

# CHALLENGE STUDIES IN HUMANS

Potential use in determining correlates of immunity

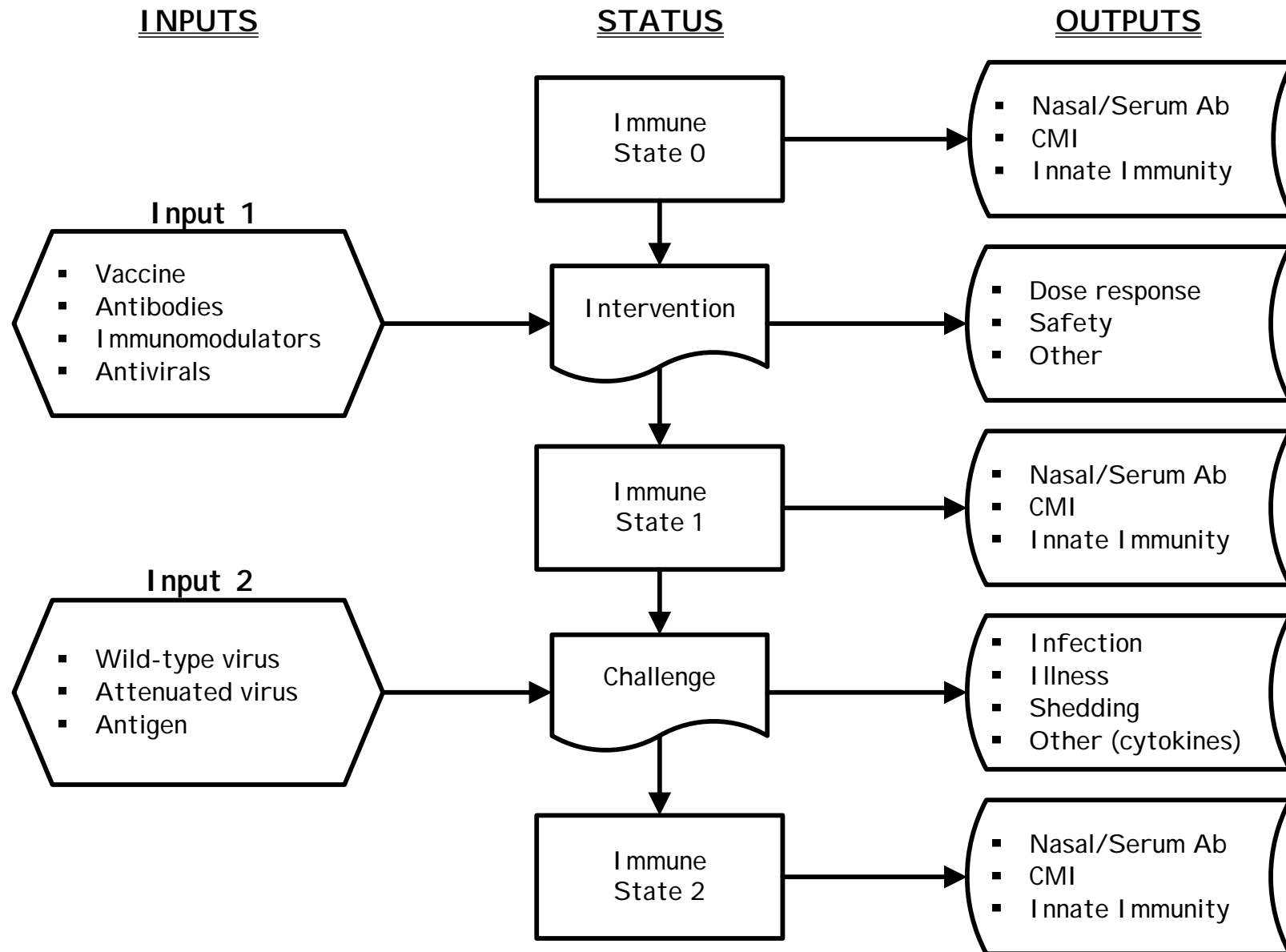
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# Potential utility of challenge models of influenza in humans

- Establishment of etiology
- Assessment of the relative attenuation of candidate live vaccines
- Proof of concept studies of antiviral agents, vaccines, immunomodulators
- Detailed measurements of the kinetics of immune or other responses
- Development of correlates of protection

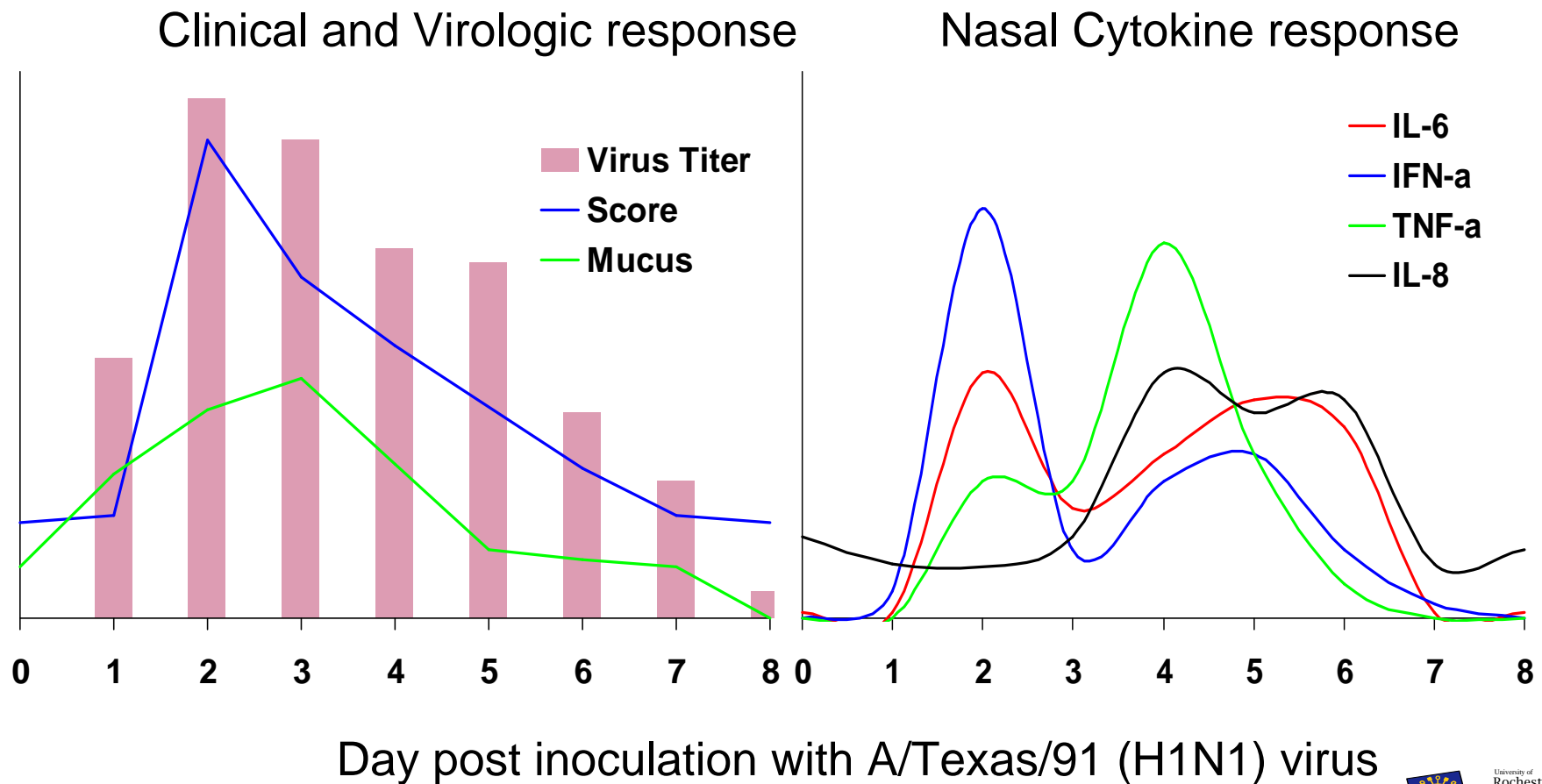
# Basic flow diagram of a typical experiment in the human challenge model



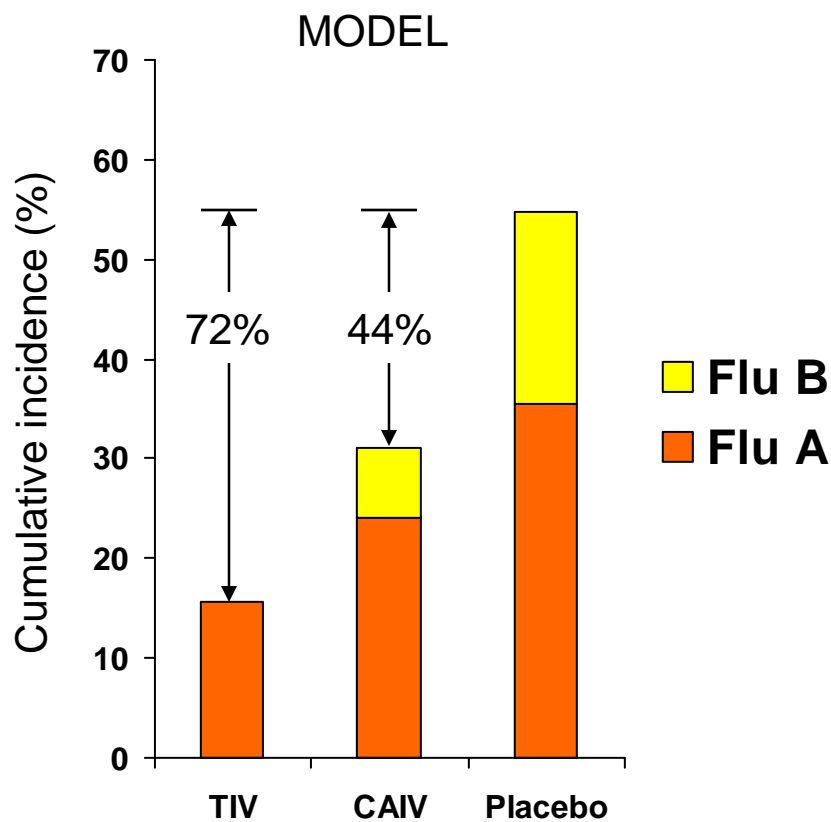
# Considerations in the experimental infection model of influenza

- Immune state 0
  - May be necessary to screen subjects for susceptibility
  - Serum antibody (HAI, Nt, NAI) have been used
- Input 2 (challenge intervention)
  - Validity for purposes of the model
  - Dose (50% human infectious dose)
  - Availability
- Output
  - Model may be intended to induce illness
  - Clinical outputs are both **Objective** (viral titers, cytokine levels, physiologic measurements) and **Subjective** (symptoms)
  - Immune outputs may or may not be well-validated

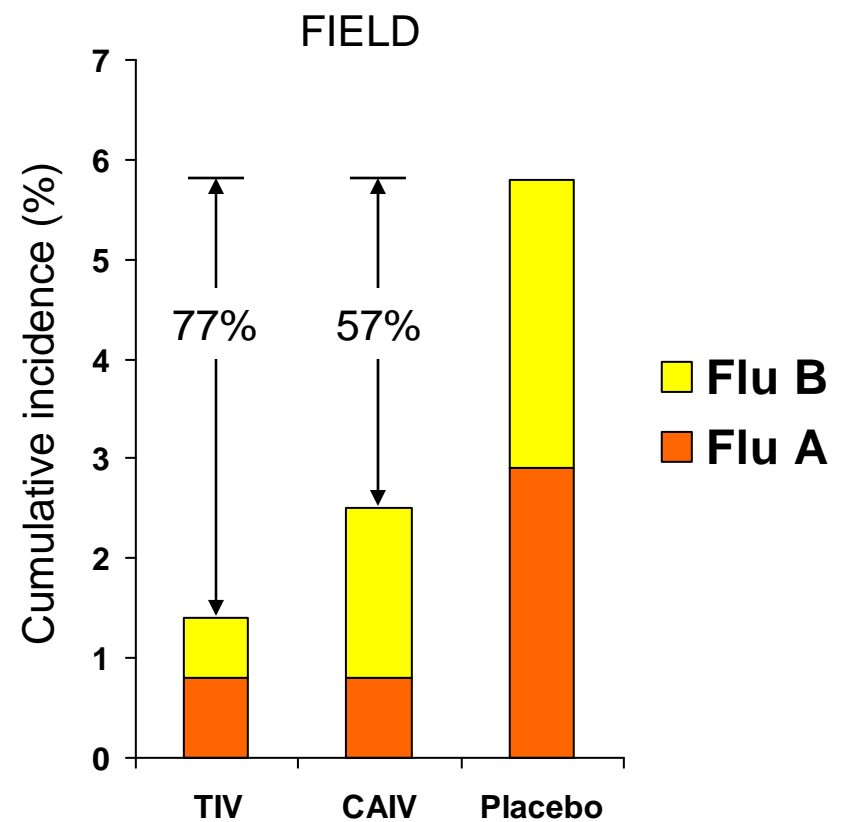
# Response to intranasal inoculation with wt influenza A virus



# Relationship between results in the challenge model and in the field

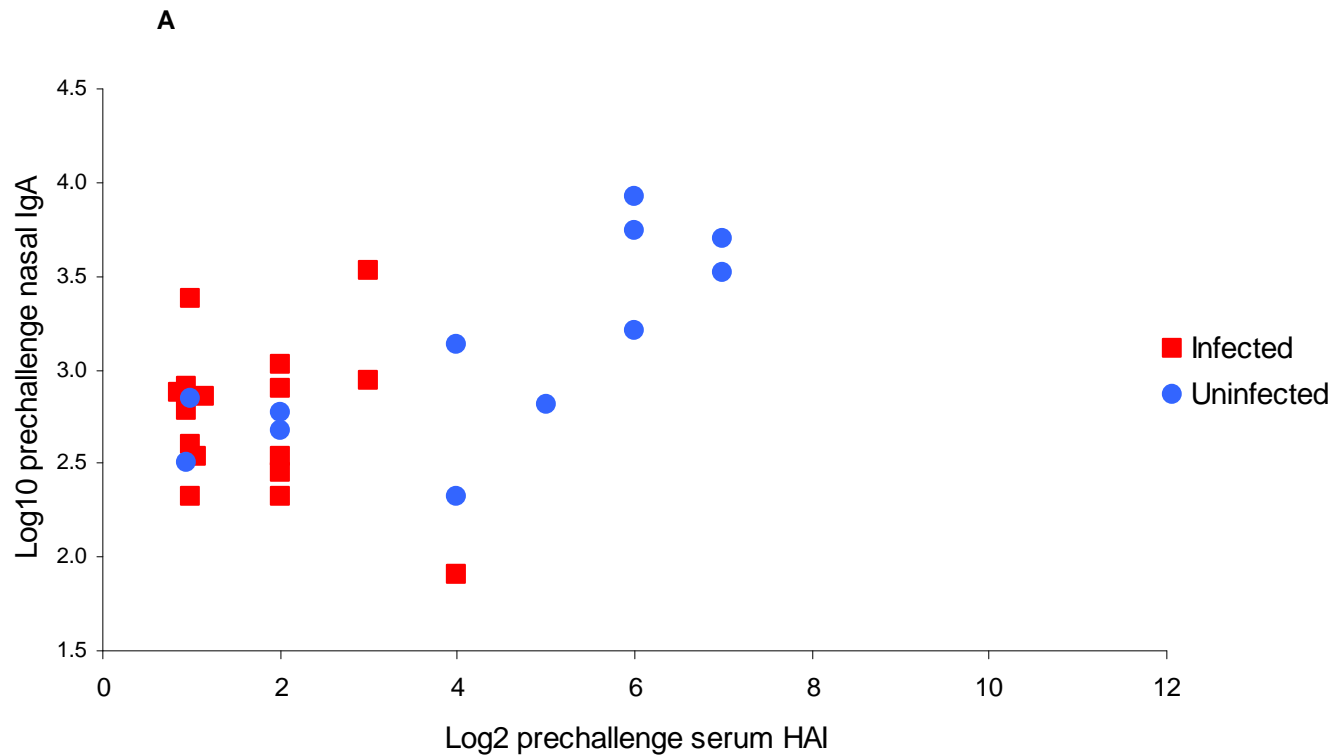


Treanor, et al Vaccine 18:899, 2000



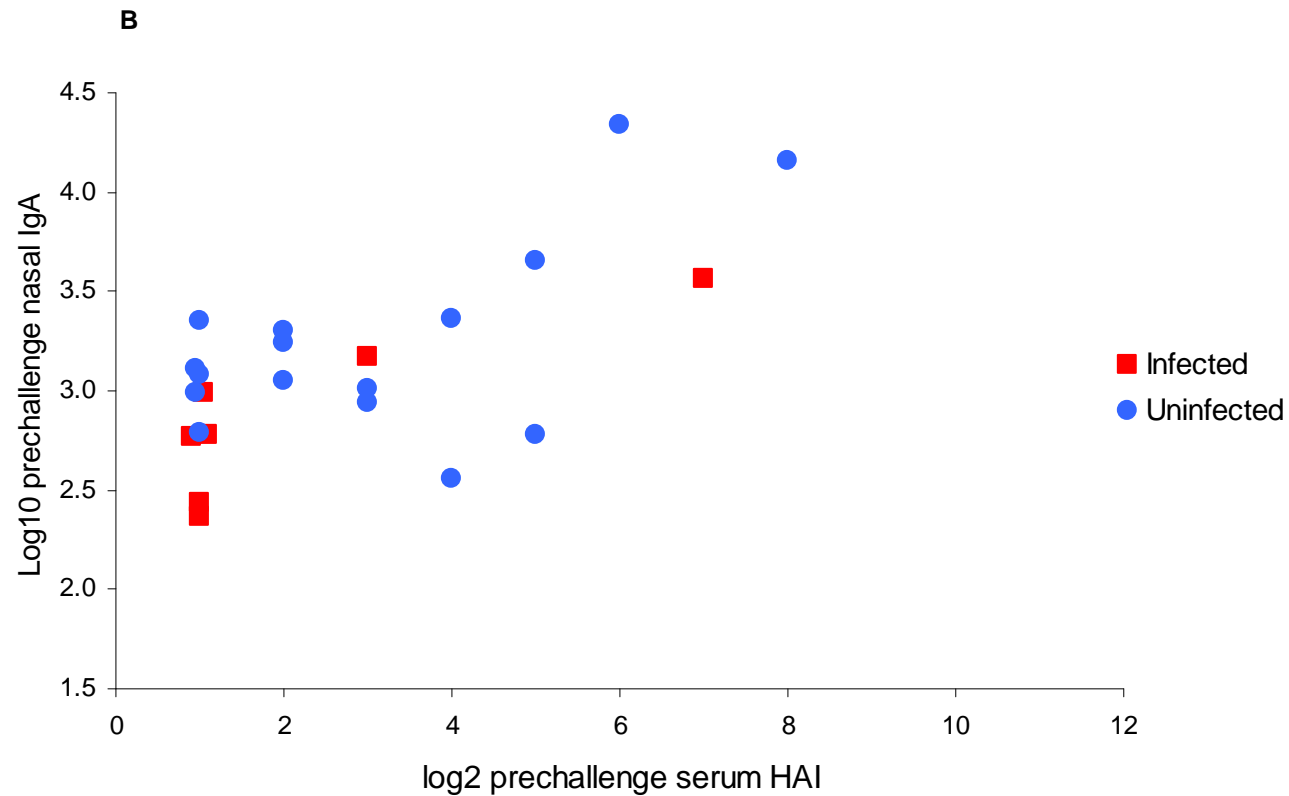
Ohmit, et al. NEJM 355:2513, 2006

## Relationship between prechallenge antibody and infection in placebo recipients



- A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2), B/Panama/9/90
- Challenge dose  $10^7$  TCID<sub>50</sub>

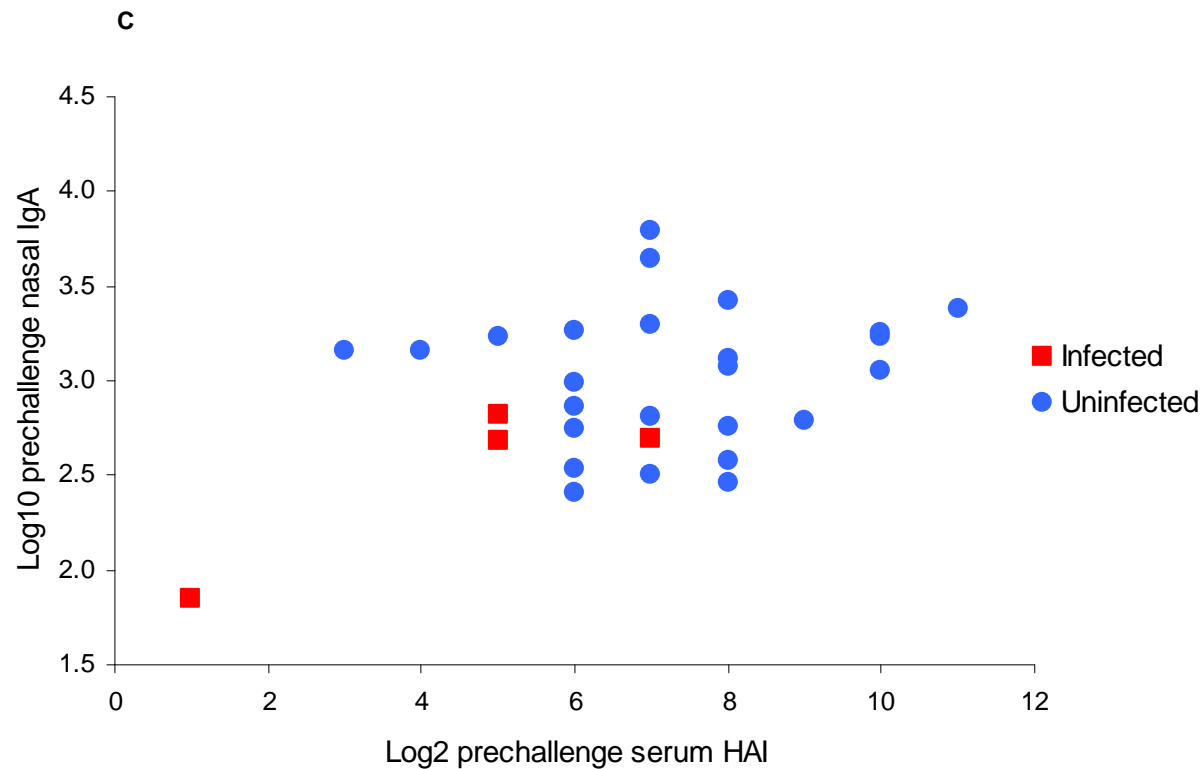
## Relationship between post vaccination (pre-challenge) antibody and infection in recipients of CAIV



- A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2), B/Panama/9/90
- Challenge dose  $10^7$  TCID<sub>50</sub>



## Relationship between post vaccination (pre-challenge) antibody and infection in recipients of TIV



- A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2), B/Panama/9/90
- Challenge dose  $10^7$  TCID<sub>50</sub>

# Relationship between prechallenge antibody and infection (virus or ab)

Pre-challenge antibody status		No. infected/Total in those challenged with			
Serum HAI	Nasal HA-specific IgA	H1	H3	B	Any
Neg	Neg	8/10	4/5	6/10	18/25 (72%)
Neg	Pos	1/6	2/4	1/2	4/12 (33%)
Pos	Neg	1/3	3/7	0/9	4/19 (21%)
Pos	Pos	0/10	1/8	0/6	1/24 (4%)

Infected is any virus shedding and/or 4-fold antibody response

HAI neg is  $\leq 1:8$

IgA neg is  $<1000$  "units" except for B which is 500 units

- A/Texas/36/91 (H1N1), A/Shangdong/9/93 (H3N2), B/Panama/9/90
- Challenge dose  $10^7$  TCID<sub>50</sub>

# Relationship between antibody and protection against *wt* challenge in adults

Source of immunity	Protection against	Serum		Nasal	
		NAI	HAI	HA Fab	HA IgA
Naturally acquired infection	Infection	<.01	NS	NS	<.05
	Illness	<.05	NS	NS	<.025
Inactivated vaccine	Infection	<.03	<.001	NS	NS
	Illness	<.003	NS	<.005	NS
Live vaccine	Infection	<.003	NS	<.025	<.025
	Illness	NS	NS	NS	NS

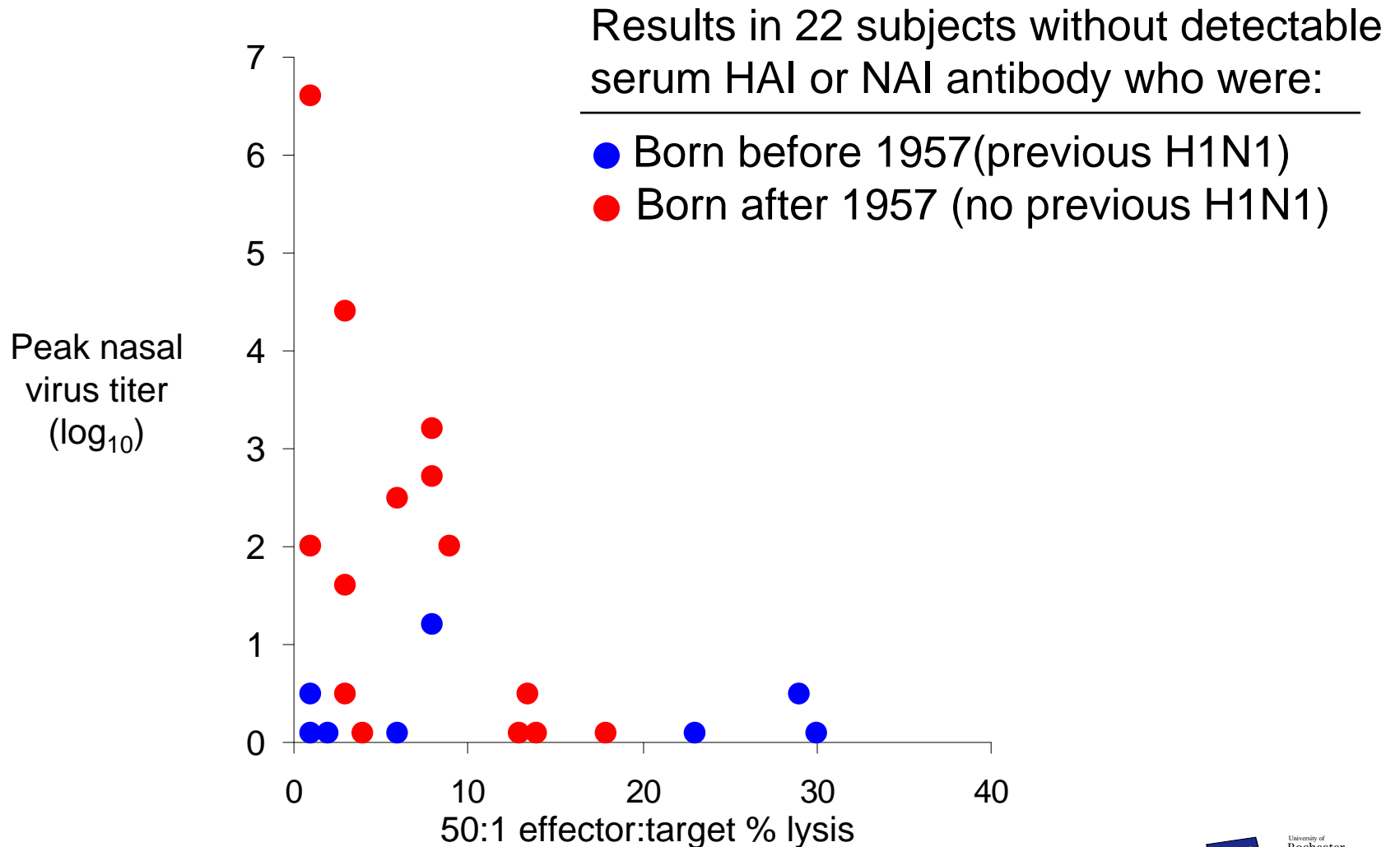
- A/Washington/897/80 (H3N2)  $10^{6.0}$  TCID<sub>50</sub>
- A/California/10/78 (H1N1)  $10^{4.0}$  TCID<sub>50</sub>

Clements et al *J Clin Micro* 24:157, 1986

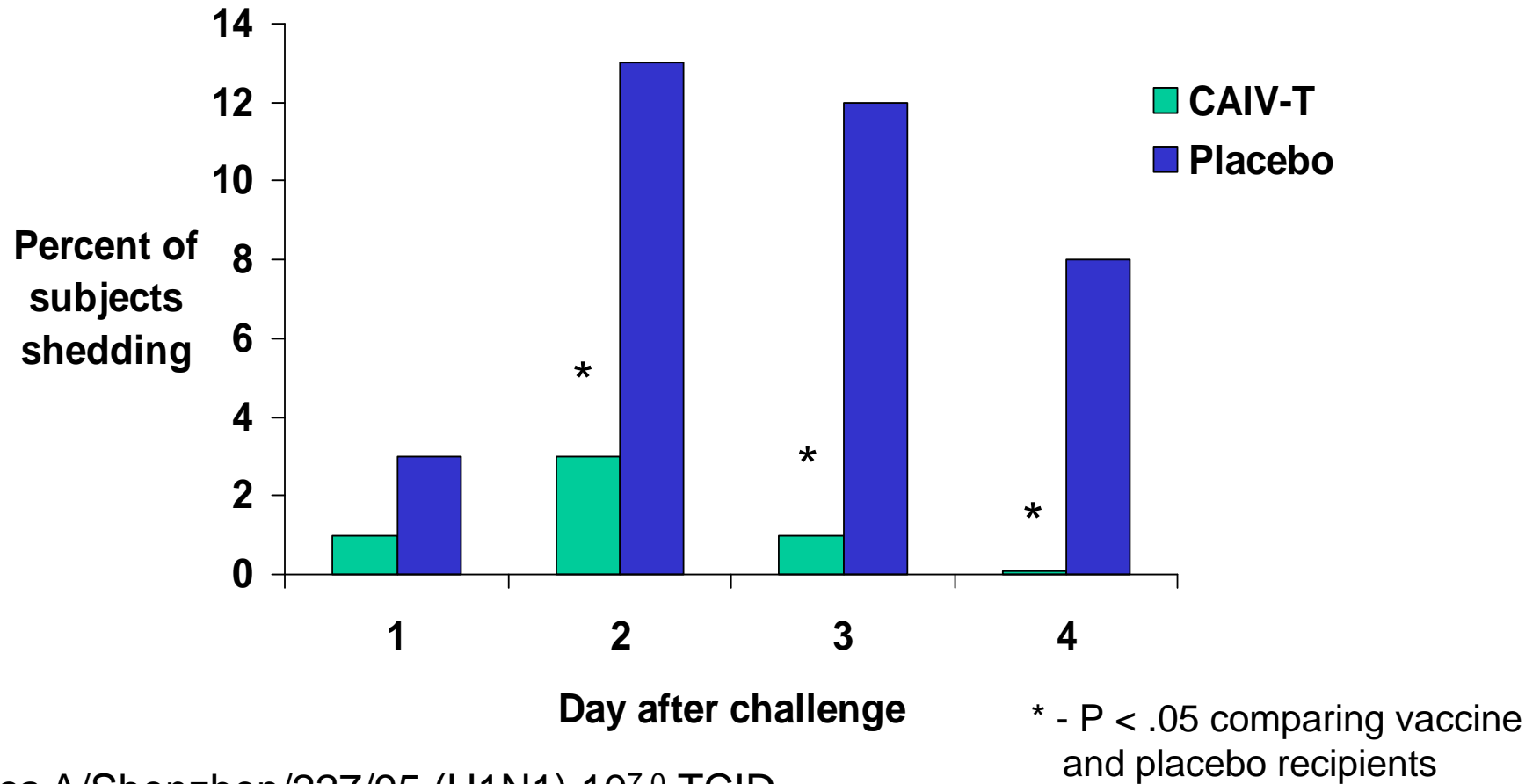


# Effect of CTL in the absence of antibody on response to viral challenge\* in adults

\* A/Munich/1/79 (H1N1)  $10^{5.0}$  EID<sub>50</sub>

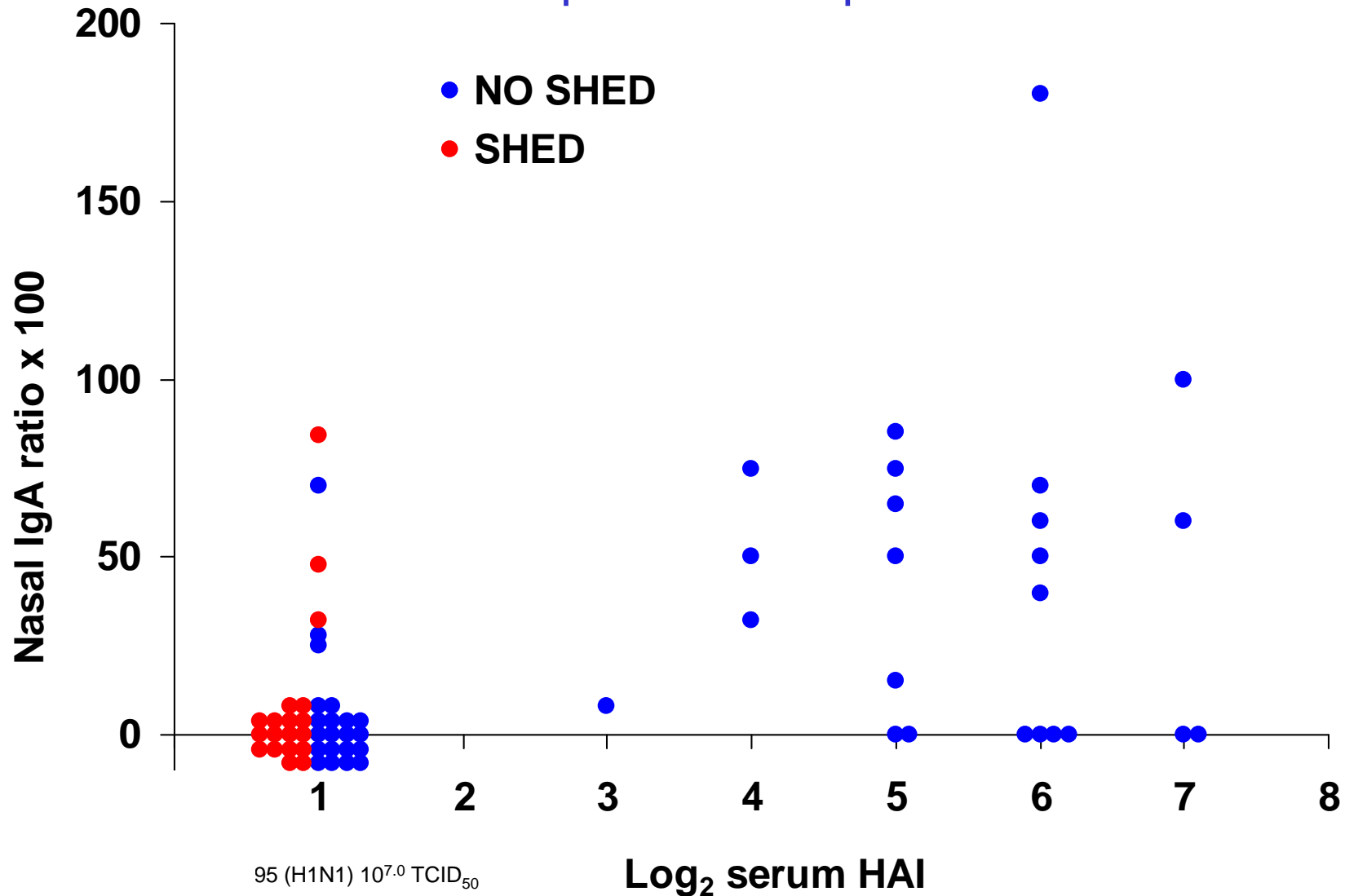


# Previous vaccination protects against viral shedding after *ca* H1N1<sup>†</sup> challenge

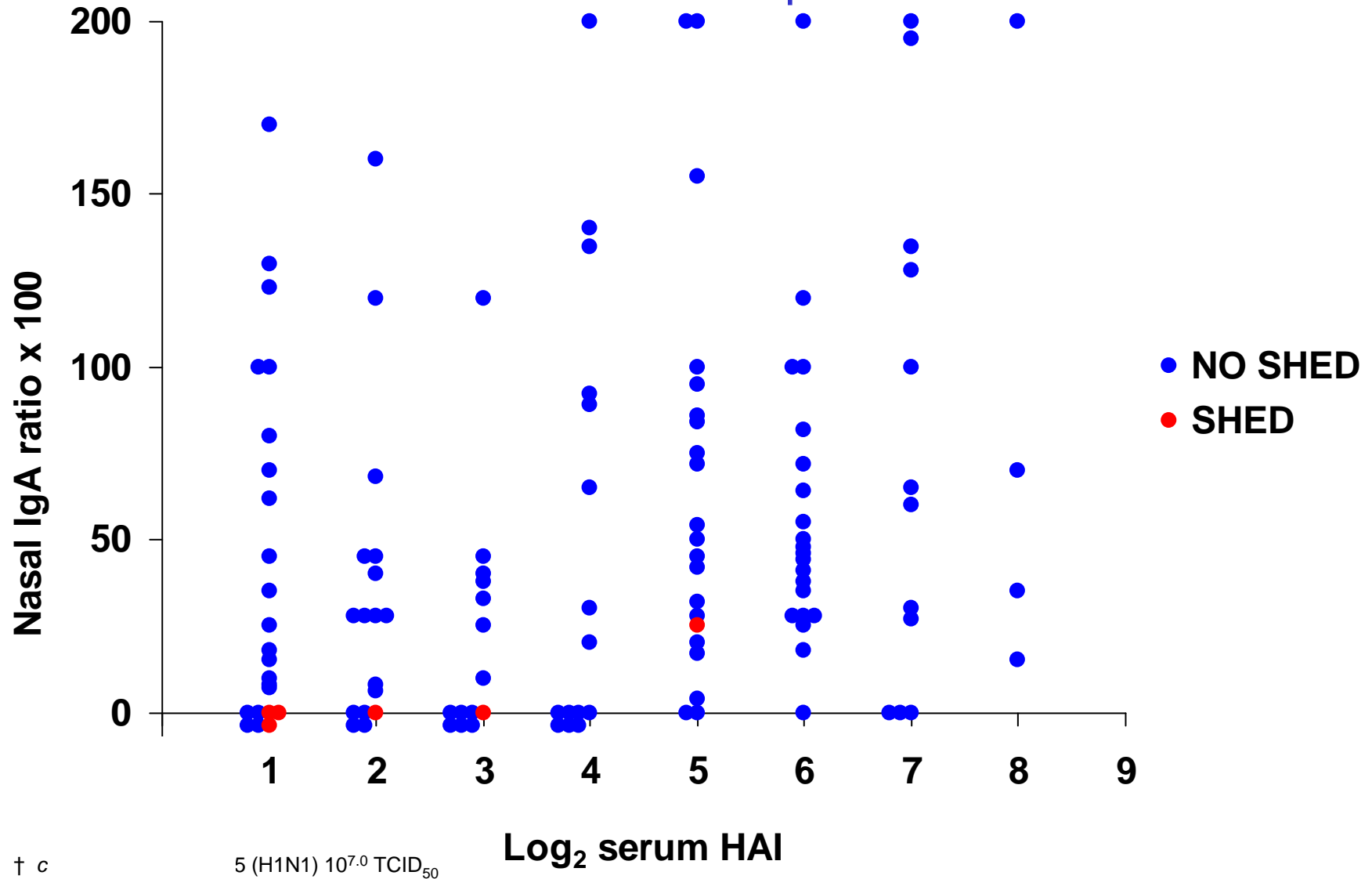


† *ca* A/Shenzhen/227/95 (H1N1) 10<sup>7.0</sup> TCID<sub>50</sub>

# Relationship between pre-challenge antibody and shedding in placebo recipients



# Relationship between pre-challenge antibody and shedding in vaccine recipients



† c

5 (H1N1) 10<sup>7.0</sup> TCID<sub>50</sub>

Log<sub>2</sub> serum HAI

# Human challenge studies and correlates of protection against influenza viruses with pandemic potential

- Challenge studies have been useful for assessing correlates for seasonal influenza
- Use for pandemic influenza would require an appropriate live, attenuated vaccine with properties of:
  - Sufficient infectivity and replication to make comparisons
  - Acceptable safety profile
- If available, such a model could be used to:
  - Validate some concepts related to antibody and protection
  - Explore novel immune mechanisms
- Significant limitations exist regarding the fidelity of an attenuated challenge model to natural infection