Japanese encephalitis vaccines: Newer vaccines and their current status.

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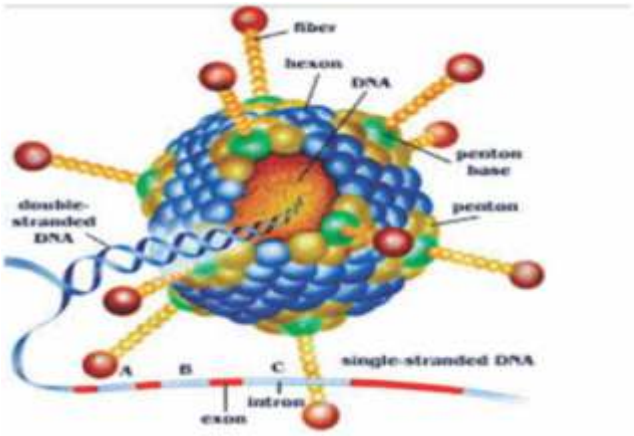
Abstract : Japanese encephalitis is a serious arboviral disease caused by virus of genus Flavivirus. Japanese encephalitis is the most common vaccine preventable virus causing encephalitis in Asia. There is no antiviral treatment for patients with Japanese encephalitis and clinical care is only supportive management.

Thus vaccination is the best prevention against Japanese encephalitis. A number of developments have occurred in the vaccines available for JE including widespread availability of inactivated Vero cell vaccine, live attenuated vaccine, live chimeric vaccine. Thus the improved access to JE vaccines and availability of newer vaccines necessitates revision of JE vaccines.

Keywords : Japanese encephalitis, Vaccination.

Introduction : Japanese encephalitis virus, a flavivirus transmitted by mosquitoes is the leading cause of encephalitis in Asia. It is a single stranded RNA virus. The JE cycle occurs between Culex tritaeniorrhynchus and vertebrates. Humans are the dead end host and no human to human transmission occurs.[1] Globally JE affects about 67,900 people each year with approximately 13,600 to 20,400 deaths worldwide. Approximately most cases are asymptomatic but in symptomatic cases, JE can be a devastating disease. Following a incubation period of 4 to 14 days, symptomatic patients can present with fever, chills, headache, myalgia and confusion. In children gastrointestinal complaints can dominate initially and 75% can experience seizures. No treatment is available and thus apart from prevention of mosquito bite, vaccination is the only method of prevention. Almost 15 vaccines are currently available for JE. All these vaccines are based on 3 virus strains. The four major type of vaccines in use are: inactvated mouse brain-derived vaccine, Chimeric vaccine, inactivated Vero cell vaccine and live attenuated vaccine.[2]



Japanese Encephalitis Virus

Inactivated Mouse Brain Vaccine : The first vaccine developed for Japanese encephalitis was inactivated mouse brain derived vaccine.

Contents : It was derived from Nakoyama and/or Beijing-1 strain by BIKEN as JE-VAX.

Dosage : 2 doses 1 to 2 weeks apart.

Age Group: It is recommended above 1 year of age.

Immunogenicity: 80% after 2 dose schedule.

Booster: 1 dose 1 year after primary schedule.

Safety: Local reactions like tenderness, swelling and redness. Systemic side effects like headache, myalgia, gastrointestinal symptoms and fever. Acute disseminated encephalomyelitis (ADEM) is reported in 1 in 50,000 to 1 in 1,00,000 doses administered.

Current Status : Mouse brain derived vaccine has been replaced by the newer vaccines due to better safety . Its production has ceased since 2005.[3]

Live Attenuated Vaccine:

Content : The live attenuated SA-14-14-2 vaccine is manufactured by the Chengdu Institute of Biological products and is being licensed in China since 1988.This vaccine is produced in primary Hamster kidney cells. It contains gelatin, saccharose, human serum albumin and sodium glutamate.

Dosage : 1 primary dose above 8 months of age.

Age Group : It can be given after 8 months of age.

Immunogenicity : Seroconvertion rate after 28 days of primary dose was about 90% to 92%.

Booster: 1 booster can be given to produce a good anamnestic response with seroprotection of 76 % to 86 %.

Safety : Local tenderness, redness, swelling. Systemic reactions like fever, vomiting, drowsiness, loss of appetite and irritability.[4]

Current Status : Available immunogenicity data indicate children vaccinated with a single dose at 8 month of age have adequate seroprotection titres at 3 years. In India a 2 dose schedule has been recommended to increase primary vaccination coverage. CD JEVAX is the available vaccine in India. No vaccine related serious local or systemic reactions nor deaths have been reported in Randomized controlled trails. Thus Live attenuated vaccines have an acceptable safety profile based on currently available data.[5]

Chimeric Vaccine:

Content : Only one product is licensed which is developed by Sanofi Pasteur marketed as IMOJEV, prequalified by WHO in September 2014. It was created using recombinant RNA technology by replacing the premembrane and envelope coding sequences of Yellow fever live attenuated 17D vaccine virus with SA-14-14-2 live attenuated JE vaccine.[6]

Dosage : 1 dose.

Age Group : It is given above 9 months of age.

Immunogenicity : High seroprotection rates one month post vaccination were reported which was about 99.3%.

Boosters : 1 booster recommended 2 years after primary vaccination which provided more seroconvertion rates than primary series of vaccination.

Safety : In children between 9 months to 18 years its safety is comparable to licensed vaccines like Hepatitis and Varicella. It had few side effects in patients like local site tenderness, redness and swelling. Significantly low side effects have been observed as compared to mouse brain-derived vaccine. As the Chimeric vaccine IMOJEV is made from Yellow fever 17D backbone so yellow fever vaccine-associated viscerotropic disease (AVD) and acute neurotropic disease (NVD) can be side effects.

Current Status: Chimeric vaccine has a over acceptable profile for vaccination from 9 month above age.[7]

Inactivated Vero Cell Vaccine:

Content : A number of inactivated Vero cell vaccines are available. The mostly marketed [virus produced in Vero cells and contain inactivated, purified virus antigen. It is alum conjugated and contains phosphate buffer saline.

Dosage : 2 primary dose series one month apart.

Age Group : It is most widely used vaccine in India and is licensed for individuals above 2 months.

Immunogenicity : In Indian studies, 2 month to 17 years of vaccinees who received age appropriate dose showed seroconvertion of about 98% within 1 month.

Boosters: 1 booster dose recommended specially in non endemic regions. In children who were not seroprotected following primary series of vaccination, the seroprotection after 1 month was observed about 100 % following booster dose.

Safety : About 3 % vaccinated had local side effects like redness, swelling. The most common vaccine related side effect are headache (19%), myalgia (13%), fatigue (10%), flu like illness (9%) and nausea (5%).[8]

Introduction of JE Vaccine in Vaccination Schedule : JE vaccine should be included in vaccination schedule of all countries where JE is recognized as a public health problem. Even if the number of cases confirmed is low, the vaccine should be considered if the factors favoring spread of JE are present. These include presence of animal reservoirs, ecological conditions supporting spread of virus etc. All the countries considering introduction of vaccine in their immunization schedule collect background data on Japanese encephalitis burden and identify target age group to be vaccinated.[9]

Age of administration and schedule : The appropriate age for vaccination should be decided so that the vaccination doses not interfere with passive maternal antibodies and also is given at the right time to provide protection as early as possible.

1. Inactivated Vero cell vaccine 2 doses are recommended after 6 months in endemic regions and after 2 months in non endemic regions.
2. Live attenuated vaccine 1 dose is given after 8 months of age.
3. Chimeric vaccine 1 dose after 9 months of age.
4. Inactivated mouse brain-derived vaccine is no longer recommended for vaccination.[10]

Co-administration of other vaccines : Data support co-administration of live attenuated JE vaccine with measles vaccine. Immunogenicity studies are needed for co-administration with MR and MMR. However, for programmatic reasons itmay be considered acceptable to co-administer live attenuated JE vaccine with MR or MMR vaccines,although data are not yet available. Following the same rationale, co-administration of MMR andchimeric vaccine is acceptable. Coadministration

of IXIARO with a range of vaccines is given to travellers. While the possible impact of coadministrationof inactivated JE vaccines with other vaccines of the childhood immunization

programhas not been systematically studied, co-administration of inactivated Vero cell vaccines with othervaccines for programmatic reasons seems acceptable.[11,12]

Vaccination In Special Situations :

1. Immunocompromised : There are very limited data in immuno compromised persons for inactivated Vero cell, liveattenuated, or chimeric JE vaccines.In the one small study of HIV-infected children not receivinganti-retroviral therapy (ART) no safety concerns were identified but the seroprotection rate wasapproximately half the rate in HIV-uninfected children (Rojanasuphot 1998).inactivated Vero cell JE vaccine can be used in HIV-infected andimmunocompromised persons, but the immune response may be lower than in healthy persons.Inactivated vaccines should be used preferentially over live or chimeric vaccines inimmunocompromised persons. However, it is not necessary to use screening tests prior tovaccinating and it should not be a deterrent to using live or chimeric vaccines during campaigns.

2. Pregnant Female : Inactivated vaccines should be used preferentially over live or chimeric vaccines in women known to be pregnant out of the same precautionary principle against using any live attenuated vaccine in pregnant women. However, it is not necessary to do pregnancy testing beforeJE vaccination.

3. Travellers : Most authorities recommend vaccination for travellers going to endemic countries, particularly but not exclusively rural areas, for more than one month, or repeat travel to such areas. As noted by WHO guidelines for International Travel and Health, "the risk varies according to season, destination, duration of travel and activities. Vaccination is recommended for travellers withextensive outdoor exposure... during the transmission season.

4. Health Care Workers : WHO defines health care workers as all persons involved in patient care such as health care professionals, residents, students, laboratory staff, administrative and service staff, as well as persons in public health acts such as field workers, epidemiologists, laboratory staff and communityhealth workers. Health care workers at high-risk in JE-endemic areas, e.g. those involved in vectorcontrol, should be vaccinated.[13]

Vaccination Impact : SAGE guidelines for evidence-based vaccine recommendations include considering the populationimpact of the vaccine and cost-effectiveness of immunization programs.

Many countries with JE surveillance systems have been able to track JE trends over time, before andafter vaccination.[14] There is clear evidence of significant impact on JE disease of population vaccination with live attenuated and inactivated mouse brain JE vaccines (Liu 2006, Upreti 2013,Zhou 2001, Chen 1992, Wong 2008, Japanese Surveillance Report 1999, Wu 1999). Disease impactstudies exclusively for inactivated Vero cell vaccines and chimeric vaccines are not yet available dueto the lack of widespread use; chimeric vaccine impact studies may now be possible in some of theendemic countries in which they are now being used.[15]

Data on the population impact of vaccination programs show significant reductions in JE cases.

When high coverage is achieved in populations at risk of disease, JE in humans can be virtually eliminated while the virus remains in circulation. Due to the continued enzootic cycle of JE virus,sustained high coverage vaccination programs are critical.

Although cost-effectiveness studies are highly dependent upon parameters such as incidence of disease and vaccine price, it has been demonstrated that vaccination programs can be highly cost effective.[16]

Future aspects of Japanese Encephalitis Vaccine:

I. Long-term immunogenicity studies to inform optimal dosing schedules for long-term protection, which may vary by location (based on natural boosting or other factors).

II. Vaccine effectiveness and impact studies (particularly for newer vaccines).

III. Development of standardized neutralization assay reagents.

IV. Further development of sensitive, specific, affordable commercial serological assays to ensure access to diagnostic testing in JE-endemic countries.

V. Co-administration of live attenuated and chimeric vaccines with other live vaccines, including MR and MMR. Co-administration of any JE vaccine with other vaccines not yet studied may also be warranted.

VI. Better description of disease severity by age, including long-term sequelae from JE disease.

VII. Guidance on how to approach JE vaccine impact assessments. This guidance should address surveillance data sources and analysis to measure JE vaccine impact, design of surveillance and special studies for impact measurement, JE laboratory diagnostics, and data collection and analysis for observational studies to measure vaccine effectiveness. WHO should take the lead on developing this guidance and making it available to countries and stakeholders.

VIII. Development of case-investigation protocols and field tools to enable strong monitoring.[17]

Conclusion : Japanese encephalitis is major public health problem in many countries in South East Asia

and the Western Pacific. Safe and effective (immunogenic) vaccines are available.

With greater access to products, including new vaccines and WHO pre qualified vaccines, and there are many opportunities to initiate or expand JE vaccination programs. Surveillance strengthening is needed to assess the burden of JE, inform vaccination strategies, and monitor the impact and effectiveness of JE vaccines. Assessments of the public health and economic impact of vaccination programs show significant reductions in JE cases and economic burden of JE. Vero cell vaccine from India JENVAC manufactured by Bharat Biotechis the most commonly used vaccine. When high coverage is achieved in populations at risk of disease, JE disease in humans can be virtually eliminated while the virus remains in circulation.

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