Immune responses to non replicating avian influenza vaccines EU experience

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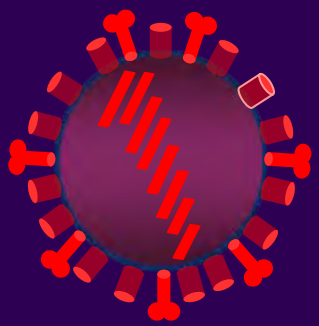
Washington

December 2007

Types of inactivated influenza vaccine

H5N1, H9N2, H2N2



→ Virus particles disrupted

H5N3, H5N1, H7N1, H2N2, H9N2

→ Purified virus surface glycoproteins (HA+NA)

H5N1

Adjuvants for parenteral administration

Goal: improved immunogenicity

Many examples

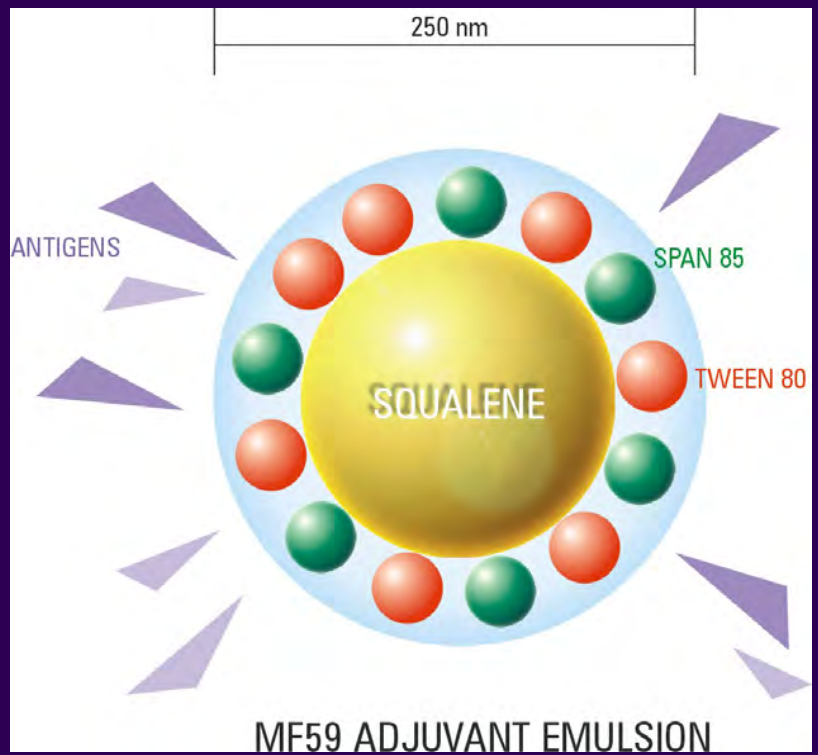
Mineral salts AlOH AlPO4

Emulsions MF59 (AS)

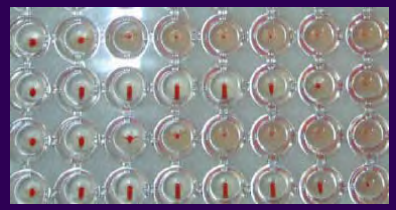
Microparticles (liposomes, ISCOMs)

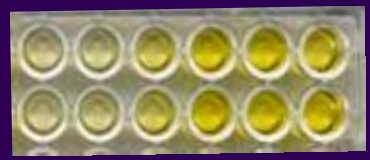
Immunostimulatory: MPL, LPS, QS-21

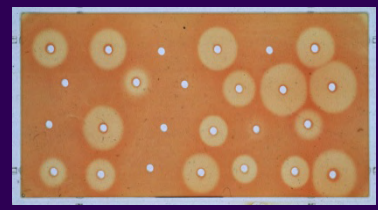
LT



Methodology for evaluation of immunogenicity







Assays: Haemagglutination-Inhibition | Virus Neutralisation | Single Radial Haemolysis

BIOASSAYS…….. All are variable between laboratories

- WHO study: HI 6-128 fold variation; VN 91-724 fold variation
- Need for standardisation
- New methods for functional antibodies
- Used due to licensing requirements, but some parallel data with other methods (WB/ELISA/ELISPOT)

Immunogenicity Criteria for Pandemic Vaccine Evaluation (<65/ ≥ 65)

European Guidelines

(CPMP/BWP/214/96)

- GMTpost/GMTpre >2.5/>2
- Post ≥ 40 in >70%/60%
- SCR >40/30%

(≥4 fold rise or increase <10 to >40 post)

Neut titre desirable

US FDA Guidelines

- Post ≥40 in >70%/60%*
- SCR >40/30%*

*Lower bound of 2-sided 95% CI

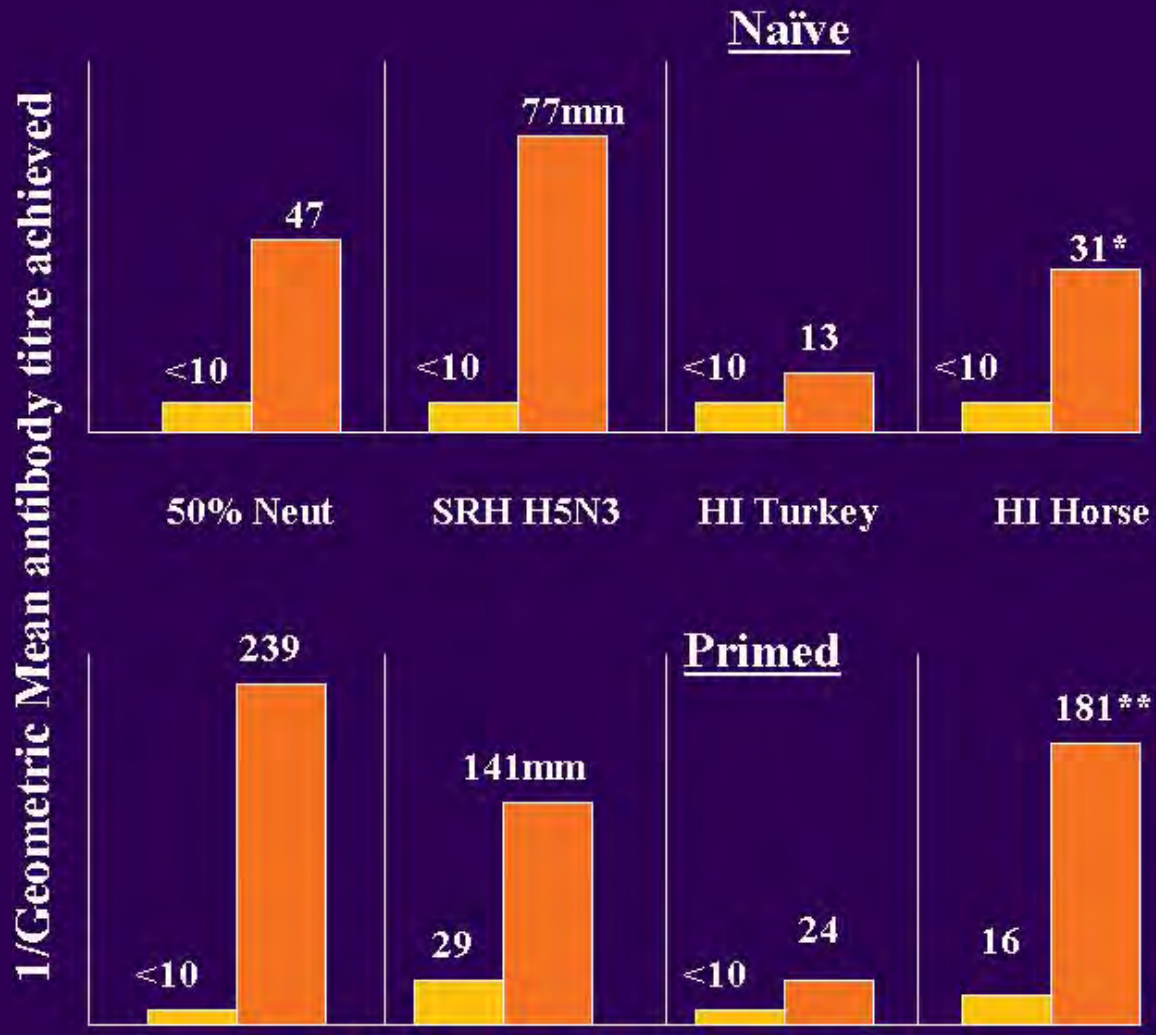
or

GMTlicensed/GMTnew ≤1.5*

SCRlicensed/SCRnew ≤10%*

*Upper bound of 2-sided 95% CI

H5N3 vaccine recipients



PRE

Pre vaccine

POST

Post vaccine

Significant difference between horse and turkey

*p<0.001

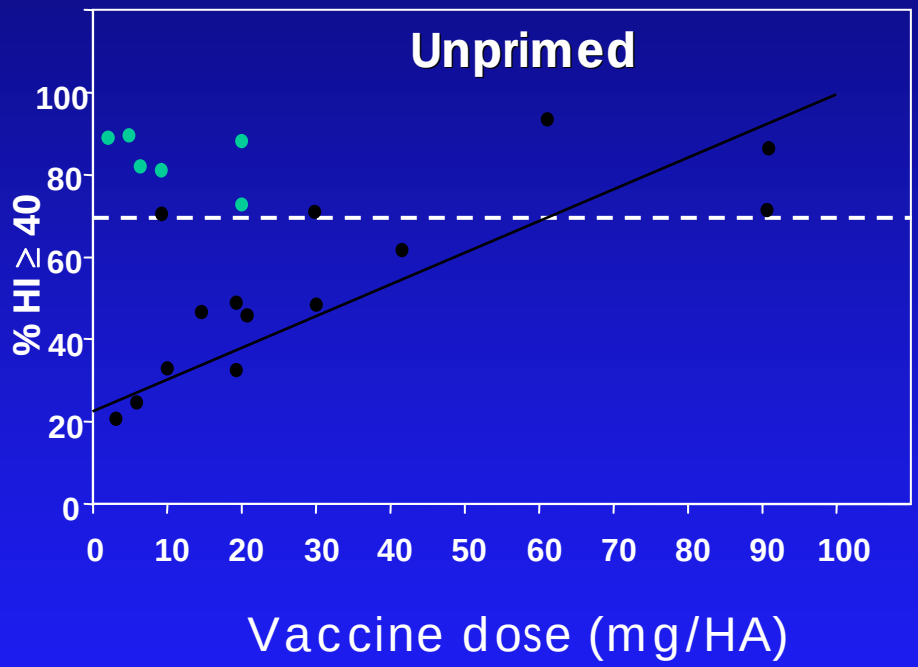
**p<0.0001

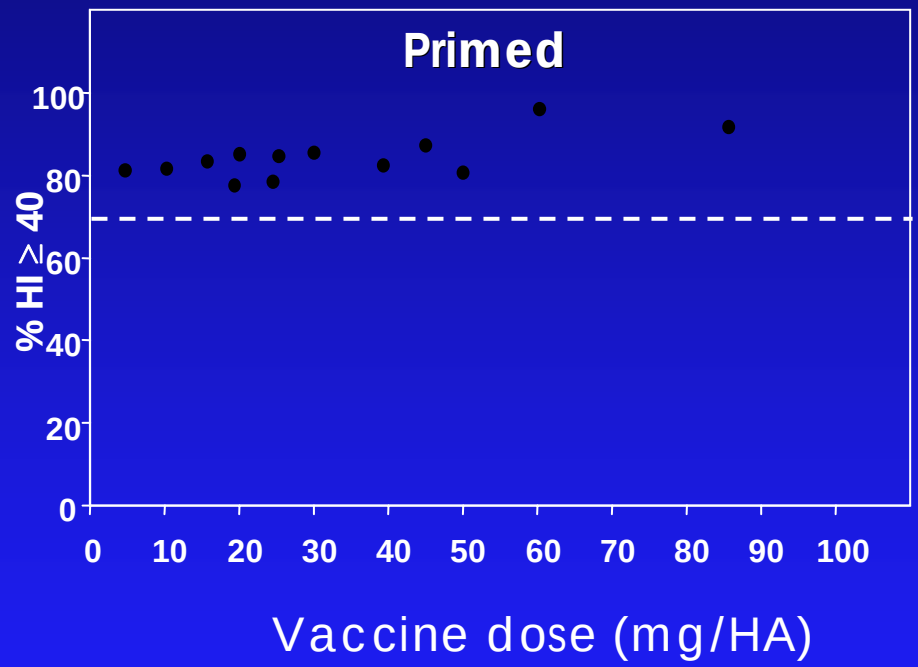
Variables

- Subtypes (H5/H7/H9/H2)
- Type of vaccine
- Vaccine substrate (egg vs cell)
- Monovalent vs Trivalent
- Parenteral vs mucosal

A/New Jersey/8/76 (H1N1) whole virus vaccine clinical trials

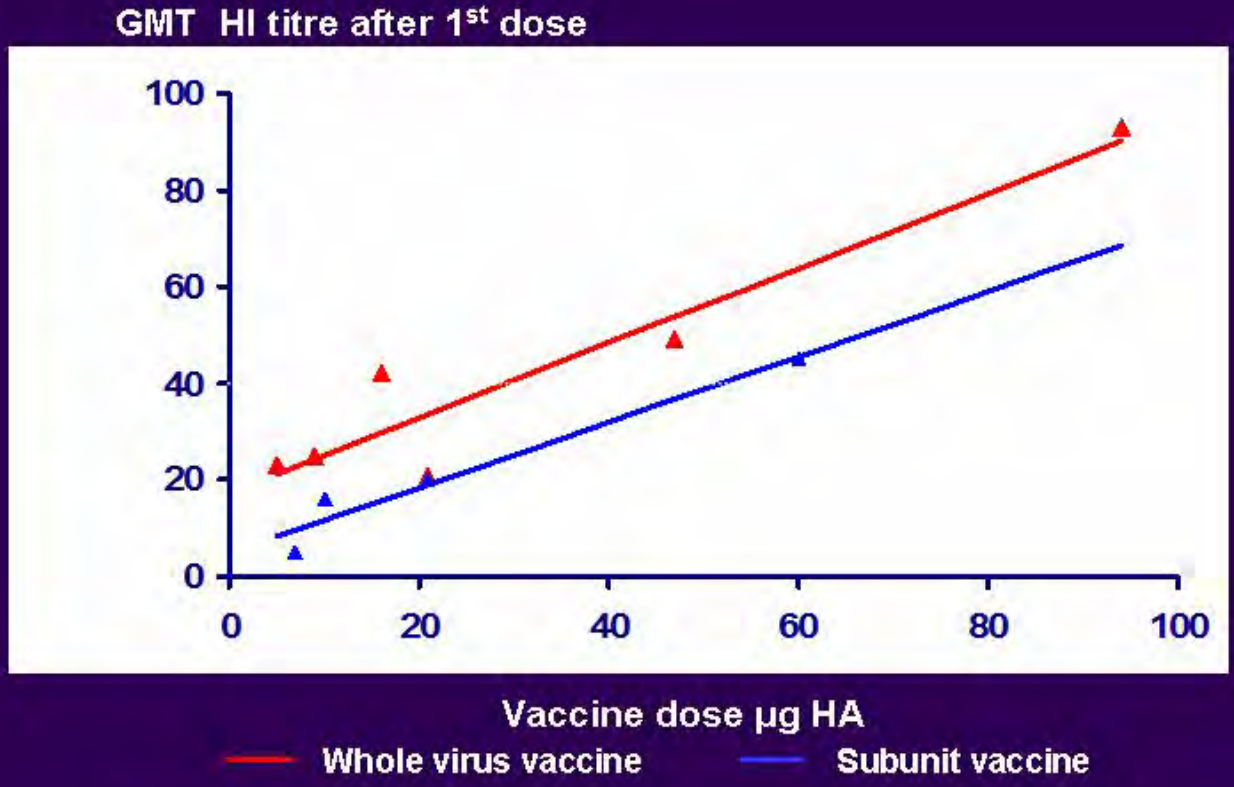
(28 trials USA, UK)





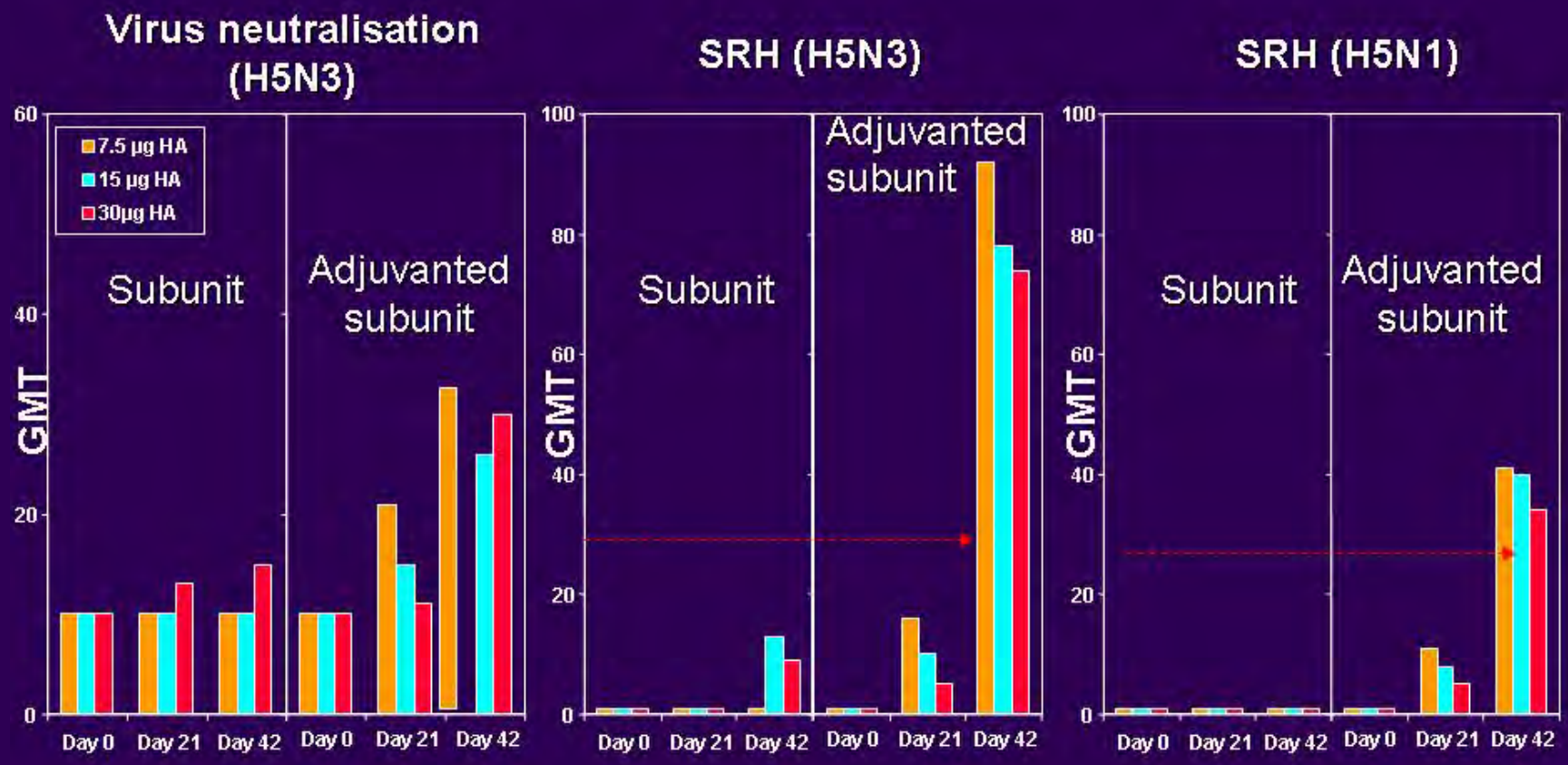
● 1 dose ● 2 doses

Comparative immunogenicity of WV & SU A/USSR/77 (H1N1) vaccine, unprimed



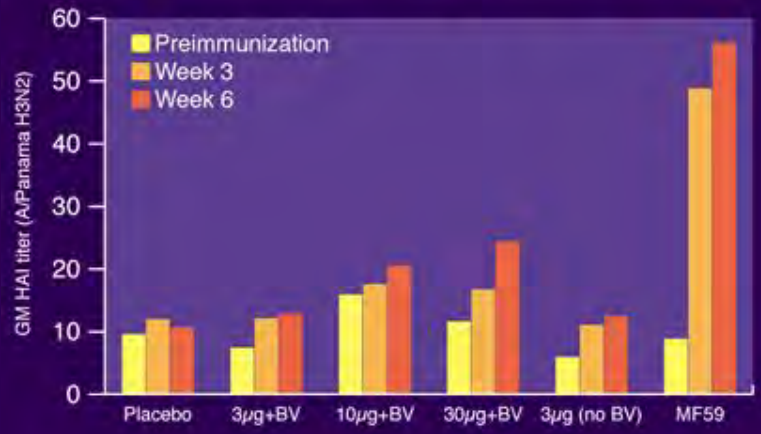
Nicholson *et al* J Biol Stand 1979;7:123-36.

A/Duck/Singapore/97 (H5N3) GM Antibody Titres

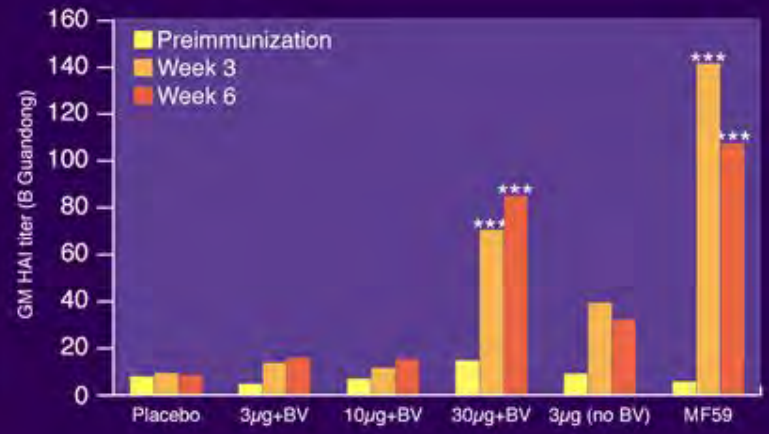


Nicholson et al, Lancet 2001

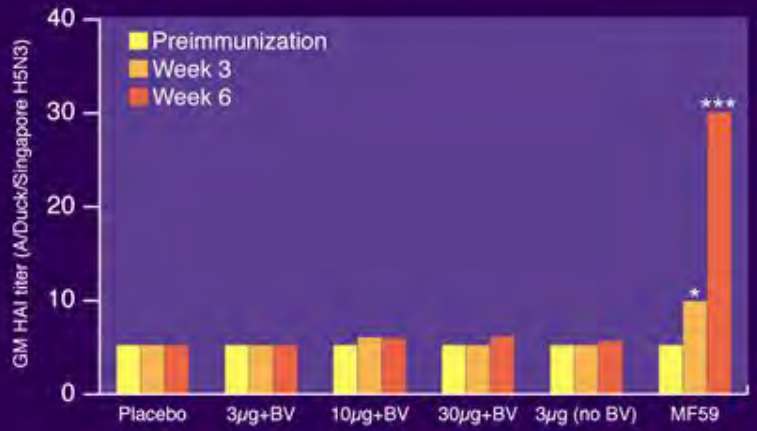
TV Inactivated Mucosal Adjuvant H3N2, B, H5N3



H3N2



B



H5N3

Stephenson et al, J Virol 2006

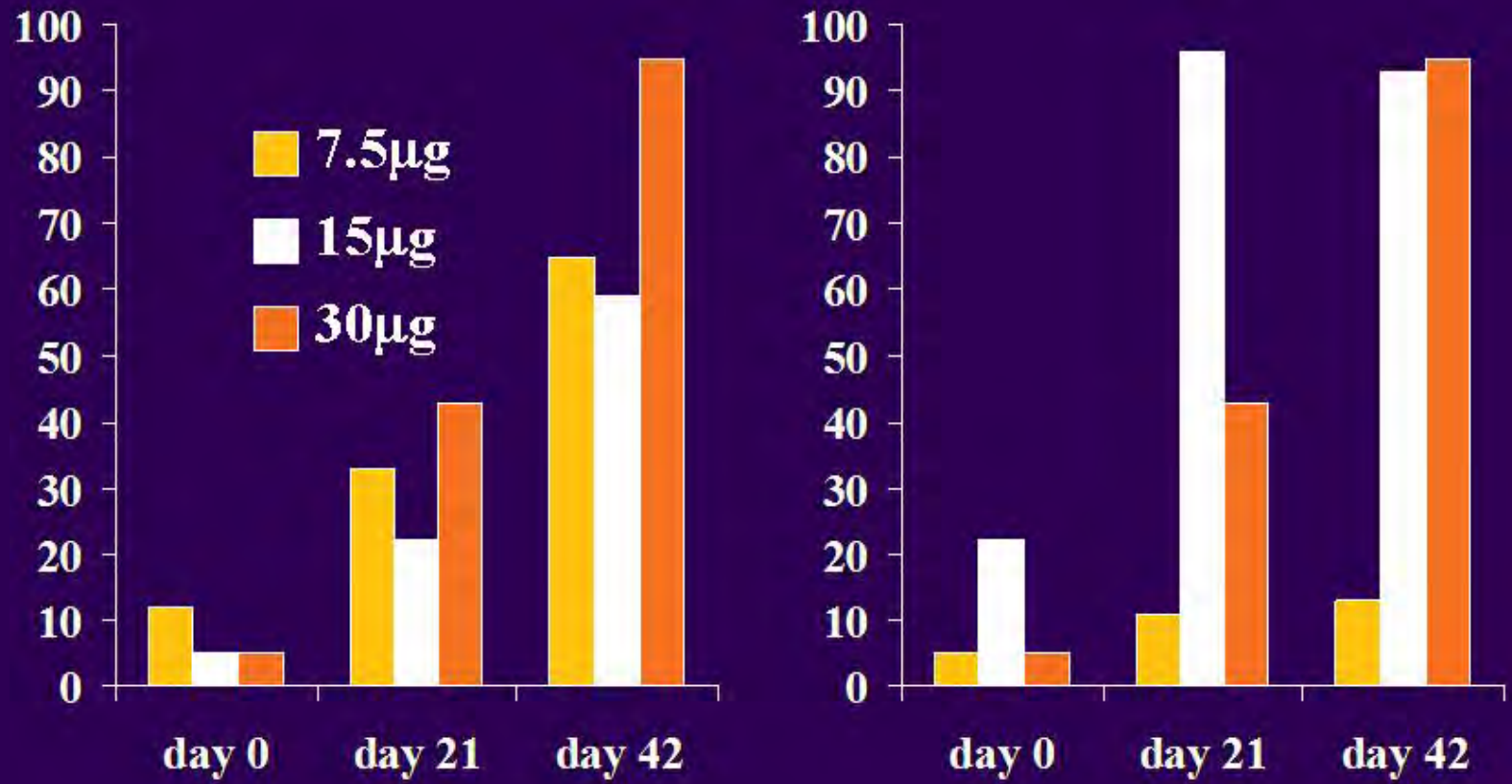
Global H5N1 Vaccine studies 2006-2008

EU H5N1 vaccine trials 2006-2007

Type of vaccine	'Compliance' with EU licensing criteria
Split vaccine no adjuvant	2 x 90 µg (USA)
Split/subunit vaccine with alum	2 x 30-45 µg
Whole virus (egg) with alum	2 x 10-15 µg
Subunit with MF59 adjuvant	2 x 7.5 µg
Whole virus Vero cell culture, no adjuvant	2x 7.5 µg
Split vaccine with AS adjuvant	2 x 3.8 µg
Whole virus vaccine with alum	1 x 6 µg

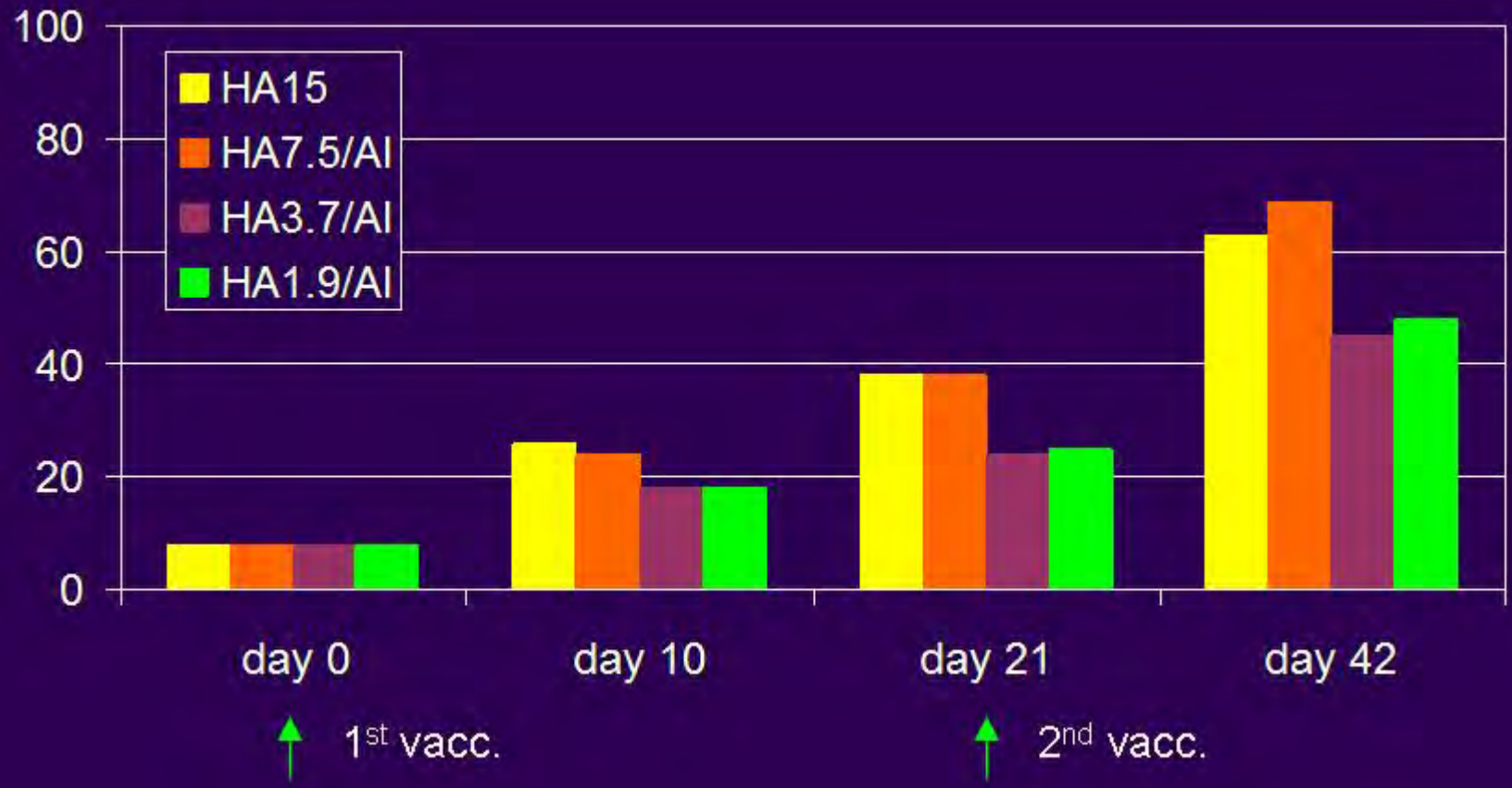
Data presented at WHO meeting, Oct 2007

H9N2 WV and SU vaccine



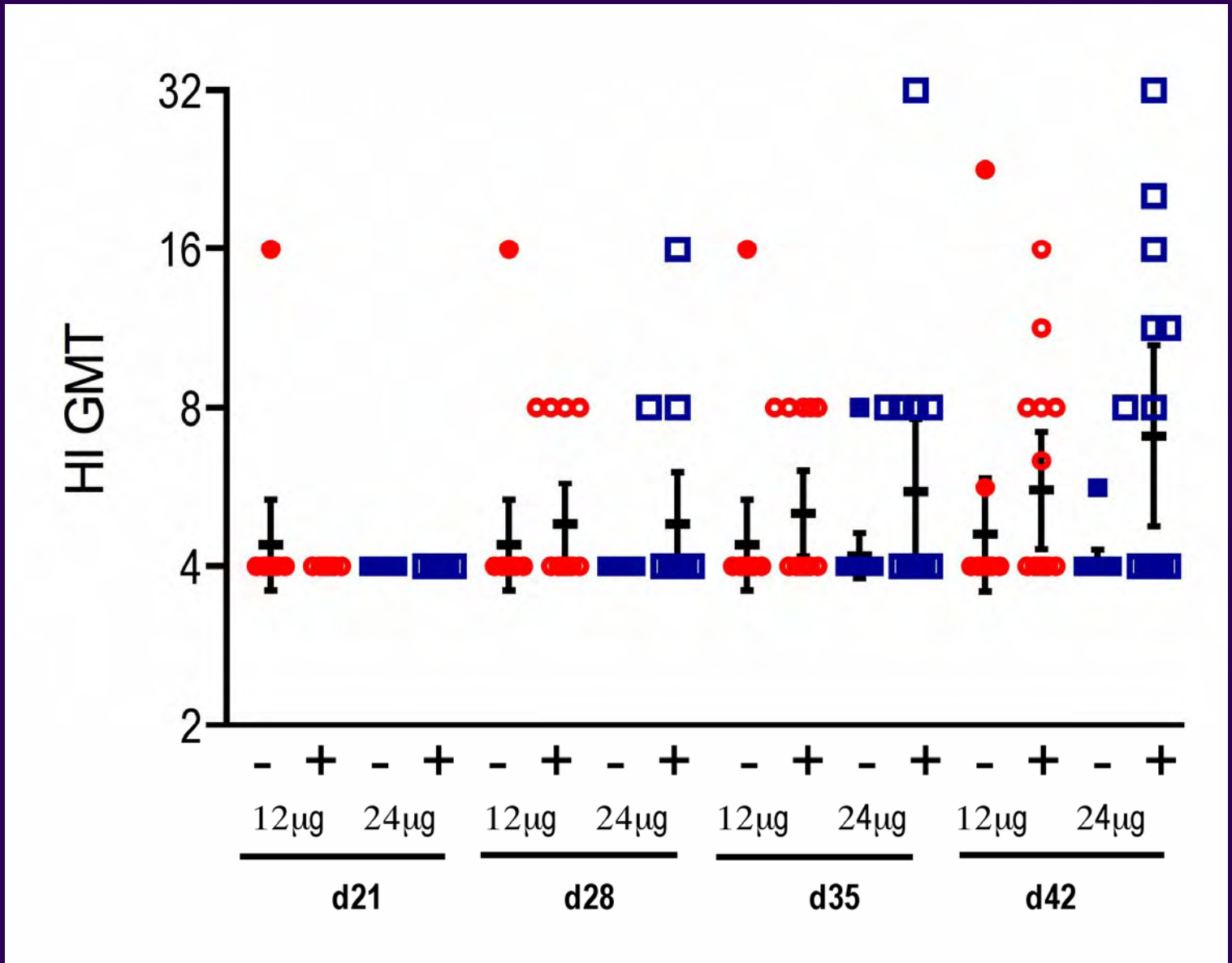
Stephenson et al, 2003

Clinical trial of H9N2 whole virus vaccine
with and without aluminium adjuvant
Geometric mean HI titres



Hehme et al, 2002

H7N1 subunit PERC6 + Alum (Cox et al, Options 2007)



Summary of detectable functional antibody responses (HI and/or MN)

Group	Vaccine	No. of volunteers detectable antibody/ total no. volunteers (% of responders)
1	12µg HA	3/14 (21%)
2	12µg HA + alum	7/14 (50%)
3	24µg HA	3/13 (23%)
4	24µg HA + alum	8/13 (62%)

Dose & adjuvant conclusions

- High antigen dose without adjuvant

- Alum adjuvant modest effect, not always predictable, dependent antigen type

- More powerful adjuvants (Mf59 & AS) show signficant antigen sparing

(2 x 5-10ugm subvirion HA possible),

not affected by trivalent formulation H5

- Whole virus vaccines may be more immunogenic

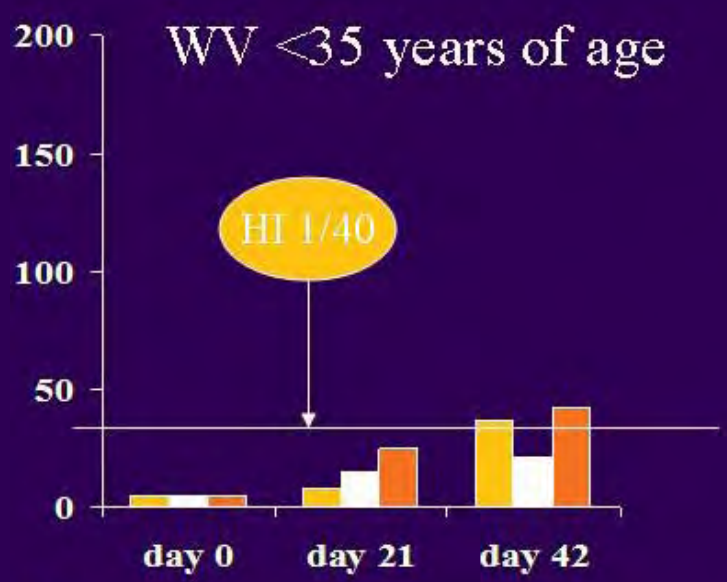
(1x 5-10ugm WV possible with/without adjuvant)

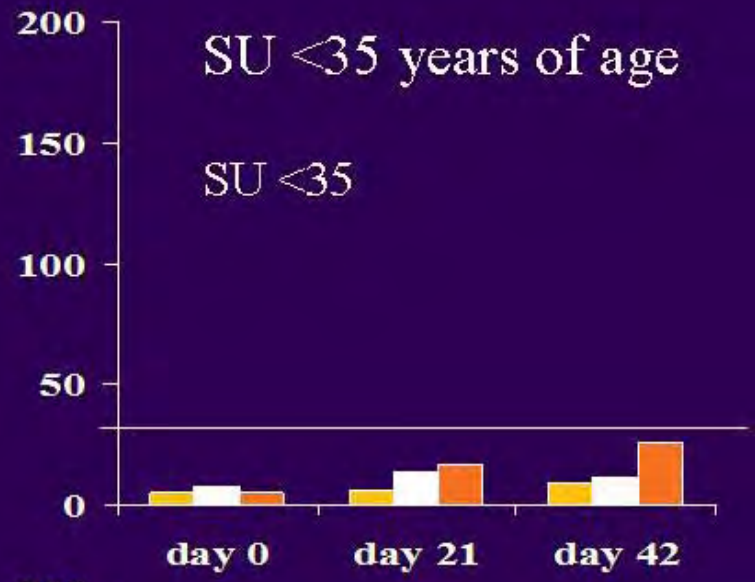
BUT....caveats re standardisation of vaccines and immunogenicity

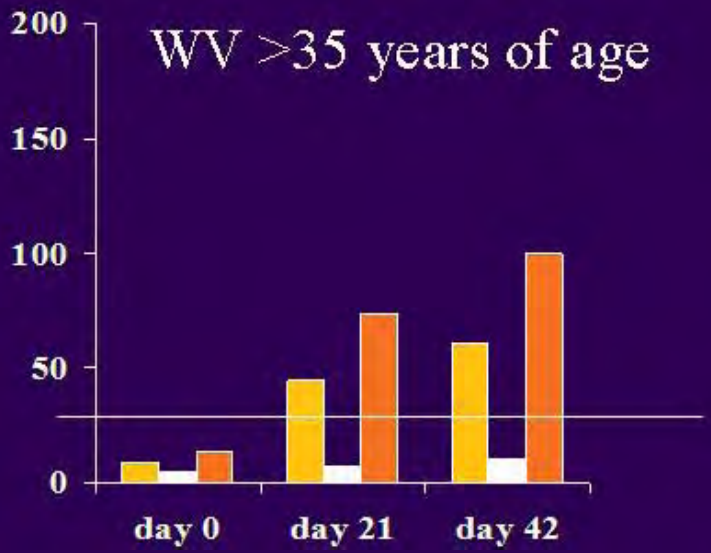
Age related responses

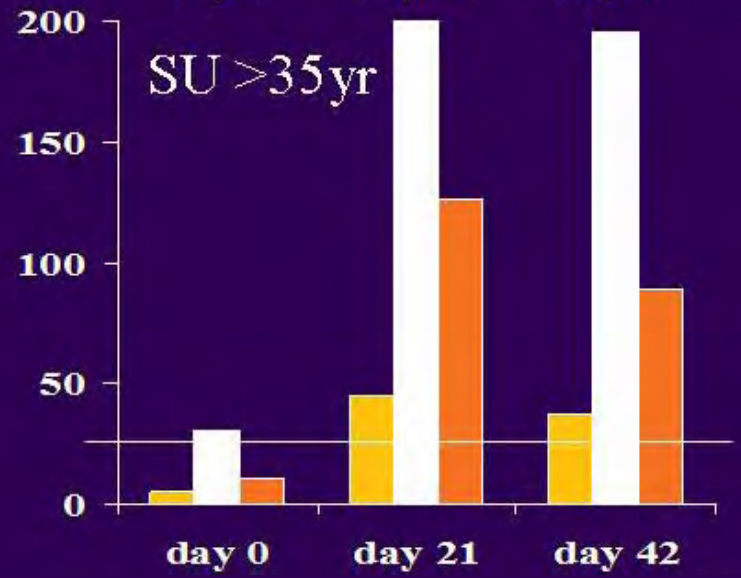
- Paediatric studies in progress In EU (commercial)
- Pre existing immunity may influence response to vaccines
- WV vaccines more immunogenic in younger people ?
- Is there useful heterosubtypic functional antibody ?

Age effect on HI responses H9N2 UK

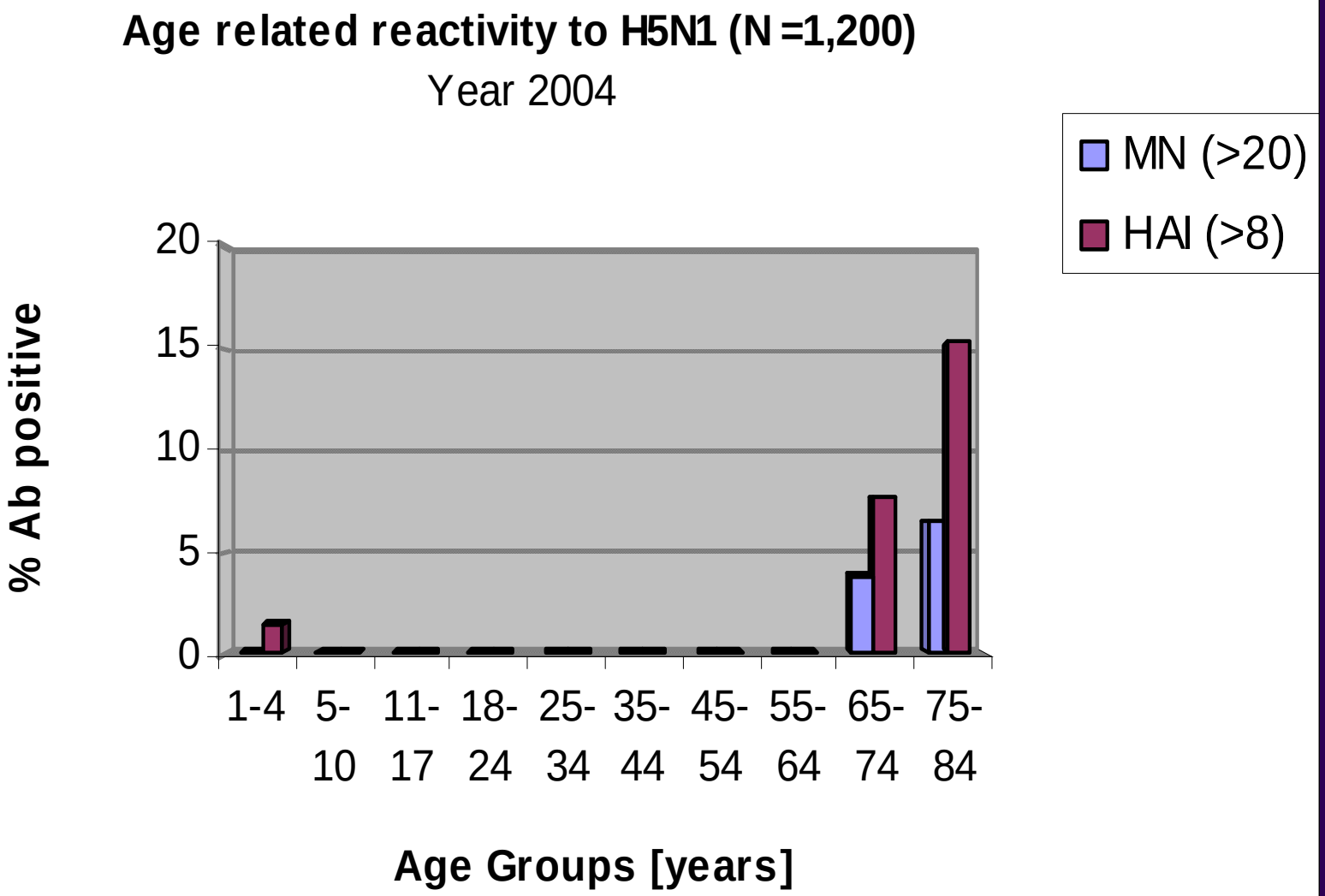








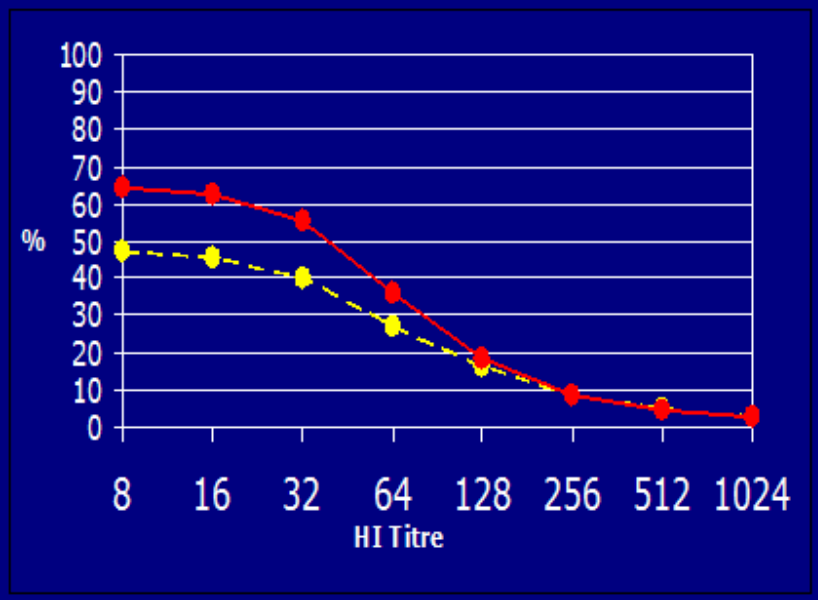
Heterosubtypic antibody ??



H5N1 Sanofi 30µg HA + Ad

Reverse cumulative HI titre distribution

Elderly with undetectable Ab titer at baseline (N=127)

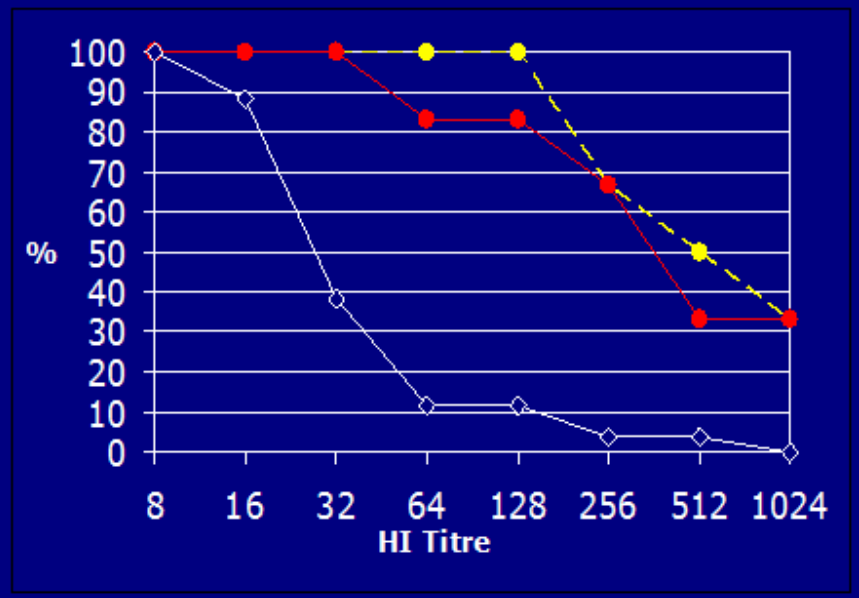


D0

D21

D42

Elderly detectable Ab titer at baseline (N=23)



Hoffenbach et al, WHO Feb 2007

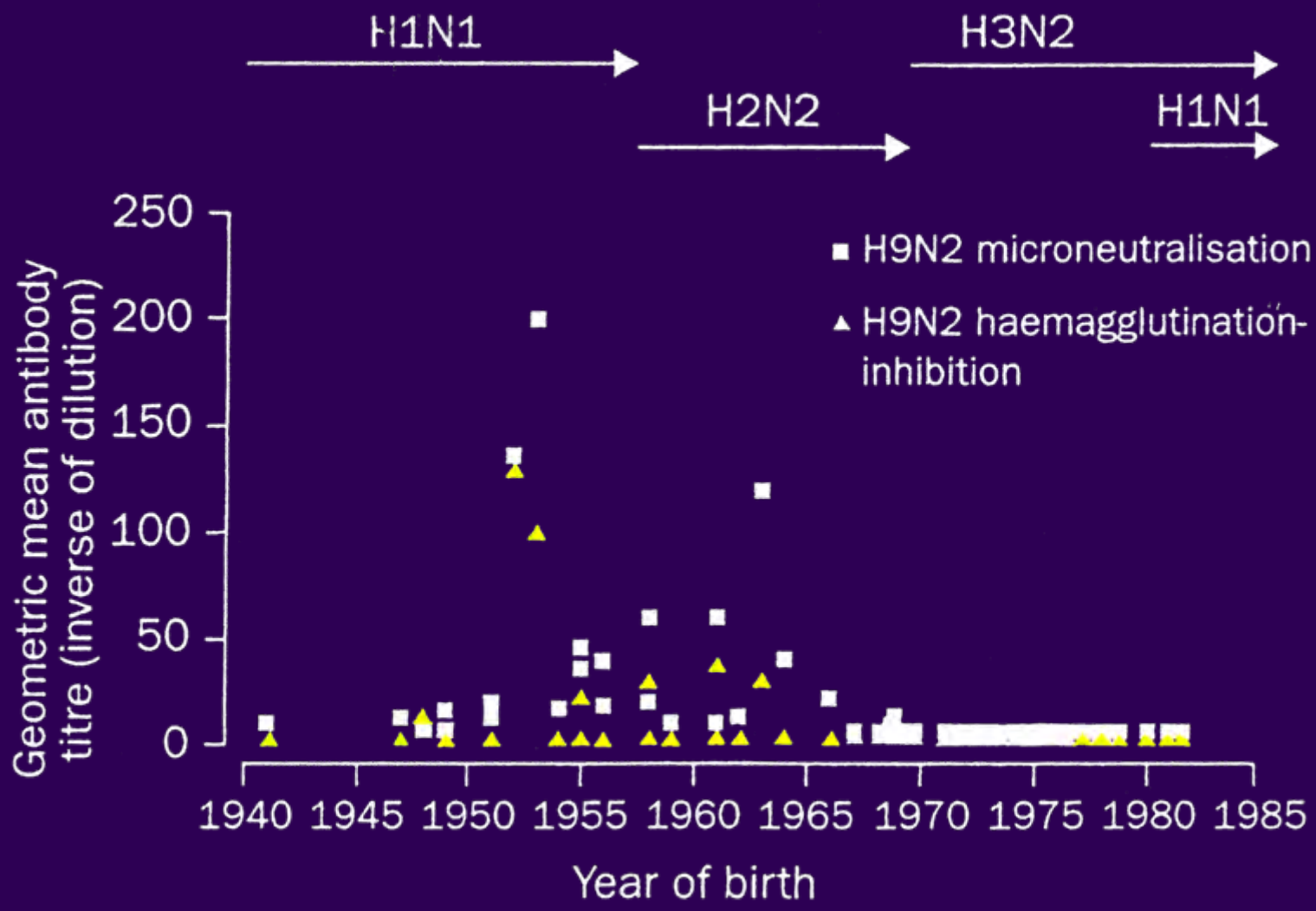
Phase II Conclusions
Elderly (France)

- Pre-vaccination anti H5 HA abs were seen in approximately 16% of the elderly population

- 2 doses (30ug SU) needed to optimize immune response in population with undetectable Ab titer at baseline

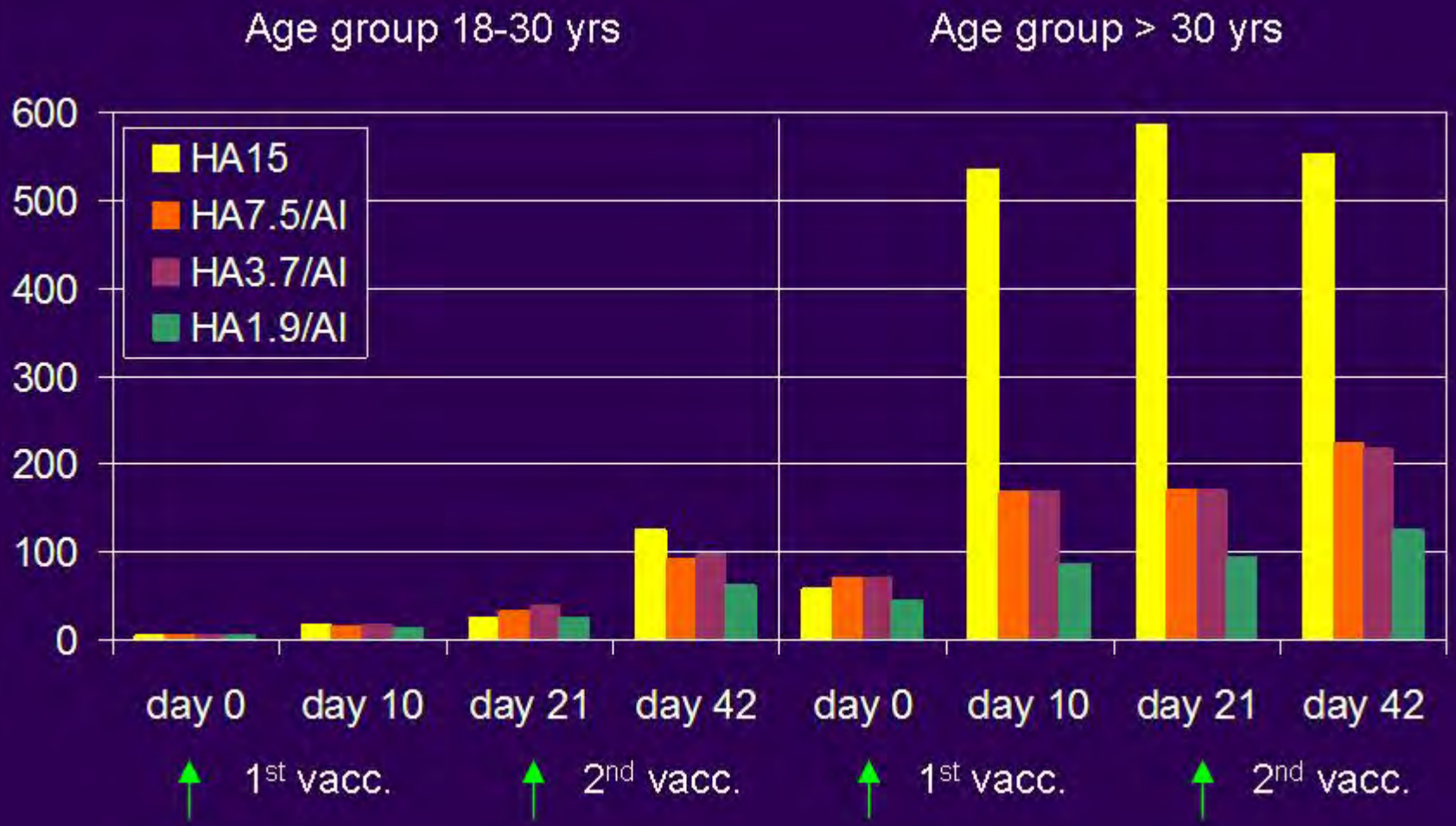
- Elderly with pre-existing titer have little benefit from 2nd dose

Pre existing Antibody ? H9



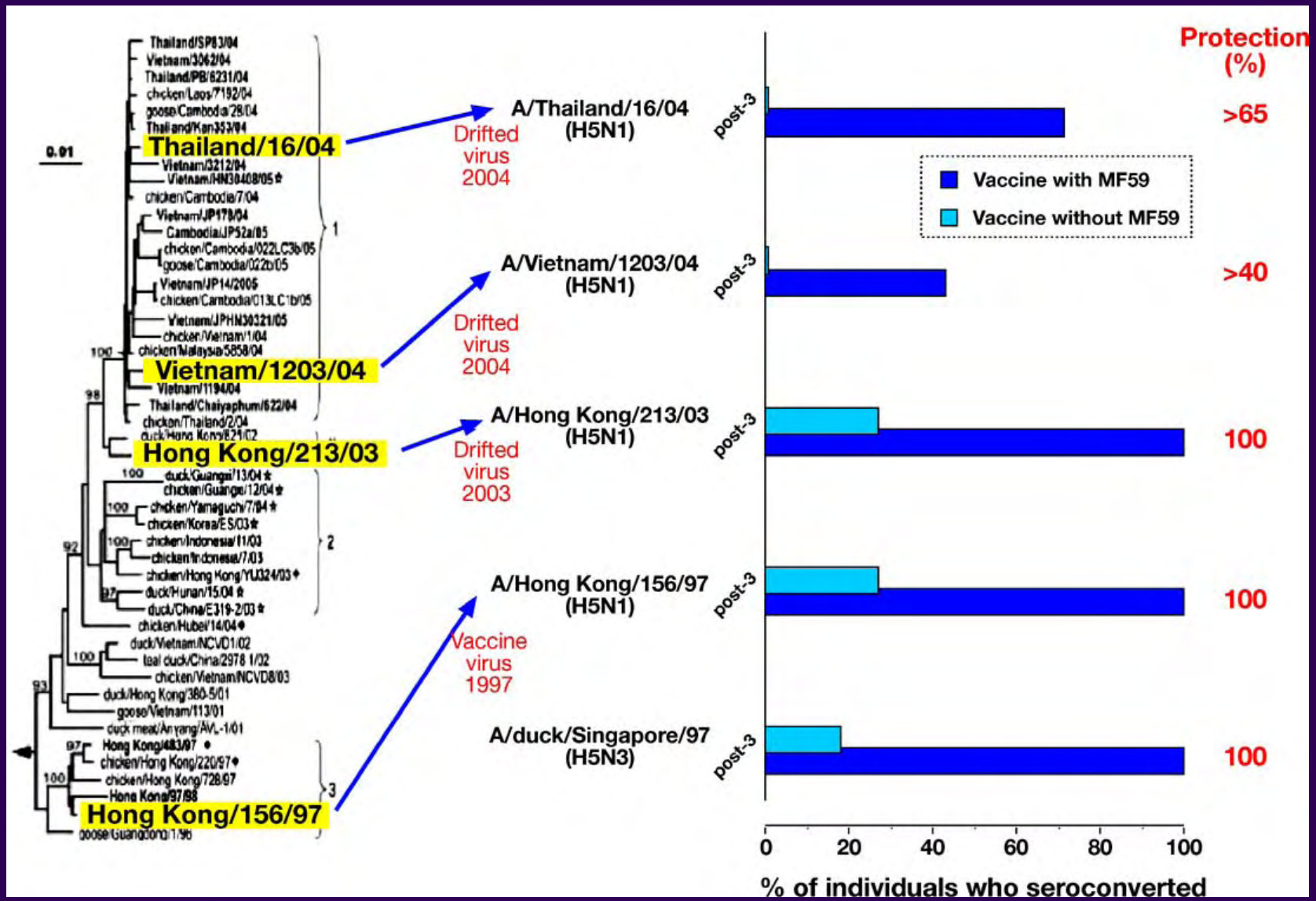
whole virus H2N2 vaccine

GM HI titre according to age

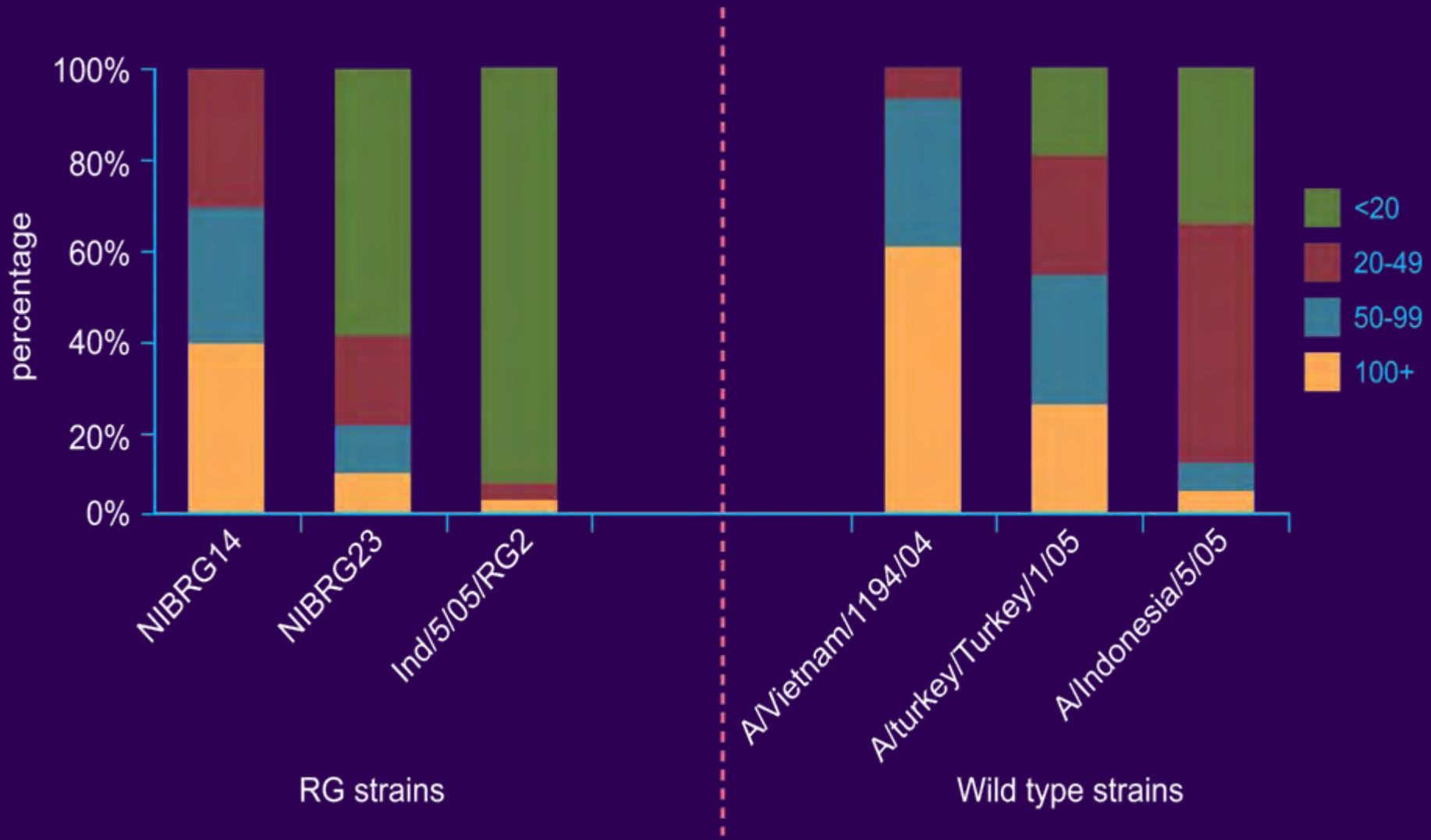


Hehme et al, 2002

Neutralisation against antigenic variants
H5N3 + MF59

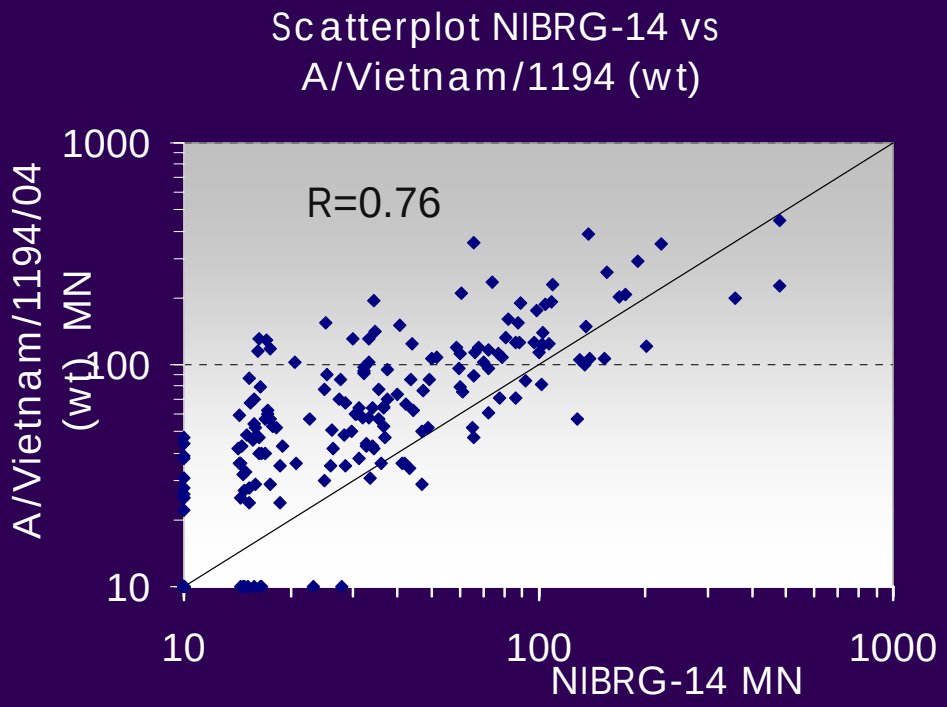


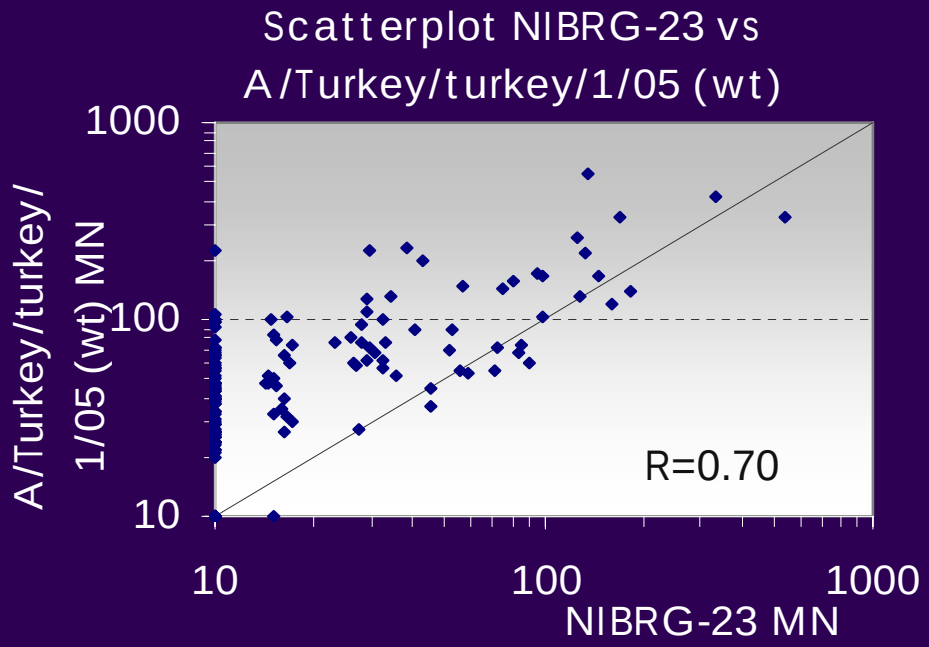
Cross Neutralisation H5N1 strains (Vietnam 1194 RG su + AL)



Hoschler et al, 2007 ISRV In Press

2. Comparison of Immune Response to Vaccine Strains and Wildtype Viruses (GPA01 subunit H5 +/- alum)

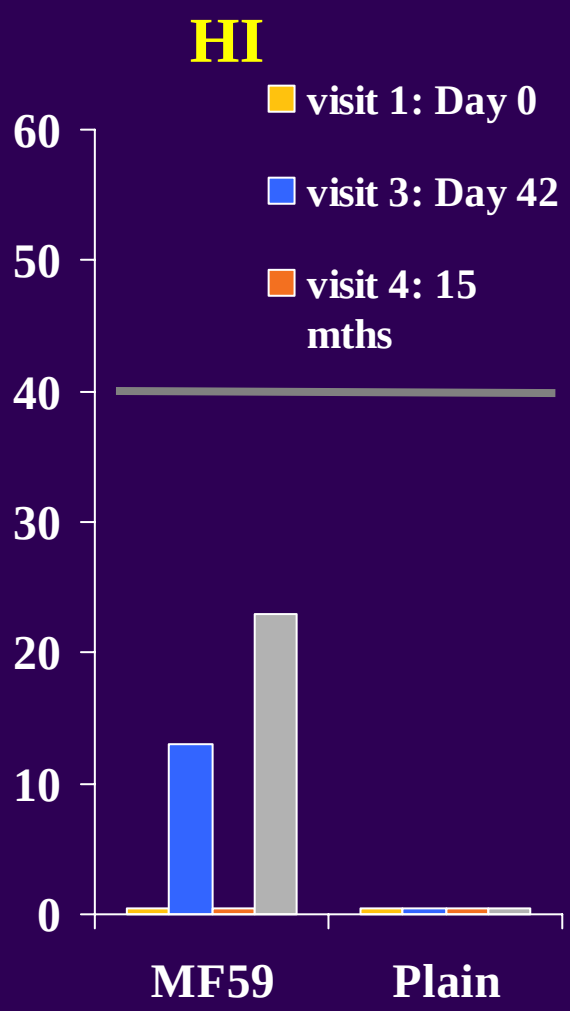


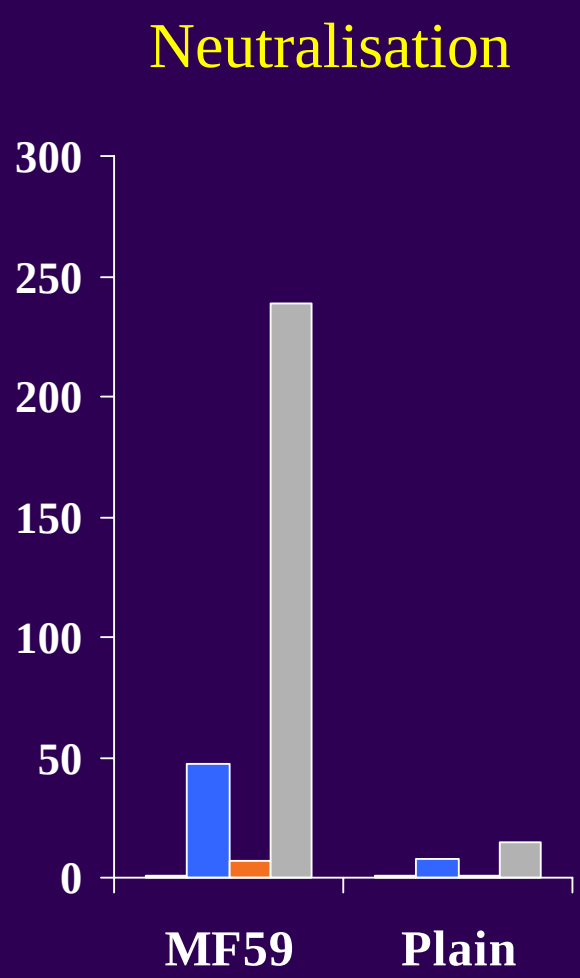


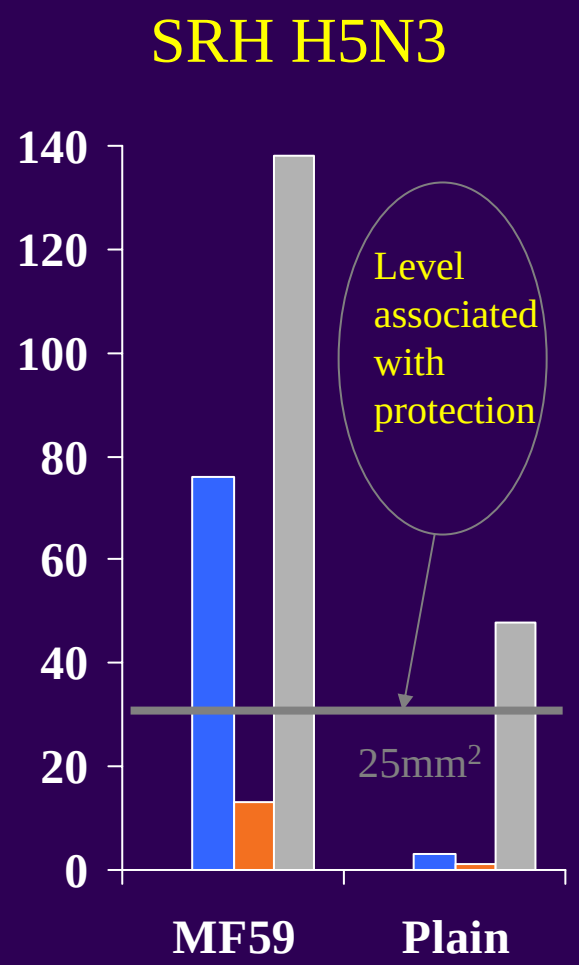
Broad response to diverse strains

- Some cross neutralisation seen with several vaccine types tested to date, in line with animal (ferret) data
- Height of Ab response important
- No advantage alum adjuvant
- Cross protection improved with MF59/AS vaccine but may be dependent on higher Ab titres

Boosting of responses in a primed population
HI, MN and SRH H5N3 titres







Stephenson et al, Vaccine 2003

Is serum antibody necessary for protection?

mice

Subtype	Vaccine strain	Serum antibody	Virus challenge		Authors
			Challenge virus	Survival	
H5N1	HK/213/03	V low	VN/1203/04	100%	*Ninomiya et al, 2007*
	VN/1203/04	V low	VN/1203/04	100%	
	None	none	VN/1203/04	0%	
H7N1	Ty/Italy/99	V low-absent - mainly IgG1	Ty/Italy/99	95%	*Hauge et al unpublished*
	None	None	Ty/Italy/99	0%	

ferrets

two doses of A/VN/1194/04 vaccine induce

100% survival against A/Indonesia/5/05 challenge

Serological Assays for detections of antibodies to avian influenza 2007

Microneut

Gold standard for detection of antibodies

Optimal results, need well matched virus

H1

Suitable for screening large no of sera/BSL 2 inactivated material

Good correlation MN. Take account of receptor specificity of virus

SRH

Needs to be optimised for recent H5N1 strains

Western Blot

Useful for confirmation...important data may accrue from careful analysis HA

False positive if used for screening

ELISA

Requires use of HA I

Needs more development

No correlate of protection

Key Messages EU trials

- Antigen sparing is possible
- Whole virus vaccines maybe more immunogenic
- Cross protection against diverse range viruses likely within subtype
- Immunity maintained after >5 years post vaccine, even if Ab decline
- Correlate of protection needs better definition for naive population.
- Effect of pre existing heterosubtypic antibody ?
- MOVE FROM HYPOTHESIS GENERATING TO TESTING