Japanese Encephalitis

Vaccine Quality

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

Cold Chain Equipment

The freeze indicator is used to warn of freezing and is packed with vaccines that are sensitive to freezing temperatures: DTP, TT, DT, Td (freezing point of -6.5°C), hepatitis B (-0.5°C), liquid Hib and their combinations (DTP-HepB, and DTP-HepB+Hib vaccines) and JE.

Every refrigerator storing vaccines should have a freeze indicator (Freeze Watch™). It is strongly recommended that one freeze indicator be placed in each cold box during vaccine transport and distribution. This is critical in places subject to low temperatures.
**Vaccine Handling**

Lyophilized mouse brain-derived (JE) vaccine is stable at 4 °C for at least 1 year.

**Schedule**

The most effective immunization strategy in JE endemic settings is a one time campaign in the primary target population, as defined by local epidemiological data, followed by incorporation of the JE vaccine into the routine immunization programme. This approach has a greater public health impact than either strategy separately (page 331.)

The most effective immunization strategy in JE-endemic settings is one time catch-up campaigns including child health weeks or multi-antigen campaigns in the locally-defined primary target population, followed by incorporation of the JE vaccine into the routine immunization programme. This approach has a greater public health impact than either strategy separately (page 339.)
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Both the mouse-brain derived and the cell culture-based vaccines are considered efficacious and to have an acceptable safety profile for use in children. However, with the mouse-brain derived vaccine, rare cases of potentially fatal acute disseminated encephalomyelitis (ADEM) and hypersensitivity reactions have been reported among vaccinated children in endemic regions and in travellers from nonendemic locations. Because of the rarity of these adverse events, and the high benefit-to-risk ratio of routine vaccination, the introduction of immunization against JE in public health programmes should not be deferred (page 332.)

The three types of JE vaccines that are currently in large scale use are considered efficacious and acceptably safe for use in children. However, following immunization with the mouse brain-derived vaccine, rare cases of potentially fatal ADEM and hypersensitivity reactions have been reported among children in endemic regions and in travellers from non-endemic locations. An increased awareness of these specific adverse events is recommended, for example when assessing the actual risk of JE for the individual traveller. However, because of the rarity of these adverse events, and the greater benefit to risk ratio of routine vaccination, the introduction of immunization against JE in public health programmes should not be deferred (page 339.)

The cell culture-based, live attenuated (JE) vaccine appears to require fewer doses for long term protection, is in most cases less expensive, and seems to represent an attractive alternative to the mouse brain-derived vaccine. However, more needs to be known on its safety and efficacy when used in immunodeficient people, as well as on the impact of co-administering this vaccine with other vaccines (page 332.)

The live attenuated vaccine induces protection for several years after 1 or 2 doses, whereas durable protection by the mouse brain-derived vaccine may require 2-3 initial doses followed by boosters at intervals of approximately 3 years. As the price per dose of the mouse brain-derived vaccine in most countries is higher than that of the live attenuated vaccine, the need for repeated doses renders the former vaccine unaffordable in many JE-endemic countries (page 339)
When immunizing children 1-3 years of age, the mouse brain-derived vaccine provides adequate protection throughout childhood following 2 primary doses 4 weeks apart and boosters after 1 year and subsequently at 3-yearly intervals until the age of 10-15 years. Equally good childhood protection is obtained by a single dose of the cell-culture based, live attenuated vaccine followed by a single booster given at an interval of about 1 year (page 332).

For epidemiological, programmatic and economic reasons, JE immunization schedules differ widely from one country to the other. In general, using the mouse brain-derived vaccine, adequate childhood protection is achieved following immunization of children as of 1 year of age with 2 primary doses 4 weeks apart followed by boosters after 1 year and subsequently at 3-yearly intervals up to the age of 10-15 years. Using the cell culture-based, live attenuated vaccine, equally good childhood protection is provided by a single dose of vaccine followed by a booster given at an interval of about 1 year (page 340).

Although experience from Thailand shows that JE vaccination of children aged 6-12 months may be highly efficacious as well, in most epidemiological settings primary immunization should be given at the age of 1-3 years. Given the mostly infrequent occurrence of JE in infancy and the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months.

In people whose immunity is unlikely to be boosted by natural infection, repeated boosters are required for sustained immunity.

Since the optimal number and timing of booster doses depend on the frequency of natural boosting with JE virus and possibly with related flaviviruses, the schedule for routine JE immunization has been difficult to standardize. Many Asian countries have adopted a schedule of 2 primary doses preferably 4 weeks apart, followed by a booster after 1 year. In some countries, subsequent boosters are recommended, usually at about 3-year intervals up to the age of 10-15 years.
For travellers aged >1 year visiting rural areas of endemic countries for at least 2 weeks, the established current practise is to administer 3 primary doses at days 0, 7 and 28; alternatively 2 primary doses preferably 4 weeks apart. When continued protection is required, boosters should be given after 1 year and then every 3 years.

(For cell culture-derived, live attenuated JE vaccine,) carefully planned studies are required to establish firm recommendations on the optimal immunization schedule.

Neither hypersensitivity reactions nor acute encephalitis have been associated with this (cell culture-derived, live attenuated JE) vaccine. However, for immunization of pregnant women or immunodeficient individuals, the live attenuated vaccine should be replaced by one of the inactivated JE vaccines until further evidence has been generated.

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The live attenuated vaccine induces protection for several years after 1 or 2 doses, whereas durable protection by the mouse brain-derived vaccine may require 2-3 initial doses followed by boosters at intervals of approximately 3 years. As the price per dose of the mouse brain-derived vaccine in most countries is higher than that of the live attenuated vaccine, the need for repeated doses renders the former vaccine unaffordable in many JE-endemic countries.
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The mouse brain-derived JE vaccine is given subcutaneously in doses of 0.5 or 1 ml (with some vaccines: 0.25 ml or 0.50 ml) the lower dose being for children aged <3 years.

Current experience, primarily from Taiwan (China) and Thailand, does not suggest reduced seroconversion rates or an increase in adverse events when mouse brain-derived JE vaccine is given simultaneously with vaccines against measles, diphteria-tetanus-pertussis (DPT) and polio as part of the Expanded Programme Immunization (EPI) programme. However, the possible impact of co-administration of the mouse brain-derived vaccine with other vaccines of the childhood immunization programme has not been systematically studied.

Adverse Event

Both the mouse-brain derived and the cell culture-based vaccines are considered efficacious and to have an acceptable safety profile for use in children. However, with the mouse-brain derived vaccine, rare cases of potentially fatal acute disseminated encephalomyelitis (ADEM) and hypersensitivity reactions have been reported among vaccinated children in endemic regions and in travellers from nonendemic locations. Because of the rarity of these adverse events, and the high benefit-to-risk ratio of routine vaccination, the introduction of immunization against JE in public health programmes should not be deferred (page 332.)

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The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)
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In general, the mouse brain-derived JE vaccine has been considered safe, although local reactions such as tenderness, redness and swelling occur in about 20% of vaccinated subjects. A similar percentage of vaccines may experience mild systemic symptoms, including headache, myalgia, gastrointestinal symptoms and fever. Acute disseminated encephalomyelitis (ADEM) temporally coinciding with JE immunization using the mouse brain-derived vaccine has been reported at frequencies corresponding to 1 case per 50 000-1 000 000 doses administered, but no definitive studies are available. Based on observations of a case of ADEM temporarily associated with JE vaccination, the recommendation for routine childhood JE vaccination has been withdrawn in Japan. However, the Global Advisory Committee on Vaccine Safety* concluded recently that there was no definite evidence of an increased risk of ADEM temporally associated with JE vaccination and that there was no good reason to change current recommendations for immunization with JE vaccines.

* See No. 28, 2005, pp. 242-247.

Occasionally (with mouse brain-derived JE vaccine,) hypersensitivity reactions, in some cases serious generalized urticaria, facial angio-oedema or respiratory distress, have been reported, principally in vaccine recipients from non-endemic areas. The reported rates of such reactions in prospective and retrospective studies are usually in the range of 18-64 per 10 000 vaccinated subjects. A complicating factor is that such reactions may occur as late as 12-72 hours following immunization. Sensitization to gelatine, a vaccine stabilizer, has been suspected in some cases in Japan, but the underlying cause remains uncertain.

The only contraindication to the use of this vaccine is a history of hypersensitivity reactions to a previous dose. However, pregnant women should be vaccinated only when at high risk of exposure to the infection. Mouse brain-derived vaccine has been given safely in various states of immunodeficiency, including HIV infection.

Neither hypersensitivity reactions nor acute encephalitis have been associated with this (cell culture-derived, live attenuated JE) vaccine. However, for immunization of pregnant women or immunodeficient individuals, the live attenuated vaccine should be replaced by one of the inactivated JE vaccines until further evidence has been generated.
Japanese Encephalitis

The Committee considered the decision taken by the Government of Japan on 30 May 2005 to suspend routine vaccination with the mouse brain-derived Japanese encephalitis (JE) vaccine currently used in Japan (3).

GACVS was advised that there is no definite evidence of an increased risk of acute disseminated encephalomyelitis temporarily associated with JE vaccine and a causal link has not been demonstrated.

The national authority recommends vaccination in high-risk areas only and for travel to endemic regions.

GACVS concluded, on the information presently available, that there is no good reason for WHO and national immunization programmes to change the current recommendations for JE vaccination for residents in and travellers to JE-endemic regions.


Global Advisory Committee on Vaccine Safety, 9–10 June 2005

The JE vaccine may cause severe delayed allergic reactions. Because of this, use of the vaccine requires careful evaluation of risks and benefits. Patients must be advised to be near a health facility for ten days after receiving the vaccine.

Immunization in practice: a practical resource guide for Health workers – 2004 update Module 2: The vaccines
Surveillance of Vaccine Preventable Disease

SAGE recommended that surveillance (for Japanese encephalitis) be conducted in accordance with the established WHO surveillance standards* and that sentinel sites be equipped to confirm diagnosis using validated and standardized diagnostic tests. There is a need to establish disease surveillance in rural areas. SAGE recommended that commercial kits for detection of JE-specific IgM be compared and validated. SAGE noted that valuable experience had been gained from linking surveillance of encephalitis to detection of acute flaccid paralysis.


Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

Improved methods of JE surveillance including standardized, JE virus-specific laboratory tests are critical for characterizing the epidemiology, measuring the burden of disease, identifying high-risk populations and documenting the impact of control measures. The recommended standards for JE surveillance are discussed in a separate WHO document. (WHO-recommended standards for surveillance of selected vaccine-preventable diseases. Geneva, World Health Organisation, 2003 (WHO/V&B/03.01))

JE surveillance is critical for characterizing the epidemiology, measuring the burden of disease, identifying high-risk areas and areas of new disease activity, as well as for documenting the impact of control measures (page 340.)

In countries having a good surveillance and laboratory framework, impact of JE vaccination on other flavivirus infections should be monitored.

Japanese encephalitis vaccines (WHO position paper)

Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation

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JE surveillance is critical for characterizing the epidemiology, measuring the burden of disease, identifying high-risk areas and areas of new disease activity, as well as for documenting the impact of control measures (page 340.)

(For cell culture-derived, live attenuated JE vaccine,) carefully planned studies are required to establish firm recommendations on the optimal immunization schedule.

Optimal national vaccination strategies depend on reliable information concerning the duration of protection and, additionally, whether repeated exposure to natural infection is required for long-term protection (following JE immunization.). Similarly, further information is needed on possible impact of cross-reacting flavivirus antibodies (e.g. dengue virus antibodies) on the outcome of primary JE immunization.

Further studies are needed to document the safety of administering Japanese encephalitis (JE) vaccine concomitantly with the measles vaccine. If the first dose of JE vaccine could be given at the same visit with the first dose of measles, this will fit better into the schedule of the national immunization programme (NIP) and may help to increase coverage.
Japanese Encephalitis

GACVS acknowledged the excellent safety and efficacy profile of the (live attenuated) SA 14-14-2 (Japanese encephalitis) vaccine but nonetheless recommended more detailed study of the following: the safety profile in special risk groups including immunocompromised people and pregnant women; whether viral shedding occurs in vaccinees and the potential implications of such shedding; further analysis of sequential or co-administration of JE and measles vaccines; the interchangeability of inactivated and live JE vaccines; the safety of vaccine administration to infants aged under 1 year; and the implications for the efficacy and safety of the vaccine in infants with maternal antibodies against JE virus.

Introduction of Vaccines

SAGE commended the efforts of countries (regarding Japanese encephalitis control) and acknowledged that immunization is the most appropriate means of controlling the disease. It also acknowledged the cost-effectiveness of the measure.

(page 216) SAGE recommended that (Japanese encephalitis) immunization strategies be guided by evidence of the burden of disease, the impact and safety of immunization and the ability to integrate JE vaccination into the EPI programme.

Interference with the immune response to other vaccinations, the number of doses required and the duration of protection need to be assessed. Efforts to continue measuring incidence of acute encephalitis syndrome and to confirm diagnoses need to be sustained.

JE vaccination should be extended to all areas where JE is a demonstrated public health problem (page 331).

With increasing availability of efficacious, safe and affordable vaccines, JE immunization should be integrated into the EPI programmes in all areas where JE constitutes a public health problem (page 339.)