Japanese Encephalitis Vaccine Market & Supply Update

UNICEF Supply Division

July 2015

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1. Summary

- UNICEF and Gavi, the Vaccine Alliance, support country introduction of Japanese Encephalitis (JE) vaccine into national immunization programmes.
- Several WHO prequalified vaccines are able to meet country programmatic requirements. However, UNICEF currently only has a long-term arrangement (LTA) with one manufacturer, producing the only vaccine deemed suitable at the time of Gavi's funding window and UNICEF's tender.
- To date (July 2015), three Gavi-eligible countries have applied to Gavi for funding to introduce the JE vaccine through initial catch-up campaigns. These introductions have a combined target population of 9.4 million children. Gavi's current forecast anticipates campaign vaccine requirements could reach more than 75 million doses by 2020 in 12 countries.[1]
- JE vaccine supply is sufficient to meet Gavi forecast demand. However, current supply is dependent on a 9-month lead-time for delivery from one manufacturer. Timely delivery is incredibly important given the seasonality of disease incidence and the necessary timing of associated catch-up campaigns.
- UNICEF concluded its 2015-2016 tender process in mid-2014. 2 million doses were awarded to one manufacturer, of which 1.8 million doses was procured. UNICEF increased the award by 8.4 million doses in April 2015 to reach 10.4 million doses on account of new country requirements being approved by the Gavi Board.

2. General Brief and Background

Japanese Encephalitis (JE) is a viral brain infection transmitted by a mosquito vector. Globally, it causes an estimated 70,000 cases and 20,400 deaths per year, and has a case fatality rate of between 20-30%.[2] It is the leading cause of viral encephalitis in Asia and the Western Pacific with endemic transmission in 24 countries and an aggregate at-risk population of 3 billion (Figure 1). There is no curative treatment for JE. Palliative care can focus on relieving severe clinical symptoms. WHO recommends that immunization of children with JE vaccines in countries with a high-risk of infection is the most appropriate and cost-effective means of controlling JE. WHO recommends introducing the vaccine through a one-time catch-up campaign, followed by integration into routine national immunization programmes. The recommended country immunization schedule depends on the profile of the chosen vaccine, local epidemiology, and EPI programmatic requirements.

Gavi's 2011-2015 strategy to accelerate the uptake and use of underused and new vaccines recommends supporting JE vaccine country introduction in eligible countries through a one-time catch-up campaign using a 1-dose schedule targeting infants and children aged from 9 months up to 15 years. Gavi support for JE vaccine introduction is predicated on an agreement that recipient countries self-finance the use of JE vaccines in routine immunization programmes following the catch-up campaign.

Gavi's Guidelines for JE Applications in 2015 can be accessed here. These guidelines highlight JE programmatic requirements to use a one-dose immunization schedule, as per WHO recommendation.[3] The vaccine currently procured is supplied in a 5-dose vial lyophilised formulation and has a 10% indicative maximum wastage rate.

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[1] Gavi, the Vaccine Alliance, *2014 Strategic Demand Forecast v.10*, Gavi, Geneva, October 2014.
[2] World Health Organization, *Japanese Encephalitis Fact Sheet*, WHO, Geneva, March 2014.
[3] World Health Organization, *Japanese Encephalitis Vaccines WHO position Paper*, WHO, Geneva, February 2015, p.85.

Figure 1 Countries or Areas with High Risk Exposure to Japanese Encephalitis

Source: WHO.

Several types of JE vaccine are currently available or under development. Their characteristics vary according to the different production technology platforms used, presentation, formulation, as well as the number of doses required to confer durable protection. JE vaccine production platforms include mouse-brain, hamster kidney or vero (monkey) cell cultures and use Beijing-1, Kolar, Nakayama, P-3 or SA 14-14-2 JE vaccine strains.

Whereas the different manufacturing methods all produce vaccines with acceptable safety and efficacy profiles, the vero cell culture-based and primary hamster kidney vaccines generally offer cost-effective longer-lasting protection with fewer doses (Table 1).

Table 1 JE Vaccine Production Platforms, Strains and Considerations

Platform	Strain Used	Type	Considerations
Mouse-brain culture	- Beijing-1 - Nakayama	- Inactivated	- Limited duration of induced protection. - Requires multiple doses. - Higher reactogenicity.
Primary Hamster Kidney	- SA 14-14-2	- Live attenuated	- Longer duration of induced protection. - Requires fewer doses.
Vero cell culture	- Beijing-1 - P-3 - Kolar (JEV 821564 XY) - SA 14-14-2	- Inactivated	- Duration of protection in endemic areas unknown. - Requires multiple dose.
Vero cell culture	- SA 14-14-2/YF17D	- Live recombinant	- Longer duration of protection expected. - Requires fewer doses.

Source: WHO.

At present, three manufacturers have WHO prequalified JE vaccines (Table 2). Chengdu Institute of Biological Products (CDIBP) is the first Chinese vaccine manufacturer to have a WHO prequalified vaccine. The Program for Appropriate Technology in Health (PATH) has been working with CDIBP to build a new manufacturing plant that meets international good manufacturing practices (GMP) standards. The facility increases the availability of new affordable vaccines.

Table 2 WHO Prequalified JE Vaccine Manufacturers

Manufacturer	WHO PQ	Present.	Formulat.	Shelf life	VVM	Cold Chain
Biological E (India)	2013	1 dose	Liquid	36 months	Type 14	14.7 cm^3
	2014	2 dose	Liquid*	36 months	Type 14	7.35 cm^3
CDIBP (China)	2013	1 dose	Lyophilised	18 months	Type 14	21.2 cm^3
	2013	5 dose	Lyophilised	18 months	Type 14	4.2 cm^3
Sanofi Pasteur (France)	2014	4 dose	Lyophilised	36 months	Type 14	2.5 cm^3

Source: WHO.

*NB: Liquid without preservative; considered by WHO to be programmatically suitable, provided that similar measures were used as for other two-dose preservative-free vaccine presentations that have been WHO prequalified - See here for further details.

All WHO prequalified vaccines use the SA 14-14-2 JE vaccine strain; though they differ in vaccine platform, type, formulation and immunization schedule (Table 3).

Table 3 WHO Prequalified JE Vaccine Technology Platforms and Specifications

Manufacturer	Platform	Strain	Type	Paediatric Schedule
Biological E (India)	Vero cell culture	SA 14-14-2	Inactivated	2 dose**
CDIBP (China)	Primary Hamster Kidney	SA 14-14-2	Live attenuated	1 dose
Sanofi Pasteur (France)	Vero cell culture	SA 14-14-2	Live recombinant	2 dose

Source: UNICEF Supply Division.

**NB: Indicated for use in infants aged 12-35 months, while other WHO prequalified vaccines indicated for use in infants aged 9 months and older.

Several other non-WHO prequalified licensed JE vaccines exist on the market, of which one anticipates WHO prequalification.

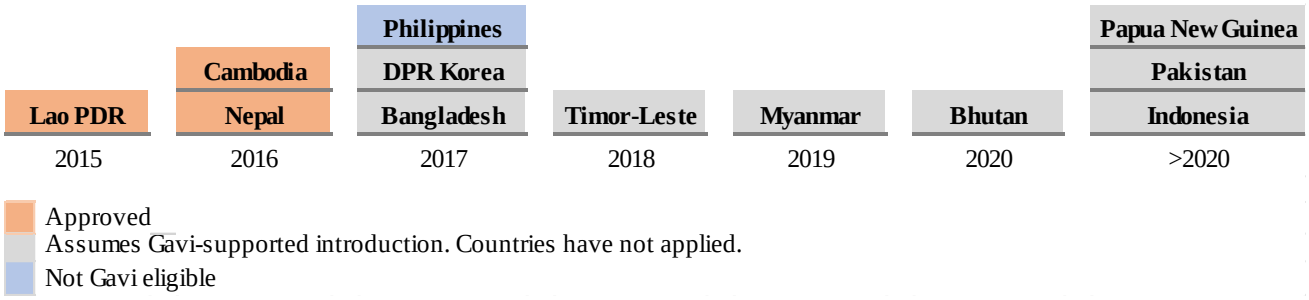
3. Current Market Situation

3.1. Demand and Forecast

At a global level, large country immunization programmes will drive the demand. India and China, for example, self-procure jointly between 33-53 million doses of JE vaccines per year to support rolling campaigns in targeted districts, as well as for use in routine immunization programmes following campaign completion.

Gavi estimates JE vaccine demand among 11 eligible and graduating countries (excluding India) and 1 non-eligible country with a high-risk of JE infections to reach more than 75 million doses for Gavi-supported introduction campaigns (strategic demand forecast (SDF) version 10). Gavi also estimates 6 million doses per year for self-financed routine programmes in countries that have had Gavi support in a campaign by 2020. Twelve countries are assumed to introduce JE vaccine and carry out catch-up campaigns through >2020 (Figure 2). Gavi has approved three countries for JE introduction. Other countries have not yet applied for support.

Figure 2 Unconstrained Country JE Vaccine Introductions 2015->2020 (Estimate)



Source: Gavi SDF v10.

Gavi's SDF v.10 forecasts through 2020 does not include Gavi support for India, Sri Lanka or Vietnam, all of which have already adopted one of the JE vaccines that are on the market. Gavi will support eligible countries that have self-financed routine programme introduction of JE vaccine for campaign extension activities if they have not vaccinated all children up to 15 years of age (e.g. Vietnam introduced in 1997; and Nepal introduced in 2006).

Gavi opened their funding window in 2014 to receive country applications for catch-up campaigns. The first application round closed in May 2014. As of July 2015, three countries (Cambodia, Lao PDR and Nepal) have submitted applications for Gavi support of JE vaccine campaigns. Lao PDR introduced JE in April 2015, having identified a requirement for 1.9 million doses, including a 10% wastage rate, for a target population of 1.61 million children. Cambodia identified a requirement for 4.5 million doses for 4.1 million children, anticipating JE introduction in 2016. Nepal identified a requirement for 4.05 million doses for a target population of 3.7 million children. JE is already in part of Nepal's national EPI and anticipates carrying out their catch-up campaign during April 2016.

In previous SDF versions, Gavi initially estimated JE campaign demand to peak in 2015 on account of Bangladesh, Cambodia and Lao PDR, and 2016 on account of DPR Korea and Myanmar. However, country application submissions have been slower than initially expected, and has resulted in lower demand, due to weak evidence for country decision-making, and fewer programme introductions during 2015/2016.

In June 2015, the Gavi Board agreed to exceptionally allow those graduating countries that entered graduation before Gavi opened the JE vaccine funding window to apply for support to introduce JE vaccines. The terms of this exceptional support will be further defined but will most likely be more limited than regular new vaccine support, reflecting the relatively advanced financing capacity of these countries. Nonetheless, these changes may have modest implications for future Gavi (and non-Gavi) demand forecasts.

3.2. Supply

While there are currently other WHO prequalified JE vaccines available in the market, GAVI guidelines at the time of the procurement specified a single dose course in a 5-dose vial as the only suitable presentation. Based on the anticipated demand, UNICEF issued a tender targeting 7.25 million doses for 2015 and 2016 (2 million doses and 5.25 million doses respectively). UNICEF awarded 2 million doses to CDIBP to cover the needs for Lao PDR, of which 1.8 million doses were procured. In April 2015, UNICEF awarded the manufacturer an additional 8.4 million doses to cover the supply needs of Cambodia and Nepal. At the time of publication, these additional doses have yet to be procured. Table 4 summarizes the current status of JE vaccine doses awarded, procured and the remaining balance.

Table 4 UNICEF JE 2015-2016 Awards and Procurement

Manufacturer	Total Doses Awarded	Doses Procured	Remaining Balance
CDIBP (China)	10,394,400	1,789,000	8,605,400

Source: UNICEF Supply Division.

The timing of JE vaccine delivery is important given JE incidence seasonality, coinciding with the rainy season and associated preventive campaigns (Table 6). Based on the factors affecting the timing of supply, UNICEF will maintain and develop a close working relationship with the manufacturer to ensure timely delivery of supplies.

Vaccine prices for each manufacturer holding an LTA with UNICEF are published. Data on JE pricing can be found here. The price for JE increased from $ 0.27 per dose in 2014 to a staircase price by volume ranging from $ 0.41 to $ 0.42 per doses in 2015, on account of a reassessment of costs of goods and production (Table 5).

Table 5 UNICEF JE Price per Dose

JE Staircase Volume	2014	2015
Price per dose	$ 0.2687	
Up to 1 million vials		$ 0.4220
1 million to 3 million vials		$ 0.4180
3 million to 5 million vials		$ 0.4140
Over 5 million vials		$ 0.4100

Source: UNICEF Supply Division.

4. Issues and Challenges

A number of considerations related to production, calendar timing and country readiness could affect Gavi JE programme vaccine supply availability. The timing and availability of vaccine supply could delay programmes by up to one year if calendar schedules are missmatched with campaign seasonality. Table 6 describes a number of challenges affecting JE vaccine supply, requiring that countries plan for this with sufficient lead-time.

Table 6 Challenges That Could Affect JE Vaccine Supply Availability and Timing

Challenges	Considerations
Forecast	JE forecast accuracy remains a challenge and is subject to country application submissions, which have been slower than expected and has lowered demand. Determining the population at risk within each country is a challenge due to lack of surveillance data, which affects the certainty in the forecast doses.
Supply	JE vaccine supply through UNICEF is currently dependent on one supplier. While the supplier has been able to meet all demand requirements, high reliance on a single supplier (which also supplies other large countries) presents a fragile supply base.
Production	The JE vaccine has a shelf life of 18 months, of which 6 months are required for release authorization, including: - End-product tests; - Quality Assurance control; - National authority-release processing time. Upon release and shipment time, only 12 months vaccine shelf life remains. The manufacturer also shuts down its vaccine production facilities for two-months a year to carry out maintenance operations, which has an impact on the vaccine production and lead-time for release and delivery.

Challenges	Considerations
Calendar timing	Programme calendar timing depends on: - Gavi applications and approval processes; - Tender process and duration; - Manufacturer production lead-time supply availability; - National authority vaccine release duration; - Campaign seasonality.
Country Readiness	Country readiness to introduce JE vaccine is uncertain and can delay introduction timing and schedules due to: - Staff training; - Cold chain requirements. - Other factors and priorities such as natural disasters.

Source: UNICEF Supply Division.

5. Steps Forward

- UNICEF is actively following the development of new JE vaccine market entrants and manufacturers with WHO prequalified vaccines to ensure an expanded supply base and increased supply security.
- UNICEF will continue to develop and maintain a close relationship with the current existing manufacturer to ensure the timely delivery of supplies and ensure compliance with UNICEF's operating procedures, as it is the first Chinese vaccine manufacturer to have a WHO prequalified vaccine and an LTA with UNICEF.
- UNICEF will communicate with countries and promote awareness of the current lead time required and limited shelf life of the JE vaccine currently procured through UNICEF, as well as implications and necessary considerations for routine programme and campaign timings.
- UNICEF, together with Gavi and partners, is reviewing JE vaccine forecast accuracy, demand and supply availability, and is assessing the need to issue a tender during the 2H 2015. UNICEF will support the procurement for catch-up campaigns supported through Gavi, and establish contractual relationships with manufacturers to supply JE vaccine country demand through Procurement Services.

For further questions or additional information, please contact:

Heather Deehan
Chief, Vaccine Centre
UNICEF Supply Division
+45 45 33 58 90
hdeehan@unicef.org

Sonia Freitas
Contracts Specialist
UNICEF Supply Division
+45 45 33 57 87
sfreitas@unicef.org

Aadrian Sullivan
Information Management
UNICEF Supply Division
+45 45 33 57 68
asullivan@unicef.org

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