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Review Article

Mayaro virus (MAYV) Disease: Past, present and future

Rajni Yadav[1,*], Megha Jha[2], Shilpi Prasad[3], Diksha Jat[4], Deepak Kumar Jain[5]

[1]*Dept. of Pharmacology, Faculty of Pharmacy, Kalinga University, Chhattisgarh, India*
[2]*Dept. of Pharmaceutical Chemistry, Pinnacle Biomedical Research Institute (PBRI), Bhopal, Madhya Pradesh, India*
[3]*Siddhi Vinayaka Institute of Technology and Sciences, Bilaspur, Chhattisgarh, India*
[4]*Dept. of Pharmacy, Oriental College of Pharmacy, Bhopal, Madhya Pradesh, India*
[5]*Dept. of Medicinal Chemistry Research Laboratory, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur, Chhattisgarh, India*

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ABSTRACT

Mayaro virus (MAYV) has haggard increasing interest as an arthropod-borne virus causes eruptions among the human populations of the Western Hemisphere and is transmitted mostly by Hemagogus mosquitoes. MAYV travels in high-density tropical forests or rural areas of Central and South America origin a disease characterized by maculopapular skin rash, high-grade fever and manifest arthralgia that in some patients can continue for extended periods following infection and may be misunderstand as chikungunya. The virus stays alive in sylvatic cycles among mosquitoes and primate reservoirs such as marmosets. Though forest-residence mosquitoes are considered as imperative vectors for MAYV, it has been shown prior to that the virus can contaminate and potentially be transmitted by the mosquitoes, *Aedes albopictus* and *Aedes aegypti.* Although only a little eruptions involving MAYV have been accounted, in the previous years the number of MAYV illness has improved in the northern and central regions of Brazil and many part of world. Disease by MAYV can make mayaro virus disease (MAYVD) which is frequently a clinically identified, sharp, feverish illness connected with extended and painful joint inflammation and swelling. MAYVD may be clinically indistinguishable from chikungunya fever, malaria, dengue, rabies, measles or other arboviral diseases. The full range of disease, routes of infection, virus shedding, sequelae and any rarer means of spread remain undefined. At present, there are no precise marketable tools for the diagnosis of MAYV and utilize of serological methods can be exaggerated by cross-reactivity and the window period. A diagnosis based on clinical and epidemiological data alone is still premature. Therefore, new entomological investigate is necessary and new extremely precise molecular diagnostic methods should be urbanized. This paper presents a systematic and present review of the published MAYV literature ranging from its original report to current eruptions and from the essential virus traits to the clinical and epidemiological traits of this disease.

1. Intriducation

Arboviruses are a varied group of naturally happening viruses that can be transmitted among vertebrate hosts by hematophagous arthropod vectors. Since 1963, this categorization has been texted by the International Nomenclature Subcommittee Viral.[1] Nowadays, above 500 viruses are cataloged in the International Catalogue of Arboviruses and other vertebrate's viruses with about 150 species of arboviruses that taint humans and domestic animals.[2] The arboviruses have a large worldwide allocation and are present in about all continents,

* *Corresponding author.*
E-mail address: rajni.yadav@kalingauniversity.ac.in (R. Yadav).

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although they happen most commonly in the tropics.[3] In South America, many epidemics have been credited to arboviruses. In meticulous, Brazil has a topography that supports the extend of such viruses due to forests that wrap more than 1/3 of its territory, high density of species that dish up as vectors and a positive climate that create perfect conditions for the preservation of the viral cycle.[4] The arbovirus perseveres in natural world through life cycles that engross a diversity of hosts including bats, reptiles, birds, rodents, primates, among others, as well as numerous arthropod vectors such as ticks, black flies, mites and horseflies, but mainly mosquitos. For mainly arboviruses, humans are unintended hosts due to their presence in forested areas. The only exclusion is the dengue virus that utilizes humans as its main host to preserve cycles in urban and peri-urban areas.[5] There are many issues that decide and influence the biological cycle of arboviruses away from hosts, such as alters in the climate and ecological habitats that force viruses to regulate to new reservoirs and vector species, which change the prevalence of human infections and can increase the risk for the repetition of disease.[6] The clinical traits of arbovirus diseases are in common similar and include arthralgia, fever, encephalitis, rash, myalgia, hemorrhagic fever.[7] The lack of specific systemic symptoms makes it difficult to identify the etiologic agent in a clinical setting and many infections most likely pass without observe in the population, which jointly represents a stern public health problem.[6–10] The family Togaviridae has only 2genera, Alphavirus and Rubivirus, but they are accountable for a broad range disease. Viruses in both genera are spherical, tiny and enclosed that gauge between 60 and 70 nm in diameter[11,12] The genus Alphaviruses includes a varied group of 29 species that are nearly internationally distributed and include three major categories: aquatic viruses, arthralgic viruses and encephalitic viruses.[12] Apart from the aquatic virus, all others have invertebrate hosts and are considered to have great significance to public health. They include several infectious agents that are important human and animal pathogens, some with the potential to be used as agents of bioterrorism.[10,13] MAYV is an arbovirus transmitted mainly by the bite of female mosquitoes of the genus Hemagogus, typically from contaminated on-human primate like monkeys to a vulnerable human. These tree-residence mosquitoes are also the vectors worried in the sylvatic cycle of yellow fever virus and though MAYV preservation competence in main reservoirs is not known, it has been noticed in nature in numerous vertebrate hosts such as sloths, rodents, birds, non-human primates and other small mammals.[14] As for yellow fever virus, MAYV can taint humans who live in the rural areas or go into these forested areas either to work or to take benefit of the environmental attractions, leading to a fever is situation described by cutaneous rash, fever and joint pain. It was 1^{st} isolated in Trinidad (1954) from blood samples of rustic workers that had existing with fever.[15] The virus is found solely in the Americas, mainly in countries with widespread tropical forests, such as Trinidad and Tobago, Cooperative Republic of Guyana, Peru, Guyana, the Republic of Suriname, Venezuela, Panama, Costa Rica, Colombia, Mexico, Bolivia and Brazil[16–18] Evidence accrued over time explains that when a virus is initiated into new environments, new species of mosquitoes might be engaged in the transmission cycle[19,20] conversely, both ZIKV and CHIKV infections appeared in the Americas and speedily spread to dozens of countries, influencing millions of people from 2013-2018. These countries could at present become high-risk areas for MAYV infection, which may likely be misdiagnosed as CHIKV infection due to their similarities.[21] MAYV is the etiological agent of mayaro fever, also recognized as mayaro virus disease. Though, mayaro fever has also been introduced to Europe, as voyagers return home from widespread areas. Considering that MAYV has been co-isolated along with yellow fever virus from the similar invertebrate and that *Aedes* spp. have been accounted to be able to transmit MAYV in certain laboratory conditions, the urbanization of MAYV is likely and it has the potential to represent a real threat to the region of the Americas, especially if viral changes lead to more effective transmission by anthropophilic, urban mosquitoes.[22]

2. History of Mayaro Virus Fever

In the Amazonian rainforest, mayaro fever is frequently known as the jungle flu.[23] This virus was 1^{st} isolated in 1954 between febrile patients from the island of Trinidad. Casals and Whitman differentiated MAYV as an arbovirus intimately related to the Semliki Forest virus[24] which was afterward long-established by *Lavergne et al.*[25] Moving MAYV among vertebrate reservoirs, humans and non-vertebrate vectors has been accounted in Panama, Suriname, Brazil, Trinidad, Tobago, Bolivia, Ecuador and Venezuela. In addition, anti-MAYV antibodies have been reported among indigenous populations of Colombia, Panama, Peru, Suriname, Trinidad, Bolivia, Brazil, and Tobago, Venezuela, French Guiana and Mexico. MAYV has also been introduced into non-endemic areas including France (from French Guiana and Brazil), Germany (from Bolivia, French Guiana and Ecuador), The Netherlands (from Suriname and Brazil) and Switzerland (from Peru).[22] In addition, Mayaro infection has been often recognized among colonists of the Trans-Amazonian Highway in South America. MAYV eruptions were accounted in the Amazonian rainforest of Belterra, Brazil, in 1978. The assault rate of MAYV between immunologically virgin populations has been explained in eruptions among Okinawan settlers in Bolivia and in Dutch military troops in Suriname. The accounted assault rate among Dutch soldiers was 5.3 per 100 person/years at danger.[26] MAYV is a significant arbovirus in the

Amazonian area of French Guiana, with a sero prevalence of 6.3% between humans and 66% between non-human primates.

3. Mayaro Virus Biology

3.1. Genomic association and viral structure

The MAYV genome is composed of a positive-strand RNA of ~11.5 kb holding two open reading frames (ORFs). The 5′-proximal ORF encodes the nonstructural proteins, whereas the 3′-proximal ORF encodes the structural proteins. The nonstructural proteins are directly translated from the genomic RNA into one polyprotein, which is cleaved into 4 nonstructural peptides (nsP1, 2, 3 and 4). The structural proteins are translated from a sub genomic mRNA (26S mRNA), thus encoding a polyprotein cleaved into 6 proteins: capsid (C), envelope (E) E1, E2, E3, 6K and transframe (Figure 1).[27] The MAYV life cycle begins with binding of the viral envelope with an unidentified cellular receptor, followed by endocytosis of the virus into the cytoplasm.[28] After the virus go into the host cell, disassembly of the core and discharge of genomic RNA occur. Once in the cytoplasm, genomic RNA is translated into nonstructural proteins. These proteins then enable the processing of genomic RNA into sub genomic mRNA and additional translation into structural proteins. These are then processed and collected into a nucleocapsid and glycoproteins, which in involvement with the plasma membrane, outcome in the budding of the new virion particles.[27]

3.2. Phylogenetic studies

It using whole-genome sequencing have classified MAYV strains into 3 genotypes:

1. Genotype D mostly detached in South America and the Caribbean
2. Genotype L, partial to North-central region of Brazil and
3. Genotype N a recently described clade found only in a localized area in Peru.[29]

Phylogenetic analyses and nucleotide sequence homologies verify that MAYV belongs to the Semliki Forest complex. Moreover, analyses on the E1 region have shown that MAYV is linked to the Una virus, the only other South American virus linked with Old World viruses.[30] Based on these results and the Alphavirus 'variety and pathogenicity, it has been suggested that alphaviruses may have an Old World origin. The genotype L appears to be restricted to Brazil, suggesting a geographic restraint on MAYV dispersal. The detail that genotype L has not been establishing in other countries suggests a sampling bias rather than true viral strain subdivision.[29]

3.3. Cellular and molecular mechanisms of pathogenicity

Most of the information concerning the cellular and molecular mechanisms concerned in alphavirus-induced arthritis arrives from studies of RRV and CHIKV. Alphaviruses appear to distribute through the host via lymphatics and microvasculature after subcutaneous inoculation by a mosquito bite.[31] The blood carries most viruses, as free virions or in the form of tainted monocytes to target organs. The spleen and liver in turn are the sites where additional viral replication occurs contributing to virus propagation. Then, the virus arrives at the muscles, bones and articular tissues and produces the acute phase of the illness, which is powerfully linked with a local inflammatory process.[32] An inflammatory infiltrate wealthy in macrophages, monocytes, natural killer cells and $CD4^+$ and $CD8^+$ T lymphocytes, affecting the muscles and joints has been reported in murine models.[33–35] The in vitro study by Cavalheiro et al.[36] demonstrated that MAYV infection of macrophages leads to apoptosis. MAYV repetition in macrophages induces tumor necrosis factor (TNF) synthesis in association with fever since TNF promotes an inflammatory profile characteristic of arthritis. Furthermore, they observed an increase of reactive oxygen species (ROS) at early points of infection, which agreed with the acute phase of viral duplication followed by TNF secretion.[36] These verdicts were established by Camini et al,[37] who establish that MAYV induces significant oxidative stress in infected HepG2 cells. Inequity in the production of ROS and the cell's inability to detoxify these hasty species may be accountable for this status.[37] Furthermore, Santiago et al.[38] demonstrated those persons with established MAYV infection elicit a strong immune response, resulting in the discharge of pro-inflammatory immune mediators. During the acute phase of infection, various pro-inflammatory innate immune factors become active, such as interleukin (IL)-6, IL-7, IL-8, IL-12p70, IL-15, IP-10 and MCP-1. The chemokine MCP-1, which controls the immigration and penetration of monocytes and macrophages, is higher during the MAYV acute phase and persists at elevated levels for up to 6 months after infection. IL-2 and IL-9 are involved in cell proliferation and are also present at high levels during the recuperative phase, whereas IL-7 and IL-13 remain eminent awaiting 3 months post infection. Throughout the chronic phase, infected patients showed increased levels of IL-1β, IL-5, IL-10, IL-12p70, IL-17, interferon (IFN)-γ and TNF-α. Other immune mediators showed higher levels in the blood compared to healthy donors (e.g., IL-1Ra, IL-6, IL-7, IL-8, IL-13, IL-17, G-CSF, IFN-γ, PDGF-BB, TNF-α, VEGF and IL-12p70) despite of the phase of MAYV infection. The profile of these inflammatory mediators has been linked with the harshness and persistence of infection. Also, diverse chemokines stayed elevated in patients that developed persistent arthralgia: G-CSF, IL-1Ra, IL-8, IL-

17, IFN-γ, MCP-1, PDGF-BB and TNF-α. VEGF was also considerably elevated 3 to 6 months post infection. Based on these findings, Santiago et al.[38] recommended that, similar to CHIKV, the MAYV immune response is mostly inflammatory during the acute phase. However, the composition of elicited immune mediators is distinct.

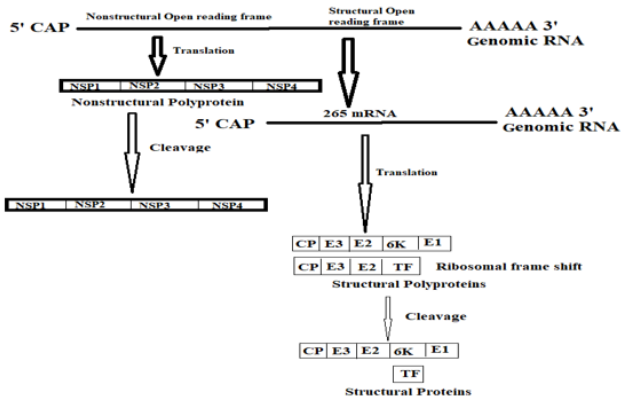

Fig. 1: Schematic diagram of the MAYV genome and proteins

4. Epidemiology

Most of the epidemiology data accessible are based on serological tests, which may be highly cross-reactive with other alphaviruses. The epidemiologic history of MAYV infection starts in 1954with its 1^{st} report in Trinidad and Tobago, when the virus was remote from blood samples of 5 rural workers that existing with a febrile disease. The virus received its name after Mayaro County, a southeastern region of Trinidad, where the cases were reported.[15] Since then, the virus has been accounted in some countries in Central and South America, usually in places with tropical forests, such as French Guiana, Venezuela, Mexico, Ecuador, Guyana, Panama, Bolivia, Peru, Suriname, Costa Rica, Guatemala, and Brazil. Imported cases are not very recurrent, but some have been accounted: North Americans visiting Peru and Bolivia; French citizens revisiting from French Guiana and Brazil; a German woman revisiting from Bolivia; a Swiss tourist visiting Peru; a Dutch couple revisiting from Suriname and some interstate imported cases in Brazil. The virus is considered widespread in some places of Brazil, such as the northern, central and western regions of the country. The 1^{st} case in Brazil was reported in 1955[39] next to Guama River, Para state and the 1^{st} plague in Brazil occurred in a village next to that river. A slight more than 2 decades after that, in 1978 in Belterra, Para, an out-break was explained with 55 established cases (43 with virus isolation and 12 with serological tests) from a total of 72 individuals with acute illness (fever and arthralgia were present in most of them).[40] Other2 eruptions have been reported by Vasconcelos et al.[41] in Conceicao do Araguaia in 1981 and Benevides in1991, both cities in Para state, northern Brazil and in Peixe, Tocantins state in 1991. In begin of 2008 an eruption broke out in a settlement in Santa Barbara and surroundings Para state. From a total of 105 individuals that reported a febrile condition in the past 30 days, 36 had IgM antibodies against MAYV.[42] It was reported the occurrence of IgM antibodies beside MAYV in 33 patients and viral genome was detected from one of them in Manaus, throughout an acute febrile eruptionin 2007-2008.[43] Also, throughout a dengue virus eruption in Mato Grosso, Central-West region of Brazil 15 out of 604 patients were positive for mayaro RNA detection during an acute febrile illness.[44] More recently, the state of Goias experienced another out-breaks of the disease and about 183 cases have been notified. From Dec. 2014 until Jan. 2016, a sum of 343 suspected cases were notified as a result of MAYV infection in Brazil, in which more than 50% were from Goias State. Some of those cases were initially reported as chikungunya infection, as both viruses are directly related to each other and there is antibody cross-reactivity in the accessible diagnostic tests. As verification for this cross-reactivity, a huge number of mayaro fever cases that occurred in this eruption were positive for both viruses by serologic tests. The rising occurrence of mayaro fever in areas of the country other than the northern region, where the illness is endemic, is a growing concern because this can point to that the virus is dispersal to other parts of the country and future epidemics may happen in Brazil in areas where healthcare workers are not common with mayaro fever clinical appearance.

5. Viral Replication

Like mostly arboviruses, the MAYV is able to taint and duplicate in cells from both vertebrates and invertebrates.[45] The mechanisms concerned in viral replication are not well known and numerous studies have tried to reveal the cellular responses concerned with infections by MAYV.[46] Studies have recognized that the morphogenesis location occurs in the cytoplasm.[47] Primary, internalization of MAYV proceeds through vesicles intended for endosomes where acidification changes the viral envelope, leading to its fusion with the endosomal membrane (Figure 2). This occasion is followed by the discharge of the nucleocapsid into the cytoplasm where ribosomes bind to the positive-sense RNA genome and start translating the encoded polyprotein.[45] The nonstructural proteins are the 1^{st} to be produced and a number of host proteins assist in the replication complex. The genome is then transcribed into a negative sense RNA whose synthesis ends 4 hrs after an infection. This negative sense is afterward used to produce a genomic 49S RNA as well as a 26S sub genomic RNA that serves as the template for the transcription of the viral structural proteins.[47] Throughout translation of the C protein, a proteolytic cleavage site is exposed that after proteolysis discharges a signal peptide for its translocation into the endoplasmic

reticulum. The envelope glycoproteins are synthesized, glycosylated in the Golgi complex and moved to the plasma membrane. Then, the capsid proteins endure self-assembly with the 49S genomic RNA and are linked with the regions containing the membrane envelope proteins. The maturation of the particles and budding happen mostly from vesicles with subsequent exocytosis of mature virions;.[48–50] Within invertebrate cells, infections can guide to the generation of inclusion bodies containing immature virions. The inclusion bodies have not been observed with budding virus. It is supposed that the discharge of virions occurs by exocytosis, due to the large aggregates of viral particles present in the extracellular medium. Exocytosis could be a significant mechanism for maintaining a state of MAYV unrelenting infection of invertebrate cells.[25]

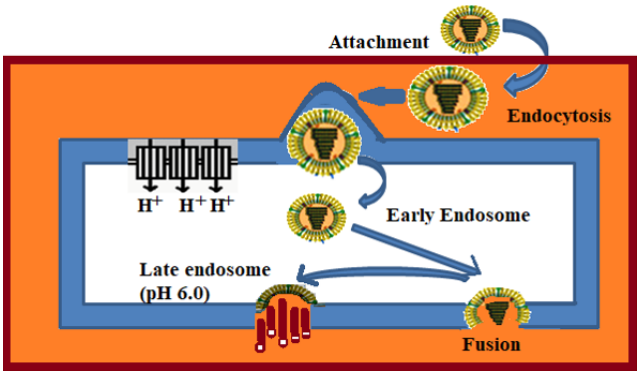

Fig. 2: Mayaro viral fusions in endosomal membrane

6. Modes of Transmission

The preservation cycle of MAYV look likes that of other arboviruses with a sylvatic cycle preserved in bloodsucking mosquitoes that serve as the vector to the wild hosts consisting of birds and non-human primates (Figure 3). Man is measured an accidental host from invading the habitat of sylvatic reservoirs.[16] From sero-epidemiological studies, the occurrence of MAYV in numerous mammalian species (agoutis, anteaters, marsupials, sloths, rodents) shows that vectors have a high aptitude to disperse the virus to a wide range of hosts, which cautions of the risks for new eruptions. It is worth noting the likely participation of synathropic animals in periurban environments.[50,51] Its major vector species is the mosquito *Haemagogus janthinomys*. However, other genera of mosquitoes are also recognized as vectors, such as *Culex* and *Psophors sabethes*. Some studies have recommended *Aedes aegypti* as a possible vector, which should be considered a chief public health problem as this mosquito is well adapted to the city environment. Also, there is the opportunity for the connection of mayaro fever with dengue through the use of the similar insect as a host.[52]

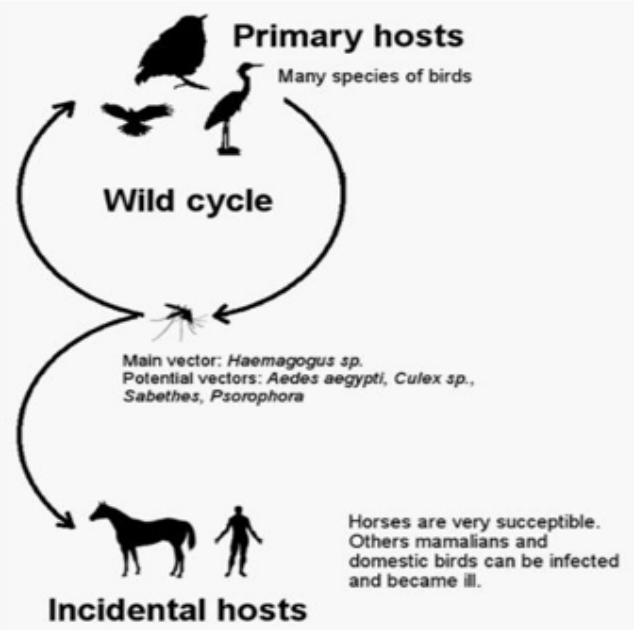

Fig. 3: Cycle of mayaro virus

7. Clinical Manifestations

The indications caused by MAYV are unfocused, mild and self-limited. Its clinical course is characteristically described as two phases: acute and subacute.[52] The acute phase is differentiated by a short, transient viremia (3-4 days), followed by an incubation period of 7-12 days, in which the systemic signs become clear. Among the common indications described in the textis a triad of sudden fever, arthralgia/arthritis and maculopapular rash often related to bleeding.[53,54] However, other indications can occur, such as retro orbital pain, headache, myalgia, vomiting and diarrhea. The fever can last 10 days and may recur after a period free of hyperthermia. This model can help to differentiate fever caused by MAYV from other arboviruses.[7] MAYV causes an acute debilitating disease and >50% of cases can be followed by long-term arthralgia. Comparable to CHIKV fever, joint pain can persevere for several months.[38] In addition, as with other Alphavirus infections, MAYV can produce harsh difficulties, such as irregular fever, neurological complications, myocarditis and even death.[55] Hemorrhagic signs are rare but have been explained by Mourao et al.[43] When an infection due to arbovirus is expected, the term ChikDenMa Zika syndrome has been recommended to indicate the common symptoms shared by CHIKV, DENV, MAYV and ZIKV infections given the pattern of co infection and co-circulation in South America. Some of these arboviruses can cause hepatitis, thrombocytopenia, lymphadenopathies and leukopenia. Particularly, there is a high possibility of misdiagnosis, particularly during early clinical stages, which constitutes a challenge.[56]

8. Diagnostic

Typically the diagnosis of mayaro fever relies only on clinical findings, which can cause MAYV to be misguided for dengue or other arboviruses.[57] The only gold standard method for MAYV diagnostic is the viral isolation from blood. However, the short viremic period can complicate the viral isolation. Typically, the viral isolation is performed in cellular culture of insect (e.g., Aedesalbopictus C6/36 strain) and mammalian cells (e.g., African green monkey kidney -Vero) or in suckling mice with intracerebral inoculation. The development of cytopathic effects requires at least 3 days.[58] Sensitive, inexpensive and easy tools as conventional polymerase-chain reaction and real time polymerase-chain reaction using generic primers for Alphavirus[59,60] or virus-specific primers are good choice for more reliable diagnosis of MAYV infections. However other methods as viral isolation or serological detections can also be used. Serological methods as enzyme-immune assays, immune fluorescence, haemagglutination inhibition or neutralization methods are useful for detection of antibodies against MAYV. IgM can be typically detected 3 days after the onset of the symptoms and persist up to 3 months, be replaced by IgG, which can persevere for years.

9. Treatment

Mayaro fever is a very incapacitating disease. In addition to the nonspecific and sublethal symptoms, it causes chronic arthralgia that may persevere for months after acute illness. As yet, similarly to other arboviruses, there are no precise drugs for MAYV fever treatment and only supportive care is accessible.[61] However, due to the pathological similarities between CHIKV and MAYV, numerous drugs used to treat chikungunya virus infection may be used to treat mayaro fever. The treatment of mayaro fever is based on pain and fever relief using analgesics (acetaminophen) and/or nonsteroidal anti-inflammatory drugs (mostly ibuprofen, diclofenac or naproxen) have also been used.[58] Corticosteroids (prednisolone, up to 40 mg/day) have been administered in a few cases; however, there is no proof of efficacy. Chloroquine (150 mg of base/day) was found to be effectual in treating the persistent and debilitating arthralgia associated with mayaro fever.[62] Treatment with ribavirin (200 mg twice per day for 7 days) has been effective relieving some signs of chikungunya fever symptoms, such as pain in the lower limbs[63] and can be useful for mayaro fever. In in vitro studies, ribavirin showed to act synergically with IFN-α inhibiting replication of CHIKV, thus could be used to inhibit replication of MAYV. Passive immunization has been proposed for the treatment of several alphavirus-mediated infections particularly for chikungunya and could be extensive to treat mayaro fever. The clinical signs and symptoms caused by mayaro virus infection are similar to those induced by other alphavirus as chikungunya and ross river viruses, therefore it is supposed that pathology of these viruses is also similar. However the effectiveness of transferred antibodies is not fully understood. In an animal model, human plasma from patients with previous CHIKV infection has high neutralizing activity in vitro. However, in B cells knockout mice, chronically infected with CHIKV, the treatment with mice polyclonal antibodies anti-CHIKV was capable to clear the infection only for a short period.[64]

10. Vaccine

Due to the limited area of MAYV circulation, there have been few efforts to develop a vaccine and as such, there is currently no licensed vaccine available for MAYV infection. Only 2 approaches to develop a vaccine have been described in the literature. The first attempt was performed in 1976 and employed a wild-type (wt) MAYV strain (strain TRVL15537) that was inactivated by formalin. This vaccine candidate was tested in immune competent CD-1 mice in a single vaccination. This strain established to be immunogenic and showed some efficacy in a lethal challenge following a passive transfer of immune mouse sera to infant mice.[65] The second vaccine candidate was based in an attenuated strain; however, the attenuation was achieved replacing the mayaro viral internal ribosome entry site (IRES) by the IRES from the encephalo myocarditis virus. The substitute of the sub genomic promoter leads to expression of the structural proteins via the IRES from the genomic RNA, which causes a reduction in the translation of these proteins. Additionally, the incompetent recognition of the IRES by insect ribosomes results in a phenotype that is unable of replicating in mosquito cells. This approach was established to be successful for the formation of other alphavirus vaccines.[66]

11. Vector Control

Due to the lack of validated vaccines, the present manage strategies for MAYV rely on reducing human contact to infected mosquito vectors. Humans are regarded as accidental hosts and MAYV is restricted to an enzootic cycle in forest/rural areas. Therefore MAYV only has the opportunity to infect individuals who make use of the areas where the mosquitoes are plentiful.[66] To prevent contact with mosquito vectors it is important to avoid these areas as much as possible. Aedes sp mosquitoes act as vectors for many arboviruses as DENV or CHIKV and due to urbanization potential can also transmit MAYV.[52] Programs for the control of these mosquitoes can be also useful not only for mayaro fever but also to control other arboviruses. Entomological and epidemiological studies must be conducted to decide the endemic areas of mayaro virus movement and the real risk of broadcast to the

population. Such studies would be useful to guide public health policies.

12. Public Health Interventions

Public health observation systems are important for the early recognition of virus outbreaks. Once recognized, it is necessary for healthcare providers and public health officials that local health authorities establish a rapid and violent control response to mosquitoes.[62] Some countries have developed and implemented an early warning system that can forecast epidemics by arbovirus derecognize high-risk zones for transmission and intensification of the agent and acquire information on meteorological and spatial factors that could influence vector dynamics[67,68] Beyond detecting the number of cases, it should be noted that voyagers can potentially act as sentinels for rising infectious diseases. MAYV infection should be considered in cases of patients who have recently visited tropical areas in South America. Regarding this finding, a partnership should be developed between public health surveillance systems and transportation companies to provide epidemiological control.[53] Digital participatory observation systems may be used to notice real-time incidence of symptoms well-matched with arboviral diseases and other tropical imported diseases. Enduring epidemiological and entomological studies should be carried out to decide MAYV endemic areas and the danger of broadcast to human hosts, particularly in countries close to regions where the disease has previously been confirmed. The interactions of the environment, including the vector, natural history of MAYV and host are reflected in Figure 4.

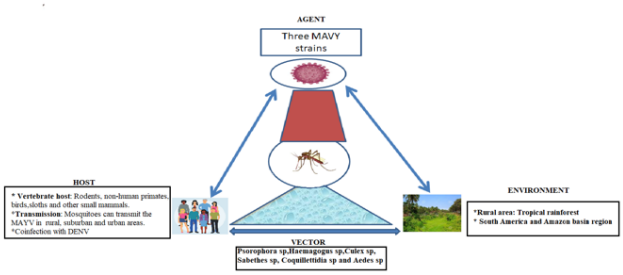

Fig. 4: Public efforts on MAYV infection should focus not only on the vector, but on the host and its environmental surrounding

13. Immune Response

Cellular and humoral immune responses are significant in the manager of primary infections with alphavirus.[12] In the cellular immune response, the active involvement of cytotoxic T lymphocytes is significant for the lysis of infected cells and to create γ-interferon for activation of macrophages for the creation of other cytokines. These responses can sway viral replication and accordingly, the severity of the disease.[46] Studies have showed the survival of antigenic sites in common among alphaviruses. Several authors have reported that, in general there are more antibodies directed against the structural protein E2 than to E1 protein, possibly because the E1 protein is more conserved. In addition, neutralizing epitopes have been explained as well as epitopes that interact with specific antibodies. For Sindbis virus, a neutralizing epitope was predictable in a linear stretch of E2 (aa 170-220) that is exclusive for alphaviruses. However, numerous epitopes are reliant of structural conformation of the protein to be reactive to antibodies, as in the example of the E1 protein. For the E2 protein, numerous studies show a need exists for denaturing or disintegration of peptides for some their interaction with host antibodies. The look and perseverance of antibody in hosts can vary significantly between patients. Also, an infection with MAYV is able of inducing antibodies IgM, which are usually transient and indicative of current infection, but may persevere for at least 90 days after the beginning of symptoms. In secondary infections, IgM creation can occur at low levels. However, IgG, which perseveres throughout the life of the host, can be an exceptional marker of the reoccurrence of an infection when establish in high levels. Infections by MAYV are increasingly being considered a severe public health problem in rustic areas and jungles of South America and can be simply puzzled with other arboviruses. There is a risk of MAYV becoming dispersed within city areas due to numerous factors: the development of ecotourism, increased tenancy and the opportunity of Aedes aegypti become a vector MAYV. Moreover, the MAYV has been slight studied and though the proteins E1 and E2 have been recognized as the mainly immunogenic in alphaviruses, small is known about the structural composition and antigenicity of other viral proteins. The applications of a variety of proteomic tools including the microarray of epitopes can clarify the recognition of antigenic determinants, their molecular structures and their interfaces with the humoral immune system to improve the knowledge on the immunogenicity of each viral protein.[69]

14. Conclusion & Future Perspective

MAYV is a neglected tropical disease that needs further investigation. It is endemic in areas of low socioeconomic determinants, which are typically described by a low investment in research, surveillance and control of outbreaks. In many of the regions where MAYV is endemic, the diagnosis of mayaro fever relies only on clinical findings, which can cause MAYV to be mistaken for DENV or other viruses resulting in an underestimation of MAYV infection rates.[57] The development of vaccines or specific drugs depends on research, which often relies on government funding. As there are presently no efforts to detect MAYV, there is little inducement to invest in MAYV

research. This fuels a vicious cycle in which low detection rates lead to few investments in the disease. Furthermore, many of the studies about MAYV present low quality, simply describing case reports. There is an imperative require for more epidemiological studies to assess the actual prevalence and incidence of this disease in South America. Currently, several in vitro studies on antiviral drugs are being conducted in animals and insect cells. Cassiaaustralis extracts,[70] bovine lactoferrin,[71] prostaglandins (PGA1 and PGB2),[72,73] cerulenin[74] and weak bases such as ammonium chloride and chloroquine[46] have been tested with some degree of achievement. The use of ribavirin has been shown to affect viral replication, although further studies are required to confirm its effectiveness.[70] Innovative techniques for diagnosis as Luminex[75] or new generation sequencing[76] have been described for several alpha virus and can be adapted for diagnosis of MAYV infections. The development of a potential vaccine for MAYV may help to control the virus; however, this is dependent on the right evaluation of its prevalence.

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16. Conflict of Interest Statement

The authors declare no conflict of interest, financial or otherwise.

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Author biography

Rajni Yadav, Assistant Professor https://orcid.org/0000-0002-6454-2562

Megha Jha, Senior Scientist

Shilpi Prasad, Principal

Diksha Jat, Assistant Professor

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