Japanese Encephalitis Vaccine: Market and Supply Update

UNICEF Supply Division

October 2021

Japanese Encephalitis Vaccine Market and Supply Update
October 2021

This note provides revised information on Japanese encephalitis vaccine market demand and supply. Several factors can affect Japanese encephalitis vaccine supply availability as the prevalence of the disease is seasonal. The timing and availability of vaccine supply could delay programmes by up to one year if calendar schedules are mismatched with procurement lead times.

1. Summary

- UNICEF and Gavi, the Vaccine Alliance (Gavi), support countries with the introduction of Japanese Encephalitis (JE) vaccines into their national immunization programmes. Over the past 15 years, significant progress has been made in the control of JE with the increased availability of safe, effective vaccines to the scaling up JE disease surveillance and implementing vaccination programmes in several endemic countries.
- The global population at risk of JE in the 24 countries where JE is endemic represents three billion people.[1] However, coverage is comparatively low as only 100 million doses of JE vaccines are supplied annually.
- Three manufacturers produce World Health Organization (WHO) prequalified vaccines. UNICEF currently only has a long-term arrangement (LTA) with one manufacturer, which produces the vaccine considered most programmatically suitable based on country preferences.
- Globally, fourteen countries have introduced JE vaccines and three of those are sub-national level. Four out of the fourteen countries have introduced JE vaccines with the support of Gavi through initial catch-up campaigns followed by routine programme immunization. Gavi-country forecasts for subsequent country introductions have not materialized since 2018. UNICEF does not anticipate any new country introductions until 2024, partly due to the impact of COVID-19, and partly due to countries not having considered or programmatically planned its introduction.
- Overall, JE vaccine supply is sufficient to meet current country demand. However, there is a long procurement lead-time of up to nine months, which remains a challenge. The timely delivery of JE vaccines is highly bound to the seasonality of disease incidence and the associated timing of catch-up campaigns.
- Following UNICEF's tender in 2018 covering the period from 2018-2022, UNICEF awarded an additional manufacturer provisional supply. However, countries have not yet expressed any interest to switch vaccines due to its programmatic features as it requires a different schedule, and there is a high difference in price.
- UNICEF together with WHO, Gavi, and PATH,[2] as well as other global partners, will continue to collaborate closely on JE vaccine local effectiveness studies and surveillance to gain more information on the burden of disease in JE endemic countries.

2. General Brief and Background

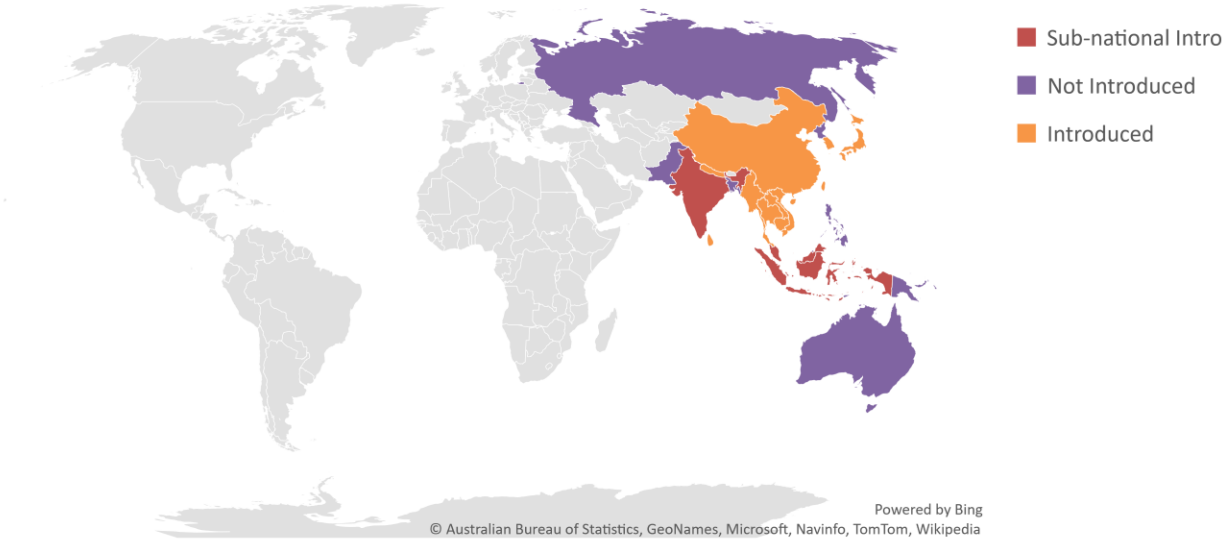
Japanese encephalitis (JE) is a viral brain infection caused by the Japanese encephalitis virus (JEV). It is a vector borne flavivirus related to dengue, West Nile, yellow fever, and Zika viruses, amongst others,[3] and is spread by mosquitoes (mainly Culex tritaeniorhynchus). It is the leading cause of viral encephalitis (inflammation of the tissues of the brain), primarily affecting children, in Asia and the Western Pacific. It is endemic in 24 countries with an aggregate at-risk population of three billion people (Figure 1, next page). It causes an estimated 70,000 clinical cases a year, of which up to 30 to 50 per cent of cases may develop permanent neurologic or psychiatric sequelae, and has a case fatality rate that can reach up to 30 per cent, resulting in between 13,600 to 20,400 deaths.[4] While JE may be traditionally considered a childhood disease, it can occur in all ages, with up to 50 per cent of cases in some countries occurring in adults. There is no antiviral treatment for JE, only palliative care focusing on relieving severe clinical symptoms, and vaccine prevention exist. WHO recommends immunizing children with JE vaccines in countries with a high-risk of infection as the most appropriate and cost-effective

[1] World Health Organization, *Japanese Encephalitis Vaccines: WHO Position Paper*, WHO, Geneva, February 2015, p. 70.
[2] PATH, formerly known as the Program for Appropriate Technology in Health, is an international, non-profit global health organization based in Seattle that focuses on innovation and developing solutions related to devices, diagnostics, drugs, health systems, and vaccines.
[3] World Health Organization, *Japanese Encephalitis Key Facts*, WHO, Geneva, May 2019.
[4] Ibid.

means of controlling JE. WHO recommends countries introduce the vaccine through a one-time catch-up campaign, followed by its integration into routine national immunization programmes in accordance with the profile of the vaccine, local epidemiology, and expanded programme on immunization (EPI) programmatic requirements.[5]

Japanese encephalitis vaccines were first developed in the 1930s. Since this period, the incidence of JE disease has fallen substantially in countries, including Japan, the Republic of Korea, and in Taiwan Province of China, due to JE vaccine use in national immunization programmes since 1965. However, as JE vaccination does not induce herd immunity, a sustained high vaccination coverage rate is required to reduce JE disease prevalence in endemic regions. However, the level of production of JE vaccines has been low and are not all programmatically suitable for campaigns and paediatric use.

Figure 1 Regions at High Risk of Exposure to Japanese Encephalitis and National introduction status



Source: WHO
Note: For some of the countries pending introduction, JE prevalence is limited to specific regions.

A literature review by WHO estimates that there are approximately 70,000 clinical cases of JE globally each year, which is significantly higher than the surveillance data system reported through WHO.[6] The data surveillance system may not capture all clinical cases, as JE cannot be easily distinguished from other encephalopathies, as it requires confirmatory testing. There may be increased risk of changes to JE prevalence from changes in geographical spread, climate change, as well as changes in agricultural practices, and ecology.[7]

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 doses.
Vero cell culture	- SA 14-14-2/YF17D	- Live recombinant	- Longer duration of protection expected. - Requires fewer doses.

Source: WHO

[5] WHO, *Japanese Encephalitis Vaccines: WHO Position Paper*, p. 84.
[6] World Health Organization, *Japanese Encephalitis Reported Cases*, WHO, Geneva, October 2020.
[7] Connor B, Bunn WB., '*The Changing Epidemiology of Japanese Encephalitis and New data: the Implications for New Recommendations for Japanese Encephalitis Vaccine*', Tropical Diseases, Travel Medicine and Vaccines, London, July 2017.

There are several different types of JE vaccines currently available or under development. Their characteristics vary according to the different production technology platforms used, their 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 cell cultures, and use Beijing-1, Kolar, Nakayama, P-3 or SA 14-14-2 JE vaccine strains (Table 1, previous page). 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.

At present, three manufacturers have seven WHO prequalified JE vaccines (Table 2). All WHO prequalified vaccines use the SA 14-14-2 JE vaccine strain; although they differ in vaccine platform, type, formulation, and immunization schedule (Table 3).

Chengdu Institute of Biological Products (CDIBP) was the first Chinese vaccine manufacturer to have its vaccine WHO prequalified. PATH worked with CDIBP to build a new manufacturing plant that meets international good manufacturing practices (GMP) standards in order to increase the availability of new affordable vaccines.

Table 2 WHO Prequalified JE Vaccine Manufacturers

Manufacturer	WHO PQ	Present.	Type	Formulation	Shelf life	VVM	Cold Chain
Biological E (India)	2013	1-dose	Inactivated	Liquid *	36 months	Type 14	14.70 cm^3
	2018	5-dose	Inactivated	Liquid	24 months	Type 14	2.50 cm^3
	2016	1-dose paediatric	Inactivated	Liquid	36 months	Type 14	14.7 cm^3
	2018	5-dose paediatric	Inactivated	Liquid	24 months	Type 14	2.90 cm^3
CDIBP (China)	2013	1-dose	Live attenuated	Lyophilised	24 months	Type 14	21.20 cm^3
	2013	5-dose	Live attenuated	Lyophilised	24 months	Type 14	4.20 cm^3
Sanofi Pasteur †	2014	4-dose	Live attenuated	Lyophilised	36 months	Type 14	2.5 cm^3

Source: WHO

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

Note †: Vaccine filling and finishing by GPO.MBP. Product owned and marketed by Sanofi Pasteur. Vaccine bulk also produced by Sanofi Pasteur.

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 doses ‡
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 doses

Source: WHO.

Note ‡: Indicated for use in infants aged 12-35 months, while other WHO prequalified vaccines indicate for use in infants aged 9 months and older.

Note §: Vaccine bulk supplied by Sanofi Pasteur, filled by GPO.MBP.

Several other licensed non-WHO prequalified JE vaccines exist on the market from manufacturers with a low interest in pursuing WHO prequalification (Table 4).

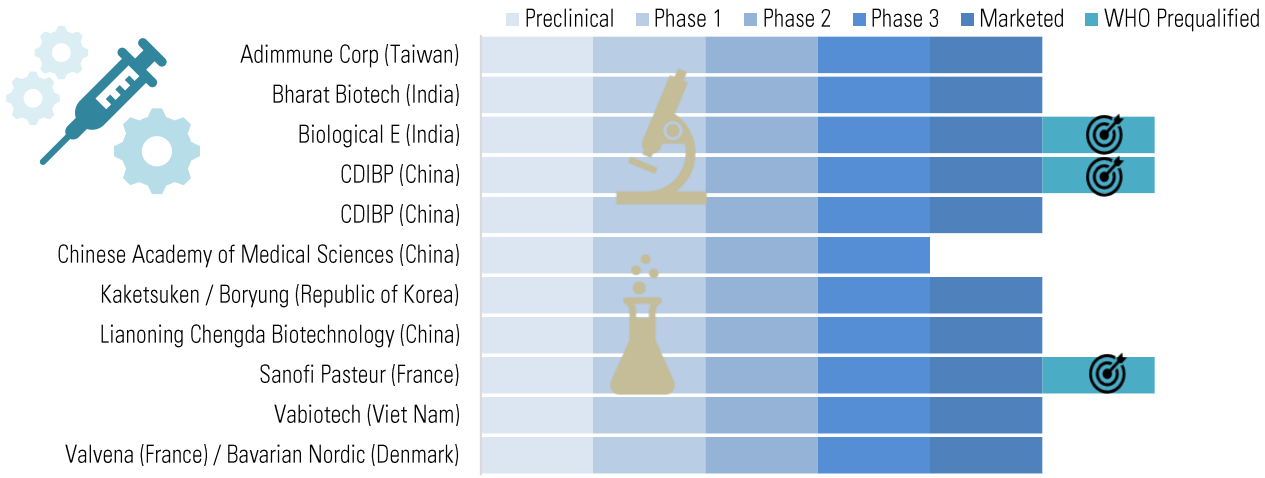
Table 4 Some Other Non-WHO Prequalified Marketed JE Vaccines

Supplier	Product
Adimmune Corp (Taiwan)	Inactivated, mouse brain
Bharat Biotech (India)	Inactivated, vero cell culture
CDIBP (China)	Inactivated, primary hamster kidney
Kaketsuken / Boryung (Republic of Korea)	Inactivated, vero cell culture, Beijing-1 strain
Lianoning Chengda Biotechnology (China)	Inactivated, vero cell culture, Beijing-P3 strain
Vabiotech (Viet Nam)	Inactivated, mouse brain
Valvena (France) / Bavarian Nordic (Denmark)	Inactivated, vero cell culture

Source: UNICEF Supply Division

Currently, there is only one known new pipeline vaccine product under development for JE (Table 5, next page), currently under clinical stage three of its development.

Table 5 Known JE Vaccine Products Pipeline Status



Source: UNICEF Supply Division

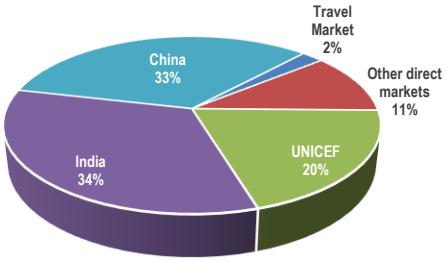
3. Innovation

There is a limited amount of activity current being taken in terms of innovative pipeline products related to JE vaccines, as most innovation has been largely met by manufacturers transitioning from mouse-brain derived vaccines in addition to products being more programmatically suitable and affordable. Manufacturers have also prequalified multi-dose vial inactive JE vaccine presentations in 2018.

4. Current Market Situation

Independent market researchers have valued the JE vaccine market to reach USD 17.93 billion in 2020, and project it to possibly reach up to USD 34.68 billion by 2028, growing at a compound annual growth rate (CAGR) of approximately eight per cent.[8] However, UNICEF considers this assessment to be extremely distorted, based on its current estimated production capacity of 100 million doses, and on a high middle-income country (MIC) price of USD 20.00 per dose, for which it could therefore only reach an estimated value of approximately USD 2 billion. Large country JE immunization programmes will drive most of the growth fuelled by increased government interest in immunizing children with vaccines in high-risk countries such as China and India. This will require increased campaigns and the inclusion of JE vaccines into national immunization plans. India and China combined currently self-procure between 50-70 million doses of JE vaccine per year for their JE vaccination campaigns in targeted districts, and for use in their routine immunization programmes upon campaign completion.

The global JE vaccine market is estimated to be 80-100 million doses annually, with production volumes fluctuating every year due to JEV demand being driven by the disease's seasonality and campaign activities. From 2014 to date, UNICEF procured up to 34.6 million doses of JE vaccines for a value of USD 14.2 million. UNICEF's market share of global JE vaccine procurement per year ranges between 2.5 per cent to 20 per cent. The higher end of its procurement represents catch up campaign activities preceding the JE vaccine's introduction. There were 14 JE vaccine manufacturers with commercial products marketed in different countries, but that number is decreasing over the years through various forms of technology transfer. UNICEF now counts there to be 11 distinct products. At present, CDIBP in China dominates global supply representing approximately 90 per cent of global demand.



Source: UNICEF Supply Division

[8] Verified Market Research, *Global Encephalitis Virus Vaccine Market Size By Strain Type , By End User, By Geographic Scope And Forecast*, Verified Market Research, Delaware, June 2021.

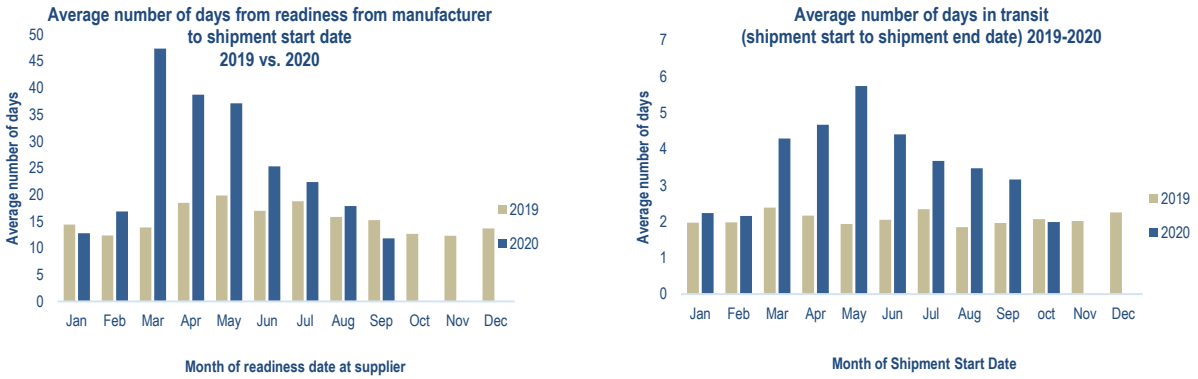
JE's endemicity and disease burden has decreased in countries as their economies have increased. High-income countries (HICs) in the JE endemic region tend to have more prevalent well-developed sanitary conditions and have been able to eradicate the disease. However, in low-income countries (LICs) and MICs, the virus exists in areas where there is a high presence of mosquitoes, pigs, and water birds in settings predominantly found in rural and peri urban areas that are associated with human activity, predominantly engaged in rice farming and rearing livestock. These serve as breeding grounds for mosquitoes.

Despite UNICEF and Gavi offering to support countries to introduce JE vaccines into their national immunization programmes, several JE endemic countries have still not applied for national introduction. This potential need for JE vaccines currently outweighs total available supply, should all endemic countries prioritise the introduction of this vaccine into their routine immunization programmes. Initial catch up campaigns would require proximately ten-times the annual requirement of JE vaccine than for routine programmes. If over the next decade a large country should get approval to introduce the vaccine, the surge in demand could result in a constrained supply of WHO prequalified vaccines.

4.1 COVID-19 Market Impact

Nearly all vaccine shipments are shipped by air, given their cold chain requirements. Following COVID-19, even though many vaccine shipments were initially affected in 2020 by national lockdown measures and the grounding of airlines worldwide, the vaccine shipments have since recovered well during 2020 (Figure 1).

Figure 1 UNICEF Vaccine Deliveries Comparison 2019-2020



Source: UNICEF Supply Division

Some delayed JE vaccine deliveries were due to shipping and logistics challenges. Following constrained transportation capacity, freight costs significantly increased, and which more than tripled due to competing demand. Chartered flights were used in some instances to deliver JE vaccine during the peak of the pandemic. While air freight analysts are quietly optimistic that air carriers are increasingly offering fixed rates, some carriers are increasing their rates considerably due to the ongoing congestion of sea freight and a shift in high demand from sea freight back to air freight. UNICEF notes that whilst carriers may offer fixed rates to UNICEF, as cargo space becomes limited, UNICEF may be forced to pay premium rates to secure space.

In addition, the lead time for some of the procurement orders for JE vaccine have also increased beyond six months due to national regulatory authorities extending their batch release procedures on account of the pandemic. There has also been a financial impact on some JE manufacturers and their liquidity (cash flow) as some report that their sales and export numbers dropped in 2020.

4.2 Demand

UNICEF and Gavi support countries to introduce JE vaccines into their national immunization programmes to accelerate the uptake and use of underused and new vaccines. Gavi's JE vaccine strategy recommends supporting countries to introduce the JE vaccine in eligible countries through a one-time catch-up campaign, using a one-dose schedule targeting infants and children aged from 9 months up to 15 years. Countries were supported by Gavi to undertake catch up campaigns to introduce and self-finance routine use of JE vaccine until 2015 when the policy changed to include funding for routine introduction.

From 2018 to date, there has not been any new country applications through Gavi seeking support to introduce JE vaccines. UNICEF recognizes that the impact of COVID-19 will have influenced how countries have had to reassess and reprioritise any decision they may have wanted to make on introducing the JE vaccine, given the context and the need to focus on COVID-19 immunization requirements. UNICEF anticipates that some countries may only prioritize new vaccine introductions after the next tender period post 2022.

Key drivers of country product preference are product presentation, dosing schedule, and price. Laos PDR was the first country supported by UNICEF and Gavi to introduce the JE vaccine with campaigns, followed by campaigns in Cambodia and Nepal (Figure 2). Upon completion of catch-up campaigns, these countries were to self-finance their national routine introductions. Despite some delays that occurred during the transition in the source of funding, national routine programmes are now sustainable. Indonesia and Myanmar were the last two countries supported by UNICEF (Myanmar with Gavi support) to introduce JE vaccines. In 2017, Gavi's policy changed to provide support for both campaign and routine programmes. All countries self-finance their JE vaccine procurement through UNICEF, except for Myanmar, and all countries use CDIBP's JE vaccine, five-dose vial presentation.

Figure 2 Overview of JE vaccine Introductions to date and expectations up to 2022

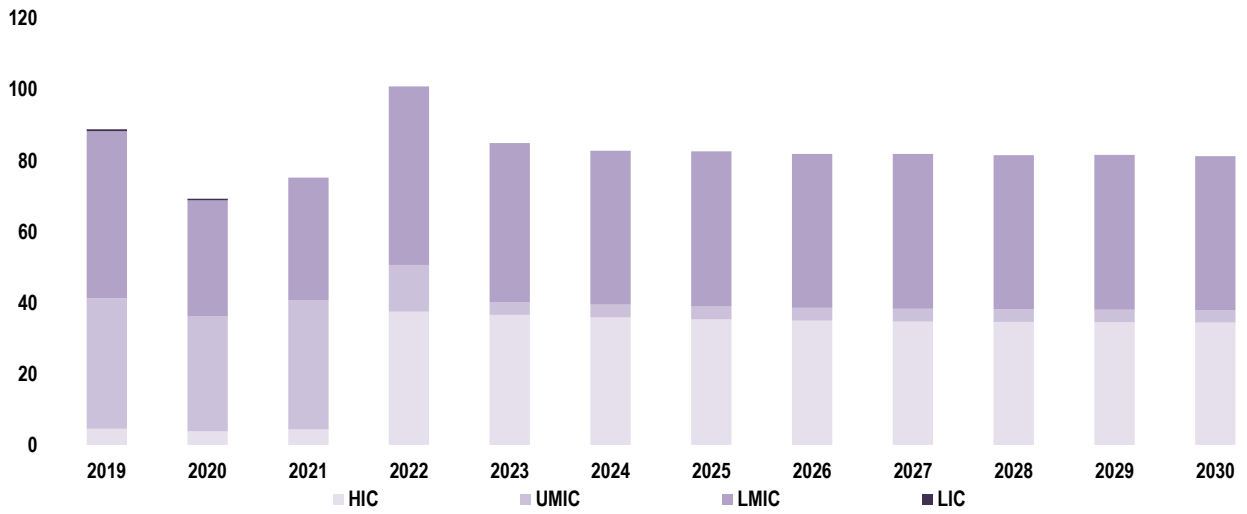
2015	2016	2017	2018	2019	2020 --- 2024	2025	2026+
Lao PDR	Cambodia		Myanmar			Bangladesh	Bhutan**
	Nepal		Indonesia*				Korea, DPR
							Pakistan
							Papua New Guinea**
							Timor-Leste**

	Introduced
Name*	Subnational introduction
	Countries eligible for Gavi support
Name**	Countries having transitioned from Gavi support

Source: UNICEF Supply Division

Data below shows the global demand by countries for JE vaccines by World Bank income group (Figure 3), which averages out at approximately 82 million doses a year. The data excludes any demand generated by the travel market; anticipated new country introductions; catch up campaigns; and any changes in demand generated by variations in the seasonality of the disease. The drop in data noted in 2020 and 2021 through to 2022 incorporates the projected disruptions in coverage due to the impact of COVID-19.

Figure 3 Global Demand by World Bank Income Group for Select Gavi-supported JE Vaccines



Source, GVMM

4.3 Supply

Current supply availability is sufficient to meet demand through UNICEF as well as globally. Manufacturers have expanded their production capacity anticipating new country introductions and the scale up of programmes in large countries. UNICEF has one LTA with CDIBP and has issued another manufacturer, Biological E, a provisional award in order to diversify its supplier base for JE vaccines (Table 6). Country product preferences are still heavily in favour of a single dose schedule in a five-dose vial presentation. As such, currently all country demand is covered by JE vaccines from CDIBP.

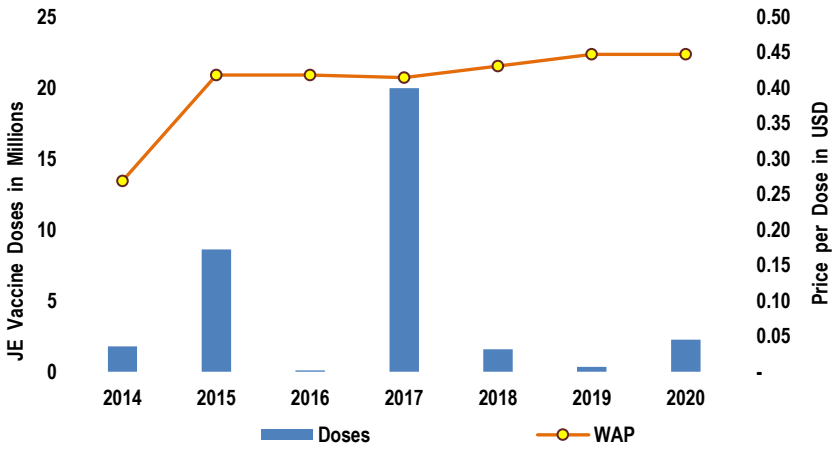
Table 6 UNICEF JE 2015-2022 Awards and Procurement

Manufacturer	Total Doses Awarded	Doses Procured	Remaining Balance
CDIBP (China)	10,394,400	1,789,000	8,605,400
BioE	N/A	0	N/A

Source: UNICEF Supply Division.

Under normal circumstances, UNICEF requires long purchase order lead times of up to six months in advance of any planned programmes in order to preposition supplies ahead of the rains season in regions where there is high incidence of JE outbreaks. Under the context of COVID-19, this can now take up to nine months. UNICEF maintains and has developed a close working relationship with JE manufacturers to ensure the timely delivery of supplies.

Figure 4 Japanese Encephalitis Vaccine Demand and Weighted Average Price per Dose through UNICEF 2014-2020

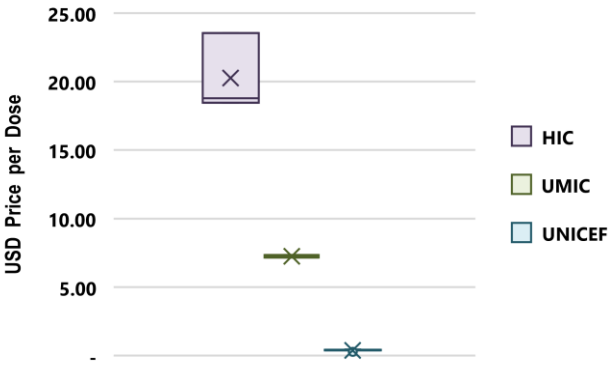


Source: UNICEF Supply Division

The demand for JE vaccines procured through UNICEF is characterized by high peaks and troughs due to the seasonal nature of disease transmission and the requirements of large campaigns prior to national routine introduction (Figure 4). UNICEF concluded its first tender for JE vaccines in 2014 with supply awarded through an LTA to one manufacturer, which was sufficient to meet country demand requirements through to 2017. A second tender was launched in 2018 covering a five-year period through to 2022.

4.4 Pricing

Figure 5 Pricing Data



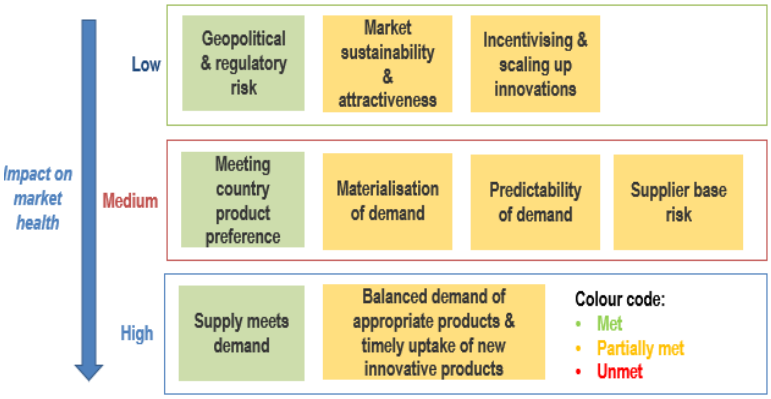
Source: GVMM

The price for JE vaccines can range between 18.00 to 23.00 USD in many HICs, and average 7.31 USD in upper MICs, which is a price that reflects predominantly the travel market, compared to 0.27-0.45 USD per dose through UNICEF (Figure 5). The price through UNICEF is accessible for countries and not only for those that have applied and been approved for support by Gavi. The price data includes a range of JE products that are not all interchangeable.

5. Healthy Market Framework

The Bill and Melinda Gates Foundation (BMGF), Gavi, and UNICEF, developed the healthy markets framework (HMF). The HMF is a tool to support market shaping and is used to assess and articulate a market's current and desired future state. UNICEF and partners use it to identify a set of attributes that measure the health of a particular market; to provide a process to value it specifically for vaccines; and to provide a framework to describe its desired state of health. The current revised HMF evaluation for JE vaccines below (Figure 6), demonstrates that the JE vaccine market is now in a moderate state of health.

Figure 6 Healthy Markets Framework for JE Vaccines 2021



Even though supply is sufficient to meet country demand and presentation preferences, with vaccines from manufacturers that are programmatically suitable in multi-dose vials, with a single dose schedule, the buffer capacity is only partially met. The buffer capacity in the short term is dependent on higher priced, and less programmatically suitable, vaccines. The JE vaccine market needs a wider diversified supplier base to mitigate individual supplier risk. All country manufacturers fall under different NRAs in Asia. India's NRA achieved functionality level 4 according to WHO classification, and therefore this attribute is considered met.

Source: UNICEF

Long-term competition is considered unmet, and the push funding investment and subsequent pricing offered to LICs limits the ability of other manufacturers to provide any significant, cost-effective competition. India's future choice of supply will also have an impact on market competition. Therefore, long-term competition is unlikely in this market, especially after any period of high demand from new introductions. Product innovation is also only partially met, after manufacturers moved away from the mouse-brain derived vaccines and current product offerings are suitable.

6. Issues and Challenges

Several factors can affect JE programme vaccine supply availability. The timing and availability of vaccine supply could delay programmes by up to one year if calendar schedules are mismatched with procurement lead times. Table 6 describes a number of challenges affecting JE vaccine supply that countries should take into consideration and plan for with sufficient lead-time.

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

Challenges	Considerations
Forecast	There is a high variance in vaccine demand from year to year, which creates economic uncertainty for manufacturers resulting in potentially unutilised left-over stock. JE forecast accuracy remains a challenge as past projections for introductions since 2018 have not materialised
Supply	JE vaccine supply through UNICEF is currently sufficient to meet demand, but it relies on one supplier. This is a risk for vaccine security as large JE endemic countries like India and China also procure from the same source.
Production	A long 'lot-release' process in China creates vaccine procurement problems. The JE vaccine has a shelf life of 24 months, of which six months are required for batch release processes. Upon its release and shipment time, only 18 months of vaccine shelf life remains.
Price pressure	The push funding support received for the development of JE vaccines by the manufacturer comes with price conditions that put a lot of pressure on the manufacturer's mark up and sustainability. Since 2014, the price of JE vaccines have increased twice, yet it is still six times lower than the next available WHO prequalified vaccine.

Source: UNICEF Supply Division.

7. Steps Forward

- Following UNICEF's issuance of a provisional award to a new JE vaccine manufacturer with WHO prequalified vaccines in 2018, to ensure an expanded supply base and increased supply security, there has been no materialized demand. UNICEF will continue to work with countries to generate demand.
- UNICEF will continue to develop and maintain close relationships with current existing manufacturer to ensure the timely delivery of supplies and improve lead time delivery.
- UNICEF will communicate with countries and promote awareness of the current lead times required and the limited shelf life of the JE vaccine currently procured through UNICEF, as well as its implications and necessary considerations for routine programme and campaign timings.
- UNICEF, together with Gavi and partners, are reviewing JE vaccine forecast accuracy, demand, and supply availability, and will assess the need to issue a new tender subsequently.
- UNICEF together with WHO, Gavi, PATH and other global partners will continue close collaboration on JE vaccine local effectiveness studies and surveillance to gain more information on burden of disease in JE endemic countries.

For further questions or additional information, please contact:

Andrew Owain Jones
Principal Adviser, Vaccine Centre
UNICEF Supply Division
+45 45 33 58 90
anjones@unicef.org

Abraham Kofi Ntow
Contracts Specialist
UNICEF Supply Division
45 45 33 59 06
akntow@unicef.org

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

Other UNICEF information notes can be found at: https://www.unicef.org/supply/market-notes-and-updates

UNICEF issues market and information notes on products and supplies that are essential for the needs of children, and by extension their families. While some products are easily available and affordable, the availability of others can be limited, or in some instances, non-existent in the quality and price required. UNICEF places a strategic focus on these supplies to shape healthy markets. UNICEF seeks to influence the market to achieve greater coverage, affordable prices, diversified supplier bases, competitive market landscapes, and product quality that is fit for purpose and in the right form for children.