

VACCINES AGAINST ARTHROPOD- BORN VIRUSES: YELLOW FEVER, ZIKA, DENGUE, ETC.

Lawrence D. Frenkel, MD

Professor, Departments of Pediatrics and Microbiology

U of Illinois College of Medicine

Member, Dept. of Immunology, Allergy, Infectious Diseases

The Children's Hospital at Saint Peter's U Hospital

A FEW ARTHROPOD-BORN VIRUSES

Deaths resulting from mosquito bites outnumber all other insect-related deaths combined. A staggering more than 1 million people die each year from diseases transmitted by mosquitoes

- Zika Virus – Vaccine being developed
- Yellow fever – Vaccine available
- Dengue – Vaccine in clinical trials
- Chikunguna virus
- West Nile virus
- Japanese encephalitis virus – Vaccines available

ARTHROPOD-BORN ZIKA VIRUS

- Zika – first isolated from monkeys in Africa in 1947
- Determined to be *Aedes* mosquito-born
- Sporadic human cases until outbreak on Yap island in Micronesia in 2007
- Appreciable outbreak in Brazil in early 2015, generally a subclinical or mild disease with fever, rash and conjunctivitis; now considered pandemic
- Association with microcephaly reported in early 2016, apparently with first trimester infection
- Sexual transmission now believed to occur

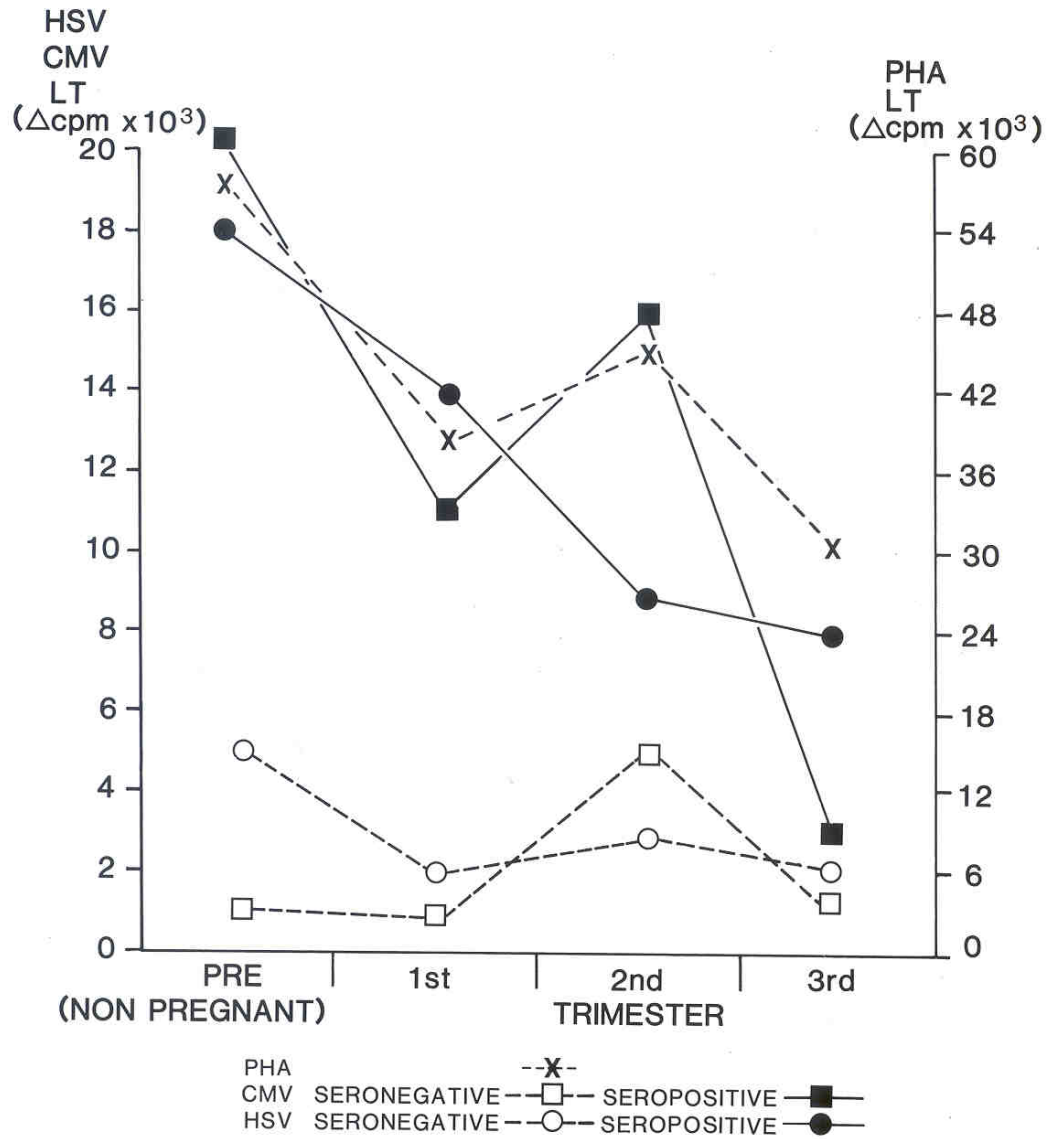
PATHOGENS ASSOCIATED WITH CONGENITAL MICROCEPHALY

- Toxoplasma gondii – No vaccine available
- *Cytomegalovirus – Two vaccines developed, none in use
- *Herpes simplex virus – Vaccine in clinical trials
- Rubella virus – Vaccine in general use
- Herpes varicella zoster virus – Vaccines in general use
- *Zika virus – No vaccine yet available

*Sexually transmitted

PATHOGENESIS OF CONGENITAL INFECTION AND AFFLICTION

- Generally, primary infection or re-infection with different strain (CMV)
- Maternal cell mediated immunity is down-regulated to prevent rejection of the fetus
- Microcephaly implies invasion and destruction of CNS tissues during first trimester of fetal development
- Microcephaly also suggests neurotropism of pathogen



LYMPHOCYTE TRANSFORMATION
 IN PREGNANT AND NON PREGNANT SUBJECTS

FIGURE 1

YELLOW FEVER

- Tends to be a rather mild disease, manifest with fever, chills, nausea, vomiting, back pain lasting for three or four days.
- In about 15% of individuals, the disease enters a second, toxic phase associated with liver involvement, jaundice (hence the name yellow fever) and hemorrhagic manifestations including bloody vomiting and bleeding of the mouth and eyes.
- This second phase is fatal in about 20% of the cases.

A Yellow Fever Epidemic

- The worst yellow fever epidemic in Angola since 1986 is rapidly spreading, including the capital, Luanda. In Angola, the epidemic began in December 2015 and the laboratory-confirmed outbreak was reported to the World Health Organization (WHO) on January 21, 2016. Angola has had 2023 suspected cases and 258 deaths as of April 26, 2016. China, the Democratic Republic of Congo, and Kenya also have reported cases arising from infected travelers from Angola.
- *JAMA*. Published online May 09, 2016.

YELLOW FEVER EPIDEMIOLOGY AND THE VACCINE

- 90% occur in sub-Saharan Africa and 10% in South America with incidence related to level of immunization and viral strains. Spread by *Aedes* mosquitoes
- Virus was first isolated in 1927
- The French neurotropic vaccine was used between the 1930's and 1982; discontinued because of encephalitic reactions to the vaccine
- The 17D "seed lot" vaccine has been used since; it is prepared in eggs and contains gelatin

YELLOW FEVER VACCINE ADVERSE EFFECTS

- Mild: headache, low grade fever, and myalgia in up to 25%
- Hypersensitivity in 1/75,000 recipients
- Since 2002, severe neurotropic events occurred in 1/20,000,000 recipients with the highest incidence in young infants
- Multiple organ system failure, especially hepatic with jaundice, occurs in 1/250,000 recipients mostly in those over 60

DENGUE FEVER

- **Dengue fever** is an acute tropical disease, the most widespread arboviral infection
- Symptoms typically include a high fever, intense headache, vomiting, severe eye pain, muscle and joint pains, and a flushed erythema with islands of pallor
- Recovery generally takes less than a week.
- In a small proportion of cases, the disease develops into the life-threatening **dengue hemorrhagic fever**, resulting from thrombocytopenia, capillary leak, and bleeding, or into **dengue shock syndrome**.
- Host factors, including tissue tropism and viral factors including virulence may determine disease progression

DENGUE FEVER EPIDEMIOLOGY

- The virus was first isolated in 1943, Dengue fever (DF) is caused by any of four closely related viruses, or serotypes (1-4) Infection with one serotype does not protect against the others
- Sequential infections, with different serotypes, put people at greater risk for hemorrhagic fever (DHF) and shock syndrome (DSS)
- 40% of the world's population live in areas where mosquito (including Aedes) transmission is possible

DENGUE VACCINE

- As of December 2015, there is no commercially available vaccine
- One is predicted to become available in Mexico, the Philippines, and Brazil in early 2016
- The vaccine is based on a weakened combination of the yellow fever virus and each of the four dengue serotypes
- Two studies of a vaccine found it was 60% effective and prevented more than 80 to 90% of severe cases
- There are ongoing programs working on a dengue vaccine to cover all four serotypes but a fifth serotype will need to be factored in
- One concern is that a vaccine could increase the risk of severe disease through antibody mediated enhancement

SIR WILLIAM OSLER

*The practice of medicine is an art, not a trade;
a calling, not a business; a calling in which
your heart will be exercised equally with your
head.*

REFERENCES

- Schuler-Faccini L, Riberio EM, Feitosa IML, et. al. Possible association between Zika virus infection and microcephaly – Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:59-62.
- Oster AM, Brooks JT, Stryker JE, et al. Interim Guidelines for Prevention of Sexual Transmission of Zika Virus — United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:120–121.
- Sabahi, F, O’Connell S, Rola-Pleszczynski M, and Frenkel LD. Qualitative and Quantitative Analysis of T. Lymphocytes During Normal Human Pregnancy. *American Journal of Reproductive Immunology* 1995;33:381-392.
- Rola-Pleszczynski, M, Frenkel LD, Fuccillo DA, et al. Specific Impairment in Cell Mediated Immunity in Mothers of Infants Due to Congenital Cytomegalovirus Infections. *Journal of Infectious Diseases* 1977;135:386-91.
- Barnett ED. Yellow Fever Epidemiology and Prevention. *Clinical Infectious Diseases*. 2007;44:850-856.
- Haelle T. Dengue Vaccine 100% Effective in Human Challenge Study. *Medscape*. March 17, 2016.