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Supremacy of Dengue Vaccine Over the Conventional Treatment: A Review

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ABSTRACT:

Nations with tropical climates experience a high number of dengue cases. Approximately 300 million individuals affect with dengue virus annually, around 1 million experiencing severe symptoms, resulting in 2 to 5% fatality rate. The virus, belonging to the Flavivirus group, has four closely related strains known as DENV-1, DENV-2, DENV-3, and DENV-4, which are capable of causing dengue fever in individuals. It is essential for the government to take swift action to control the spread of dengue infections. With conventional treatment of dengue there are several ADR such as severe hepatic injury, acute liver failure, allergic reactions like fever, chills, tremor etc. Therefore, one should move towards vaccine for dengue with minimal ADR. Currently, there is a vaccine known as Dengvaxia that offers protection against the dengue virus. Dengvaxia is limited to regions with high prevalence of dengue fever, despite concerns raised by the World Health Organization (WHO). Two vaccines are in the process of being tested in the last phase of trials. DENVax is the name of the vaccine created by the US CDC and Invitrogen, which is currently licensed to Takeda. The TV003/TV005, created by the US NIAID, is another choice of vaccine. Various types of vaccines, including live-attenuated vaccines, purified-inactivated viruses with adjuvants, DNA vaccines, subunit vaccines, and heterologous prime/boost strategies, are examined in these studies. The aim of this review article is that to give an update on vaccine strategies of dengue fever over the conventional treatment of dengue with minimum side effect.

Introduction-

Dengue is a critical illness that can result in death in certain circumstances. It is the result of four distinct strains of the flavivirus: DEN-1, DEN-2, DEN-3, and DEN-4. The Asian DEN-2 and DEN3 types typically cause severe illnesses. The virus can be transmitted between people by Aedes aegypti and Aedes albopictus mosquitoes. Severe dengue infection can lead to rapid and severe illness in patients, yet the exact cause remains unknown. The severity of the illness appears to be influenced by the immune system, genetic factors, and the virulence of the virus[1]. In regions with high temperatures, dengue is a significant public health issue due to its high prevalence. As outbreaks continue to occur one after another, the number of incidents increases. The occurrence of dengue outbreaks is closely related to the changes in weather that occur during the rainy season. A disease spreading can impact many individuals[2].

Phases of Dengue-

Dengue infection develops in three separate stages[3]:

1. Febrile Phase-

Usually lasts 2-7 days. The patients develop a sudden high fever, with their face and skin becoming red, along with body aches, muscle and joint pain, eye discomfort, light sensitivity, and a headache. During this phase, distinguishing between dengue and other fevers can be

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challenging. An individual may experience bleeding under the skin or in the mouth. A swollen and painful liver is possible[4].

2. **Critical Phase-** It usually begins 3 to 8 days after the onset of the illness, as the fever starts to recede. The following indicators typically appear before a person enters a state of shock. Discomfort or pain in the abdomen, Constant vomiting, Buildup of medical fluid (such as ascites or pleural effusion). Spontaneous bleeding of the mucosa. Sluggishness or agitation. Increase in hematocrit with a fast drop in platelet count; liver enlargement >2 cm. It typically requires 1-2 days for a considerable volume of plasma to escape from the bloodstream. It is important to monitor an individual with a plasma leak for signs of circulatory collapse, including cold extremities, a weakened pulse, and slow capillary refill[5].

3. **Recovery Phase-** During the recovery phase, the body stops leaking plasma and bleeding, vital signs stabilize, and the extra fluids are taken in by the body. Occasionally, a fresh rash may appear as you begin to improve, usually within a few days. It can endure for approximately one to five days." Improvement generally occurs within a span of two to four days. It is common for adults to feel extremely worn out for an extended period after their recovery[6].

Complication with Management Of Dengue-

Symptomatic management-

It is advisable to offer plenty of fluids and administer paracetamol as necessary to reduce a fever. It is

recommended to avoid taking more nonsteroidal anti-inflammatory drugs.

Adverse drug reactions with paracetamol in dengue-

Pregnancy can cause damage to the baby's liver and hinder its growth and development. Raise the risk of severe hepatic injury, Acute liver failure, Drug-induced liver disease, Hepatoxicity, Raise the risk of severe hepatic injury[7].

Use of intravenous N-acetylcysteine in dengue haemorrhagic fever with acute liver failure-

N-Acetylcysteine (NAC) was administered to a patient suffering from severe dengue fever and liver issues, leading to their improvement. The Ceylon Medical Journal published this information in 2012. After getting admitted, N-acetyl cysteine (NAC) was administered upon the onset of liver encephalopathy symptoms on the sixth day of the fever. A limited amount of individuals with dengue fever and acute liver failure have been examined, and just a handful of them have experienced complete recovery[8,9]. The absence of a known treatment makes liver failure from dengue fever a significant concern[10]. NAC might assist individuals experiencing severe liver failure from non-acetaminophen causes by enhancing cardiac function, increasing oxygen delivery to bodily tissues, or aiding in the repair of the damaged liver. Early administration of NAC during liver failure has the potential to offer assistance, though there are occasions where it may not be effective[11].

Fluid resuscitation

Take in as much liquid as you are able to through drinking. In cases where a patient's illness prevents them from consuming liquids, intravenous fluids are administered as an alternative. The initial recommendation is to administer fluids through a needle in the vein, starting with 0.9% saline solution. Giving fluids at a steady speed is not recommended. Instead of this, adjustments should be made by consistently monitoring the fluid levels in the blood vessels during the crucial phase[12].

Side effect with IV fluid-

Typical indications of an allergy include fever, chills, and tremors. Patients with low blood volume may experience kidney damage. Failure to metabolize lactate effectively can lead to significant liver complications[13].

Blood products-

Those with significant bleeding or a dangerously low platelet count often require platelet donations from another person. The platelets provided to patients suffering from shock syndrome quickly diminish in the body. The outcome is directly affected by the quantity of platelets given during a transfusion. Following a

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transfusion, there is a rise in the number of platelets in the bloodstream, but this increase can have negative consequences. Although we haven't conducted a formal study, it seems that administering plasma to individuals with dengue shock may raise their platelet levels. Individuals experiencing significant bleeding require blood transfusions, yet there is a lack of official data on their frequency of utilization[14].

Side effect with blood product- A blood transfusion may lead to a fever caused by an allergic response, without causing harm to red blood cells, Pulmonary edema, Bacterial sepsis, Alloimmunization, Platelet refractoriness, Complications from blood transfusions including infections and lung damage[15].

Antibiotics

Although Cefpodoxime is effective and generally safe for children, some may experience stomach issues, skin rashes, or allergic responses. The virus is responsible for causing dengue fever and there are no specific medications available to treat it. It leads to an elevated body temperature, intense head pain, and discomfort in the muscles and joints. Preventing mosquito bites is crucial in order to avoid getting dengue. According to the WHO's criteria for determining causation, it is likely that Cefpodoxime Proxetil was the cause of the bloody diarrhea and red rashes, as they disappeared after the treatment ceased[16].

VACCINE STRATEGIES

Dengue Vaccine Development

Currently, there is no medication available for curing dengue. Controlling the insects that carry the disease is crucial for prevention. It is essential to develop a dengue vaccine quickly in order to prevent people from contracting the disease. Developing a dengue vaccine has faced two major challenges. Initially, DENV antibodies can provide some level of protection against various DENV infections, but severe dengue symptoms typically occur when a second, distinct infection exacerbates the initial one[17]. In 2019, the World Health Organization identified dengue as one of the ten most significant health risks. According to the WHO, a vaccine is necessary to curb the transmission of dengue[18].

Dengue vaccine- Dengvaxia

The knowledge that there are vaccinations for the dengue virus is now widely known. The vaccine Dengvaxia or CYD-TDV has been granted authorization for use in multiple countries. Sanofi Pasteur, a pharmaceutical company in France, is the owner of the product. The safety and efficacy of the dengue vaccine is verified by the World Health Organization (WHO). The effectiveness of the CYD-TDV vaccine (CYD14 and CYD15) has been evaluated through Phase III clinical studies in various countries, using the Randomised Controlled trials approach[19]. Dengvaxia vaccines effectively produce a strong immune response to the four types of dengue virus and are well received by the body. Based on this information, we can deduce that the CYD-TDV dengue vaccine contains a less potent version of the virus. The flavivirus-17D vaccine is produced using a variation of the yellow fever virus known as YF-17D. Dengvaxia has not undergone testing on individuals above the age of 60[20].

Effect On Fertility, Pregnancy and Lactation-

There has not been a thorough investigation into the topic of getting pregnant. The reproductive abilities of female rabbits were not impacted by the administration of Dengvaxia medicine before mating. Pregnant women are advised to avoid getting the Dengvaxia vaccine. Women who have received a Dengvaxia shot should delay pregnancy for four weeks after the vaccination. Pregnant women have not been included in the study of the vaccine. The vaccine for dengue disease may be ineffective in children aged 2 to 5. There is concern that vaccinated children are still falling seriously ill from dengue. Children below the age of nine were not supposed to receive the dengvaxia vaccine[21].

Contraindications-

Individuals who have experienced adverse effects from the Dengvaxia vaccine or a similar vaccine should refrain from receiving Dengvaxia. People who had an adverse allergic reaction to Dengvaxia should avoid taking it again. It is unacceptable for the immune system to have issues with fighting off infections get the dengvaxia vaccine treatment. Included are individuals who are undergoing treatments that suppress the

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immune system, such as chemotherapy or high levels of corticosteroids for a minimum of two weeks. People with symptoms of HIV or a weak immune system should not be given Dengvaxia. Dengvaxia is not recommended for pregnant women[22].

Dengvaxia®: Current Status and Controversies Currently-

Dengvaxia® has been approved for use in 20 different countries. The vaccine was shown to prevent 93% of severe dengue cases and decrease hospitalization due to dengue by 80% in extensive studies conducted in Asia and Latin America over a 25-month period. There is a significant controversy surrounding Dengvaxia® at the moment. The vaccine has resulted in the deaths of 10 children in the Philippines. Following the issues in the Philippines, an organization of specialists from the WHO recommends that only individuals with prior dengue infections should receive Dengvaxia®. In accordance with the recommendations of the CHMP, a committee within the European Medicines Agency focusing on human medicine[23]. Sanofi Pasteur has been given permission to distribute Dengvaxia® in European countries with high rates of dengue fever, beginning December 19, 2018, despite concerns about the vaccine[24]. The USFDA has prioritized the use of the vaccine in the US and its territories, such as the Virgin Islands, Puerto Rico, and Guam, due to their high dengue rates. A burden is a weighty responsibility or hardship that is hard to bear[25]. According to Sanofi Pasteur, blood samples were not gathered before the vaccine was administered in the third phase of the study to assess previous dengue infection[26].

TAKEDA'S TAK-003-

The new dengue vaccines contain specific components of the dengue virus. Takeda's dengue vaccine contains a less potent version of the DENV-2 virus along with components from DENV-1, DENV-3, and DENV-4[27]. Takeda has developed the most cutting-edge vaccine for dengue fever compared to all other vaccines in production. Research on this topic has been ongoing since 2010 and is currently the subject of a long-term investigation. An international research study is being conducted to assess the effectiveness of various treatments for children aged 4 to 16[28]. The vaccine's effectiveness varied across different virus types, and further investigation showed that it might not work as well against DENV-3 in the early stages. The treatment's effectiveness was most notably reduced for the youngest group of children (4-5 years old)[29].

Efficacy of Takeda's TAK-003-

The impact of DENV-1 and -2 was observed in the TAK-003 group. An additional injection could potentially enhance the effectiveness of the vaccine. The results of a phase 2 trial examining the administration timing of the vaccine revealed that individuals without pre-existing antibodies experienced a significant increase in immunity when receiving the second dose 12 months after the initial dose. Individuals who received their second dose three months later experienced heightened vaccine efficacy[30].

Targeted Mutagenesis Based Live-Attenuated Vaccine-

The initial testing of this tactic was carried out by the Lab of Infectious Disease at NIAID, NIH in Maryland, USA. This potential vaccine is a combination of four weakened DENV strains that have had their genetic material altered to remove 30 nucleotides. It comes from a specific area of the mRNA, known as the 3' untranslated region. We named the weakened forms of the DENV-1 and DENV-4 viruses DEN130[31,32].

Inactivated virus

An inactivated virus offers the notable benefit of being highly safe to use. Clinical trials have only tested a small quantity of purified formalin inactivated virus (PIV) so far. In Phase I testing, WRAIR's DENV-1 PIV combined with aluminum hydroxide was evaluated. When tested with ELISA and neutralization tests, the vaccine proved to be both safe and effective in generating antibodies[33]. In the first phase of their research, scientists investigated the four-part PIV vaccine to identify the most effective dosage and additional components (alum versus AS01E versus AS03B)[34].

Recombinant Subunit Vaccine-

The main aim of the Subunit DENV protein vaccine is to develop a vaccine by employing a particular portion of the virus and diverse approaches for creating that portion, such as employing E. coli, yeast, and insect cells. The proteins were purified and then mixed with

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adjuvants known as ISCOMATRIX and alhydrogel. The V180 vaccine underwent testing in a small clinical study to determine its safety and effectiveness at varying dosages, while also being combined with supplementary components for improved efficacy[35].

Dengue DNA Vaccine-

DNA vaccines are progressing at a slower rate compared to other methods due to their inability to induce a robust immune response. The introduction of a plasmid into a cell results in the production of an antigen, triggering the immune system to mount a defense[36,37]. MHC class I molecules are present on the surface of the cell. The USA's Naval Medical Research Center has used DNA to produce a vaccine for the DENV-1 virus[38]. This was accomplished by inserting genes from the DENV-1 virus into a compact piece of DNA known as a plasmid vector. The effectiveness of a vaccine named D1ME100 in preventing DENV-1 was assessed in a medical trial. Nonetheless, only a small proportion of the vaccinated individuals had a limited amount of antibodies capable of combatting dengue[39,40].

Other Vaccine Candidates-

Developing a dengue vaccine involves several stages to ensure its safety and official approval. A major concern is the inadequate number of animal models displaying the same symptoms as humans. The dengue virus can only replicate inside the bodies of mice that have specific immune system receptors missing. Scientists have recently created mice with human-like characteristics by introducing human cells into them[41]. Generating fresh blood cells in mice that have compromised immune systems. NSG or BALB/c-Rag2null IL2rγnull are both examples of this. BRG is useful for researching vaccines and gaining knowledge about disease formation[42,43,44].

VACCINATION PROGRAMMES-

The CYD-TDV vaccine has shown to be successful in preventing dengue illness in those over 9 years of age. The symptoms and hospital visits for dengue fever can be reduced by 10% to 30% over the course of 30 years with the help of the CYD-TDV vaccine. By comparing individuals who received the vaccine with those who did not, this was discovered. Many different math models. This information is limited to comparisons and cannot be relied upon for making detailed country-specific research-based decisions[45].

Conclusion-

Dengue can affect anyone, but individuals living in areas with high occurrences of the disease are more susceptible. This infection is a concern for everyone in society and should be monitored closely. Several vaccines are currently in development to mitigate the severity of dengue virus infection. The Dengvaxia vaccine, which has been approved in a number of European and Asian nations, is the only vaccine that has been permitted by the WHO to be released up to this point. Pre-clinical and phase 3 clinical trials are still ongoing for other vaccine candidates. The initial vaccine for dengue, known as Dengvaxia, received approval in various countries in 2015/2016. The efficacy of the CYD vaccine in protecting against DENV-2 is less effective compared to other dengue types, however, the production of antibodies and immunity development are comparable or superior to others. Further research on T cells and specific neutralizing components may be necessary to develop better protection against a threat. Although there are obstacles, it is encouraging to witness the advancements in research and development for a dengue vaccine, showing promising outcomes.

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