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Review Article

Current recommendations for the Japanese encephalitis vaccine

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Abstract

Japanese encephalitis (JE) is a mosquito-borne flavivirus infection and an important cause of encephalitis in most of Asia and parts of the western Pacific. Most people infected with the JE virus (JEV) are asymptomatic or seemingly suffer from a nonspecific, flu-like illness; in others, JE can cause illness ranging from fever and headache to severe encephalitis. Although it can cause significant morbidity and mortality, JE is a vaccine-preventable disease, and vaccination programs have proven most effective in preventing and diminishing the burden of disease. Such JE vaccines have been available for decades with four types of JE vaccines—live attenuated SA14-14-2 vaccine, inactivated mouse brain-derived vaccine (JE-MB), inactivated Vero cell culture vaccine (JE-VC), and live attenuated chimeric vaccine (IMOJEV)—and are currently used in most countries. In some Asian countries such as Japan, China, Taiwan, Korea, and Thailand, immunization programs have been conducted for children and so the ongoing incidence of JE has declined considerably in recent decades. Until quite recently, the primary JE vaccine in use internationally has been the JE-MB, which is now commonly replaced by cell culture-based vaccines.

Keywords: inactivated mouse brain-derived vaccine (JE-MB); inactivated Vero cell culture vaccine (JE-VC); Japanese encephalitis (JE); live attenuated chimeric vaccine (IMOJEV); live attenuated SA14-14-2 vaccine

1. Introduction

Japanese encephalitis (JE) is the most common vaccine-preventable cause of encephalitis in Asia. It is responsible for an estimated 67,900 JE cases annually, has a 20–30% fatality rate and leaves neurologic or psychiatric sequelae in 30–50% of survivors.[1] JE virus (JEV) is a single-stranded RNA virus that belongs to the genus *Flavivirus* and is transmitted to humans through the bite of an infected mosquito, primarily *Culex* species. Fortunately, it cannot spread directly from person to person. JEV is transmitted in an enzootic cycle between mosquitoes and vertebrate hosts, mainly pigs and wading birds. Overall, humans are incidental or dead-end hosts in the JEV transmission cycle. Because immunization is the major contributing factor to the decrease of JE, the World Health Organization (WHO) recommends that the JE vaccine be incorporated into immunization programs in all areas where the disease is a public health problem.[2,3]

2. Epidemiology

JE is the main cause of viral encephalitis in many Asian countries; it is endemic with seasonal distribution in parts of China, the Russian Federation's south-east, and South and South-East Asia. To date, there has been no local transmission of JEV detected in Africa, Europe, or the Americas. There are a reported 30,000–50,000 clinical cases of JEV annually, with an estimated mortality ranging from 10 to 15,000 deaths.[4,5] It is more common in rural areas where regular rice cultivation and flood irrigation occurs. In some developed Asian countries, use of the JE vaccine has dramatically decreased cases of

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the disease found in children. However, JE is still seen in adults, particularly the elderly.[6] In data derived from populations in Taiwan and Thailand, the incidence of JE was noted to be 1.8 to 2.5 per 100,000 among unvaccinated children during placebo-control JE vaccine trials, whereas unvaccinated children in trials in China had an incidence of 5.7 to 64 per 100,000.[7−9]

According to the Taiwan Centers for Disease Control (Taiwan CDC), transmission of JE in Taiwan occurs mostly between the months of May and October, and annually peaks between June and July. Since Taiwan began routine use of the JE vaccination in 1968, the annual confirmed case number over the last decade has been between 20 and 40, including 0−2 deaths; the average age of patients in Taiwan with JE exceeds 20.[10] Due to the loss of vaccine-derived immunity in Taiwan, declining JE antibody prevalence ranged from 49% in primary school to 38% in junior high school, 34% in junior college, and 29% in university students.[11] For people who travel in Asia, the risk for JE is very low but varies by season, activities, travel destination, and duration of stay. The overall incidence of JE is estimated to be < 1 case per 1 million among people who travel from non-endemic countries to Asia.[2−4]

3. Clinical features

JE is primarily a disease that afflicts children but can occur among people of any age. People infected with JEV mainly are asymptomatic; infection is symptomatic in less than 1% of cases, and typically involves severe encephalitis. The incubation period of JE is 5−15 days,[2,3] and its earliest symptoms are lethargy, fever, headache, abdominal pain, nausea, and vomiting. Prodromal symptoms can evolve over several days to 1 week, when characteristic mental changes, focal neurological deficits, movement disorders and generalized weakness may develop over the next few days, thereafter advancing to progressive confusion, delirium, and coma. A minority of patients develop signs of increased intracranial pressure, such as papilledema and hypertension. Additionally, movement disorder such as nonstereotypical flailing, ataxia, or tremor may be present initially. Like Parkinson's syndrome, choreoathetosis, rigidity, masked facies, and other extrapyramidal signs may manifest later in the illness. Furthermore, 85% of children and 10% of adult develop focal or generalized seizure and multiple seizure and status epilepticus associated with a poor outcome.[12]

Laboratory studies disclose moderate leukocytosis with a left shift, mild anemia and hyponatremia. Cerebrospinal fluid (CSF) findings include mild to moderate pleocytosis, lymphocyte predominance, slightly elevated protein, and a normal ratio of CSF to plasma glucose. Imaging studies with electroencephalogram have revealed a pattern of diffuse slow waves with periodic lateralized epileptiform discharges (PLEDS). Magnetic resonance imaging (MRI) exhibited diffuse white matter edema, and abnormal signals in the thalamus, basal ganglia, cerebellum, midbrain, pons, and spinal cord. Thalamic lesions are the most commonly described abnormality.[12]

4. Treatment

Currently, there is no specific antiviral treatment for JE. Therapy for JE consists of supportive care and management of complications. The optimum way to prevent JE is to avoid mosquito bites. It is well understood that JE is a vaccine-preventable disease with four types of vaccines now available for active immunization. Vaccination programs have been proven the most effective in preventing and diminishing the burden of disease. All travelers to countries where JE occurs are at risk for JEV exposure and should take precautions to avoid mosquito bites. Because the risk of JE varies based on destination, duration of stay, activities, and seasonal patterns of disease in the areas to be visited, JE vaccination is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season.[13,14]

5. Type of JE vaccines and schedule

The four available JE vaccines are registered worldwide and used in national immunization programs for different age groups. Each of the vaccines incorporates a different vaccination schedule and booster dose requirement: (1) inactivated Vero cell culture vaccine (JE-VC) (IXIARO); (2) inactivated mouse brain-derived vaccine (JE-MB) manufactured in countries other than Japan; (3) a cell-culture-derived (primary hamster kidney) live attenuated vaccine based on the SA 14-14-2 strain manufactured in China; and (4) a live attenuated chimeric vaccine based on the genes of yellow fever 17D backbone combined with Vero cell propagated SA 14-14-2 strain (IMOJEV). Vero cell culture-derived inactivated vaccine based on the Beijing-1 strain (JEBIK-V and ENCEVAC) are manufactured for local use in Japan. Until quite recently, the main JE vaccine used internationally has been the inactivated JE-MB, which is effective in persons $\geq$ 1 years and administered in early childhood in two primary doses, with four to six additional boosters at various intervals until 15 years of age.[13−15] The Nakayama strain of JEV, isolated from the CSF of a patient in 1935 and maintained by continuous mouse brain passage, has been the principal strain used in JE-MB produced throughout Asia.[16] However, the JE-MB vaccine is now commonly replaced by cell culture-based vaccines.[13,14] A new JE vaccine containing Beijing-3 (P3) vaccine strain grown in primary hamster kidney (PHK) cells was developed in China in 1968.The two new generations of JE vaccines, IXIARO and IMOJEV, have recently been licensed for routine use by countries in Europe, America, and Asia.[17] A further overview of these vaccines used against JE is provided in Table 1.

6. Recommendations for the use of JE vaccine

The WHO recommends that the JE vaccine be incorporated into immunization programs in all areas where there is a risk of JEV transmission. According to information derived from a survey of JE vaccine programs, 11 (46%) of the 24 countries with JEV transmission risk had a JE immunization program in

Table 1
Summary of current available JE vaccines.

Vaccine features	Live attenuated	JE-MB	JE-VC		Live attenuated chimeric
			With aluminum adjuvant	Without adjuvant	
Strain	SA14-14-2	Nakayama-NH Beijing-1	SA14-14-2	Beijing-1	SA14-14-2
Trade name		JE-VAX	IXIARO/JESPECT	JEBIK-V[a] ENCEVAC[b] TC-JEV[c]	IMOJEV
Manufacturer	Chengdu Institute	BIKEN	Intercell biomedical	BIKEN	Sanofi- Pasteur
Licensed	1988	1954-Japan 1993-US	2009[d]	JEBIK-V(2009) ENCEVAC(2011) TC-JEV(2013)	2010
No. of doses for primary series	1 dose	2 doses	2 doses Day 0 and 28	3 doses Day 0, 7, and 28	1 dose
Schedule age first shot	8 mo	15–27 mo	2 mo	36 mo	≥12 mo
Booster	At 2 years and 6–7 y	12 mo after primary series, aged >5 y	Aged ≥17 y,12 mo after primary series.	12–24 mo and thereafter every 3 y	Not yet
Total doses	3	4	3	5	1
Route	SC	SC	IM	SC	SC
Country	China Japan Thailand Hong Kong	Taiwan Thailand South Korea	Europe, USA, Canada, Switzerland, Singapore, Hong Kong, and Australia	Japan Korea[e]	Australia Thailand

IM = intramuscular; JE-MB = inactivated mouse brain-derived JE vaccine; JE-VC = inactivated Vero cell culture-derived JE vaccine; SC = subcutaneous.
[a] Japan, BIKEN/TAKEDA.
[b] Japan, Kaketsuken.
[c] Korea, Boryung/Star-Bio.
[d] Licensed in 2009 for aged ≥17 years and in 2013 for aged 2 months through 16 years.
[e] Targeted use in March 2014.

2012. Ten (4%) countries included a JE vaccine in their routine vaccination schedule, and one country conducted annual vaccination campaigns. The scheduled age at which children were first vaccinated ranged from 8 months to 3 years.[1]

Use of the JEV vaccine was recommended for travelers spending 1 month or more in endemic area during the JEV transmission season, and laboratory workers with a potential for exposure to infections JEV.[18]

The vaccine should also be considered for: (1) short-term (<1 month) travelers to endemic areas during the transmission season, if they plan to travel outside an urban area and their activities will increase the risk of JEV exposure; (2) travelers going to an area with an ongoing JE outbreak; (3) travelers going to endemic areas who are uncertain of their specific destinations, activities, or duration of travel.[18]

However, the JEV vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JEV transmission season.[18]

Precautions and contraindications include: (1) persons who have had severe (life threatening) allergic reaction following a previous dose if any JE vaccine is a contraindication to administration of subsequent dose; (2) pregnant women due to a lack of information. FDA classifies JE-VC as "pregnancy category B" drug and JE-MB as a " pregnancy category C" drug. To date, no specific information is available on the safety of JE vaccine in pregnancy; (3) although breastfeeding per se is not a contraindication to vaccination, whether JE-VC or JE-MB is excreted in human milk remains unknown and thus should be accordingly approached with caution.[18]

7. Efficacy of JE virus vaccine

In Taiwan, a 30-year duration evaluation of the JE-MB vaccine conducted in 1999 showed that the efficacy of completing at least two doses of the JE vaccine was 96.98%; the efficacy of children between the ages of 1 to 14 years completing one, two, and three doses of immunization were 85.59%, 91.07%, and 98.51%, respectively.[19] An earlier study suggests that 91% of children developed protective neutralizing antibodies after receiving two doses of primary immunization.[8] An international meta-analysis combining the results of 10 studies which included both randomized controlled trials and observational studies showed that 99% of children and 98% of adults have seroprotection at 1 month. Another smaller meta-analysis of five other studies combined showed that 92% of children and 91% of adult were seroprotected at between 5 and 6 months after the two-dose primary vaccination with JE-VC.[20] Three studies conducted a randomized controlled trial in the United States which showed a vaccine effectiveness of 94% and 99% was observed at 14 days and 1 month, respectively, after a single dose of IMOJEV vaccine was administered. No booster effect was noted with the second dose administered more than 30 days later.[21] This IMOJEV vaccine still has a protective effect even 5 years after receiving a single dose of the vaccine.[22]

8. Cost-effectiveness of JE virus vaccine

Use of the JE vaccination is the most effective JE prevention strategy, and cost effectiveness analyses of the JE vaccination

have been conducted in Thailand and China. In Thailand, incorporated routine immunization with JE vaccine at 18 months (costs US$ 2.28/person) would prevent 124 cases (per 100,000 people), with a cost-effectiveness of US$ 15,715.00, and would save US$ 72,922.00 (in treatment costs, disability care, and loss of future earnings) for each prevented JE case.[23] In Shanghai, China, a cost-effectiveness analysis estimated that vaccination with inactivated P3 vaccine would prevent 420 JE cases and 105 deaths, saving 6456 disability-adjusted life−-years per 100,000 people. A similar number of cases and deaths were prevented by immunization with live attenuated SA 14-14-2 vaccine. Both vaccines resulted in cost savings compared with no vaccination, but the live vaccine would result in a greater cost saving (US$ 512,456.00 per 100,000 people versus US$348,246.00) because it requires fewer doses.[24]

9. Adverse reactions

Local symptoms of pain, swelling, and redness were the most commonly reported adverse reactions in 20% of people, and 10% of people suffered general side effects such as fever, chills, headache, rash, and muscle pain.[18,25] JE-VC contains protamine sulfate which is a compound known to cause hypersensitivity in some people. The JE-MB vaccine contains thimerosal, proteins of neural origin and rodent origin, which can cause hypersensitivity in some people.[13,14] In Japan, a survey between 1957 and 1966 found 26 temporally neurologic-related events (meningitis, convulsions, demyelinating disease, polyneuritis), but the rates of JE immunization and comparison with controls were not available.[7] Surveillance data from 1965 through 1989 in Japan suggested neurologic adverse events rates in children of 1 to 2.2 per million doses.[7,26,27] There is no specific information regarding the safety, immunogenicity, or efficacy of JE-VC and JE-MB vaccine in pregnant women and in breastfeeding women.[14]

In conclusion, since JE continues to be a significant cause of morbidity and mortality, the WHO recommends that the JE vaccine be incorporated into immunization programs in all areas where JE is a public health problem. Taiwan started to implement the JE vaccination program for younger children in 1968 and the vaccine coverage rate in Taiwan is above 90%. Earlier successful implementation of the JE vaccination program has proven that active immunization is most effective for prevention of JE. The JE vaccine has a good safety record and large clinical trials have shown that the two new JE vaccines, IXIARO and IMOJEV have a demonstrated level of safety and generate a potent immune response. To prevent further spread of JEV infection and reduction of disease incidence, vaccination is the single most important preventive measure.

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