Yellow Fever: A Review

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Objectives

- Describe the epidemiology and clinical manifestations of yellow fever
- Discuss indications and contraindications to yellow fever vaccination
- Understand new research into fractional dosing, potential treatments, and vector control

Pre-Test

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A. Malaria
B. Respiratory syncytial virus
C. Chagas disease
D. Hepatitis C

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Yellow Fever

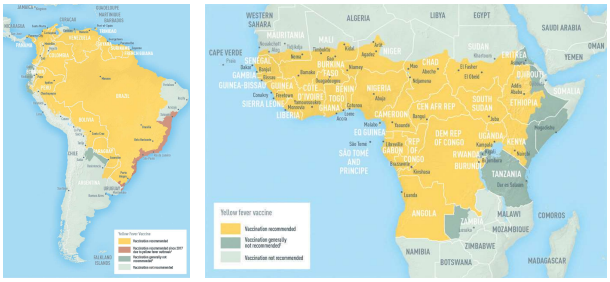
Source: http://www.panamahistorybits.com/article.asp?id=2012-04-26b

Overview

- Yellow fever virus (YFV) is an enveloped, single-stranded positive-sense RNA virus
- Family *Flaviviridae*, prototype of genus *Flavivirus*
- Other members of the genus *Flavivirus* include:
  - **Dengue virus (DENV)**
  - **Zika virus (ZIKV)**
  - Japanese encephalitis virus (JEV)
- Related to hepatitis C virus and **chikungunya virus (CHIKV)**

Overview

- Yellow fever virus (YFV) is endemic in 47 countries across sub-Saharan Africa and South America
  - 34 countries in Africa and 13 in South America
- Estimates for burden of disease vary:
  - 200,000 to 1.8 million infections annually
  - 50,000 to 300,000 severe infections
  - 20,000 to 180,000 deaths
  - Vast majority of deaths occur in Africa but the case fatality rate in South America is higher (40-60% compared with 20%)



Source: https://www.cdc.gov/yellowfever/maps/index.html

Overview

- Transmission Cycles
  - Jungle (Sylvatic):
    - Hosts: Non-human primates (NHP), humans are incidental hosts
    - Vectors: *Aedes spp.*, *Haemogogus spp.*, and *Sabethes spp.* mosquitos
  - Intermediate (Savannah):
    - Hosts: NHPs and humans
    - Vectors: *Aedes spp.* mosquitos
    - Only in Africa
  - Urban:
    - Hosts: Humans
    - Vector: *Aedes aegypti* mosquito

History of Outbreaks

- Virus originated in Eastern/Central Africa roughly 1500 years ago
- Spread to West Africa and then to the Americas in the 1400-1800s
  - via the Trans-Atlantic slave trade
- Large outbreaks in the 1700-1800s in North America and Europe
  - as far north as Boston and Dublin
- Vector control efforts eliminated urban yellow fever in the Americas
  - facilitated construction of Panama Canal which France had previously abandoned
- No documented outbreaks in Asia despite appropriate vectors/hosts

Recent Outbreaks-Africa

- In December 2015, an outbreak started in Angola
  - Spread to Democratic Republic of the Congo and Kenya
  - 1000 confirmed cases and 7000 suspected ones
- 11 unvaccinated Chinese workers in Angola returned home to China where they presented with symptoms of yellow fever
- 30 million doses of vaccine were needed to control the outbreak
  - The global stockpile is set at 6 million doses
  - Employed fractional-dosing program to increase coverage
- Ongoing outbreak in Ebonyi state-Nigeria with 36% case fatality rate

Recent Outbreaks-South America

- Between January 2016 and December 2018, yellow fever was confirmed in seven countries in South America
  - 723 infections and 237 deaths
- Outbreak preceded by large die-off of NHP hosts
  - similar die-off seen in 2008
- Wave of infection moved towards populous coastal cities in Brazil where yellow fever was eliminated 70 years prior
- YFV isolated from *Ae. albopictus* in 2017, never documented before

Eliminate Yellow Fever Epidemics (EYE)

- Developed by the WHO following the Angola/DRC outbreak
- Goal is to eliminate yellow fever epidemics by 2026
  - Need 1.4 billion doses of vaccine to accomplish
- Three objectives:
  - "(1)Protect at-risk populations;
  - (2) prevent international spread and
  - (3) contain outbreaks rapidly"
- Employed to respond to outbreak in Brazil and ongoing outbreak in Nigeria

Clinical Manifestations

- Categories of infection:
  - Subclinical infection
  - Non-specific febrile illness
    - Fever, headache, vomiting, myalgias
  - Potentially fatal liver disease and hemorrhagic fever
    - Jaundice, hemorrhage, SIRS, organ failure
- 90% of infected individuals develop subclinical/non-specific illness

Clinical Manifestations

- Course of infection in symptomatic individuals:
  - Period of infection (3-6 days after bite of an infected mosquito)
  - Period of remission
  - Period of intoxication (10-15% proceed to severe disease)
- Case fatality rate similar to Ebola and Marburg

Diagnosis

- Clinical findings:
  - Leukopenia
  - High fever with bradycardia (Faget's sign)
  - Transaminitis (AST > ALT, correlates with disease severity)
- Serology
  - Limitation: cross-reactivity among the flaviviruses
- Nucleic acid tests
  - Limitation: primarily limited to regional and national laboratories
- Lack of rapid and accurate point-of-care test
  - -Reverse-transcription loop-mediated isothermal amplification (RT-LAMP) shows promise

Treatment

- No specific treatment currently exists
- Supportive care (intensive if available)
- New research has shown that sofosbuvir may be a treatment option
  - Binds NS5b of flaviviruses
  - Interferes with replication in hepatic cells
  - Sofosbuvir is converted to its active metabolite in the liver
  - Demonstrated effectiveness against DENV, ZIKV, and CHIKV
  - Greatest effect seen when given prophylactically

Vaccine

- Yellow fever vaccine is a live, attenuated virus with rare side effects
  - Yellow-fever vaccine-associated neurotropic and viscerotropic disease (YEL-AND/YEL-AVD)
- Indications
  - Persons nine months or older traveling/residing in areas at risk for yellow fever transmission
- Contraindications
  - Age less than 6 months
  - Thymus disorders
- Precautions
  - Age six to eight months and age 60 years or older
  - Pregnancy

Vaccine Updates

- WHO guidance:
  - As of 2016, one-time dose is considered to provide lifelong immunity
- Fractional-dosing
  - Employed to control outbreaks in Brazil and in multiple African countries
  - Lack of standard virus concentration in vaccine (only minimum requirement)
  - Unknown duration of effectiveness
    - Some new data eight and ten years after vaccination

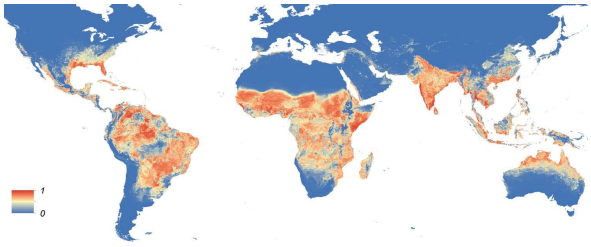
Vaccine Updates

- Supply in the United States:
  - Sanofi Pasteur is the only approved manufacturer and is transitioning to a new production facility
  - Anticipated to resume production of YF-Vax in 2020
  - Stamaril (also produced by Sanofi Pasteur) made available through FDA's Investigational new drug (IND) program
  - Clinics offering Stamaril can be found here: https://wwwnc.cdc.gov/travel/page/search-for-stamaril-clinics

Vector Control

- Integrated *Aedes* management
  - Integrated surveillance
  - Vector control
  - Community engagement and mobilization
  - Collaboration
- Climate change
  - Increased geographic range of both *Ae. aegypti* and *Ae. albopictus*

Predicted Global Distribution of *Ae. aegypti*



Source: https://elifesciences.org/articles/08347

Travel

- 4 billion people flew in 2017, expected to double in next 20 years
- Air travel in Asia represents 1/3 of all air travel
- Lack of enforcement of IHR
  - 67% of flyers from yellow-fever endemic areas traveling to at-risk cities were not required to show proof of vaccination
  - 77% of flyers traveling to endemic areas were not required to show proof of vaccination
- Unknown number of foreign workers in at-risk areas
- Counterfeit certificates

The Risk to Asia

- Mystery why yellow fever is not present in Asia
  - Competent vectors, hosts, and environmental conditions
- Genetic differences in NHPs and humans impacting disease severity
  - Historical examples: Tennessee, British and Indian troops in Africa
- Cross-protective immunity between flaviviruses
- Competence of *Ae. albopictus* as a vector
- 2 billion people at risk

The Role of Family Physicians

- Educate our patients and communities
- Promote routine vaccination programs
- Discuss travel plans and history during clinical encounters
- Advocate for public health

Summary

- Yellow fever virus could follow path similar to other arboviruses
- Sylvatic cycle prevents elimination
- Safe and effective vaccine is “available”
- New diagnostic tests and treatments are on the horizon
- Coordinated response needed to control vector and prevent spread
- If the virus spreads to Asia, the global health system is unprepared

Post-Test

1) Which of the following individuals should receive the yellow fever vaccine before he or she travels?

A. A 46 year-old healthy man who is visiting Ghana and previously received the vaccine twenty years ago.
B. A healthy five month-old infant traveling with her family to northern Brazil.
C. A 27 year-old healthy pregnant woman visiting Nigeria.
D. A 35 year-old HIV-positive man with a CD4 count of 450/mL traveling to South Africa.

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Post-Test

2) Which individual should receive a waiver letter in lieu of yellow fever vaccination?

A. A 58 year-old woman with diabetes traveling on an adventure holiday to Cameroon.
B. A 42 year-old man with a history of thymectomy visiting Paraguay.
C. A 27 year-old woman with rheumatoid arthritis on prednisone 5mg/day visiting family in Brazil.
D. A 10 month-old traveling with family on holiday in Angola.

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Questions?

Thank you!

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