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An Insight to Japanese Encephalitis: A Descriptive Review

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ABSTRACT: Japanese encephalitis (JE) is a life-threatening vector-borne disease of central nervous system caused by Japanese encephalitis virus (JEV). JE virus is single-stranded RNA virus belonging to family *Flaviviridae.* JE virus is transmitted by zoonotic chain cycle between amplifying hosts such as wading birds and pigs, and the mosquitoes (*Culex tritaeniorhynchus),* where humans are accidently infected and are the dead-end host of virus life cycle. JE is observed to be the dominant cause of mortality in world mainly in Asian countries. For endemic areas, JE is considered as disease of children but in newly invaded areas, children and adults both are affected due to absence of antibodies. Non-specific febrile illness, encephalitis or meningitis are the symptomatic manifestation of JEV infection. MRI and autopsy studies revealed that JE majorly affects thalamus, brainstem, corpus striatum and spinal cord regions. Aspiration, seizures, hyperglycaemia and raised intracranial pressure are main cause of JE like motility. Due to absence of any antiviral drugs JE can be managed by preventive measures and supportive cares. Various classes of vaccines are developed such as Mouse brain-derived inactivated vaccine, Vero cell-derived inactivated vaccine, live recombinant vaccine like (Chimeric) and Live-attenuated cell cultured-derived vaccine to control JE. Control of JE is significantly linked to the wider matter of education, hygiene, environment, and economy.

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INTRODUCTION:

Inflammation of the brain parenchyma that can be caused by infection or autoimmunity disorder which results in severe neural dysfunction is known as encephalitis [1,2]. Whereas Inflammation of the brain specifically due to viral infection is termed as viral encephalitis and the permanent damage inside the brain is the most serious potential complications of viral encephalitis. Focal neural signs and seizures will differentiate encephalitis from encephalopathy [3]. Japanese encephalitis virus (JEV), one of the leading public health issues not just due to high mortality rate

but also because of serious neuro-psychiatric sequence that bound lifelong support amounting in the direction of reasonable socio-economic loads [4,5]. The arthropod borne virus JEV is transferred in an enzootic cycle among *Culex tritaeniorhynchus* mosquitoes and vertebrate hosts, specifically pigs (Sus scrofa domesticus), horses and Aves [6-8].

Domestic pigs are crucial turn up host for virus transmission to human population. Unlike polio and small pox complete elimination of JE is not possible due to enzootic nature of transmission [9]. Acute encephalitis syndrome (AES) is manifestation of JEV infection but due to various possible causes of AES, laboratory confirmation becomes more important for exact diagnosis of JE which is a very difficult task because of very low viremia. Isolation of virus through cell/tissue culture, antibody detection, and antigen detection is some of the common diagnostic procedures for JEV [10]. Neural dysfunction, Cephalalgia, altered level of consciousness, seizure, swelling of optical disc (Papilledema), focal deficits, etc., along with some systemic indications like joint and muscular pain, gastrointestinal and respiratory systems related problems are the common symptoms of JEV [11,12]. Virus, main etiologic factor of Japanese encephalitis, diffuses into cerebrospinal fluid (CSF) via blood circulation and attack brain tissue [13].

The additional very common viral encephalitis vectors are Enterovirus (non- polio), Herpes virus 1 and Herpes virus 2 and Arbovirus. Seasonal flu, cytomegalovirus, Human herpes 6 [HHV-6] and Epstein Barr virus [EBV] are other pertinent causes [14]. Geographical locations, season, patient immunology level and viral genetic mutations over time decide variations in the frequency of the particular agent for Japanese Encephalitis [1]. Explosion of JE were registered at Japan at late 1800s and the first was confirmed in 1924 at Japan and in Indian in 1955 in Madras [15,16]. It was observed that nearly 67,900 JE cases are reported annually in JE-endemic countries, in which China alone contributes nearly half of these cases [17]. It was estimated that in WHO's Western Pacific region and South East Asian regions nearly 3 billion population reside in 24 countries are under risk of JE infection [14,18]. Yearly frequency of Japanese encephalitis was evaluated to be in range of 50,000 to 75,000 cases, depends upon the age, group, geographical area and immunity status of the patient [19,20]. Approximately 20 to 30 % of clinical JE cases are fatal and about 30 to 50 % case patients survive but suffer serious neural cognitive complications. Vaccination is only scheme to evolve long term sustain safety against JEV infection due to lack of antiviral therapy [21,22]. This review summarizes the brief discussion on JEV, its pathogenesis, transmission cycle, and recent advances in treatment approaches against this viral infection including different vaccines.

VIROLOGY:

Japanese encephalitis virus belongs to family *Flavivirdae* and genus flavivirus [23,24]. JEV is prototype virus of its serotaxonomical group [25,26]. Like other flaviviruses, structure of JEV is small, spherical shaped having diameter size of 50 nm (Fig 1). It contains an electron dense core of diameter about 30nm which is covered by a lipid bilayer envelope. The genome of JEV is single-stranded, linear and positive-sense RNA of nearly 11 kb length. The RNA genome is enclosed in nucleocapsid which in turn coded by a protein called capsid protein C. Nucleocapsid and core is surrounded by a small lipoprotein envelope [27]. The genome of JE virus is monopartite and is linear with single stranded RNA (ssRNA) genome along with positive polarity. At the 5' end RNA contains 5' cap (m7g5'ppp5'A) and polyadenylate tail is absent. As a large polyprotein a single and long open reading frame (ORF) is translated by genomic RNA also known as messenger RNA (mRNA). Virions are associated with three viral proteins named, E (envelope), C (capsid), M (membrane) proteins. Among these, major surface protein is E protein (50kd) interacts with virus receptor and mediates the fusion of virus–cell membrane. M protein (26 kd) is small fragment of prM protein and it is important for viral maturation into infectious form. The highly basic protein is C protein (11 kd) and it takes part in ribonucleo protein complex formation with packed genomic RNA [28].

TRANSMISSION CYCLE:

Japanese encephalitis virus is a flavivirus which causes zoonotic disease called Japanese encephalitis. Mosquitoes, specifically Culex species plays an important role in transmission chain of JEV (Fig 2). Wading birds like egrets, herons and ducks are host of virus [7,29,30]. domestic pigs are major amplifying host of JEV, Increased JE cases can also be associated with increased density of domestic pigs in that area [31,32]. Humans and horses are referred as Dead-end host of JEV but, sometimes they develop encephalitis and having fatality rate more than 30 % [33,34].

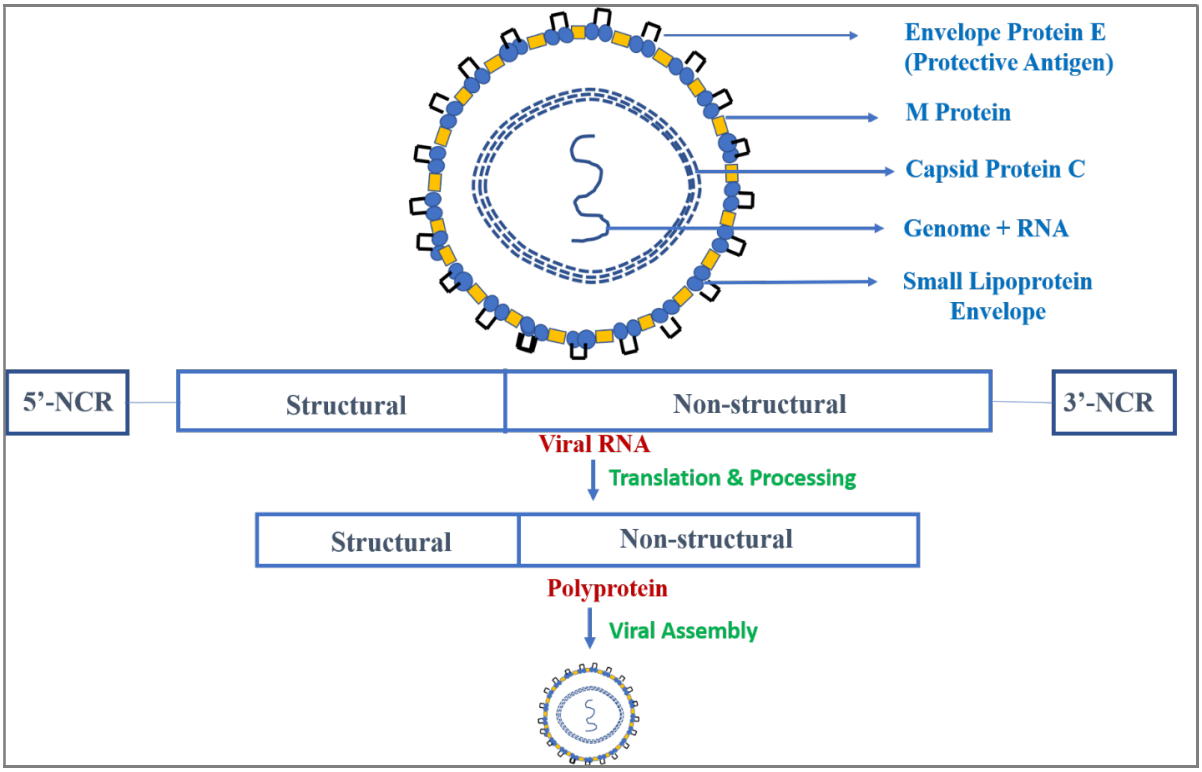

Fig 1. Structure of Japanese Encephalitis Virus.

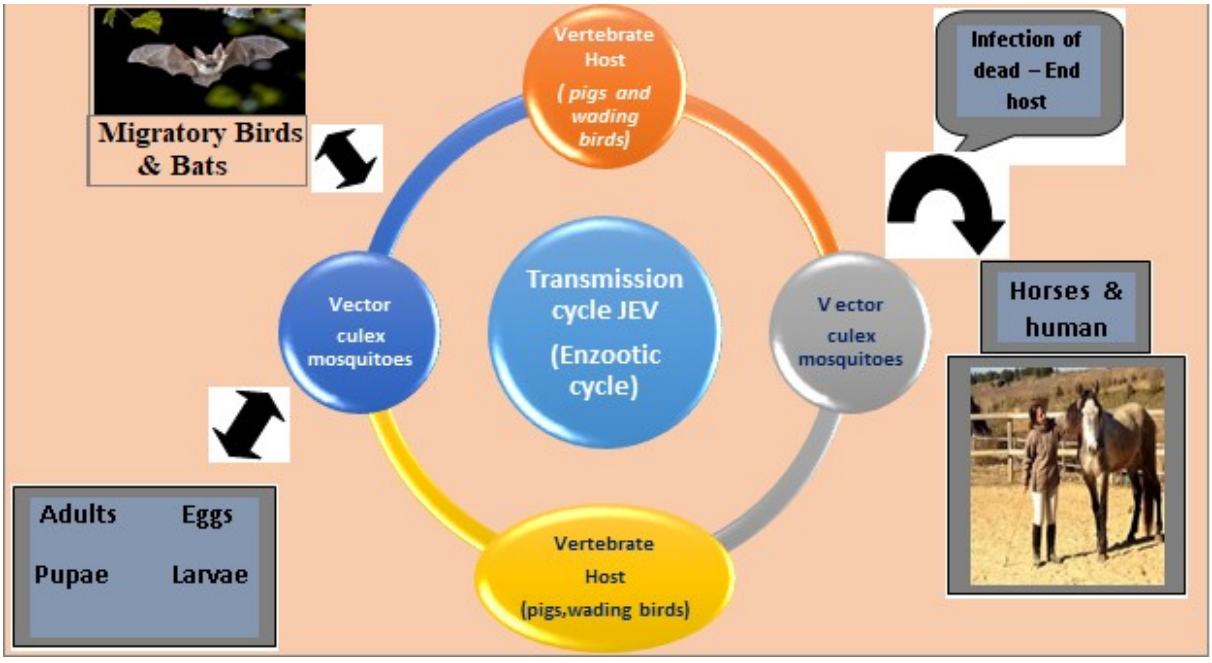

Fig 2. Japanese Encephalitis Virus transmission cycle.

In rice field of rural areas, the vector of JE virus like *Culex tritaeniorhynchus* go through larval development therefore Japanese encephalitis can be considered as a rural disease [7,28]. In the infection chain of JEV domestic pigs and feral plays a peculiar role therefore, considered as an important carrier of virus. Domestic pigs are susceptible host but, clinical manifestations are milder and then after body temperature normalized symptoms reduces and ultimately disappeared [35,36]. However, it was observed that in pregnant pigs the viruses cross the blood-placenta barrier and responsible for the death of piglets in uterus due to viral infection [37]. Pigs transmit the virus in vector-free mode among themselves through mucous exposure and corresponding micro-droplets [38]. Infected pigs act as JEV reservoir, which are capable to contribute JEV transmission in temperate climates throughout the year and originate epidemic events in hotter and wetter seasons which also accelerated viral

transmission from pigs to mosquitoes [35,39]. In tropical and sub-tropical regions mosquitoes particularly Culex and Aedes species transmits the virus from birds to susceptible mammals and humans [40]. Transmission of virus from human to others via vectors are not reported but it can transmit via blood transfusion from infected person to healthy person [35].

PATHOGENESIS:

Japanese encephalitis virus has an incubation period of 6 to 16 days. The virus must introduce to central nervous system to cause encephalitis and the process is termed as viral Neuro-invasiveness and replication of virus to cause CNS damage is known as Neuro-virulence [10,41]. For treatment and prevention of JE, it is important understand the pathogenic mechanism of the disease [42,43]. A recent study on mouse model of JE elaborates that JEV entry inside CNS occurs earlier to blood brain barrier (BBB) dysfunction. Inflammatory secretions like cytokines and chemokines reduces the tight junction expression proteins, which ultimately enhance the BBB permeability [44].

When infected mosquito, bites in skin, virus gets replicated and then transmitted to localized lymph nodes. Langerhans dendritic cells (present in skin) are reported to reinforce the viral replication in case of most of the flavivirus infections [45,46]. Now, viral frequencies intensify peripherally which causes transient viremia before entering in CNS [47].

During primary viremia, extra neural tissues are seeded by viral molecules. Striated muscles, Muscular tissue, lymphoid organs, connective tissue, myocardial cells and glands are major extra neural sites of viral replication [23]. Monocytes are type of white blood cells whose infiltration is an indication of central nervous system (CNS) inflammation, as well as viral infection. Monocyte enters into the infected brain and then transformed into dendritic cell, macrophages and microglial cells. After transformations these cells took part in number of potent effector activities, which include T-cell stimulation, the production and release of various pro-inflammatory mediators along with reactive oxygen species (ROS), these are attentive viral contamination and clearance. However, in some cases immune-mediated pathology is achieved due to unbalanced and badly controlled migration and effector functions which ultimately resulting tissue damage and eradication during infection [48] (Fig 3). The clinical signs and symptoms of most of the infections are depends on whether or not the sensitive or prone cells of CNS are accessed by virus. The signs can be mild in case of limited infection to extracellular tissues, therefore to understand the pathogenesis of any viral diseases the prime important part to find and understand the mechanism of virus penetration inside the CNS [23].

Various mechanism through which JEV enters into CNS are Direct endothelial cell infection and later transcellular release of JEV into brain parenchyma, Trojan horse mechanism (Migration of infected peripheral immune cells in CNS), Entry through paracellular route following disintegration of the BBB, Retrograde transport and From blood to CSF viral translocation [49-51].

In basement membrane of CNS beside endothelial cell, Pericytes are located which releases IL-6 to reinforce the permeability to BBB and ultimately leads to ZO-1 reduction. These events accelerate BBB permeability due to inflammation caused by JEV inside the CNS. Pro-inflammatory mediator TNF-alpha which enhance BBB permeability released by microglia and increased secretion of mediators like interleukin-6, CCL5 which are released from co-culture of endothelial and astrocytes cells to increased tight junction permeability. Hence BBB permeability amplified by JEV infection inside the brain [52]. Stimulation of paracellular infection by MCs was also observed, the entry of neurotropic viruses can be attained by compromising the BBB, due to pro- inflammatory response the tight junctions between endothelial cells becomes leaky [49].

THERAPEUTIC APPROACH:

Specific drug treatment for JEV infection is not available and only vaccines are not much effective against all isolated clinical JE viruses [53]. Protection and incubation of the airways decreased the risk of conditions like aspiration pneumonia and hypoxia. Oxygen supply should be maintained and patient should have elevated head posture to reduce the increased intracranial pressure.

Hydration status should be assessed carefully and re-hydration therapies should be maintained appropriately. Anti-inflammatory and corticosteroids has been examined in which dexamethasone at higher dose was unable to produces significant protective effect on acute infected JE patients, whereas glucocorticoid drug methylprednisolone was studied on patients suffering from viral encephalitis was found to be beneficial might be due to its anti-inflammatory activity [54].

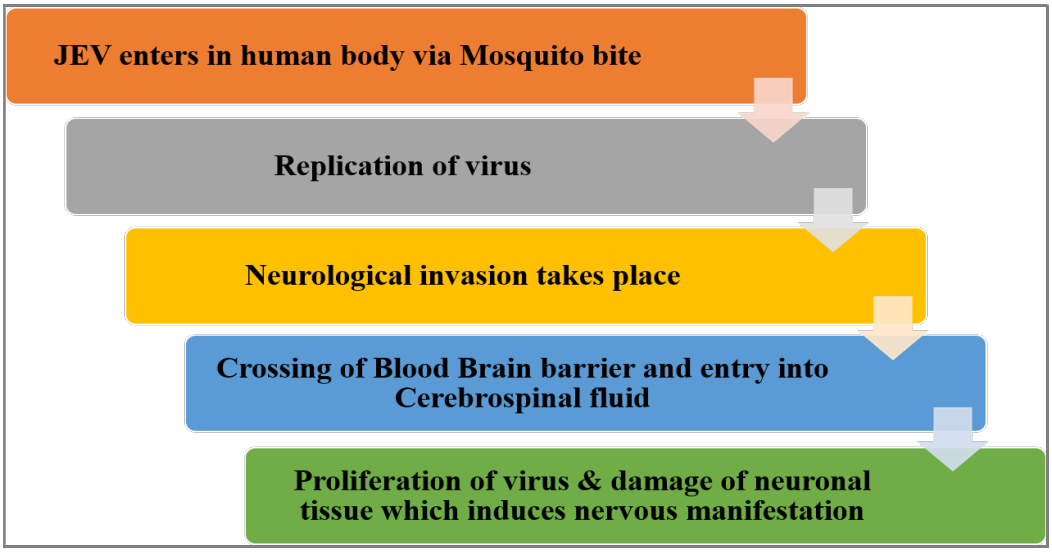

Fig 3. Typical schematic diagram of Neuro-virulence of Japanese Encephalitis Virus.

Table 1. Summary of 4 different types of Japanese Encephalitis vaccines.

Vaccine type	JEV strain	Number of doses	Vaccine name	Route of administration
Mouse brain-derived inactivated vaccine	Nakayama/ Beijing-1(P1)	3 doses	JE-VAX	Subcutaneous
Vero cell-derived inactivated vaccine	Beijing-1(P1)	2 doses 4 week apart (0.25, 0.5 ml)	JESPECT, JEEV	Intramuscular
Live recombinant vaccine like (Chimeric)	SA14-14-2	1 dose	Chimerivax-JE, JE-CV	Subcutaneous
Live-attenuated cell cultured-derived vaccine	SA14-14-2	1 dose	SA-14-14-2	Subcutaneous

To treat JE disease interferon therapy did not faces great success. Clinical trial result of oral administered drug ribavarin was also not very encouraging. A phenolic compound rosmarinic acid which is extracted from various *Labiatae* herbs and alignan compound arctigenin were found to be effective in reducing JEV-induced neuronal death, active caspase activity, microglial activation and triggers the proinflammatory mediators in JEV infected mice of GP78 strain. A broad-spectrum antibiotic Minocycline which is used as antiviral drugs was also found to have anti-JEV action due to its potency to decreases neuronal apoptosis,caspase activity and microglial activation [55]. Some cardiac glycosides like ouabain and digoxin was found to be effective against JEV infection by inhibiting Na^+/k^+ATPase which blocks infection at the replication stage and it was reported that ouabain significantly decreased the morbidity and mortality induced by JEV in a BALB/c mouse [56]. In an investigation, Ca^{2+} channel blocker Manidipine was found to be protective against JEV mediated lethality by reducing the viral load inside the brain [57]. Preventive strategies can play an important role in management of JE disease. Measures include vector control, change in agriculture practices and environmental manipulations, centralized pigs' production can contribute towards depletion in JE cases. Vector abundance increases the risk of human infection which in turn linked with agricultural practices. Increasing the use of natural pesticides can be effective to control vector population in agricultural field and use of neem- coated urea can control larvae of JE vector in rice field ecosystem. Other measures like mosquito repellent coils, creams, oils are widely used to prevent mosquito bites. Curtains and pyrethroid-impregnated bed nets have been reported to reduce man-mosquito contact [58].

VACCINES:

Due to lack of any specific antiviral treatment so far, it is mainly managed via preventive measures and with supportive therapies [59]. Based on mode of transmission,

JE infection can be prevented through 4 main strategies like by avoiding mosquito bites, mosquito control, human immunization and pig's immunization [60-63]. And among all human immunization is more actively acceptable method to get long-term protection against JE. Currently on the basis of the genotype 3 virus strain near about 15 JE vaccines are in use. JE vaccines are categorized into 4 major classes that are Mouse brain-derived inactivated vaccine, Vero cell-derived inactivated vaccine, Live recombinant vaccine like (Chimeric) and Live-attenuated cell cultured-derived vaccine [6,58]. JE vaccines are reported to have good safety profile and absolute contraindication is still not listed. Inactivated JE vaccines are recommended for immunocompromised patients. The WHO recommends JE vaccination for even those areas which have less confirmed JE cases but have potential chances for outbreak due to suitable environmental condition supporting the JE transmission [64]. Now cell culture-derived vaccines are commonly replaced the inactivated mouse brain-based vaccine (IMB vaccines) and SA14-14-2 stain of JE is a live attenuated vaccine is generally used in china, India, Sri Lanka, and in many Asian countries [65]. Four different types of Japanese Encephalitis vaccines were summarized in Table 1. Other than human vaccination such as vaccination of pigs, surrounding locality management to control vector population, and vector control through chemical agents, mosquito net etc. are the little preventive measures that can support in reduction of JE burden [58].

CLINICAL TRIALS:

Worldwide there are approximately 11,412 patents are enlisted related to Japanese encephalitis vaccine out of which 9042 patents demonstrates JE vaccine compositions [66], and 71 clinical trial studies on Japanese encephalitis vaccine are reported out of which 62 trails are successfully completed [67] but, unfortunately till now JE is incurable disease which cause severe health related issue globally. One of the clinical trials demonstrates the comparative study between the live attenuated JE chimeric virus vaccines (IMOJEVTM) and JE live attenuated vaccine (SA-14-14-2) and non-inferiority antibody response is observed after 28 days of administration of one dose of both of the vaccines in toddlers [68]. Likewise in another study, a single dose of (JE-CV) the JE chimeric virus vaccine is found to be non-inferiority in comparison of a single dose of JE life attenuated vaccine SA-14-14-2 after 28 days of administration of both vaccines in toddlers and infants this study also elaborate the safety profile of vaccines and all other severe adverse effects up to 6 months of administration [69]. The research institute for tropical medicine of Philippines conducts a clinical trial on infants of age 8 month to 11 month and they observed that when JE vaccine SA-14-14-2 is co-administered with measles vaccines, the long-term safety and efficacy was reported [70]. Likewise, in China, a trail study was conducted on Measles-Rubella vaccine (MR) and attenuated JE SA-14-14-2 in which both the vaccines are co-administrated to healthy infants of 8 months to compare the immunogenicity of measles vaccine administrated alone or along with LJEV vaccine. The study also explains the safety and tolerability of SA-14-14-2 JE attenuated vaccine along with MR vaccine in infants [70]. There are other clinical studies which are under process to study the efficacy and safety of various JE vaccines.

CONCLUSION:

JE is a serious public health issue especially for eastern and southeastern Asian countries. JE is Arthropod-borne life threatening neuronal disease, which causes swelling of brain and affects 50,000-75,000 peoples annually all over the world. The vector mosquito exhibits a significant role in transmission chain of JEV and pigs are amplifying host which accelerates the rate of infection in an area. Human are accidently infected and considered as death-end host of JEV life cycle. JEV firstly multiplies its number in RE-system of human body then by using various mechanisms JEV enters in CNS and neurological invasion of virus takes place. In brain virus proliferates which results in neuronal tissue damage which further induces nervous manifestations. In milder infection fever, vomiting, headache, neck stiffness are common symptoms which might be developed into severe symptoms like mental status changes, weakness, movement disorders, seizures and other neurological disorders. Specific treatments has not been reported but hospitalization for close observations and supportive care are generally required. Some medicines are used according to symptoms of patients to manage JE severity. Various vaccines like JE-VAX, JESPECT, Chimerivax-JE, SA-14-14-2 etc. are used to prevent JE and Now cell culture-derived vaccines are commonly replaced the inactivated mouse brain-based vaccines, whereas SA-14-14-2 stain of JE is a live attenuated vaccine is generally used in India, china, Sri

Lanka, and in many Asian countries. The main victims of Japanese encephalitis are poor and vulnerable population lives in rural areas and the main reasons are limited health care capital and resources along with endemic zones with less vaccination coverage. So, in the meantime the cost-effective therapies and vaccination strategies are basic requirement to control JE disease.

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