

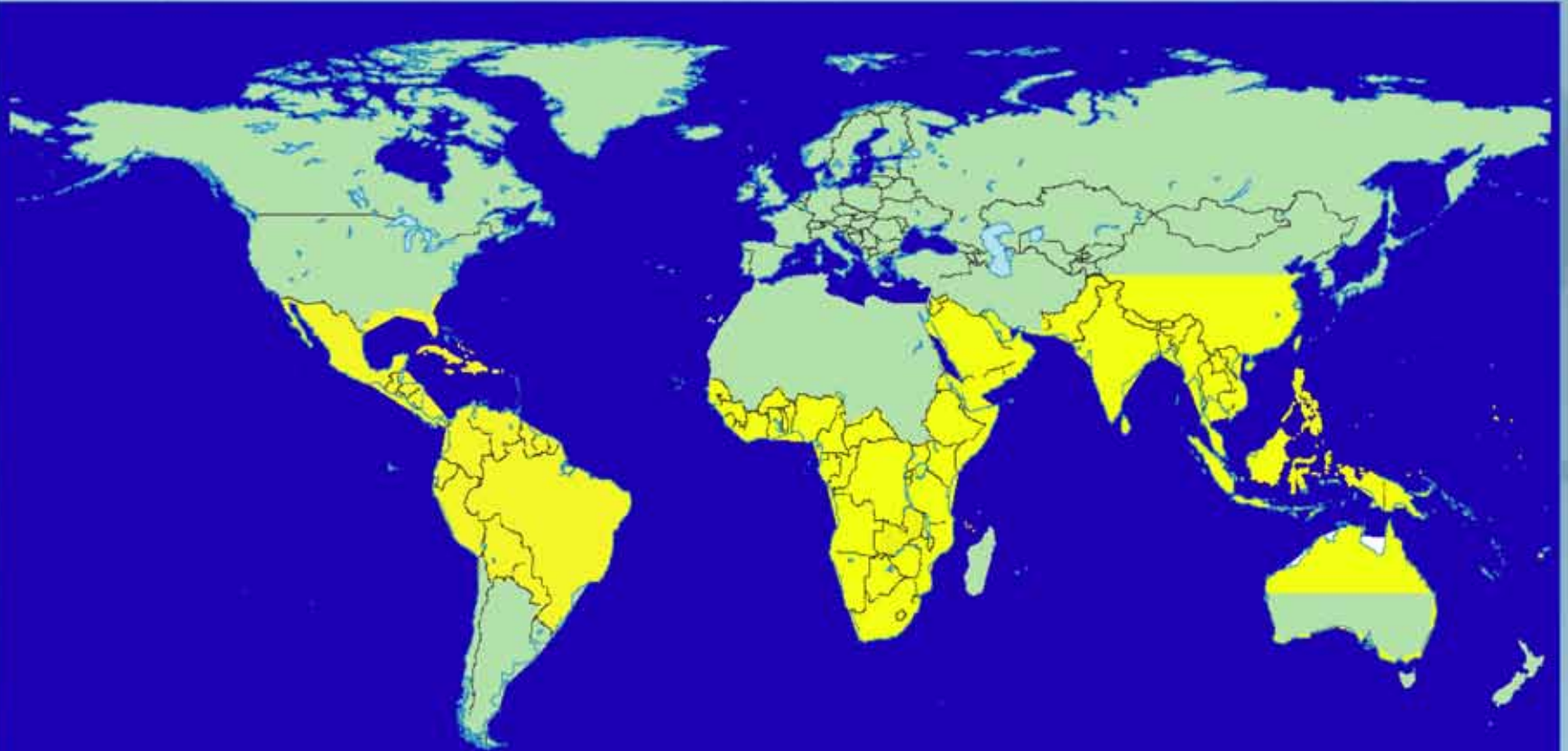
HURDLES FOR DENGUE VACCINES

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Global Spread of Dengue



Countries with active dengue transmission by

Population at risk = ~ 3.5 billion

Aedes aegypti

In 2014, possibly 3.0 – 3.5 billion humans will live in countries where one or more dengue viruses are endemic.

>/= 2.5 BILLION MAY BE SUSCEPTIBLE TO ONE OR MORE DENGUE VIRUSES

**SANOFIPASTEUR EXPECTS TO
LICENSE A TETRAVALENT THREE-
DOSE DENGUE VACCINE BY 2014**

**THEIR FRENCH FACILITY HAS A
PRODUCTION CAPACITY OF 100
MILLION DOSES/YEAR.**

**AT 100 MILLION DOSES A YEAR, 30
MILLION PERSONS CAN BE
VACCINATED/YEAR.**

The Task Ahead

- Create an enabling environment to:
 - Accelerate licensing and introduction of dengue vaccines.
 - Learn how to achieve protection when vaccinating the partially immune.
 - Optimize use of vaccines by using dengue vaccines strategically.

GOOD NEWS!

**SEVERE DENGUE IS RARE.
ONLY 2 - 4% of SECONDARY
DENGUE INFECTIONS
ARE HOSPITALIZED**

First Goal of Vaccination

- Protect those persons who have been infected by one dengue virus.

Primary Dengue Infections

- Approximately 50 million/year.
- One-half are in adults.
- In adults predominantly overt, causing DF and in older adults with pre-existing conditions, more severe disease.
- In children, predominantly mild or silent.

Second Goal of Vaccination

- Protect against primary infection disease.
- Protect against primary infection “sensitization.”

Dengue Protection in Real Life

- Homologous protection.
- Heterologous protection

Homologous Immunity

- ANTIBODIES

- Passive antibodies protect against homologous challenge (Simmons et al Phil J Sci 44:1-252, 1931).
- Protect against homologous challenge (Sabin AB AJTMH 1:30, 1952).
- Persist for life (Halstead SB AJTMH 23:974, 1974).

Heterologous Immunity

- ANTIBODIES
 - DENV 1 infection cross protects against DENV 2 for three months (Sabin AB AJTMH 1:30, 1952).
 - Pre-illness monotypic-immune sera in Bangkok school cohort neutralized DENV 2 in primary monocytes (Kliks SC et al AJTMH 40: 444, 1989).
 - DENV 1 sera from Iquitos, Peru neutralized American genotype DENV 2 (Kochel T et al Lancet 360: 310, 2002).
 - Heterologous protective immunity wanes with passage of time (Guzman MG et al EID 13:282, 2007)

Heterologous Immunity

- TWO OR MORE DENGUE INFECTIONS PROTECT AGAINST DHF/DSS
 - Antibodies raised presumably are directed at epitopes commonly expressed by all four dengue viruses.
 - Mechanism and kinetics of protection by heterotypic neutralizing dengue antibodies not well studied.

**MULTIPLE DOSES OF
TETRAVALENT DENGUE
VACCINES RAISE
HETEROTYPIC
NEUTRALIZING ANTIBODIES**

**IMPLEMENTING DENGUE
VACCINATION:**

**LET'S USE DENGUE
VACCINES PROACTIVELY**

Strategy

- Use protective synergy from broadened antibody responses to vaccination of partial dengue-immunes.
- Vaccinate to stop transmission
- Vaccinate to protect the unvaccinated or those who cannot easily be reached by vaccines.

**THIS SAME STRATEGY WAS
USED TO ERADICATE
SMALLPOX**

**THIS STRATEGY
REQUIRES HERD IMMUNITY**

What is known about herd immunity in dengue?

- Dengue 1 stopped in Cuba in 1979 at around 50% antibody prevalence (house index \sim 70%).
- Dengue 1 stopped in Iquitos, Peru in 1995 at around 80% antibody prevalence (house index $>$ 95%)

Protecting Infants/Avoiding ADE: Herd Immunity

- Herd immunity for all 4 dengue viruses estimated at 80%
 - Ferguson et al Phil Trans R Soc Lond B 354: 757-768, 1999

DENGUE NEUTRALIZING ANTIBODIES, RAYONG THAILAND, 1980

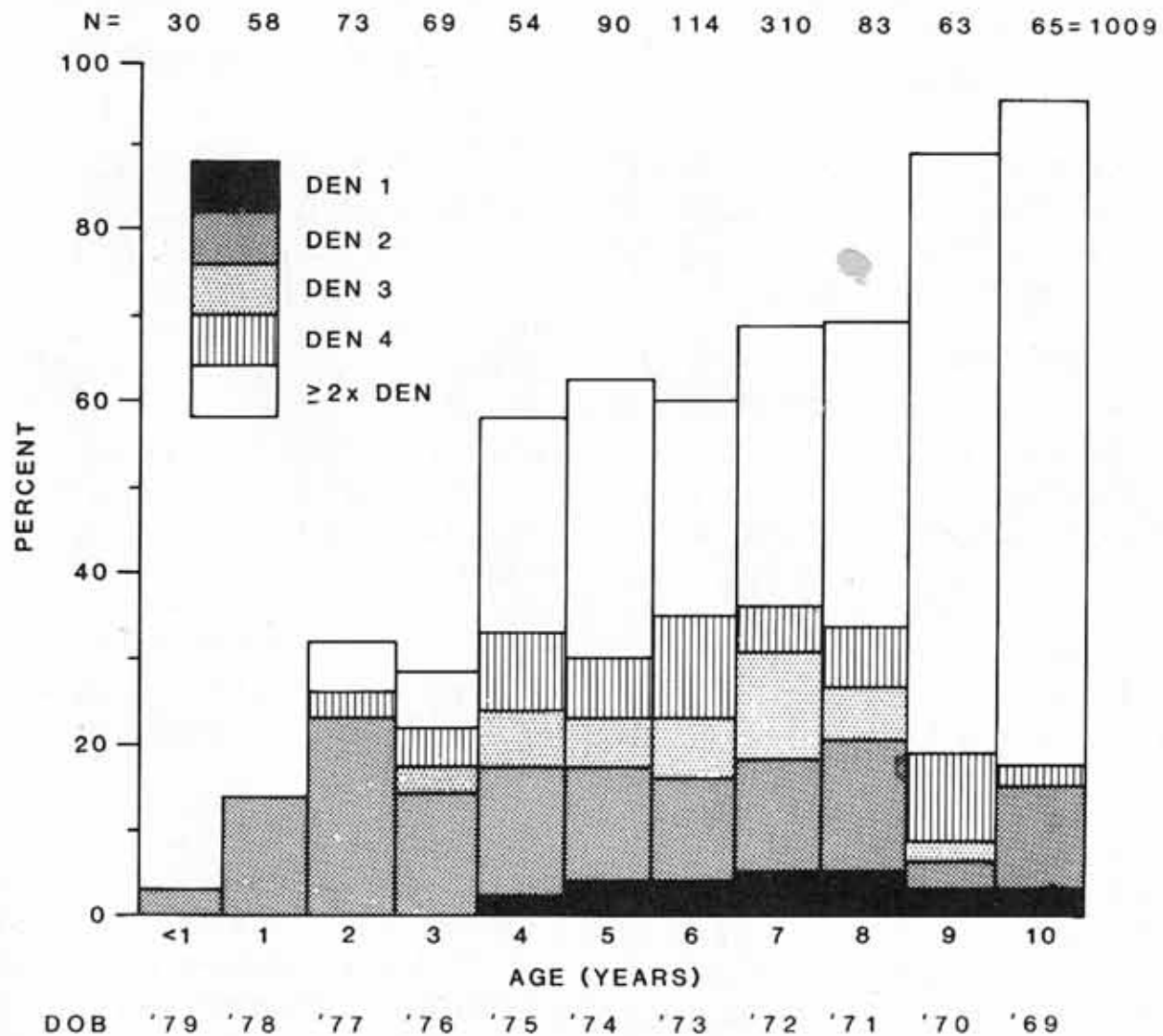


Figure 2. Prevalence of neutralizing antibodies (DEN 1, DEN 2, DEN 3, DEN 4, and ≥2x DEN) by age group and date of birth, Rayong, Thailand, 1980.

**UNLIKE MEASLES, FOR
DENGUE THERE IS
EFFECTIVE AND
ACHIEVABLE HERD
IMMUNITY**

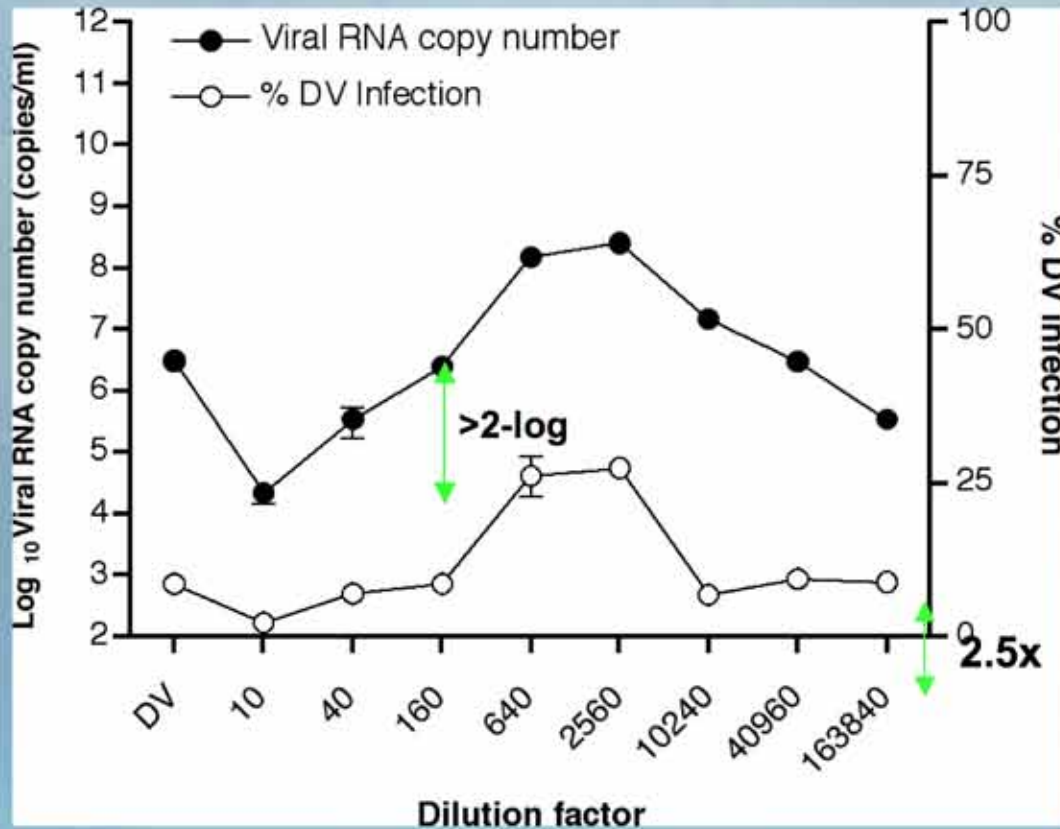
**Still, it is important to avoid
ADE as a post-vaccination
event.**

**Need to defend against post-
vaccination ADE thru better
understanding**

New Paradigm

- **EXTRINSIC ADE**
 - 3 X increase in number of infected monocytes/macrophages
- **INTRINSIC ADE**
 - 10-20 X increase in virus production per infected cell.

Increased viral production with ADE in Mature DC



Serum dilution factor

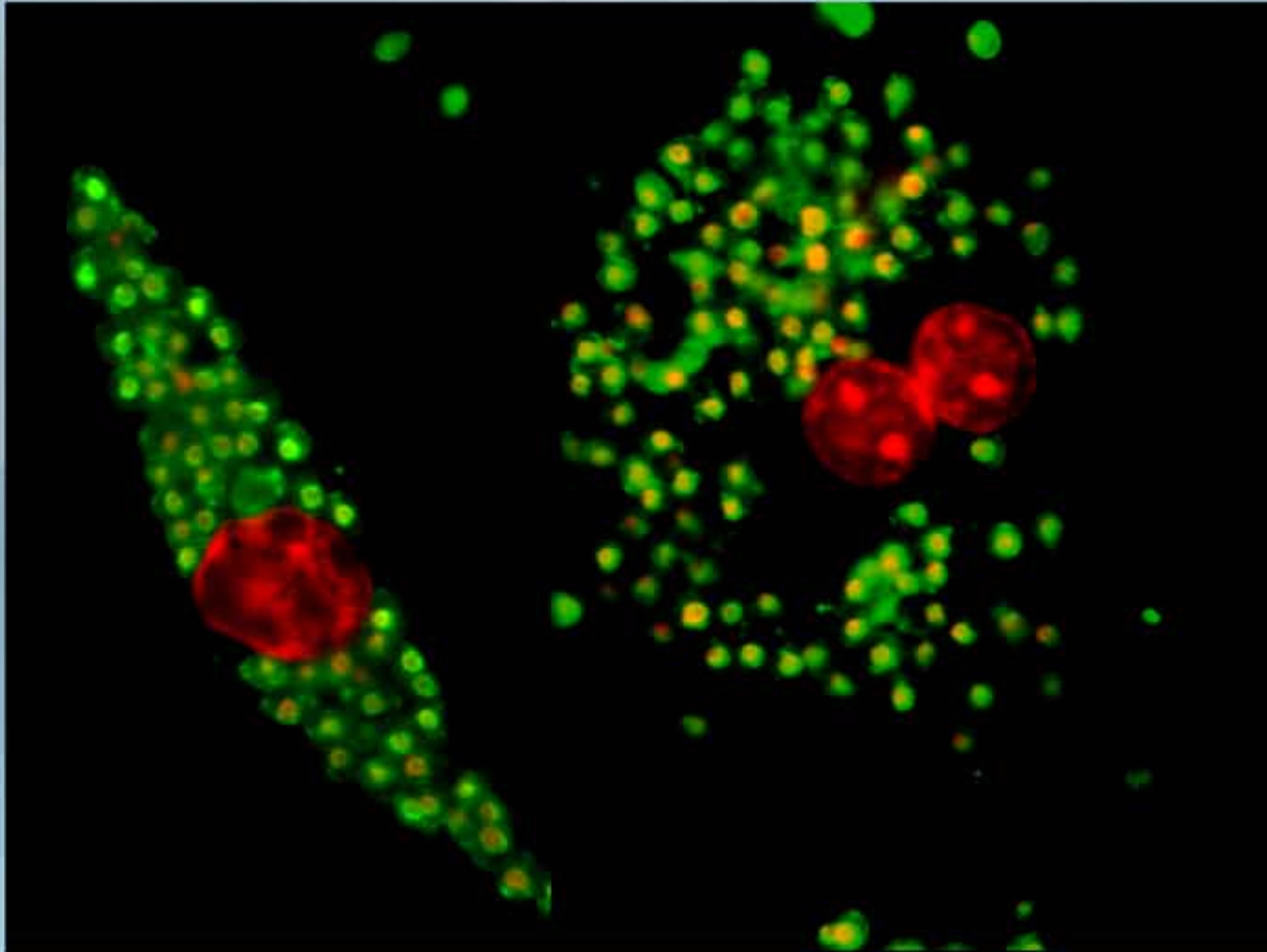
Marovich, M. personal communication

Intrinsic ADE

- Observed with wide taxa of organisms capable of replicating in monocytes/macrophages.
- Requires attachment of non-protective “enhancing” IgG antibodies.
- Enhancing immune complex ligates Fc Receptor which sends signal via tail.
- May be a central role for IL-10.

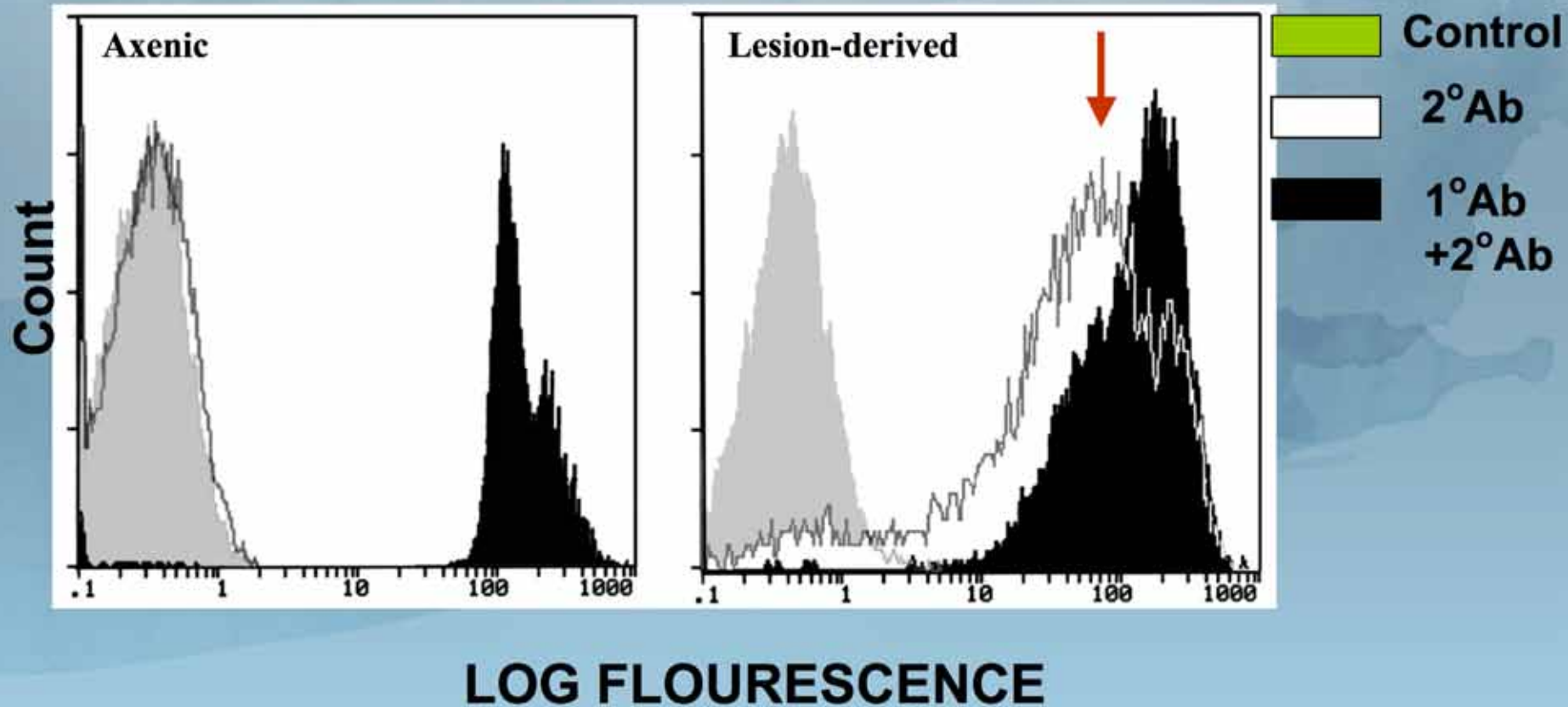
Analogy to human and experimental leishmaniasis

Leishmania-macrophage interactions....



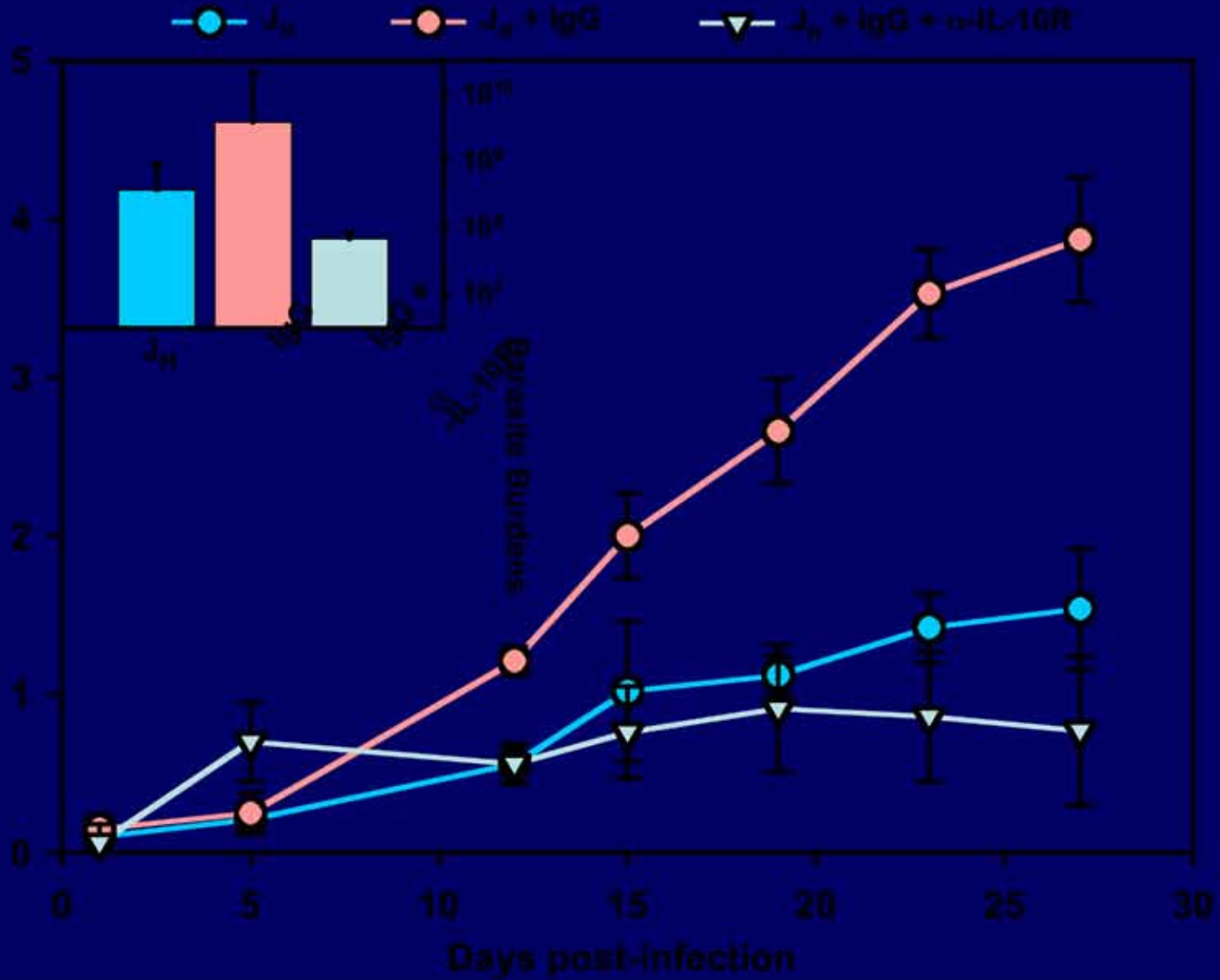
L. amazonensis amastigotes have host IgG on their surface

Lesion-derived amastigotes are coated with host Ig



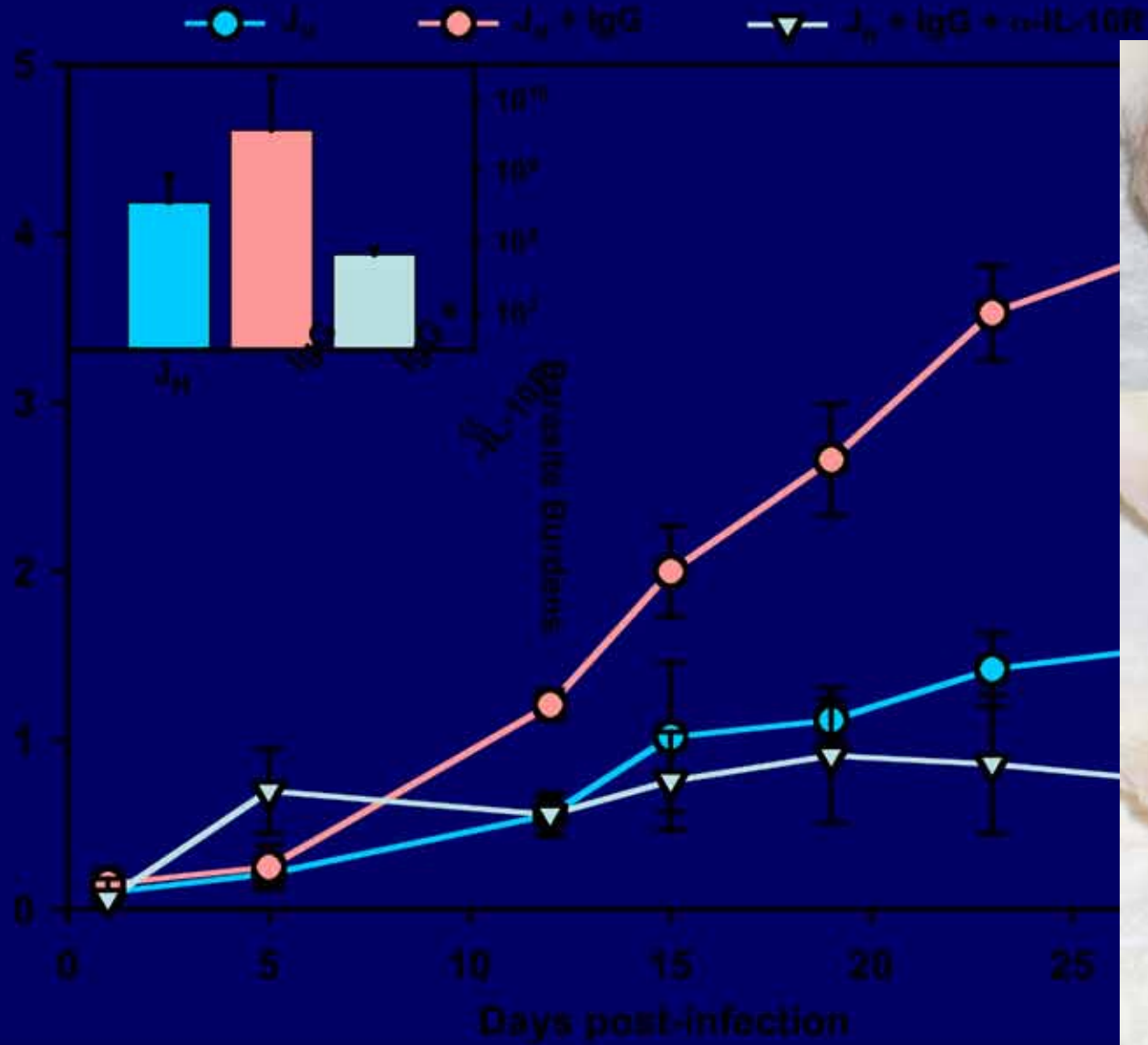
Mosser, D personal communication

IgG Reconstitution of J_H Mice and the Effect of α -IL10R



Mosser, D. personal communication

IgG Reconstitution of J_H Mice and the Effect of α -IL10R



i ADE

- New method to measure “protective” role of dengue antibodies.
- i ADE responses differ between primary human monocytes and macrophages.
 - Boonnak et al J Virol (in press)
- Recent reviews:
 - Halstead SB et al Lancet Infect Dis 10:710, 2010
 - Ubol et al Clin Vacc Immunol Dec 2010

A mouse model for antibody-enhanced dengue virus infection and disease.

**Scott J. Balsitis, Katherine Williams,
P. Robert Beatty, and Eva Harris**

Shresta et al J Virol 80: 10208, 2006

Balsitis et al. PLoS Pathogens 6: e 1000790, 2010



Required to Control Dengue

- Tetravalent vaccine that will raise heterotypic protective antibodies.
- Continue vaccinations until transmission stops.
- Political will
- Money

Role of DVI

- Study vaccine requirements in susceptibles vs partial immunes. Use partial immunity proactively.
- Measure herd immunity in sites for vaccine introduction.
- Contribute to implementation of regulatory/manufacturing standards.
- Improve and standardize dengue diagnostics.
- Support burden of illness estimates.
- Advocate for introduction/use/funding of vaccine purchases.

DVI

- A product development partnership
- Founded in 2001 as the Pediatric Dengue Vaccine Initiative.
- Now, consortium of WHO, Sabin Vaccine Institute, JHSPH, IVI
- Funding:
 - Rockefeller Foundation (early)
 - Gates Foundation

Vaccine Access

- Better information
 - Estimate disease and economic burden of dengue.
 - Comparative economic studies: vaccine vs vector control vs treatment.
 - Estimate effects of vaccine strategies.
- Prepare for vaccine introduction

Vaccine Access

- Prepare for vaccine introduction.
 - Strengthen regulatory pathways.
 - Advocacy
 - Regional networks of country leaders (Dengue Prevention Boards)
 - Enhanced communication
 - Develop dengue vaccine investment case.
 - Develop dengue vaccine implementation strategies.
 - Develop mechanisms/funding to sustain dengue vaccine programs.