

Clinical Trials of Pandemic Vaccines: Key Issues

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Inactivated vaccine approach

- Proven technology
 - Used successfully in 1957 and 1968
 - Abundant efficacy data in both pandemic and interpandemic years
 - Very safe, with large safety database
- Manufacturing capacity exists in potentially large scale
- Licensing would be relatively straightforward

Inactivated vaccine approach

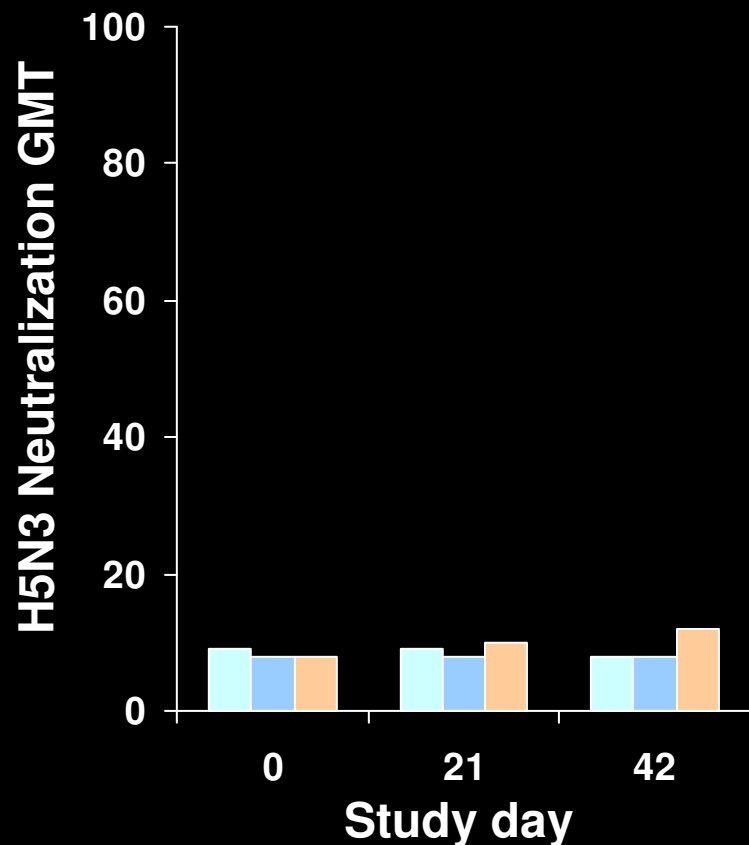
- Unlikely to induce mucosal immunity
 - May be less effective in preventing spread
- Protection may be strain specific
 - Little if any cellular immune response
- Requires multiple doses
- Manufacturing capacity limited by availability of eggs and capacity for expansion limited
 - Cell culture strategies might circumvent this problem

Recent clinical evaluations of potential pandemic viruses

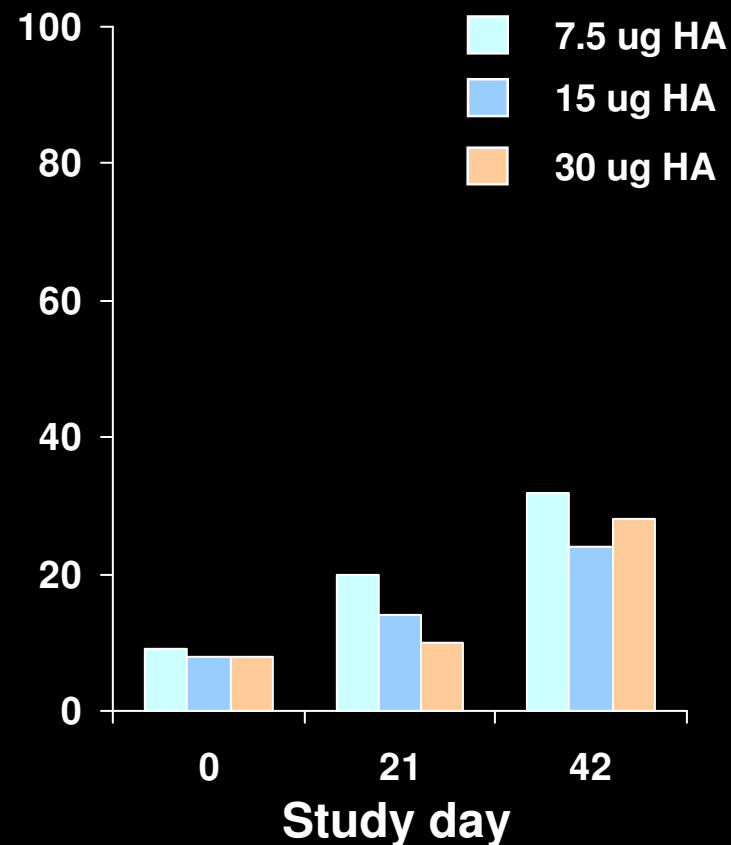
- Duck Singapore/97 (H5N3) as a vaccine for Hong Kong/97
- Recombinant, baculovirus-expressed HA of A/Hong Kong/156/97 (H5)
- Whole virion A/Singapore/1/57 (H2N2) and A/Hong Kong/1073/99 (H9N2)
- Whole virion and subunit A/Hong Kong/1073 (H9N2)

Egg-grown Duck/Singapore

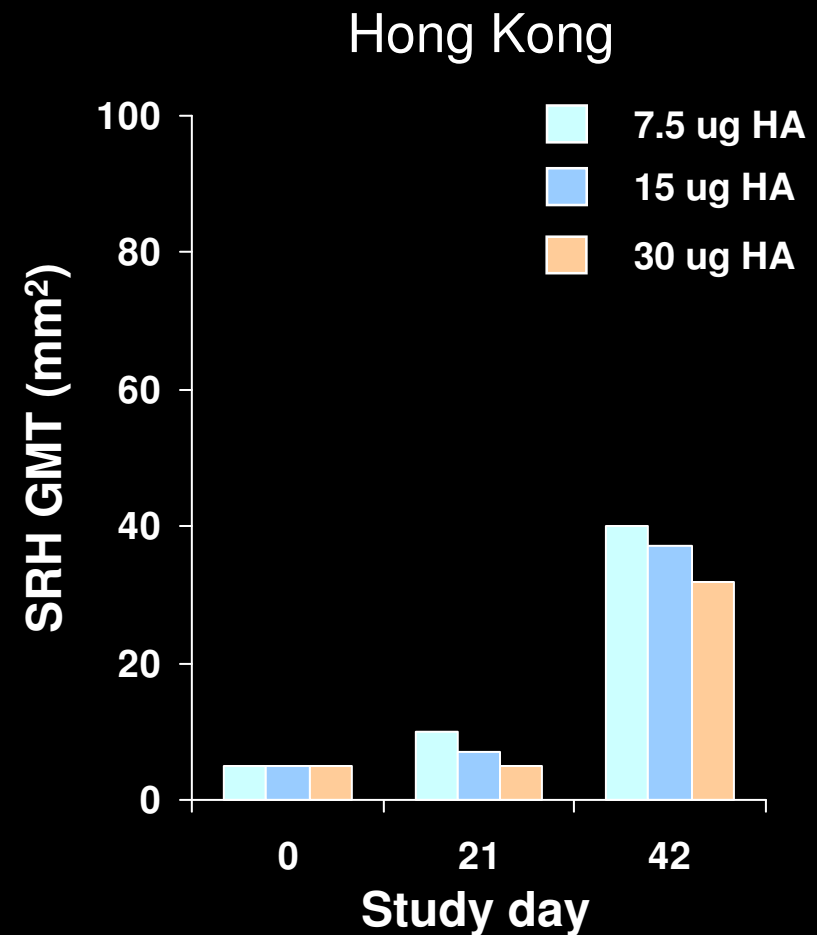
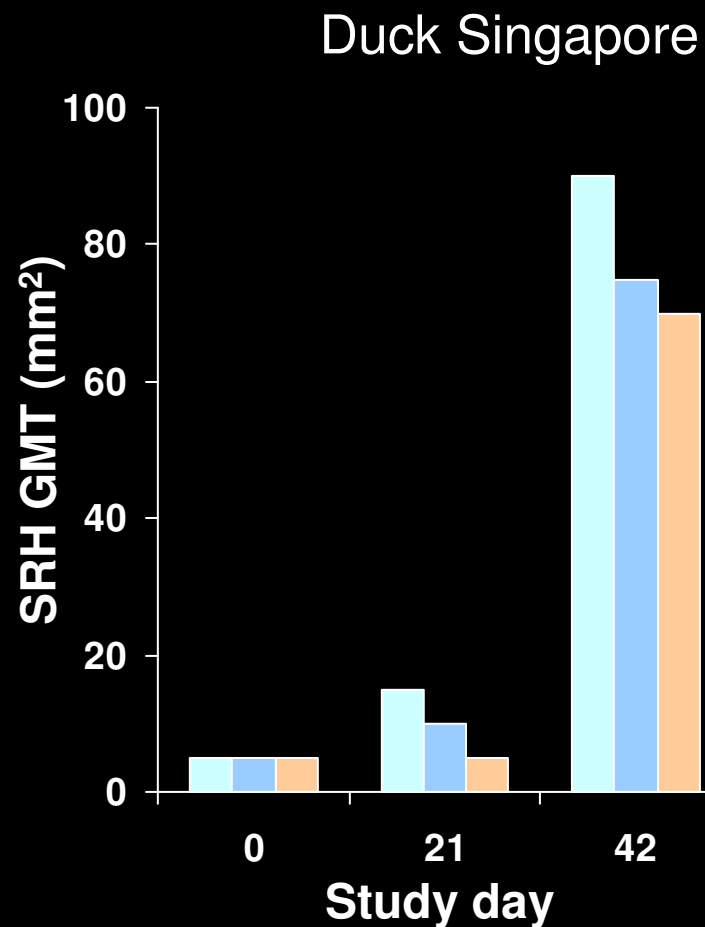
No adjuvant



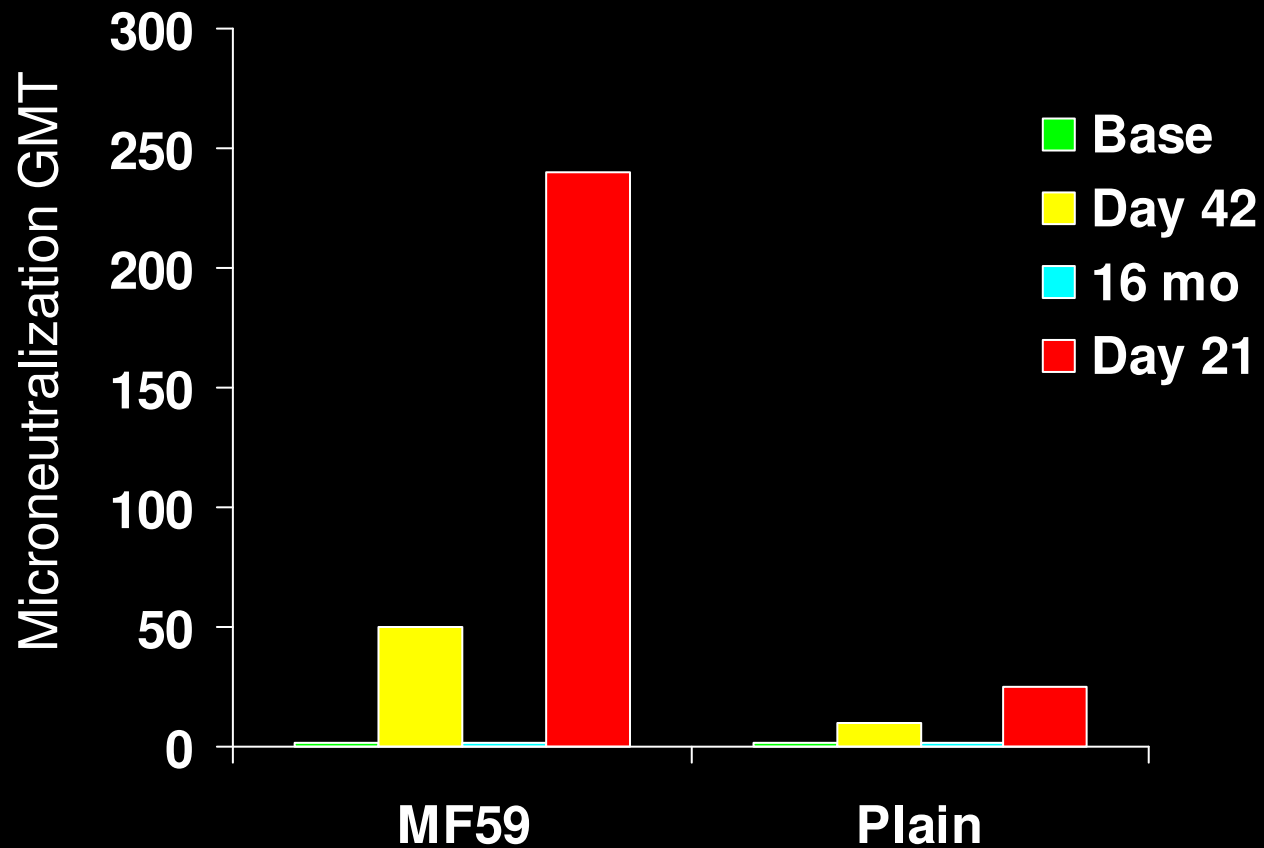
MF59 adjuvant



Egg-grown Duck/Singapore



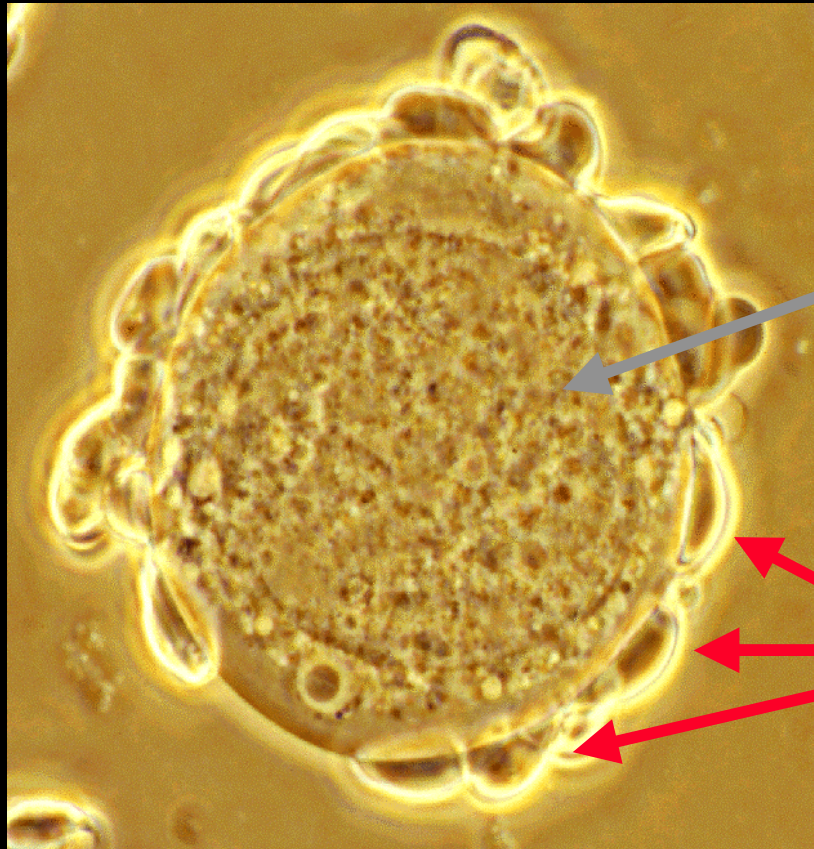
Reimmunization with Duck/Singapore



Key issues [1]

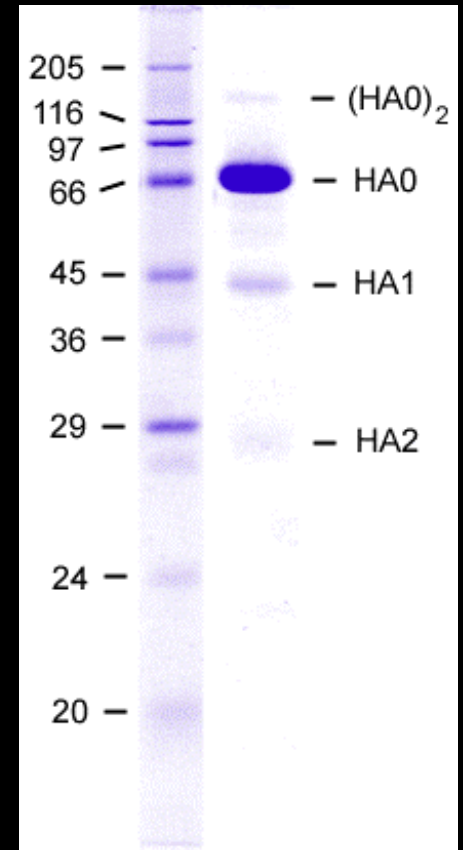
- Development of standardized, validated surrogate markers of protection
- Responses to inactivated vaccines may be very strain specific – evaluation of strategies to broaden responses
- Adjuvants should be evaluated. Ratio of antigen to adjuvant may be important
- Pre-pandemic priming dose with heterologous variants should be explored
- Dose responses relationships may not be obvious

Recombinant rHA H5 Vaccine



Insect cell
expressing
rHA

RBCs

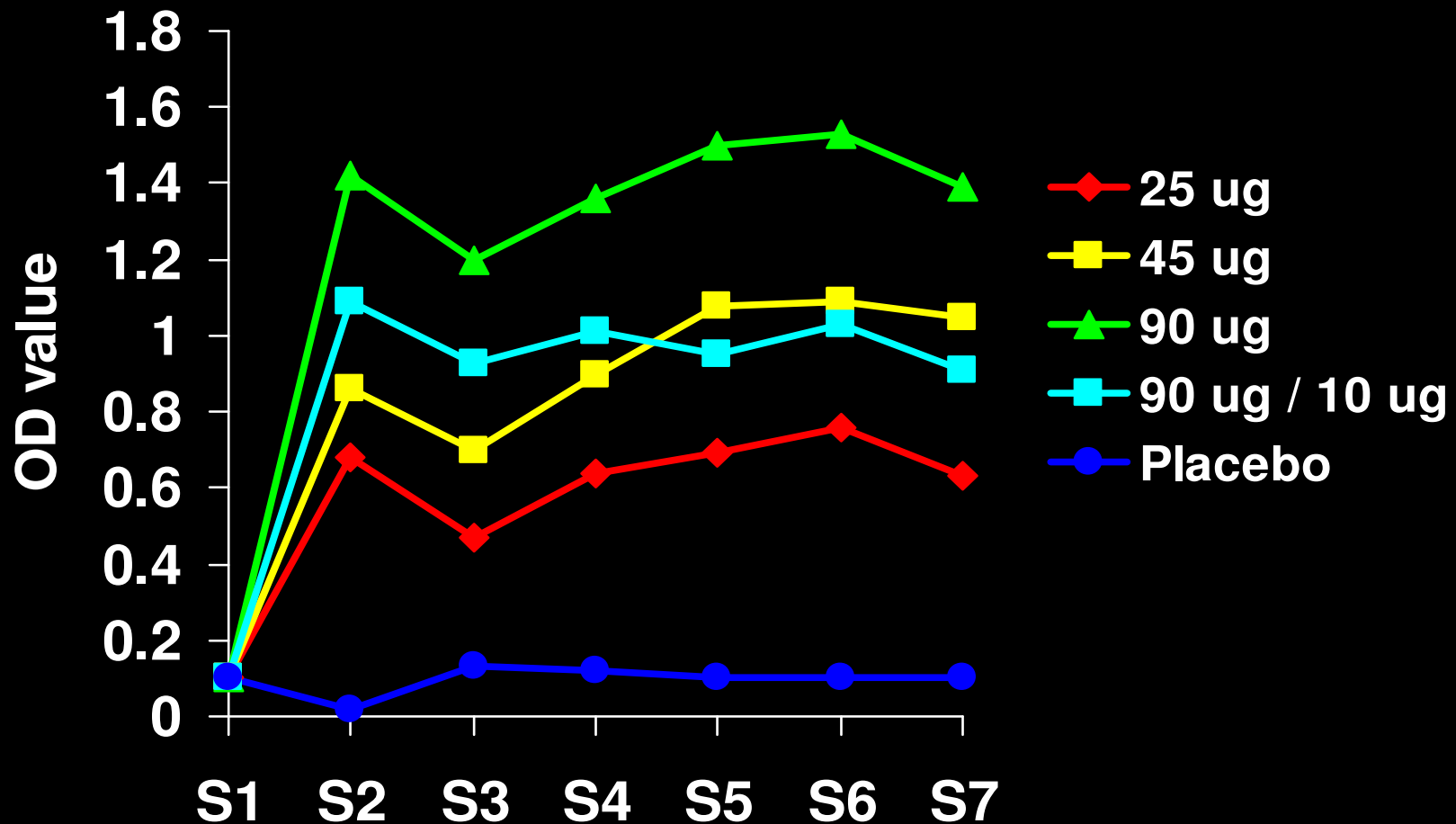


Purified rHA H5
SDS-PAGE

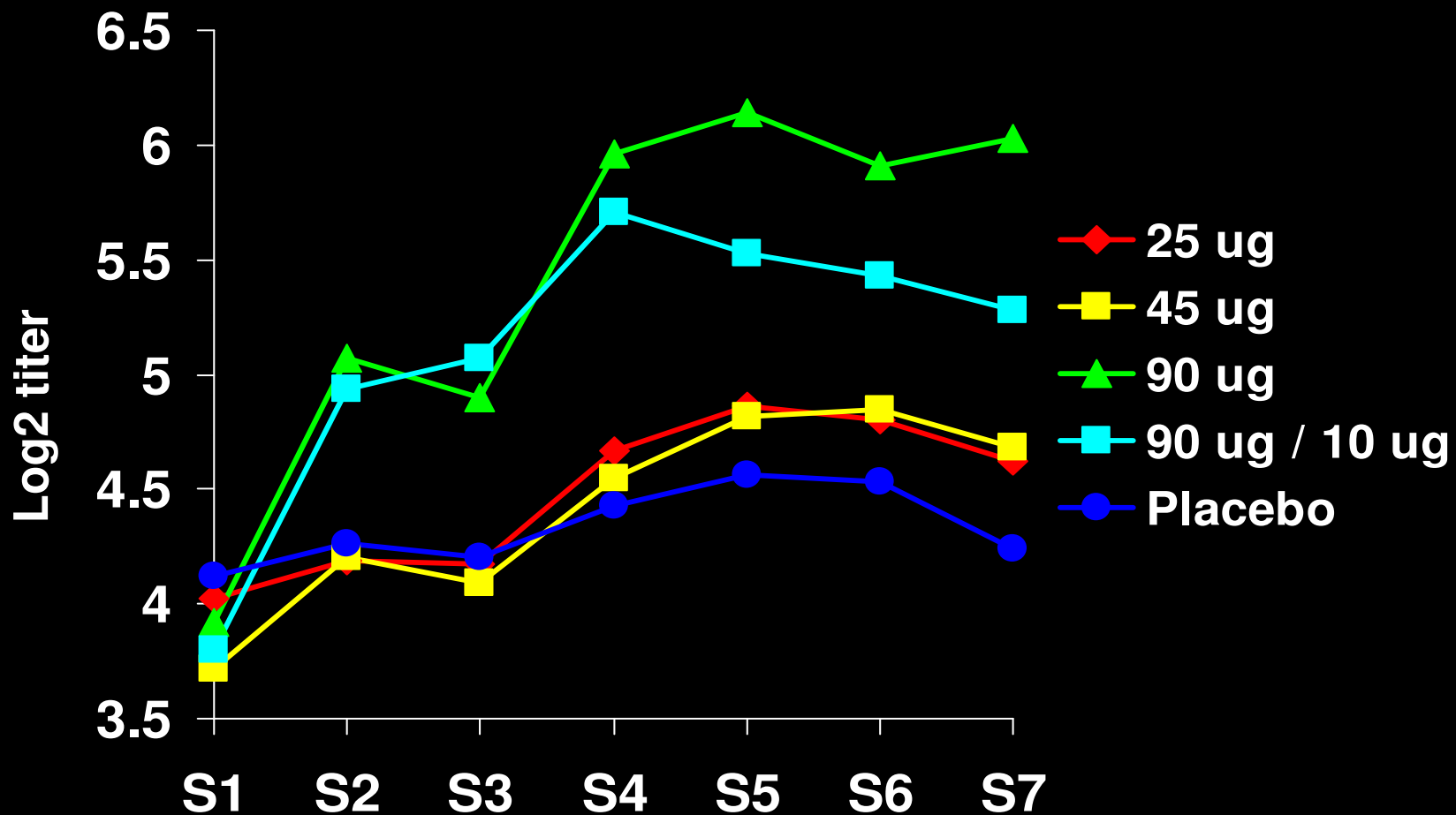
Phase I evaluation of rH5

- Randomized to interval between doses (21, 28, or 42 days) and then to dose groups (90 ug, 45 ug, 25 ug, 90/10 ug, placebo) - Total of 15 groups
- Vaccine or placebo administered in total of 1 mL by i.m. injection
- Sera before and 14 days after dose 1, and before and 7, 14, 21, and 28 days after dose 2

ELISA vs. A/HK/156 virus



Neutralization titers



Response rates

Percent of subjects responding by the following tests after 1 or 2 doses

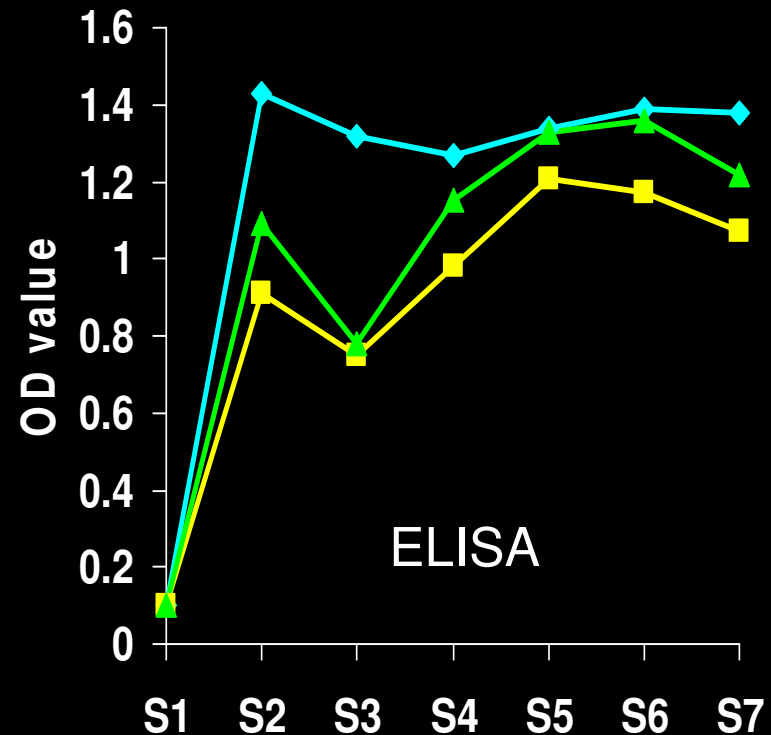
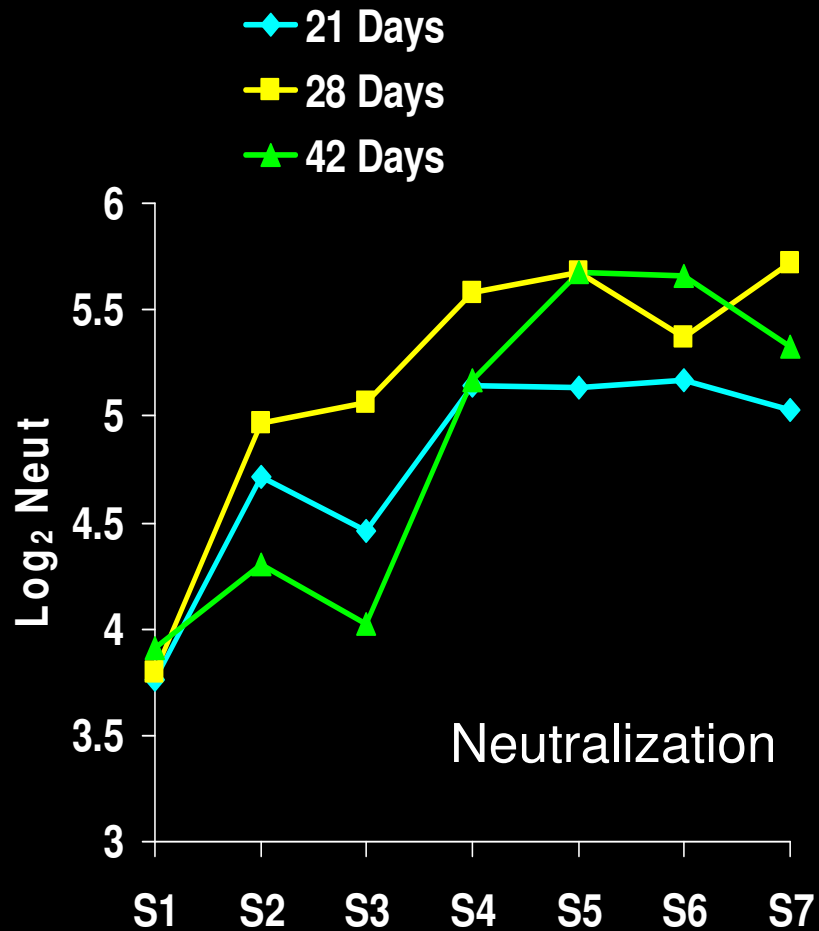
Dose	No. of subjects	156 ELISA		483 ELISA		Neutralization	
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
25 ug	29	42	55	33	42	3	24
45 ug	29	45	67	42	71	3	28
90 ug	30	73	87	50	75	21	57
90 ug/ 10 ug	30	63	63	83	75	30	43
Placebo	28	0	0	10	15	7	7

156 ELISA: increase of 0.8 OD units or more

483 ELISA: 2-fold or greater increase in unitage

Neutralization: 4-fold or greater increase to a titer of 1:80 or greater, confirmed with positive Western blot

Effect of interval



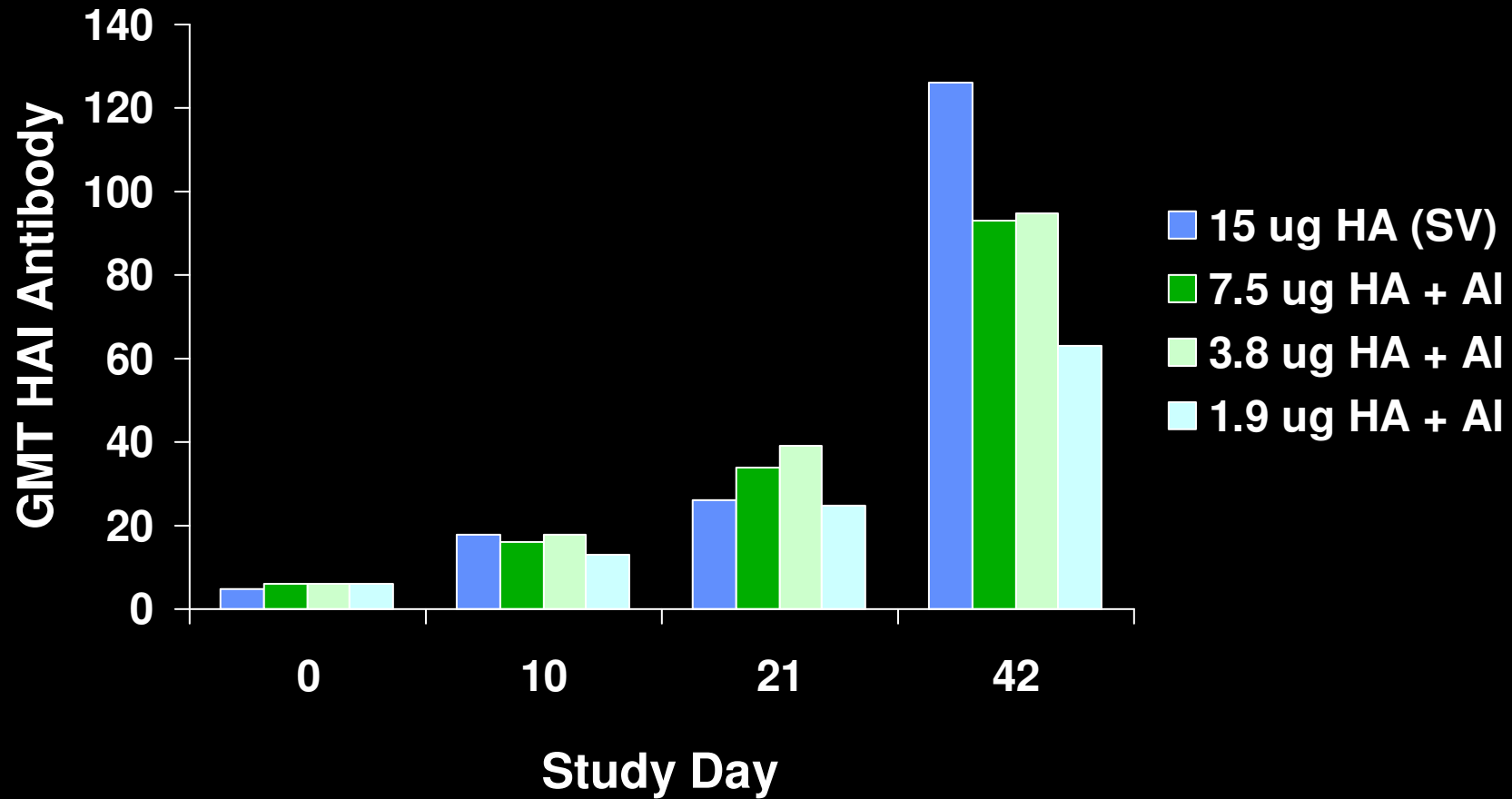
Critical issues [2]

- Development of validated high-throughput tests
- Interval does not seem to be important
 - Shorter intervals result in more rapid effect
 - Effects on duration of antibody are not known
- Expressed HA proteins are not a validated strategy for influenza control
 - Studies to demonstrate efficacy against conventional influenza

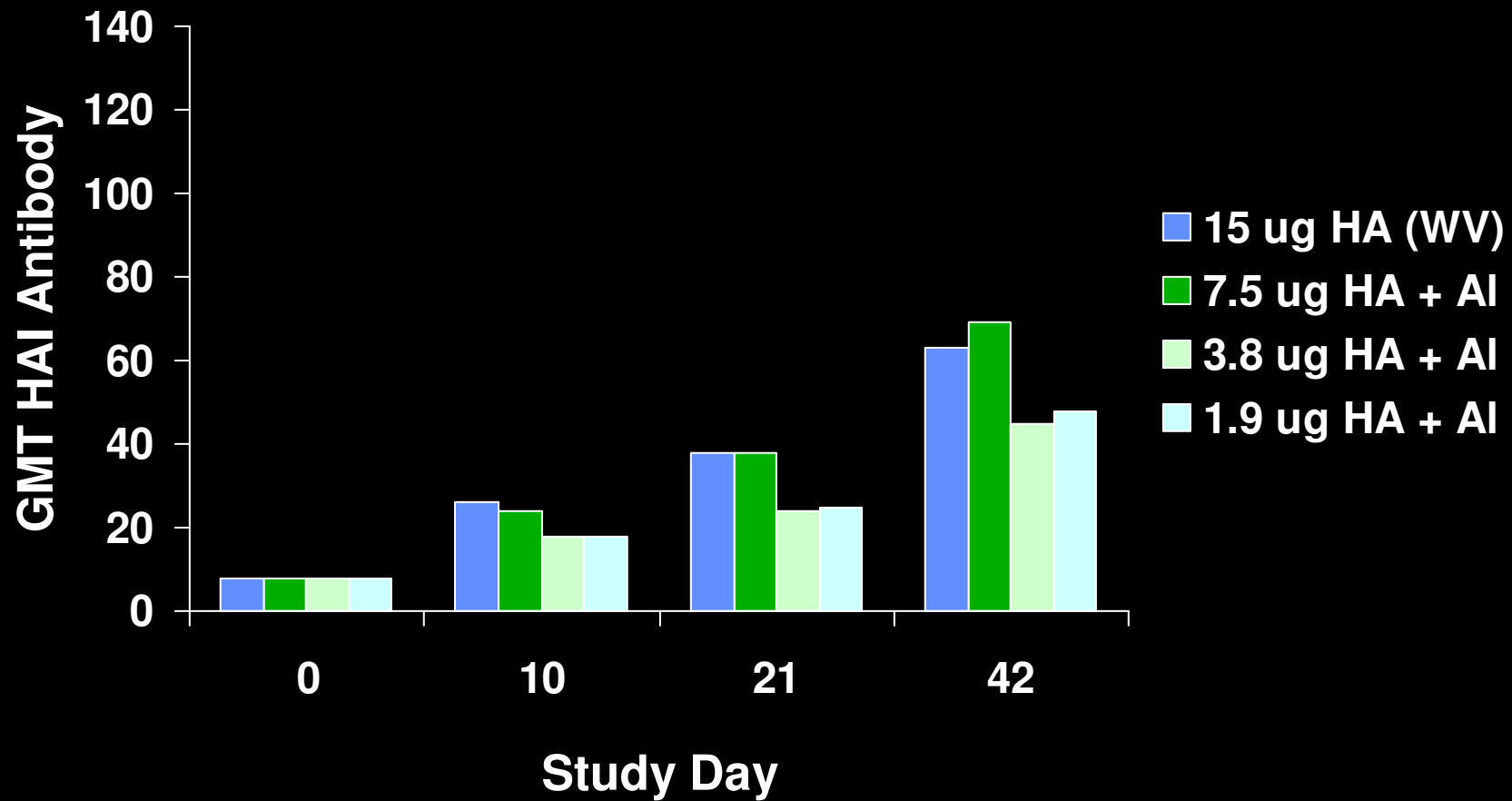
Critical issues [3]

- Is the H5 HA intrinsically less immunogenic?
 - Studies in humans are small and limited
 - Some experiences in animal models with less than expected results
 - Might be assay issue
 - Mechanism unclear

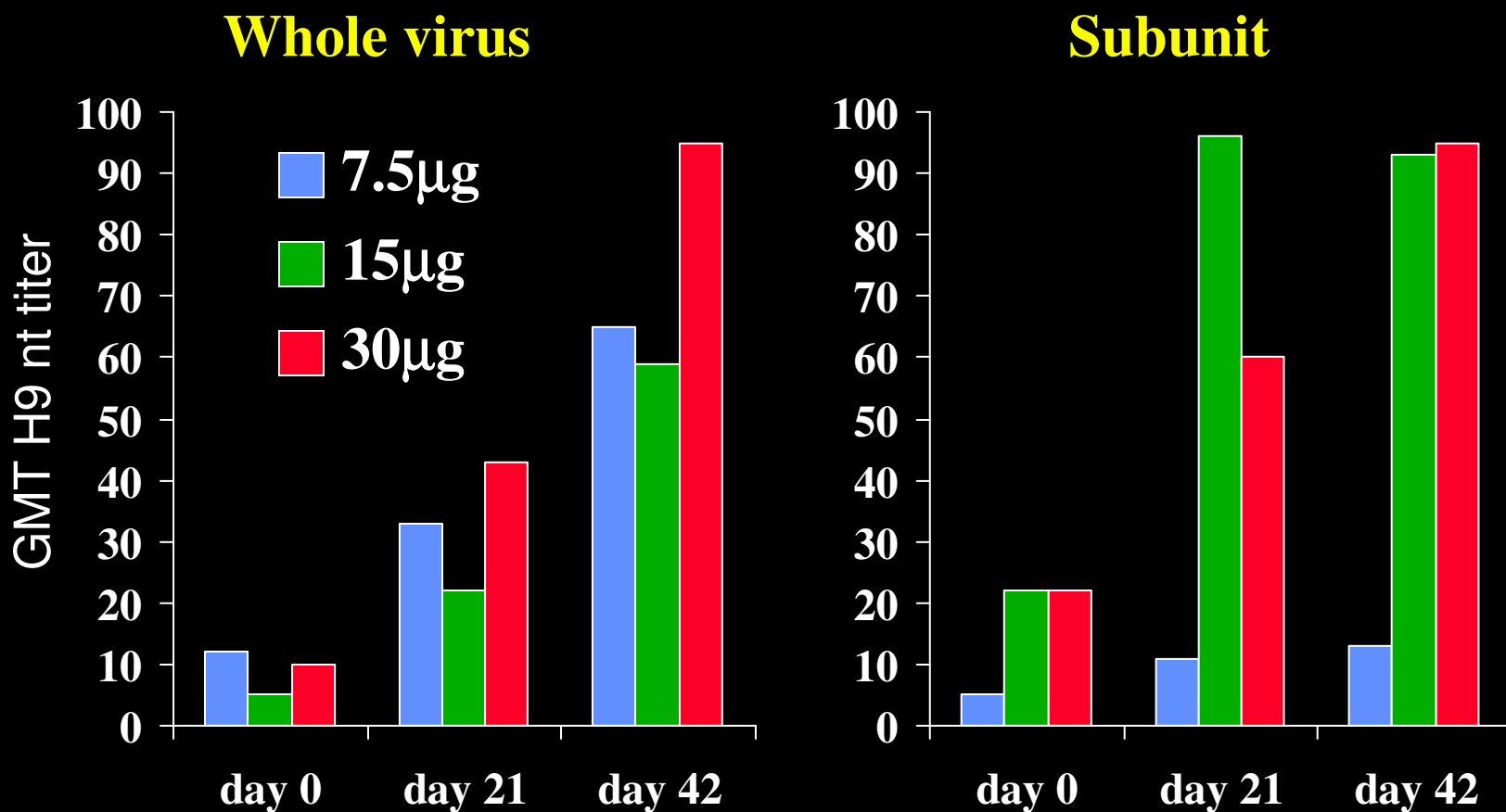
Evaluation of whole virus H2N2 vaccine with alum



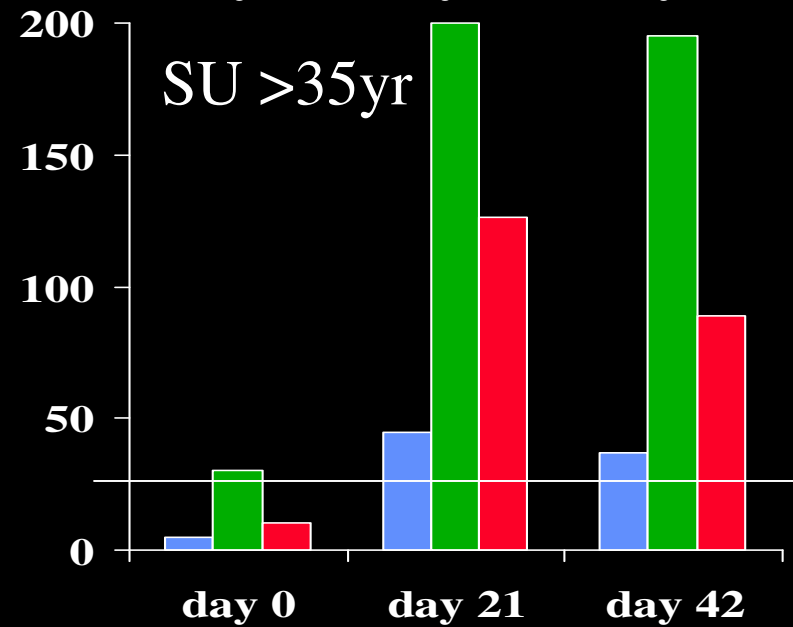
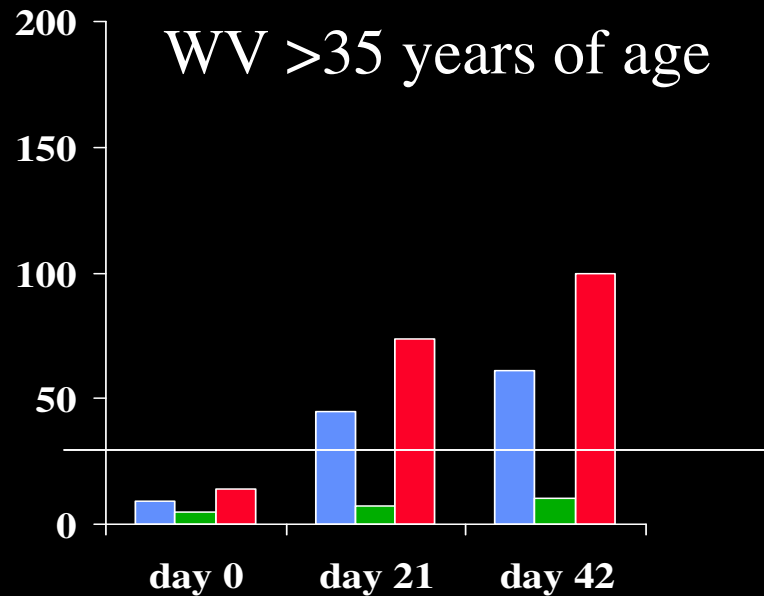
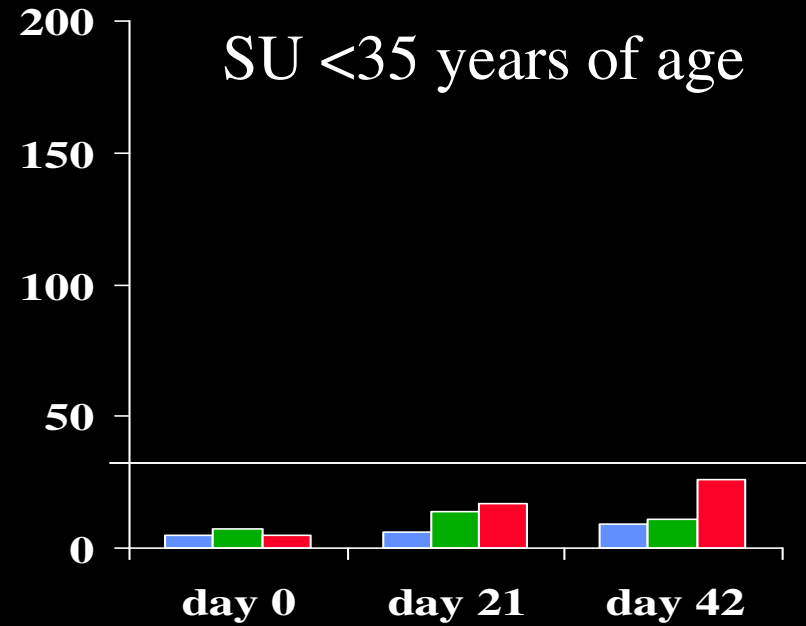
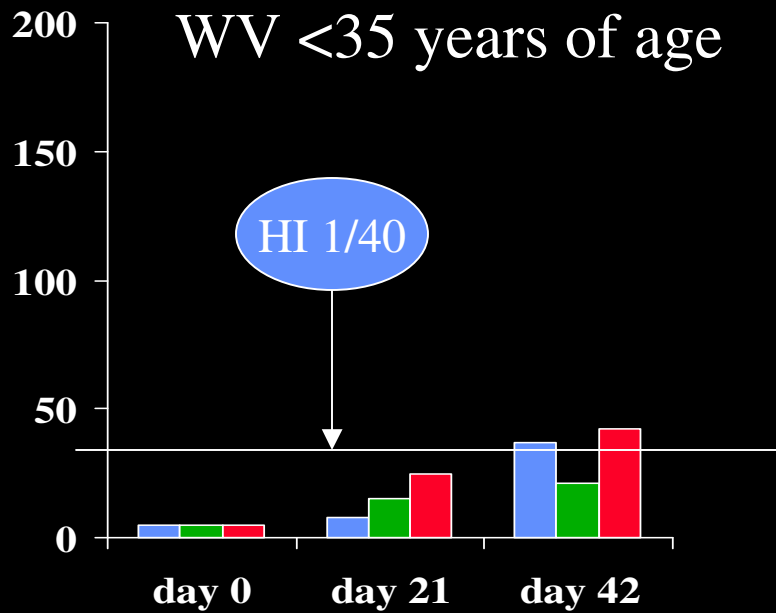
Evaluation of whole virus H9N2 vaccine with alum



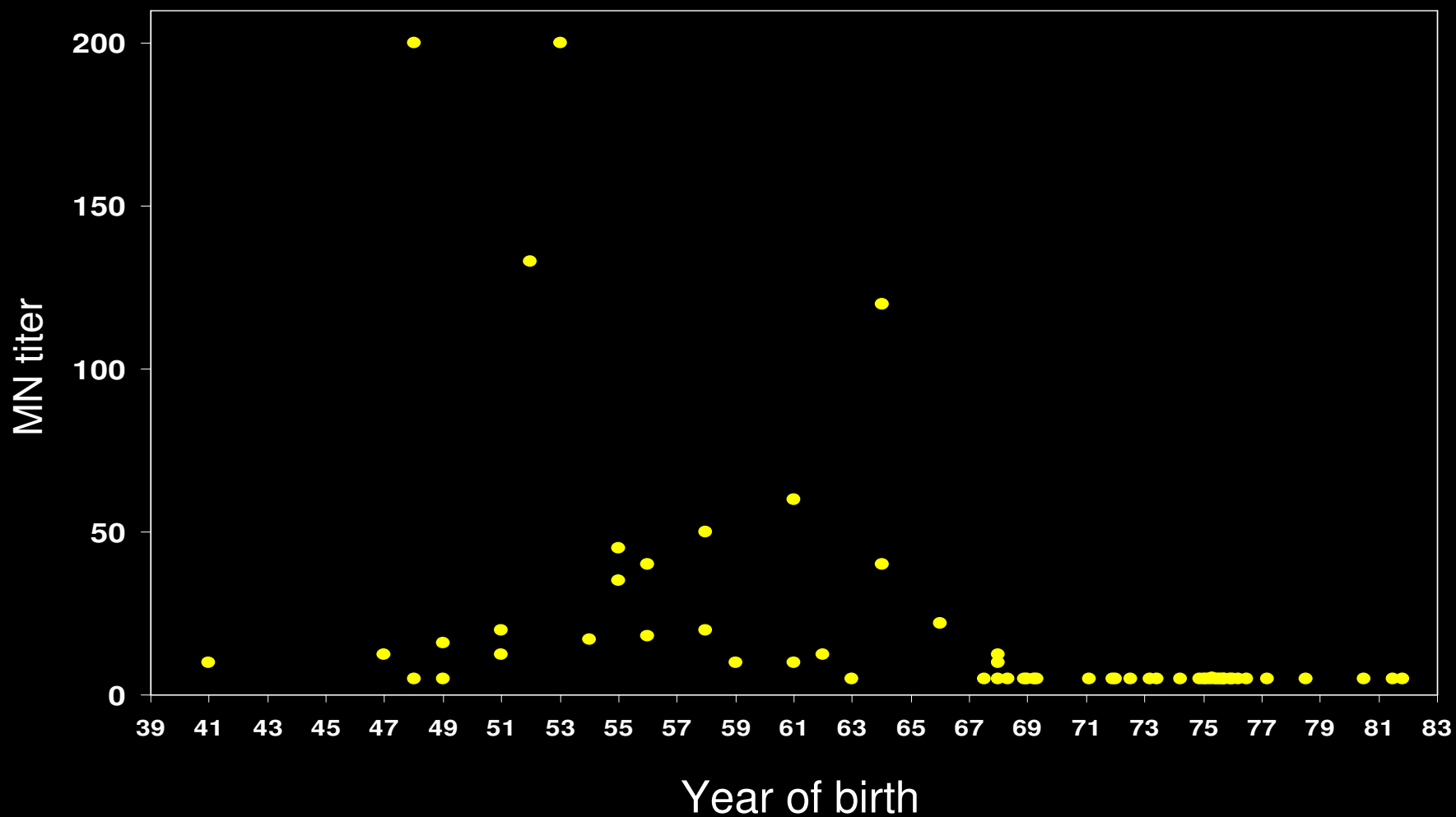
Geometric mean 50% MN (H9N2) antibody titres to WV and SU vaccines



Age effect on GMT HI responses



Effect of H2N2 exposure on H9N2 neutralizing antibody



Stephenson Lancet 362:1959, 2003

Critical issues [4]

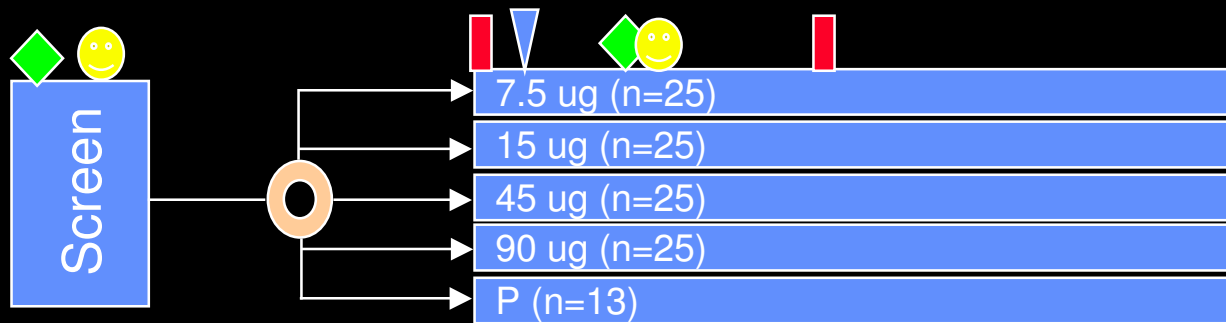
- Dose-sparing role of adjuvants should be evaluated by direct comparison of adjuvanted and non-adjuvanted vaccine
- Do potential production advantages of WV vaccine warrant further evaluation?
- Impact of prior exposure to related HA should be considered
- Optimal testing strategy and results may differ between subtypes

Current H5 vaccine candidates

- Seed virus reverse genetically engineered A/Vietnam
- Manufactured by Sanofi Aventis and Chiron
- Subunit vaccine
- Represent new strain manufactured with licensed manufacturing

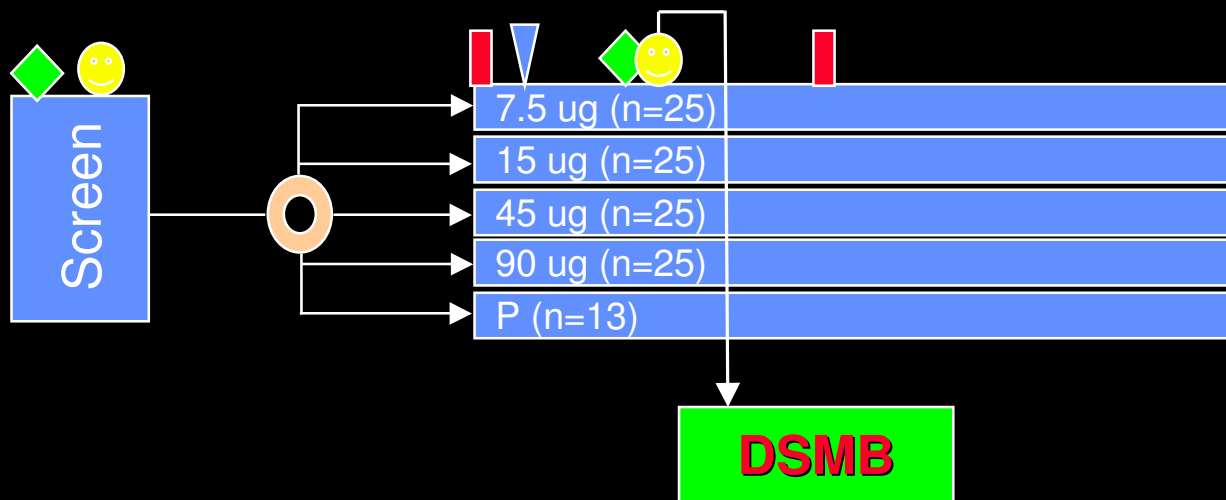
Development plan – H5N1

◆ Clinical evaluation 😊 Safety labs ▼ Vaccine ■ Immunogenicity



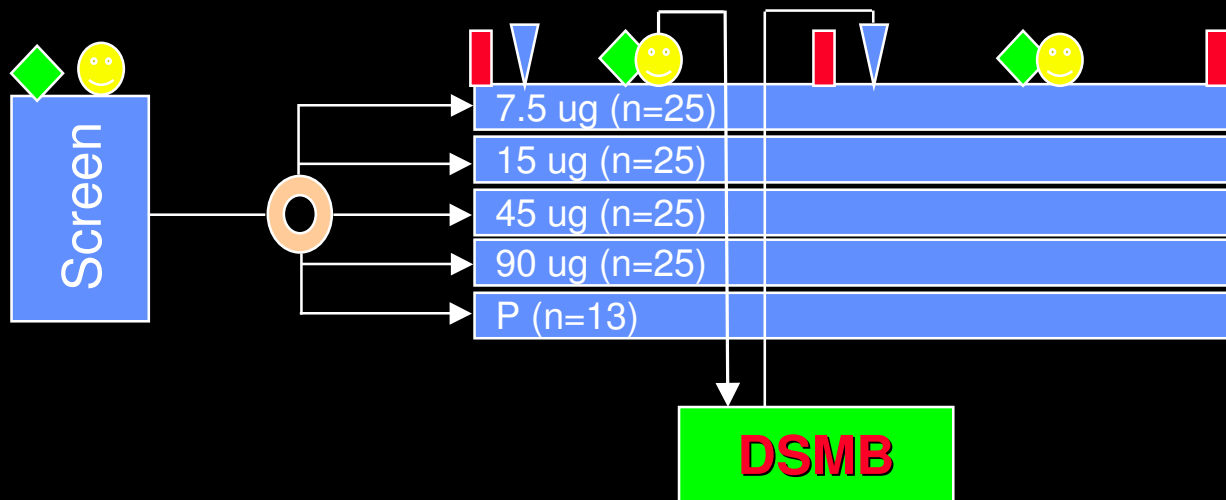
Development plan – H5N1

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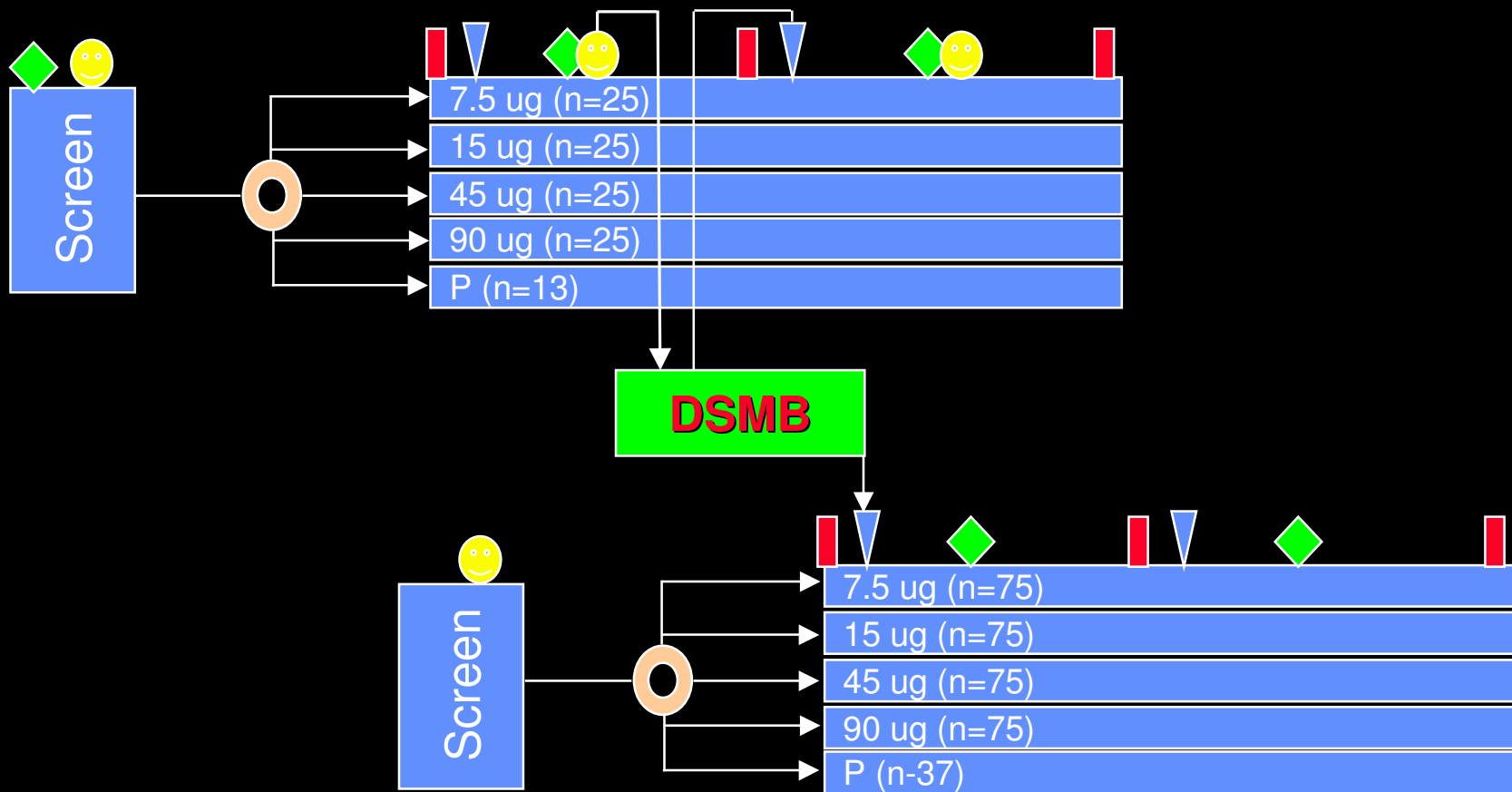
Development plan – H5N1

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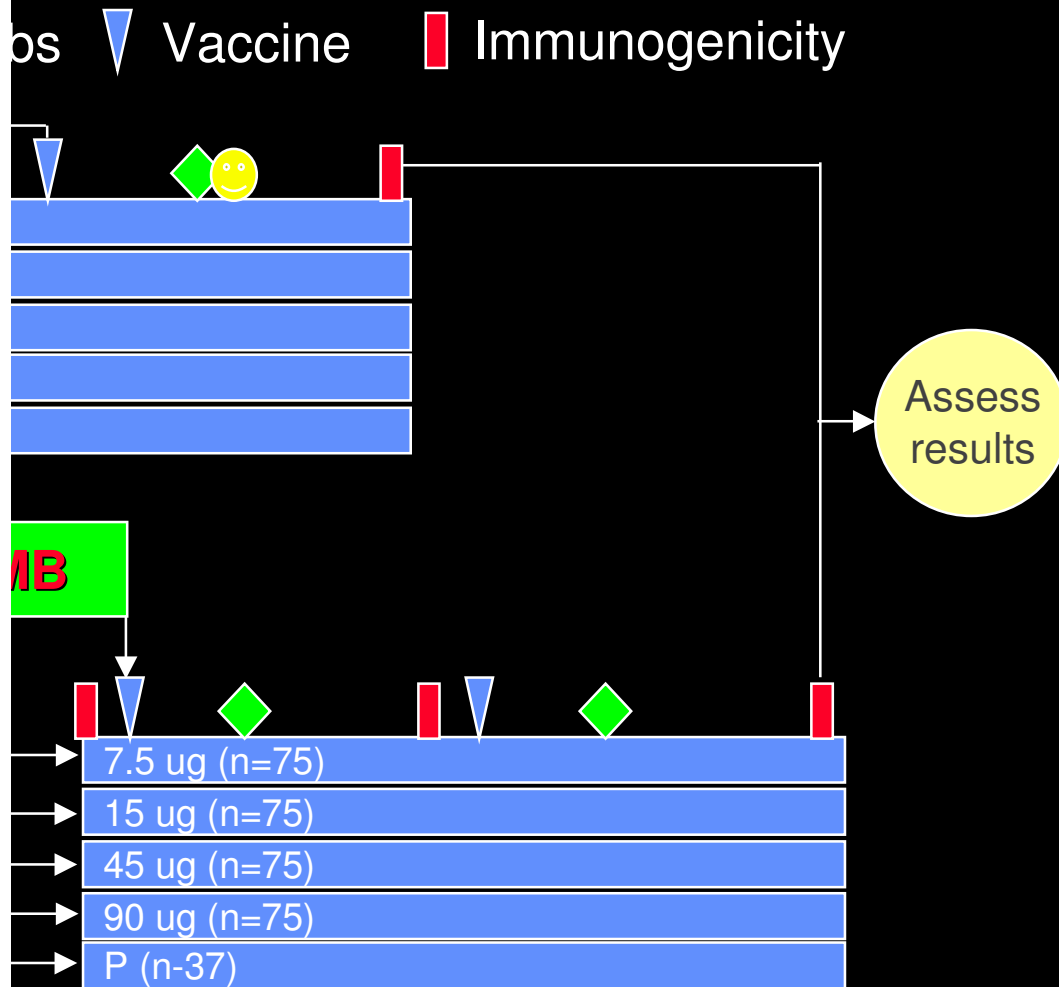


Development plan – H5N1

◆ Clinical evaluation ☺ Safety labs ▼ Vaccine ■ Immunogenicity

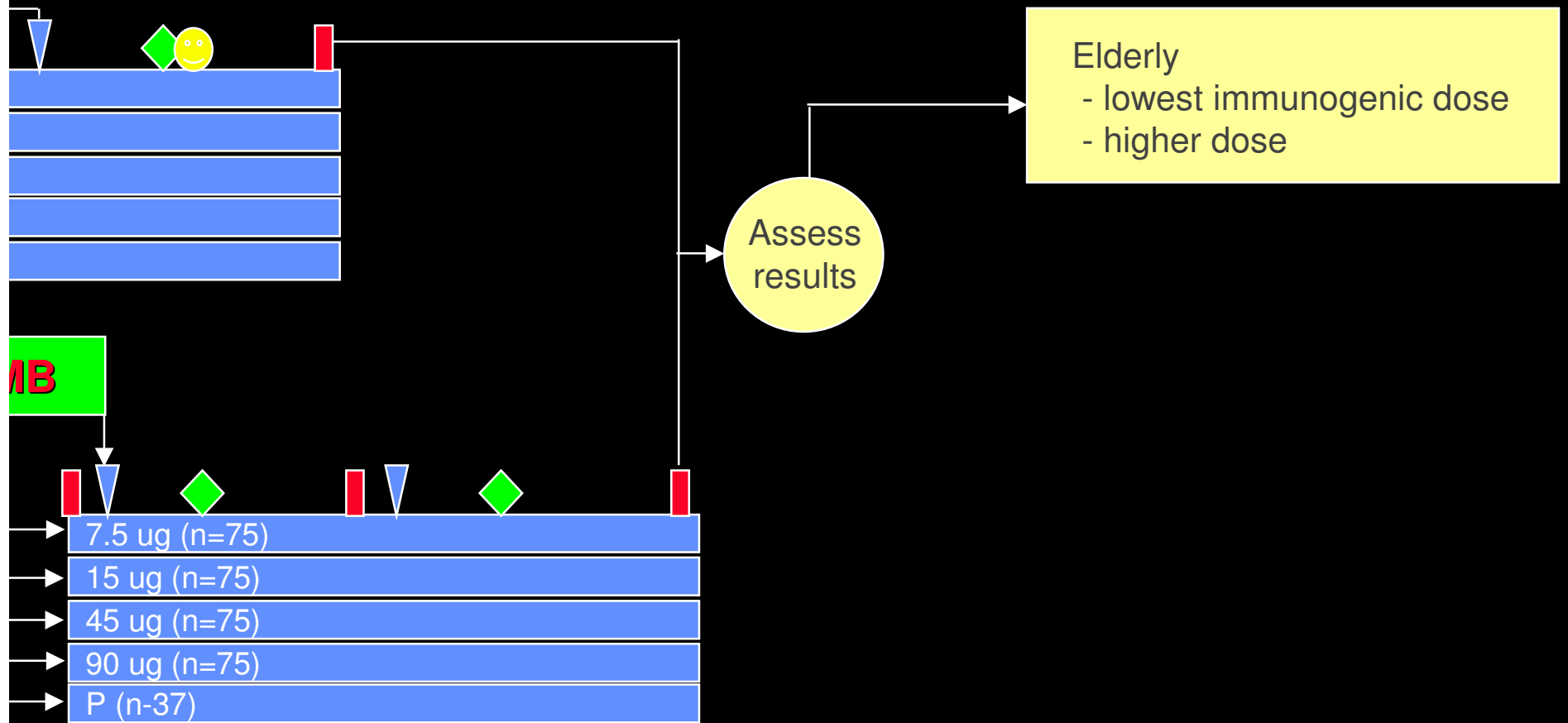


Development plan – H5N1



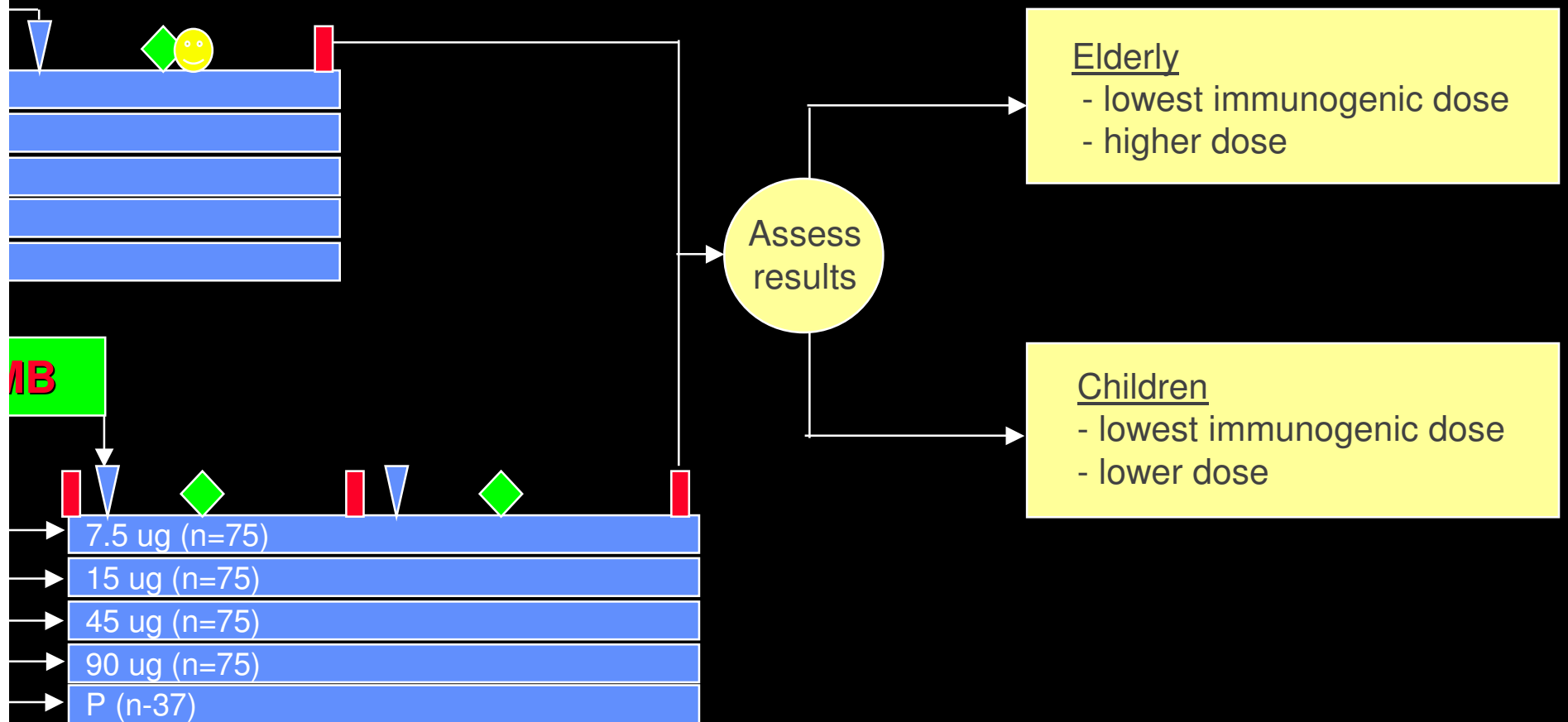
Development plan – H5N1

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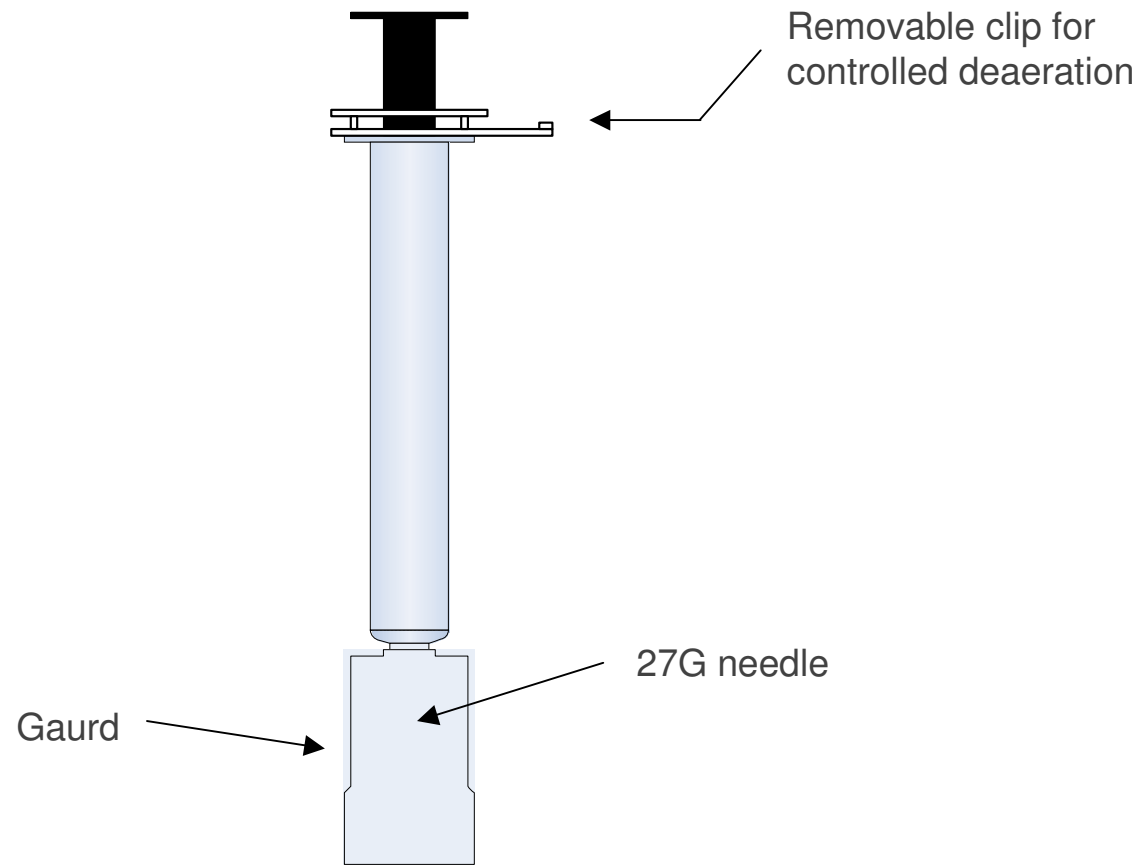
Evaluation of inactivated vaccines: Objectives

- Determine the lowest dose resulting in a potentially protective immune response in the greatest proportion of people with an acceptable level of safety.
- Gain experience with the logistical issues involved in producing a pandemic vaccine

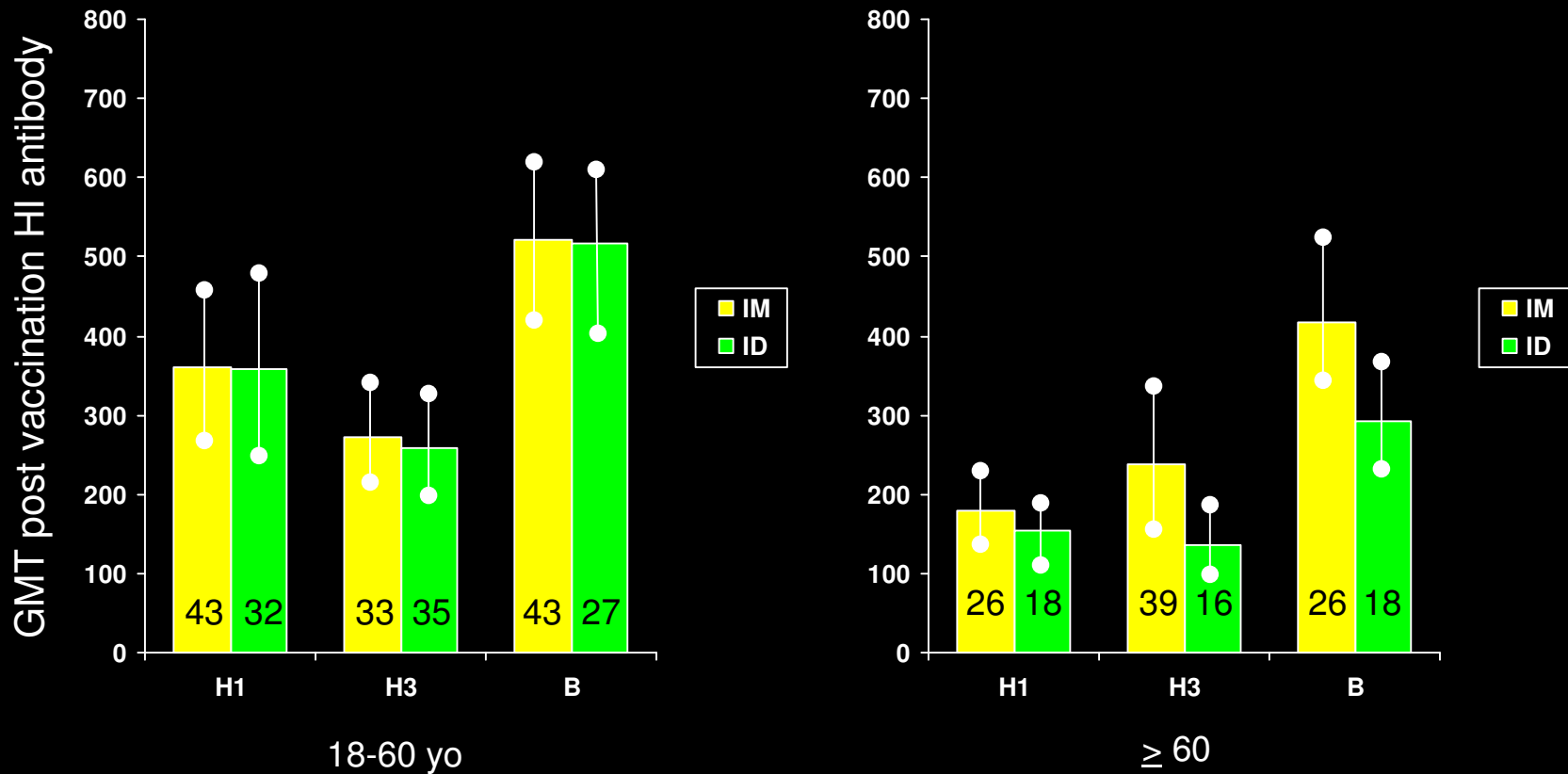
Find the lowest dose

- Whole virus vs. subunit
- Egg grown vs. cell culture or other substrates
- Adjuvants
 - Alum and MF59 are currently licensed
- Schedule and route of administration
 - Intradermal, transcutaneous, intranasal

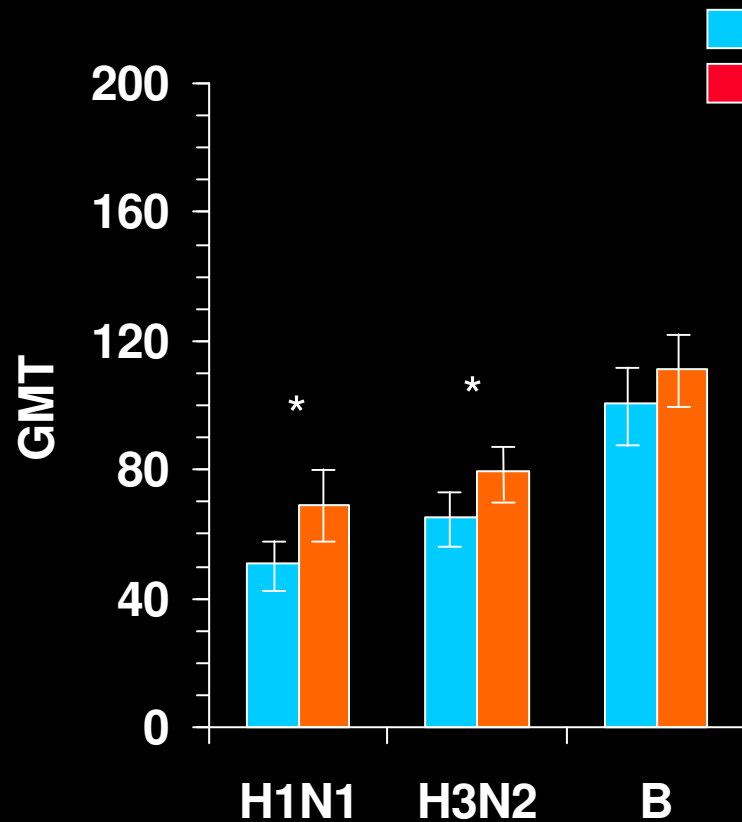
Device for intradermal vaccination



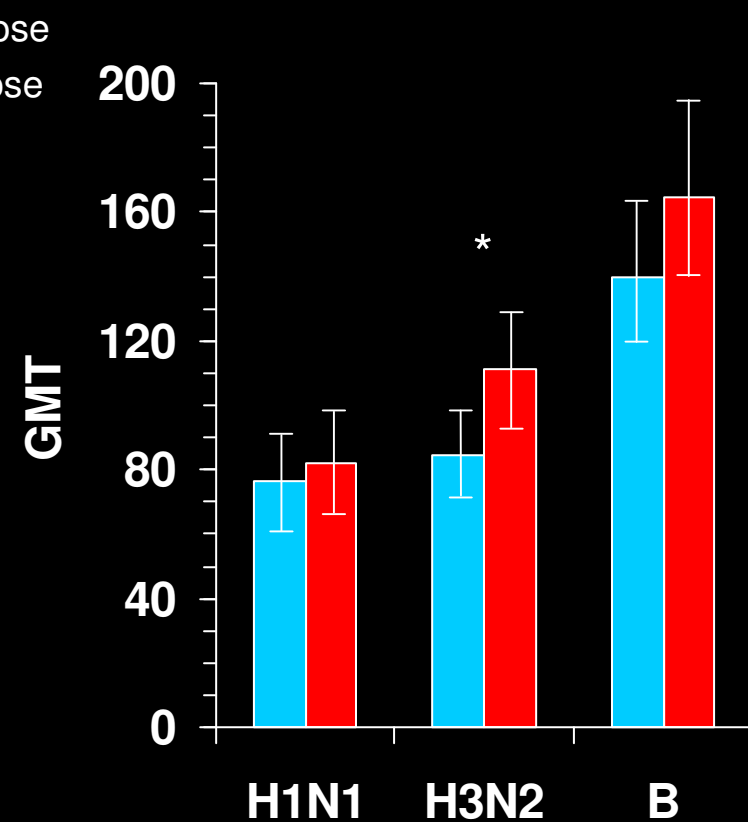
Intradermal vaccination: post vaccination GMT and response rate (%)



Responses to 15 ug or 7.5 ug IM in adults



Subjects with history of vaccination in the last three years



Subjects with no history of previous vaccination in the last three years

Determine the immune response

- Assays: HI assay insensitive for avian viruses
 - Neutralization
 - SRH
- Protective levels not defined
- Role of mechanisms other than serum antibody are unknown

Protect the greatest proportion of people

- Majority of studies will be done in healthy adults
- Safety and immunogenicity may be different in children
- Evaluation of priming strategies
- Need to evaluate pandemic vaccines in groups that respond poorly to conventional vaccine

Acceptable level of safety

- Defining acceptable safety parameters
- Considerations of sample size related to detection rates for rare events
- Safety considerations may favor conventional (licensed) approaches
- Tolerability may be different in different populations

Evaluation of live attenuated vaccines (CAIV)

- Highly immunogenic in susceptible populations
 - Critical need to define correlates of immunity
- Potential use of low doses
 - Studies should evaluate full range
- Induction of mucosal immunity might reduce transmission
 - Development of challenge models

Evaluation of live attenuated vaccines (CAIV)

- Potential cross protection
 - Evaluate responses to range of antigenic variants
- Not licensed in all populations
 - Critical need to expand safety database
 - Define correlates of immunity that could be extended to elderly
- Concerns regarding transmission and reassortment
 - Clearly define conditions of deployment, expected shedding patterns, and biologic behavior of reassortants

Experimental Approaches

- Nasal inactivated vaccines
- Cross protective peptides/epitopes
- Virus-like particles
- Alternative live vaccines
- Vectored approaches
- DNA Vaccines

Considerations for alternate approaches

- Validation in clinical studies
- Extensive safety evaluation
- Specific markers of efficacy
- Individualized development strategy
- Need for early determination of potential advantages against conventional approaches