# Yellow Fever Review

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# Disclosure Information

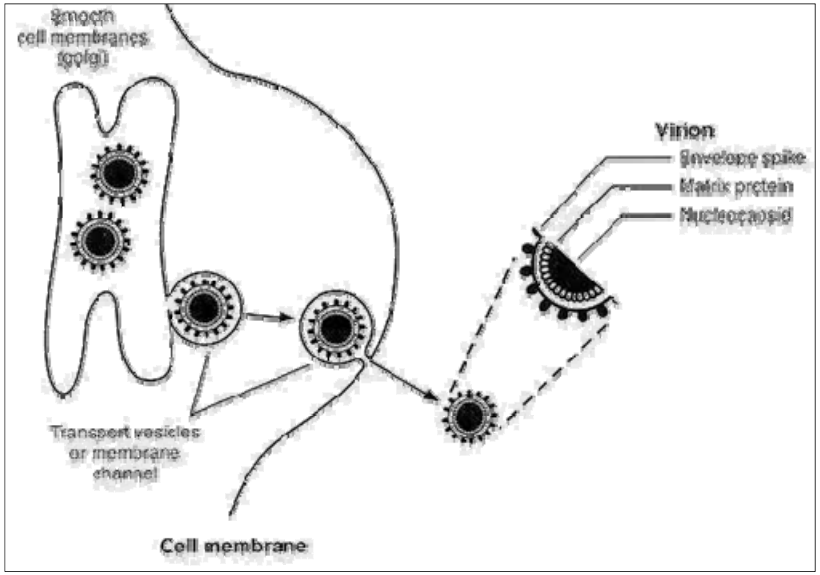
- I have **no** financial relationships to disclose.
- I will **not** discuss off-label use and/or investigational use in my presentation.
- The research and opinions in this paper are of the author and are not the views of the Department of Defense.

# Outline

- Etiology and Flavivirus Review
- Historic Significance
- Epidemiology
- Clinical Presentation
- Vaccine (Prevention)
- Questions

# Yellow Fever Virus

- *Flaviviridae* family, Genus Flavivirus
- (+) ssRNA enveloped virus
  - Replicate in the cytoplasm




- Flavivirus RNA encode for 10 proteins
  - 3 structural proteins and 7 non-structural proteins

Baron et al, Medical Microbiology, Chapter 54,1996

# Question

- Yellow Fever is the "prototypical Flavivirus." Which of the following virus is **NOT** in the *Flaviviridae* family?
  - A: Dengue
  - B: Mosquito-bourne encephalitis (JE, WNV, St. Louis)
  - C: Hepatitis C
  - D: Tick-bourne encephalitis
  - E: Sinbis, WEE, VEE, EEE, Chikungunya

# *Flaviviridae* Family

**Family**

*Flaviviridae*

**Genus**

- Flavivirus
  - -Yellow Fever
  - -Dengue (1-4)
  - -Japanese encephalitis
  - -St. Louis encephalitis
  - -West Nile encephalitis
  - -Murray Valley encephalitis
  - -Tick-bourne encephalitis
  - -Omsk Hemorrhagic Fever
- Pestivirus
  - Non-arthopod Veterinary diseases
- Hepacivirus
  - HCV, HGBV

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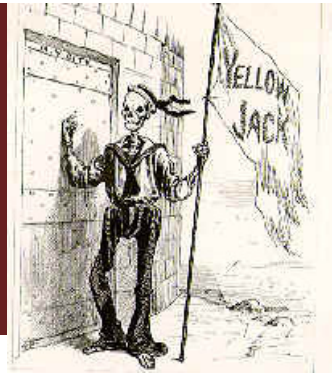
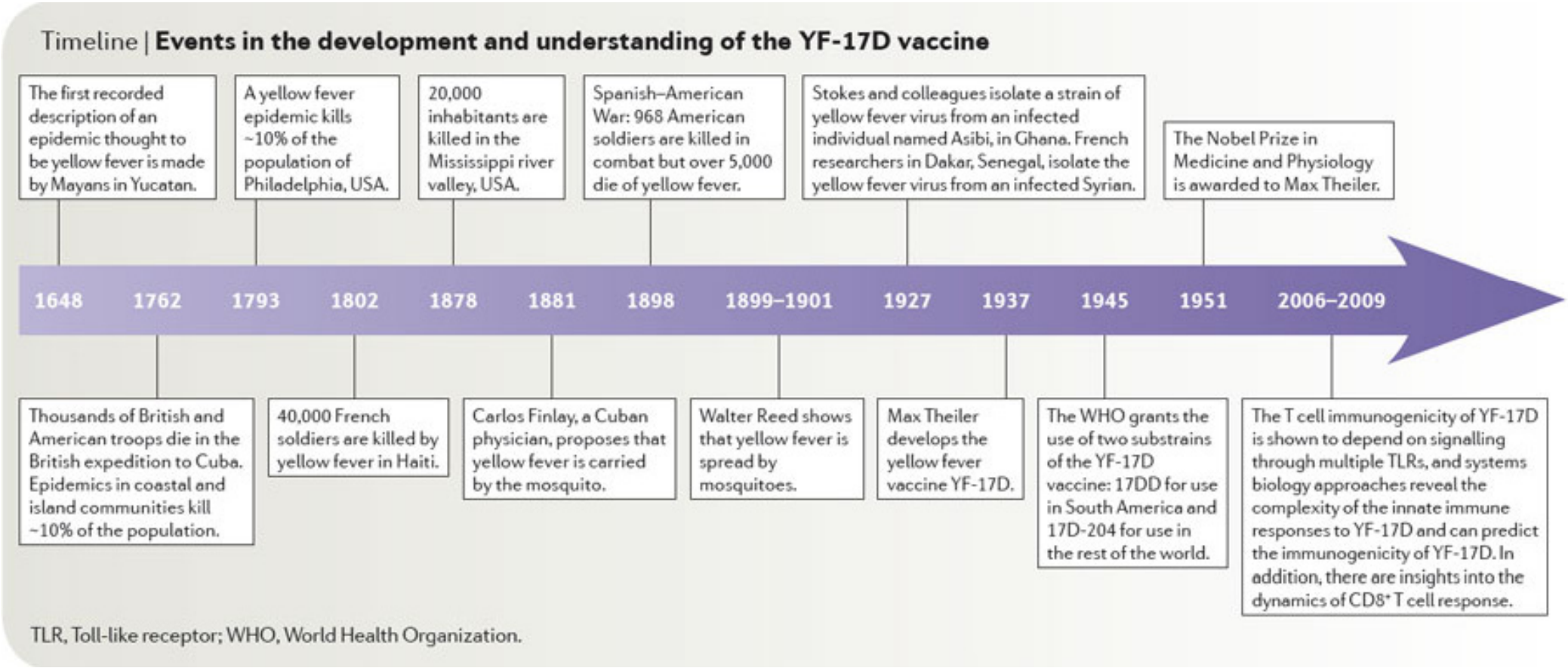
# Historic Importance



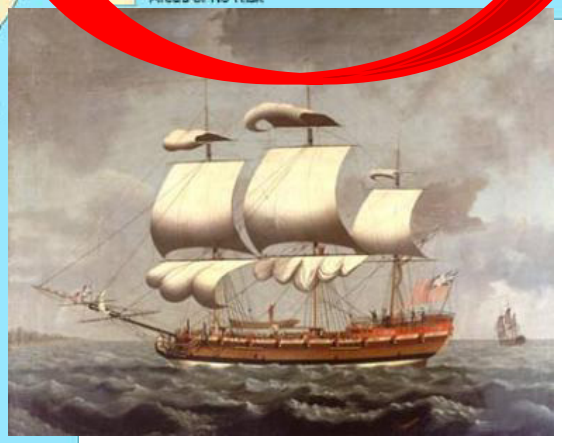

- First described in the 1600's in the New World
- Imperial Britain's "white man's grave"
  - Fever was romanticized by Coleridge in the *Rime of the Ancient Mariner*[1]
  - Likely the disease in Wagner's *The Flying Dutchman*
- First human disease shown to be due to a "filterable agent" by MAJ Walter Reed

[1] Debbie Lee, **Slavery and the Romantic Imagination, Ch 3.** (available on Google Books)

# Yellow Fever Vaccine Timeline




Nat Rev Immunol. 2009 Oct;9(10):741-7. Epub 2009 Sep 18.



Mosquito larvae carried in ship's water barrels spread the virus to the Americas

Maps from http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.aspx

**The physical atlas of natural phenomena**
by Alexander Keith Johnston, F.R.S.E., F.R.G.S., F.G.S.
William Blackwood and Sons, Edinburgh and London, MDCCCLVI
Also posted on www.iayork.com

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# Transmission Cycles

- Sylvatic (jungle) transmission
- Savannah cycle
- Urban Cycle

# Sylvatic cycle

- Transmission between nonhuman primates and mosquito species
- African sylvatic cycle:
  - *Ae. africanus* is the principle vector
- American sylvatic cycle:
  - *Haemagogus* sp. is the principle vector
  - Human infections peak during rainy season Dec-May
  - Dead monkeys may herald local sylvatic YF activity
  - Primary method of human transmission in Americas
- Demographic: mostly males age 15-45yo

Barrett A., Higgs S.: Yellow fever: a disease that has yet to be conquered. *Annu Rev Entomol* 52. 209-229.2007

# Savannah Cycle

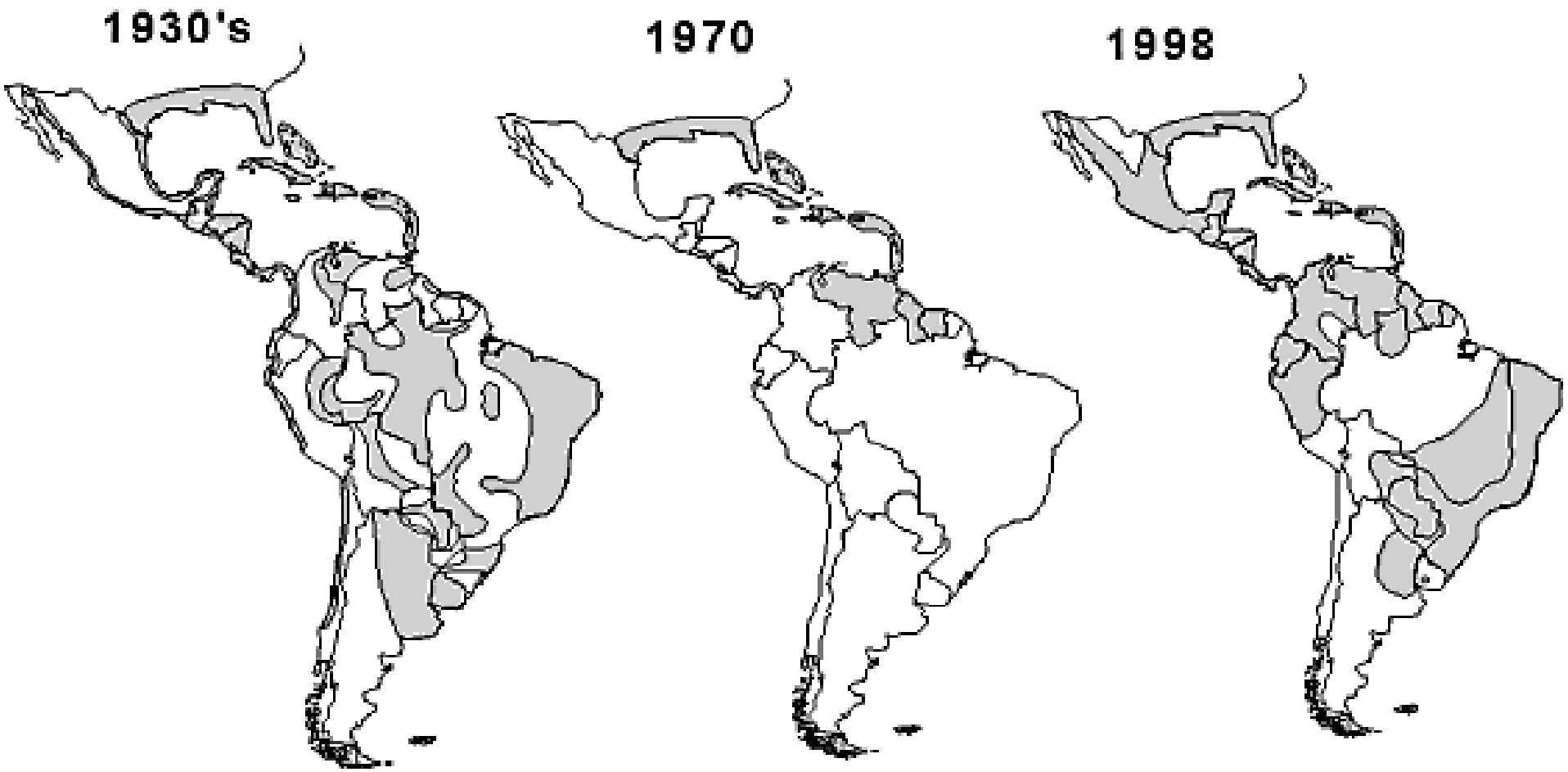
- An intermediate cycle between Sylvatic and Urban described in Africa
- Characteristic:
  - non-*Ae. aegypti* vector
  - Epidemics occur
- Demographic: both sexes and all ages

# Urban Cycle

- Associated with epidemics and substantial morbidity and mortality
- *Ae. aegypti* is the principle vector
- Elimination of *Ae. aegypti* in the Americas led to elimination of Urban YF
- Demographic: both sexes and all ages

Staples J.E., Monath T.P.: Yellow fever: 100 years of discovery. *JAMA* 300. (8): 960-962.2008

# Resurgence of *Ae. aegypti*




Gubler DJ . Resurgent Vector-Borne Diseases as a Global Health Problem. EID 1998 Jul-Sep;4(3):442-50.

# East African YF epidemiology

- Differences in regional epidemiology
  - 7 genotypes of YF distributed across Africa
- Eastern and Central Africa have few YF epidemics
  - Usually associated with periods of civil unrest
  - Also with large population movements into areas with endemic YF
- Large *Urban* YF epidemics are less common in East Africa

Ellis B.R., Barrett A.D.: The enigma of yellow fever in East Africa. *Rev Med Virol* 18. (5): 331-346.2008

# West African YF epidemiology

- West Africa genotypes I and II are prevalent
- Epidemic YF is historically more common
- May occur during stable socio-political times and without mass movements of people

Ellis B.R., Barrett A.D.: The enigma of yellow fever in East Africa. *Rev Med Virol* 18. (5): 331-346.2008

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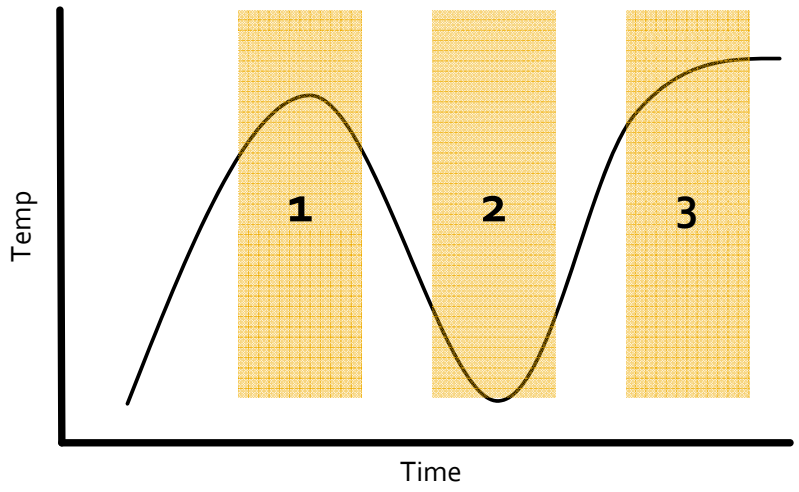
# Spectrum of Clinical Illness

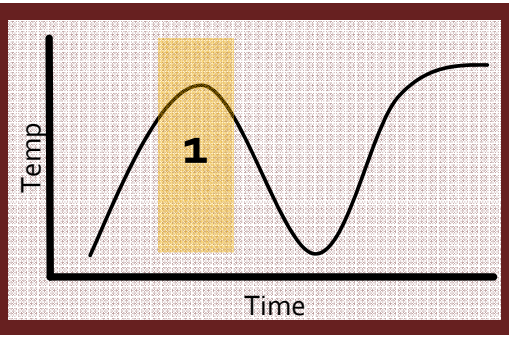
- Subclinical infection
- Abortive, nonspecific febrile illness w/o jaundice
- Life-threatening disease with fever, jaundice, renal failure and hemorrhage

# Clinical Presentation

- Incubation period of 3 to 6 days
- Majority of infections are inapparent or mild
- Severe cases classically pass through 3 phases:
  1) Infection
  2) Remission
  3) Intoxication



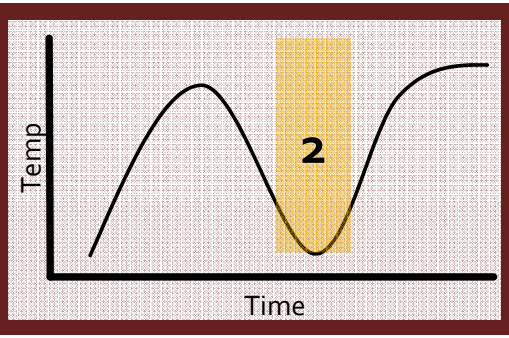
# 3 Phases: Infection




- Mild YF will only pass through this phase
- Acute febrile illness of short duration often <48H
- Characterized by:
  - Fever, headache, mylagias, other mild constitutional sx
  - Proteinuria my be present
  - Leukopenia (1.5 – 2K) with relative neutropenia
  - Faget's Sign: bradycardia in relation to fever
    - Classically described in YF, but found in other tropical diseases

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London, England:Elsevier; 2004.

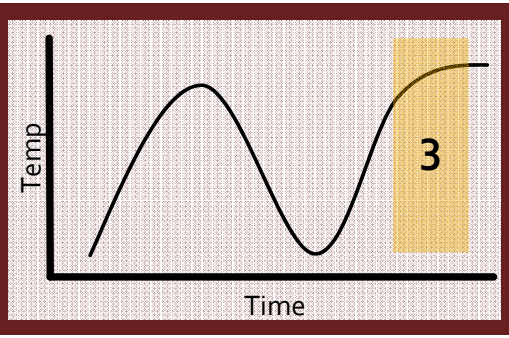
# 3 Phases: Remission




- Seen in severe cases
- Diminishment of fever
  - With improvement in clinical status
- Lasting up to 24-48 hours
- In very severe YF cases, remission period may be short or absent

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London, England:Elsevier; 2004.

# 3 Phases: Intoxication




- Severe and widespread necrosis in liver
  - Jaundice – clinical sign c/w case-fatality rate 20-50%
- Myocardial and Renal dysfunction

- Ultimately leading to **Hemorrhagic Fever**:
  - Hepatic failure, encephalopathy, hemorrhage
  - Hematemesis is characteristic
  - Laboratory Findings:
    - Leukopenia (low WBC) and thrombocytopenia (low platelets)
    - elevated liver enzymes and abnormalities on clotting tests

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London, England:Elsevier; 2004.

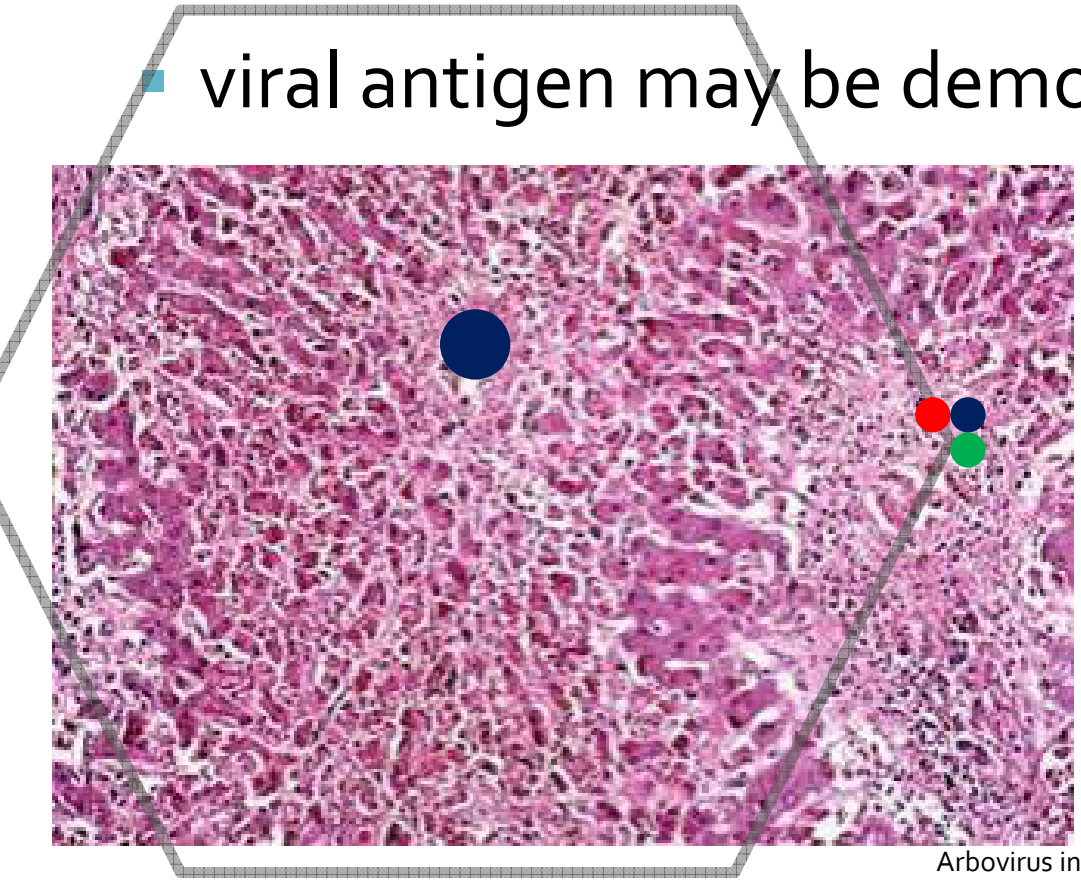
# Diagnosis

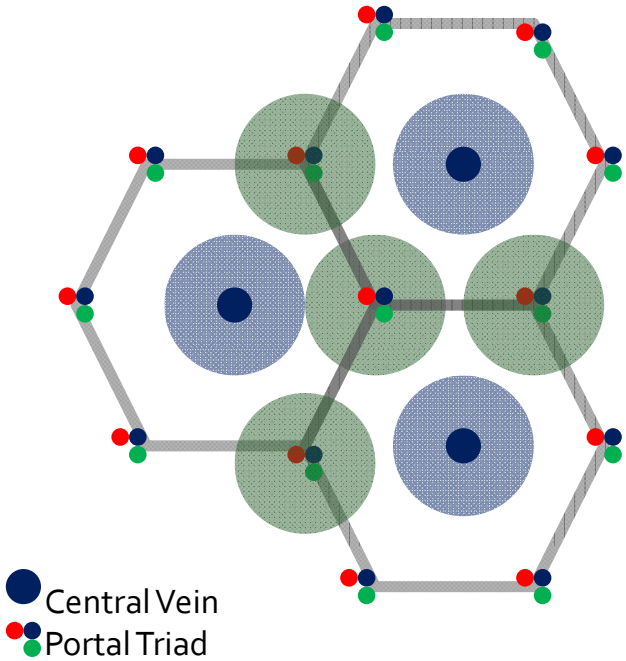
- Clinical Diagnosis
  - h/o travel to endemic area within the incubation period

- Advanced Diagnostics:
  - Virus Isolation (culture)
  - Rapid Diagnostics
    - PCR
      - use with caution as antigen may not be detected late in disease
    - Antibody or Antigen detection (ELISA)
      - IgM for acute phase, coupled with convalescent antibodies (IgM/IgG)
    - Neutralization Ab are more specific for YF

# Liver Histology: Autopsy or Biopsy

- mid-zonal coagulative necrosis
  - with sparing of periportal hepatocytes
  - minimal inflammation is seen
  - viral antigen may be demonstrated within hepatocytes






Picture from alarabiya.net

Arbovirus infections. Manson's Tropical Diseases. 21st Edition. London, England:Elsevier; 2004.

# Treatment Overview

- Supportive Care -- **no specific therapy**
  - Maintain nutrition and prevent hypoglycemia
  - NG tube to prevent gastric distention
  - Treatment of hypotension (IVF, pressors)
  - Supplemental oxygen
  - Correction of bleeding abnormalities
  - Dialysis
  - Treatment of secondary infections
  - Treatment of DIC

  - **PROTECT FROM FURTHER MOSQUITO EXPOSURE**

# Alternative Treatments

- Stress-dose Steroids not clearly indicated
- Ribavirin is active against YF *in vitro*
  - Monkeys model showed no benefit
  - Hamster model with improved formulation did show benefit

J Nat Prod 1992 Nov;55(11):1569-81.
Am J Trop Med Hyg 2004 Sep;71(3):306-12.

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# Yellow Fever Control

- *Ae. aegypti* control is critical to control of YF
  - Elimination of *Ae. aegypti* results in complete control of urban cycles
  - Also controls Dengue transmission
- Vaccine critical to control in endemic zones
  - Sylvatic YF cannot be eliminated
- Vaccine also critical in keeping YF out of areas susceptible to re-emergence
  - Areas with vector (*Ae. aegytpi*) and host (human)

# Yellow Fever Vaccine

- 2 live-attenuated YF vaccines were developed
- Both developed from serial passage of human-derived YF
  - FNV: passage in mouse brain
  - 17D: passage in chicken embryo tissue

# Yellow Fever Vaccine: FNV

- Between 1939-52 administered to nearly 40 million people in West Africa
- Effectively reduced YF incidence in the region

- Associated with large numbers of encephalitis cases in children
  - Vaccine not recommended for children less than 10yo
  - Manufacture discontinued in 1980

WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.

# Yellow Fever Vaccine: 17D

- Has remained in continuous use since 1936
  - Over 400 million doses given
- Long-lasting immunity
  - Countries may require boosting every 10 years
  - Studies have shown neutralizing Ab decades after dose
    - 81% of US WWII veterans with Ab after more than 30 years


1. WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.
2. Poland JD, Calisher CH, Monath TP. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59:895-900.

# Yellow Fever Vaccine: Use in Endemic Countries

- WHO recommends incorporation into routine infant and child immunizations
  - Given between 9 and 12 months of age
  - Severe YF more common in infants and young children in outbreaks of YF in endemic zones

- 32 of 44 countries endemic for YF have partial or national expanded programs for YF immunization
  - Despite this, coverage less than 50% in these countries

WHO. Yellow fever vaccine. www.who.int/vaccines/en/yellowfever

# Yellow Fever Vaccine: Emergency Vaccination Campaigns

- Surveillance is important in the detection of YF outbreaks
- Largest mass vaccination campaign:
  - Southern Mali in April 2008
  - 6000 HCP and 2000 volunteers vaccinated 6 million
- In mass vaccination vaccine can be given to children as young as 6 months (instead of 9mo)
  - *Manufacturer contraindicates use in infants <9mo*

WHO. Mali: 6 million vaccinated against yellow fever. 2008 at: www.who.int/features/2008/mali_vaccine/en/.
Health information for international travel, 2008. Atlanta: CDC, 2007.

# Yellow Fever Vaccine: Contraindications

- Three major contraindications:
  1. Immunosuppression (YF Vaccine is a Live Virus)
  2. Age younger than 6 months
  3. Allergy to eggs

  - History of thymus disorder
    - Including myasthenia gravis, thymoma, or prior thymectomy

- Caveats:
  - HIV not a strict contraindication (unless pt has AIDS)
  - Should be *avoided* in pregnancy / breast feeding
  - Should be *avoided* acute or febrile illness

WHO. Vaccine-preventable diseases and vaccines. In: International travel and health, 2008.

# Yellow Fever Vaccine: YF-associated Viscerotropic disease

- First recognized in 2001
- Incidence: 0.3 to 0.4 per 100,000 vaccinated persons
  - Some vaccine lots may have higher rates
- Presents 2-5 days after YF vaccine
  - Febrile illness with multi-organ failure
  - Indistinguishable from natural YF disease
- 60% case fatality rate

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:6077-82.

# Yellow Fever Vaccine: YF-associated Viscerotropic disease

- Higher Risk population:
  - Individuals older than 60 yo
  - Individuals with thymus disorders
  - Primary vaccination in non-immune individuals
- Risk seems to be much lower in infants / children
  - Incidence of 1 case per 10million doses in routine child immunizations

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:6077-82.

# Yellow Fever Vaccine: YF-associated Neurotropic disease

- Rare: incidence 0.4 per 100,000 vaccinations

- Mulitple presentations:
  - Post-vaccine encephalitis
  - Autoimmune involvement of central and peripheral nervous system
    - Including Guillain-Barre syndrome

Adverse event reports following yellow fever vaccination. Vaccine 2008;26:6077-82.

# Yellow Fever Vaccine: Encephalitis in Infants

- Young infants at increased risk
- Has led to the lack of recommendation consensus for infants 6-8 months who need vaccine

WHO. The Immunological Basis for Immunization Series. Module 8: Yellow Fever.

# Yellow Fever Vaccine: Risks for Travellers

- Risk of illness / death for a 2-week stay
  - West Africa is 50 per 100,000 / 10 per 100,000
  - South America is 5 per 100,000 / 1 per 100,000

- These are rough guidelines based on the risk to indigenous populations, during peak transmission

CDC website: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.aspx

# Yellow Fever Vaccine: Recommendations for Travelers

- HCP giving advice must remain current in YF endemic regions
  - Review current maps (WHO, CDC, TRAVAX)
  - Carefully scrutinize itinerary to best determine risk
- Balance risk of YF exposure and YF immunization
- If vaccination is *only* to satisfy an international requirement (as opposed to decreasing risk of infection), efforts should be made to obtain a waiver letter.

# Careful Scrutiny of Itinerary

- Example of travel to Argentina
- YF risk is isolated in the North
- Only parts of provinces affected

Map from Travax Encompass

# Yellow Fever Vaccine Waiver

**Figure 2-2. Example International Certificate of Vaccination or Prophylaxis (ICVP) medical contraindication to vaccination**

**MEDICAL CONTRAINDICATION TO VACCINATION**
**Ceontre-indication médicale à la vaccination**

This is to certify that immunization against
Je soussigné(e) certifie que la vaccination contre

_____ for
(Name of disease – Nom de la maladie) pour

_____ is medically
(Name of traveler – Nom du voyageur) est médicalement

contraindicated because of the following conditions:
contre-indiquée pour les raisons suivantes:

_____

_____

_____

_____
(Signature and address of physician)
(Signature et adresse du médecin)

Image available on CDC website: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.aspx

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