Immune response in children and adults to influenza vaccination

(NIH/ NIAID U19 Grant: Protective mechanisms against pandemic respiratory virus)

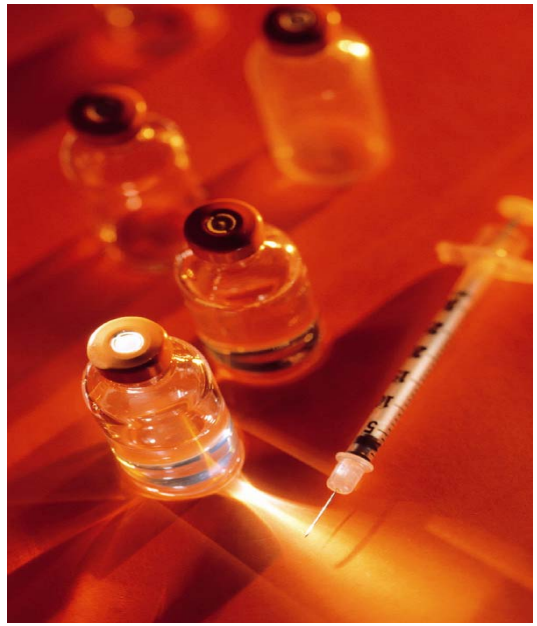
Co-Directors Ann Arvin and Harry Greenberg

FDA/NIH/WHO Workshop: Immune Correlates of Protection against Influenza A

12/10/07

Influenza Vaccines Approved in the United States

- **Trivalent Inactivated Vaccine (TIV)**
  - Traditional vaccine
  - Delivered by intramuscular injection
  - Purified HA and NA
- **Live-attenuated Influenza Vaccine (LAIV)**
  - New vaccine
  - Delivered by intranasal administration



Both vaccines have similar efficacy in healthy adults and older children.

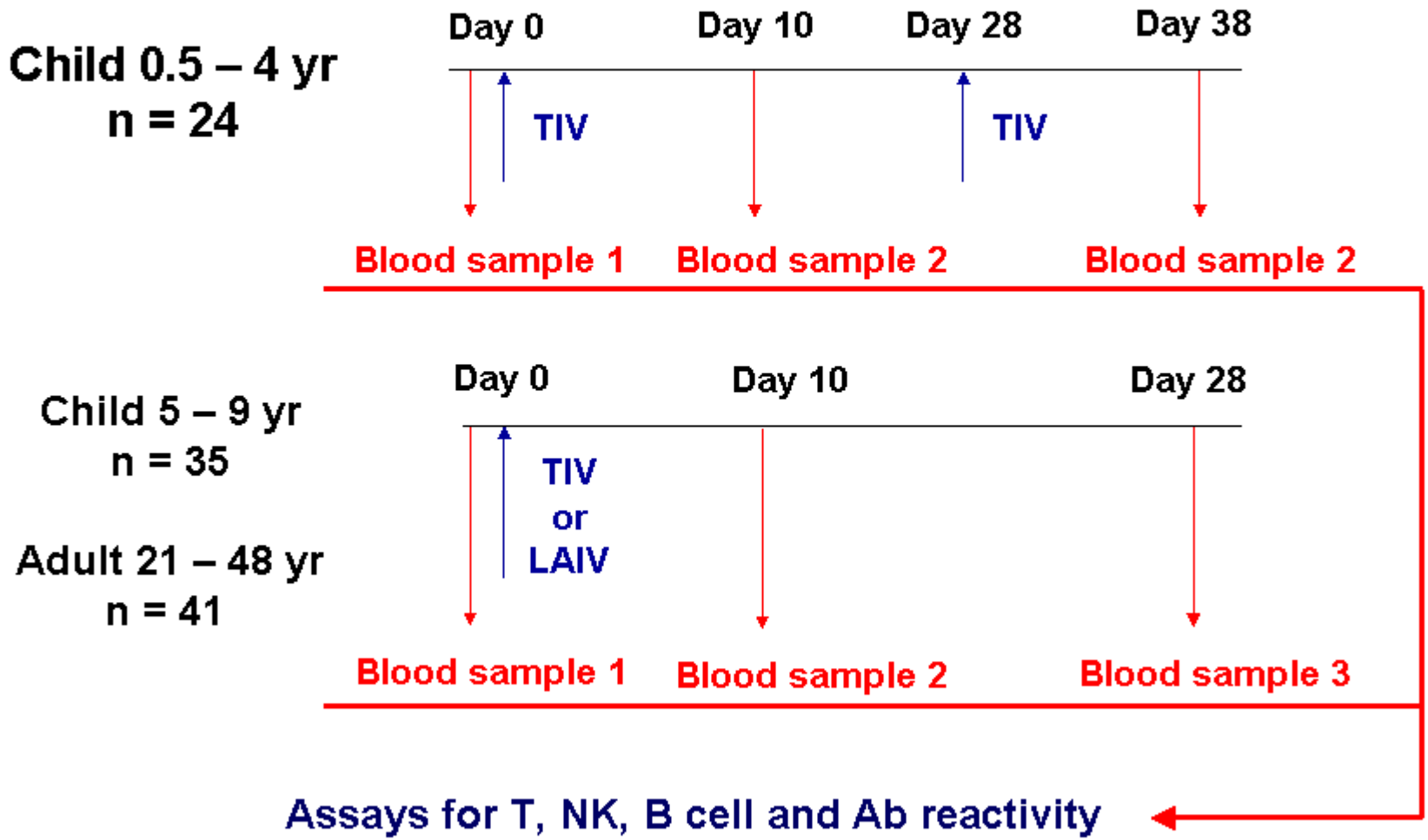
Beyer WE, Vaccine 2002;20:1340-53

LAIV has greater efficacy than TIV in younger children.

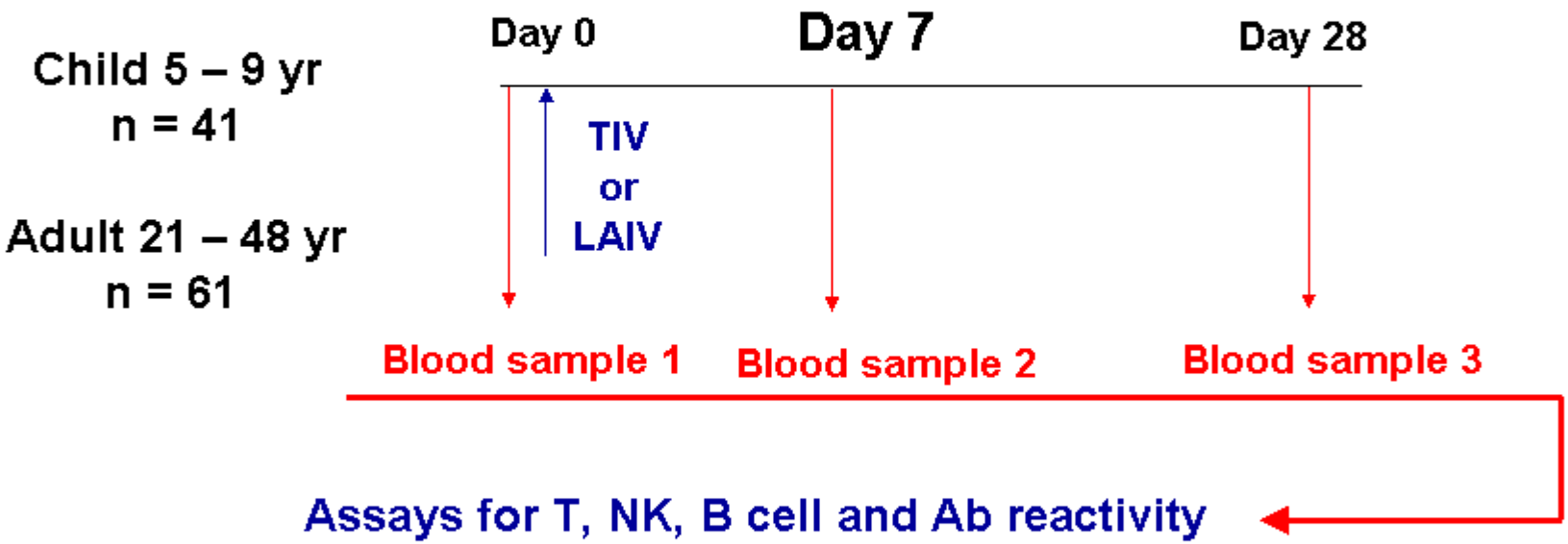
Belshe RB, N Engl J Med. 2007:356:685-96

Study design

2004 – 2005 flu season (year 2)



Study design
2005 – 2006 flu season (year 3)



Assays for T, NK, B cell and Ab reactivity

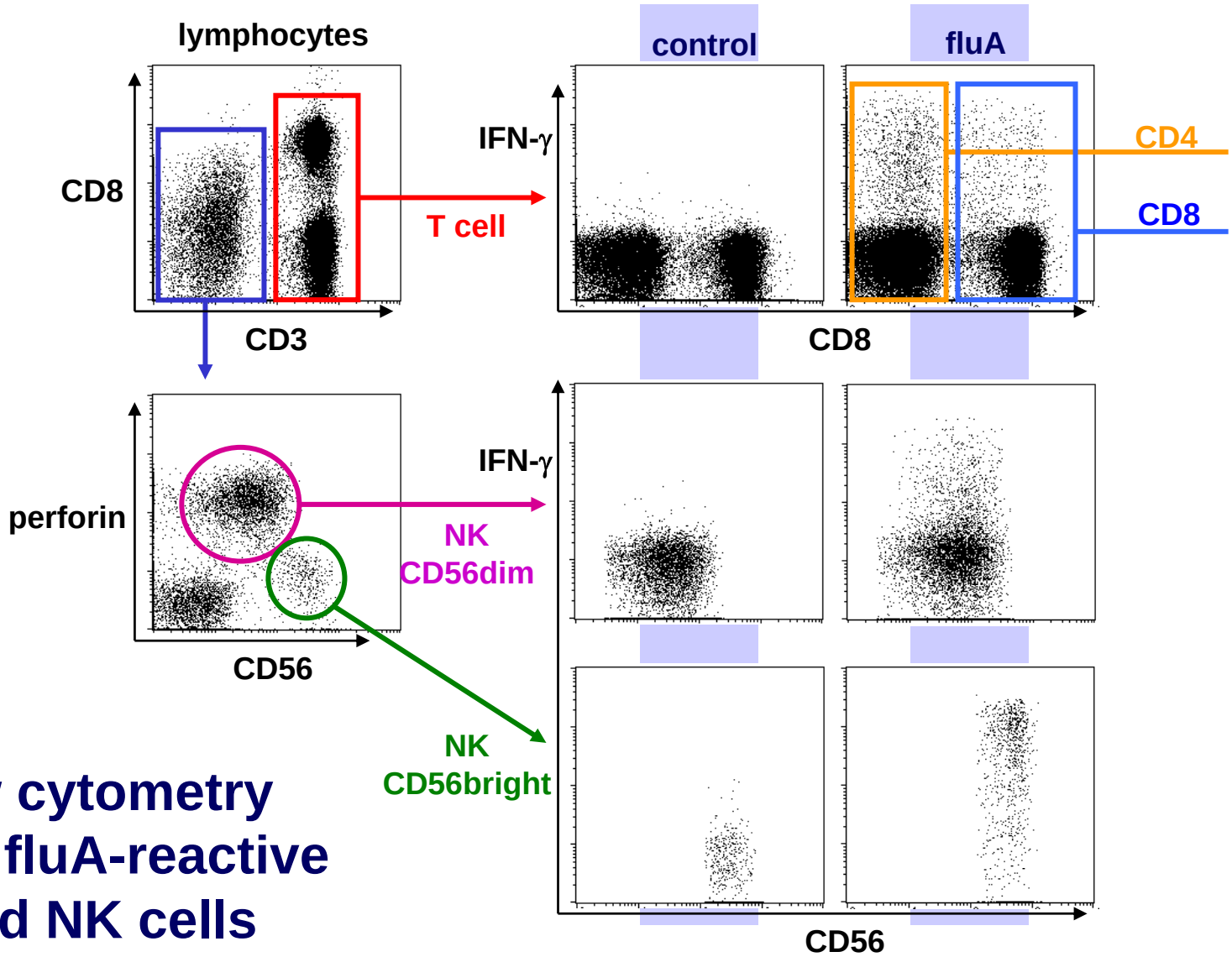
- **IFNγ flow cytometry**
  % and phenotype of fluA-specific CD4 and CD8 T cells
  % of fluA-reactive CD56hi and CD56lo NK cells

- **ELISPOT**
  % of flu-specific memory IgG and IgA B cells (days 0 & 28)
  # of flu-specific IgG and IgA Ab secreting cells (day 7 or 10)

- **Serology**
  Neutralizing Ab
  HAI

PBMC / flu virus
or control

17 h

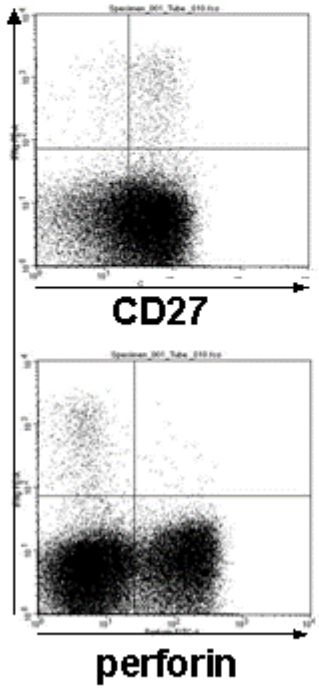


IFN-γ flow cytometry assay for fluA-reactive T cells and NK cells

Phenotypic analysis of fluA-specific T cells

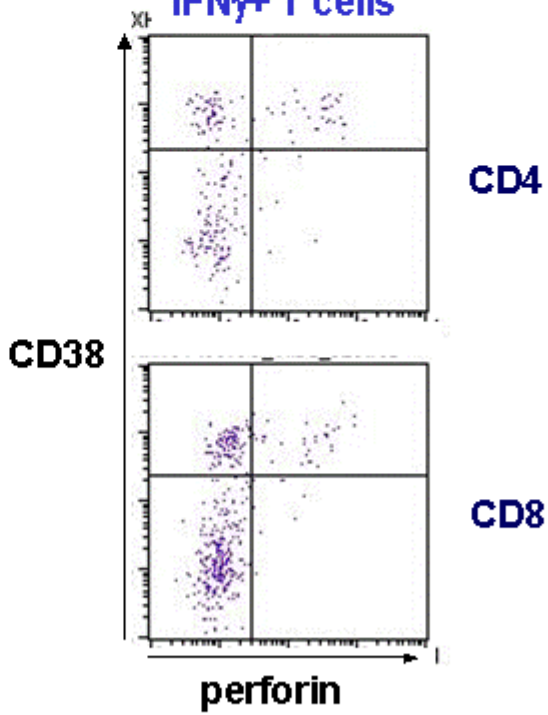
PBMC / fluA, 17 h

CD8 T cells



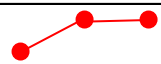
PBMC / fluA, 17 h

IFNγ+ T cells



Quantitative and phenotypic changes of fluA-specific IFNγ+ T cells after vaccination

Days 0, 10, 28 (year 2 data set)

vaccine	T cell subset	age (year)	0 - 4	5 - 9	21 - 48
TIV	CD4	% of CD4 T			
	CD8	% of CD8 T			
		% CD27+			
		% perforin+			
LAIV	CD4	% of CD4 T	N.D.		
	CD8	% of CD8 T	N.D.		
		% CD27+	N.D.		
		% perforin+	N.D.		

d0 10 28

Vaccination changes % and/or phenotype in children

Vaccination changes phenotype but not % in adults

Summary 1

Influenza vaccination induces quantitative and/or phenotypic changes in flu-specific T cells

The effect of vaccination on flu-specific T cells varies with type of vaccine and age of vaccinees

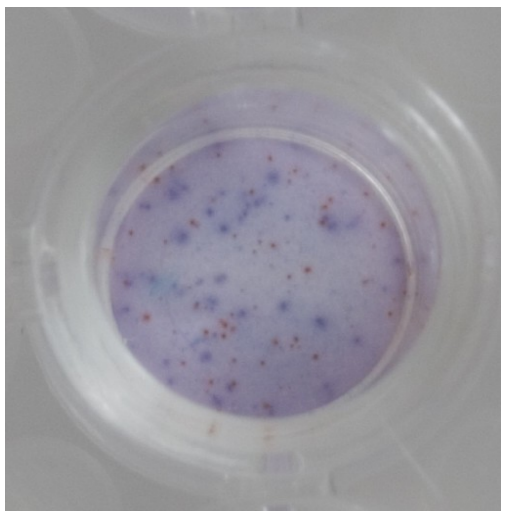
Effector B cell (ASC) and memory B cell assays

Effector B cell assay

PBMC

↓

ELISPOT for influenza-specific antibody secreting cells (ASC)



IgA: Red spot
IgG: Blue spot

Memory B cell assay

PBMC

↓

Cultured for 5 days with
Pokeweed mitogen
CpG oligonucleotide
Staphylococcus aureus Cowan

↓

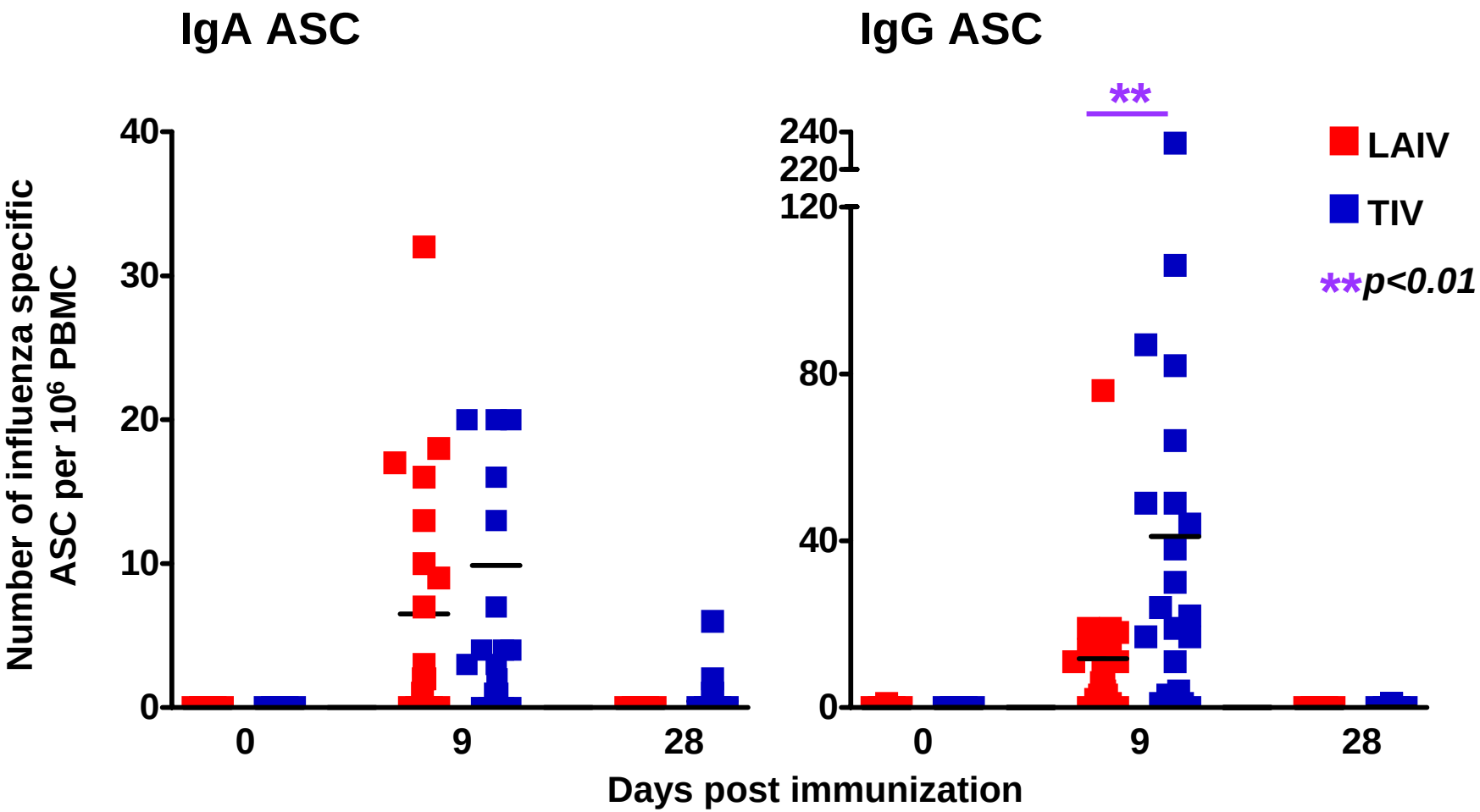
ELISPOT for flu-specific IgA and IgG ASC

ELISPOT for total IgA and IgG ASC

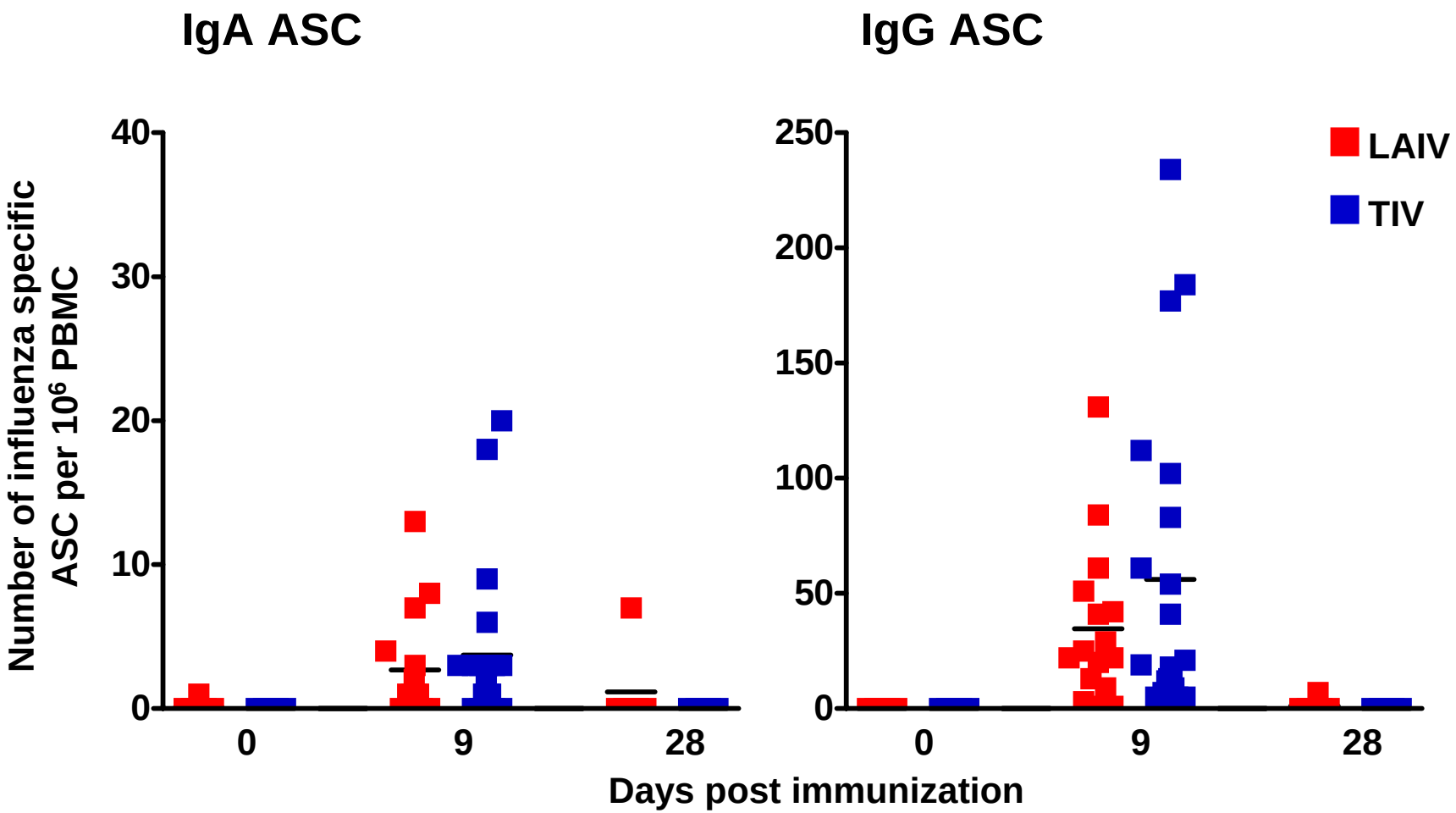
↓

% of flu-specific memory B cells

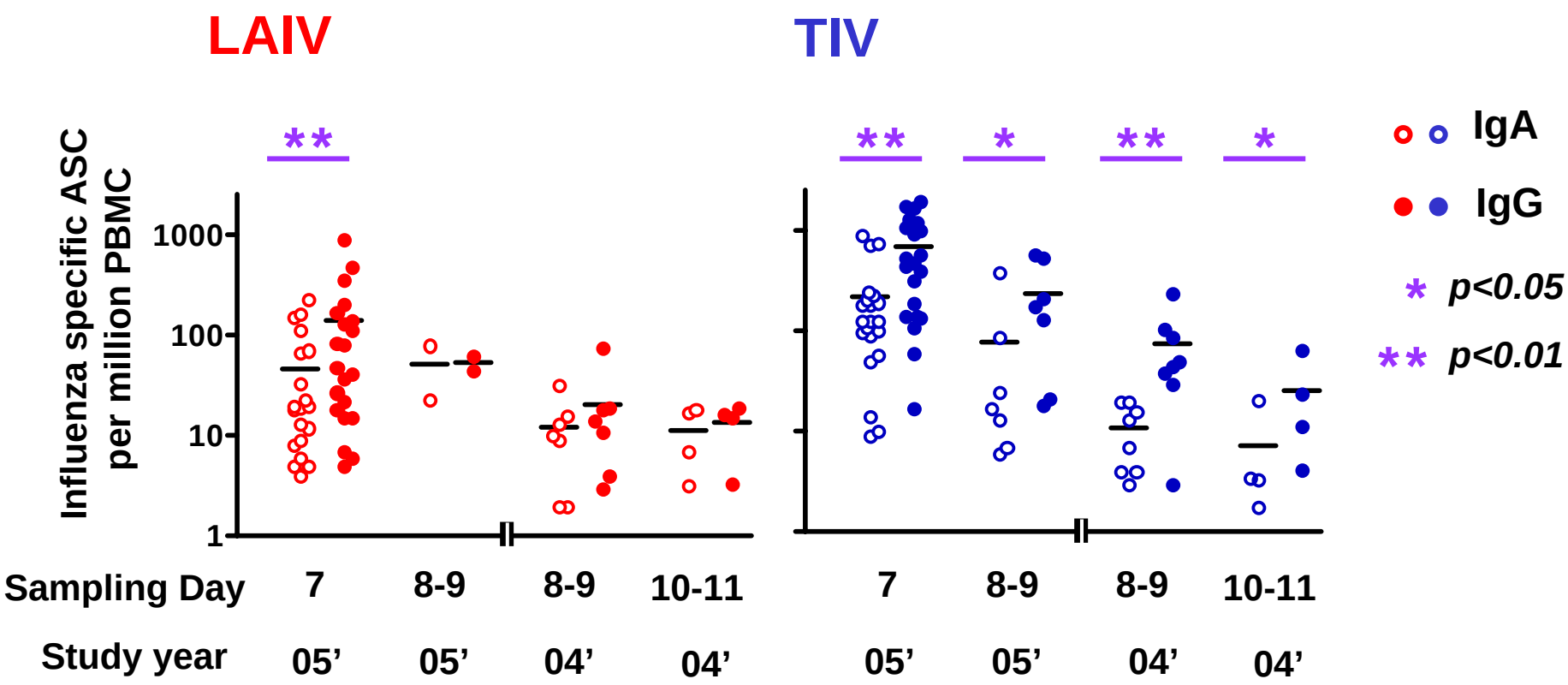
Number of flu-specific ASC after TIV or LAIV vaccination: adults



Number of flu-specific ASC after TIV or LAIV vaccination: children aged 5 – 9 yr



Flu-specific ASC on different days after vaccination (responders)



Comparison of responses ("take" rate) after LAIV or TIV immunization measured by ASC VS. HAI

Percentage of responders	IgA ASC ≥ 2	IgG ASC ≥ 2	HAI for H3N2 ≥4 folds
LAIV	77.0 *	90.0**	50.0
			**
TIV	97.0	100	85.7

* *p<0.05* ** *p<0.01*

The ASC IgG B cell "take" rates following TIV and LAIV are similar.

The serum HAI "take" rates following LAIV are significantly lower than TIV.

The ASC B cell "take" rates are higher than HAI rates after LAIV.

Summary 2

TIV and LAIV induce effector B cell responses. In children the 2 vaccines are similar. In adults the 2 vaccines are similar for IgA ASC but IgG B cells are more numerous after TIV

LAIV induced a less sharp peak ASC responses than TIV immunization.

ASC "take" rates are higher than HAI "take" rates in LAIV recipients, especially the repeat vaccinees.

Both vaccines induced increases in memory IgG B cells but TIV induced greater increases. Prior year vaccine status did not affect baseline memory B cell levels.

3. Comprehensive analysis:

What host and vaccine factors predict CD4 T cell, CD8 T cell and antibody responses to vaccination?

Parameters considered:

Immune parameters (pre- and post-vaccination)

- Flu-specific IFN-γ+ CD4 T cells
- Flu-specific IFN-γ+ CD8 T cells
- Flu-specific memory IgG cells
- Flu-specific memory IgA cells
- Flu-specific serum Ab (HAI)

Age of vaccinee : adult or children

Type of vaccine : LAIV or TIV

Immune responses to vaccination

- day 0 to day 28 fold change of flu-specific T cell and Ab levels

Predictor for CD4 T cell response to vaccination

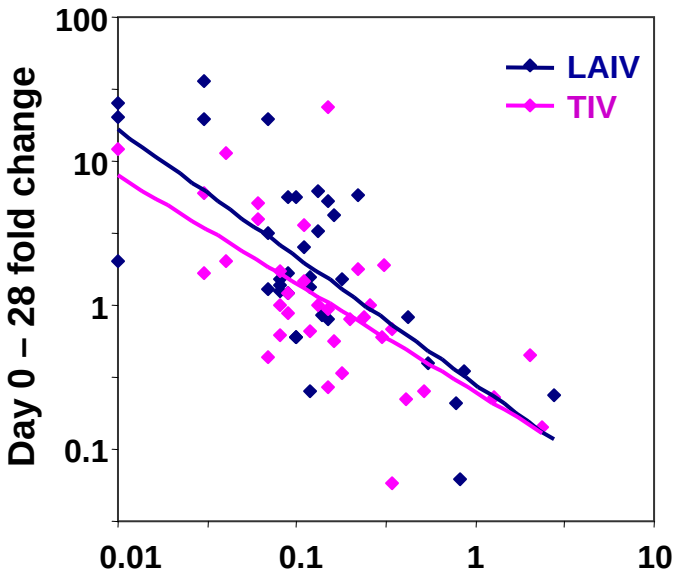
Identified candidates with yr. 2 data

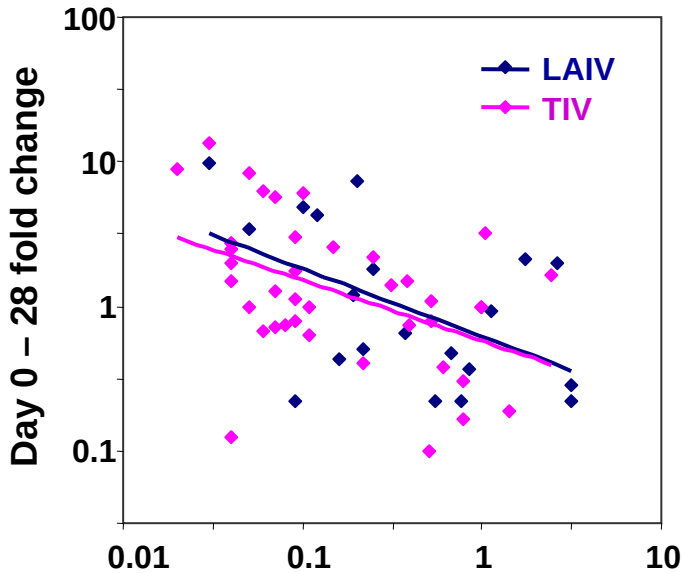
- **Baseline flu-specific CD4 level (100%)**
- **Vaccine type (38%)**

Mean Adjusted R^2 = 0.48

Verified predictors with yr. 3 data

- **Baseline flu-specific CD4 level**
  P = 0.0003





Baseline % of flu-specific CD4 T cells

Summary 3

- The baseline level of flu-specific antibodies and the type of vaccine (TIV vs LAIV) are significant predictors for antibody responses to influenza vaccination

- The baseline level of flu-specific memory CD4 T cells is a significant predictor for CD4 and CD8 T cell responses to influenza vaccination