Distinct priming effect of live attenuated vs inactivated influenza vaccines in repeated influenza vaccination

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Background

- **Influenza epidemic and pandemic are serious public health problems**
  - **Average annual flu-related death- ~23,000 (USA)**
  - **Annual direct medical cost - $10 billion, lost earnings - $16 billion, total economic burden - $87 billion (USA)**

Background

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- **The best protection against influenza is provided by flu vaccines**
- **B cell/Ab responses to influenza vaccination are associated with flu vaccine effectiveness**

Limitations of current influenza vaccination

- limited efficacy in the elderly
  - lower Ab response after vaccination

- limited efficacy for antigenically mismatched strains and need for annual re-vaccinating
  - lower cross-reactive Ab activity to variant strains

Controversy in efficacy of repeated IIV immunization

- **Hoskins study (1979)**
  Annual vaccination of school children with inactivated influenza A vaccine conferred no long-term advantage – "Hoskins paradox"

- **Keitel study (1997)**
  Repeat influenza vaccination provided continual protection

CDC recommendation since 2010:

Annual flu vaccination starting at age of 6 months

Flu vaccine effectiveness could be affected by prior season vaccination

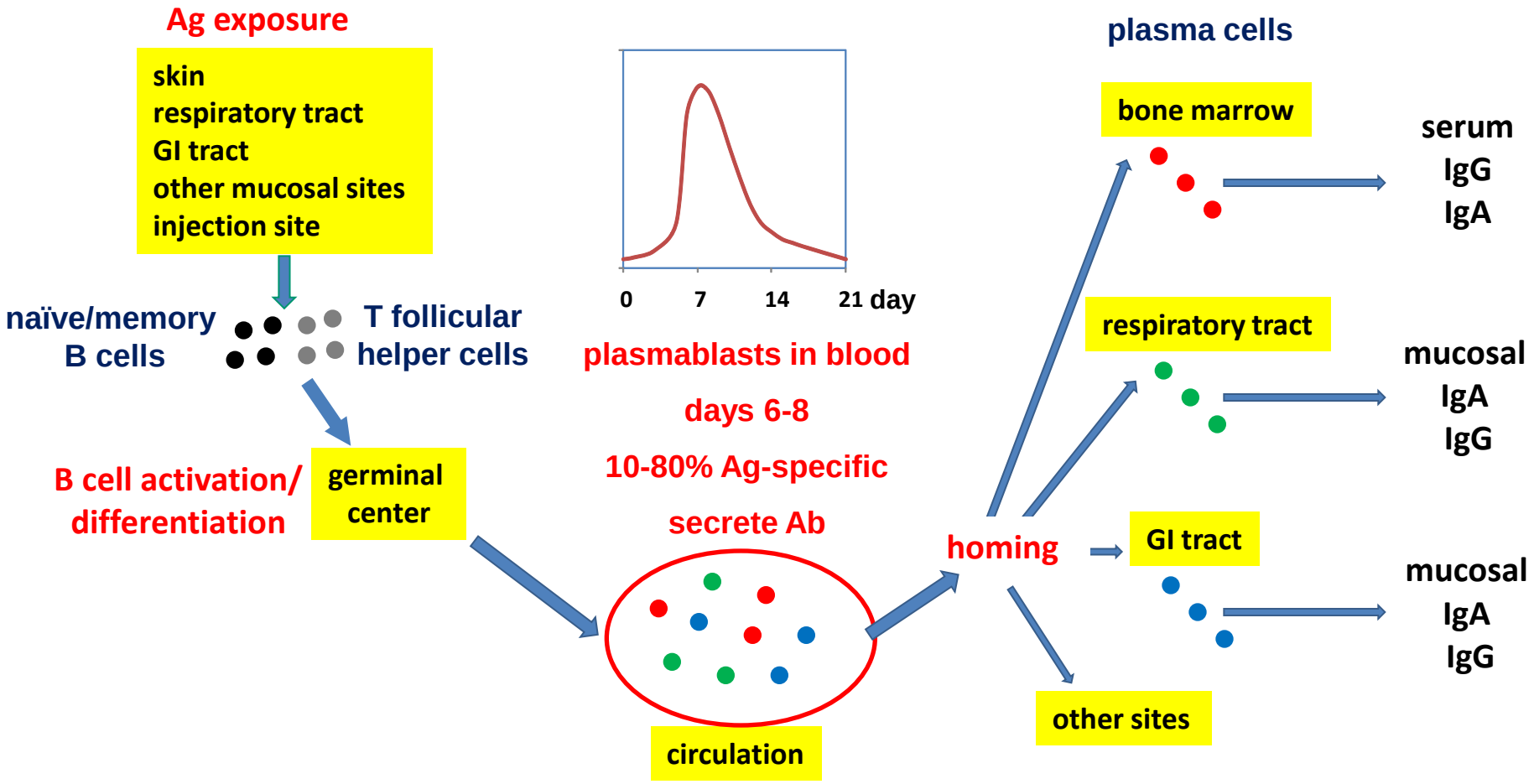
Skowronski 2012
Ohmit 2013
Sullivan 2013
Thompson 2014
Amer 2015

Skowronski 2014
Ohmit 2014a
Ohmit 2014b
McLean 2014
Ohmit 2015

Limitations of serum-based assays for Ab response

- interference from pre-existing Abs in the circulation
- no access to Ab-producing cells – plasma cells in BM

Plasmablast response to infection/vaccination



Plasmablast (Ab Secreting Cell, ASC)-based analyses for B cell responses

- **Phenotype – conventional flow cytometry/CyTOF**
- **Number – ELISPOT (total and vaccine-specific ASCs)**
- **Ig gene sequence – repertoire study, by next-G sequencing (deep sequencing)**
- **Ab function – recombinant mAb**
- **Ab function – Plasmablast-derived Polyclonal Ab (PPAb)**

Two types of licensed influenza vaccines
IIV and LAIV

Inactivated Influenza Vaccine (IIV)
(>6 months)

Similar or somewhat better efficacy than LAIV in adults

Live Attenuated Influenza Vaccine (LAIV)
(2 – 49 years)

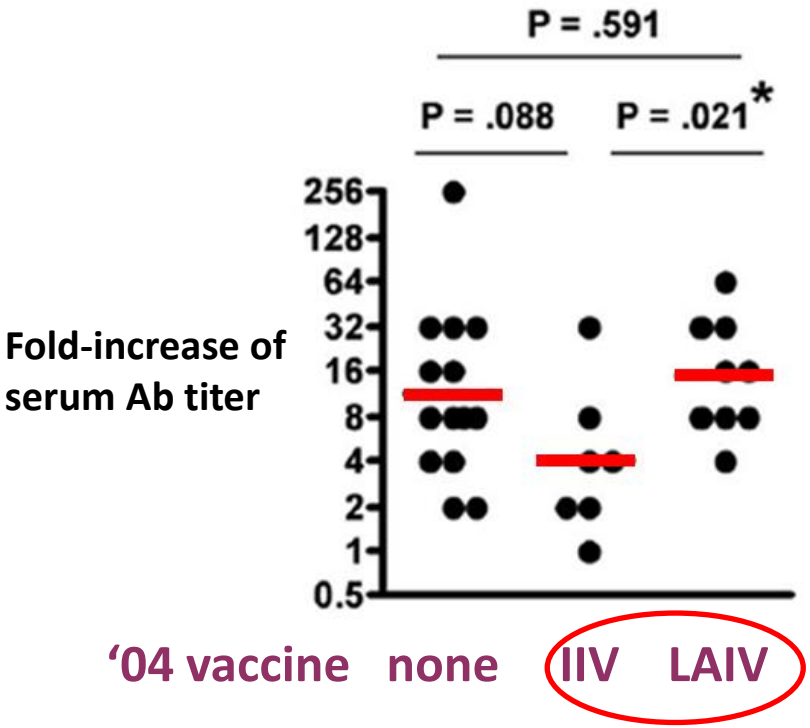
Better efficacy than IIV in children, especially for mismatched strains

B cell and Ab responses: LAIV vs IIV

Serum neutralization Ab response	LAIV < IIV
Frequency of vaccine specific IgA and IgG ASC	LAIV < IIV
IgG and IgA PPAb titer	LAIV < IIV
Yield of IgA or IgG per ASC	LAIV = IIV
IgG and IgA PPAb avidity	LAIV = IIV
IgA/IgG ratio	LAIV > IIV
Relative NP-specific plasmablast response	LAIV > IIV
Relative hererovariant ASC reactivity	LAIV > IIV

Sasaki et al. 2014 JID

H3N2-specific serum Ab response after 2005 IIV immunization – Distinct priming effect of LAIV vs IIV



Sasaki et al. 2008

Predominant circulating flu strains
2009 - 2014

	2009	2010	2011	2012	2013	2014
	A/H1N1pdm09 (A/California/7/09)	A/H3N2	A/H3N2	A/H3N2	A/California/7/09	A/H3N2

Seasonal flu vaccine composition and predominant circulating flu strains 2009 - 2014

Vaccine	2009	2010	2011	2012	2013	2014
H1N1	A/Brisbane/59/07	A/California/7/09	A/California/7/09	A/California/7/09	A/California/7/09	A/California/7/09
H3N2	A/Brisbane/10/07	A/Perth/16/09	A/Perth/16/09	A/Victoria/361/11	A/Victoria/361/11	A/Victoria/361/11
B	B/Brisbane/60/08	B/Brisbane/60/08	B/Brisbane/60/08	B/Wisconsin/1/10	B/Massachusetts/2/12	B/Massachusetts/2/12
					B/Brisbane/06/08 (in LAIV)	B/Brisbane/06/08 (in LAIV and IIV4)
Predominant Circulating strain	**A/H1N1pdm09 (A/California/7/09)**	**A/H3N2**	**A/H3N2**	**A/H3N2**	**A/H1N1pdm09**	**A/H3N2**

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B	B/Brisbane/60/08	B/Brisbane/60/08	B/Brisbane/60/08	B/Wisconsin/1/10	B/Massachusetts/2/12	B/Massachusetts/2/12
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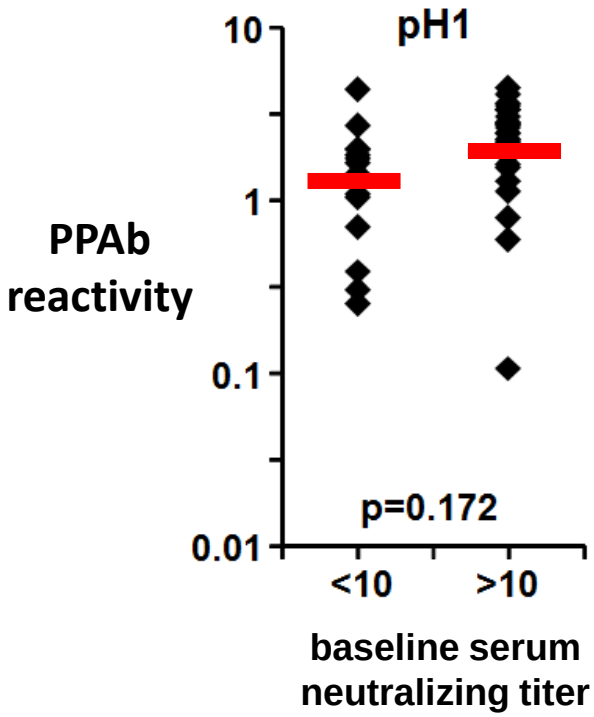
Repeated vaccination study

2010/2011
Baseline serum titer
1st immunization
IIV

2012
2nd immunization
IIV

Distinct priming effect of natural flu infection vs IIV



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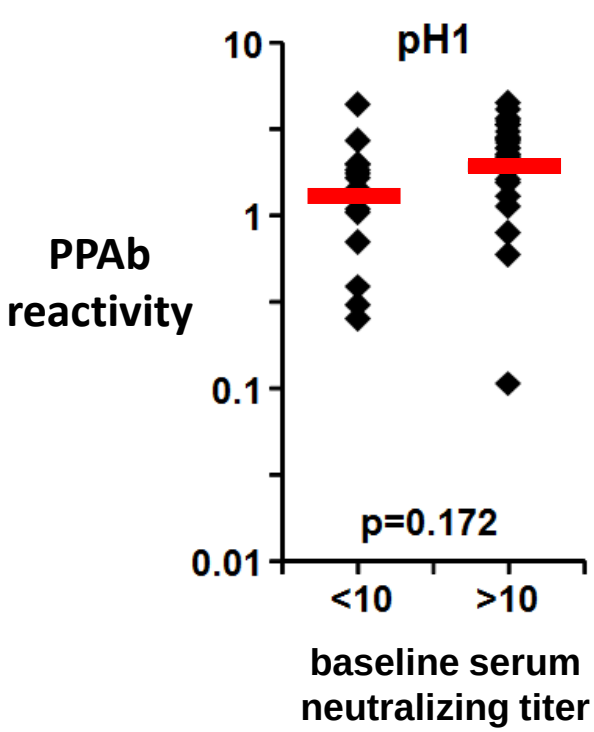

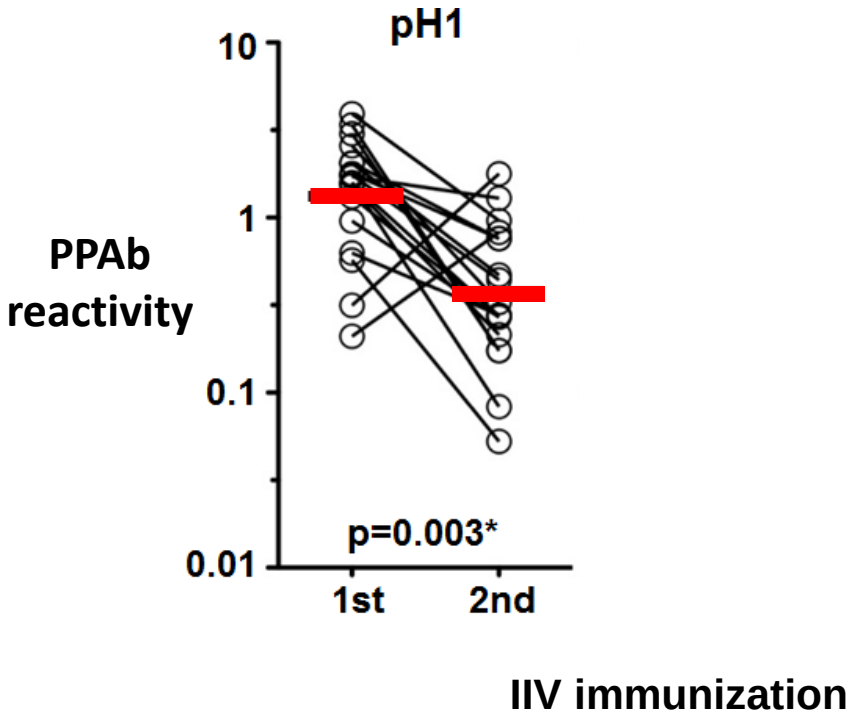

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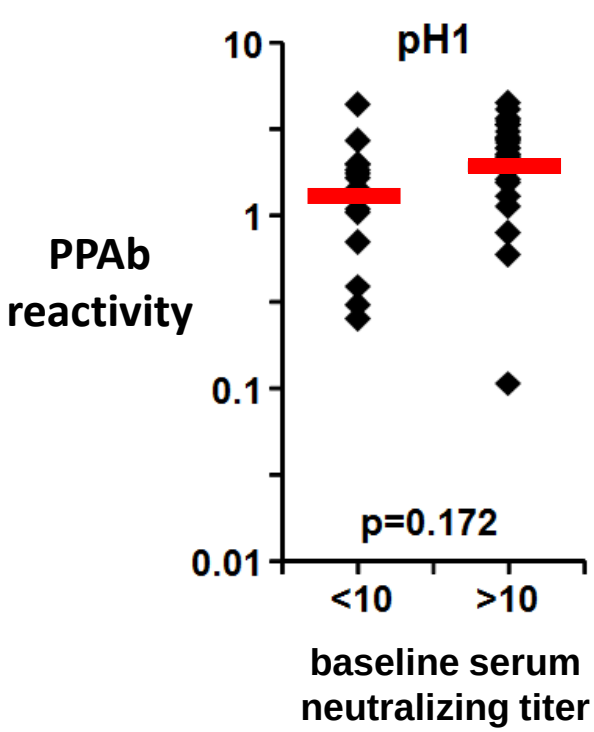
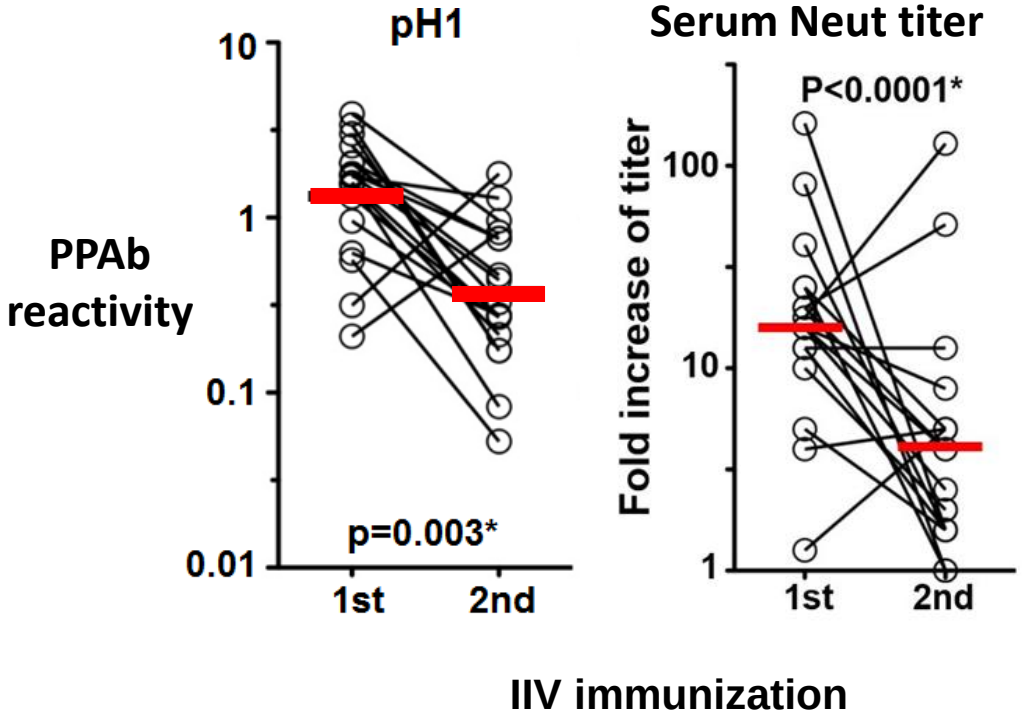
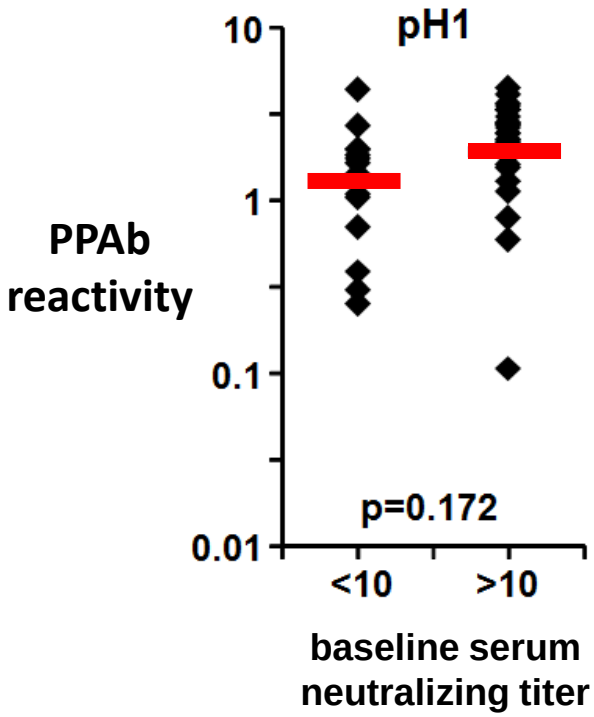


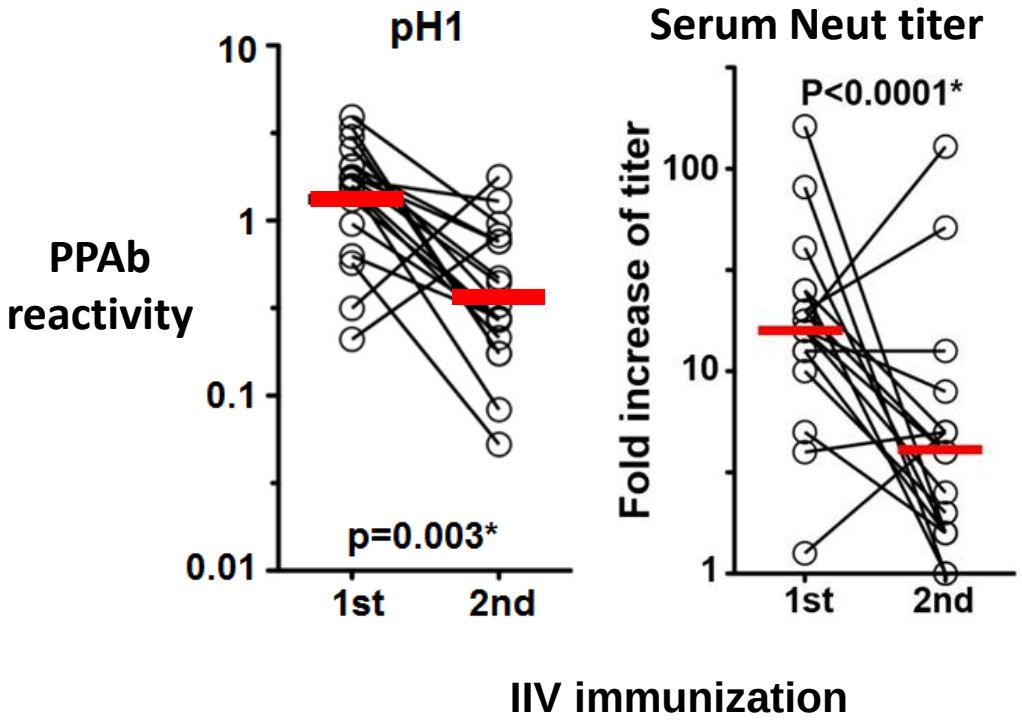


Distinct priming effect of natural flu infection vs IIV

Natural infection did not affect the Ab response to subsequent IIV immunization

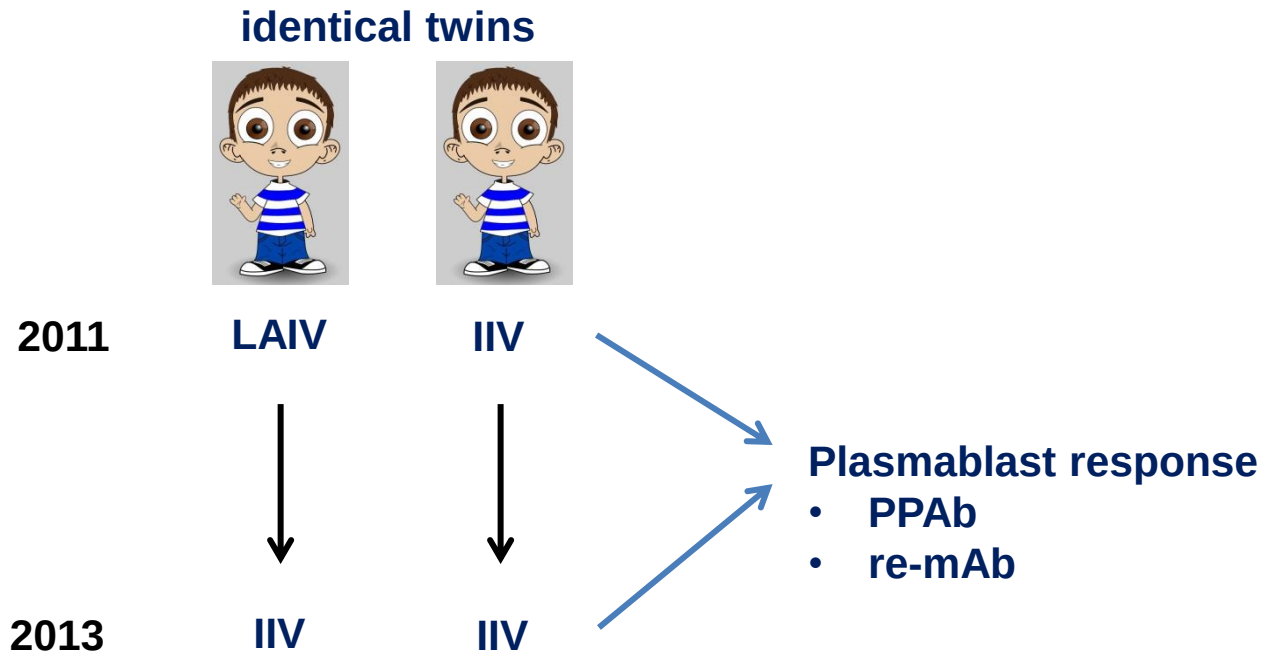


Repeated IIV immunization resulted in reduced Ab response

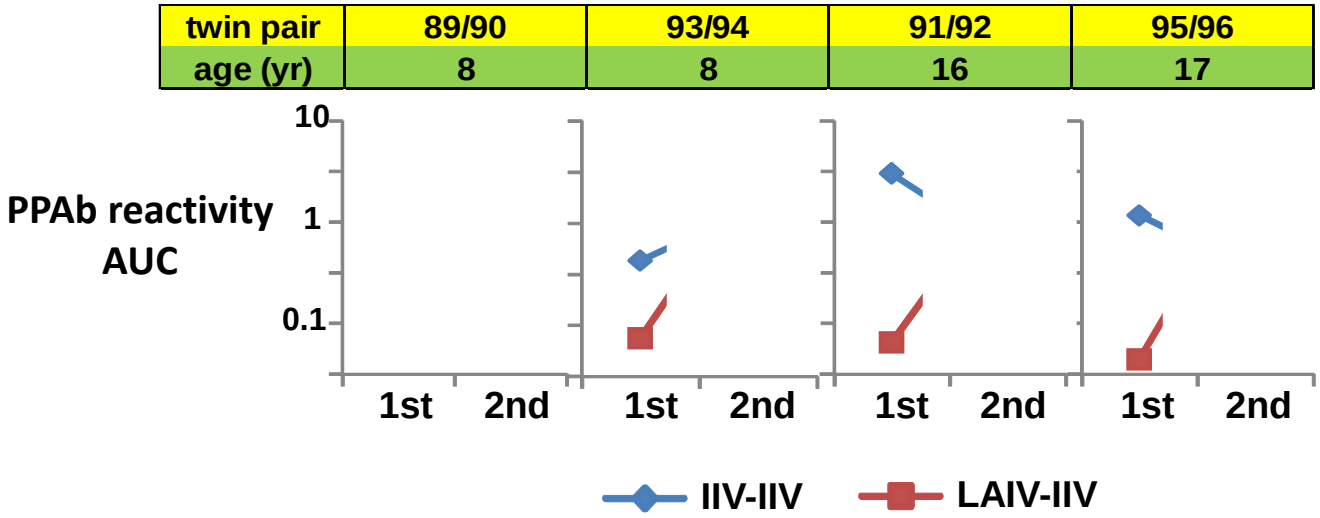


He et al. JID 2015

Priming effect of LAIV vs IIV in identical twin children



PB response in repeated flu vaccination: MZ twins 8-17 years



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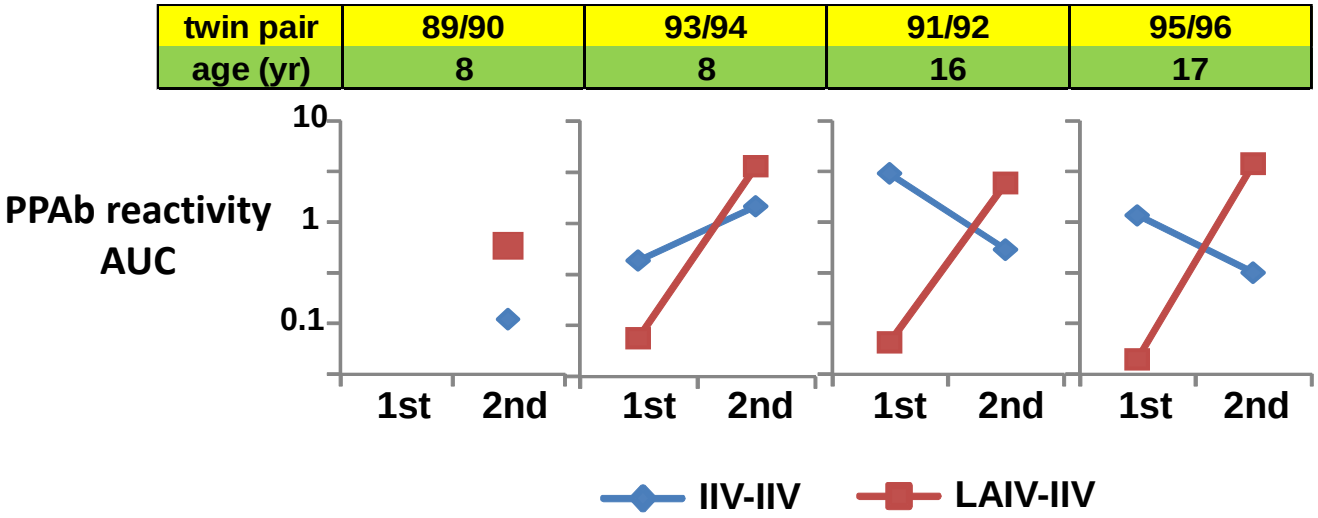

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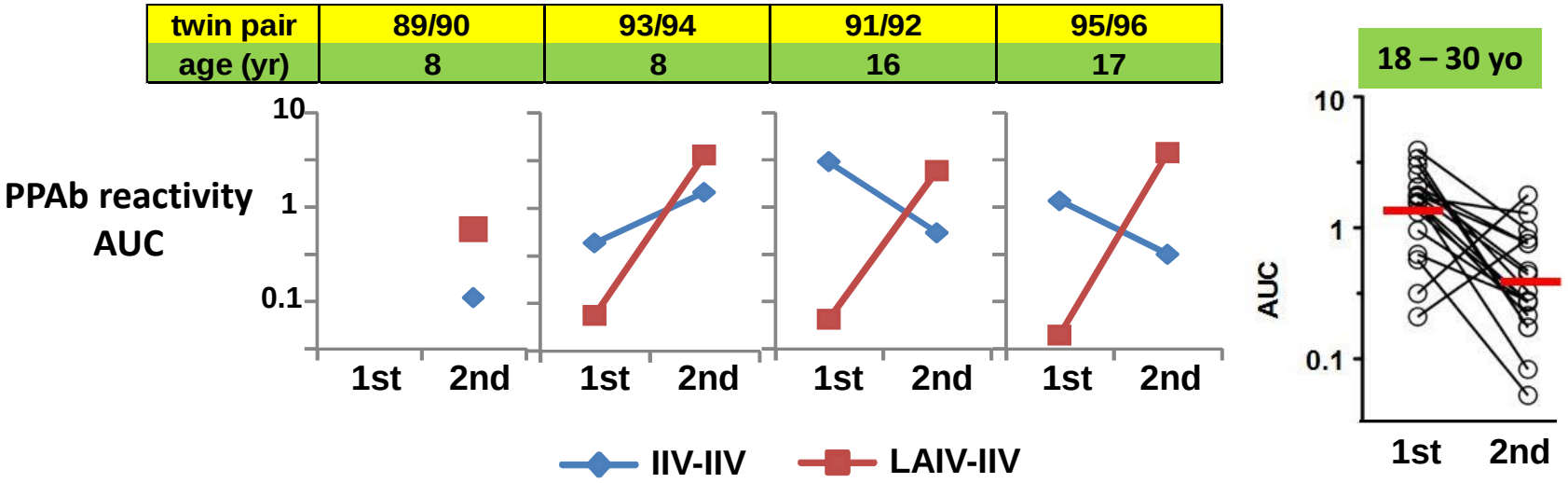
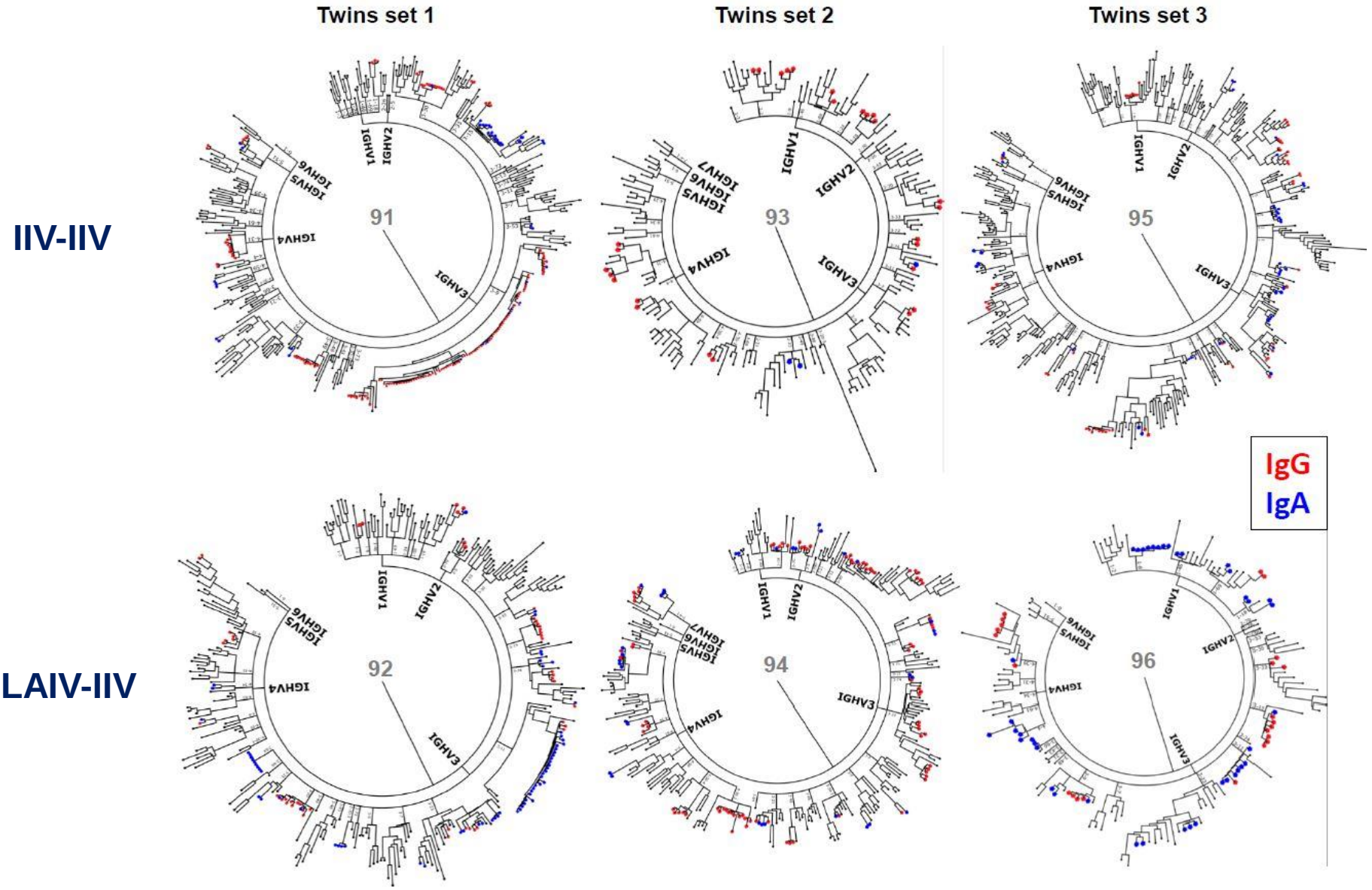


Clonal structure of plasmablast repertoire in LAIV/IIV-immunized twins



Conclusion

- First IIV immunization resulted in reduced B cell response to subsequent IIV immunization
- Natural infection by wild type flu virus and LAIV immunization did not result in reduced B cell response to subsequent IIV immunization

Current CDC recommendation:

Annual flu vaccination starting at age of 6 months
= ~80 doses of flu vaccines per lifetime

Limitations of the current influenza vaccines

- **Limited efficacy in the elderly**
- **Needs for annual re-vaccination**

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