Update from the Japanese encephalitis (JE) vaccine work group

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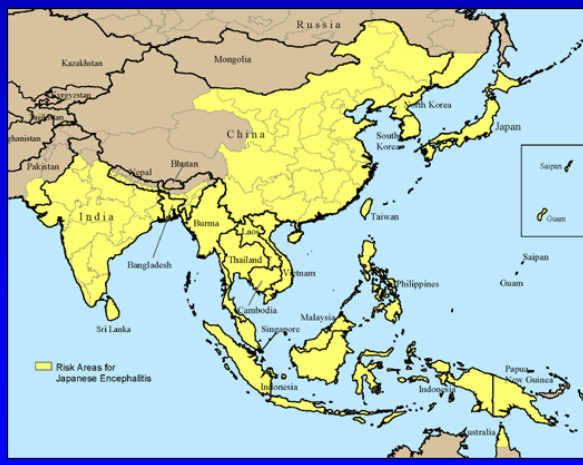
Japanese encephalitis virus (JEV)

- Mosquito-borne flavivirus
- Leading cause of encephalitis in Asia
- 35,000-50,000 encephalitis cases annually
- No antiviral therapy; only supportive care
- 20-30% case fatality for encephalitis
- 30-50% of survivors have significant neurologic sequelae



JEV transmission cycle

Enzootic cycle of JEV

Infection of

"Dead End" hosts

Japanese encephalitis (JE) epidemiology

- Rural disease associated with rice production
  - Mosquitoes feed mostly outdoors at night
- Most cases among children
  - Adults have protective immunity
- Two seasonal patterns
  - Temperate areas: Summer/fall epidemics
  - Tropical areas: Sporadic disease

Estimating JE risk for travelers to Asia

1. Prolonged travel to rural areas during JEV transmission season
   - Extrapolate rates from resident children or non-immunized U.S. military in endemic areas
   - 10 to 200 cases per 1 million persons per week

2. Minimum estimates based on published cases from 1973-2008
   - 43 JE cases among travelers reported in past 36 years
   - 15 U.S. travel-related cases (6 military, 9 civilians)
   - 2 to 5 million U.S. travelers to Asia per year
   - <1 case per 1 million trips to Asia

CDC

JE among travelers from non-endemic countries, 1973-2008

- 43 cases reported in literature
- 36 (84%) report demographic information

Median age (Range)	31 yrs (1 – 81)
Male	19 (53%)
Received JE vaccine	0 (0%)
Outcome	
Died	5 / 32 (16%)
Disabled	11 / 32 (34%)

Risk factors for JE among travelers from non-endemic countries, 1973-2008

- 43 cases reported in literature
- 24 (56%) report travel itinerary information

Duration of travel	
≥4 weeks	17 (71%)
2 to 3 weeks*	5 (21%)
<2 weeks*	2 (8%)
Onset in June-September	13 (52%)

*All "short-term" travelers visited rural or agricultural areas

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 term travelers may still be at risk if itinerary includes outdoor or nighttime exposure in rural areas
- Short-term travel restricted to major urban areas confers very minimal risk for JE

CDC

Inactivated mouse brain-derived JE vaccine

- Current formulations developed in 1960s
- Used to effectively control JE disease in several Asian countries
- JE-VAX® licensed in U.S. since 1992
- Manufactured by Biken (Osaka, Japan)
- Distributed in U.S. by sanofi pasteur (Swiftwater, PA)

Randomized controlled efficacy trial of inactivated mouse brain-derived JE vaccine, 1984-85

- Randomized >65,000 children (1-14 yrs) in Thailand
- Received 2 doses of JE vaccine or tetanus toxoid
- Evaluated efficacy at 2 years

	JE vaccine (N=43,708)	Tetanus tox (n=21,516)	Efficacy (95% CI)
JE cases	2	11	91% (70–97%)

Hoke. N Engl J Med 1988.

Seroconversion with mouse brain-derived JE vaccine in susceptible persons from non-endemic countries

Study	2 doses	3 doses
Henderson 1984	5 / 14 (36%)	42 / 47 (89%)
Poland 1990	91 / 118 (77%)	71 / 72 (99%)
Sanchez 1990	16 / 20 (80%)	25 / 25 (100%)
DeFraites 1999	-- --	470 / 470 (100%)

Incidence of hypersensitivity reactions following inactivated mouse brain-derived JE vaccine

Country	Cases	Denominator	Incidence 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.	38	14,249 vaccinees	266

Plesner 2003; Takahashi 2000; Berg 1997; CDC 1993

Hypersensitivity reactions among 14,249 U.S. Marines receiving inactivated mouse brain-derived JE vaccine

	(n=38)
Clinical features	
Urticaria, angioedema, or wheezing	27 (71%)
Pruritus only	11 (29%)
Hospitalized	2 (5%)
Median days to onset (Range)	
1st dose	1 (1-7 days)
2nd dose	4 (1-14 days)

Berg. Clin Infect Dis 1997

CDC

Causes of hypersensitivity reactions to inactivated mouse brain-derived JE vaccine

- Hypersensitivity reactions more likely in persons with a history of anaphylaxis, urticaria or allergies
- IgE antibodies against the gelatin stabilizer may be responsible for some of these allergic reactions

Berg 1997; Plesner 2000; Sakaguchi 2001

Rates of neurologic events following inactivated 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

Neurologic events reported following inactivated mouse brain-derived JE vaccine

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

Matsukura 1980; Ohtaki 1992; Ohtaki 1995; Sohn 2000; Takahashi 2000; Matsui 2002; Ferguson 2007; Plesner 2000; Plesner 2003

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
- Rare severe adverse events following JE vaccine

Current ACIP recommendations

"JE vaccine is NOT recommended for all travelers to Asia."

"JE vaccine should be offered to persons spending ≥1 month endemic areas during the transmission season, especially if travel will include rural areas."

"Under specific circumstances, vaccine should be considered for persons spending <30 days in endemic areas, e.g., travelers to areas experiencing epidemic transmission and persons whose activities, such as extensive outdoor activities in rural areas, place them at high risk for exposure."

JE-VAX availability in the U.S.

- In 2005, Biken discontinued production of JE-VAX®
- In 2007, sanofi estimated that remaining supplies for civilian travelers would be exhausted by mid-2008
- In June 2008, sanofi obtained 25,000 additional doses from the DoD stockpile for use in civilian travelers
- Estimate enough supply to last through the 1st quarter 2009
- To prolong availability, sanofi continues to restrict purchase to current customers and limit orders to 9 doses per month

Licensing a new JE vaccine in the U.S.

- Availability of several effective JE vaccines in Asia makes a controlled efficacy trial unethical and impractical
- Plaque reduction neutralization test (PRNT) titer of ≥1:10 accepted as an immunologic correlate of protection for JE
- New JE vaccines for the U.S. will be licensed based on:
  - Comparative PRNT immunogenicity study showing "non-inferiority" of new vaccine to licensed vaccine
  - Safety evaluations of the new vaccine in ~5,000 subjects

Hombach. Vaccine 2005; Markoff. Vaccine 2000.

CDC

Inactivated Vero cell-derived JE vaccine (IC51)

- IC51 (Ixiaro®) manufactured by Intercell (Vienna, Austria)
- BLA filed with FDA in December 2007
- Initial indication will be for use in adults (≥18 years)
- Novartis will distribute vaccine for U.S. civilians

Inactivated JE vaccines in the U.S.

	JE-VAX	IC51
Substrate	Mouse brains	Vero cells
JEV strain	Nakayama-NIH	SA 14-14-2
Adjuvant	None	Aluminum hydroxide
Stabilizer	Gelatin	None
Preservative	Thimerosal	None
Preparation	Lyophilized	Liquid
Route	Subcutaneous	Intramuscular
Primary series	3 doses (0, 7, 30 days)	2 doses (0, 28 days)
Age group	≥1 yr	≥18 yrs

IC51 pivotal clinical trials

- Non-inferiority of IC51 (n=361) vs. JE-VAX (n=364)
- Safety and tolerability of IC51 (n=1,993) vs. placebo (n=657)
- Persistence of neutralizing antibodies at 6 and 12 months
- Kinetics of neutralizing antibodies
- Co-administration of IC51 and hepatitis A vaccine
- Pooled safety at 6 mos after receiving IC51 (n=3,558)

Tauber.J Infect Dis 2008; Schuller Vaccine 2008; Tauber Lancet 2007.

CDC

Comparative immunogenicity trial of 2 doses of IC51 to 3 doses of JE-VAX

	IC51 (N=361)	JE-VAX (n=364)
$PRNT_{50}$ ≥1:10*	98%	95%
Geometric mean titer*	245	102

*SA 14-14-2 used as the target JEV strain for PRNT assay

Tauber. Lancet 2007.

Pivotal safety trial for 2 doses of IC51

Adverse events	IC51 (N=1,993)	Placebo* (n=657)
Any	1,173 (59%)	372 (57%)
Medically attended	254 (13%)	80 (12%)
Serious	10 (0.5%)	6 (0.9%)
Terminated study	12 (0.6%)	5 (0.8%)

*Aluminum hydroxide adjuvant

Tauber. J Infect Dis 2008.

ACIP WG conclusions

- IC51 is a promising vaccine for travelers
  - Two dose schedule (0 and 28 days)
  - Good immunogenicity and reactogenicity profile
  - No gelatin or murine protein; likely fewer adverse events
- IC51 has been studied in <5,000 recipients and the possibility of rare adverse events cannot be excluded
- Post-licensure studies and surveillance data will be important to further evaluate safety in a larger population

JE vaccine for U.S. children

- IC51 will initially be licensed for adults (≥18 yrs)
- IC51 will be evaluated in children in Asia then U.S
- JE-VAX will remain the only JE vaccine approved for use in children for at least 2-3 years
- Sanofi plans to maintain a stockpile of JE-VAX for use in children until 2010

ACIP WG activities

- Monitor availability of JE vaccine for U.S. travelers
- Work with HHS, DoD, and sanofi pasteur to mitigate possible supply issues
- Present revised recommendations at February 2009 meeting
- Address future availability of JE vaccine for U.S. children

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