黃熱病及黃熱病疫苗

衛生署 疾病管制局
中區傳染病防治醫療網
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YFV History

Dr. Walter Reed

- Outbreak in Philadelphia
- Spanish American War-1898
- Dr. Carlos Finlay
- Dr. Walter Reed
- Bold Experiment

Dr. Carlos Finlay

Outbreak in Philadelphia, 1793

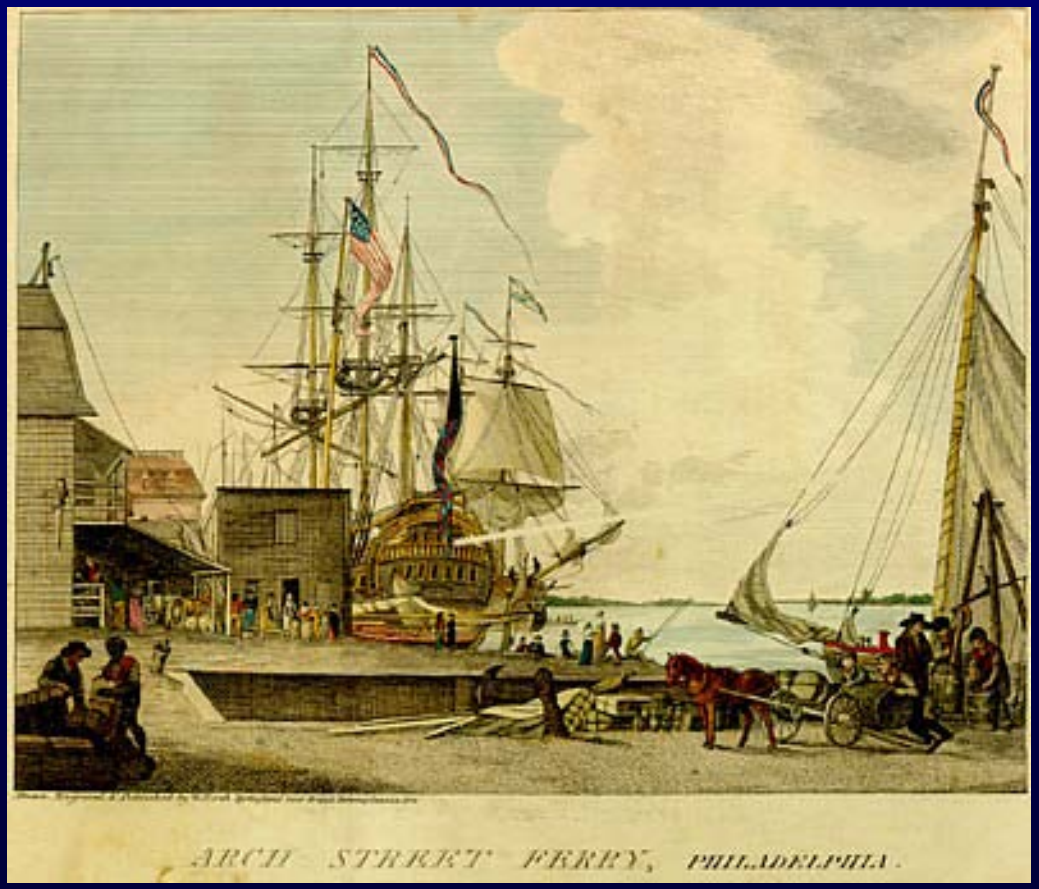
Outbreak in Philadelphia, 1793: I

- 1793年8月1日到11月9日期間，美國賓州費城當時只有五萬人口，卻因為黃熱病而死掉五千人。
- 九月底就已經有二萬人逃離費城，疫情死亡的高峰出現在十月，到了十一月開始結霜後，蚊子沒法生存，疫情才告終止。
- 但當時並不知道蚊子是傳播的元兇，要到十九世界末才了解黃熱病是經由蚊子傳染。

Outbreak in Philadelphia, 1793: II

- 費城市長及一個24人委員會共同在費城布希丘(Bush Hill)上建立了一個熱病醫院醫治病人。由於當時發現黑人好像比較不會生病，因此號召當地黑人成立照顧團隊，照顧病患及清理屍體。
- 後來發覺黑人的死亡率其實跟白人差不多，整體也死了240人。 這一結果讓當地人更加恐慌。
- 鄰近的城市如巴的摩爾、紐約，都拒絕費城來的難民，並對費城來的物品實施檢疫。

1793費城黃熱病病例最早出現地



Spanish American War, 1898

Spanish-American War

- **美西戰爭**又稱**西美戰爭**是1898年美國為了奪取西班牙的加勒比海殖民地進而控制加勒比海而發動的戰爭。
- 在美西戰爭期間, 黃熱病肆虐, 美國軍醫沃爾特・列德跟三個助理醫生James Carroll、Aristides Agramonte 以及Jesse Lazear通過用自身進行實驗的方式找到了疾病爆發的原因。他們在另一位醫生品嚐病人嘔吐物來證明黃熱病非傳染性疾病的基礎上開展研究, 認為病毒是通過昆蟲叮咬而非人類接觸進行傳播。為了證明這一發現, 三位助理醫生在去古巴實地考察的途中讓蚊子盡情叮咬, 使試驗得以繼續。但他們也因此付出了代價:Lazear在試驗過程中失去生命, 而Carroll長期患有併發症, 最終53歲便與世長辭。

In 1881, Carlos Juan Finlay, a physician in Havana, first proposed that yellow fever was a mosquito-borne illness, which subsequently was proven by Walter Reed and colleagues.

U.S. Army doctor Discovered the Cause of Yellow Fever
August 27, 1900

Research and Walter Reed

Walter Reed, M.D., (1851-1902) was an American Army surgeon who led the team which proved the theory first set forth in 1881 by the Cuban doctor and scientist **Dr. Carlos Finlay** that yellow fever is transmitted by mosquitoes rather than direct contact. The risky but fruitful research work was done with human volunteers, including some of the medical personnel such as **Clara Maass** and surgeon **Jesse W. Lazear** Walter Reed Medal winner who allowed themselves to be deliberately infected and died of the virus. All this lead to the elimination of Yellow Fever from Cuba and allowed the final construction of the Panama Canal.

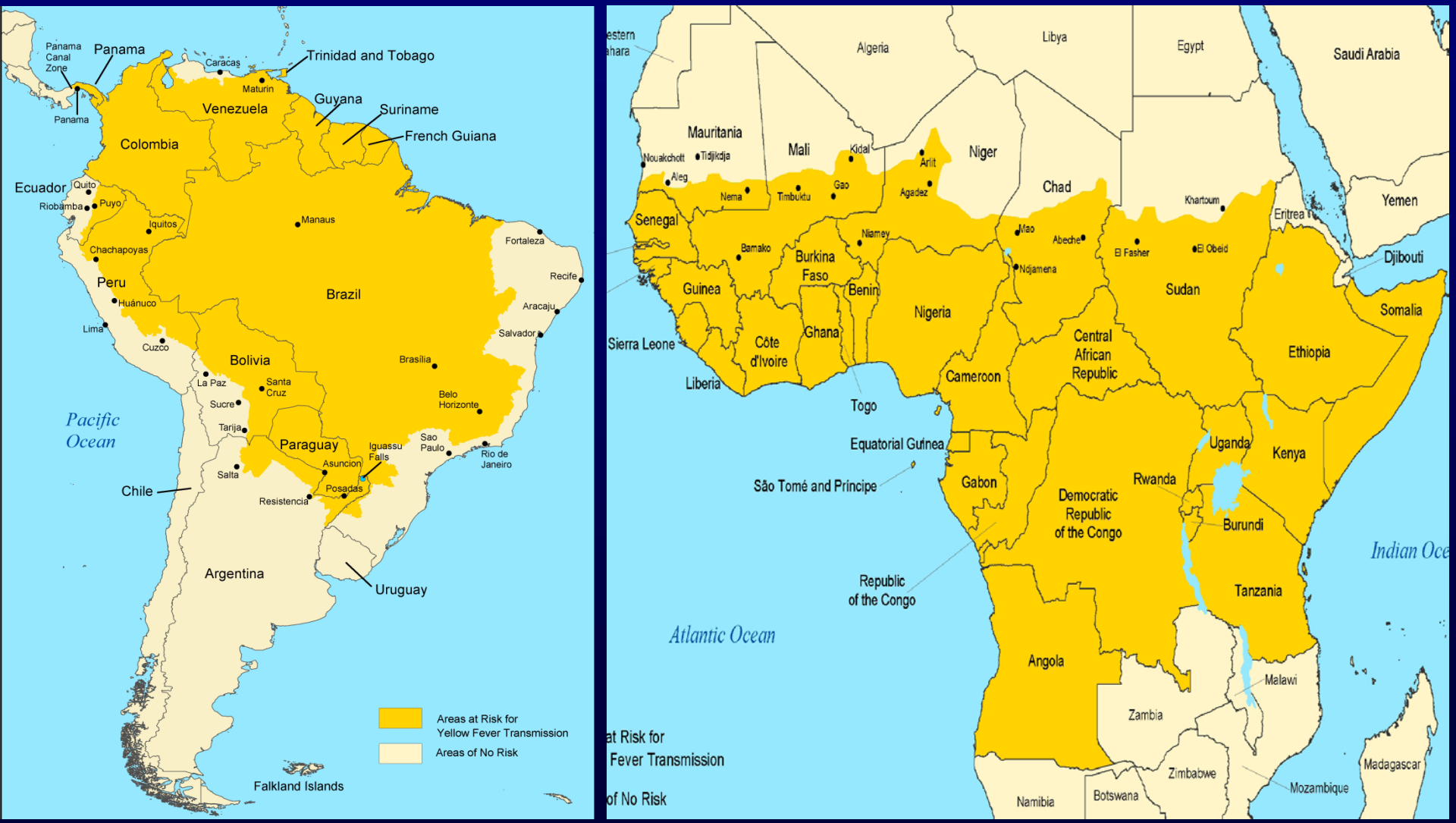
Clara Maass

On August 14, 1901, Maass allowed herself to be bitten by infected mosquitoes for the seventh time Maass once again became ill with yellow fever on August 18 and died on August 24. Her death roused public sentiment and put an end to yellow fever experiments on humans.

Yellow Fever (YF)

- Caused by yellow fever virus (*Flavivirus)*
- Transmitted predominantly by *Aedes* mosquitoes
- Endemic in equatorial Africa and South America
- Estimated 200,000 cases and 30,000 deaths annually
- Overall case-fatality rate in Africa 23%

Worldwide Distribution of Yellow Fever

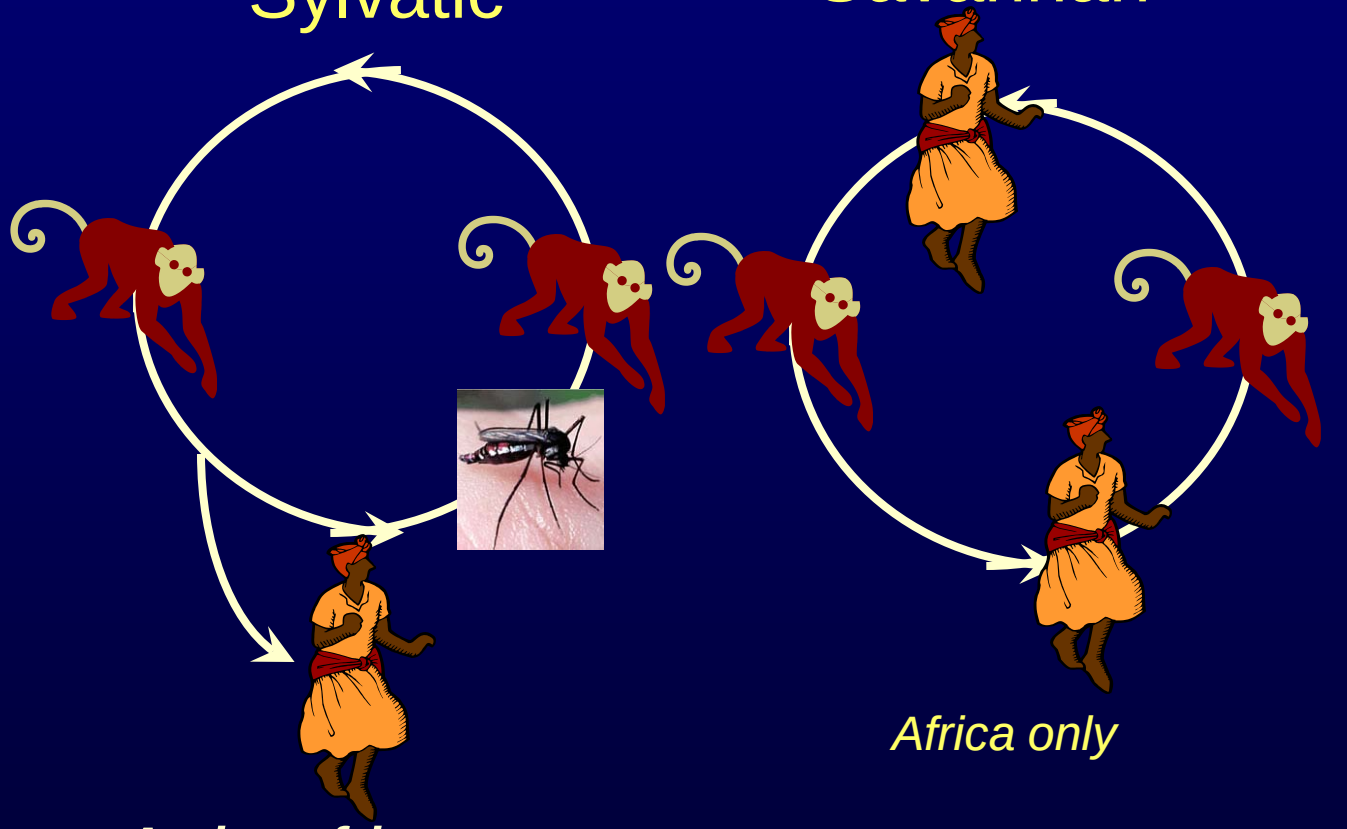


YF Virus Transmission Cycles in Africa

Jungle/
Sylvatic

Intermediate/
Savannah

Urban

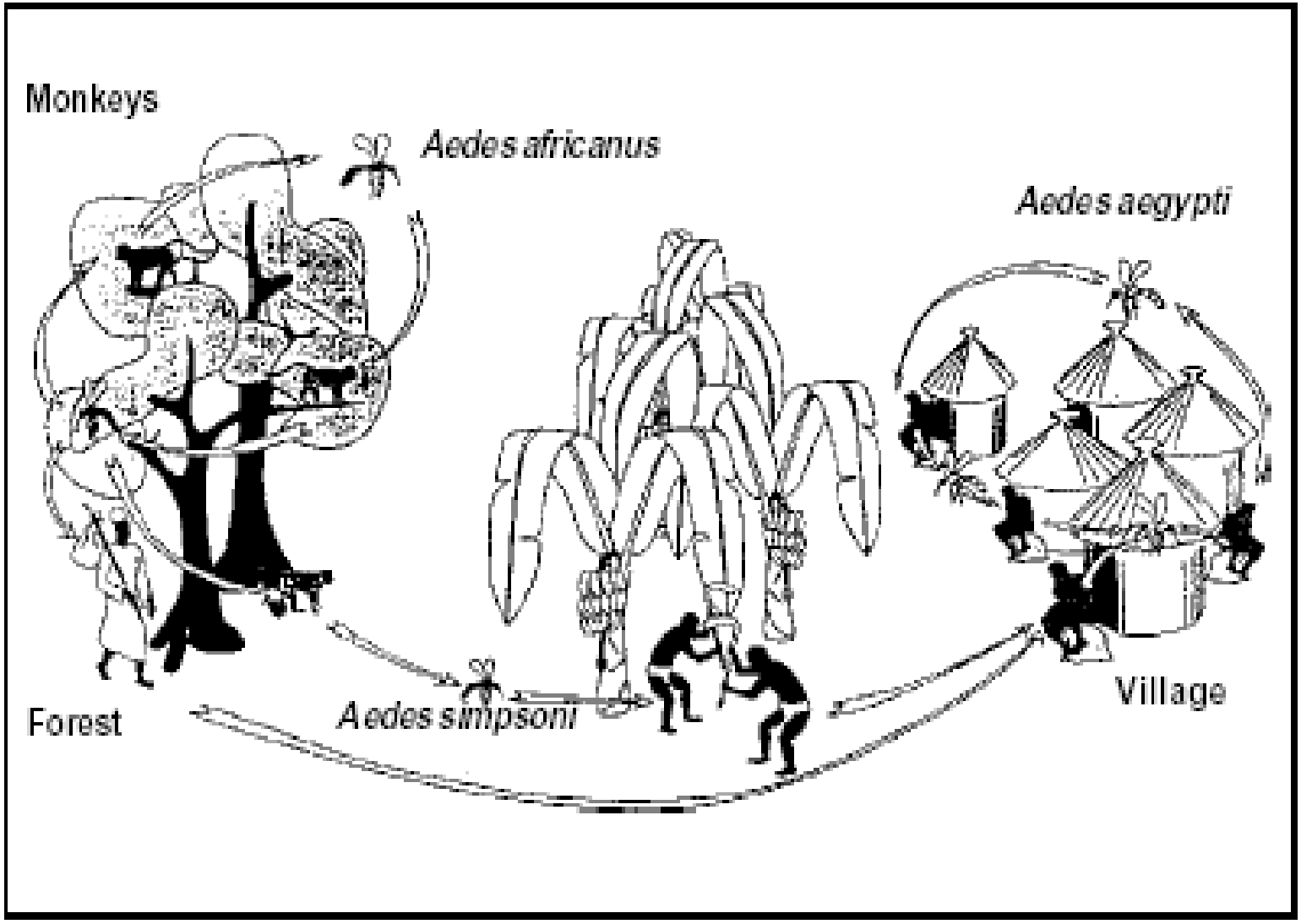


Africa only

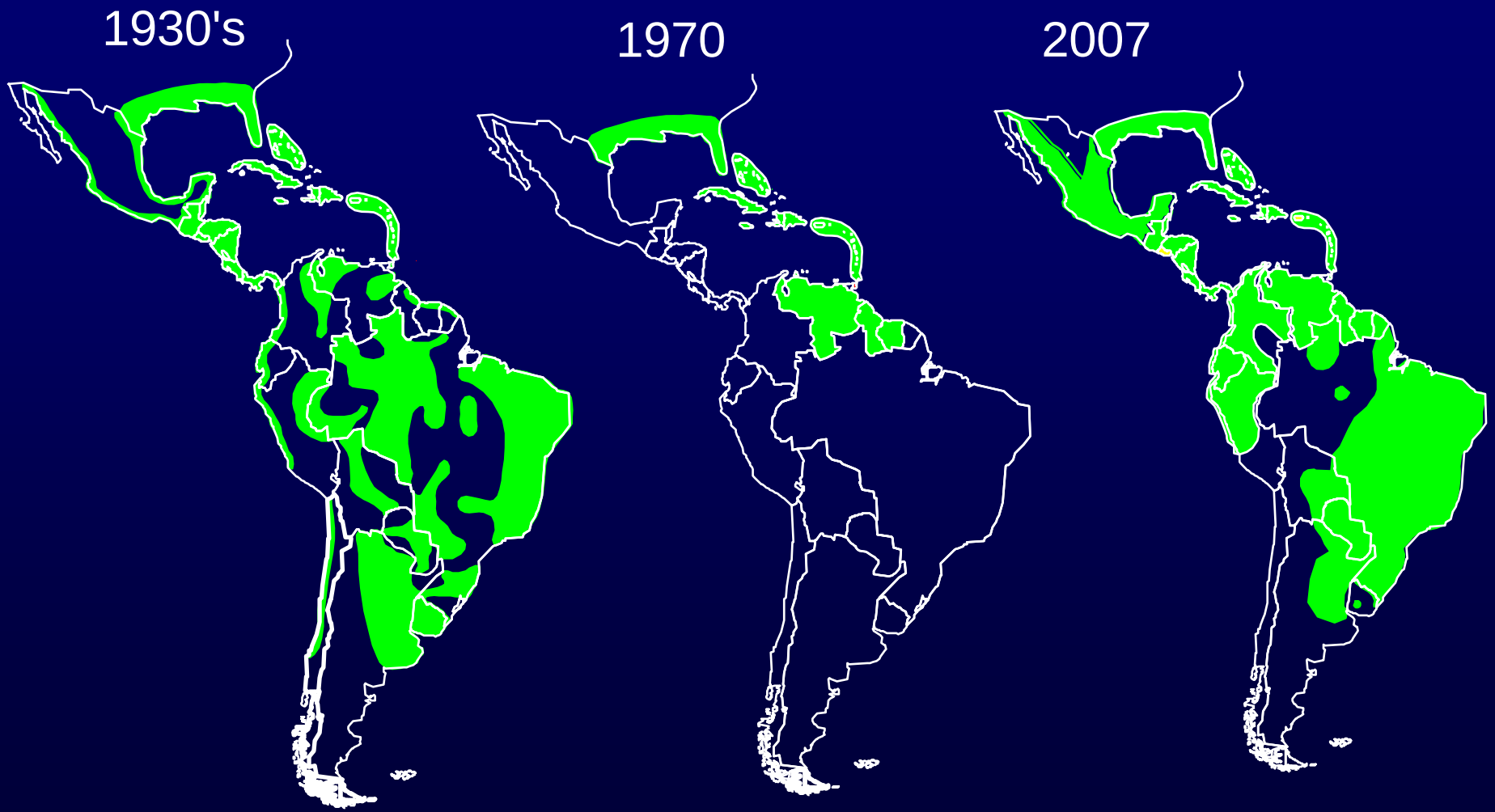
***Aedes africanus* spp.**
***Haemagogus* spp.**
***Sabethes* spp.**

Semi-domestic
***Aedes* spp.**

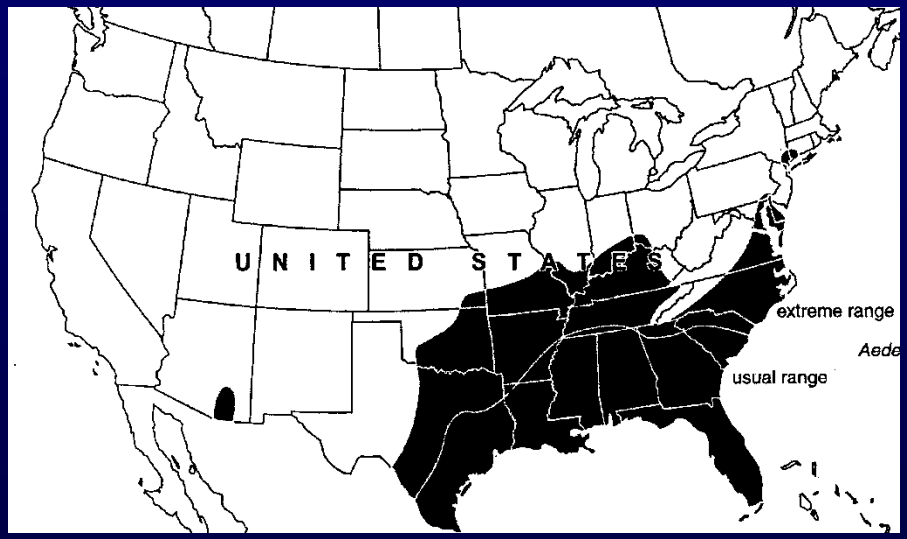
Aedes aegypti


Monkeys
Aedes africanus
Aedes aegypti
Forest
Aedes simpsoni
Village

Aedes aegypti Distribution in the Americas



Ae. aegypti – United States

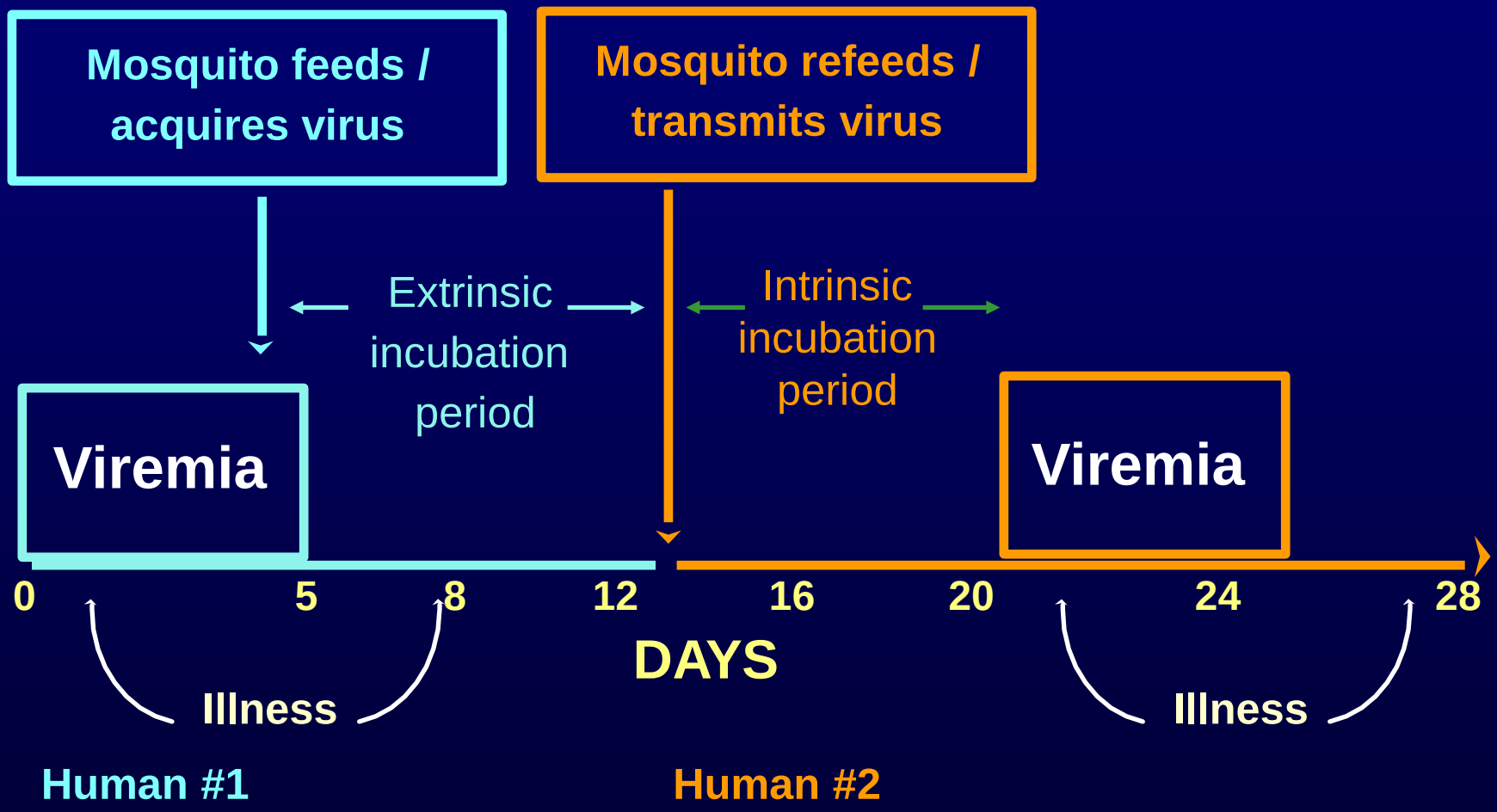


Darsie RF and Ward RA. Identification and Geographical Distribution of the Mosquitoes of North America, North of Mexico. Gainesville, FL: University Press of Florida; 2005: 226

Role of humans in yellow fever transmission

- Incubation period of 2-6 days
- Human become viremic; capable of infecting mosquitoes
  - Shortly before onset of fever and for the first 3–5 days of illness
  - Virus has been found in the blood up to 17 days after illness onset
- The extrinsic incubation period in *Ae. aegypti* is 9–12 days
  - Once infected, mosquitoes remain so for life

Timeline of yellow fever transmission



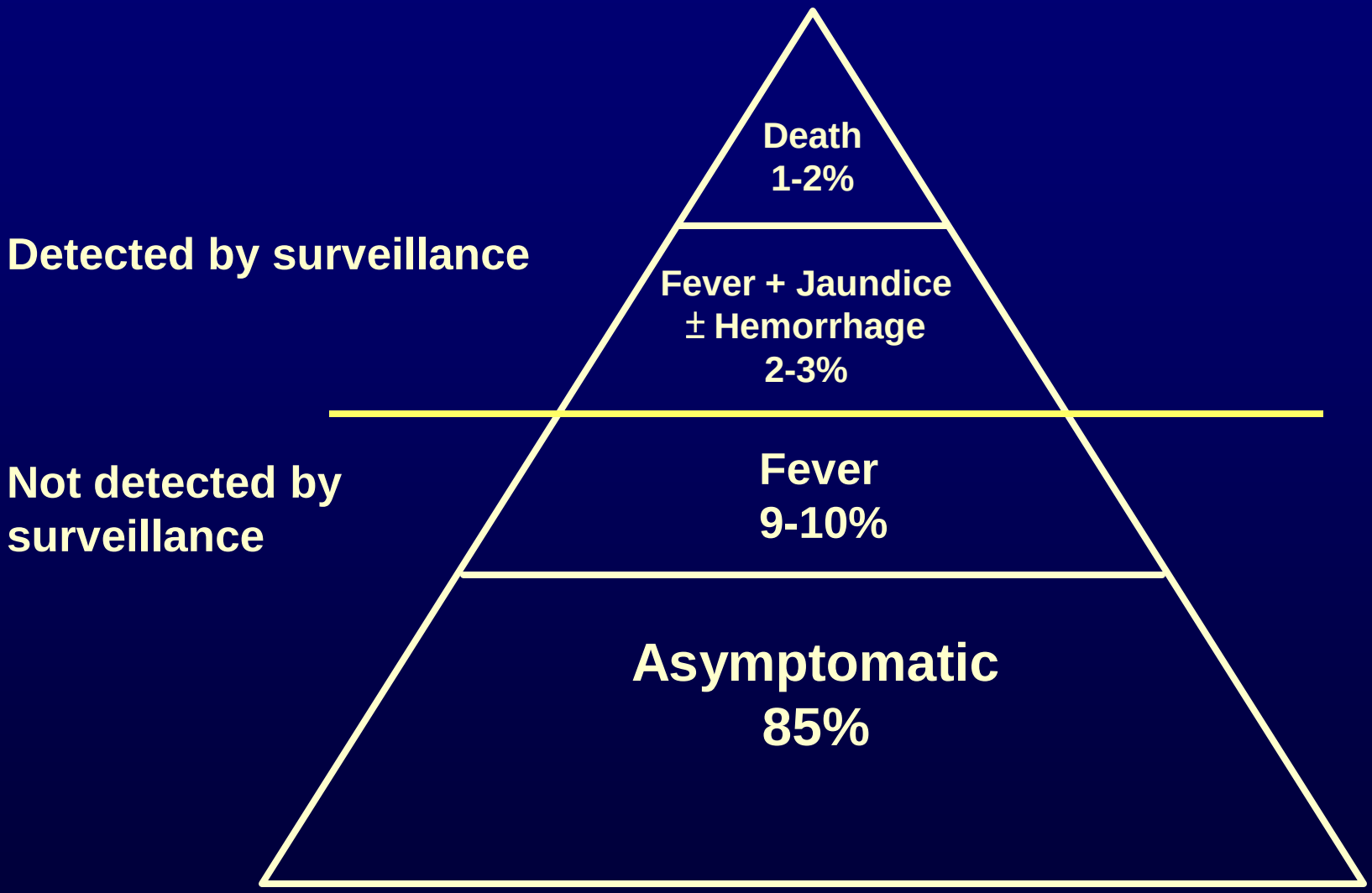
Three Stages of YF

- Early stage: Headache, muscle and joint aches, fever, chills, loss of appetite, vomiting, and jaundice are common.
- Period of remission: After 3 - 4 days, fever and other symptoms go away.
- Period of intoxication: Multi-organ dysfunction occurs.

Symptoms

- Jaundice
- Headache
- Fever/chills
- Vomiting (blood)
- Muscle aches
- Hemorrhaging
- Seizures
- Arrhythmia
- Delirium
- Decreased urination
- Red eyes
- Coma

YF Clinical Presentation



Incubation period of 2-6 days

Monath, Lancet Infect. Dis. 2001;1:11-20

Diagnostic Testing for Yellow Fever

- Laboratory diagnosis usually accomplished by testing of serum for antibodies
  - ELISA on serum samples to detect YF-specific IgM and IgG antibodies
  - Confirmatory (plaque reduction neutralization testing, PRNT) testing is needed due to cross-reactive flaviviral antibodies (e.g., dengue, WNV)
- Acute samples often positive for virus by viral isolation or viral RNA detection through RT-PCR
- Post-mortem samples should be obtained
  - Frozen – viral isolation and RNA detection
  - Fixed – IHC staining

YF Treatment, Prevention and Control

- Treatment
  - No specific anti-viral treatment
  - Supportive therapy

- Prevention and Control
  - Vaccination
  - Mosquito control

Immunity to Yellow Fever

- Natural disease provides life-long immunity
- Sporadic disease occurrence and deadly nature does not allow for high levels of immunity
- Most areas have no previous immunity and minimal cross protective immunity to YF
- Yellow fever 17D Vaccine
  - Live attenuated viral vaccine
  - Given every 10 years

Development of 17D Vaccine

- Asibi strain obtained in 1927
- Passed hundreds of times through monkeys, mosquitoes, mouse and chicken embryonic tissue
- Two strains currently used in vaccine development
  - 17DD – separated at passage 195 then subsequently passed to 286/7; strain used in Brazil
  - 17D-204 – separated at passage 204 then passed to 233-239 depending on vaccine; strain used outside Brazil (US, France, Dakar, Switzerland, Russia, China)

Current 17D Yellow Fever Vaccines

- All produced in eggs
- Differ in substrain, passage level, stabilizers, salt, diluent
- All are heterogeneous mixtures of virion subspecies
- Seed-lot system limits vaccine lots to single passage from secondary seed
  - Developed in 1941 secondary to encephalitis cases noted following vaccination
    - Vaccine ‘redeveloped’ neurovirulence with passages beyond the current levels

Currently Available 17D Vaccines

- WHO prequalified
  - Bio-Manguinhos, 17-DD, Brazil
  - sanofi pasteur, Stamaril®, 17D-204, France
  - Pasteur Institute Dakar, 17D-204, Senegal
- Local consumption
  - sanofi pasteur, YF-Vax®, 17D-204, USA (used in USA and Canada)
  - Vaccine produced in China (17D, Rockefeller Foundation) and Russia (17 D-204)
- Previous production
  - Chiron, Arilvax®, 17D-204, United Kingdom
  - 17 D-204 in India, Colombia, Australia, S Africa
- Anticipated production
  - Berna, Flavimune®, 17D-204 (former Robert Koch Institute)

Yellow Fever Vaccine Requirements

- Most endemic countries require proof of vaccination for all travelers coming from other endemic areas
- Certain countries with the vectors but without the disease require proof of vaccination for all travelers from endemic areas
- The United States has no vaccine requirement for entry

Indications for YF Vaccine

- For persons ≥ 9 months of age
  - Planning travel to or residence in an endemic area
  - Planning travel to a country with an entry requirement
- Needs to be given ≥ 10 days prior to arrival in endemic area
- Revaccination at 10 year intervals

Use of 17D Vaccine

- From 1937-2008 over 500 million doses have been given to humans
- No placebo controlled studies of efficacy
- Incidence of yellow fever among laboratory workers and in endemic areas declined after vaccination began

Common Adverse Events

- Fever, headache, backache 3-7 days after vaccination: 5%-15%
- Injection site inflammation 1-5 days after vaccination: 1%-30%
- Mild neutropenia – one study
- AST elevation: 4% – one study
- Variable with study

Serious Vaccine Adverse Events and Rates

- Overall reporting rate for serious adverse events is 4.7 per 100,000 doses*
- Three primary serious adverse events
  - Anaphylaxis – 0.8-1.4 per 100,000 doses
  - Neurologic disease – 0.4-0.8 per 100,000 doses
  - Viscerotropic disease – about 0.3-0.4 per 100,000 doses

* VAERS data from 2000-2008; accepted for publication *Vaccine*

Neurologic Disease

- Absolute number of cases is unknown
- Onset 11 days following vaccination (2-28 days)
- Most common presentation is meningoencephalitis
  - Others: GBS, ADEM, bulbar palsy, Bell's palsy
- More common following initial vaccination
- Rarely fatal
  - One death in a HIV-positive patient with CD4 count < 200/mm^3 in Thailand
  - One death in a healthy 3-year-old child in US
  - Three deaths with neurologic symptoms in Kenya during 1990's mass vaccination campaign

Viscerotropic Disease

- Severe illness similar to wild-type disease with vaccine virus proliferating in multiple organs
- Over 40 cases since first recognized in 2001
- Onset 3 days following vaccination (1-8 days)
- Seen after initial immunization with YF vaccine
- Reported after use of most 17D vaccines
- Sex and age distribution

Sex	% total	Mean age	Age Range
Female	37% (14)	30	4-79
Male	63% (24)	58	11-79

- 53% mortality

Diagnostic Testing for Serious VAERs

- Neurologic disease
  - Detection of vaccine virus (RNA or isolation) or YF-specific IgM antibodies in CSF
  - YF-specific IgG antibodies in CSF or IgM and IgG antibodies in serum are not diagnostic
  - GBS and ADEM diagnosis of exclusion
- Viscerotropic disease
  - Detection of vaccine virus in serum either > 7 days post vaccination or exceeding 3 log10 pfu/mL
  - Post-mortem detection of vaccine virus in tissues
  - Antibody testing not diagnostic as Ab response is usually intact in patient with viscerotropic disease

Special Interests

- Pregnancy
  - Brazilian vaccine campaigns (early in pregnancy)
    - Studies of 340 infants
      - No increase in major malformations
      - Increase in minor malformations (skin naevus)
    - Studies of 480 pregnant women
      - 98.7% developed a protective immune response
- Breastfeeding
  - Breastfeeding as route of transmission to an infant with YF vaccine associated neurotropic disease
- HIV
- Immunosuppressant medication
  - TNF-alpha inhibitors and interferon therapy

YF Vaccine Contraindications

- Infants < 6 months of age
- Hx of hypersensitivity to
  - Eggs
  - Chicken protein
  - Gelatin
- Immunosuppression from illness or drugs
- Hx of thymus disorder
- Current radiation therapy

YF Vaccine Precautions

- Adults ≥ 60 years of age
- Infants 6-8 months of age
- Asymptomatic HIV infection
- Pregnancy
- Breastfeeding

Use of Yellow Fever Vaccine in U.S.

- Advisory Committee on Immunization Practices (ACIP) periodically reviews and provides recommendations for yellow fever vaccine use in the United States
- Last guidelines updated in 2002

  http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5117a1.htm
- Working group currently updating the guidelines
- Anticipated updated guidelines in late 2009/early 2010

Risk-Benefit of Vaccination

- Risk of acquiring yellow fever for travelers
  - Africa: Estimated 50 per 100,000 per 2 week stay during peak transmission from July–October
    - Average annual risk closer to 10 per 100,000 per 2 weeks (lower risk during “off season”)
  - South America: Estimated 5 per 100,000 per 2 week stay
- Risk of serious adverse event >70 years old
  - Any serious event: 12.6 per 100,000 doses
  - YEL-AVD: 2.3 per 100,000 doses

International Health Regulations – 2005

- Allow countries to require proof of YF vaccination for entry
- Goal is to prevent importation and indigenous transmission of YF virus
- Proof of vaccination must be documented on *International Certificate of Vaccination or Prophylaxis (ICVP)*
- YF vaccine is only vaccine currently required under International Health Regulations
  - Traveler without proof of vaccination can be detained for 6 days (incubation period)

Requirements versus Recommendations

- *Requirements*
  - Permitted by IHR
  - Established by individual countries for entry
  - To prevent importation and transmission of YF virus
  - Subject to change at any time
- *Recommendations*
  - Advice given to prevent YF infections in travelers
  - Based on best available YF epidemiologic data
  - Subject to change depending on disease conditions
  - CDC and WHO are harmonizing recommendations

Medical Waivers for YF Vaccination

- If YF vaccine is medically contraindicated
  - Complete “Medical Contraindication to Vaccination” on ICVP
  - Give traveler signed, dated, and stamped exemption letter on physician's letterhead stationary
  - Inform traveler of increased risk of YF with nonvaccination
  - Counsel traveler about mosquito prevention measures
- Issuance of waiver does not guarantee its acceptance by destination country
- Traveler should consider contacting destination country embassy for further guidance

Mosquitoes Do Not Read Medical Waivers!

- Unvaccinated travelers going to endemic areas could be at significant risk of contracting YF
- During 1970-2002, 9 cases of YF reported in unvaccinated travelers to endemic countries (8 fatal)
- Options for travelers with contraindications or precautions to YF vaccine
  - Get YF vaccination and travel to endemic area — *risky*
  - Get waiver and travel to endemic area — *risky*
  - No vaccine and no travel to endemic area – *least risky*

Personal Protection Measures

- Vaccination
- Use insect repellant on exposed skin
  - DEET
  - Picaridin
  - Oil of lemon eucalyptus
  - IR3535
- Wear long sleeves, long pants, hats, socks
- Treat clothes with permethrin
- Stay in well-screened or air conditioned accommodations