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Review Article

Global Impact of Mosquito-borne Alphaviruses on Humans: Their Spread and Rehabilitation

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A B S T R A C T

Alphaviruses of the family *Togaviridae* are mostly arboviruses with worldwide distribution and are maintained in nature by reservoir hosts and mosquitoes in an enzootic cycle. Spillover events occur in the form of local outbreaks or epidemics involving human beings. These may cause arthritis or encephalitis which might be fatal. We have comprehensively reviewed the structure of the human pathogenic alphaviruses with the functions of individual proteins, and the life cycle events of alphaviruses with a special emphasis on the difference in these events in the case of vectors and hosts, and diseases produced by them along with the pathogenesis. Molecular-level studies of these viruses, the phylogenetic evolutionary events, and various measures being taken to prevent or control the infections caused by these viruses in humans are also discussed in this review article. The recent outbreaks of alphaviral infections demand in-depth knowledge of virus-host interaction at the molecular level and the development of better drugs to control the infections.

Keywords: Alphavirus, Disease, Host, Phylogenetic, Vaccine, Vector

Introduction

Viruses, the obligate intracellular parasites, are of various types depending on the nature of their genetic material (genome) like RNA viruses (single-stranded or double-stranded), DNA viruses, or retroviruses. They rely on host cellular machinery to replicate and synthesise viral components. The newly identified viruses differ in their pathogenicity and may be responsible for illnesses ranging from mild to serious.[1] Viruses can be transmitted in various modes through vectors, e.g., mosquitoes, ticks, fleas, or through air, water, food, fomites, blood transfusion, close contact such as sexual transmission etc.[2] A majority of alphavirus species have been reported to infect mammals as well as birds. The carrier organism responsible for the spread of alphaviruses is the mosquito.[3] Alphaviruses commonly pathogenic to human beings are Barmah Forest Virus (BFV), Chikungunya Virus (CHIKV), O'nyong-nyong virus (ONNV), Sindbis Virus (SINV), Semliki Forest Virus (SFV), Ross River virus (RRV), and Mayaro virus (MAYV). They cause febrile illness with rash and arthritis. Encephalitis-causing alphaviruses are Venezuelan equine

encephalitis virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), and Western equine encephalitis virus (WEEV). Alphaviruses can be divided into two groups based on their geography (origin), severity of infection, and mechanism of infecting the host. The two groups are called new-world alphaviruses and old-world alphaviruses. Viruses like SINV, SFV, and CHIKV that use nsP2, one of the non-structural proteins (nsP) to downregulate host transcription, cause arthralgia, and have low mortality rates, come under the group old-world viruses. The new-world group of viruses downregulates the host cell transcription with the use of their Capsid Protein (CP) causing more fatality. This group includes viruses like VEEV and WEEV, which are major causes of sleeping sickness.[4] Another classification is based on antigenic cross-reaction. The two glycoproteins E1 and E2 form the basis of various serological tests.[5] There is a risk of future outbreaks of these viruses in different geographical areas due to the adaptation of these viruses to different mosquito vectors even with a single mutation (e.g., CHIKV IOL lineage with mutation E1-A226V adapted to a new vector *Aedes albopictus*, which is prevalent in cooler geographical areas in contrast to *Aedes aegypti*). So, to prevent such outbreaks and develop better preventive and therapeutic strategies against alphaviruses, there is a need to review these viruses in detail.

Structure of Alphavirus and Functions of Its Various Components

Structure

Alphaviruses have an icosahedral structure, approx. 70 nm diameters and a 5'capped and 3' polyadenylated genome. Alphavirus particles show a Svedberg coefficient of 280S and a buoyant density of 1.15–1.22 g/cm^3 in a sucrose gradient.[6] The viral genome ranges from 9.7 to 12 kb in length with an intergenic sequence connecting two Open Reading Frames (ORFs).[7,8]

In most of the alphaviruses, out of the two ORFs, 5' ORF (7 kb) encodes a polyprotein consisting of four non-structural proteins namely nsP1, nsP2, nsP3, and nsP4, which are involved in a replicative complex. The sub-genomic RNA (26s) of 4 kb encodes for an organisational protein, which is divided to form E1, E2, E3, Capsid (C), and 6k/TF as shown in Figure 1, interacting to form a virion envelope.[8] The surface of the virion particle has 80 trimeric spikes of heterodimers of E1 and E2 glycoproteins.[9] The positive sense single-stranded RNA genome of SINV allows a relatively large genome packaging capacity for proteins up to 5 kb.[10] WEEV is a hybrid with sequences derived from the Sindbis virus.[11] In VEEV, there are five structural proteins, which are considered as main targets for the acquired immune system.[12]

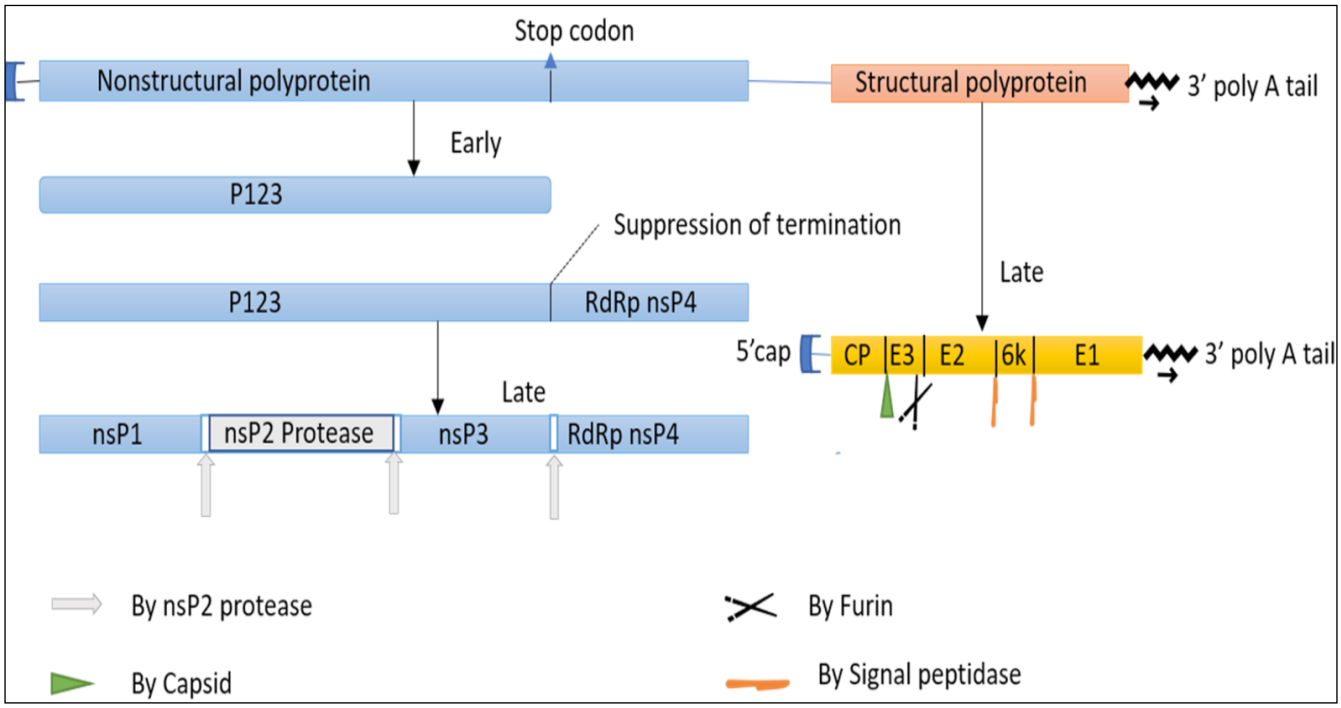

Figure 1.Event of Viral RNA Translating into Non-structural and Structural Polyproteins During the Early and Late Phases of Infection. The Non-structural Polyprotein is further Processed into Various Non-structural Proteins (nsP1, nsP2, nsP3 and nsP4) and Structural Polyprotein is Cleaved into Capsid Protein (CP), 6K, and Envelope Glycoproteins (E1, E2, and E3).[7]

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Functions

Non-Structural Proteins

Non-structural protein nsP1 is the major anchor protein of the replication complex and has guanine-7-methyl transferase (MTase) and guanylyl transferase properties required to enclose the viral RNA.[13] nsP2 has RNA helicase activity and acts as a viral protease for non-structural polyproteins.[14] nsP2 has a methyl transferase-like domain[15] in addition to its helicase and protease activity. It also obstructs the synthesis of host cellular macromolecules, thereby hindering various antiviral responses.[16] Non-structural protein, nsP3 , is essential for the function of RNA replicase although its function needs to be explored further.[17] GDD motif in nsP4 suggests that it has RNA polymerase function.[18]

Structural Proteins

Structural proteins capsid comprises three domains. Domain I (1–80 amino acids), in association with domain II (81–113 amino acid residues), helps genomic RNA and domain III (114–264 residues) in proper folding. Domain III of capsid protein has serine protease activity of CP.[19] Another important protein among structural proteins is 6k. It is a protein with a molecular weight of 6000 Da. About 30 copies of 6K are incorporated into virions[20] which perform palmitoylation at conserved cysteine residues, leading to the formation of infectious particles.[21] Dey et al. reported the structure of the 6K protein of CHIKV for the first time using techniques like electrophysiology, confocal and electron microscopy, and molecular dynamics simulations and found it to be an ion channel-forming protein.[22] E3 protein helps in efficient particle assembly and mediates spike folding and activation; E1 protein initiates the interaction between viral and host endosomal membrane; and E2 is responsible for interaction with host cell receptors.[7]

Hosts and Vectors of Alphaviruses

The spread of most alphavirus infections between the hosts is carried by a mosquito, except the Buggy Creek virus and the Southern elephant seal virus. The vectors for these two viruses are swallow bugs and seal lice, respectively.[23] The primary vectors for SINV reported in Finland were *culex* and *culiseta*, whereas grouse and passerines were the amplifying hosts in northern Europe. Migratory birds might also be playing a role in spreading the disease.[24]

ONNV is transmitted by *Anopheles gambiae* or *Anopheles funestus,* with humans thought to be the only natural hosts. Heat shock cognate 70B protein of mosquitoes has been reported to suppress the replication of ONNV, so these mosquitoes act as asymptomatic vectors.[25] The most common mosquitoes transmitting RRV are *Ochlerotatus vigilax*, *Ochlerotatus camptorhyncus*, and *Culex annulirostris*.[26] The main vertebrate hosts for RRV are non-migratory macropods like kangaroos, wallabies, New Holland mice, and flying foxes.[27] The first isolation report on BFV from vector *Culex annulirostris* came in 1974 in the state of Victoria in Barmah Forest and from southwest Queensland Australia simultaneously.[28,29] MAYV in forest areas is transmitted by the mosquitoes of genus *Haemagogus*, but it can also be transmitted by *Aedes aegypti* making it a potential threat to the health of people[30] shown in Table 1.

Table 1.Hosts, Vectors and Diseases related to the Alphaviruses

Name of Alphavirus	Natural/ Reservoir Host(s) (Confirmed/ Putative)	Common Vectors (Confirmed/ Putative)	Diseases in Humans
Barmah Forest Virus (BFV)	Brushtail possums, horses	*Culex annulirostris, Aedes vigilax*[29]	Fever, rash, myalgia, arthritis
Chikungunya Virus (CHIKV)	Baboons, Cercopithecus monkeys	*Aedes aegypti, Aedes albopictus*[31]	High fever, severe joint pains, chronic recurrent polyarthralgia
Eastern Equine Encephalitis Virus (EEEV)	Birds,[27] horses	*Culiseta melanura*[32]	Encephalitis, muscle pain, fever
Mayaro Virus (MAYV)	Marmosets[33]	*Heamagogus janthinomys*[34]	Self-limited dengue-like illness along with long-lasting arthralgia
O'nyong-nyong Virus (ONNV)	Not known	*Anopheles funestus, Anopheles gambiae*[35]	Fever, rash, polyarthritis (weakness of joints), lymphadenitis etc.

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Ross River Virus (RRV)	Marsupials like kangaroos, wallabies, New Holland mouse, flying fox[27]	*Aedes vigilax, Aedes camptorhynchus, Culex annulirostris, Aedes notoscriptus*[36]	Arthritis, rash, lymphadenitis
Semliki Forest Virus (SFV)	Horses, monkeys	*Aedes abnormalis group, Aedes argenteopunctatus,*[37] *Aedes africanus, Aedes aegypti*[38]	Mild disease in humans (used as a model virus for research)
Sindbis Virus (SINV)	Birds	*Culex torrentium, Aedes cinereus, Culiseta morsitans*[39]	Arthralgia, fever and rash
Venezuelan Equine Encephalitis Virus (VEEV)	Rodents, birds, horses	*Culex taeniopus, Aedes taeniorhynchus*[40]	High fever, headaches, fatal for immunocompromised individuals
Western Equine Encephalitis Virus (WEEV)	Birds, humans, horses	*Culex tarsalis*[41]	Rare, Western equine encephalitis

The reported vector for EEEV is *Culiseta melanura* maintaining a bird-mosquito-bird cycle,[25] and a possible bridge vector is Ae. *vexans*[31]. The vector for WEEV is primarily *Culex tarsalis*. A cycle of wild birds and mosquito infectivity is maintained, with mosquitoes acting as vectors and birds as reservoirs.[11]

Transmission of Alphavirus between Host and Vector

After a blood meal, the alphavirus in mosquito vector interacts with the mid-gut epithelial cells, enters into the cells via a receptor-ligand interaction,[14] replicates there, and escapes into the haemolymph (Figure 2) from where it can reach other tissues. The importance of the E2 glycoprotein of the virus in this interaction was evident when a SINV strain MRE16 infected the *Aedes aegypti* mosquito efficiently after a blood meal, but its variant i.e., MRE16sp (sp-small plaque) was found to poorly infect the mosquito after a blood meal. Genomic sequencing of both these types indicated deletion of 90 nucleotides in E2 glycoprotein spanning the 3' end of the coding region for putative cell receptor binding domain (CRBD) in MRE16 sp. Infectious clones were prepared with or without deletion or with partial deletion to understand the role of this deletion and a reduced midgut infection and a lower spread of infection in *Aedes aegypti* were reported from deletion mutants but intrathoracic inoculation led to the production of similar viral titers with all clones in the mosquito. This was indicative of the important role of E2 CRBD in MRE16 in mid-gut infectivity in Aedes aegypti.[14] On reaching the salivary glands, it replicates and can be transmitted into a vertebrate host through the saliva of the vector.[42,43]

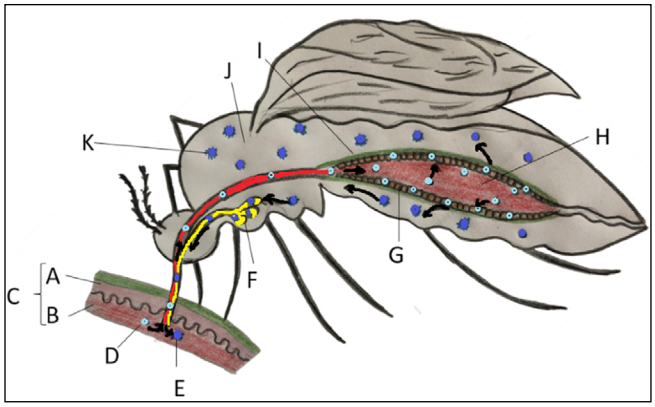

Figure 2.A Diagrammatic Representation of Alphavirus Entering and Leaving the Mosquito (Vector) (A: Epidermis, B: Dermis, C: Skin of the Host, D: Virus Particle Entering the Blood Meal of Mosquito, E: Virus Particle Entering the Host through the Saliva of Mosquito, F: Salivary Gland, G: Midgut Epithelium, H: Blood Meal, I: Basal Lamina, J: Haemocoel, K: Virus Particle)

Mosquito saliva containing enough virus particles transmits the virus during feeding by enhancing vasodilation and preventing blood coagulation in the host.[44] SFV was inoculated subcutaneously alone and also with mosquito bites of *Aedes aegypti* in a mouse model. The bite had a significant impact on enhancing virus replication probably due to delayed innate immune activation, neutrophil influx, and late response of bite-associated genes; although there was no effect on skin antiviral immune response.[45]

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Life Cycle of Alphavirus

Attachment of Virus to Host Cell Receptors

The virus induces its attachment to the host cell receptors via E1 and E2 glycoproteins.[46] Various receptors have been reported including divalent metal ion transporter natural resistance-associated macrophage protein (dNRAMP) in Drosophila cells and adult flies and NRAMP2 in mammalian cells (SINV),[47] Laminin receptors (SINV) in mammalian and mosquito cells[48] and heparan sulfate proteoglycan[49,50]. SFV and RRV use dendritic cell-specific ICAM-3-grabbing non-integrin (DC-sign)[51] and collagen-binding alpha1 beta1 integrin respectively. E2 glycoprotein is a highly conserved host cell recognition protein among various species of alphaviruses. Their unique properties include ubiquitous nature, species tropisms, and expression of proteins like NRAMP2.[48]

Entry and Release of Nucleocapsid

Binding with the receptor is followed by endocytosis in a clathrin-dependent manner[52] as shown in Figure 3, except for MAYV using caveolin-coated pits[53]. Low pH levels of the endosome induce the expression of the fusion peptide of E1 and virion's structural rearrangement.[54] The entry of fusion peptide into an endosomal membrane helps nucleocapsid (NC) to enter into the cytoplasm. The viral RNA is reported to assemble viral replicase complexes on lysosomal and endosomal membranes.[55,56] After the initial processing of non-structural polyprotein, P123 + nsP4, and nsP1 + P23 + nsP4 form early replication complexes responsible for synthesising negative-strand RNA.[57] The last cleavage event at the P2/3 junction forms mature nsPs, which form positive strand replication complexes along with host cell proteins. The synthesis of the minus-strand marks the initial stage of infection, followed by the synthesis of sub-genomic RNA and a plus-strand[9] as shown in Figure 3.

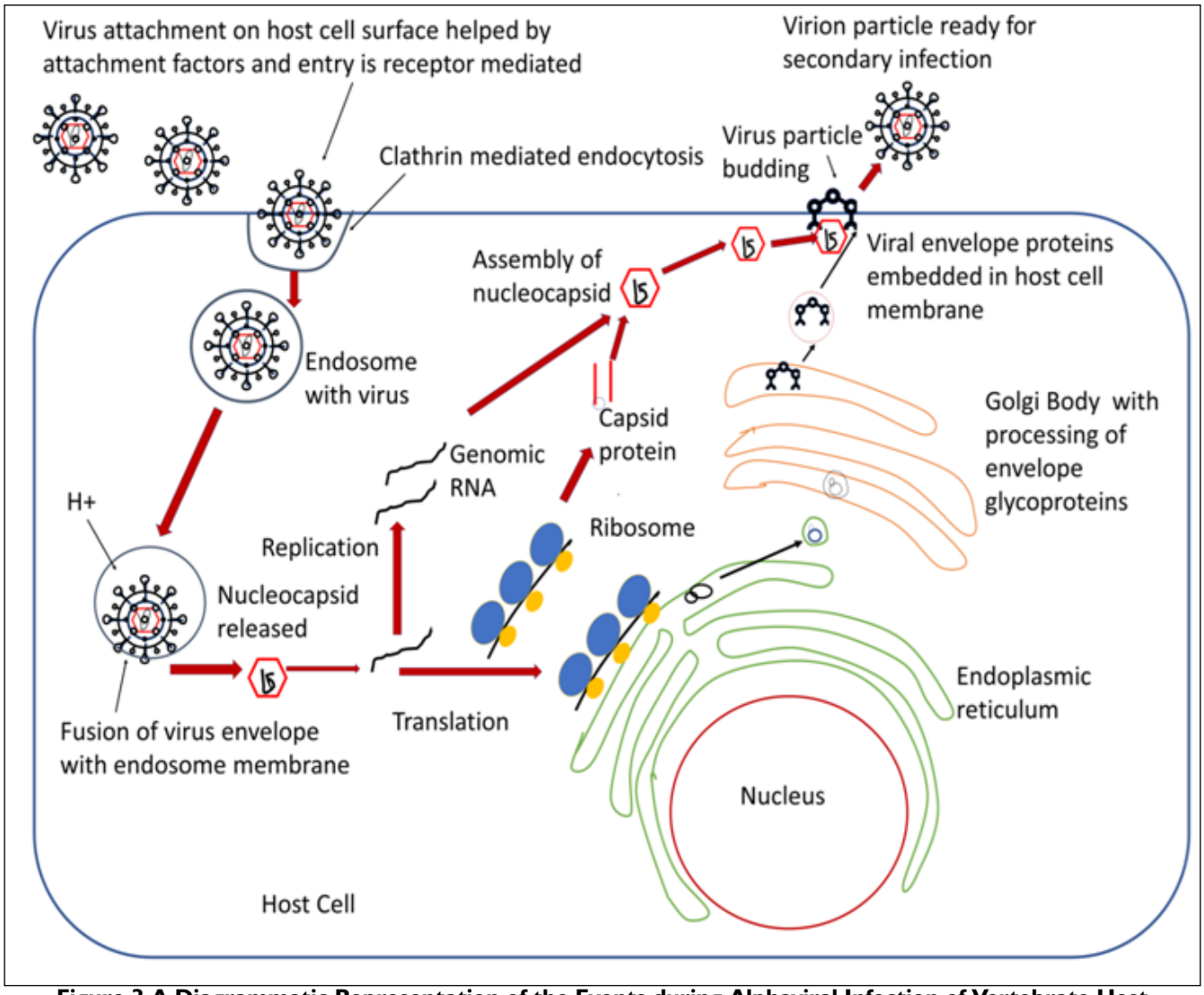

Figure 3.A Diagrammatic Representation of the Events during Alphaviral Infection of Vertebrate Host Cells

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Formation, Transport, and Budding of Viral Particles

Translation of structural proteins occurs from sub-genomic RNA. Capsid protein gets cleaved from the structural polyprotein co-translationally[8] and then a full-length viral RNA along with NCs assembles from 120 dimers of capsid proteins,[58] and E1, pE2 (E2 precursor protein), and 6K enter the plasma membrane via a secretory pathway after exiting the endoplasmic reticulum (Figure 3). The cleavage of pE2 into E2 and E3 with the help of furin initiates viral infection.[59] NCs' interaction with the cytoplasmic domain of E2 helps it to get enclosed by E1/ E2 icosahedral structure.[7] 6K protein forms cation-selective ion channels in mammalian host cells.[60] Jose et al. have reported live cell imaging and electron microscopic analysis of replication complexes to study the life cycle of alphavirus.[61]

Diseases Caused by Alphaviruses

WEEV, EEEV, and VEEV can produce lethal encephalitis in horses and humans with variable progression of the disease. The overall case-fatality rate of WEEV is 4%.[11] EEEV infection is responsible for very few cases per year in the US, with encephalitis cases showing high mortality (30%–70%) and neurological sequelae in survivors.[62,63] An epizootic disease is mostly produced by VEEV with 1% mortality.

Arthritogenic alphavirus infection leads to fever, skin rash, myalgia, and arthralgia.[64] A case of fatal SFV neurovirulent laboratory strain causing meningoencephalomyelitis and the death of a laboratory worker has been previously reported.[65] Avirulent strains cause non-lethal demyelinating disease for about 30 days.[66] ONNV infection is characterised by fever, symmetrical polyarthralgia, lymphadenopathy, maculopapular rash, joint pains, redness and pain in the eyes, and general malaise (usually self-limiting).[67] BFV causes disease just like RRV but with milder symptoms. BFV is also a pathogen of public concern.[68]

Pathogenesis of Disease in the Susceptible Vertebrate Host

The pathogenesis of the alphaviral diseases in humans can be attributed partly to the direct cytopathic effects of the virus particles invading the host cells and partly to the inflammatory and immune responses generated because of the alphavirus infection. Studies in SFV-infected adult mice have shown the ability of alphavirus to cross the blood-brain barrier and have confirmed their presence in endothelial cells of the brain.[69] These viruses are also reported to spread through infected blood cells, like leukocytes, monocytes, and WBCs or through olfactory neuroepithelium, tooth pulp and subsequent spread through trigeminal nerve.[70] It has been reported that mutation of E2 glycoprotein at position 55 where glutamine is replaced by arginine reduces the neuroinvasive capacity while a single amino acid, Thr at position 538 in nsP1 protein was vital for neurovirulence in adult mice replacing threonine with isoleucine at this position in nsP1 attenuated neurovirulence.[71] In RRV disease, a cell surface marker F4/80 for monocytes and macrophages at the peak time of the disease with decreased viral titers pointed to the role of macrophages in damaging the muscle tissue.[72,73] In new-world alphavirus encephalitis, various regions of the brain show symmetric or asymmetric lesions.[74]

Basis for Maintenance of Infectivity in Mosquito Vector

The basic difference in the virus entry into the invertebrate (insect) cell is that the virus envelope fuses with the plasma membrane leading to penetration and uncoating of virus particles rather than endocytosis as seen in vertebrate cells and is proved by an experiment using WEEV and three strains of Culex tarsalis.[75] Alphavirus protein interaction with cellular factors is indicative of different activities in vertebrate and invertebrate hosts as proven using engineered viruses with tagged non-structural proteins.[76] Virus maturation can occur in different ways in cultured insect cells. It can be very similar to the process in the cultured vertebrate cells, with budding on the cell surface and nucleocapsid inside the cytoplasm or the budding at the cell surface as observed in a few cells.[77] In Aedes albopictus cell populations, clones of individual cells differed in producing virions. Cells producing lower yields did not show cytopathic effects and maintained their function in the presence of virus replication, suggestive of the maintenance of infective virus particles in the mosquito cells during the interepidemic period.[78] The whole insect shows no harmful effects of virus infection and passes the virus transovarially to their offspring, whereas vertebrate cells show cytopathic effects on alphavirus infection due to shut shutdown of the transcription and translation machinery.[79]

Molecular Studies of Alphaviruses

Certain experimental studies have revealed the importance of point mutation in the genome sequence of alphaviruses, which might be responsible for attacking the immune system of the host organism inducing an immune response. Genes sequence analysis of SINV strain S.A.AR86 along with three mutant strains showed a single point mutation in E2 glycoprotein where asparagine replaced serine in the native strain. Mutant virions contained pE2 rather than E2 and lost

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the ability to bind to R6 and R13 E2-specific monoclonal antibodies.[80] The importance of a stop codon in altering the level of infectivity of alphaviruses was revealed in a study for the first time indicating the functional significance of the Opal stop codon in the ONNV genome on the infectivity of virus in a natural mosquito host (*Anopheles gambiae*). Mutants were created with point mutations replacing arginine between nsP3 and nsP4 with stop codons, i.e., opal, ochre, or amber. Mutant having stop codon opal upstream of nsP4 increased the infectivity of ONNV to double compared to the normal virus strain having arginine at the corresponding position.[42] To understand the events during the budding of the virus particles, a pseudoatomic model of SINV was constructed at 7 Ångström resolution with a focus on the sites of interaction between CP and transmembrane E1 and E2 glycoproteins. Three contact regions between the cytoplasmic domain of E2 (cdE2) and CP were identified, which are important for virus assembly.[81]

The functional importance of glycoprotein E3 was explored by constructing chimeric viruses with E3 protein swapping between alphavirus species belonging to the same clade and between species belonging to different clades. Intraclade chimaeras produced infectious viruses at the same rate as the parent virus, whereas the rate was reduced for interclade chimaeras.[82] To study the infection pattern in *Anopheles gambiae*, the vector was infected in *vitro*. The experiment showed that the increase in infection was controlled by the nsP3 region similar to the wild-type ONNV. In chimaera, when nsP3 of ONNV replaced the nsP3 region from CHIKV, the infection rate in *Anopheles gambiae* increased from 0% to 63.5%.[83] The role of Sorting Nexin 5 (SNX5), a host factor, in the replication of alphaviruses was reported. Also, virions expressed in all host cells showed the presence of SINV nsP2.[84]

Phylogenetics

A phylogenetic analysis of alphaviruses was performed to discover their origin. The phylogenetic trees of alphaviruses constructed by including E1 and E2 genes were very different from the ones constructed according to non-structural gene sequences. Phylogenetic analysis based on the E1 gene tree shows that new-world viruses like WEEV have extended from old-world virus complexes like SINV. Another phylogenetic study had shown an independent divergence of EEEV and VEEV species and no relation to old-world virus complexes like SFV, CHIKV, and RRV.[85]

Phylogenetic analysis has evaluated the genetic distinctiveness of Venezuelan alphaviruses which were isolated between the years 1973 and 1999. Studies showed the dominance of the VEEV subtype IAB strain a decade after an epidemic took place. Faragher and Dalgarno identified RRV of three genetic types with each having two subtypes with no link to the source i.e., host/ vector or geographical origin.[86] A lot of variations were found in the 3' untranslated regions of the sequences of RRV belonging to three genetic types. Genome-scale phylogenetic analysis of RRV revealed that the lineages diverged from a common ancestor 94 years ago. The findings did not support the earlier geographic distribution. Further genomic sequencing from a wide spatiotemporal range was suggested to monitor the evolution of RRV.[87] The phylogenetic analysis revealed a slow evolution of EEEV and its constant presence and transmission among the animals in Florida. The virus possessed tenacity with high genetic divergence.[88] Although studies on phylogenetic analysis of alphaviruses are being conducted, there is a need to understand the basis of this evolution by comparing the codon and AA usage in alphaviruses and their respective hosts and vectors.

Epidemiology of Alphaviruses

In August 2004, the CHIKV infection was transmitted by *Aedes* mosquitoes in tropical Africa and Asia.[89] In 2015, at least 25,000 suspected cases and almost 3,500 laboratory-confirmed cases of CHIKV were reported in India, and in 2018–2020, the number of suspected cases rose to 170,000 with 27,120 confirmed cases in India. Outbreaks of CHIKV were reported in 2017 in Bangladesh and Pakistan, in 2019 in Myanmar, and in 2018–2020 in Thailand. Most of these outbreaks were due to *Aedes aegypti*-adaptive mutations in the ECSA strain.[90] In 2013, the first local transmission of the chikungunya virus was reported in the Western Hemisphere, beginning with an indigenous case in Saint Martin. Before the Saint Martin case, the only confirmed case of chikungunya in America was a traveller.[91] In 2010, a virulent disease of febrile infection with arthralgic manifestations was detected in countries of South America. The infectious agent was a rebounded South American alphavirus i.e., the Mayaro virus (MAYV).[35,92] Seventy-seven instances were reported in total and 19 were shown as seropositive. This virus normally infects men and women living close to enzootic transmission foci due to anthropogenic incursions as shown in Table 2.[93]

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Table 2.Epidemics Caused by Some Mosquito-borne Alphaviruses

Name of the Virus	Name of City/ Country where Epidemic Occurred	Year of the Epidemic/ Death Toll	Probable Cause of the Epidemic	Preventive Measures taken for Stopping the Epidemic
CHIKV[89]	Kenya, Comoros Islands, La Reunion, Seychelles, Mayotte, Mauritius, India, Southeast Asia	2004–2006 6 million cases in > 40 countries, 237 deaths in the Indian Ocean islands	Unusual dry and warm conditions, stagnant water, increased tourism, non-existent herd immunity E1-A226V mutation was identified in ECSA genotype enhanced transmission by *Aedes albopictus.*	Control of vectors by insecticides larvicides, personal protection
CHIKV[91,94]	Saint Martin Island, spread throughout the American continent	2013 > 2 million cases in 50 countries	CHIKV of Asian genotype responsible, *Aedes aegypti* and *Aedes albopictus*, population naïve to CHIKV, intense movement of people	Avoid mosquito bites, physical barriers like topical repellents, bed nets
MAYV [95]	Portuguesa, Venezuela (South America)	2010 77 cases	A new genotype N closely resembling genotype D infected persons residing near enzootic transmission foci	Use of insecticides, using natural enemies to reduce the vector density, isolating viraemic individuals
MAYV[93]	Brazil	2014–16 343 cases, antigenic cross-reactivity might underestimate the MAYV cases.	*Aedes aegypti, Aedes albopictus,* and *Culex quinquefasciatus* could act as vectors for MAYV and humans could act as amplifying hosts and might be responsible for establishing an urban cycle of transmission for MAYV.	No specific antivirals, cases treated with NSAIDs and corticosteroids, the vaccine is in the preclinical stage of development.
MAYV[33,96]	French Guiana (France)	2020 13 cases (9 out of 13 cases were in urban settings)	The urban transmission cycle still needs to be explored. If established, then additional measures would need to be considered to prevent further outbreaks.	Suppress mosquito bites, avoid outdoor activities during peak activity hours of Heamogogus (*sylvatic vector*)
VEEV [95]	Iquitos, Peru	2006 > 100 cases, 2 deaths, seroprevalence of 23% in Iquitos urban population	Unclear, increase in vector abundance and rate of transmission in the forest and urban spillover, unusually high river levels and high Culex (Mel.) ocossa prevalence	-

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SINV[97]	Finland	2002 597 cases	Mosquito bites, handling sick/ dead animals, more outdoor activity	-
SINV[98]	Finland	2012 189 cases, 2018 71 cases	Different strains from mosquitos and patient sera were obtained indicating transfer between different regions of Europe, high summer temperature, precipitation, and a thick layer of snow during summer	-
RRV[89]	Southeast Queensland (Australia)	2015 9544 cases	High temperature and rainfall, abundance of *Culex. annulirostris* and *Ae. procax,* multiple reservoir hosts	Mosquito control, avoidance of bites
RRV[99,100]	New South Wales, Victoria, Western Australia	2017 6928 cases	High temperature and rainfall, abundance of *Cx. Annulirostris* and *Ae. Procax*, multiple reservoir hosts an unusually high number of *Ochlerotatus camptorhynchus,* more rainfall, outdoor activities	Mosquito control, avoidance of bites reducing vector population, educating people to reduce exposure
BFV	Victoria (Australia), Tasmania	2002 47 laboratory-confirmed cases, 2019		
ONNV[35]	Nicla border camp in Western Côte d'Ivoire (Western Africa)	2003 31 cases in a refugee camp	-	The movement of refugees to North America was delayed to control the epidemic.

CHIKV: Chikungunya virus, MAYV: Mayaro virus, VEEV: Venezuelan Equine Encephalitis virus, SINV: Sindbis virus, RRV: Ross River virus, BFV: Barmah Forest virus, ONNV: O'nyong-nyong virus

In addition, during an epidemic of dengue virus in Mato Grosso, midwestern Brazil, 15 of 604 patients responded positively to the detection of MAYV RNA during acute febrile illness.[101,102] A total of 343 suspected cases were observed in Brazil following MAYV infection from 2014 to 2016, of which more than 50% occurred in the state of Goias as mentioned in Table 2.[102] The increasing prevalence of MAYV disease outside the northern regions is of growing concern because the virus is spreading to other regions and may indicate a possible future epidemic in Brazil.

One of the severe epidemic infections reported in South America is Venezuelan equine encephalitis (VEE). In early 2006, VEEV infection was discovered through a fever surveillance programme at a hospital in Iquitos, Peru. An antibody prevalence study was performed in the urban area of Iquitos to identify the risk factors for VEEV infection in the city. In addition, entomological investigations were carried out to identify whether VEEV vectors were present in the city. The result of the study observed that more than 23% of Iquitos inhabitants possessed neutralising antibodies to VEEV, which was found to be significantly associated with an increased prevalence of antibodies due to age, safe practices like bed net use, travelling at night, and the participant's job. Studies suggested that VEEV infections occur frequently in pastoral areas, though the spread is also occurring in the urban areas of Iquitos, and hence more research is needed to estimate exactly which vectors and reservoirs are involved in the disease.

An arthropod-covered RNA virus, SINV, belongs to the *Alphavirus* genus of the Togaviridae family. The first report on SINV came from a group of virus vectors, *Culex pipiens* and *Culex univittatus.*[103,104] In Finland, outbreaks

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occur every seven years, with hundreds or thousands of reported cases, but no pertinent information is available on factors associated with clinical infection of SINV.[105] RRV has been reported from the Western Pacific regions and Australia and is considered to be the most common cause of mosquito-borne disease in Australia.[106] One of the largest reported outbreaks of RRV infection was reported in the year 2015 with more than 10,000 patients. Barmah Forest virus (BFV) disease originated from the forest of Barmah which is similar to the Ross River virus (RRV) which causes the epidemic arthritis.[100,107] Since 1988, BFV has been reported in Western Australia, Queensland, New South Wales, Northern Territory, and Victoria. Occurrences of BFV without RRV occurred in New South Wales in 1994/1995 and in 1993 in Australia.[108]

ONNV is an alphavirus transmitted mainly by bites of the African protozoan vector of malaria namely *Anopheles funestus* and *Anopheles gambiae* (Table 1).[35,45,109] It was first isolated in the year 1959 in Uganda and has been reported to cause outbreaks in many sub-Saharan regions of Africa.[110] Precautionary measures are no different from those already taken to combat malaria infection. No effective vaccine or drug has been created so far.

Status of Prevention and Control Measures

Pharmacotherapy currently available for alphaviruses is a combination of ribavirin and interferon, which is relatively inefficient, and some anti-inflammatory drugs for symptomatic relief. There are still no FDA-approved drugs or vaccines specifically targeting alphaviruses. Table 3 highlights some of the molecules that have shown anti-alphaviral activity.

Progress in Vaccine Development

For encephalitis-causing viruses, various formulations of the inactivated virus have been tested, which include different mechanisms of inactivation and routes of administration. A mixture of three species i.e., WEEV, EEEV, and VEEV are inactivated by formalin, 1,5-iodonaphthyl azide, or ɤ-irradiation. Different routes used were intramuscular, subcutaneous, or intranasal. Immunogenic effects and protective efficacy varied depending on the above factors. Viral replicon particles (VRP) are based on an attenuated strain of VEEV (V3014) into which structural protein-coding genes can be inserted. In WEVEE (trivalent vaccine candidate), expression of alphavirus glycoproteins with a deletion in the pE2 furin cleavage site is involved. The efficacy of the vaccine was observed in a lethal mouse model for all three viruses. Against alphaviruses, a variety of virus-like particles (VLPs) are being pursued for vaccination.[111] A phase 2 trial on a CHIKV VLP vaccine PXVX0317, an aluminium hydroxide-adjuvanted formulation, was conducted in the USA between 2018 and 2020 to evaluate the efficacy and immunogenicity among CHIKV naive individuals belonging to the age group of 18–45 years. The trial was well endured and generated a strong and long-lasting serum nullifying immune response against CHIKV which could last up to two years. A phase 3 clinical trial on adjuvanted PXVX0317 with a single injection is being conducted at present.[112] The effects of binary ethylenimine-inactivated (BEI) RRV in diminishing the infectivity of the Ross River virus were studied in mice by immunising them intramuscularly with the BEI-inactivated virus. Antibodies were generated that neutralised RRV in vitro and mice also did not develop viraemia when challenged with live virus intravenously.[96] A formal- and UV-inactivated whole RRV vaccine grown in animal protein-free cell culture was tested for its efficacy and immunogenicity in animal models. Active immunisation with these vaccine-induced antibodies prevented viraemia in adult mice and protected the IFN-a/b receptor knockout mice from death and diseases.[113]

Present Status of Anti-alphaviral Drug Therapeutics

Difficulty in assessing the population at risk generates the need to evaluate and develop post-exposure treatment methods to control alphaviral infections. The drugs being developed are either targeting different proteins of the virus or altering the host-targeted immune response to viral infections like immunomodulation (Table 3).

Table 3.Anti-alphaviral Molecules and Their Potential Targets with Half-maximal Effective Concentration

Alphavirus	Anti-viral Molecules	Target	EC_{50} (µM)
CHIKV	Neoguillauminin A[114]	Protein kinase C	17.70
	Lobaric acid[115]	Non-structural protein 1	5.30–16.30
	Harringtonine[116]	Viral genome replication	0.24
	Ivermectine[117]	Unidentified target	0.60
	Abamectin[117]	Unidentified target	1.50
	Prostratin[118]	Protein kinase C	0.20–8.00
	Berberine[119]	Extracellular signal-related kinase	1.80 ± 0.50

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EEV	ML336[63]	Unidentified target	3.60
	Tomatidine[120]	Viral replication	10.00
	Citalopram[120]	Viral replication	20.00
	Dibenzylamines[121]	Protein synthesis	0.89
MAYV	Favipiravir[122]	Viral replication	4.50
	Suramin[123]	Unidentified target	124.00
	Quercetin[124]	Protein synthesis	10.00 ± 0.70
	Cassia australis extract[125]	Viral replication	2.30
	Punica granatum extract[126]	Unidentified target	12.30
ONNV	Rev-erbα/β[127]	Viral replication	10.00
	Quercetin[128]	Viral RNA	10.00
RRV	Pentosan polysulfate[129]	Unidentified target	4.50
	Geranial[130]	Virus replication	45.11 ± 2.46
	Citronellol[130]	Virus replication	23.43 ± 0.14
SFV	Chloroquine[131]	Unidentified target	2.00
	Amantadine[131]	Unidentified target	2.50
	Monensin[132]	Viral replication	6.00
SINV	Hesperetin[132]	Unidentified target	20.50
	Naringenin[133]	Unidentified target	14.90
	Beclin[134]	Viral replication	-
	Ivermectin[117]	Viral replication	0.60
	Abamectin[117]	Viral replication	1.50
	Berberine[117]	Viral replication	1.80

CHIKV: Chikungunya virus, EEV: Equine Encephalitis virus, MAYV: Mayaro virus, ONNV: O'nyong-nyong virus, RRV: Ross River virus, SFV: Semliki Forest virus, SINV: Sindbis virus

For the first time, anti-VEEV agents were identified using an *in silico* structure-based drug development technique. These agents inhibited capsid protein recognition by nuclear transport protein importin (IMP) α/β1. One of the compounds reduced VEEV replication but was inactive against a mutant VEEV lacking IMP α/β1-C interactions. Laboratory studies assessed four analogues of ML336 (a benzamidine) and three of them were tested in an *in vivo* study. BDGR-4, one of the analogues of ML336, when given to mice exposed to VEEV TrD (Trinidad Donkey strain) after 24 hours and 48 hours of exposure, provided 100% and 90% protection from the lethal disease, respectively. A specific mutation in nsP4 provided resistance to VEEV against BDGR-4.[72] So, the tendency of viruses to mutate also poses a problem in developing specific antiviral drugs. Peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) - antisense drug products were designed. The drug was effective against multiple strains of VEEV and could prove to be a very effective therapeutic agent against VEEV and other alphaviruses. Since these drugs are less effective when given post-exposure (in vivo) and the cases in humans are usually sporadic, it needs further exploration to develop the drug molecules, which are more efficient in controlling the infection post-exposure.[135]

Fifty-one betulin derivatives were assessed against SFV and SINV. The susceptibility of positive-stranded RNA viruses towards the derivatives of betulin and the absence of early toxicity and inhibitory effects on SFV and SINV make these compounds potential therapeutic candidates.[136] Doxycycline and ribavirin were found to have synergistic anti-CHIKV effects *in vitro*. Doxycycline, by binding to E2 glycoprotein, inhibits the conformational change in E2 required for binding to cell surface receptors.[107] Antiviral dioxane-based compounds have been constructed to recognise the hydrophobic region of the capsid protein of

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SINV using computational methods.[137] They hindered 50% of viral replication at a concentration of 40 µM, with no signs of toxicity. So, further studies can be done to develop antivirals against this target. Chloroquine works against multiple viruses like SINV, SFV, and CHIKV by increasing the pH of the endosome,[137] but its efficacy could not be proven in vivo for SFV and in CHIKV-infected patients. *In vitro* studies have proven that the antiapoptotic protein Bcl-2 prevents apoptosis in SFV and SINV-infected cells.[102] IFN-ɤ (Interferon-gamma) has also been demonstrated to help in clearing SINV from neurons by hindering viral transcription, reducing viral protein synthesis, and assisting in the recovery of cellular protein synthesis.[138]

N-methyl-D-aspartate (NMDA-a glutamate receptor) antagonists have been identified as protective agents against SINV-induced death of neurons, but not in mice,[104] whereas α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) antagonist talampanel provided protection against the fatal disease,[137] by decreasing CNS inflammation. Two important antagonists of SINV include naloxone (an opioid receptor antagonist) and minocycline (a tetracycline derivative).[138] They inhibit SINV infection by decreasing cytokine interleukin-1. A flavonoid-based chemical obtained from Salacia crassifolia shows antiviral activity against the capsid protein of MAYV. It was also subjected to bioassays (*in vitro*), which supported its potential as an antiviral agent inhibiting the effects of viral infection and low cytotoxicity with potency almost twice that of ribavirin.[30]

Various drugs against alphaviruses, which are under investigation, are in the preclinical trial stage. There is still no effective FDA (Food and Drug Administration) approved specific antiviral drug available against alphaviruses.

Conclusion and Future Perspectives

Although a lot of work is under progress to understand the mechanisms used by alphaviruses to adapt to a variety of natural hosts and vectors, there is no study as per the current information, regarding the genomic adaptation of the majority of these alphaviruses to different hosts in terms of codon and AA usage. The recent emergence of infections caused by these alphaviruses necessitates the in-depth study of these viruses at the molecular level. Future exploration of encephalitic alphaviruses at the molecular level for understanding genetic diversity and the structure of their envelope proteins will be of great help in developing specific drugs/ vaccines. The aerosol route of transmission generates the need to develop measures against encephalitic viruses. Due to the multiplicity of natural hosts and vectors for alphaviruses, we need to understand the genome dynamics of these viruses in relation to their hosts.

Authors' Contributions

MS: Review of literature, and building the draft of the manuscript; NRS: Conception of the idea of this article and gap identification in the existing studies, editing of the manuscript; JG, MAK: Compilation of the manuscript; AB, SK, GS: Technical review of the manuscript.

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15. Abbreviations: SINV: Sindbis virus, SFV: Semliki Forest virus, MAYV: Mayaro virus, ONNV: O'nyong-nyong virus, RRV: Ross River virus, BFV: Barmah Forest virus, CHIKV: Chikungunya virus, VEEV: Venezuelan Equine Encephalitis virus, EEEV: Eastern Equine Encephalitis virus, WEEV: Western Equine Encephalitis virus, CP: Capsid protein, nsP: non-structural protein, ORF: Open Reading Frame, TF: Transframe, ICAM: intracellular adhesion molecule, CRBD: cell receptor binding domain, NMDA N: methyl-D-aspartate, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

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