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

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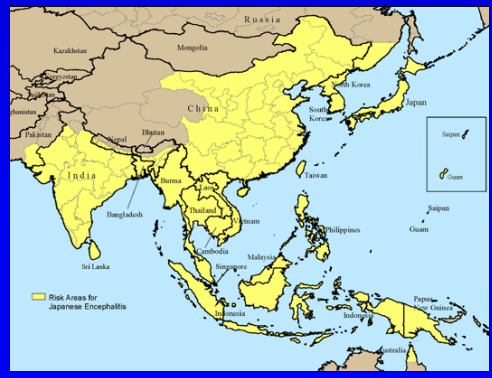
JE virus

- Mosquito-borne flavivirus
- Closely related to dengue and West Nile viruses
- Leading cause of encephalitis in Asia



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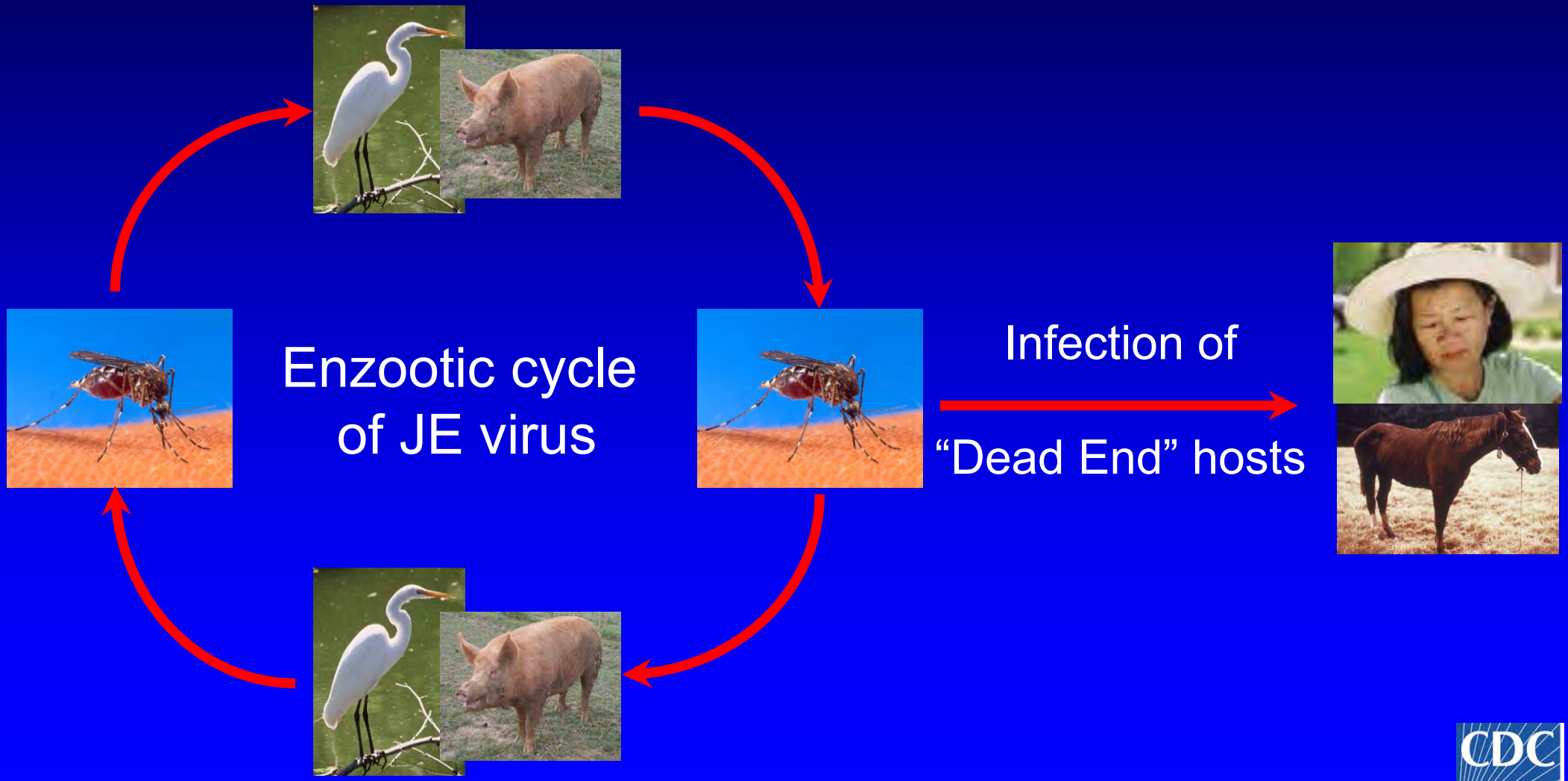
JE virus transmission cycle



Culex tritaeniorhynchus

- *Culex* mosquitoes primary JE virus vectors
- Evening- and nightime-biting mosquito
- Feed most often outdoors
- Larvae found in rice fields and marshes
- Greatest densities from June-November

JE virus infections in humans

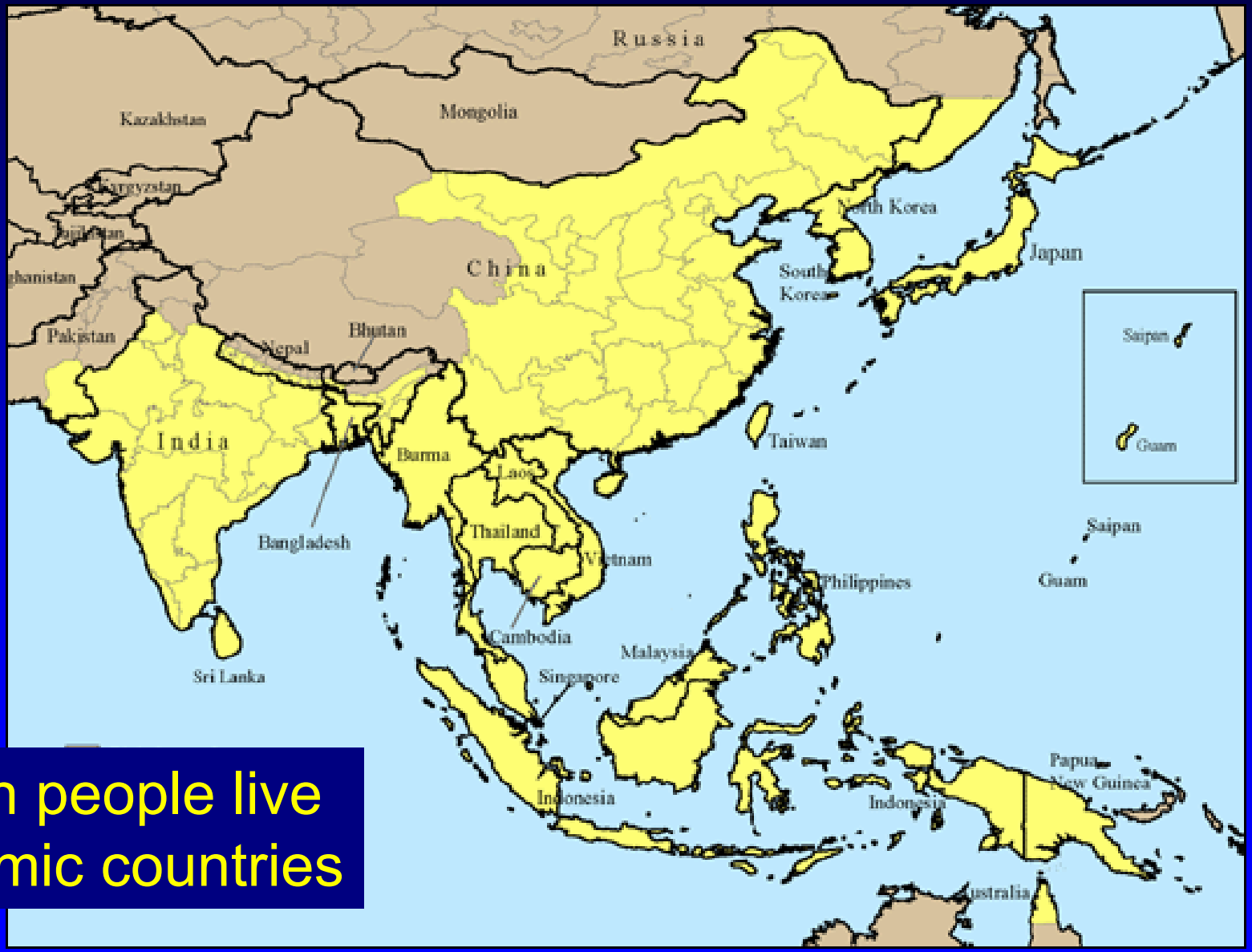
- Most are asymptomatic
  - <1% infected people develop clinical disease
- Clinical disease is often severe
  - Estimated 68,000 JE cases annually
  - 20%-30% case fatality
  - 30%-50% of survivors have sequelae
- No antiviral therapy; only supportive care

CDC

JE epidemiology

- Highest risk in rural agricultural areas
  - Transmission often associated with rice production
  - Ecologic conditions may occur near urban areas
- Highest incidence among children
  - 5 to 50 cases per 100,000 children per year
  - Adults in high transmission areas often immune
- Seasonality varies by region
  - Temperate: Seasonal peaks with large outbreaks
  - Tropical: Sporadic or year round

Geographic range of JE virus



3 billion people live in endemic countries

CDC

JE vaccine programs in endemic Asian countries

Comprehensive

- China
- India
- Japan
- South Korea
- Nepal
- Sri Lanka
- Taiwan
- Thailand
- Vietnam

Partial

- Cambodia
- Laos
- Malaysia
- North Korea

None

- Bangladesh
- Bhutan
- Brunei
- Indonesia
- Myanmar
- Papua New Guinea
- Philippines
- Timor Leste

CDC

JE among travelers from non-endemic areas

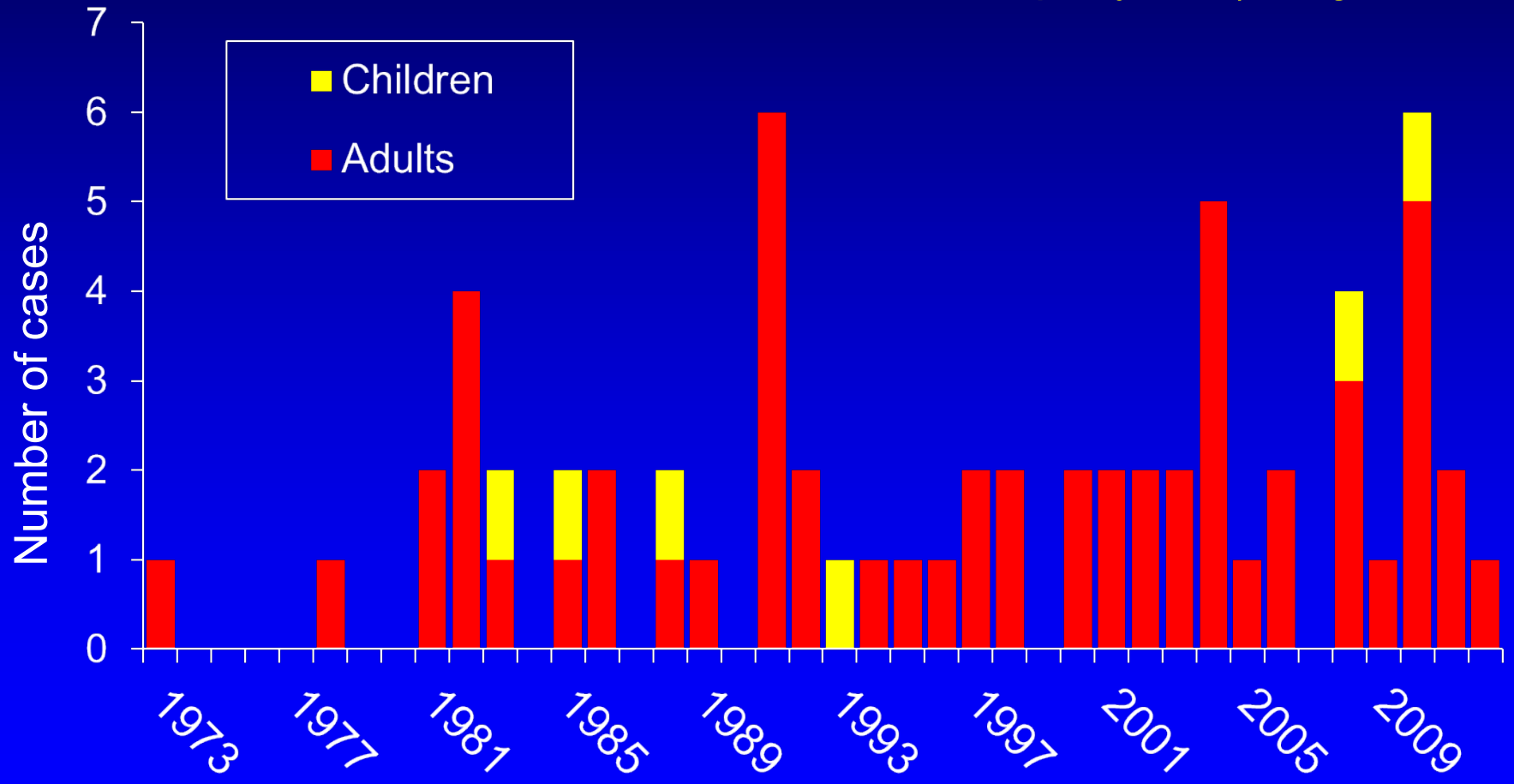
- For most travelers, the risk for JE is very low but it varies based on destination, duration, season, and activities
- >300 JE cases reported among U.S. military personnel during the Vietnam and Korean Wars
- From 1973-2012, 65 cases of travel-associated JE among persons from non-endemic areas reported in literature*
  - 6 (9%) cases in children <17 years of age

*Includes reports that are in press or submitted for publication

CDC

Year of travel-associated JE cases, 1973–2012 (N=63)*

Median 1 case per year (Range: 0-6 cases)



*Two cases occurred before 1993 but specific year not reported

CDC

Sex of travel-associated JE cases, 1973–2012

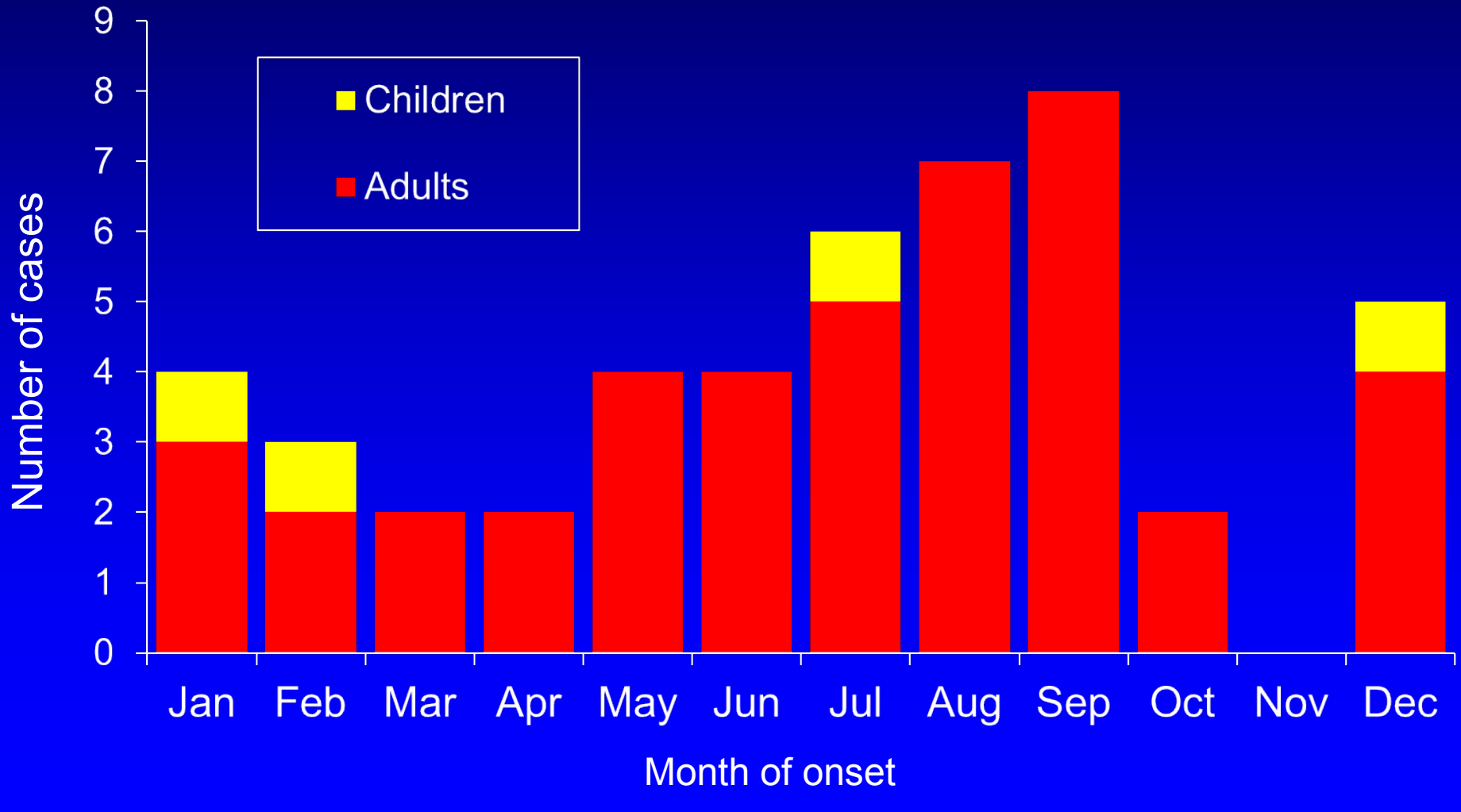
	All ages (N=65)	Adults (N=59)	Children (N=6)
Male	54%	54%	50%
Female	40%	39%	50%
Unknown	6%	7%	--

Age group of travel-associated JE cases, 1973–2012

Years	All ages* (N=65)	Adults (N=59)	Children† (N=6)
<20	11%	2%	100%
20–39	37%	41%	--
40–59	18%	20%	--
≥60	20%	22%	--
Unknown	14%	15%	--

*Median 34 years (Range 1–91 years)
†Median 9 years (Range 1–11 years)

Month of onset of travel-associated JE cases, 1973–2012 (N=47)



Outcomes of travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
Died	20%	19%	33%
Survived			
Sequelae	43%	42%	50%
No sequelae	23%	25%	0%
Unknown	14%	14%	17%

Probable countries of acquisition of travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
Thailand	32%	36%	--
China	14%	15%	33%
Indonesia	14%	12%	--
Philippines	11%	10%	17%
Japan	6%	7%	--
Vietnam	5%	2%	33%
Other	12%	14%	--
Unknown	6%	5%	17%

CDC

Country of citizenship for travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
United States	29%	27%	50%
Sweden	11%	12%	--
Germany	9%	10%	--
Australia	6%	3%	33%
Italy	5%	5%	--
Norway	5%	5%	--
Netherlands	5%	5%	--
Other	31%	32%	17%

Type of traveler for travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
Tourist	62%	59%	83%
Expatriate	18%	19%	17%
Soldier	9%	10%	--
Unknown	11%	12%	--

Itineraries for reported travel-associated JE cases, 1973-2012 (n=47)

Duration of travel		(N=47)
≥1 month		30 (64%)
2 – 4 weeks	"Short-term"	13 (27%)
1 – 2 weeks	"Short-term"	4 (8%)

Rural exposure for short-term travelers	(N=17)
Extensive rural travel	4 (24%)
Short trips to rural areas	10 (59%)
Primarily coastal areas	3 (18%)
Urban areas only	0 (0%)

Epidemiology of JE among travelers compared to resident populations

- Similarities
  - Associated with rural exposures in endemic areas
  - High case fatality and sequelae
- Differences
  - Age distribution reflects exposed travelers
  - Seasonal variation less apparent
  - Occur in areas with few recognized cases due to poor surveillance or routine vaccination
  - Incidence usually lower but depends on itinerary

CDC

Limitations of using travel-associated JE cases to estimate risk

- Numerator incomplete or not representative of all cases
  - Published cases not identified
  - Cases not diagnosed, reported, or published
  - Missing travel details for many cases; especially prior to 1992
  - Reported cases may be clinically or epidemiologically different
- Denominators unknown
  - Total numbers of travelers to Asia
  - Proportion of travelers with long-term or high risk itineraries
  - Proportion of travelers who are immunized

CDC

Survey of U.S. travelers to JE-endemic areas in 2007

- Surveyed 1,691 U.S. travelers boarding direct flights to Asia
- 25% reported higher JE risk itineraries
  - 20% planned to spend ≥1 month in Asia
  - 5% spend <1 month but majority of time in rural areas
- 11% of higher risk travelers reported receiving JE vaccine
- 2% of lower risk travelers reported receiving JE vaccine

Duffy. J Travel Med. In press

CDC

Estimated incidence of JE for travelers to Asia

1. Extrapolate from unimmunized children in endemic areas
   - 50 to 500 cases per million children per year
   - Assuming equal risk throughout year
   - 1 to 10 cases per million travelers per week

2. Minimum estimates based on published cases from 1973-2012
   - 19 U.S. travel-related cases in 40 years
   - 5.5 million entries of U.S. travelers to Asia in 2004
   - <1 case per million trips to Asia

CDC

Summary of JE risk for travelers to Asia

- Overall risk of JE for travelers is very low but varies based on destination, duration, season, and activities
- Prolonged travel in rural areas with active JE virus transmission may confer similar risk as 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 minimal risk for JE

CDC

JE vaccines licensed in the United States

- Inactivated mouse brain-derived JE vaccine (JE-MB)
  - Trade name: JE-VAX
  - Manufactured in Japan by Biken
  - Distributed in United States by Sanofi
  - No longer produced or available
- Inactivated Vero cell culture-derived JE vaccine (JE-VC)
  - Trade name: IXIARO
  - Manufactured in Scotland by Intercell Biomedical
  - Distributed in U.S. private market by Novartis
  - Only JE vaccine currently available in the United States

CDC

JE-MB timeline

- Developed and manufactured in Japan in 1940-50s
- Used to control JE in several endemic countries in 1960-70s
- 91% efficacy in a randomized controlled trial in >65,000 children in Thailand in 1984–86
- Licensed in U.S. for use in people ≥1 year of age in 1992
- Neurologic and hypersensitivity reactions described in 1990s
- Biken discontinued production in 2006
- All remaining doses expired in 2011

CDC

JE-VC timeline

- Licensed for use in adults in the United States, Europe, and Australia in 2009
- ACIP recommendations for adults (≥17 years of age) approved in June 2009
- Booster dose recommendations approved in February 2011

JE-VC efficacy and licensure

- No efficacy data for JE-VC
  - Availability of several effective JE vaccines in Asia made a controlled efficacy trial impractical and unethical
  - JE virus plaque reduction neutralization test (PRNT) titer ≥10 is an established immunologic correlate of protection*
- JE-VC licensed based on:
  - Non-inferiority of neutralizing antibody response compared to JE-MB
  - Safety evaluations in ~5,000 adults

*Hombach. Vaccine 2005; Markoff. Vaccine 2000.

JE vaccines components and administration

	JE-MB	JE-VC
JEV strain	Nakayama-NIH	SA_{14}-14-2
Preparation	Lyophilized	Liquid
Adjuvant	None	Aluminum hydroxide
Stabilizer	Gelatin	None
Preservative	Thimerosal	None
Primary series	3 doses (0, 7, 30 days)	2 doses (0, 28 days)
Route	Subcutaneous	Intramuscular

Comparative non-inferiority study of JE-VC and JE-MB

	Days			
	0	7	28	56
JE-VC (N=428)	X	Placebo	X	$PRNT_{50}$
JE-MB (N=435)	X	X	X	$PRNT_{50}$

$PRNT_{50}$ = 50% plaque reduction neutralization test

Tauber. Lancet 2007.

Immunogenicity of JE-VC (2 doses) vs JE-MB (3 doses) at day 56*

	JE-VC (n=361)	JE-MB (n=364)	p-value
$PRNT_{50}$ ≥1:10	98%	95%	NI
Geometric mean titer	245	102	<0.05

NI = Non-inferior

*Per protocol analysis; prevaccination $PRNT_{50}$ <1:10 for all subjects

Tauber. Lancet 2007.

Severe local and systemic adverse events within 7 days after vaccination at days 0 and 28

	JE-VC (N=428)	JE-MB (n=435)
Severe local		
Pain/ tenderness	<1%	1%
Redness*	1%	11%
Swelling*	1%	5%
Systemic		
Headache	26%	29%
Myalgia	21%	16%
ILI	13%	13%
Fatigue	13%	11%

*p<0.01

Tauber. Lancet 2007.

Safety and tolerability of JE-VC vs placebo

	Days		
	0	28	56
JE-VC (n=1,993)	X	X	Adverse events
Placebo (n=657)*	X	X	Adverse events

*Phosphate buffered saline with 0.1% aluminum hydroxide

Tauber. J Infect Dis 2008.

CDC

Adverse events within 56 days after first dose

Adverse events	JE-VC (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%)

*Phosphate buffered saline with 0.1% aluminum hydroxide

Tauber. J Infect Dis 2008.

Studies evaluating duration of protection after JE-VC primary series and response to a booster dose

- Three studies evaluated duration of JE-VC seroprotection*†‡
  - Of 495 subjects total, 17-42% had no detectable neutralizing antibodies at 12-15 months after the 2-dose primary series
- In two of the studies, subjects received booster dose at 11-23 months after the primary series†‡
  - Of 238 subjects total, all were seroprotected at 1 month after booster
  - 98% remained protected at 12 months after booster

Schuller. Vaccine 2008; †Dubischar-Kastner. Vaccine 2010; ‡Eder. Vaccine 2011.

CDC

JE-VC post-licensure safety data

- Since 2009, several hundred thousand doses total have been distributed in the United States, Europe, and Australia*
- No important safety concerns have been identified in passive post-licensure surveillance

*Schuller. Vaccine 2011.

JE-VC summary

- The only JE vaccine licensed and available in the U.S.
- Licensed for use in adults based on non-inferiority comparison and immunologic correlate of protection
- Good immunogenicity and reactogenicity profile in ~5,000 adults clinical trials
- No safety concerns identified to date in post-licensure surveillance
- Costs ~$200 per dose

JE vaccine considerations for U.S. travelers

- Risk of JE disease for most travelers is very low
- Risk varies based on location, duration, season, activities
- JE is a severe disease with substantial morbidity & mortality
- There is no specific treatment
- Safe and effective vaccine is available
- Vaccine is expensive
- Does not prevent importation or spread of JE virus

ACIP recommendations for JE vaccine (June 2009)

1. Travelers to JE-endemic countries should be advised of the risks of JE disease and the importance of measures to reduce mosquito bites
2. JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season
3. JE vaccine should be considered for short-term travelers to endemic areas if they will travel outside of an urban area and their activities will increase the risk of JE virus exposure
4. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season

CDC. MMWR 2010.

CDC

ACIP recommendations for a booster dose of JE-VC (February 2011)

- If ≥1 year since the primary series, a booster dose may be given prior to potential JE virus exposure
- Data on the need for and timing of additional booster doses are not available

CDC. MMWR 2011.

JE vaccine for children in the United States

- No JE vaccine is licensed and available in the United States for use in children <17 years of age
- JE-VC has been evaluated in three pediatric clinical trials (two in endemic areas and one in travelers)
- In July 2012, Intercell submitted a BLA amendment to FDA for use of JE-VC in children aged 2 months–16 years
  - Action due date May 2013
- Pediatric indication approved by EMA in February 2013

JE Vaccine Workgroup plans for June 2013 ACIP meeting

- Present JE-VC pediatric clinical trial data
- Present and vote on proposed recommendations and evidence-based ratings for use of JE-VC in children

ACIP JE Vaccine Workgroup members

ACIP

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