

**Repeated mucosal exposures of NHPs using lower  
SIV/SHIV challenge doses to study vaccine-elicited  
protection from transmission**

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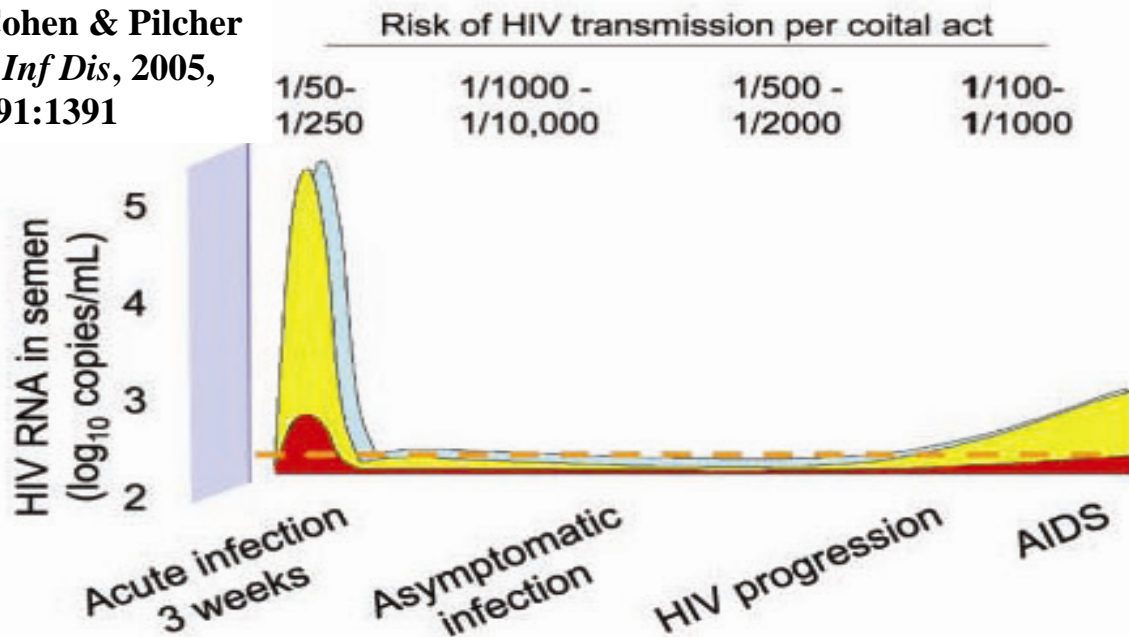
**Division of HIV/AIDS Prevention**

**National Center for AIDS, STD, and TB Prevention**

**Centers for Disease Control and Prevention**

# Repeated mucosal challenge of non-human primates

Adapted from:  
Cohen & Pilcher  
*J Inf Dis*, 2005,  
191:1391



**As a model for mucosal transmission, can we develop a repeated-exposure approach in NHP?**

- **More analogous to human mucosal exposures**
- **Physiologic, realistic inoculum dose**

## Repeated mucosal challenge of non-human primates

### Mucosal challenge parameters

- **Animals and route:** Female and male Rhesus and Pig-tailed macaques; vaginal and rectal exposures
- **Challenge virus and inoculum:**  
SHIV-SF162p3 ( $3.5 \times 10^5$  vRNA copies per exposure)  
SIVmac251 ( $1.3 \times 10^7$  vRNA copies per exposure)
- **Frequency and duration:** weekly mucosal exposures until systemic infection is achieved (as determined by plasma vRNA)

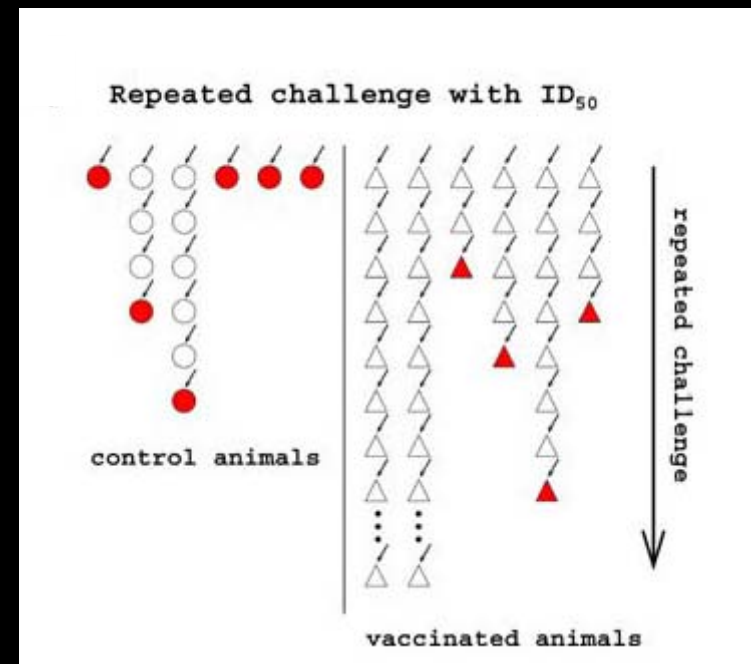
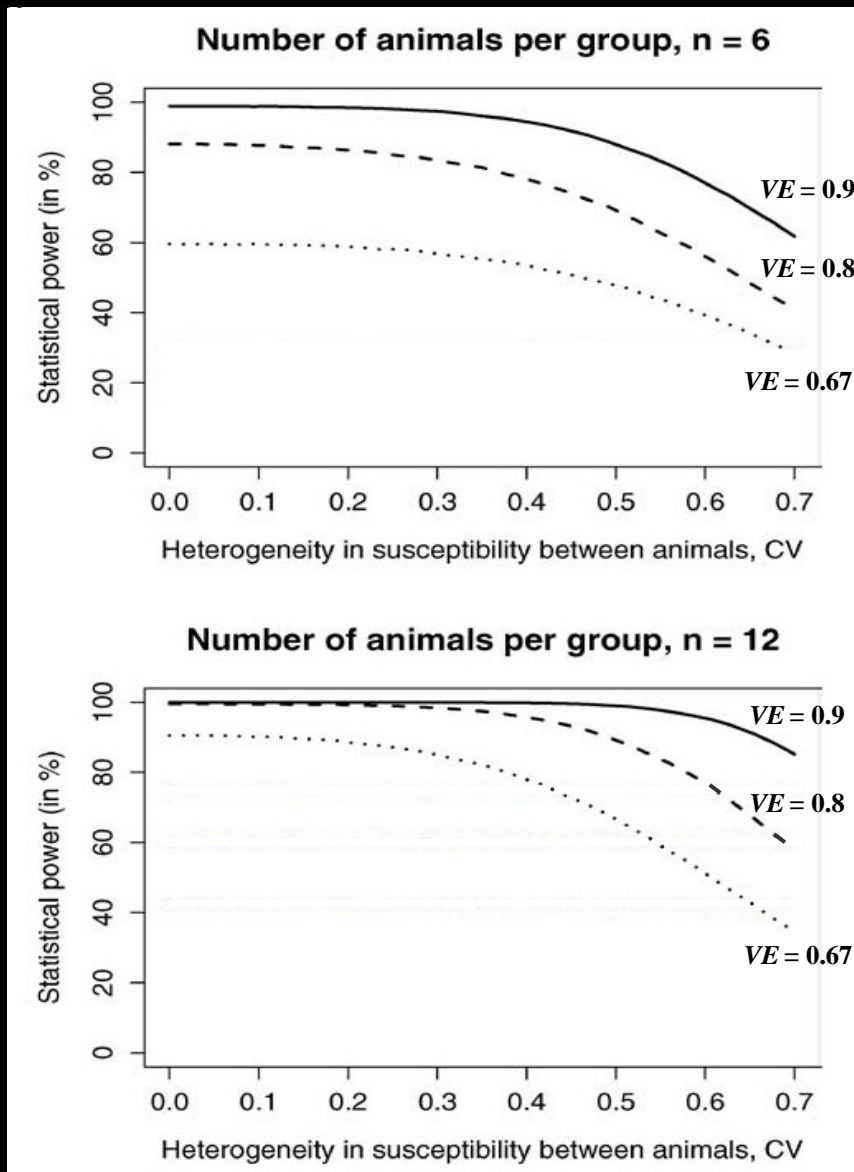
Ellenberger, *et al.*, *Virology*, 2006, 352:216

Kim, *et al.*, *J Med Primatol*, 2006, 35:210

Otten, *et al.*, *J Infect Dis* 2005, 191:164

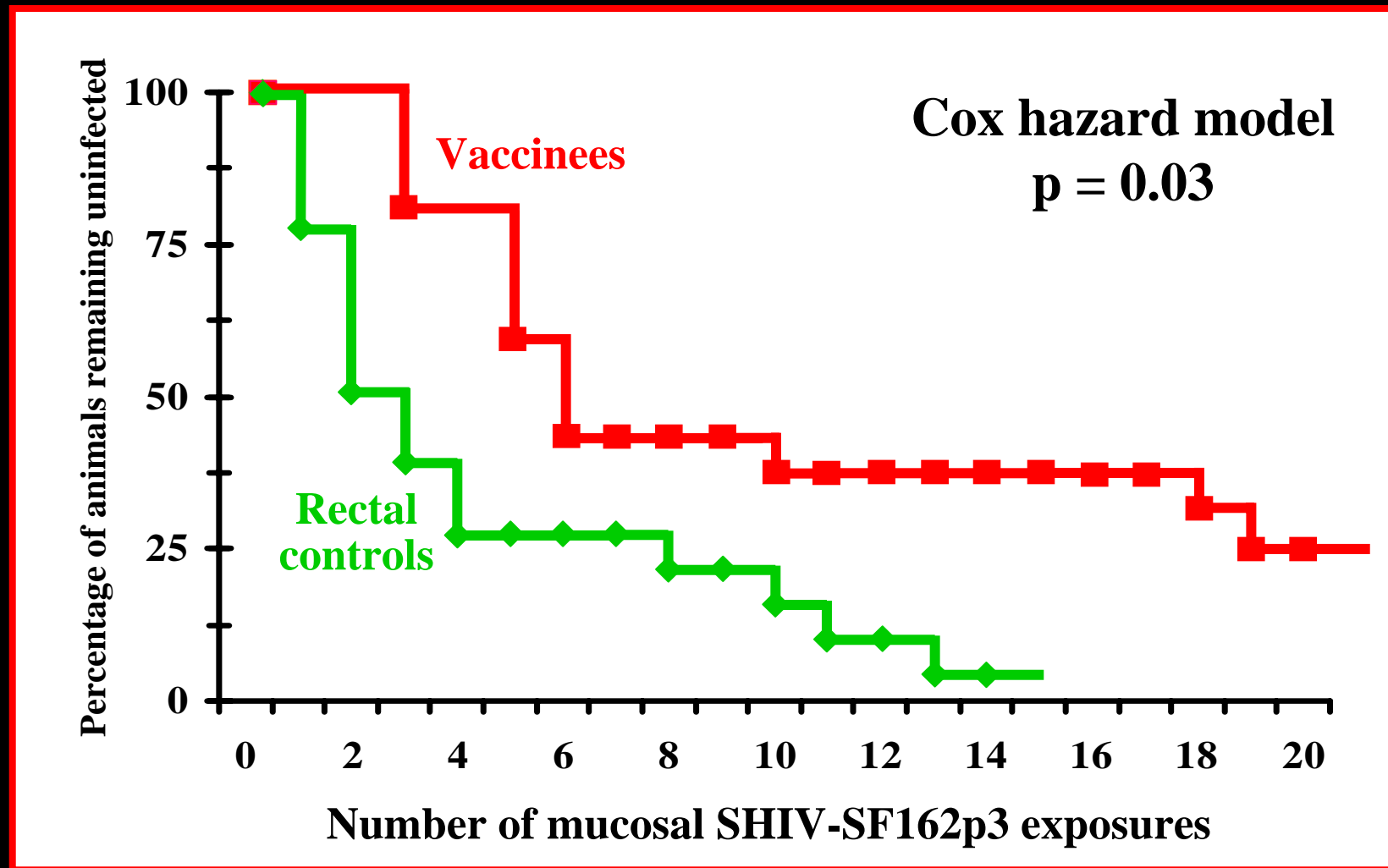
Subbarao, *et al.*, *J Infect Dis*, 2006, 194:104

# Repeated mucosal challenge of non-human primates



Adapted from:  
Regoes, Longini, Feinberg, & Staprans  
*PLoS Med*, 2005, 2:798

# Repeated mucosal challenge of DNA+MVA immunized animals



Adapted from Ellenberger, *et al.*  
*Virology*, 2006, 352:216

# Calculation of maximum likelihood of vaccine efficacy (*VE*)

$$VE = 1 - (pv/pc)$$

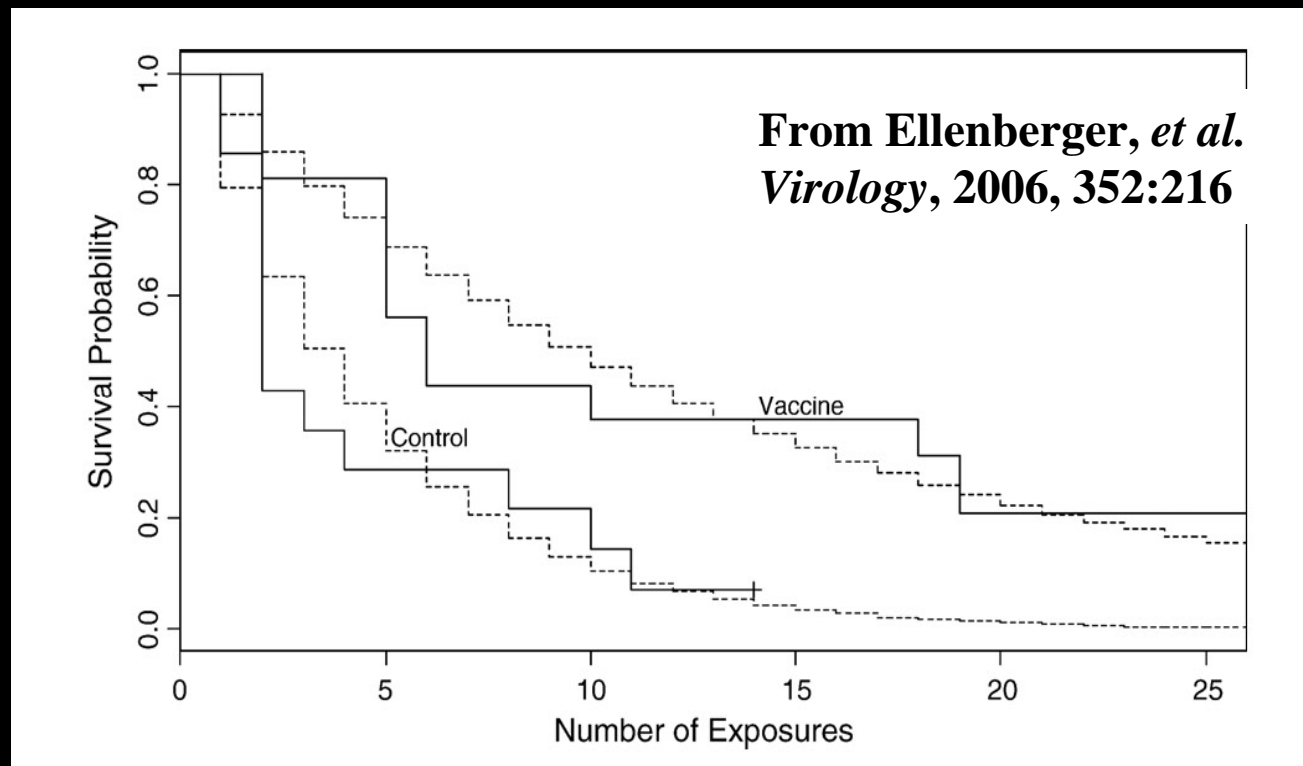
**pv** = probability of infection per exposure for vaccinees

**pc** = probability of infection per exposure for controls

$$VE = 0.64 \text{ (95\% CI = 0.26 - 0.83)}$$

**64% reduction in probability of per exposure  
infection imparted by vaccination**

# Repeated mucosal challenge of DNA+MVA immunized animals

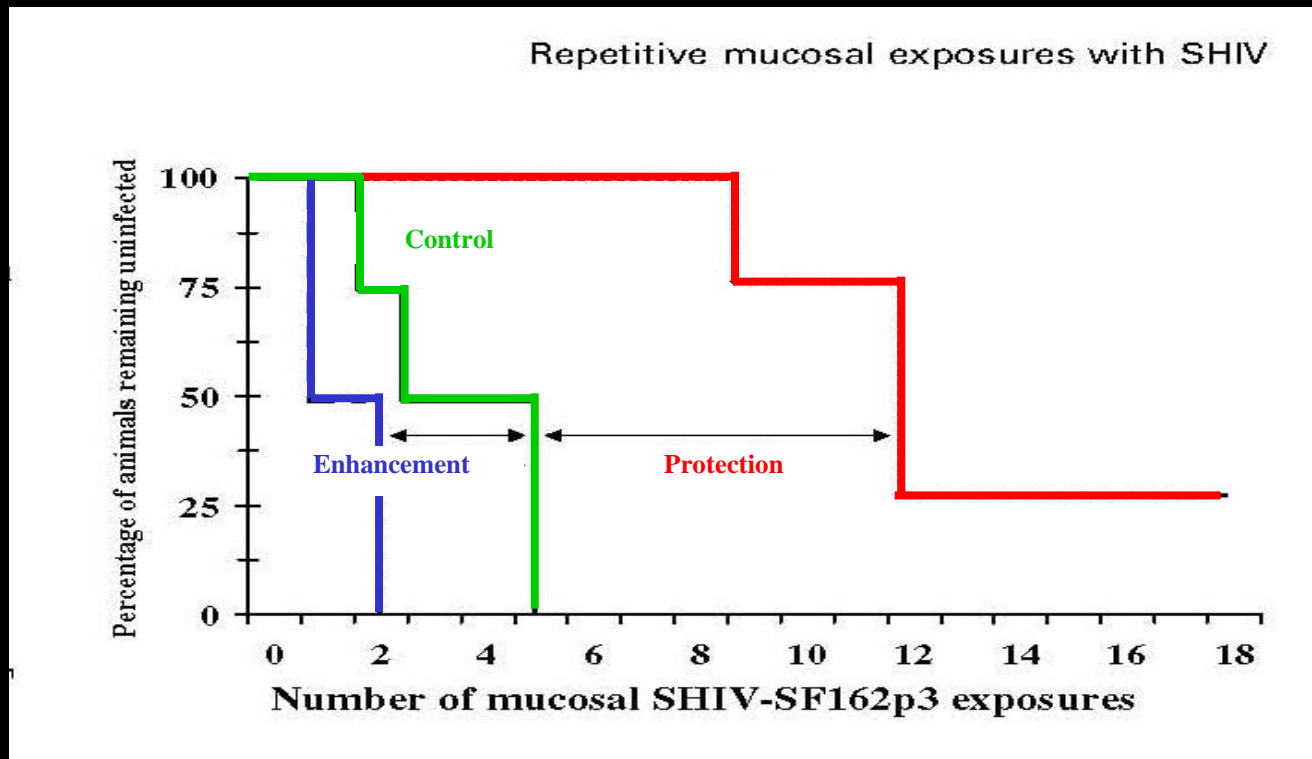


## Vaccination-associated delay of infection:

- Allowed an estimation of vaccine efficacy ( $VE=0.64$ )
- Allowed a calculation of per-exposure probability of infection (2.6-fold less)
- Allowed an indication of vaccine mechanism (leaky vs all-or-none)

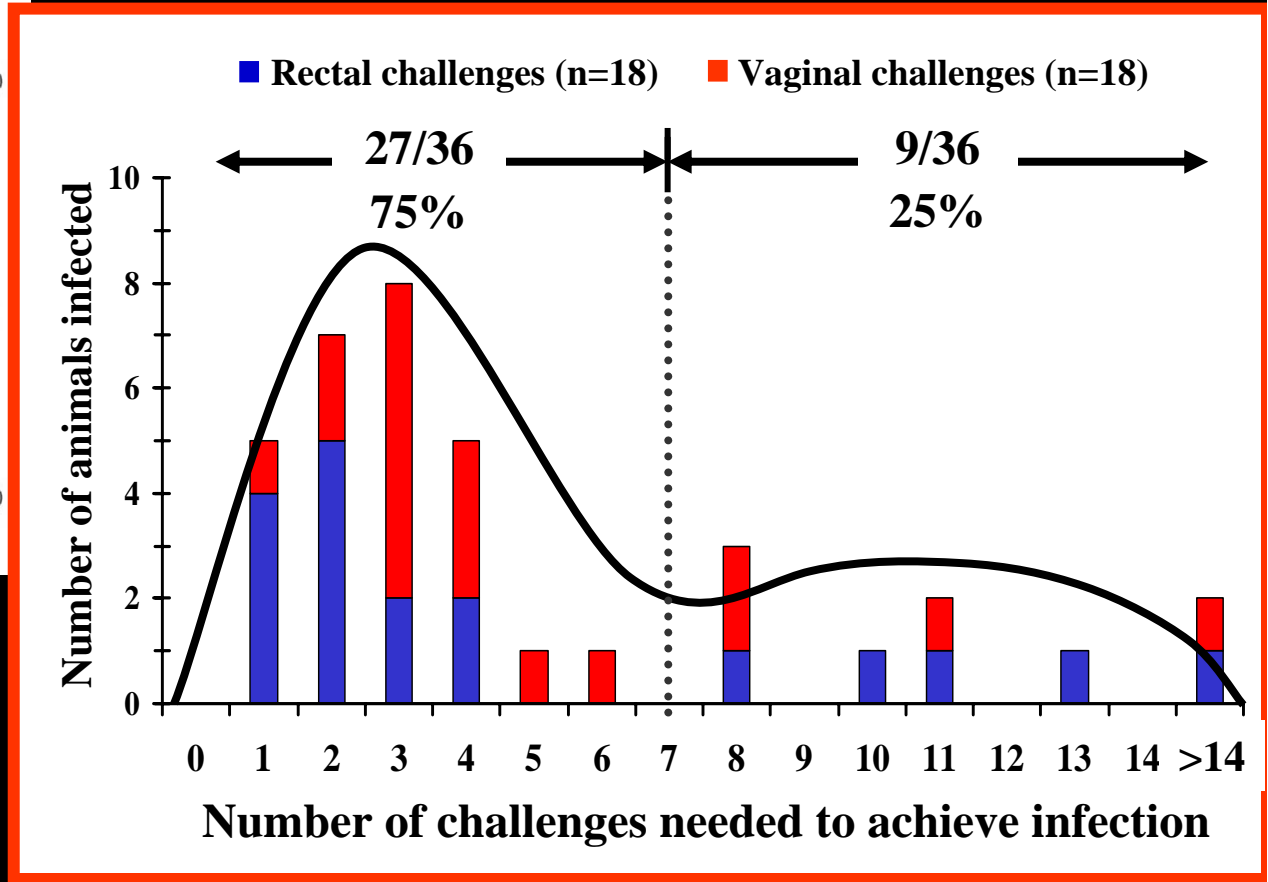
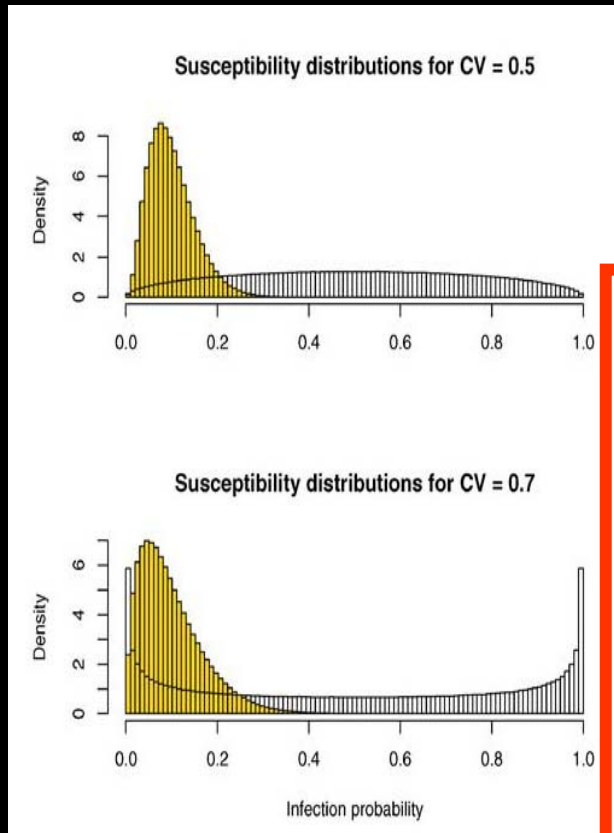
# Repeated mucosal challenge of non-human primates

## Application to study vaccine safety



From Kim, *et al.*, *J Med Primatol*,  
2006, 35:210

# Repeated mucosal challenge of naïve control animals

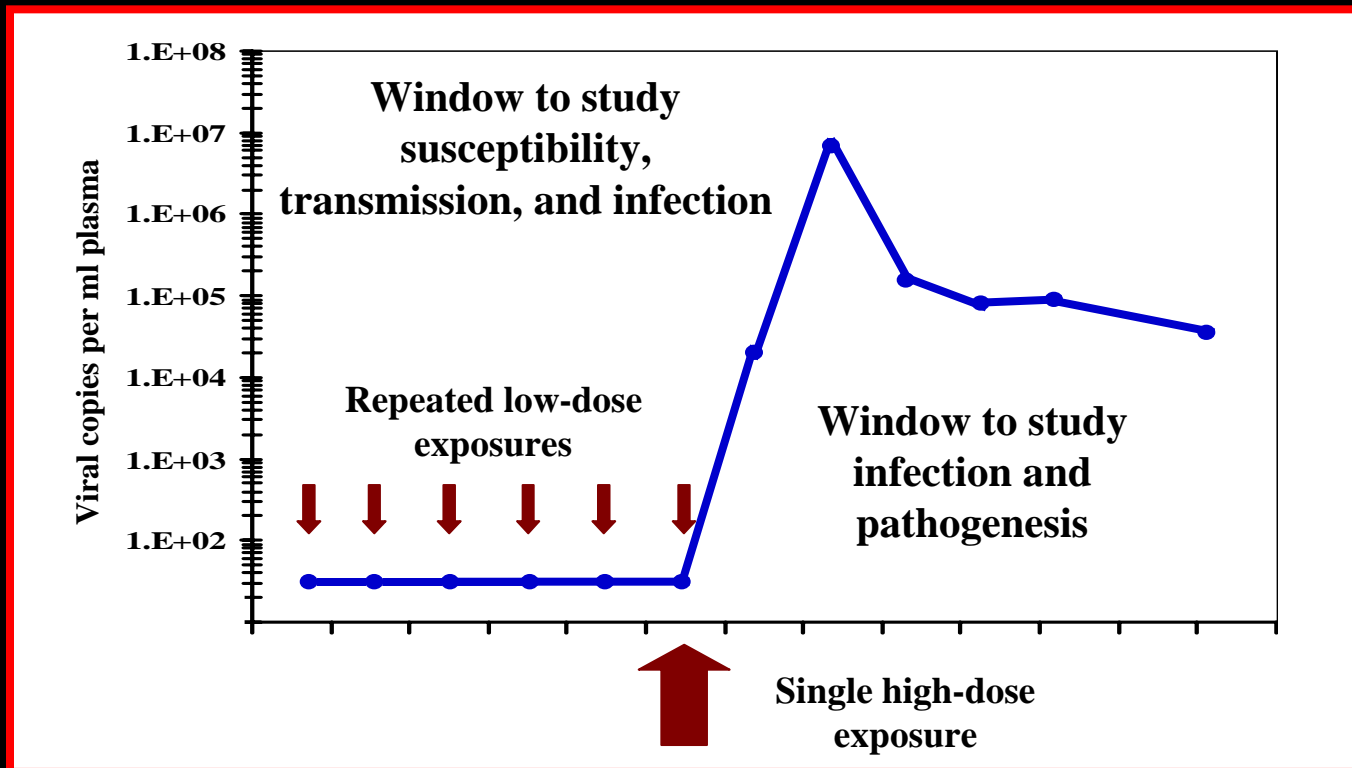


From Regoes, *et al.*  
*PLoS Med*, 2005,  
2:798

Adapted from Kim, *et al.*, *J Med Primatol*, 2006, 35:210



# Repeated mucosal challenge of non-human primates



## Advantages

- More realistic and representative
- Estimate vaccine efficacy
- Allow period of vaccine recall
- Demonstrate vaccine safety
- Study natural resistance to infection

## Limitations

- Longer follow-up time
- Variability in time to infection
- Uncertainty regarding point of infection
- May create exposure effect