

Immune Responses of Healthy Subjects to a Single Dose of Intramuscular Inactivated Influenza A/Vietnam/1203/2004 (H5N1) Vaccine After Priming With an Antigenic Variant.

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Background

- Non-adjuvanted, inactivated subvirion H5N1 vaccine required two 90 mcg doses to elicit neutralizing antibody in more than half of subjects
- In one study, a third dose of inactivated A/Duck/Singapore/97 (H5N3) vaccine 16 months after a priming series resulted in significant boosting
- Pre-priming might generate better immunity, allowing a single dose strategy in face of emerging pandemic. However, any emergent pandemic virus will likely represent antigenic variant from the priming virus
- We took advantage of a previous study evaluating a baculovirus recombinant H5 A/HK/156/97 (clade 3) vaccine performed in 1998 to evaluate effect of boosting with a single dose of subvirion A/VN/1203/04 (clade 1) vaccine.

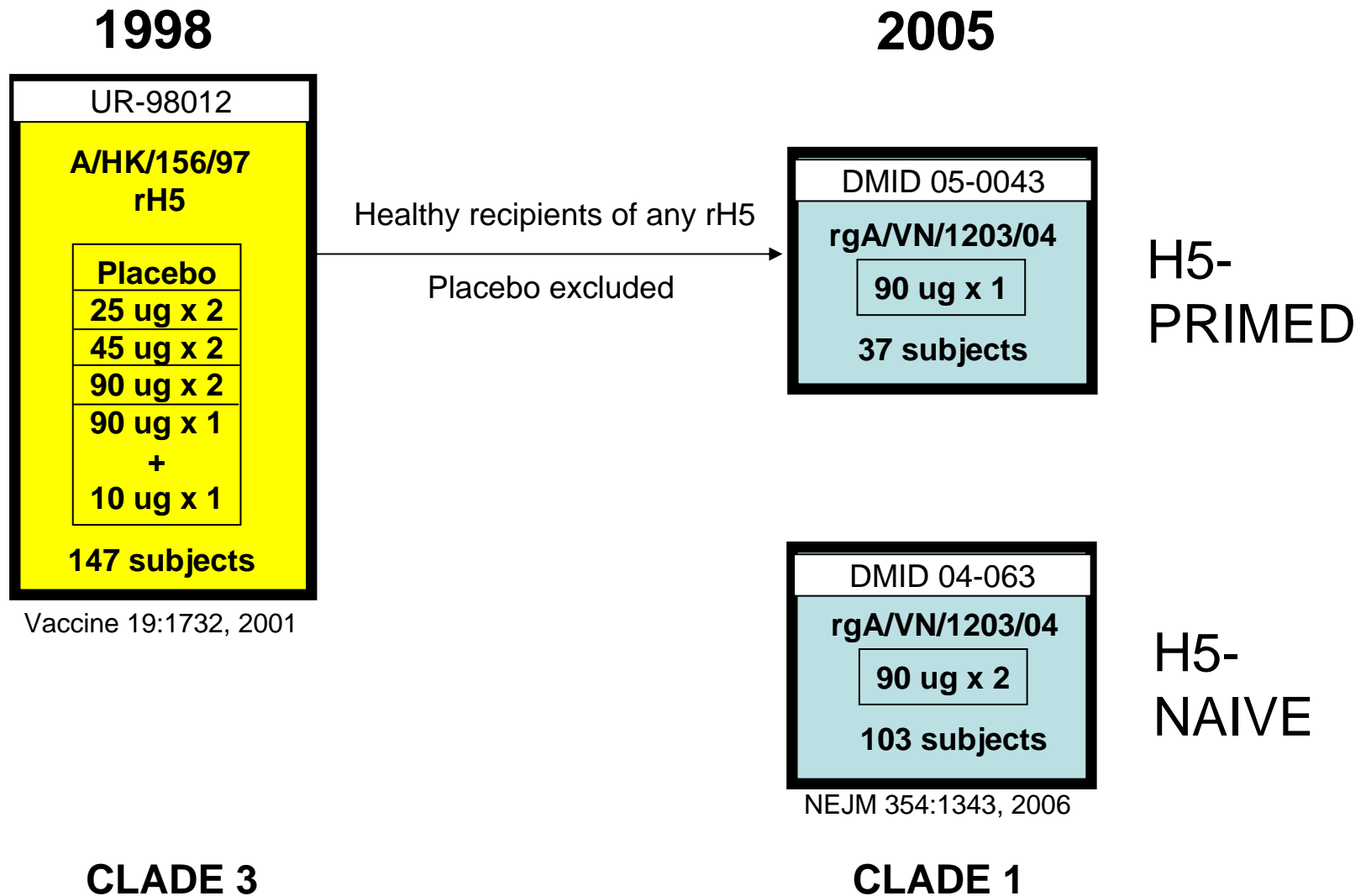
Objectives

- Determine the ability of a clade 3 H5 recombinant vaccine to prime for immune responses to a subsequent clade 1 H5 subvirion vaccine in healthy adults
 - Comparison of responses in H5 primed subjects to those of H5 naïve subjects
- Determine the safety of revaccination with a clade 1 vaccine in primed subjects

Methods

- Subjects: participants in 1998 study who received a clade 3 rH5 vaccine baculovirus-expressed recombinant H5 vaccine (A/HK/156/97, Clade 3)
- Vaccine: single 90 mcg dose of subvirion rgA/Vietnam/1203/04 x PR8 (clade 1) vaccine
- Safety diary card x 7 days, all adverse events recorded over 56 days
- Serum HAI and MN antibody tested at days 0, 28, and 56
- Results compared to responses to one (primary analysis) or two (secondary analysis) 90 mcg doses of clade 1 vaccine in naïve subjects

Evaluation of priming with an antigenic variant: schematic of study design



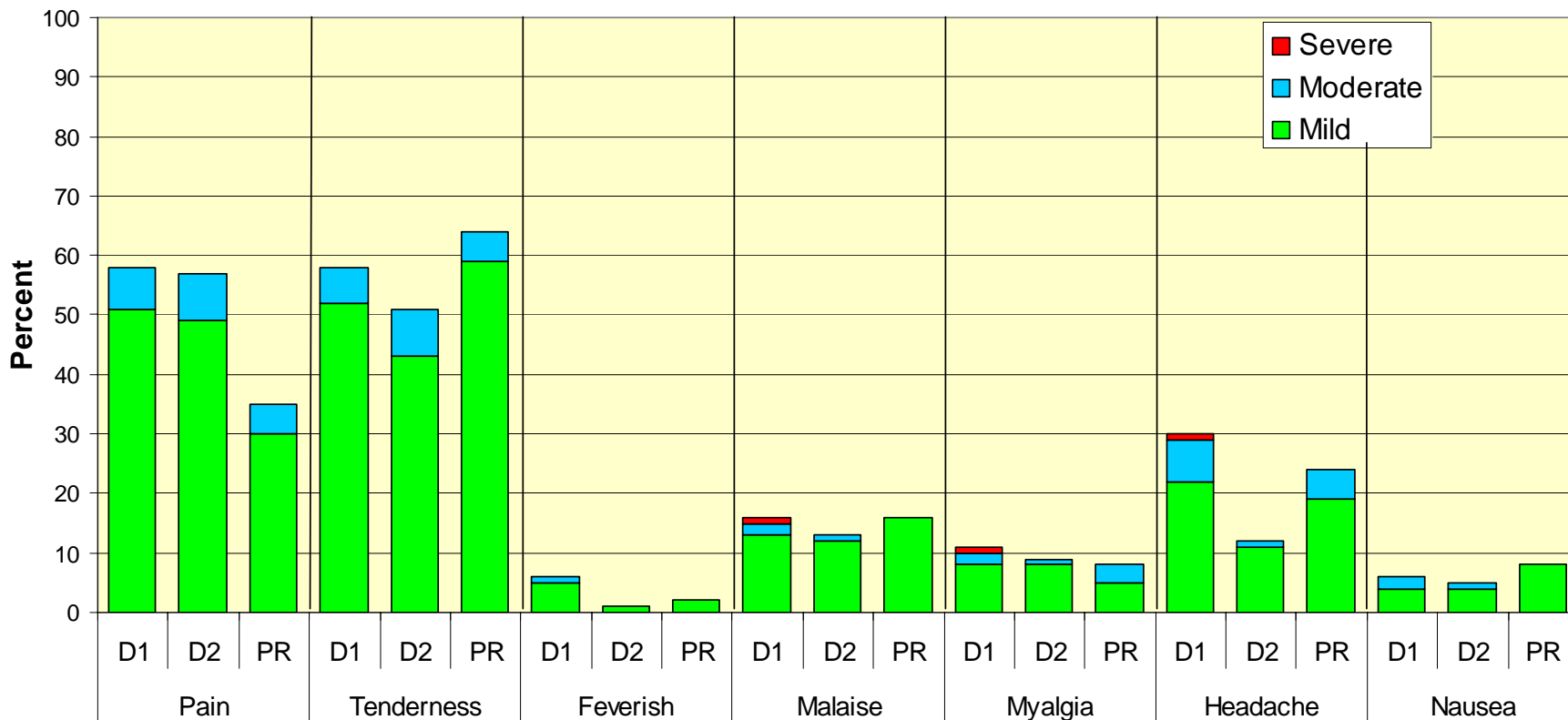
Demographics

H5 NAIVE
(DMID 04-063)
n=103

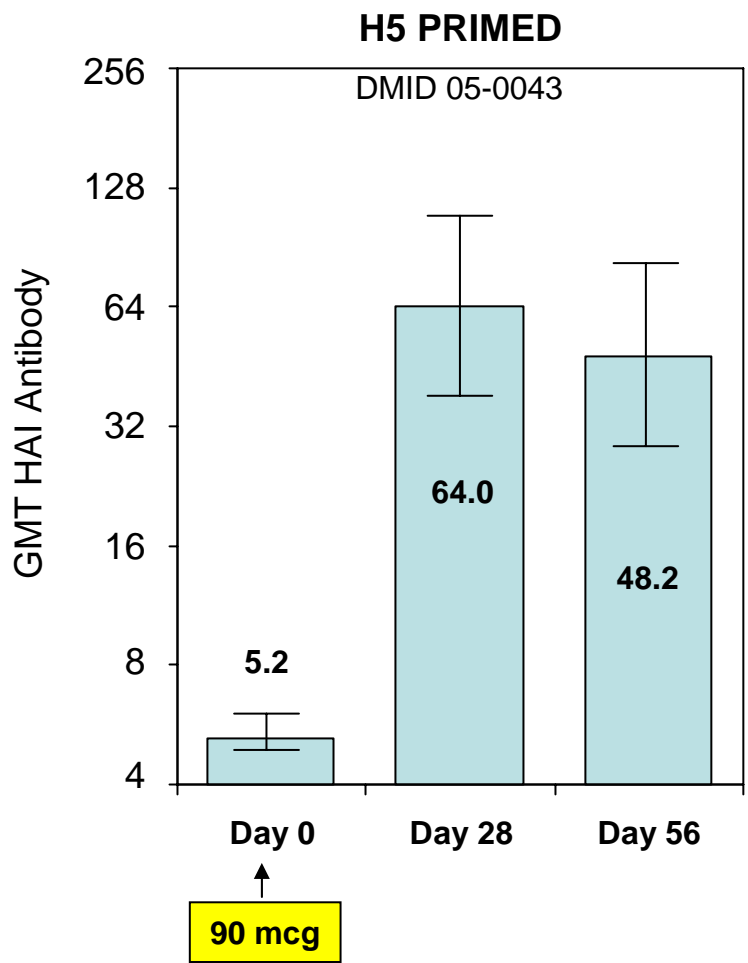
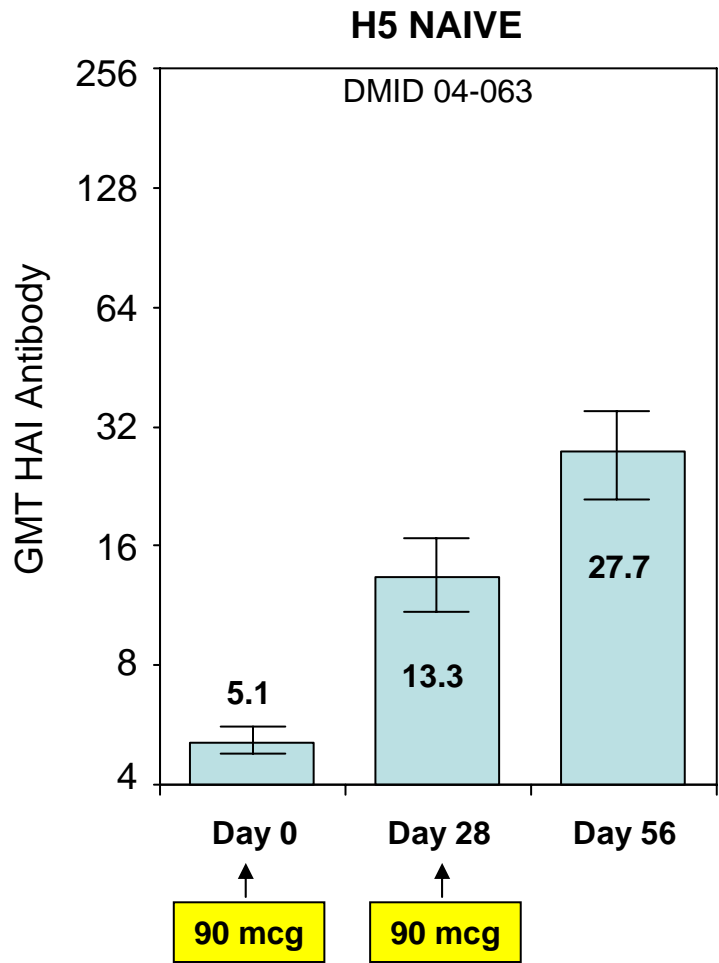
H5 PRIMED
(DMID 05-0043)
n=37

White	84 (82%)	35 (95%)
Black	11 (11%)	2 (5%)
Asian	8 (8%)	0 (0%)
Pacific Islander	0 (0%)	0 (0%)
Multiracial	0 (0%)	0 (0%)
Hispanic	13 (13%)	0 (0%)
Female	55 (54%)	23 (62%)
Age (median, range)	38 (18-64)	42 (33-51)

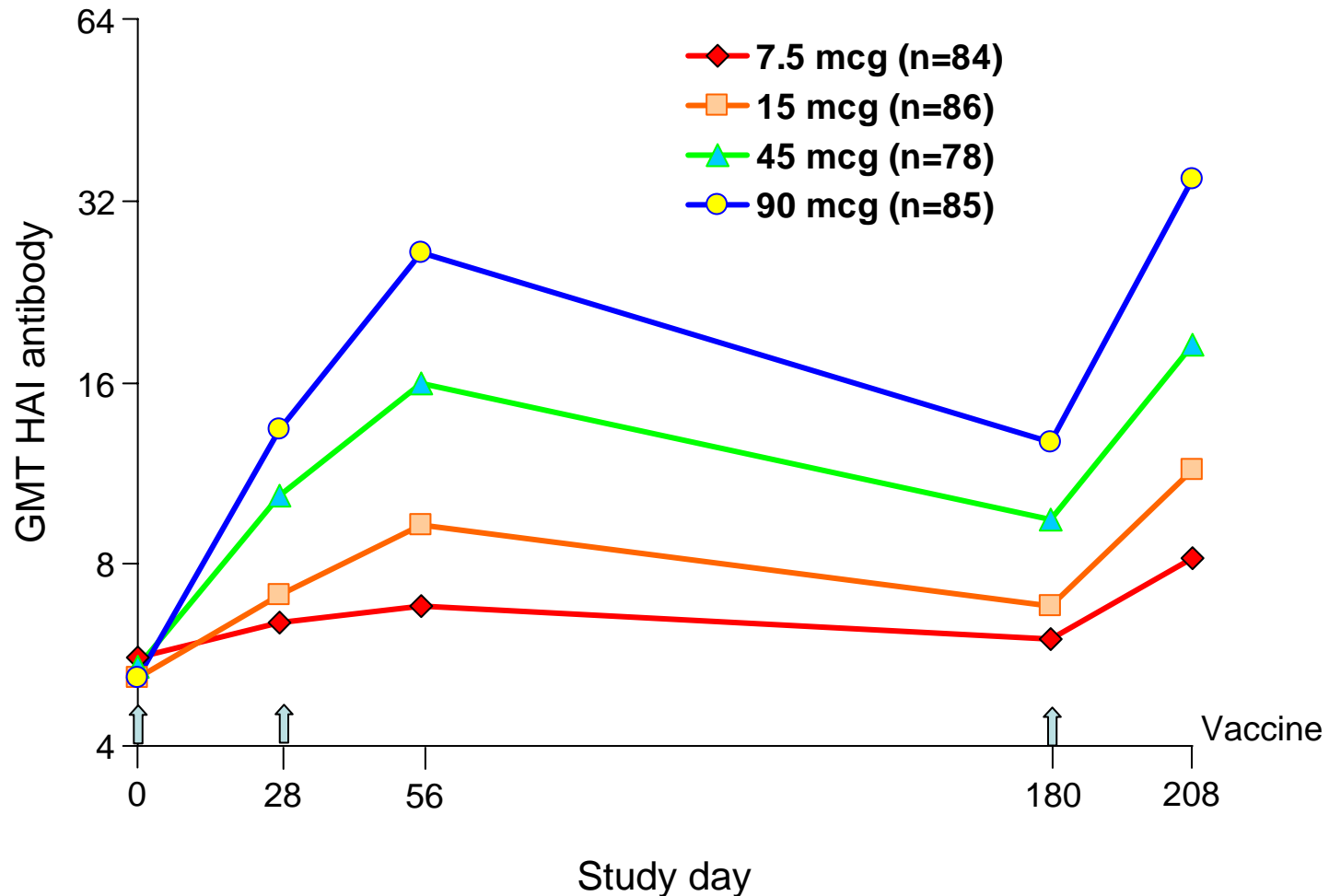
Rates and severity of reactogenicity after 1 (D1) or 2 doses (D2) in naïve subjects and after one dose in H5 vaccine-primed (PR) subjects



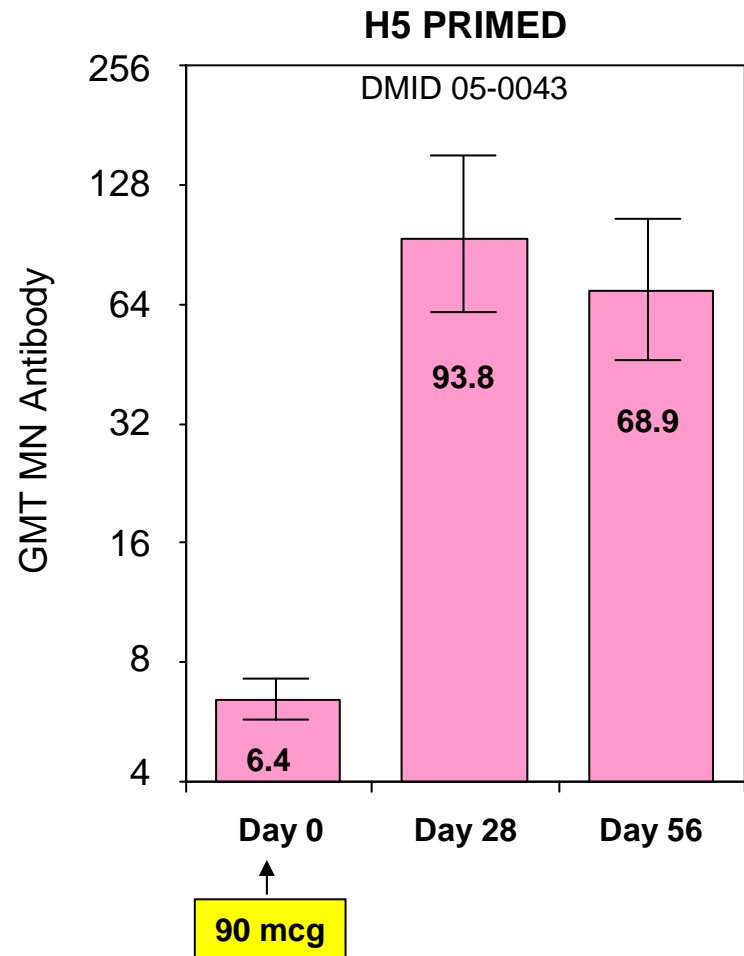
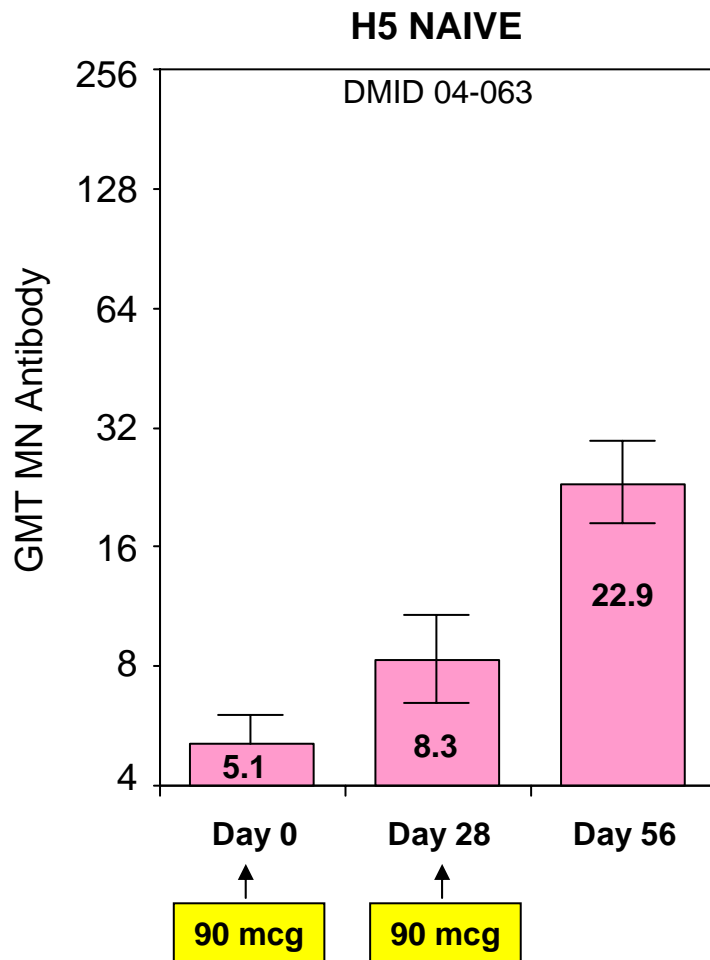
Serum hemagglutination-inhibition (HAI) titers following one or two doses of H5 vaccine in naïve subjects or following a single dose in H5 vaccine-primed subjects



Response of healthy adults to a third dose of subvirion H5 vaccine (study DMID 05-0090)



Serum microneutralization assay (MN) antibody responses following one or two doses of H5 vaccine in naïve subjects or following a single dose in H5 vaccine-primed subjects



Rates of serum HAI and MN antibody responses and proportion achieving a titer of 1:40 or greater after one or two doses of H5 vaccine in naïve subjects or after one dose in H5 vaccine-primed subjects

Group	Result 28 days after:	Percent responding* (95% CI)		Percent ≥1:40 (95% CI)	
		HAI	MN	HAI	MN
H5 naïve	Dose 1	23 (15, 33)	10 (5, 18)	24 (16, 34)	11 (6, 19)
	Dose 2	43 (33, 54)	41 (32, 52)	44 (34, 55)	42 (33, 53)
H5 primed	Dose 1	68 (50, 82)	76 (59, 88)	70 (53, 84)	76 (59, 88)

* Response defined as 4-fold or greater increase in titer from baseline. For the HAI assay, a response also must achieve a titer of 1:40 or greater

Effect of the priming dose of recombinant H5 vaccine administered in 1998 on responses to 90 mcg of H5 vaccine in 2006

Response to a single dose of H5 vaccine in 2006

1998 Priming Dose	N	HAI		MN	
		GMT	Response* n (%)	GMT	Response* n (%)
25 ug x 2	12	63.5	7 (58%)	195.6	10 (83%)
45 ug x 2	7	155.1	6 (86%)	304.5	6 (86%)
90 ug x 2	8	42.1	5 (63%)	174.5	7 (88%)
90 ug/10 ug	10	48.7	7 (70%)	134.5	9 (90%)

* Response defined as 4-fold or greater increase in titer from baseline. For the HAI assay, a response also must achieve a titer of 1:40 or greater

Relationship between response in 1998 and response in 2005

Response to a single dose of H5 vaccine in 2006

Response to rH5 in 1998 [^]		HAI		MN	
		GMT	Response* n (%)	GMT	Response* n (%)
No	27	44.3	17 (63%)	67.7	22 (81%)
Yes	10	172.5	8 (80%)	226.3	10 (100%)

[^] Response in 1998 was defined as 4-fold or greater increase in MN titer to a titer of 1:80 or greater, accompanied by positive WB

* Response defined as 4-fold or greater increase in titer from baseline. For the HAI assay, a response also must achieve a titer of 1:40 or greater

Conclusions

- The antibody responses to a single dose of non-adjuvanted vaccine support the hypothesis that previous vaccination with a clade 3 H5 vaccine primed for responses to a clade 1 H5 vaccine
- Antibody responses to a single booster dose exceeded those seen after two or three doses in naïve subjects, and were more evident than those seen with the original recombinant vaccine. The reasons for such vigorous responses to revaccination are unclear:
 - Priming may have generated long-lived memory CD4 cells and/or memory B cells
 - Results should be interpreted with caution because of small sample sizes
- Revaccination was well tolerated, with a safety profile similar to vaccination of naïve subjects

Conclusions

- Further studies to evaluate different priming schedules and to verify priming between clade 1 and clade 2 viruses are needed
- If the results were confirmed in larger studies, then pre-pandemic vaccination programs could be considered for some populations (first responders, HCW, military)

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