

Navigating vaccine introduction: a guide for decision-makers
JAPANESE ENCEPHALITIS (JE)

Module 3

**WHICH JE VACCINE
SHOULD MY
COUNTRY USE?**



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ABOUT THIS GUIDE

Japanese encephalitis (JE), a viral infection of the brain, is transmitted to humans by mosquitoes. Because these mosquitoes usually live in areas with standing water, such as rice fields, and the pigs and birds that are part of the JE transmission cycle are common in the countryside, people in rural areas are most at risk. It begins like the flu and can progress to a brain infection, killing up to 30 percent of its victims and leaving up to half of its survivors with permanent brain damage such as memory loss, impaired cognition, paralysis, seizures, the inability to speak, and other mental disorders. Providing lifelong care for survivors is a significant financial strain on families and on government health care systems. Although there is no treatment to cure JE, several safe and effective vaccines are available to prevent infection. In areas where JE is recognized as a public health priority, the World Health Organization (WHO) recommends implementing a one-time JE vaccination campaign focused on the at-risk population followed by incorporation of JE vaccine into routine immunization.¹

The modules in this guide are designed to help country decision-makers understand the evidence around when to consider introducing JE vaccines, the potential benefits, how to incorporate JE vaccines into their country's immunization program, and how to monitor and evaluate the vaccines after introduction. The resources and evidence included focus on JE vaccines that are WHO-prequalified.



KEY TAKEAWAYS • Module 3

- Three JE vaccines have been prequalified by WHO as safe, effective, and acceptable for procurement by United Nations agencies.
- Vaccination programs using any of the WHO-prequalified JE vaccines would provide lifesaving protection from JE for your country's children.
- Each vaccine has different dosing and administration requirements, which can impact costs and vaccine introduction logistics. The number of required doses is an important cost driver of vaccination programs.
- Live vaccines that provide significant protection and potentially life-long immunity after a single-dose primary injection have some advantages over inactivated vaccines, including lower operational costs for delivery. WHO-prequalified inactivated vaccines, however, may have higher efficacy.

MODULE

3

Which JE vaccine should my country use?

After confirming the JE disease burden and considering cost-effectiveness of JE vaccination in your country, you will need to decide which vaccine to use. Three JE vaccines are WHO-prequalified as high-quality, safe, effective, and available for procurement by United Nations (UN) agencies. This module provides information on the safety, immunogenicity, effectiveness, and dosage requirements of these vaccines.

WHO-prequalified JE vaccines

WHO prequalification is a process that uses a transparent, scientifically sound assessment to help ensure that medical commodities such as vaccines for high-burden diseases meet global standards of quality, safety, and efficacy in order to optimize use of health resources and improve health outcomes. As of mid-2016, three JE vaccines have been prequalified (Table 1). WHO has reviewed the manufacturing process and clinical testing and prequalified these vaccines as high-quality, safe, and immunogenic. As with all WHO-prequalified vaccines, they are available for procurement by UN agencies.

TABLE 1. WHO-PREQUALIFIED JE VACCINES

IMAGE	TRADE NAMES (abbreviation)	VACCINE TYPE	MANUFACTURER	DOSES (WHO REC.)	COUNTRIES WHERE VACCINE IS LICENSED*
	CD.JEVAX®, RS.JEV® (CD-JEV)	Live attenuated; uses SA 14-14-2 strain	Chengdu Institute of Biological Products (China)	1	Cambodia, China, India, Laos, Malaysia, Myanmar, Nepal, South Korea, Sri Lanka, Thailand, Vietnam
	IMOJEV®, ChimeriVax-JE™ (JE-CV)	Live recombinant; uses genes from SA 14-14-2 and yellow fever	GPO-MBP Co., Ltd. (Thailand)	1	Australia, Brunei, Hong Kong, Malaysia, Myanmar, Philippines, Singapore, Thailand
	JEEV® (JEEV)	Inactivated, Vero cell-derived; uses SA 14-14-2	Biological E (India)	2	India

*Licensure as of June 2016. Subject to change.

Non-prequalified JE vaccines

In addition to the three WHO-prequalified JE vaccines, more than ten other JE vaccines are made. All are inactivated and derived from either infected mouse brains or cell cultures. Although mouse brain-derived vaccines are effective, in 2006, WHO recommended mouse brain-derived vaccines be replaced by newer JE vaccines. This was due to safety concerns as well as the variability of manufacturing, higher price, and need for repeated doses and boosters, which often

make mouse brain-derived vaccines unaffordable in many JE-endemic countries. Except for JEEV (Table 1), these inactivated, cell culture-derived JE vaccines have not been WHO-prequalified as of mid-2016 and often have limited or no international distribution. Because non-prequalified vaccines are not eligible for UN procurement, they will not be discussed further in this module.

JE vaccine safety

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How is vaccine safety evaluated?

Vaccine safety is evaluated by monitoring adverse events following immunization (AEFIs), or medical incidents that occur during a specified period after vaccination. AEFIs can include pain at the injection site, allergic reactions, fevers, seizures, and other symptoms. An AEFI is classified as serious if it results in death, hospitalization, or disability. In clinical trials, safety is determined by comparing AEFIs after participants receive the vaccine under trial to AEFIs after a placebo or another vaccine. Population-based AEFI surveillance of licensed vaccines is also important to identify rare events that may not appear in clinical trials. Causality is determined by an expert review that classifies AEFIs according to whether they are:

- most commonly, a coincidence (e.g., due to an illness or event unrelated to vaccination);
- due to an immunization error (e.g., inappropriate vaccine handling or administration); or
- most rarely, due to a problem with the vaccine product itself (e.g., a low-quality batch of vaccine from the manufacturer).

All WHO-prequalified JE vaccines are considered safe, have very few serious adverse events following immunization (AEFIs) attributed to them, and are considered safer than older, mouse brain-derived vaccines. WHO's 2015 position paper on JE vaccines states that all three prequalified vaccines have acceptable safety profiles.¹

Due to its long history and widespread use in China and India, CD-JEV has the largest safety database of the three prequalified vaccines.² In a 2014 review of population-based AEFI surveillance in Guangdong Province, China, only 36 serious AEFIs were reported among 23.3 million infants vaccinated with CD-JEV.³ According to a 2016 AEFI review in India, of the over 145 million children under 15 who have been immunized with CD JEV in 20 Indian states between 2006 and mid-2016, only 53 AEFI deaths were reported and none of them were caused due to the vaccine.⁴ While passive surveillance systems often result in underreporting of AEFIs, WHO has reviewed both population-based and clinical trial safety data for CD-JEV on multiple occasions and has confirmed the vaccine's acceptable safety profile.¹

Due to limited widespread use, the other prequalified JE vaccines have less safety data. While population-based AEFI studies of JE-CV have not been performed, clinical trials in children and adults suggest that it has a safety profile similar to CD-JEV and superior to the mouse brain-derived vaccines.^{5,6} JEEV's safety has only been studied in a few clinical trials in India. However, JEEV is made using the same vaccine strain and cell line and inactivated in the same way as the non-prequalified JE vaccine IXIARO® as part of a technology transfer. Because IXIARO® has been studied extensively in clinical trials and population-based AEFI surveillance,⁷ WHO extends IXIARO's® safety profile to JEEV due to the quality of the data and the degree of similarity between IXIARO® and JEEV.

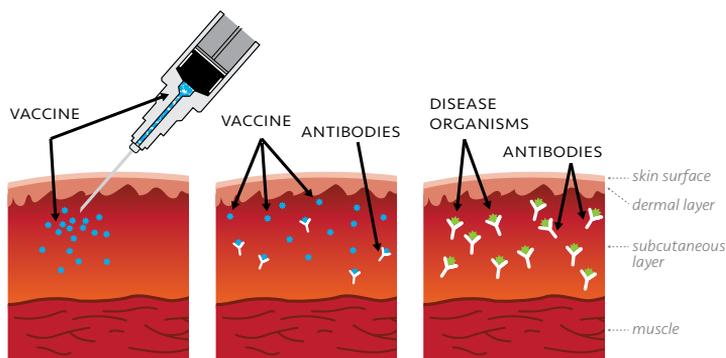
WHO states that more safety data are needed for prequalified JE vaccines.⁸ In particular, CD-JEV could benefit from more safety data about its use in adults, JE-CV from population-based AEFI surveillance studies, and JEEV from safety data following co-administration with measles vaccine. Safety data from pregnant women or immunocompromised persons would be useful for all of these vaccines.

FIND OUT MORE



What is vaccine immunogenicity?

Vaccine immunogenicity is a vaccine's ability to elicit a protective immune response to a disease-causing organism (pathogen). After vaccination, the immune system becomes prepared to fight the pathogen contained in the vaccine by creating proteins called antibodies. If the pathogen is encountered again, these antibodies will bind to it, preventing it from attacking cells while also triggering other immune cells to destroy the pathogen. A vaccine is considered to be immunogenic if the concentration of pathogen-specific antibodies in a person's blood rises to a protective level after vaccination.



JE vaccine immunogenicity and effectiveness

All three WHO-prequalified JE vaccines have been found to be highly immunogenic in clinical trials in both JE-endemic and non-endemic settings. Across clinical trials for these vaccines, 80 to 100 percent of those vaccinated developed antibody concentrations that are considered protective against JE disease.^{3,9}

Vaccine effectiveness studies, which differ from immunogenicity studies by looking at the ability of the vaccine to protect against disease in real-world settings, have only been completed for CD-JEV in JE-endemic areas. In JE-endemic parts of Nepal, among persons vaccinated during CD-JEV campaigns when they were

TABLE 2. WHO-RECOMMENDED DOSING AND AND ADMINISTRATION REQUIREMENTS FOR WHO-PREQUALIFIED JE VACCINES

JE VACCINE	DOSES IN PRIMARY SERIES	AGE RANGE	DOSAGE	BOOSTER	ADMINISTRATION
CD-JEV	1	≥8 months	0.5 ml	No	Subcutaneous
JE-CV	1	≥9 months	0.5 ml	No	Subcutaneous
JEEV	2 (4 weeks apart)	1–49 years	12–35 months: 3µg 3–49 years: 6µg	No*	Intramuscular

* India's national regulatory authority has not approved an indication for a booster dose of JEEV for adults or children. However, Valneva recommends a booster of IXIARO® 12 months after primary immunization for adults residing in JE-endemic areas. Similar recommendations will likely be made for JEEV. Additionally, a Phase III trial of IXIARO® in children showed a pronounced booster response when a dose was delivered 12 months following the primary series.¹⁰

1 to 15 years old, effectiveness was 98.5 percent one year after immunization¹¹ and 96.2 percent after five years.¹²

JE vaccine dosing requirements

When considering JE vaccine introduction, it is important to consider the recommended dosing regimen, the number of doses in a primary series, and whether a booster dose is required (Table 2). Vaccines that require multiple doses in the primary series or need booster doses will incur greater costs due to the purchase of more vaccine and greater operational costs of vaccinating the same person on multiple occasions.

Because of the programmatic costs to administer multiple doses, a vaccine requiring only one dose without a booster shot may be more cost-effective for some countries. For more information on the cost-effectiveness of JE vaccines, please see *Module 2: Is JE vaccination cost-effective?*.

References

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As this module shows, all three of the currently WHO-prequalified JE vaccines are safe and immunogenic. Vaccination programs using any of the WHO-prequalified JE vaccines should provide protection from JE for your country's children with very little risk of AEFIs. Your country's choice of vaccine may be based on a variety of cultural, political, and economic factors unique to your country, but when choosing a JE vaccine, it is helpful to:

1. **Prioritize WHO-prequalified vaccines.** The WHO prequalification process works with national regulatory authorities to ensure that vaccines are manufactured in high-quality conditions and are safe, immunogenic, and effective. WHO-prequalified vaccines are eligible for procurement by UNICEF and other United Nations agencies that purchase vaccines for low- and middle-income countries and development partners such as Gavi, the Vaccine Alliance.
2. **Consider dosing schedules and administration requirements.** These requirements can have major implications on the immunization supply chain, logistics of delivery, and cost. All of these items can affect the overall cost-effectiveness of vaccination. Additionally, countries should consider how JE vaccination schedules would fit into existing childhood immunization schedules to optimize delivery of multiple childhood vaccines.
3. **Inquire about vaccine cost and availability.** Vaccine costs vary widely from country to country based on supply and demand and distribution agreements. As a result, it is not possible to compare these costs at a global level. Reach out to your WHO regional office, UNICEF, in-country vaccine suppliers, or vaccine manufacturers for more information about specific JE vaccine costs and availability for your country.

Your country's choice of vaccine will have far-reaching implications for introduction. For guidance on how to develop a JE vaccine introduction plan, see *Module 4: How should my country introduce JE vaccines?*





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