Overview on Japanese Encephalitis

Introduction

The leading cause of viral encephalitis in Asia is mosquito borne arboviral Japanese Encephalitis (JE) (1). JE is an inflammatory disease that affects the central nervous system causing acute inflammation of the brain. The virus is transmitted in an enzootic cycle among mosquitoes, primarily C. tritaeniorhynchus, and vertebrate- amplifying hosts, which include domestic pigs and Ardeid (wading) birds. Humans are considered dead end hosts as infected humans do not transmit the virus to the biting mosquitoes (2). This is because viremia is transient with low levels of circulating virus. Historically JE is known to have originated in Malay Archipelago (3). The virus evolved in several thousand years, into different genotypes (I–V) and spread across Asia. There are five genotypes which have been identified by the researchers. Their geographical distributions are: Genotype I includes isolates from Korea, India, Cambodia, Laos, and northern Thailand (4), Genotype II, from Malaysia, Sarawak, Indonesia, southern Thailand, and northern Australia (5), Genotype III, from Japan, Taiwan, China, India, Sri Lanka, Nepal, Vietnam, and the Philippines (6), Genotype IV from Indonesia (7), Genotype V, which includes isolates with a restricted distribution in India in addition to genotype I and II. It is the last genotype to be identified (8). The first clinical case of JE was recorded in 1871 in Japan (9). The first clinical case of JE in India was observed in 1955 at Vellore (10). There have been reports of several outbreaks, the most fatal outbreak was reported in 2005, wherein around 1700 people mostly children were killed and several thousands were disabled (11). Press Trust of India has reported the death toll in 2013 as 358 due to JE virus (12). The scientific survey conducted by the doctors who treated the JE virus affected areas shows that the affected patients were poor people hailing from mostly rural areas.
**Virus Structure**: JEV is a relatively small (~50 nm diameter) spherical virion that encapsidates a nonsegmented RNA genome of positive-sense polarity (13). The single strand of positive-sense RNA comprises of a single open reading frame capped by a 5'UTR 95 bp long and a 3'UTR 580 bp long (14). This ~11 kb viral RNA encodes a single polyprotein, which is cleaved by viral and cellular proteases into three structural proteins (capsid, C; membrane, M; and envelope, E), and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (15). The E glycoprotein (53-55 kDa) is the principal target for neutralization in *vitro* and *in vivo* by specific antibodies (16). The nonstructural protein NS1 (39 to 41 kDa) is a glycosylated protein, which is derived from the polyprotein by an N-terminal cleavage involving a novel host protease (15). NS1 is believed to be involved in the assembly and release of virions (17). NS2A and NS2B are low-molecular-weight proteins that are found to be involved in the processing of other viral proteins (18). NS3 protein (68 to 70 kDa) is conserved among flaviviruses and has protease and nucleotide triphosphatase/helicase activities (19). In JEV infected cells, NS3 is associated with microtubules and tumor susceptibility gene, and plays an important role in viral RNA packaging, intracellular trafficking of viral components and viral assembly. Therefore, NS3 has been considered to be responsible for development of novel potent therapeutic substances. NS4A and NS4B are small proteins whose functions are not clear, although they are involved in the membrane localization of NS3 and NS5 through protein-protein interactions (15), or in the formation of genomic RNA replication complex (20). NS5 protein (103 to 104 kDa) is the largest and most conserved protein and is considered to be the viral RNA polymerase with both methyl transferase and RNA-dependent RNA polymerase (RdRp) activities (21).

**Clinical Implications**: Based on serological studies in endemic areas and medical histories, JE virus infection may be asymptomatic in humans. It has been estimated that, 1 to 3 per 1,000 infected humans may show clinical manifestations in the form of illness that includes evidence of virus-induced inflammation in the cerebrum, cerebellum and spinal cord (22). Typically, symptoms start suddenly following a variable incubation period of 2 days to 2 weeks and a nonspecific viral prodrome. The earliest symptoms seen during the prodromal stage include lethargy, fever (23), headache (24), abdominal pain, nausea, and vomiting. Neurologic manifestations are seen in the late stage which include meningal (meningitis) (25), parenchymal (encephalitis), or spinal cord (myelitis) involvement. Among infected children, 50%–85% develop focal or general seizures compared to 10% of adult cases. Seizures have been associated with poor clinical outcome. Although JE is often a mild disease, leading to an uneventful recovery, some cases rapidly progress to severe encephalitis with mental disturbances, general or focal motor abnormalities, and progressive coma (26).

**Treatment**: There is no specific treatment for Japanese encephalitis and the available treatment is supportive in nature (23). There are no reported cases of JEV being a communicable disease and therefore patients need not be isolated. Different approaches are being made for treatment at various stages of disease like design of chemotherapeutic drugs against virus and use of vaccines in preventing the disease.

**Chemotherapy**: An effective chemotherapeutic strategy against any viral infection is based on either 1) blocking the virus-coded function or 2) inhibition of cellular processes necessary for viral replication. The problem with the second approach is that it also hampers normal cellular function, but it is advantageous in a way that the therapy is active against all the viruses belonging to the same genus. Moreover, development of resistance against this type of chemotherapy is rare. The JEV chemotherapeutic drugs, which are tested, come under three different categories; viz; viral replication inhibitors, anti-inflammatory or anti-apoptotic drugs, interferon inducers (27).
Modern therapies: More modern therapies against the infection include the interferon therapy wherein the interferons induce production of effector proteins in cells, which inhibit various stages of viral replication, assembly, or release. In vitro studies in human trials have showed that interferon therapy is effective against JEV and other arboviruses, including West Nile virus (28). Anti-sense therapy is the use of RNA interference technology. It is also reported that a single siRNA (small interfering RNA) treatment could suppress viral infection across species (29).

Monoclonal antibody therapy has reported varied efficacy of MAbs targeted against specific JEV antigenic epitopes. Fully human or humanized MAbs against JEV might be practical and can generate cost-effective reagents for preventing or modifying the pathophysiological implications of JE (27).

Vaccination: Vaccination against infectious diseases is one of the most successful medical interventions in history. In the recent years, advances have been made in the understanding of the mechanisms underlying the induction of protective immune responses to infectious agents especially in viral infections. The most important factor is the identification of the key parameters that are responsible for the long lasting immune response induced by viruses, which has been identified and can now be exploited for the development of safe and efficacious vaccines. Four key parameters which form the basis of the strong immunogenicity of the viruses are i) particulate nature, ii) highly repetitive structures, iii) ability to induce innate immunity and iv) the relative length of time the immune system is exposed (30). For Japanese encephalitis, the aim of vaccination is to induce circulating neutralizing antibodies that can prevent invasion of the central nervous system during the viremic phase of JE virus infection.

Different vaccines for JEV are available for many years and their use has reduced the incidence of JE in many countries. But with the decrease in the incidence of the disease and the appeal for mass immunization in the epidemic regions has triggered concerns regarding the adverse events following immunizations. The present review focuses on (a) existing vaccines for JEV with their merits and demerits, (b) the published literature on latest developments in vaccine development and (c) vaccines presently in various stages of development (Table 1). The vaccines available for JEV can be broadly classified as (i) inactivated vaccines (mouse brain derived, PHK and vero cell derived), (ii) live attenuated vaccines and (iii) recombinant vaccines.

I. Inactivated vaccines

(1) Inactivated mouse brain–derived vaccine: The first inactivated vaccines were prepared in 1954 and were based on formalin-inactivated Biken vaccine, grown in adult mouse brain. The Biken vaccine uses Nakayama-NIH strain of JE virus, originally isolated in 1935 from an infected human. Three- to five-week-old mice were chosen to grow the virus, as virus yields were very high and cell culture systems were very limited at that time. Each mouse brain produced the equivalent of 4–10 doses of vaccine. The vaccine derived from mouse brain is used both as a liquid or lyophilized product and has been available in Japan since 1973. For several decades, this JE vaccine was available in the United States and Europe (BIKEN, distributed by Sanofi Pasteur as JE-Vax).

(2) Inactivated vaccine cultivated on primary hamster kidney cells: This is an inactivated vaccine cultivated on primary hamster kidney cells. The Beijing-3 strain was the main variant of the vaccine used in the People’s Republic of China from 1968 until 2005 (31). This vaccine only requires 1–2 doses to confer long-lasting immunity. The vaccine is made available at a highly competitive price to low-income countries.

There are problems associated with the presently used Japanese encephalitis vaccine and they include: a) Induction of unwanted adverse neurological reactions caused by the
nature of mouse brain-derived vaccine, b) Loss of follow-up for the third vaccination caused as a result of the long interval between vaccinations, c) The vaccines are expensive as there are only few manufacturers, d) JE vaccine is associated with local reactions and mild systemic side effects (fever, headache, myalgias, and malaise) in about 20% of vaccines, (32), e) Serious allergic reactions, including generalized urticaria, angioedema, respiratory distress, and anaphylaxis, have occurred within minutes of vaccination lasting upto one week after immunization, f) No data are available on the safety and efficacy of JE vaccine among infants less than 1 year of age, during pregnancy (33), on simultaneous administration with Diptheria, Tetanus and Pertussis (DTP) vaccine and effect of administration of other vaccines, drugs (e.g., chloroquine, mefloquine), or biologicals (34).

(3) Inactivated vaccines grown on vero cells: The IC51 (IXIARO; in Australia and New Zealand, JESPECT) vaccine is a purified, formalin-inactivated, whole virus JE vaccine developed by Intercell AG, Austria. The product was licensed for use in the United States, Australia, and Europe in 2009. The vaccine is based on a SA14–14-2 virus strain passaged 8 times in primary dog kidney cells, cultivated in Vero cells, and formulated with 0.1% aluminum hydroxide. Vero cells maintained in serum-free medium were selected as the manufacturing cell substrate. The absence of serum allows for a simplified purification process and, potentially, a superior safety profile. As an added safety advantage, this vaccine does not require additional stabilizers or additives (35).

JEEV™ is a second generation inactivated Japanese Encephalitis vaccine based on the SA 14-14-2 virus strain developed by Biological E, India, launched in 2012. It is a purified formalin inactivated vaccine adsorbed onto aluminium hydroxide. The vaccine’s safety and efficacy has been established through multiple studies on Indian subjects and is licensed by the Drug Controller General of India (DCGI). JEEV™ is indicated for active immunization against Japanese encephalitis in adults and children.

JENVAC is another vero cell derived purified inactivated JEV vaccine manufactured by Bharat Biotech, India. JENVAC is the first vaccine to be manufactured in the public-private partnership mode. The virus strain for this vaccine was isolated from the blood sample collected from an encephalitic patient admitted to Government Hospital in Kolar district, Karnataka between Nov-Dec, 1981 and characterized by the National Institute of Virology at Pune (36). JENVAC received manufacturing and marketing approvals from the Drug Controller General of India after its successful clinical trails and the product is available in the market since late 2013. It can be administered as a single dose vaccine during epidemics for mass vaccination campaigns and as a two dose vaccine during the routine National immunization programme in endemic regions.

II. Live attenuated vaccines: A live attenuated JEV vaccine developed in China (SA14-14-2; Chengdu Institute of Biological Products) (31). It is reported that this vaccine strain was developed by passing wild-type strain SA14 in primary hamster kidney cell culture. Following 114 passages of SA14 in primary hamster kidney cell culture, an attenuated derivative, 12-1-8, was isolated. This virus was given additional passages in primary hamster kidney cell culture in different laboratories to generate two sub strains, SA14-2-8 and SA14-5-3. The former was used as a veterinary vaccine in horses whereas the latter was evaluated in humans. Although both viruses were attenuated, neither was sufficiently immunogenic with seroconversion rates below 50% following one dose of vaccine. Subsequently, SA14-5-3 was given additional passages in primary hamster kidney cell culture to derive strain SA14-14-2. This virus has proved to be highly attenuated yet immunogenic. It has been successfully used as a vaccine in the People’s Republic of China with over 100 million children vaccinated. Currently, the vaccine is administered as a two-dose regimen, one year apart, with the

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first dose given at one year of age. The World Health Organization is currently developing criteria for the manufacture of live attenuated JE vaccines for its use anywhere in the world. Since the virus is attenuated; there is no clinical disease and there are no lesions following direct inoculation into the brains of monkeys or mice. There are no reported cases of reversion to virulence. The molecular basis of attenuation of SA14-14-2 has been investigated by comparing the nucleotide sequence of the genomes of wild-type SA14 and SA14-14-2. The two viruses differ by 57 nucleotides encoding 24 amino acid substitutions. Reverse genetics studies indicate that the envelope protein is a major determinant of the attenuation, in particular, amino acid 138 (37).

III. Recombinant Vaccines in various stages of development : The recombinant vaccines, presently at different stages of development can be classified into five categories namely, i) the recombinant protein based ii) the recombinant virus based iii) the DNA vaccine based iv) the bioinformatics based v) the nanobiotechnology based approach for vaccine development.

(1) The recombinant protein based vaccines : The structural and nonstructural proteins of JEV are being explored as vaccine targets. Different expression platforms like bacteria (E. coli), yeast (Saccharomyces and Pichia), baculovirus and mammalian cell lines are being used for developing new vaccine candidates. Mason et al in 1989 (38), synthesized small fragments of JEV E protein with trp fusion proteins in E. coli and reported that E protein segment containing residues from 303 to 396 was the shortest epitope capable of reacting with various JEV neutralizing monoclonal antibodies. Saini et al in 2003 (39), reported neutralizing antibodies in mice by expressing the epitopes of E protein in Jhonsongrass mosaic virus coat protein that formed virus like particles (VLP). Bhasker et al in 2009 (40), expressed E protein in Saccharomyces cervisiae and showed the production of antigen specific and non-neutralizing antibody response in mice. Xua et al in 2011 (41), have succeeded in construction of one recombinant baculovirus BacSC-E expressing His6-tagged E with the baculovirus envelope protein gp64, transmembrane domain (TM) and cytoplasmic domain (CTD). Vaccination of mouse and swine with recombinant baculovirus BacSC-E successfully induced neutralizing antibody response and protective immunity towards a lethal challenge of the JEV. Tafuku et al in 2011 (42), expressed JEV E domains (I, II and III as domains I through III (D1-3), domains I and II (D1-2) and domain III (D3) and nonstructural protein 1 (NS1) in Escherichia coli, and administered to BALB/c mice via the intranasal (i.n.) route. The E protein, but not the NS1, induced JEV-specific serum IgG with virus-neutralization capacity in vitro. When mice were lethally challenged with JEV, intranasal immunization with D1-3, D1-2, D3, or a mouse brain-derived formalin-inactivated JE vaccine conferred complete protection, while an 80% protection was observed in the NS1 immunized mice. Li et al in 2012 (43), concluded that purified JEV NS1 from Drosophila S2 cells in a native glycosylated multimeric form induced T-cell and antibody responses in immunized C3H/HeN mice. Mice vaccinated with 1 μg NS1 with or without water-in-oil adjuvant were partially protected against viral challenge and higher protection was observed in mice with higher antibody titers.

(2) Recombinant virus based vaccines : Recombinant viruses have the ability to induce both cell mediated and humoral immunity. The foreign gene product is amplified during virus infection thus increasing antigen exposure. Foreign antigens thus expressed are processed and presented to the immune effector cells resembling natural infection. Konishi et al in 1992 (44), constructed recombinant NYVAC (a highly attenuated recombinant vaccinia virus constructed by deletion of its 18 open reading frames) expressing JEV proteins prM and E with or without the NS1. Nam et al in 1999 (45), constructed a Modified Vaccinia Ankara (MVA) recombinant expressing the prM and the E proteins of JEV. Mice inoculated with NYVAC

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generated Cytotoxic T Lymphocytes and mice inoculated with MVA recombinant produced JEV neutralizing antibodies and the immunized mice were completely protected from a lethal JEV challenge. Lipenga et al in 2008 (46), constructed and characterized the immune responses conferred by recombinant adenoviruses (rAd) expressing JEV E epitopes (six amino acid residues 60–68, 327–333, 337–345, 373–399, 397–403 and 436–445 in E, designated TEP). To prove the protective efficacy of the recombinants, it was administered on swines and found to be highly effective in insulating them from viral challenge with IM rAd-TEP. These findings indicate that rAd-TEP can be a potential vaccine for preventing JEV infection. Wang et al in 2012 (47), constructed a recombinant MVA carrying multi-epitope (B-cell, CTL and Th) gene of JEV (rMVA-mep) and demonstrated the vaccine efficacy in a mouse challenge experiment.

ChimeriVax-JE virus is produced using infectious clone technology based on insertion of pre-membrane (prM) and envelope (E) genes from SA JE, SA14–14-2 virus into the nonstructural genes of YF 17D viral strain as the viral “backbone”. The resulting chimeric RNA was electroporated into Vero cells. Progeny virus particles contain JE-specific antigenic determinants that elicit neutralizing antibodies as well as cytotoxic T lymphocytes. YF 17D was chosen as backbone to the chimera because of its proven record of safety and efficacy (48). In 2011 Ishiwaka et al (49), demonstrated that a single-cycle West Nile virus (WNV) named RepliVAX WN could be used to produce a chimeric Japanese encephalitis (JE) vaccine (RepliVAX JE) by replacing the WNV prM/E genes with those of JEV. They also demonstrated that replacement of WNV NS1 gene in RepliVAX JE with that of JEV (producing TripliVAX JE) could produce a superior vaccine. TripliVAX JE elicited higher anti-E immunity and displayed better efficacy in mice than RepliVAX JE. Furthermore, TripliVAX JE displayed reduced immune interference caused by pre-existing anti-NS1 immunity.

(3) Plasmid DNA-based JEV vaccines: This vaccine is usually a plasmid DNA capable of synthesizing a protective immunogen from a given pathogen. DNA vaccines have ability to generate a broad range of immune responses which include the induction of antibodies, generation of CD4+ helper T lymphocytes and CD8+ cytotoxic lymphocytes. In 1998 Lin et al (50), showed that immunization of mice with DNA expressing NS1 alone was sufficient to protect mice but could not raise detectable neutralizing antibodies against JEV. Chang et al in 2000 (51), showed that intramuscular immunization of mice with plasmid DNA synthesizing the prM and E proteins of JEV elicited protective immunity in mice and 70% of them survived lethal JEV challenge. Chien et al in 2001 (52), concluded that intramuscular immunization induced the Th-1 type of immune responses, whereas the gene gun immunization induced Th-2 type response. Such vaccines have shown considerable success albeit with some shortcomings in terms of not evoking sufficient neutralizing antibody titers. Therefore the present attention has shifted towards the improvement of DNA vaccine modulated through several immunological adjuvants, such as the use of liposomes (53), inclusion of CpG motif (54), co-expressing cytokines and costimulatory molecules along with the target gene (55), exploring different routes of administration of vaccine (56), targeting the vaccine to specific cells (57) or endosomal/lysosomal compartment (58).

In 2009 Bharti et al (59), have evaluated the efficacy of E gene as a DNA vaccine candidate in rhesus monkey and showed the generation of neutralizing antibodies and prime the immune system effectively against further JEV infections.

IV. Bioinformatics based approach for vaccines development: The development of different software tools in the field of immunology gave birth to the field of immunomics which is nothing but the abridging of immunology with bioinformatics (60). Immunomics gave rise to the reverse vaccinology approach as analysis starts with the information contained in a computer instead of with growing pathogens (61, 62). Role
Table 1

<table>
<thead>
<tr>
<th>S.No</th>
<th>Type of vaccine</th>
<th>Substrate</th>
<th>Strain</th>
<th>Producer</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Inactivated and purified</td>
<td>Mouse brain</td>
<td>Nakayama</td>
<td>Biken-Japan</td>
<td>Production stopped by 2005 and all stocks expired by 2011.</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Green Cross-Korea</td>
<td>Vabiotech-Vietnam</td>
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<td></td>
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<td>Beijing 1</td>
<td>Kaketsuken-Biken-Japan</td>
<td>Keased production</td>
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<td></td>
<td></td>
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<td>Kitasota-Japan</td>
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<tr>
<td></td>
<td></td>
<td>Primary Hamster Kidney</td>
<td>P3 strain</td>
<td>Several manufacturers in China</td>
<td>Previously China's principal vaccine</td>
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<tr>
<td></td>
<td>(PHK) cells</td>
<td></td>
<td>Beijing 1</td>
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<td></td>
<td></td>
<td>Vero cells</td>
<td>SA-14-14-2</td>
<td>IC51-Novartis-Intercell</td>
<td>JESPECT-Australia, IXIARO, Elsewhere</td>
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<td></td>
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<td>821564 XZ, Bharat</td>
<td>Biotech, India</td>
<td>JENVAC</td>
</tr>
<tr>
<td>2.</td>
<td>Live attenuated</td>
<td>Primary Hamster Kidney</td>
<td>SA-14-14-2</td>
<td>Chengdu Institute of</td>
<td>The use of PHK cells is gradually being replaced by vero cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(PHK) cells</td>
<td>Beijing-3 strain</td>
<td>Biological products, China</td>
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<tr>
<td>3.</td>
<td>Live attenuated, Chimeric</td>
<td>Yellow fever</td>
<td>SA-14-14-2</td>
<td>Acambis with Sanofi Pasteur</td>
<td>ChimeriVax-JE</td>
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<tr>
<td></td>
<td></td>
<td>17D vectored, Vero cells</td>
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</table>

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of epitope mapping in finding a new vaccine for Japanese encephalitis virus is of great interest lately. Specific sequences coding for epitopes and cytokine enhancing factors can be incorporated into viral vectors or DNA vaccines. The focus can be on the immunogenic protein already used in vaccine production. Despite the protein's availability, it is still difficult to find a new epitope. Classical techniques are time consuming process hence bioinformatics tools like Epimatrix and Conservatrix can be of help in this direction. Conservatrix (63), is a sequence matching and counting tool, can be used to compare the sequence of every 10-amino-acid-long peptide in a given sequence database (e.g. one isolate of a virus) for identity with every 10-amino-acid-long sequence of another sequence database (e.g. another strain of the same virus). This can be used to identify broadly conserved (across-clade) epitopes. Conservatrix can be configured to allow amino acid substitution at non-anchor positions. The algorithm has been used to map highly conserved T-cell epitopes in variable genomes. Since Japanese encephalitis is a viral infection, the favorable epitope should be a specific T cell epitope which has an important role in
immunogenicity via the T cell immune system. Existing vaccines have been developed mostly against pathogens that show no or limited antigenic variation. With immunomics one can search the entire genetic repertoire for protective antigens, thus increasing by several orders of magnitude the number of antigens available for vaccine development. The combination of epitope-mapping informatics tools with new sensitive in vitro screening methods has driven many new vaccine approaches.

V. Nanobiotechnology based vaccines:
Another upcoming approach is in the field of nanobiotechnology. This field in the domain of vaccinology is being used to develop synthetic vaccine carrier/delivery systems. These vaccine carrier systems mimic pathogen structure and are also engineered to show chemotaxis at immunization sites. There are two methods by which one can deliver the vaccines; the first being a method to provide a depot for an immunostimulatory compound that attracts APCs to immunization sites and the second method is to deliver the vaccines in the form of particles that are internalized by the infiltrating immune cells. Examples include the alginate microspheres used to deliver the chemotactants and antigen entrapped nanoparticles. In vitro studies have demonstrated that the chemotactant can readily diffuse out of the particles and attract dendritic cells. In contrast, the antigen-loaded nanoparticles do not leave the alginate microparticles, but antigen that is accessible at the surface of the particle can be extracted and presented by dendritic cells. The delivery of antigens is also being done by skin patches. Two general approaches have been used with skin patches, one by using a dry formulation in the patch and second the delivery of an adjuvant using the patch, followed by injection of conventional vaccine at the same site. Such approaches ensure that both antigen and adjuvant are delivered to the same population of antigen presenting cells. Particulate delivery systems can specifically target the adjuvant effect to the key cells of the immune system thereby reducing systemic distribution and minimizing induction of adverse reactions. Small unilamellar liposomes have a significant potential as delivery systems for the co-administration of antigens (peptides, lipopeptides) and of immunostimulatory adjuvants, including CpG oligonucleotides or DNA encoding antigens and/or immunostimulatory sequences. Advantages of nanotechnology include uniformity, reproducibility, and precision in the synthesis and manufacture of candidate compounds. Combined with novel pharmacokinetics and the possibility of targeted therapy, nanotechnology-based vaccines may prove superior to existing vaccines and have the potential to open therapeutic avenues for treating JEV.

Conclusions
JE has remained a tropical disease uncommon in the West. With rapid globalization and climatic shift, JEV has started to emerge in areas where the threat was previously unknown. Scientific evidence predicts that JEV will soon become a global pathogen and cause worldwide pandemic. A considerable percentage of JEV outbreaks occur in developing countries. Therefore it is the responsibility of the scientific communities, governments and WHO to find drugs that could reach the unprivileged masses to contain JEV. JE is a vaccine-preventable disease with numerous options now available for active immunization. Aggressive and responsible vaccination programs should greatly diminish the burden of disease. In India vaccination against Japanese encephalitis are administered in areas where the disease is hyper-endemic. Protection at personal level would also help to reduce the menace of JE.

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