Vaccines to Mitigate Risk During Travel

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Learning Objectives

1. Highlight 6 common travel vaccines
2. Understand the geographic locations or epidemiology of the 6 vaccine-preventable diseases
3. Become familiar with the current vaccine recommendations for these travel vaccines
Protection During Travel
### Licensed Travel Vaccines in US

- Yellow Fever
- Typhoid
- Hepatitis A
- Japanese Encephalitis
- Cholera
- Meningococcal
- Rabies

- Poliovirus
- Influenza
- Tetanus
- Measles, Mumps, Rubella
- Hepatitis B
- Pneumococcal
- Varicella
Beware of insect bites...
Yellow Fever (YF)

- Caused by a Flavivirus
- Transmitted by mosquito bite (*Ae. aegypti*)
- Yellow Fever causes 200,000 cases of clinical disease and 30,000 deaths each year
- Substantial underreporting, due to rural nature

1. WHO. Yellow Fever fact sheet, no. 100
2. Weekly Epi Rec 1990; 65: 213
Yellow Fever: Epidemiology

Geography

- Sub-Saharan Africa
  - 87% cases and 50% case-fatality ratio
- Tropical South America
  - 13% cases and 20% case-fatality ratio

Seasonality

- All-year but peaks with mosquito breeding
- **South America**: peak rainfall, humidity, temp = Jan-May
- **West Africa**: late rainy season to early dry season = July-Oct
Yellow Fever: Clinical Presentation

- Majority of human infections are asymptomatic, but spectrum can be mild to severe
- Incubation 3-6 days
- **Initial stage**: Abrupt fever and severe headache; nonspecific flu symptoms
- Recovery period or brief remission (viremia present): 1 day
- **Toxic phase** (15%): F, N/V, myalgia, arthralgia, jaundice, epigastric pain, renal insufficiency, and cardiovascular instability (viremia often not present)
  - Multi-organ failure with bleeding diathesis.
  - Case-fatality ratio 20-50%; especially with severe yellow fever with hepatorenal dysfunction
Yellow Fever: Risk and Prevention

Risk to Traveler

- 2-week stay for unvaccinated traveler:
  - **West Africa**
    - 50 illnesses per 100,000\(^1\)
  - **South America**
    - 5 illnesses per 100,000\(^1\)

Prevention

- Clothing barrier
- Insect repellant (DEET)
- Vaccination

  - There is no specific treatment, limited to supportive care
# Globally Available Yellow Fever Vaccines

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>WHO pre-qualify</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur, France</td>
<td>1987</td>
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<tr>
<td>Institut Pasteur de Dakar, Senegal</td>
<td>1999</td>
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<tr>
<td>Bio-Manguinhos, Brazil</td>
<td>2001</td>
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<tr>
<td>FSUE Chumakov, Russia</td>
<td>2009</td>
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</tbody>
</table>
Yellow Fever Vaccine in US

YF-Vax® (Sanofi Pasteur)

- Live, attenuated 17D-204 strain
- Single parenteral dose, 0.5 mL
- Approved: age ≥9 months
- International Certificate of Vaccination valid beginning 10 days after the date of vaccination

International Health Regulations (IHR)
- WHO World Health Assembly in May 2014: changed term of validity of certificate to lifetime (i.e., no booster doses necessary).
- Change entered into force legally June 2016
- ACIP recommendations (Feb 26, 2015)
- 10 year boosters not required
Current Recommendations

A single primary dose is adequate for most travelers (no booster)

Booster, every 10 yrs:
• HIV persons
• Lab workers routinely handling YF virus (if cannot measure YF-neut ab)

Booster dose, prior to travel for:
• Pregnant women (regardless of trimester)
• Immunocompetent persons w/ hx HSCT

Consider booster q10yr:
• High-risk (prolonged duration in highly endemic area)
Yellow Fever Vaccine:
Contraindications and Precautions

Contraindications
• Hypersensitivity to vaccine components: egg/chicken proteins, gelatin, latex (vial stopper)
• Prior anaphylaxis with vaccination
• Immune deficiencies
  symptomatic HIV, CD4 <200, malignant neoplasms, transplantation, etc.
• Infants age <6 months

Precautions
• Age 6-8 months or Age ≥60 years
• Pregnancy and breastfeeding
• Asymptomatic HIV and CD4 200-499
Yellow Fever Vaccine: Safety and Adverse Effects

• 10-30% mild systemic reactions
  – low-grade fever, headache, myalgia

• Hypersensitivity
  – 1.8 cases/100,000 doses

• Vaccine-associated Neurologic Disease (YEL-AND)
  – 3-28 d post-vax: Meningoencephalitis, GBS, bulbar/Bell palsy
    Overall: 0.8 cases/100,000 doses
    Age 60-69: 1.6 cases/100,000 doses
    Age ≥70: 2.3 cases/100,000 doses

• Vaccine-associated Viscerotropic Disease (YEL-AVD)
  – Viremia w/multi-organ involvement (63% case fatality)
    Overall: 0.4 cases/100,000 doses
    Age 60-69: 1.0 cases/100,000 doses
    Age≥70: 2.3 cases/100,000 doses
Yellow Fever Vaccine: Protection

- In endemic populations (assuming vaccine coverage of 60-80% of population):
  - Within 10 d 80-100% immunity
  - After 30 d ≥99% immunity\(^1\)

Among vaccinated travelers from industrialized countries: One case, non-fatal (Spain to West Africa, 1988)\(^2\)

3. Fig. WHO 2015
Yellow Fever outbreak in Angola- (12/2015-7/2016)

- 3,818 suspected cases
- 879 lab-confirmed infections
- 369 deaths
- Exported cases:
  - Dem Rep Congo, n=74
  - Kenya, n=2
  - China, n=11
- Yellow Fever mass vaccination campaign (initiated 2/2/16)
  - 18 million doses (by mid-June 2016)

China:
Of 5 with vaccination status info, all 5 cases did not have Yellow Fever vaccine
Beware of risk through ingestion...
Typhoid (& Paratyphoid)

• Human host-restricted bacterial pathogen
• *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi)
  – *S.* Typhi: 22M illnesses and 200,000 deaths per year
• serovars Paratyphi A, B, or C (*S.* Paratyphi).
  – *S.* Paratyphi: 6M illnesses

❖ Nontyphoidal *Salmonella* (NTS) include: *S.* Enteriditis and *S.* Typhimurium
  – Transmission: fecal-oral

Bull WHO 2004; 82:346-353
Typhoid: Epidemiology

- Associated with poor sanitation and lack of access to clean water
- World-wide distribution
  - High Incidence >100 cases / 100,000 person years
  - Medium 10-100 cases / 100,000 person years
- Highest risk: Southern Asia (6-30x higher than other regions)
- No seasonality

Bull WHO 2004; 82:346-353
Typhoid: Clinical Presentation

• Incubation 6-30 days
• **Insidious Onset:** gradual fatigue and fevers (102-104°F); abdominal pain, headache, malaise, anorexia, chills
• Without therapy: illness duration 3-4 weeks
• **Classic Presentation:**
  1st week - *stepwise* fever w/ bradycardia (pulse-temp dissociation)
  2nd week - abdominal pain and “rose spots”
  3rd week – hepatosplenomegaly, intestinal bleeding, perforation
• 15% serious complications: Intestinal hemorrhage, perforation, peritonitis, septic shock
• **Chronic Carrier State:** 1-6% infections; excrete organisms >1 year
  More common in women and those with cholelithiasis or abnormal biliary tract
Typhoid: Risk to Traveler

- CDC data, all travelers during 1994-1999:¹
  1,027 typhoid cases, 3 deaths
  - Risk associated with length of stay
  - Risk associated with location
    - 53% Indian subcontinent
    - 17% Mexico/Central America
    - 7% Caribbean
    - 3% Africa
    - 4% other

- CDC data, travelers to SE Asia during 2008-2011:²
  602 typhoid and 142 paratyphoid A cases
  5% typhoid cases and 20% paratyphoid cases were vaccinated

¹CID 2004; 39: 186-91
²Vaccine 2014; 32: 3577-9
Typhoid: Prevention & Treatment

Prevention:
- Safe food and water
- Vaccination

Treatment:
- Rehydration
- Prompt Antibiotics
  - First Line: Fluoroquinolones, 3rd Gen Cephalosporin, azithromycin
  - Beware: FQ resistance in SE Asia!
- Surgery - ileal perforation
- Corticosteroids
Globally Available Typhoid Vaccines

Parenteral vaccine:
- Typhoid Vi capsular polysaccharide
  - Typherix® (GSK), Typhim Vi® (SP), TypBar® (Bharat), Shantyph (Shanta), Typho-Vi® (BioMed), Zerotyph™ (Boryung, S. Korea), Typhevac® (Shanghai)
- Typhoid Vi conjugate (TT)
  - Peda-typh™ (BioMed, India)
- Combination: ViCPS+Hepatitis A
  - Hepatyrix® (GSK), Vivaxim® (SP)

Oral vaccine:
- Live Attenuated
  - Vivotif® (PaxVax)
Typhoid Vaccines Available in US

Typhim Vi® (Sanofi Pasteur)
- Purified Vi capsular polysaccharide (Vi PS)
- Single parenteral dose, 0.5 mL
- Approved: age ≥2 years
- Booster every 2-3 years

Vivotif® (Crucell-PaxVax, Inc)
- Live, attenuated bacterial strain (Ty21a)
- 4 oral doses, spaced alternating days
- Approved: age ≥6 years
- Booster every 5-6 years
Typhoid Vaccine:
Contraindication/Precautions

**Typhim Vi®**
- Hypersensitivity to vaccine components: typhoid polysaccharide, phenol, PBS
- Prior anaphylaxis with vaccination

Delay for concurrent acute febrile illness

**Vivotif®**
- Hypersensitivity to vaccine components
- Prior anaphylaxis with vaccination
- Immune deficiencies

Delay for concurrent acute febrile illness

*Efficacy reduced with concurrent antibiotics*
Typhoid Vaccine: Safety & Adverse Effects

Typhim Vi®
• 70-77% injection site pain, mild
• 42% headache
• 35% fatigue
• 1% fever

Vivotif®
• 6% abdominal pain
• 6% nausea
• 5% headache
• 3% fever
• 3% diarrhea
• <2% vomiting
• 1% skin rash

No transmission recorded
No vaccinemia or reversion events reported
Typhoid Vaccine: Protection

**Typhim Vi®**
- Nepal field trial (1986-88): 75% protection against typhoid fever
- South Africa field trial (1985-88): 55% protection against typhoid fever
- India field trial (2004-6): 61% protection
- Meta-Analysis (2007): 55% cumulative efficacy at 3 years

**Vivotif®**
- Egypt field trial (1978-81): 96% protection
- Chile field trials (1982-87): 59% protection, two-doses
- 67% protection, three-doses
- Indonesia field trial (1986-89): 79% protection, three-doses
- Meta-Analysis (2007): 51% cumulative efficacy at 3 years

Protection in US travelers using either vaccine (2008-11): 80% vaccine efficacy

1. NEJM 1987; 317: 1101-4
3. NEJM 2009; 361: 335-44
5. JID 1982; 145: 292-5
6. Vaccine 1990; 8: 81-4
Hepatitis A (HAV)

• Positive-stranded RNA virus
  – *Picornaviridae* family, *Heparnavirus* genus

• Primarily human host-restricted pathogen
  – Some non-human primate sp. hosts

• Single serotype
  – 4 genotypes, but not important for biology

• Transmission: fecal-oral
HAV: Epidemiology

- Associated with poor sanitation and hygiene
- Decline in US with vaccination
- World-wide distribution
- Highest risk: Sub-Saharan Africa, South Asia
- Intermediate risk: Central & South America
- No seasonality

Above: CDC Statistics & Surveillance
Below: CDC 2005 data
HAV: Clinical Presentation

- Incubation period: average 28 days (range 15-50 days)
- Age <6 years: majority asymptomatic, 10% jaundice
- Older than 6 yrs: >70% jaundice
- Abrupt Clinical Illness:
  - Fever, fatigue, loss of appetite, nausea, vomiting, joint pain, abdominal pain, dark urine, clay-color stools, jaundice
- Duration: usually 2 months, 10-15% prolonged/relapsing up to 6 months
- Case-Fatality: Overall 0.3% (1.8% for age >50 yrs)
HAV: Risk to Traveler

- CDC, estimated HAV cases (endemic and travelers):¹
  - 2011 – 2,700 cases
  - 2012 – 3,000 cases
  - 2013 – 3,500 cases

- Swedish travelers (1997-2005),²
  - 636 travel-related cases
  - East Africa, 14.1 cases /100,000 person months
  - Middle East, 5.8 cases /100,000 person months
  - Indian subcontinent, 5.6 cases/ 100,000 person months
  - Risk highest among those Visiting Friends & Relatives (VFR)

- Dutch travelers (2003-2011),³
  - 2,094 total cases, 931 (44%) from travel
  - Attack rate during 2003-2005, 7.5 per 100,000 travelers
  - Attack rate during 2009-2011, 3.5 per 100,000 travelers

¹ CDC Statistics & Surveillance
² J Travel Med 2009; 16:233-8
³ J Travel Med 2015; 22: 208-11
Globally Available HAV Vaccines

Inactivated vaccines:

- Monovalent
  - Avaxim® (SP), Havrix® (GSK), Vaqta® (CSL/Merck)
- Combination: HAV+ViCPS
  - Hepatyrix® (GSK), Vivaxim® (SP)
- Combination: HAV+HBV
  - Twinrix® (GSK)
- **Live Attenuated vaccine:**
  - H2 & L-A-1 strains (China)
HAV Vaccines Available in US

**Havrix® (GSK)**
- Inactivated
- Approved since 1995

**Adults:**
1 ML IM at 0 & 6-12 m

**Children (1-18 y):**
0.5 mL IM at 0 & 6-12 m

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**Vaqta® (Merck)**
- Inactivated
- Approved since 1996

**Adults:**
1 ML IM at 0 & 6-18 m

**Children (1-18 y):**
0.5 mL IM at 0 & 6-18 m

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**Twinrix® (GSK)**
- Inactivated
- Approved since 2001

**Adults:** 1 mL IM

**Children not “approved”**

*Standard* dosing:
0, 1, 6 m

*Accelerated Dosing:*
0, 7, 21-30d; 12 m

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Since 2006, routine vaccination of children age ≥1 year*

* MMWR 2006; 55: RR-7
HAV Vaccines:
Contraindications/Precautions

• Prior anaphylaxis with vaccination
• Hypersensitivity to a vaccine component: viral antigen, aluminum hydroxide adjuvant, neomycin
• Latex, vial stopper and syringe plunger
• No special precautions for the immunocompromised
HAV Vaccines:
Safety & Adverse Effects

**Adults:**
- Injection site soreness (56%)
- Headache (14%)
- Malaise (7%)

**Children:**
- Injection site soreness (15%)
- Feeding problems (8%)
- Headache (4%)
- Injection site induration (4%)
HAV Vaccines: Protection

• Protective antibodies:¹
  – First dose, ≥94% adults and ≥97% children
  – Second dose, 100% adults and children

• Havrix® Thailand field trial:²
  – Efficacy 94% (CI 79-99%) after 2 doses, 1 m apart

• Vaqta® New York trial:³
  – Efficacy 100% (CI 87-100%) after 1 dose

1. 1. MMWR 2006; 55: RR-7
2. 2. JAMA 1994; 271: 1328-34
3. 3. NEJM 1992; 327: 453-7
HAV Vaccines: “Off Schedule”

Delayed second dose:

• Adults, Two-dose, 18 months apart: 100% protective antibody after second dose\(^1\)

• Children, Two-dose, 4-8 years apart: 100% protective antibody after second dose\(^2\)

2. J Travel Med 2004; 11:120-1
Japanese Encephalitis (JE)

- Caused by a Flavivirus
- Transmitted by mosquito bite (*Culex* sp.)
- JE is estimated to cause ~68,000 clinical cases each year\(^1\)
- Most important cause of viral encephalitis in Asia and Western Pacific
- Substantial underreporting\(^2\), due to rural nature

JE: Epidemiology

Geography
Asia & Western Pacific
  – Rural agricultural areas (e.g., rice farming)
  – 20-30% case-fatality ratio

Seasonality
  • Temperate: peaks summer and fall
  • Tropics: all year with peaks during rainy (monsoon) season
JE: Clinical Presentation

• <1% of JE infection develop clinical illness
• ~1 in 200 infections result in severe disease

• Incubation 5-15 days
• **Initial stage**: Fever, Headache, Vomiting
• Progression to **Severe disease** (days): encephalitis, mental status changes, neurological symptoms, movement disorders, seizures (children especially), or death

• Among those with encephalitis, 20-30% fatality
• Among those recovering from acute illness, 30-50% survivors have residual neurologic, cognitive, or psychiatric symptoms
JE: Risk and Prevention

Risk
- Endemic incidence, 1.8 cases per 100,000 residents
- Estimated incidence among unvaccinated travelers to Asia <1 case per 1 million travelers
- 7 documented US traveler cases (1973-2011)

Prevention
- Clothing barrier
- Insect repellant (DEET)
- Vaccination
  - There is no specific treatment, limited to supportive care

2. CDC Yellow Book 2014
Globally Available JE Vaccines

Inactivated vaccine:
• Vero cell, alum-adjuvanted (Intercell) – N. America, Australia, Europe
• Vero cell (Beijing-1 strain) - Japan

Live Attenuated vaccine (Chengdu Inst. Biol Products):
• SA_{14}-14-2 strain - China, India, Nepal, Korea, Sri Lanka, Thailand

Live Chimeric vaccine (SP):
• YF 17D backbone - Australia & Thailand
JE Vaccine in US

Ixiaro® (Intercell)
- Inactivated, whole-virus
- Vero cell culture-derived
- SA_{14-14-2} attenuated strain
- Approved (2009):
  - Age $\geq$ 3 years
    - Two parenteral doses, 0.5 mL, spaced 28 days
  - Age 2 months to <3 years
    - Two parenteral doses, 0.25 mL, spaced 28 days
  - Booster dose after 1 year

*JE-Vax (inactivated mouse brain-derived vaccine) is no longer produced, expired May 2011*
JE Vaccine

Contraindications
• Severe Allergic Reactions to vaccine components: protamine sulfate
• Prior anaphylaxis with vaccination

Precautions
• Hypersensitivity to vaccine components
• Immunocompromised may have diminished protection
JE Vaccine: Adverse Effects

Adults:
• Injection site pain (25%)
• Headache (20%)
• Myalgia (10%)

*Better tolerated than JE-Vax*

Children (1-3 years):
• Fever (20%)

Infants (1-11 months):
• Injection site redness (15%)
• Fever (20%)
• Irritability (15%)
• Diarrhea (10%)
JE Vaccine: Protection

• Thailand field trial of JE-MB\(^1\)
  – Efficacy 91%

• Taiwan, trial of JE-MB, 30-years experience
  – Efficacy 97\(^2\)
  – Incidence 1967 (pre-vaccination), 2.05 cases per 100,000\(^3\)
  – Incidence 2003, 0.11 cases per 100,000\(^4\)

• Neutralizing antibody (PRNT50) of ≥1:10 is a reasonable surrogate of protection\(^5\)

1. NEJM 1988; 319: 608-14
2. Vaccine 2006; 24: 2669-73
3. AJTMH 1999; 61: 78-84
5. FDA, 16 May 2013 and Vaccine 2005; 23: 5205-11
“Off Label”
JE Vaccine: Accelerated Schedule

• Vaccination should be completed at least 1 week prior to potential exposure
• JE Accelerated Schedule: phase 3 study of Ixiaro and rabies1
  – Day 1 (JE/Rab), Day 4 (Rab), Day 8 (JE/Rab)
  – Non-inferior, rapid short-term protection for up to 2 months
    99% seroprotection in accelerated schedule
    100% seroprotection in routine schedule
JE Vaccine: Booster Doses

- JE Booster Doses
  - Current recommendation: single booster at 12-24 months
  - 76 months (6.3 years) after booster dose, 96% (64 of 67) maintained PRNT Ab
In the News: Flaviviruses

- Dengue, Japanese Encephalitis, Tick-borne Encephalitis, West Nile, Yellow Fever, Zika
  - Transmitted by mosquito bite (Ae. aegypti)
  - No therapies
  - Vaccines available for: YF and JE only

- Prevention with DEET-containing insect repellent
Cholera

- *Vibrio cholerae*
- Serogroups O1 (and O139)
  - Serotype Inaba or Ogawa
  - Biotype El Tor or Classical
- Rapidly dehydrating diarrhea
- 1.4-4.3 million cases and 28,000-142,000 deaths annually\(^1\)
- Transmission: fecal-oral

WHO, July 2015
Cholera Epidemiology

- **Pandemics**
  - Currently 7th (since 1961)
- **Epidemics**
  - Example: post-earthquake Haiti in 2010
- **Endemic**
  - Example: India, Nigeria, DRC, Tanzania, Kenya, Ethiopia, Bangladesh

Ali, Bull WHO 2012; 90:209
Globally Available Cholera Vaccines

- Oral inactivated monovalent
  Dukoral® (Crucell)
- Oral inactivated bivalent
  Shanchol™ (Shantha)
  Euvichol® (EuBiologics)
- Oral, live monovalent
  Vaxchora™ (PaxVax)
Cholera Vaccine in US

Vaxchora™ (PaxVax)

- Live, attenuated O1 classical Inaba strain (CVD 103-HgR)
- Single-dose
- Approved age 18-64 years
- Licensed June 10, 2016
- ACIP Recommendation (June 22, 2016)1
  - “Cholera vaccine (CVD 103-HgR, Vaxchora™) is recommended for adult (18-64 years old) travelers to an area of active cholera transmission”
- No booster recommended at this time
Cholera Vaccine: Protection

Primary Efficacy (Mod-Severe Diarrhea)

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<tr>
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<th>Vaccine 10-Day</th>
<th>Vaccine 3-Month</th>
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</thead>
<tbody>
<tr>
<td>Vaccine Efficacy</td>
<td>90.3%</td>
<td>79.5%</td>
</tr>
<tr>
<td>95% CI</td>
<td>62.7-100</td>
<td>49.9-100</td>
</tr>
</tbody>
</table>

Chen, CID 2016
Cholera: High Risk Populations

Risk of Infection:
• Travelers visiting friends and relatives
• Long-term travelers (e.g., expatriates)
• Travelers who do no follow safe food and water precautions and personal hygiene (e.g., adventure backpacking)
• Healthcare, aid, relief, and response workers with direct contact with cholera patients

Risk of Poor Outcome with cholera:
• Travelers without ready access to rehydration therapy and medical care
• Blood type O
• Pregnant
• Immunocompromised
• Chronic cardiovascular or renal disease
Meningococcal Meningitis

- Neisseria meningitidis
- 6 major serogroups: A, B, C, W-135, X, and Y
- Incidence: (cases/100,000 population)
  - Americas, Europe, Australia 0.3-3/100K
  - Sub-Saharan Africa 10-1000/100K

"Meningitis Belt"
Dry season (Dec – June)
5-10% of population are carriers
Serogroup A>>C,X,W
Meningococcal Vaccines in US

- Monovalent, group B (Bexsero®, Trumenba®) Combination – C, Y, Hib-TT (MenHibrix™)
- Quadrivalent Polysaccharide (Menomune®)
- Quadrivalent Conjugate (Menactra®, Menveo®)

Photo: James Gathany – CDC
Meningococcal Vaccines for Travel

To Saudi Arabia (within 3 yrs of travel)
• Age >2 yr 1 dose, Quadrivalent vaccine
• Age 3 m – 2 yr 2 doses, Men A containing vaccine

To endemic & hyperendemic area, during dry season
• 2 m – 55 yr quadrivalent (MCV)
• >55 yr quadrivalent (MPS)
• Booster dose after 5 years
• Children 9 m – 23 m, two doses 8-12 wks apart

1. MMWR 2013; 62:1-22
2. CDC Yellow Book 2016
ACIP References

• Yellow Fever - MMWR 2015; 64: 647-650
• Typhoid - MMWR 2015; 64: 305-308
• Hepatitis A - MMWR 2007; 56: 1080-1084
• Cholera - pending
• Meningococcal - MMWR 2013; 62: 1-27
Questions?