Review of Japanese encephalitis (JE) and JE Vaccine Work Group plans

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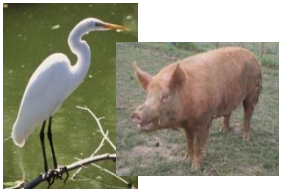
JE virus

- Mosquito-borne flavivirus
- Leading vaccine-preventable cause of encephalitis in Asia
- *Culex tritaeniorhynchus* mosquitoes primary JE virus vectors
  - Evening- and nighttime-biting mosquitoes
  - Usually feed outdoors
  - Commonly breed in rice fields

Endy TP, Nisalak A. Curr Top Microbiol Immunol 2002.

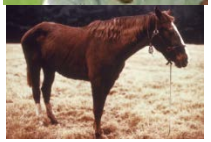
JE virus transmission cycle

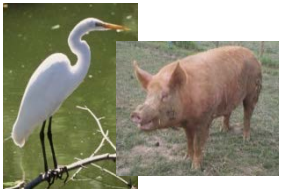


Enzootic cycle of JE virus

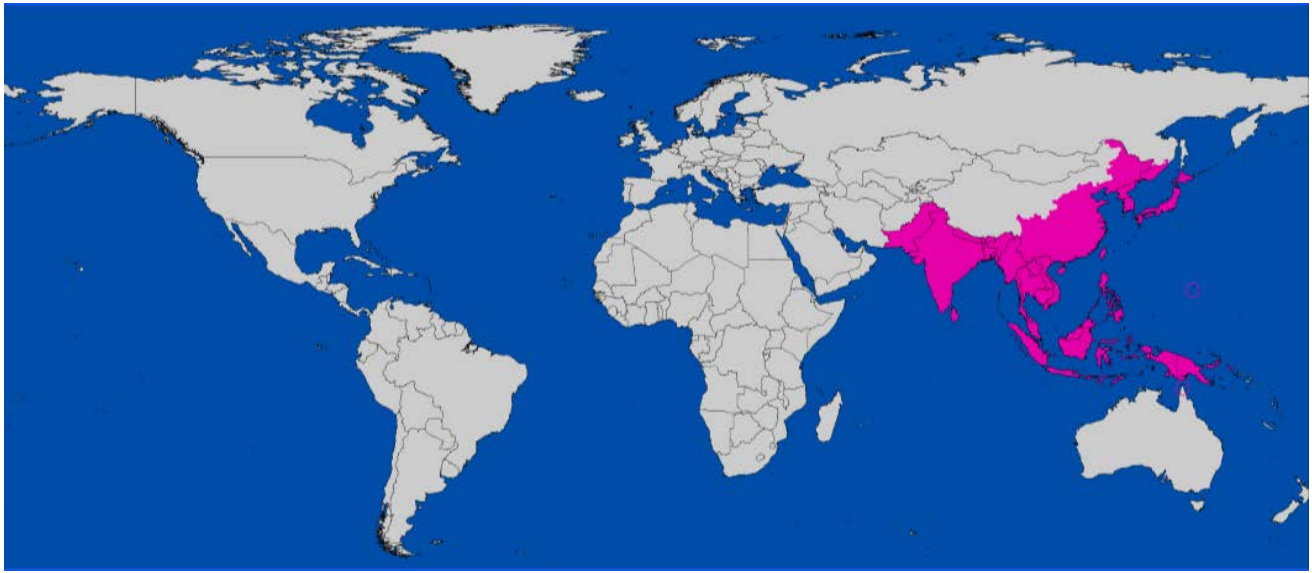
Infection of

"Dead End" hosts





Approximate global distribution of JE virus



- Only occurs in Asia and Western Pacific
- 3 billion people live in endemic countries

JE virus infections in humans

- Most infections are asymptomatic
  - <1% infected people develop neurologic disease
- Clinical disease is often severe
  - 20%–30% case fatality
  - 30%–50% of survivors have sequelae
- No antiviral therapy; only supportive care

Vaughn DW, Hoke CH. Epidemiol Rev 1992.

JE epidemiology in endemic countries

- Estimated 68,000 disease cases annually in Asia
- Overall incidence 1.8 per 100 000 population
- Highest risk in rural agricultural areas
- Seasonality varies by region
  - Temperate: Seasonal peaks with large outbreaks
  - Tropical: Year round
- National vaccination programs in some endemic countries

Campbell GL, et al. Bull World Health Organ 2011.

JE among travelers from non-endemic areas

- Risk of JE for most travelers is very low but varies based on travel destination, duration, season, and activities
- Overall incidence estimated < 1 case per million travelers
- In the United States, in 25-year period following licensure of JE vaccine in 1992, 12 travel-associated cases reported (< 1 case per year)

Hills et al. CDC Yellow Book 2018.

Inactivated Vero cell culture-derived JE vaccine (Ixiaro®, Valneva)

- Only JE vaccine licensed and available in the US
- Licensed for adults in 2009 and children in 2013
- Licensed based on ability to induce JE virus neutralizing antibodies as surrogate for protection
- Good immunogenicity and reactogenicity profile in pre-licensure studies
- No safety concerns to date in post-licensure surveillance
- Approximately $600 for 2-dose primary series

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 costs $600 for 2-dose primary series
- Rare serious adverse events
- Does not prevent importation or spread of JE virus

ACIP recommendations for JE vaccine

- Travelers to JE-endemic countries should be advised of risks of JE
- All travelers should take precautions to avoid mosquito bites to reduce risk of JE and other vector-borne diseases
- JE vaccine recommended for travelers who plan to spend a month or longer in endemic areas during JE virus transmission season, including expatriates and recurrent travelers
- JE vaccine should be considered for shorter-term travelers to endemic areas if itinerary will increase the risk of JE virus exposure
- JE vaccine not recommended for short-term travelers whose visit restricted to urban areas or times outside of transmission season

CDC. MMWR 2010.

ACIP JE Vaccine Work Group objectives

- Review newly available safety and immunogenicity data for JE vaccine
- Review epidemiology and risk of JE in travelers
- Review ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler risk data
- Update MMWR Recommendations and Reports

Work Group presentations to ACIP since 2015

- Safety
  - Adverse events reported to VAERS, 2012-2016
  - Post-marketing adverse event surveillance among U.S. military personnel
- Immunogenicity
  - Immunogenicity in adults ≥65 years of age
  - Accelerated dosing schedule
  - Concomitant administration with rabies vaccine
  - Duration of protection following primary series and booster dose
- Review of epidemiology and risk of JE in U.S. travelers

Current Work Group activities: JE vaccine cost-effectiveness analysis

- JE vaccination cost-effective or cost-saving for local populations in JE endemic countries
  - Incidence higher and substantially lower cost vaccines
- No JE vaccine cost-effectiveness studies among travelers
  - Given low disease incidence and high cost vaccine not expected to be cost-effective
- Rationale for JE vaccine cost-effectiveness analysis
  - Provide perspective on numbers needed to be vaccinated and cost per case averted
  - Compare relative costs of vaccination for travelers with different itineraries and disease risk

Remaining Work Group objectives to be addressed at upcoming ACIP meetings

- Present cost-effectiveness analysis
- Review recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler risk data
- Perform updated GRADE analysis
- Present draft of updated MMWR Recommendations & Reports

Additional JE vaccine updates

- Submissions under review at FDA
  - Pediatric booster dose
  - Accelerated primary schedule

Thank you