

JAPANESE ENCEPHALITIS (JE) VACCINE

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Japanese encephalitis vaccine WG members

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ACIP JE vaccine work group objectives

- Review newly available safety and immunogenicity data for inactivated Vero cell culture-derived JE vaccine (JE-VC)
- Review epidemiology and risk of JE in travelers
- Review ACIP recommendations for use of JE vaccine in consideration of updated data
- Update MMWR Recommendations and Reports

October 2018 ACIP session

- Presented Evidence to Recommendations framework for updated JE vaccine recommendations
- Reviewed accelerated dosing schedule data in adults
- Reviewed booster dose recommendations
 - Strengthen current permissive recommendation
 - Expand to include children aged <17 years

Overview of today's session

- Background and review of JE and JE vaccine
- Review and vote on
 - Updated recommendations for U.S. travelers
 - Accelerated primary series in adults
 - Booster dose recommendations
- Conclusion and next steps

Background and review of JE and JE vaccine

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Japanese encephalitis (JE)

- Caused by a mosquito-borne flavivirus
- Occurs in most of Asia and parts of Western Pacific
- Leading vaccine-preventable cause of encephalitis in Asia



JE virus infections in humans

- Most infections 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

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 as vector breeds in rice fields

JE risk among U.S. travelers

- Risk of JE for most travelers is very low
 - Varies based on travel destination, duration, season, activities, and accommodations
- JE vaccine first licensed in the United States in 1992
 - From 1993–2017, 12 JE cases reported among U.S. travelers or expatriates
 - 4–5 million U.S. citizen trips to Asia annually
 - Estimated risk <1 case per million trips to Asia

Travel duration and exposures for U.S. traveler JE cases

- Among 12 JE cases reported in U.S. travelers
 - 8 (67%) cases: Duration of travel ≥ 1 month
 - 3 (25%) cases: Shorter travel but rural exposure for ≥ 1 night
 - 1 (8%) case: No information

JE-VC (Ixiaro)

- Manufactured by Valneva Austria GmbH
- Only JE vaccine licensed and available in the US
- Licensed for
 - Adults aged ≥ 17 years in 2009
 - Children aged ≥ 2 months in 2013
- Schedule
 - Primary series: 2 doses administered 28 days apart
 - Booster dose (adults): >1 year after primary series

JE-VC efficacy and correlate of protection

- No efficacy data for JE-VC
- Established immunologic correlate of protection
 - JE virus 50% plaque reduction neutralization test (PRNT₅₀) titer ≥ 10
- Licensed based on non-inferiority compared to licensed mouse brain-derived JE vaccine

ACIP recommendations for use of JE vaccine

2009: Recommendations approved for JE vaccine use in U.S. travelers

2013: Recommendations reviewed following pediatric licensure of JE-VC but no changes made

Rationale for current review of ACIP JE vaccine recommendations

- Routine review of existing recommendations
 - Consider newly available safety, immunogenicity, and travelers risk data
- Update MMWR Recommendations and Reports
 - Incorporate previously published policy notes, and new data, indications, and dosing schedules

Updated JE vaccine recommendations for U.S. travelers

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Minor changes from current JE vaccine recommendations

- Additional information on factors that increase JE risk to assist providers with decision-making
- Longer-term travel no longer specifically defined as a cut-off of ≥ 1 month
- Removed consideration of vaccination for travelers to an area with an ongoing JE outbreak
- Small wording changes to address questions raised

Recommendations for the prevention of JE among U.S. travelers (1)

“JE is a very low risk disease for most U.S. travelers to JE-endemic countries. However, some travelers will be at increased risk of infection based on their planned itinerary. Factors that increase the risk of JE virus exposure include: 1) longer duration of travel, 2) travel during the JE virus transmission season, 3) spending time in rural areas, 4) participating in extensive outdoor activities, and 5) staying in accommodations without air conditioning, screens, or bed nets (**Box**).”

BOX. Factors that increase risk for JE among travelers (1)

Duration

- Highest incidence of disease has been reported among longer-term travelers.
- Although no specific duration of travel puts a traveler at risk for JE, longer-term travel increases the likelihood that a traveler might be exposed to an infected mosquito.
- Longer-term travel includes cumulative periods in endemic areas, such as frequent travelers, and persons residing in urban areas who are likely to visit higher risk rural areas.

Season

- JE virus transmission occurs seasonally in some areas, and year-round in other areas.
- Information on expected JE virus transmission by country is available on the CDC website (see Japanese encephalitis chapter in CDC Health Information for International Travel [the Yellow Book]). These data should be interpreted cautiously because JE virus transmission varies within countries and from year to year.

BOX. Factors that increase risk for JE among travelers (2)

Location

- Highest risk occurs from mosquito exposure in rural or agricultural areas.
- Mosquitoes that transmit JE virus typically breed in flooded rice fields, marshes, and other stagnant collections of water.
- Some cases have been reported among travelers to coastal areas or resorts located in or adjacent to rural or rice growing areas.
- JE can occur in large, focal outbreaks indicating extensive active JE virus transmission in those areas.

Activities

- The mosquitoes that transmit JE virus feed most often in the outdoors, particularly from sunset through dawn, so examples of activities that increase risk include:
 - Outdoor recreation such as camping, hiking, trekking, biking, rafting, fishing, hunting, or farming.
 - Spending substantial time outdoors, especially during the evening or night.

Accommodations

- Accommodations without air conditioning, screens, or bed nets increase risk of mosquito exposure.

Recommendations for the prevention of JE among U.S. travelers (2)

“Healthcare providers should assess each traveler’s risk for mosquito exposure and JE virus infection based on their planned itinerary, and discuss ways to reduce their risk. All travelers to JE-endemic countries should be advised to take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms.”

Recommendations for the prevention of JE among U.S. travelers (3)

“For some people who might be at increased risk for JE based on travel duration, season, location, activities, and accommodations, JE vaccine can further reduce the risk for infection. The decision whether to vaccinate should be individualized and weigh the: 1) risks related to the specific travel itinerary, 2) likelihood of future travel to JE-endemic countries, 3) high morbidity and mortality of JE when it occurs, 4) availability of an effective vaccine, 5) possibility, but low probability, of serious adverse events following vaccination, and 6) traveler’s personal perception and tolerance of risk.”

VOTE: Proposed JE vaccine recommendations

“JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (e.g., ≥ 1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas.

JE vaccine also should be considered for shorter-term (e.g., < 1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations (**Box**). Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities.

JE vaccine is not recommended for travelers with very low risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside of a well-defined JE virus transmission season.”

JE-VC accelerated primary series for adults aged 18–65 years

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Timeline of events

March 2009

- FDA approved JE-VC for use as 2-dose primary series administered at 0 and 28 days

October 2015

- Manufacturer presented data to ACIP for alternate accelerated primary series (0 and 7 days) in adults

December 2017

- Manufacturer submitted BLA amendment to FDA

October 2018

- FDA approved the accelerated primary series
- Work group re-presented data to ACIP

Data supporting the accelerated schedule

- Randomized trial among adults aged 18–65 years
 - Conducted at seven study sites in Europe
 - JE-VC administered with rabies vaccine
 - Non-inferiority of accelerated schedule on days 0 and 7 compared with conventional schedule on days 0 and 28
- Phase II study among adults aged 18–49 years
 - JE-VC administered on days 0, 14, and 28, or days 0 and 28
 - Data on seroprotection rate at 14 days after 2 doses on days 0 and 14

Immunogenicity of two JE-VC doses administered on days 0 and 7 versus days 0 and 28

	0 and 7 days	0 and 28 days
28 days after dose 2		
Seroprotected	203/206 (99%)	157/157 (100%)
Geometric mean titers	690	299
1 year after dose 2		
Seroprotected	188/199 (94%)	132/154 (86%)
Geometric mean titers	117	39

Immunogenicity of two JE-VC doses administered on days 0 and 14 versus days 0 and 28

	0 and 14 days	0 and 28 days
14–28 days after dose 2		
Seroprotected	22/23 (96%)	21/22 (95%)
Geometric mean titers	328	327

JE-VC dose and primary vaccination schedule varies by age

- 2–35 months: Two 0.25mL doses administered on days 0 and 28.
- 3–17 years: Two 0.5mL doses administered on days 0 and 28.
- 18–65 years: Two 0.5mL doses administered on days 0 and 7–28.*
- >65 years: Two 0.5mL doses administered on days 0 and 28.

*Only age group for which an accelerated schedule is approved.

VOTE:

Proposed new recommendation for primary series schedule in adults aged 18–65 years

“In adults aged 18–65 years, the primary vaccination
schedule is two doses administered on days 0 and 7–28.”

JE-VC booster doses

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Timeline of events

September 2010

- FDA approved JE-VC booster dose for ages ≥ 17 years

February 2016

- Manufacturer presented data to ACIP for booster dose in children

June 2017

- Manufacturer submitted BLA amendment to FDA

April 2018

- FDA approved pediatric booster dose

October 2018

- Work group re-presented data to ACIP

Current ACIP recommendations for JE-VC booster dose for adults aged ≥ 17 years

“If the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure.”

Topics for consideration

- Lower recommended age for booster dose to include children
- Strengthen current permissive booster dose recommendation

Data supporting the booster dose for children

- One open label randomized trial among children aged 14 months to 17 years
- Conducted in JE-endemic country of Philippines
- Included 300 children randomized to receive or not receive a booster dose
- Booster dose administered at 11 months after 2nd dose of 2-dose primary series

Immunogenicity following a booster dose in children aged ≥ 14 months

28 days after booster

Seroprotected 148/148 (100%)

Geometric mean titer 2,067

2 years after booster

Seroprotected 143/143 (100%)

Geometric mean titer 350

WG conclusion on recommended age for booster dose

- **Modify the current recommendation for JE-VC booster to include children**

Data supporting strengthening the current permissive booster dose recommendation

- At 12–15 months after the 2-dose primary series, 58%–83% seroprotected (3 studies)
- Studies conducted in Europe where tick-borne encephalitis (TBE) vaccine is available
- TBE virus is a flavivirus related to JE virus and there may be a boosting effect between JE and TBE vaccines
- Manufacturer conducted post hoc analysis that stratified subjects by TBE vaccination status

Immunogenicity after two doses JE-VC by TBE vaccination status

	1 year	5 years
Seroprotected		
TBE vaccine	82/89 (92%)	67/78 (86%)
No TBE vaccine	69/92 (75%)	30/47 (64%)
GMTs		
TBE vaccine	48	45
No TBE vaccine	35	29

WG conclusion

- After a 2-dose primary series, long-term seroprotection rates lower in people who have not received TBE vaccine
- TBE vaccine is not available in the United States
- Among U.S. travelers, duration of protection following JE-VC booster dose likely similar to subjects not administered TBE vaccine
- Permissive booster dose recommendation should be strengthened

VOTE:
**Proposed new recommendations
for JE-VC booster dose**

“A booster dose (i.e., third dose) should be given at ≥ 1 year after completion of the primary JE-VC series if ongoing exposure or re-exposure to JE virus is expected.”

Next steps for JE Vaccine Work Group

JE vaccine WG activities

- MMWR Recommendations and Reports on JE vaccine for U.S. travelers to be published
- JE WG activities now completed

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