# ACIP Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines Work Group

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**February 26, 2014**

# JE and YF Vaccines Work Group Members

**ACIP members**

Joseph Bocchini (Chair)

Lorry Rubin

**Liaison representatives**

Cody Meissner (AAP)

Robert Schechter (AIM)

**CDC Leads**

Erin Staples (NCEZID/DVBD)

Marc Fischer (NCEZID/DVBD)

***Ex Officio* members**

Doran Fink (FDA)

Jesse Geibe (DoD)

Michael Holbrook (NIH)

Lewis Markoff (FDA)

Pat Repik (NIH)

**Invited consultants**

Elizabeth Barnett

Alan Barrett

Lin Chen

Myron Levin

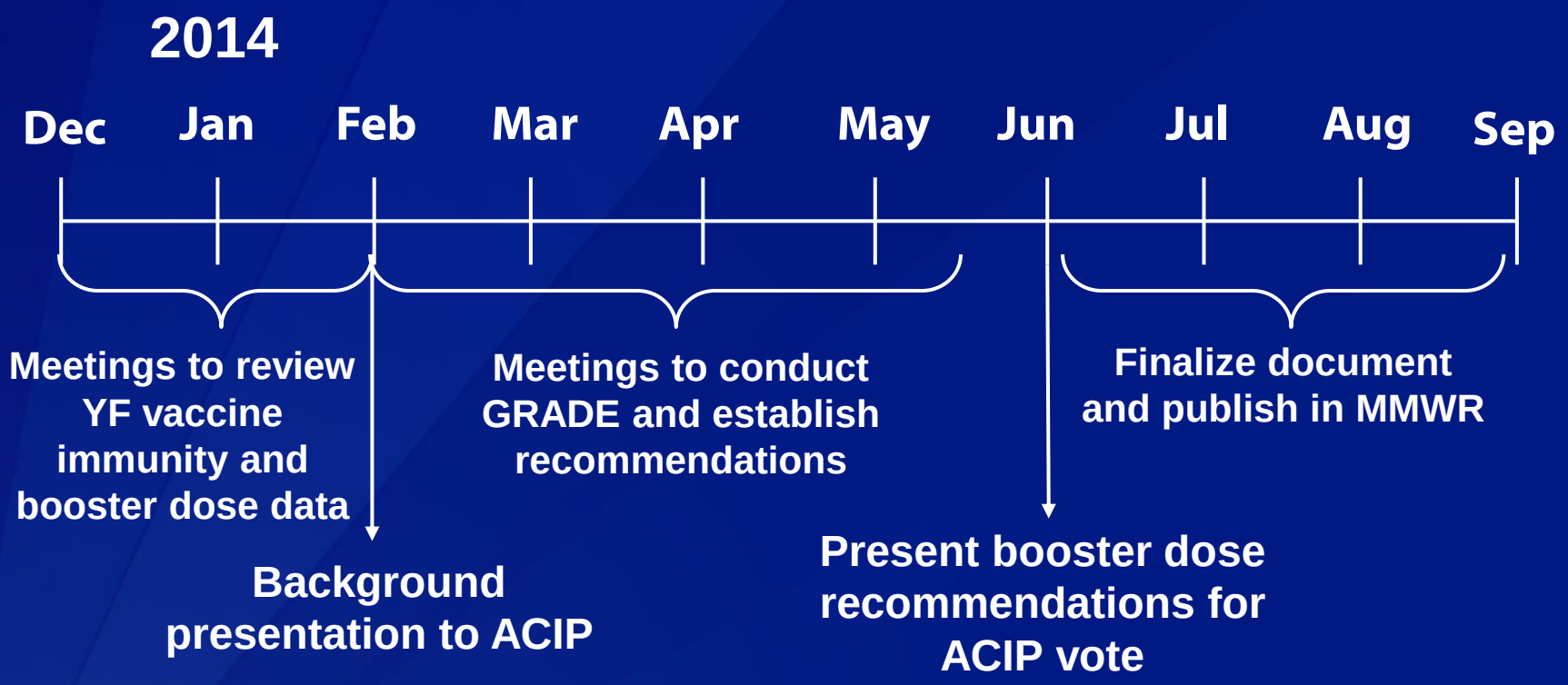
David Shlim

Mary Wilson

# JE and YF Vaccine Work Group: Objective and Plans

- Develop recommendations regarding YF vaccine booster doses in travelers and laboratory workers
- Use GRADE approach to assess YF vaccine data
  - Long-term immunogenicity
  - Vaccine failures
  - Serious adverse events

# Timelines for Work Group*




*Proposed; timelines may be impacted by work group discussions

# ACIP Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines Work Group: Background of YF disease, YF vaccine, and recent vaccine developments

J. Erin Staples, MD, PhD
Arboviral Disease Branch, Division of Vector-borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, USA

# Arboviral Diseases Branch

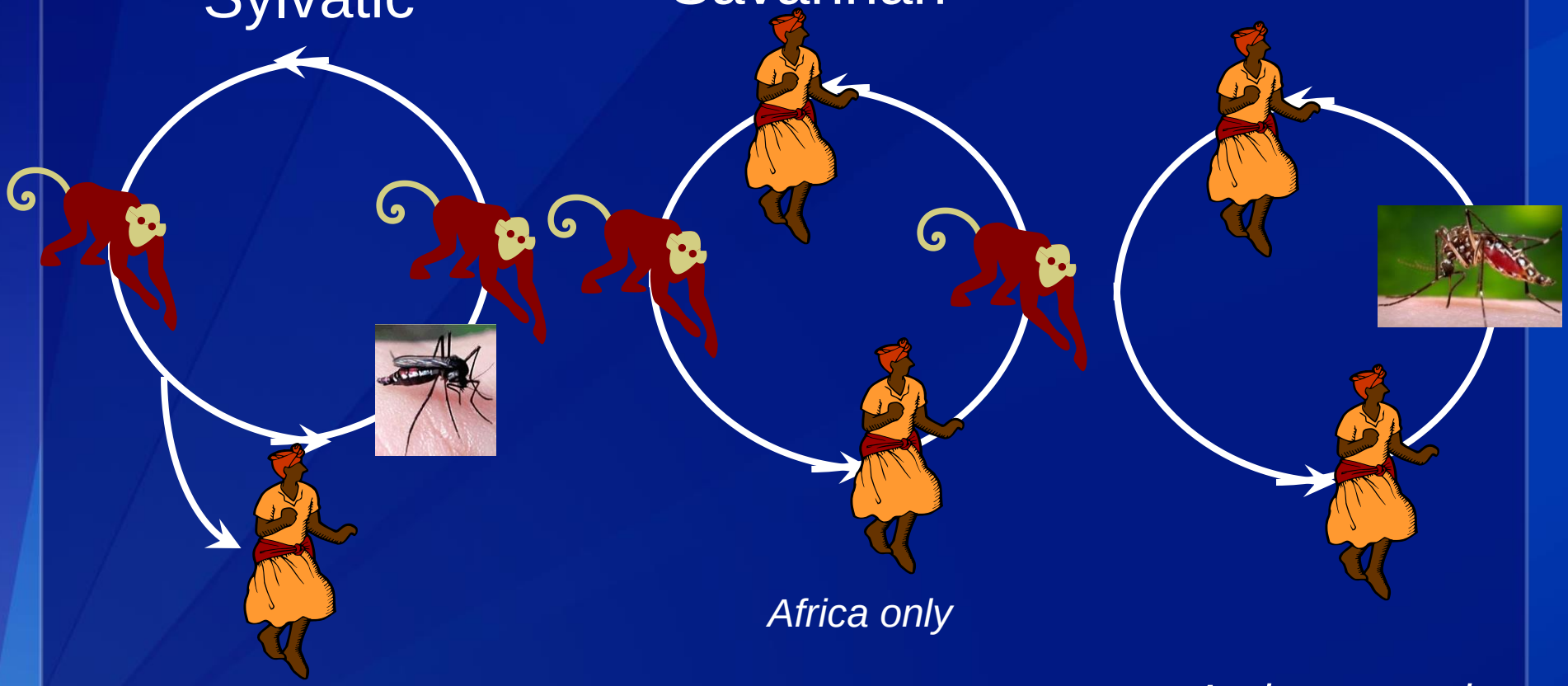
- Located in Fort Collins, Colorado
- Responsible mosquito and tick-borne viral diseases
  - Yellow fever, Japanese encephalitis, and West Nile viruses

# YF Disease Background

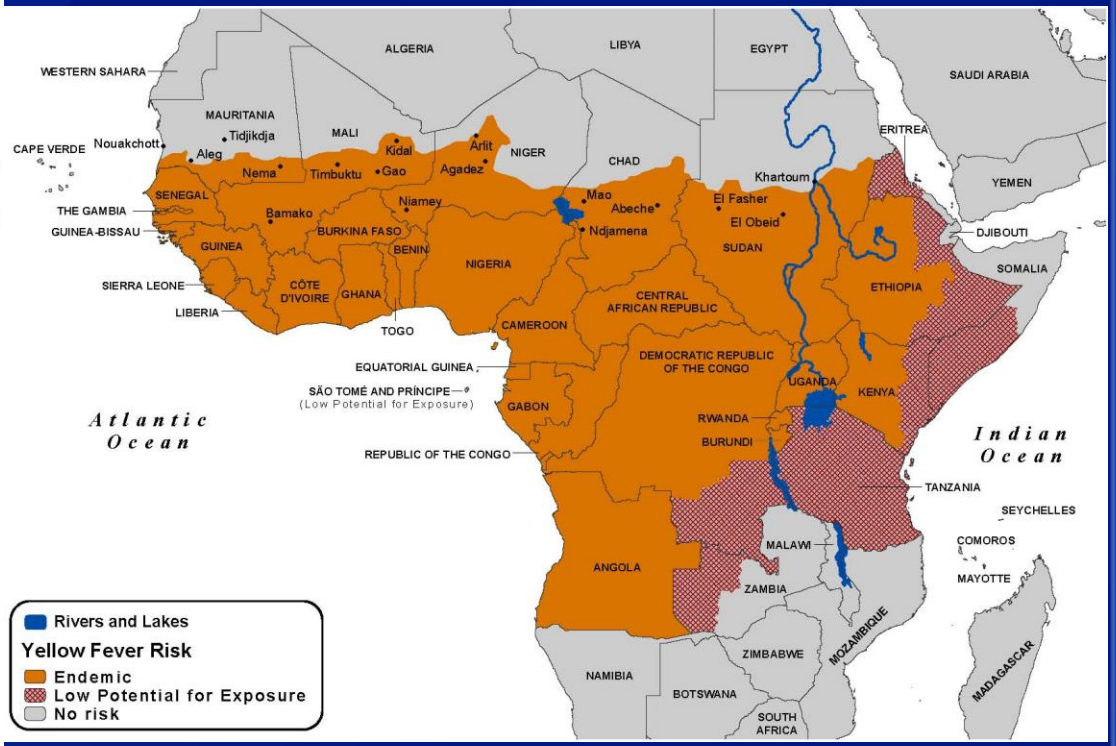
# YF Overview

- Caused by YF virus (*Flavivirus)*
- Virus transmitted predominantly by *Aedes* mosquitoes
- Endemic in equatorial Africa and South America
- Estimated 200,000 cases and 30,000 deaths annually

# YF Virus Transmission Cycles

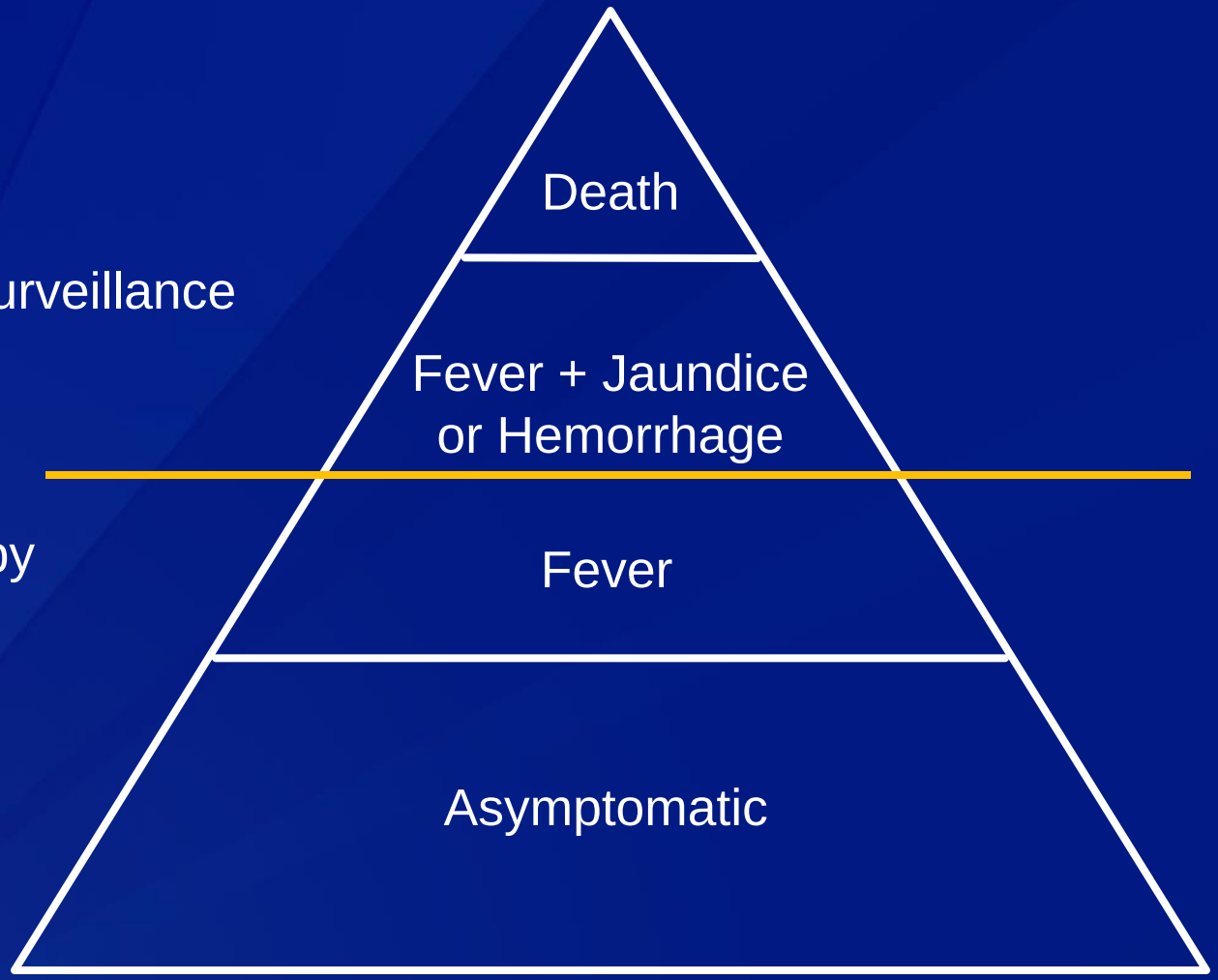


# Worldwide Distribution of YF


Jentes ES, et al. *Lancet Infect Dis* 2011; 11: 622–632

# YF Clinical Presentation




Detected by surveillance

Not detected by surveillance

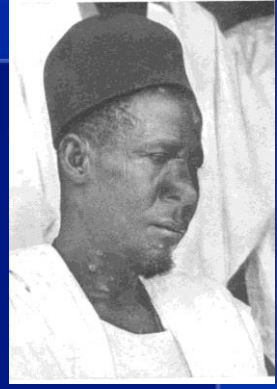
Incubation period of 2-6 days

# YF Treatment, Prevention, and Control

- Treatment
  - No specific anti-viral treatment
  - Supportive therapy
- Prevention and control
  - Mosquito control
  - Vaccination

# YF Vaccine Background

# Development of YF Vaccine



- Asibi strain obtained in 1927
- Passed >200 times to develop live attenuated viral vaccine, 17D vaccine
- Two distinct substrains used in vaccines today*
  - 17DD – produced in Brazil
  - 17D-204 – used by manufacturers outside Brazil
- All vaccines produced in embryonated eggs but differ in substrain, passage level, and stabilizers

*17D-213 substrain, a derivative of 17D-204, also exists as reference stock maintained by WHO for new manufacturers or source of emergency production

# Currently Available YF Vaccines


- WHO prequalified
  - Bio-Manguinhos, 17-DD, Brazil
  - sanofi pasteur, Stamaril®, 17D-204, France
  - Pasteur Institute Dakar, 17D-204, Senegal
  - Chumakov Institute, 17D-204, Russian Federation
- Local use
  - sanofi pasteur, YF-Vax®, 17D-204, USA (used in USA and Canada)
  - China National Biotech Group, 17D-204, China

# Use and Immunogenicity of YF Vaccine

- From 1937-2013 over 600 million doses have been administered
- No placebo controlled studies of efficacy
- Incidence of YF among lab workers and in endemic areas declined after vaccination began
- >99% of vaccinated persons develop antibody response at 28 days post vaccination

# Common Adverse Events for YF Vaccine

- Fever, headache, backache 3-7 days after vaccination: 5%-15%
- Injection site inflammation 1-5 days after vaccination: 1%-30%

# Serious Adverse Events (SAEs) and Rates for YF Vaccine

- Overall reporting rate for SAEs in U.S. population is 4.7 per 100,000 doses distributed*
- Three primary SAEs
  - Anaphylaxis – 0.8-1.4 per 100,000 doses
  - Neurologic disease – 0.4-0.8 per 100,000 doses
  - Viscerotropic disease – 0.3-0.4 per 100,000 doses

*Lindsey et al. *Vaccine* 2008; 26: 6077–6082.

# YF Vaccine-Associated Neurologic Disease

- Spectrum of illnesses due to either direct viral invasion of CNS or autoimmune mediated
  - Most common presentation is meningoencephalitis
  - Others: GBS, ADEM, bulbar palsy, Bell's palsy
- Absolute number of cases is unknown
- Onset median 11 days (2-28 days) post vaccination
- Rarely fatal with five death noted
- Reported predominantly after initial vaccination

# YF Vaccine-Associated 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 median 3 days (1-8 days) post vaccination
- Tends to affect younger females and older males though age range between sexes is similar
- 63% case-fatality rate
- Reported only after initial immunization

# Yellow Fever Vaccine Requirements and International Health Regulations (IHR)

- Most endemic countries require proof of vaccination for all travelers from endemic areas
- Certain countries with vectors but without disease require proof of vaccination for all travelers from endemic areas
- United States has no vaccine requirement for entry
- Only vaccine covered under IHR (2005)
  - Can detain traveler without proof of vaccination for 6 days (incubation period)

# Status Update of YF Vaccine Recommendations

# Current ACIP YF Vaccine Recommendations

- Last work group formed in 2008 to update previous recommendations
  - Update YF epidemiology
  - Include information on IHR (2005)
  - Update vaccine safety data
  - Add/improve wording for vaccine precautions and contraindications
- Updated recommendations published July 2010

# ACIP Recommendations for Use of YF Vaccine in Travelers

- Recommended for persons aged ≥9 months who are traveling to or living in areas at risk for YF virus transmission
- Because of the risk of serious adverse events, health-care providers should vaccinate only persons who are at risk for exposure to YF virus or require proof of vaccination for country entry
- Single subcutaneous dose; IHRs require revaccination at intervals of 10 years to boost antibody titers

# Contraindications and Precautions to YF Vaccine Administration

## Contraindications

- Allergy to vaccine component
- Age <6 months
- Symptomatic HIV infection or CD4+ counts <200/$mm^3$
- Thymus disorder
- Primary immunodeficiencies
- Malignant neoplasms
- Transplantation
- Immunosuppressive and immunomodulatory therapies

## Precautions

- Age 6-8 months
- Age ≥60 years
- Asymptomatic HIV and CD4+ counts 200-499/$mm^3$
- Pregnancy
- Breastfeeding

# WHO YF Vaccine Recommendations

- SAGE formed YF vaccine work group in 2011
  - Need for booster dose every 10 years to maintain protection against YF
  - Safety of YF vaccine in selected special populations
  - Co-administration of YF and other vaccines
- Updated position paper published in July 2013

# SAGE YF Vaccine Booster Dose Presentation – April 2013

# Overview of YF Vaccine Immunity

- No YF vaccine efficacy studies have been performed
- Several observations supported protective effect
  - Reduction in lab-acquired infection in vaccinated workers
  - Only unvaccinated persons developed disease following vaccine introduction
  - Disappearance of cases in outbreaks when campaign conducted
  - Protection of monkeys against virulent virus challenge by neutralizing antibodies generated in response to vaccination
- Monkey studies have determined $\log_{10}$ neutralization index (LNI) of ≥0.7 correlates with protection[1]
  - Correlates using more common plaque reduction neutralization test (PRNT) not established

1. Mason. Appl Microbiol. 1973; 25: 539.

# YF Vaccine Immunogenicity and Booster Dose

- >99% of vaccinated persons develop neutralizing antibodies at 28 days post vaccination
- 10 year booster dose interval established in 1965
- Booster interval based on 2 studies documenting ~80% of recipients with neutralizing antibodies around 10 years post vaccination

# Findings of Systematic Review Conducted for SAGE on YF Vaccine Booster Dose

- At 10-20 years post vaccination, high proportion (>90%) of vaccine recipient with neutralizing antibodies
- In persons vaccinated >20 years previously, ~80% have detected neutralizing antibodies
- Neutralizing antibodies detected as long as 60 years post vaccination
- Twelve vaccine failures documented within 5 years of initial vaccination

# Additional SAGE Working Group Considerations on YF Vaccine Booster Data

- YF disease noted only in unvaccinated persons during outbreaks (e.g., Nigeria)
- Data suggest role innate and cell-mediated immunity in initial and memory immune response

# SAGE Working Group Issues and Concerns with YF Vaccine Booster Dose Data

- Different PRNT levels used in published studies
- Lack of understanding of protective immunity
  - Neutralizing antibodies associated with protective immune response
  - Significance of innate and cell-mediated immunity unknown
- Natural boosting likely to occur in endemic areas
  - Travelers vs laboratory personnel vs endemic populations
- Limited data suggest certain populations might have lower seroconversion rates or more rapid Ab decay

# Summary of Key Findings of SAGE Working Group on YF Vaccine Booster Doses

- No efficacy studies performed; neutralizing antibodies used as surrogate
- Current booster dose recommendation of every 10 years from IHR in 1965 and based on limited data
- Majority of vaccine recipients develop antibody titers and will maintain titers for several decades, possibly life-long
- Very few primary vaccine failures reported; no secondary vaccine failures reported
- Both innate and cell-mediated immunity contribute to initial and memory immune response

# Updated SAGE YF Vaccine Recommendations

- “A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary.”

# Questions and Discussion

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