Update from the Japanese encephalitis (JE) vaccine working group

Patricia Stinchfield, RN, MS, CPNP
Chair, ACIP JE vaccine working group

ACIP Meeting
February 28, 2008

ACIP JE vaccine working group members

Brad Biggerstaff, CDC
Paul Cieslak, ACIP
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Marc Fischer, CDC
Bob Frenck, AAP
Patrick Garman, DoD
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Mark Gershman, CDC
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Patsy Stinchfield, WG Chair
Denise Werker, PHAC
Melinda Wharton, CDC

Issues for JE vaccine working group (1)

Issue

- The only JE vaccine licensed for use in the U.S. is no longer being produced
- Sanofi Pasteur estimates that available supplies of the vaccine may be exhausted as early as mid-2008

Working group tasks

- Monitor availability of JE vaccine for U.S. travelers
- Work to mitigate possible supply issues

Issues for JE vaccine working group (2)

Issue

- Intercell filed a BLA in Dec 2007 for a new JE vaccine
- New vaccine will be licensed for use in adult travelers

Working group tasks

- Draft ACIP recommendations for use of new JE vaccine in adult travelers
- Address future availability of JE vaccine for U.S. children

JE vaccines working group activities

- Interagency WG formed in March 2006
- ACIP WG formed in October 2006
- Three meetings and regular conference calls
- Regular updates from manufacturers regarding currently licensed and two new vaccines
- Working with HHS, DoD, and sanofi pasteur to offset potential supply issues

Agenda for ACIP meeting

JE vaccine for U.S. travelers (15 min)	Marc Fischer (CDC)
JE vaccine availability in the U.S. (5 min)	Phil Hosbach (sanofi)
New JE vaccine for adult travelers (20 min)	Eric Tauber (Intercell)

Information and discussion only.

No ACIP recommendations or vote.

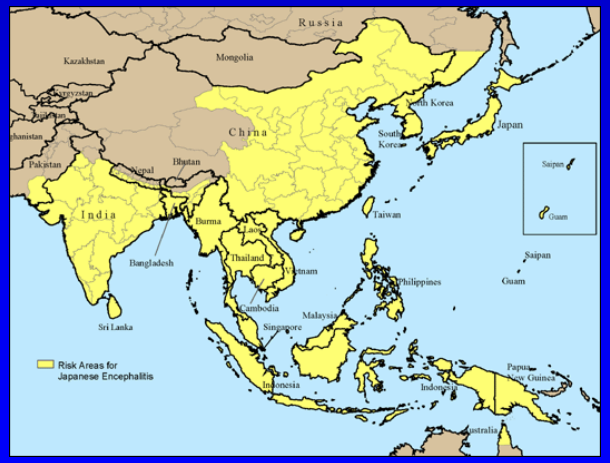
Japanese encephalitis (JE) vaccine for U.S. travelers

Marc Fischer, MD, MPH
Arboviral Diseases Branch
DVBID, NCZVED, CDC

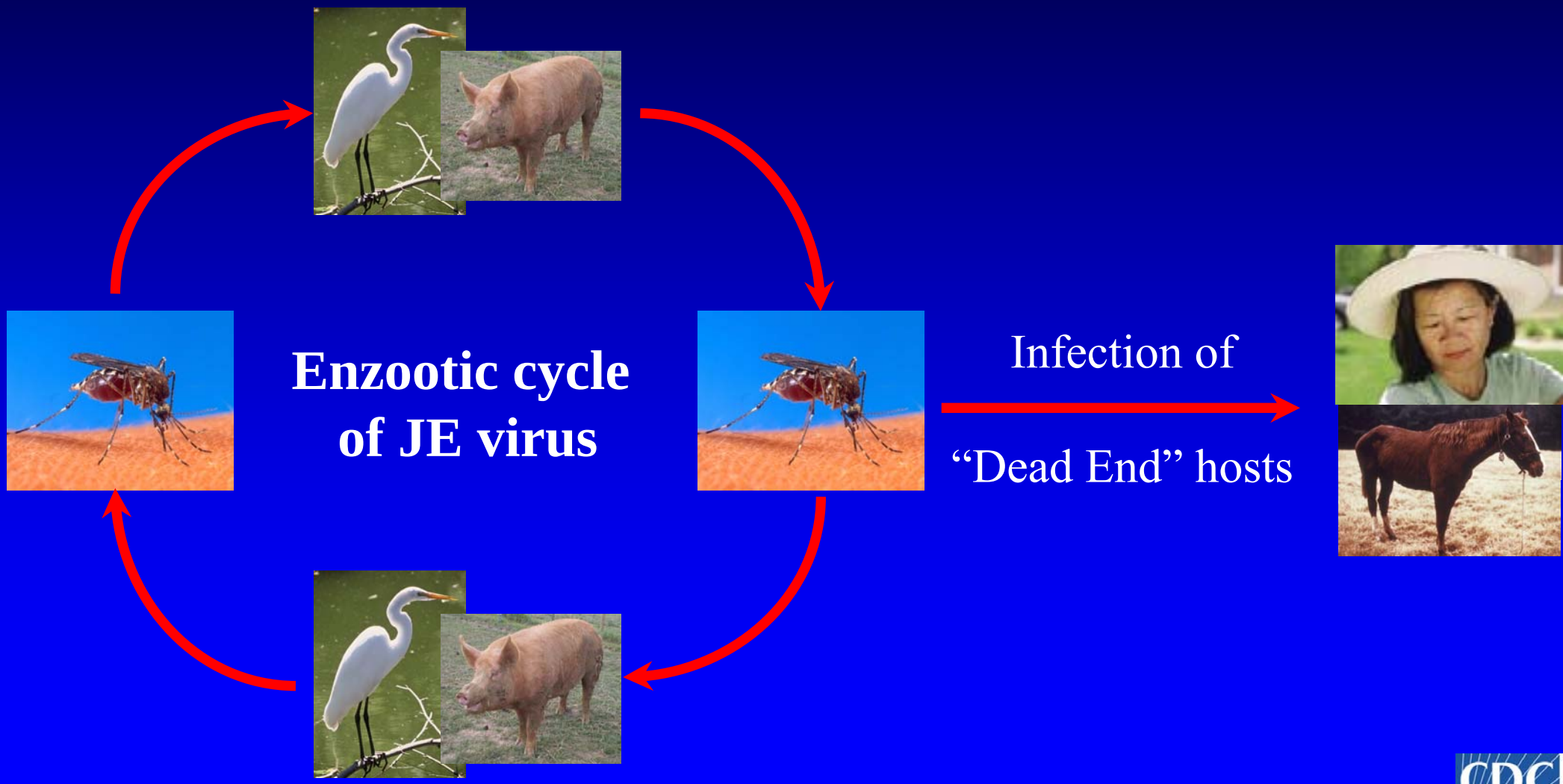
ACIP Meeting
February 28, 2008

Japanese encephalitis (JE) virus

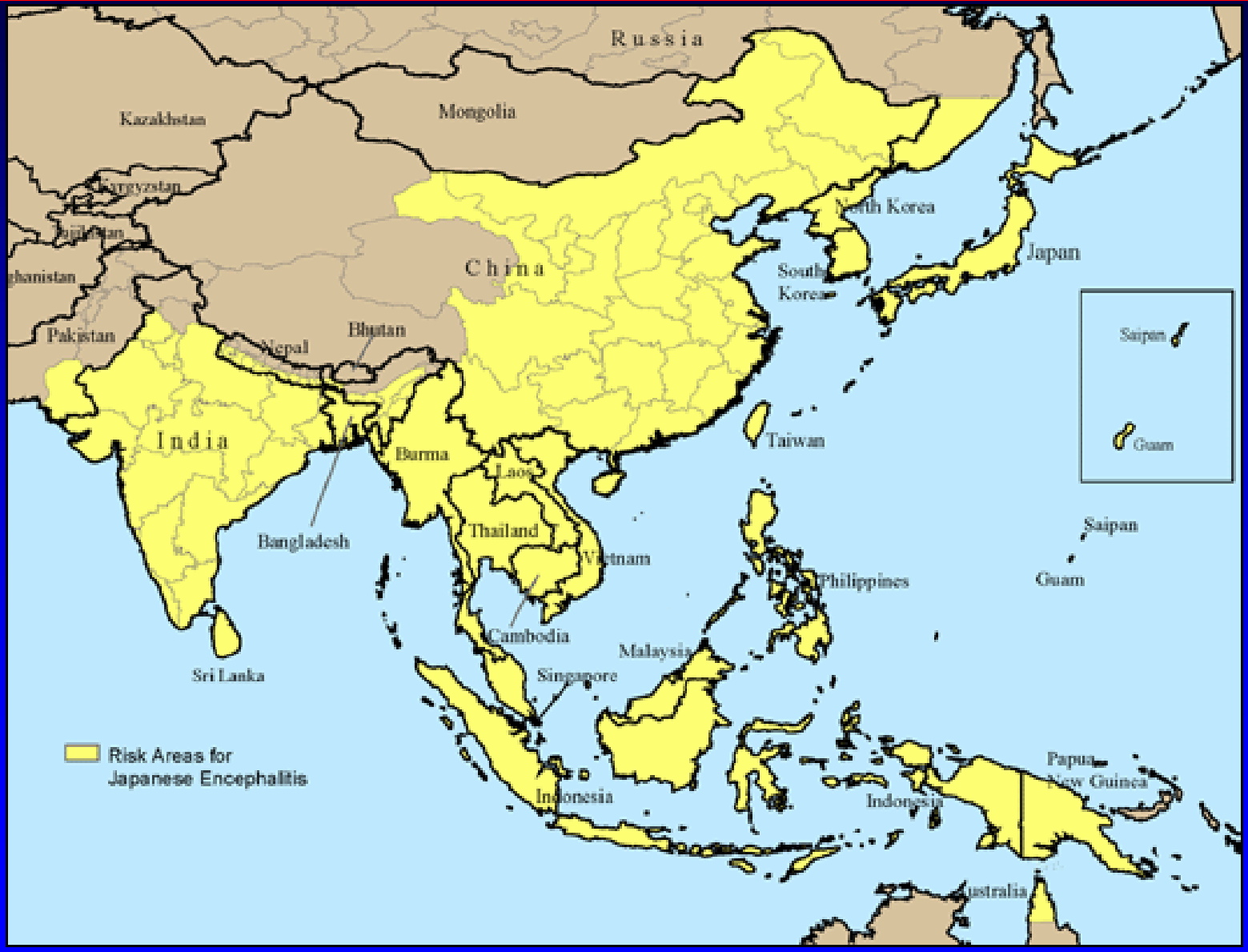
- Mosquito-borne flavivirus
- Closely related to West Nile virus and St. Louis encephalitis virus
- Leading cause of encephalitis in Asia



JE virus transmission cycle

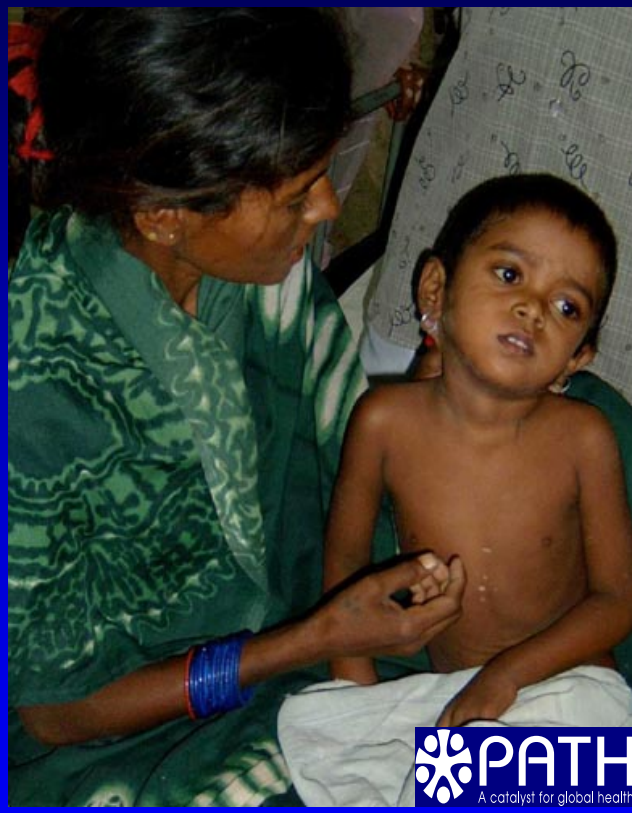


Geographic range of Japanese encephalitis



Japanese encephalitis burden of disease

- Most JE virus infections asymptomatic
- 15,000-50,000 encephalitis cases annually
- Likely underestimate of true burden
- No antiviral therapy; only supportive care
- 20-30% case fatality for encephalitis
- 30-50% of survivors have significant neurologic sequelae



CDC

JE epidemiology in Asia

- Most cases among children <15 years of age
- Two seasonal patterns
  - Temperate areas: Summer epidemics
  - Tropical areas: Sporadic disease
- Rural disease associated with rice production

Estimating JE risk for travelers to Asia

1. Extrapolate risk from residents during transmission season
   - 10 to 200 cases per 1 million persons per week
   - Consistent with rates in non-immunized U.S. military

2. Crude estimates based on published cases from 1973-2007
   - 39 travel-related JE cases reported in literature
   - All had prolonged travel (>30 days) or visited rural areas
   - 12 U.S. residents (6 military, 6 civilians)
   - ~5 million U.S. resident entries into Asian countries per year
   - <1 case per 1 million trips to Asia

CDC

Classifying JE risk for travelers to Asia

- Overall risk of JE for travelers is very low but varies based on season, destination, duration, and activities
- Prolonged travel in rural areas with active JEV transmission likely similar risk as for the susceptible resident population
- Shorter trips may confer increased risk if there is extensive outdoor or nighttime exposure in rural areas
- Short-term travel restricted to major urban areas confers very minimal risk for JE

Inactivated mouse brain-derived JE vaccine

- Only JE vaccine licensed in the U.S.
- Used to effectively control JE disease in several Asian countries since the 1960s
- Licensed in U.S. since 1992 for adults and children (≥1 year)
- Manufactured by Biken (Japan); Distributed by sanofi pasteur
- 91% efficacy at 2 years after two doses in randomized controlled trial performed in 65,000 children in Thailand
- Three dose series administered on days 0, 7, and 30

CDC

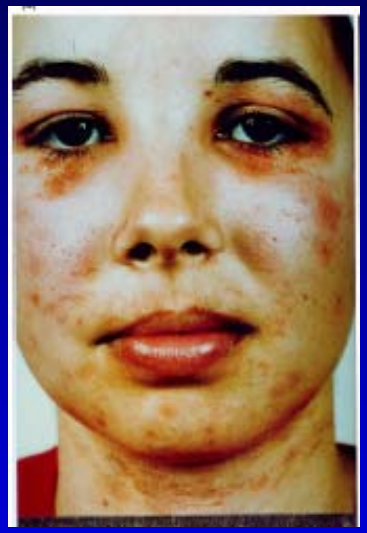
Adverse events following mouse brain JE vaccine

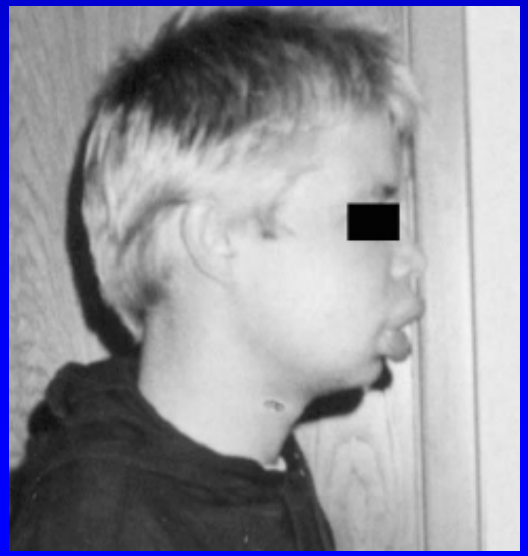
Local reactions (erythema, tenderness, swelling)	20%
Mild systemic (fever, headache, diarrhea)	10-30%
Hypersensitivity (urticaria, angioedema)	20-600 per 100,000
Neurologic (encephalitis, seizures, neuropathy)	0.1-2.0 per 100,000

Halstead. In: Vaccines (Eds. Plotkin et al.) 2004:919-958.

Allergic hypersensitivity reactions to mouse brain-derived JE vaccine

- Urticaria and angioedema of the extremities, face, and oropharynx
- Some recipients have bronchospasm, respiratory distress, or hypotension
- Up to 10% patients hospitalized





Plesner. Vaccine 2000.

Allergic hypersensitivity reactions to mouse brain-derived JE vaccine

- Reactions may be delayed after vaccination
  - 1st dose: Most reactions occur within 48 hours
  - 2nd dose: Median 3 days; Range up to 14 days
- Allergic reactions may be associated with a gelatin stabilizer used in the vaccine
- Few deaths temporally associated with recent JE vaccination
  - None had allergic signs or symptoms
  - Received other vaccines or medications simultaneously

Rates of allergic hypersensitivity reactions to mouse brain-derived JE vaccine

Country	Cases	Denominator	Rate per 100,000
Japan (NARRS)	71	9,400,000 doses	1
U.S. (VAERS)	51	813,822 doses	6
Sweden	1	15,000 vaccinees	10
U.K.	1	1,950 vaccinees	50
Denmark	21	41,500 vaccinees	50
Australia	7	4,000 vaccinees	200
U.S.	223	37,100 vaccinees	600

Plesner 2003; Takahashi 2000; Berg 1997; CDC 1993

Neurologic events temporally associated with mouse brain-derived JE vaccination

- Paresthesia
- Seizures
- Encephalopathy
- Gait disturbance
- Guillain-Barre Syndrome
- Acute disseminated encephalomyelitis (ADEM)

Rates of neurologic events following mouse brain-derived JE vaccine

Country	Cases	Denominator	Rate per 100,000
Japan (1965-73)	NA	vaccinees	0.1
Japan (1996-98)	17	9,400,000 doses	0.2
U.S. (1993-98)	2	813,822 doses	0.2
Denmark (1983-96)	10	384,000 doses	2.6

Takahashi 2000; Plesner 1998

CDC

Balancing risk and benefit of JE vaccine

- JE has high case-fatality and substantial sequelae
- There is no specific treatment
- Effective vaccine is available

- Risk of JE disease among travelers is low
- Risk varies based on season, duration, location, activities
- Adverse events following mouse brain-derived JE vaccine

Current ACIP recommendations

1. Offer JE vaccine to travelers spending ≥1 month in an endemic area during the JEV transmission season

2. Consider JE vaccine for shorter stays if the travel will include extensive outdoor activity in rural areas

3. Short-term travelers whose visits are restricted to major urban areas generally should not be advised to receive the vaccine

Availability of the currently licensed JE vaccine in the U.S.

- JE vaccine licensed for use in the U.S. is no longer being produced
- DoD uses 70-80% of the JE vaccine in the U.S. and has stockpiled enough vaccine for 3-5 years
- Sanofi pasteur estimates that remaining supplies for civilian travelers may be exhausted by mid-2008

Evaluating new JE vaccines

- Two new JE vaccines have been evaluated in clinical trials in the U.S.
- Availability of several effective JE vaccines in Asia makes a controlled efficacy trial unethical and impractical
- New JE vaccines for the U.S. will be licensed based on:
  - Immunologic correlate for protection
  - Neutralizing antibody titer ≥1:10
  - "Non-inferiority" comparative immunogenicity trial
  - Large scale safety evaluations of the new vaccine

CDC

New inactivated cell-derived JE vaccine

- Developed and manufactured by Intercell (Austria)
- Clinical trials completed in U.S. and Europe
- BLA filed in December 2007
- Earliest licensure will be last quarter of 2008
- Initial indication will be for adults (≥18 years)

JE vaccine availability for U.S. travelers

- Remaining supplies of existing JE vaccine for civilian travelers may be exhausted by mid-2008
- New JE vaccine not be available until late 2008
  - Not available for the Beijing Olympics (Aug 2008)
  - Not licensed for children until at least 2010
- Without further action, there will be a gap in the availability of JE vaccine for U.S. travelers in 2008 or 2009
- Lack of availability for children may persist for several years

CDC

Activities for CDC and ACIP WG

- Monitor availability of JE vaccine for U.S. travelers
- Work with HHS, DoD, and sanofi pasteur to mitigate possible supply issues
- MMWR to educate participants and travelers to Beijing Olympics regarding JE and JE vaccine
- Draft ACIP recommendations for use of new JE vaccine in adult travelers (April or October 2008 meeting)
- Address future availability of JE vaccine for U.S. children

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