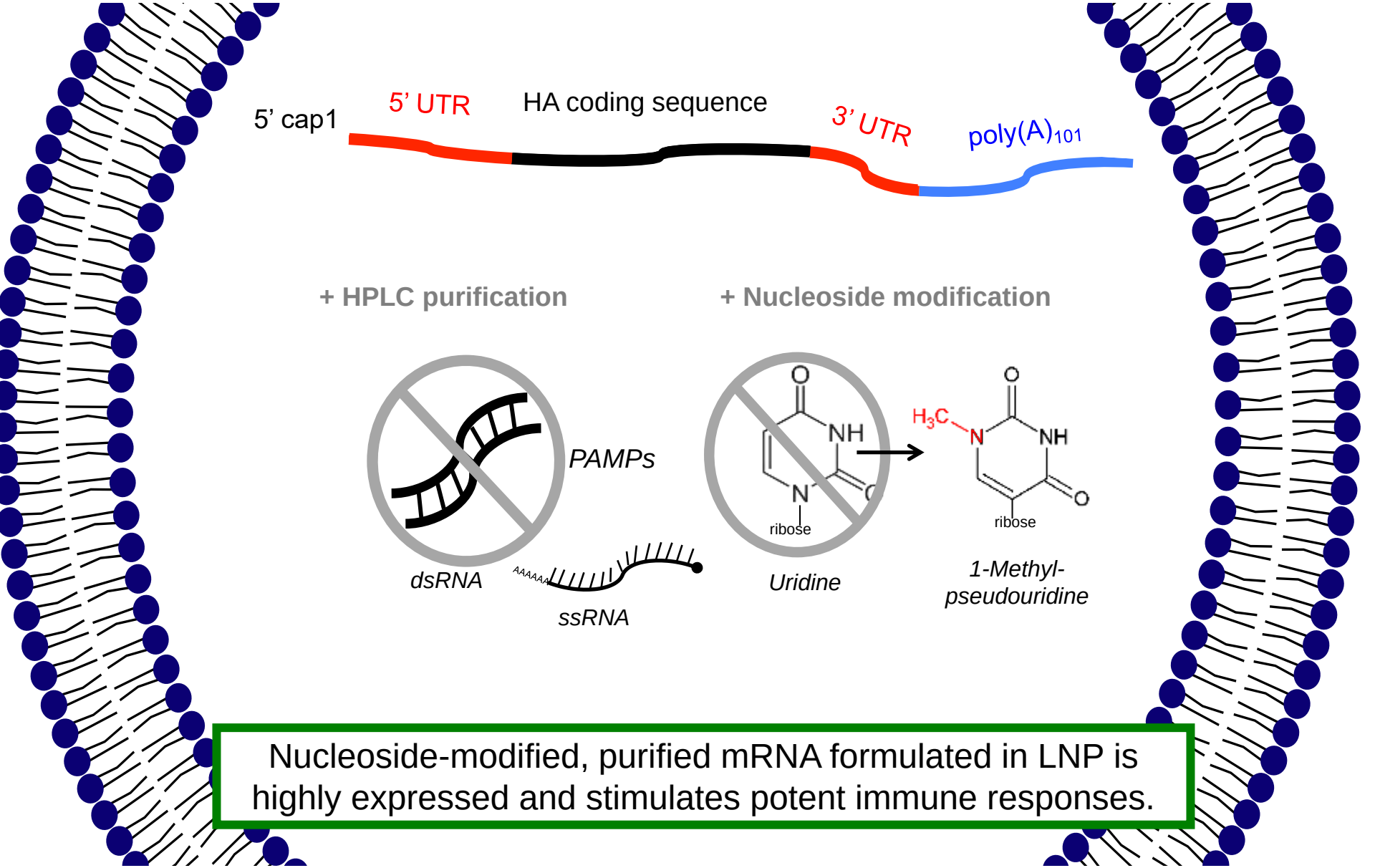
	Log2 HAI titer OR (95% CI)	Log2 stalk titer OR (95% CI)
HAI only	0.75 (0.60, 0.94)	
Stalk only		0.87 (0.75, 1.00)
HAI + Stalk	0.78 (0.63, 0.97)	0.91 (0.79, 1.06)

Controls: n = 116 Cases: n = 63

HA stalk-based vaccines will need to elicit high levels of Abs

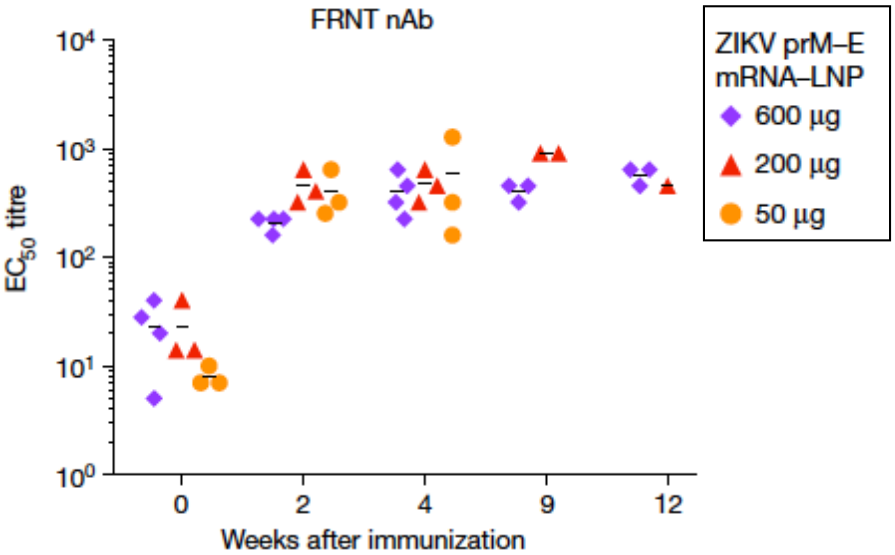


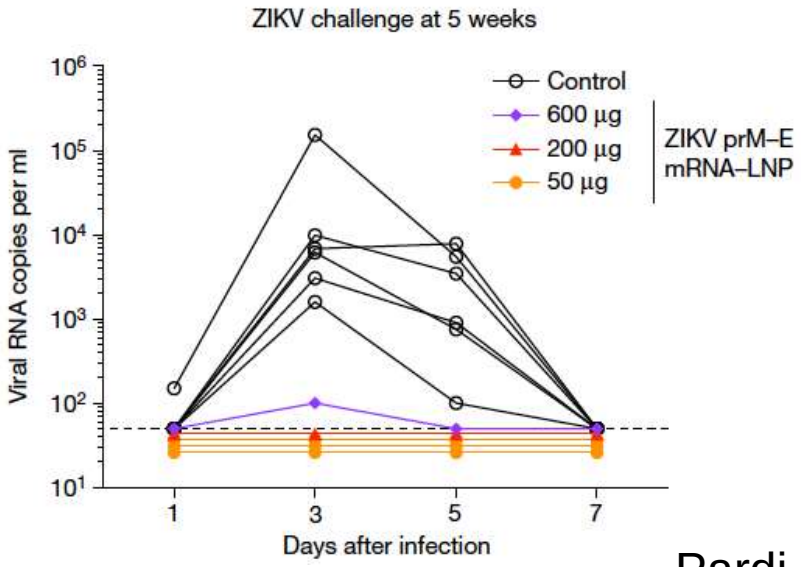
mRNA: the influenza vaccine of the future



Nucleoside-modified, purified mRNA formulated in LNP is highly expressed and stimulates potent immune responses.

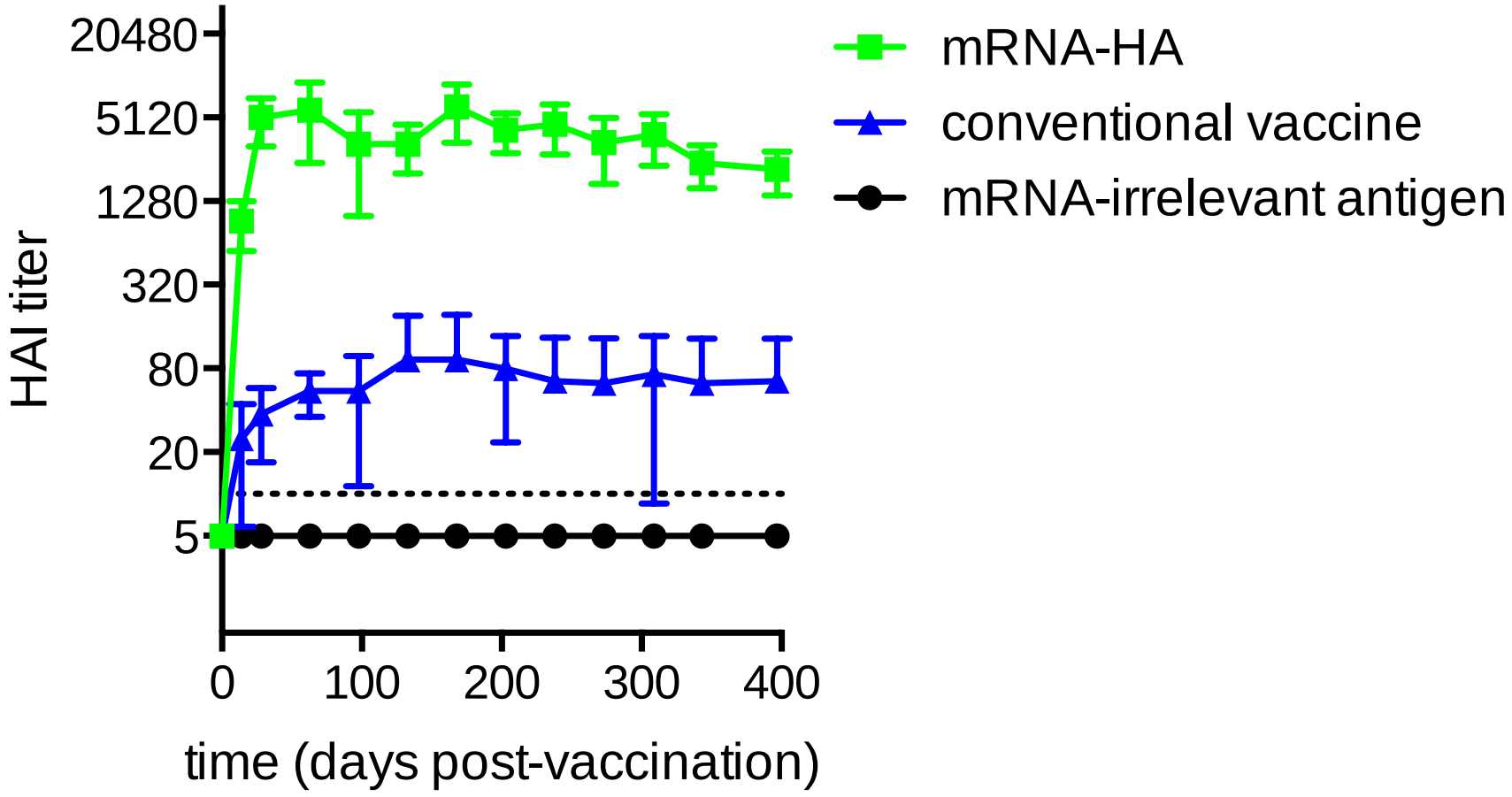
mRNA-based ZIKV vaccine protects rhesus macaques





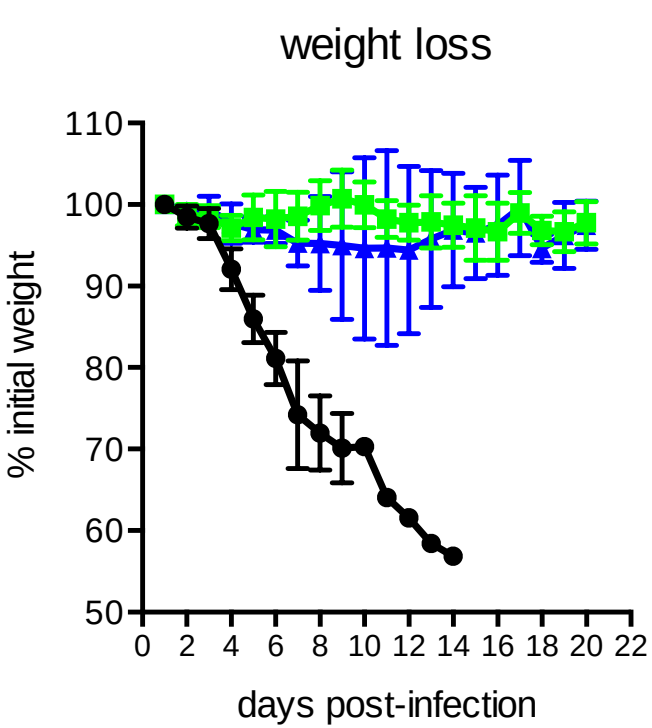
Pardi et al. *Nature* 2017

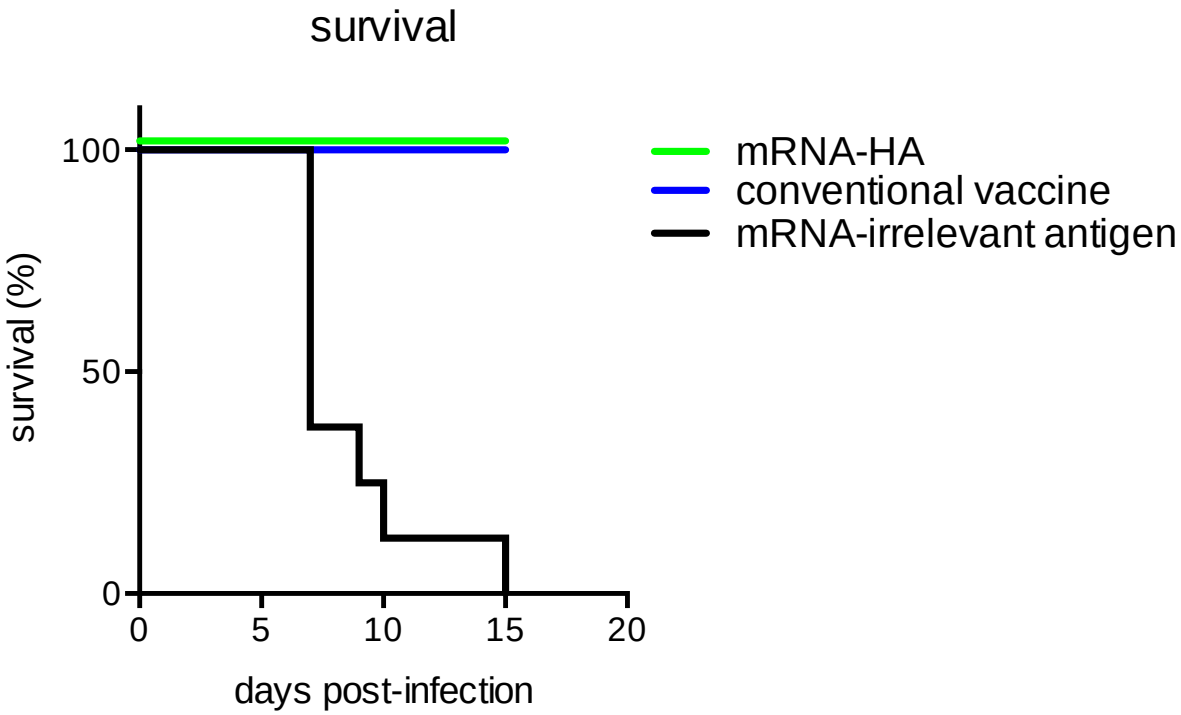
mRNA vaccine elicits a long-lasting antibody response



Pardi et al. *unpublished*

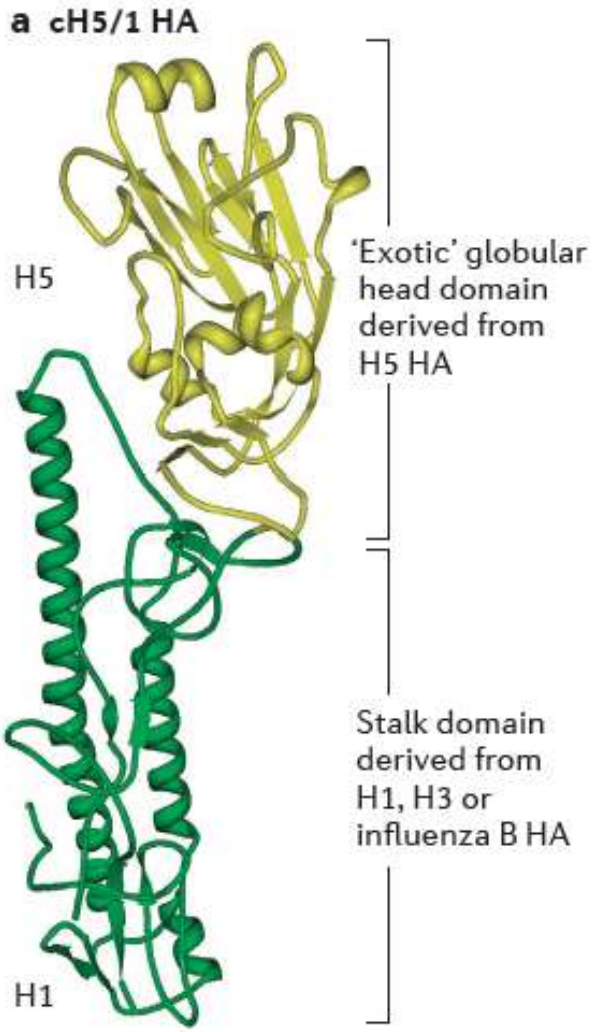
mRNA vaccine elicits a protective immune response



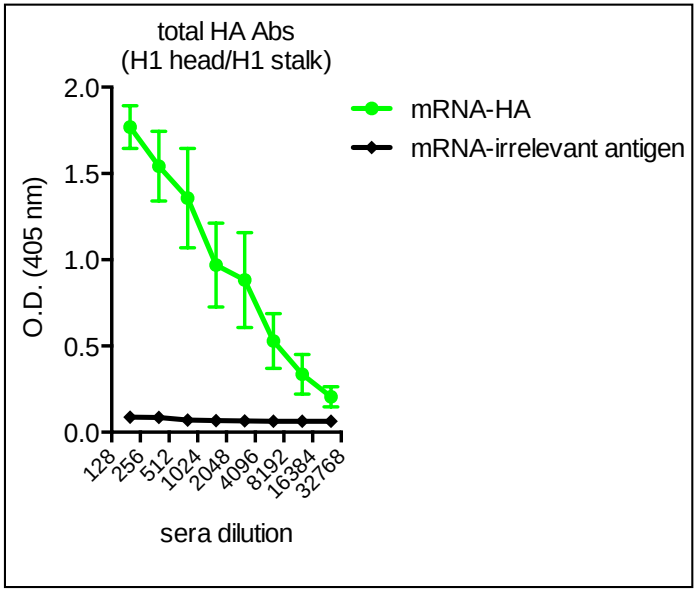


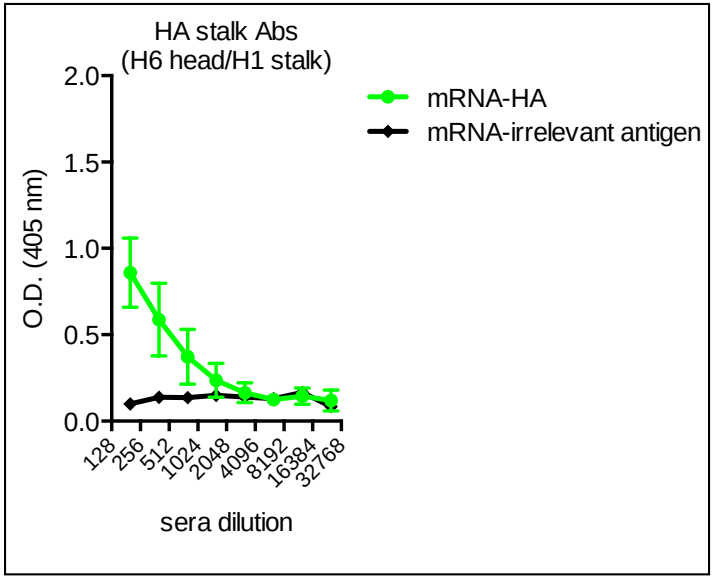
Pardi et al. *unpublished*

mRNA vaccine elicits HA head and HA stalk Abs



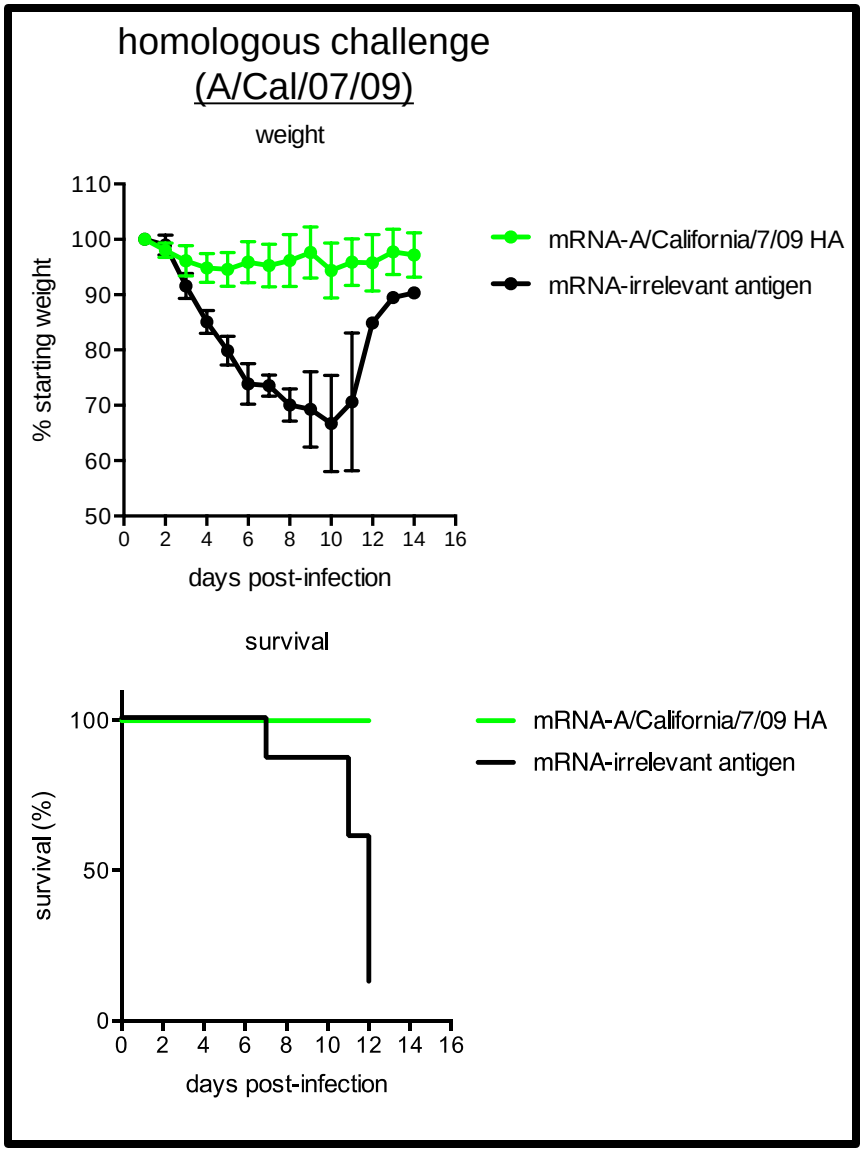
Krammer and Palese, *Nature Reviews* 2015

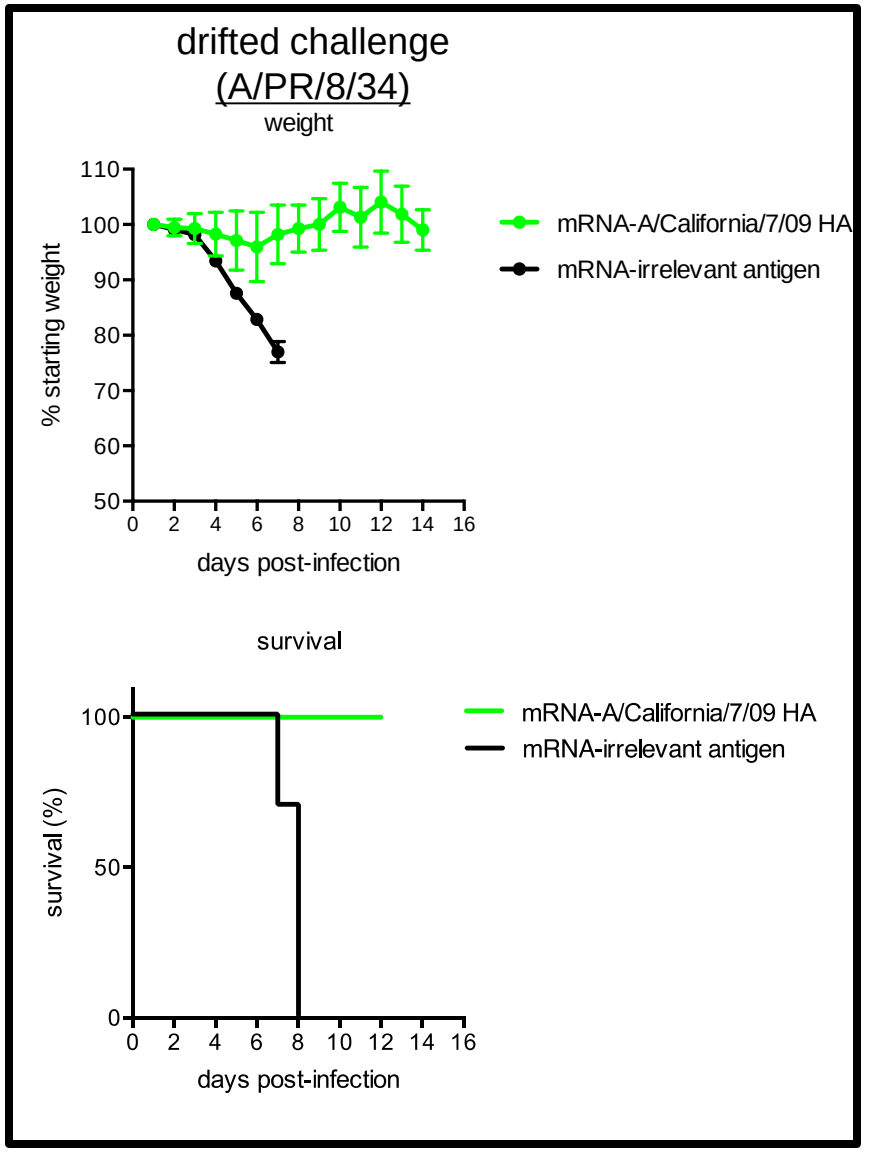




Pardi et al. *unpublished*

mRNA vaccine protects against homologous and drifted influenza virus strains





Pardi et al. *unpublished*

Main points

- Early childhood immunological imprints shape the specificity of antibody responses against new influenza virus strains
  - This is clearly the case with H1N1 viruses
  - This appears to be the case with H3N2 viruses
- Egg-adaptive mutations likely led to low vaccine effectiveness last year
- HA stalk Abs are not at sufficiently high levels in most individuals to protect against seasonal influenza virus
- mRNA vaccines might be a good alternative to conventional influenza vaccines—it is unclear why they elicit such high levels of Abs

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