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 for severe disease 20-50%
Virus Transmission Cycles in Africa

- **Intermediate/Savannah**: Semi-domestic Aedes spp.
- **Urban**: Aedes aegypti

_Africa only_
Aedes aegypti
Distribution in the Americas

1930's

1970

2007
Ae. aegypti – United States

Role of Humans in Yellow Fever Transmission

- Incubation period of 2-6 days
- Humans 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

Mosquito feeds / acquires virus

Extrinsic incubation period

Viremia

Illness Human #1

Mosquito refeeds / transmits virus

Intrinsic incubation period

Viremia

Illness Human #2
YF Clinical Presentation

- Asymptomatic: 85%
- Fever: 9-10%
  - Fever + Jaundice ± Hemorrhage: 2-3%
  - Death: 1-2%

Incubation period of 2-6 days

Diagnostic Testing for Yellow Fever

• Testing of serum for antibodies
  – ELISA to detect YF-specific IgM and IgG antibodies
  – Confirmatory 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
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

- Residents in 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:
  – 17DD – strain used in Brazil
  – 17D-204 – strain used outside Brazil (US, France, Dakar, Switzerland, Russia, China)
Current 17D Yellow Fever Vaccines

- All produced in eggs
- Differ in sub-strain, passage level, stabilizers, salt, diluent
- All are heterogeneous mixtures of virion subspecies
- Seed-lot system limits vaccine lots to single passage from secondary seed
  - Vaccine ‘redeveloped’ neurovirulence with passages beyond the current levels
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 U.S. and Canada have no vaccine requirement for entry
Indications for YF Vaccine

• For persons $\geq 9$ 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 $\geq 10$ days prior to arrival in endemic area

• Revaccination at 10 year intervals
Use of 17D Vaccine

- 1937-2008: > 500 million doses
- 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

• 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: 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/mm³ 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 60 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
- > 60% mortality
Use of Yellow Fever Vaccine

• ACIP provides recommendations for yellow fever vaccine use in the U.S.
  – Updated guidelines in 2010
    http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5907a1.htm?s_cid=rr5907a1_e

• CATMAT
  – Updated 2010
YF Vaccine Contraindications

- Allergy to vaccine components
- Infants < 6 months of age
- Altered Immune Status
  - Thymus disorder associated with abnormal immune cell function
  - HIV with severe immune suppression
  - Other immunodeficiencies
  - Immunosuppressive and immunomodulatory therapies
YF Vaccine Precautions

- Adults $\geq 60$ years of age
- Infants 6-8 months of age
- Asymptomatic HIV infection
- Pregnancy
- Breastfeeding
Revised recommendations for HIV

• Symptomatic HIV infection or CD4 lymphocytes <200/mm³ — contraindication
• Asymptomatic HIV infection and CD4 lymphocytes 200–499/mm³ — precaution
• Asymptomatic HIV infection and CD4 lymphocytes >500/mm³ — vaccinate if itinerary truly poses yellow fever risk
• If vaccinating an HIV-infected person, consider measuring neutralizing antibody response to vaccination before travel
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
  – 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)
**INTERNATIONAL CERTIFICATE OF VACCINATION OR PROPHYLAXIS**

This is to certify that [name] **Josephine Doe**

Date of birth: **12 March 1970**

Nationality: **Canadian**

National identification document (if applicable): **Passport**

Signature: **Josephine Doe**

Has on the date indicated been vaccinated or received prophylaxis against: **Yellow fever**

In accordance with the International Health Regulations.

<table>
<thead>
<tr>
<th>Vaccine or prophylaxis</th>
<th>Date</th>
<th>Signature and professional status of supervising clinician</th>
<th>Manufacturer and batch no. of vaccine or prophylaxis</th>
<th>Certificate valid from:</th>
<th>Official stamp of the administering centre</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yellow fever</strong></td>
<td><strong>15 August 2007</strong></td>
<td><strong>John Smith R.N.</strong></td>
<td><strong>sanofi pasteur Lot# C035AA</strong></td>
<td><strong>25 August 2007</strong></td>
<td><strong>PHAC ASPC</strong></td>
</tr>
</tbody>
</table>
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
Medical Waiver Section of ICVP

CERTIFICATE
OF MEDICAL CONTRAINDICATION
TO VACCINATION

This is to certify that [name] Josephine Doe

date of birth 12 March 1970

nationality Canadian

cannot be vaccinated against (name of disease or condition)

Yellow fever

because of the following reason:

Severe allergy to eggs

Issued to | Délivré à
Josephine Doe

Ca

<table>
<thead>
<tr>
<th>Certificate of Medical Contraindication to Vaccination</th>
<th>Certificate de Contré-Indication Médicale à la Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated vaccine</td>
<td>Date</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>15 August 2007</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Signature]

[Date]

[PHAC + ASPC]
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
CDC Travelers’ Health (TH) Website

- [www.cdc.gov/travel](http://www.cdc.gov/travel)

- Comprehensive information source for TH
  - Destinations
  - Vaccinations
  - Diseases
  - Finding a TH clinic

- Continually updated with travel notices and news

- Contains online version of CDC Yellow Book
Harmonization of Recommendations and Risk Maps
Informal Working Group on the Geographic Risk of YF (WG)

• Meeting since September 2008

• Systematically re-evaluate areas at risk for YF

• Harmonize YF risk maps and country specific recommendations
Two Step Process:
Step I

• Harmonize CDC / WHO maps
Use of Vegetation Data from Satellite Imagery—Africa

Barren or sparsely vegetated
Use of Elevation Data—South America

Elevation limit of 2,300 m
Yellow Fever, countries or areas at risk

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization/CDC
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

©WHO 2008. All rights reserved.
Published Maps

- 2009 WHO ‘Green Book’
- 2010 CDC ‘Yellow Book’
Two Step Process:
Step II

Systematic Country Review:

• Countries without risk classification changes
• Countries with risk classification changes
### YF Risk Classification Criteria

<table>
<thead>
<tr>
<th>YF Risk Classification</th>
<th>YF vectors and NHP present</th>
<th>Human or NHP YF cases reported</th>
<th>Human serosurvey evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic</td>
<td>Yes</td>
<td>Repeatedly</td>
<td>High levels of infection</td>
</tr>
<tr>
<td>Transitional</td>
<td>Yes</td>
<td>Reported at long intervals</td>
<td>Evidence of infection</td>
</tr>
<tr>
<td>Low</td>
<td>Yes</td>
<td>None</td>
<td>Low levels of infection</td>
</tr>
<tr>
<td>No</td>
<td>Yes or No</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

---
No Change in Previous Risk Classifications

### Africa
- Angola
- Benin
- Burkina Faso
- Burundi
- Cameroon
- Central African Republic
- Congo
- Cote d’Ivoire
- Equatorial Guinea
- Gabon
- The Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Liberia
- Nigeria
- Rwanda
- Senegal
- Sierra Leone
- Togo
- Uganda

### Americas
- Guyana
- Suriname
- French Guiana
Countries with Risk Classification Changes, Proposed 2010

**Africa**
- Democratic Republic of Congo
- Eritrea
- Ethiopia
- Kenya
- Sao Tome and Principe
- Somalia
- Tanzania
- Zambia

**Americas**
- Argentina
- Brazil
- Colombia
- Ecuador
- Panama
- Paraguay
- Peru
- Trinidad and Tobago
- Venezuela
Preliminary Conclusions

• Risk maps → vaccination maps
• Low risk areas: “Areas with low potential for exposure”
  • Vaccination not generally recommended
• Final report due 2011
• New maps published
Yellow Fever Vaccination

- **Recommended**
- **Generally Not Recommended**
- **Not Recommended**

* Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler’s risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).
* Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler’s risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).
Yellow Fever Vaccine Module
Yellow Fever Provider Training Module

- Developed by CDC Travelers’ Health Branch
  - Web-based
  - Free
  - Duration 2-3 hours
  - Continuing education credits offered
- Distribution to state health departments for oversight within their jurisdictions
- Used by Scotland for certification
- Being adapted by PHAC
Yellow Fever: Information for Healthcare Professionals Advising Travelers

• Content presented in multiple ways
  • Interactive, multimedia
  • Case studies, videos, knowledge questions, maps

• Includes two lessons
  • Lesson 1: Yellow Fever: History, Epidemiology, and Vaccine Information
  • Lesson 2: The Pre-Travel Consultation and Best Practices for Yellow Fever Vaccine Providers and Clinics
Lesson 1:

- The history of yellow fever
- Global epidemiology of yellow fever
- Safe and appropriate use of the vaccine
- The precautions and contraindications to yellow fever vaccination
- How to recognize both the common and rare adverse events associated with yellow fever vaccination
Lesson 2:

- Pre-travel consultation
- Process for becoming a designated yellow fever vaccination provider in the US
- Best practices for providers and clinics that give yellow fever vaccination
- International Certificate of Vaccination and Prophylaxis (ICVP)
Lesson 1

Lesson 2
Questions

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.