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A COMPREHENSIVE REVIEW ON VIRAL ZOONOSIS: EMPHASIZING ON PATHOGENESIS, DIAGNOSIS, TREATMENT, PREVENTION STRATEGIES AND FUTURE PERSPECTIVES

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ABSTRACT: Zoonoses are human diseases caused by animal pathogens or animal diseases that are transmissible to humans. They are caused by all types of pathogenic agents, including bacteria, parasites, fungi, viruses, and prions. Zoonotic diseases can be transmitted to humans by infected saliva, aerosols, contaminated urine or feces, and direct contact with the animal or pathogenic microbes. Furthermore, transmission can also occur through animal vectors (*e.g.*, tick bite, and insects like mosquitoes or flea). The zoonotic microbes continue to evolve and adapt with tremendous acceleration and expansion of global trade, human movement, and population. Control of zoonotic diseases and protection of public health are challenging tasks as the world population is increasing proportionately. Newly emerging viruses such as the Ebola virus, severe acute respiratory syndrome (SARS)-, Middle East respiratory syndrome (MERS)-coronavirus, and the avian influenza virus, H1N1 virus, Nipah virus, Zika Virus, and now Covid-19 are serious threats to public health and have become a global concern. The prevention of these infections depends on improved diagnosis and highly effective therapeutics/ prophylactics. In this review, most important zoonotic infections, along with their specific etiology, transmission (role of wild-life) manifestations and epidemiology and control/preventive measures, are described so as to create awareness of the scientific/public health community.

INTRODUCTION: Zoonotic pathogens identified are mostly viral origin and are emerging and reemerging. Zoonotic viral infections are grouped based on the type of infection they produce in the natural host. Since zoonotic diseases can easily be transmitted to a man in several ways, they target persons who work closely with animals; this plays a big role in zoonotic transmission.

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Such persons working with animals include veterinarians, slaughterers/butchers, farmers, researchers, pet owners (*e.g.*, through bites and/or scratches of owners of indoor pet-animals), and animal feeders in animal companies using animal products, *via* animals used for food (*e.g.*, meat, dairy, eggs, birds, infected domestic poultry, and other birds). They continue to cause health hazards in most parts of the world and are economically important and public health concern. The collective effort of professionals from medical and veterinary and others is necessary to combat these zoonotic infections.

The majority of virus infections are asymptomatic and do not cause disease. Only a tiny number of

infections cause serious or life-threatening consequences. Occasionally, known viruses appear to change their behavior, suddenly causing outbreaks of diseases. Such viruses are known as emerging viruses, and frequently the cause of a new disease is when a virus switches host species and begins to infect another, and changes in human activities also result in the emergence of new or previously unrecognized diseases. Emerging infectious diseases (EIDs) are a significant burden on global economies and public health [1-3]. Their emergence is thought to be driven largely by socio-economic, environmental, and ecological factors [5-9]. This review focused on the mentioned infectious diseases by describing general information, signs and symptoms, transmission ways, prevention, and treatment of the infection.

2. Newly Emerging Viruses: Many new and emerging RNA and DNA viruses are zoonotic or have zoonotic origins in an animal reservoir that is usually mammalian and sometimes avian. Not all zoonotic viruses are transmissible (directly or by an arthropod vector) between human hosts. Series of recent emerging infectious disease outbreaks, including the 2014 Ebola virus disease (EVD) epidemic in West Africa and the continuing Zika virus disease epidemic in the Americas, has underlined the need for better understanding of which kinds of pathogens are most likely to emerge and cause disease in human populations. Many, although not all, emerging infectious diseases are caused by viruses, and these frequently emerge from non-human host reservoirs [10-12].

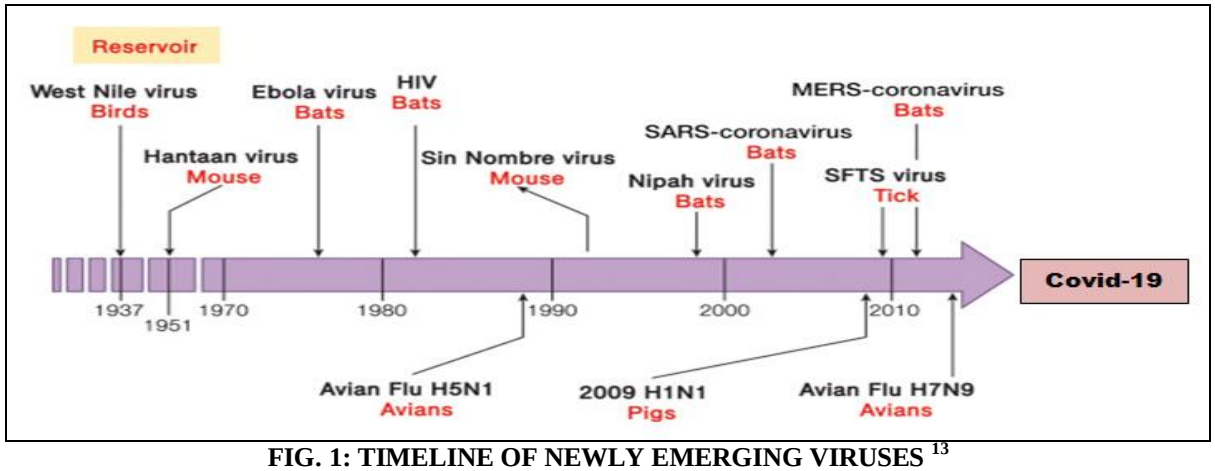

FIG. 1: TIMELINE OF NEWLY EMERGING VIRUSES [13]

TABLE 1: VIRUSES (N = 37) THAT ARE KNOWN OR SUSPECTED OF BEING TRANSMISSIBLE (DIRECTLY OR INDIRECTLY) BETWEEN HUMANS BUT TO DATE HAVE BEEN RESTRICTED TO SHORT TRANSMISSION CHAINS OR SELF-LIMITING OUTBREAKS *

Genome, virus family	Virus name
	Single-stranded RNA (ambisense)
Arenaviruses	Guanarito, Junin, Lassa, Lujo, Machupo, Sabia, Dandenong,* lymphocytic choriomeningitis*
Bunyaviruses	Andes, Bwamba, Crimean-Congo hemorrhagic fever, Oropouche, Rift Valley, severe fever with thrombocytopenia syndrome
	Single-stranded RNA (positive sense)
Flaviviruses	Japanese encephalitis,* Usutu,* West Nile*
Coronaviruses	Middle East respiratory syndrome
Togaviruses	Barmah Forest, o'nyong-nyong, Ross River, Semliki Forest, Venezuelan equine encephalitis
	Single-stranded RNA (negative sense)
Filoviruses	Bundibugyo Ebola, Lake Victoria Marburg, Sudan Ebola
Paramyxoviruses	Nipah
Rhabdoviruses	Bas-Congo, rabies*
	Double-stranded RNA
Reoviruses	Nelson Bay, Colorado tick fever*
	Double-stranded DNA
Adenoviruses	Titi monkey
Herpesviruses	Macacine herpesvirus 1
Polyomaviruses	Simian virus 40
Poxviruses	Monkeypox, Orf, vaccinia

*Human transmission of these viruses is known only by iatrogenic or vertical routes

Since the 1970s, newly emerging viruses of unknown origins have been continuously discovered **Fig. 1**. The first outbreak of the Ebola virus occurred in 1976 in Zaire and Sudan. AIDS was first described as acquired immunodeficiency syndrome among homosexual males in 1981, and its culprit was soon identified in 1983 as HIV. SARS, a respiratory disease caused by SARS-CoV, was first reported in Hong Kong in 2003. More recently, a novel coronavirus, Middle East respiratory syndrome-coronavirus (MERS-CoV), was discovered in 2012 in Saudi Arabia. Newly emerging viruses, such as the Ebola virus, the WNV, the Nipah virus, and SARS-CoV, will be described in this chapter. HIV will be covered in a separate chapter due to its huge impact on the global community.

2.1. West Nile Virus (WNV): West Nile Virus (WNV) was first isolated in a woman in the West Nile district of Uganda in 1937. The WNV outbreak in the USA (1999-2010) highlighted that importation and establishment of vector-borne pathogens outside their current habitat represent a serious danger to the world [14-16].

West Nile virus belongs to the family Flaviviridae, a large family of positive-strand RNA viruses with 3 main genera (flavivirus, hepacivirus, and pestivirus). Among the more than 70 viruses in the genus flavivirus, several neurotropic and hepato-tropic viruses Human infection is most often the result of bites from infected mosquitoes. Mosquitoes become infected when they feed on infected birds. The virus eventually gets into the mosquito's salivary glands. During later blood meals (when mosquitoes bite), the virus may be injected into humans and animals, where it can multiply and possibly cause illness. The virus may also be transmitted through contact with other infected animals, their blood, or other tissues [15] **Fig. 2**.

Infection with WNV is either asymptomatic (no symptoms) in around 80% of infected people; symptoms include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis. Serious illness can occur in people of any age; however people over the age of 50 and some immunocompromised persons (for example, transplant patients) are at the highest risk for getting severely ill when infected with WNV. The incubation period is usually 3 to 14 days [16, 17].

West Nile virus can be diagnosed by a number of different tests [18]:

- IgG antibody seroconversion (or a significant increase in antibody titers) in two serial specimens collected at a one-week interval by enzyme-linked immunosorbent assay (ELISA).
- IgM antibody capture enzyme-linked immunosorbent assay (ELISA).
- Neutralization assays.
- Viral detection by reverse transcription-polymerase chain reaction (RT-PCR) assay, and
- Virus isolation by cell culture.

Treatment is supportive for patients with neuro-invasive West Nile virus, often involving hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections. No vaccine is available for humans.

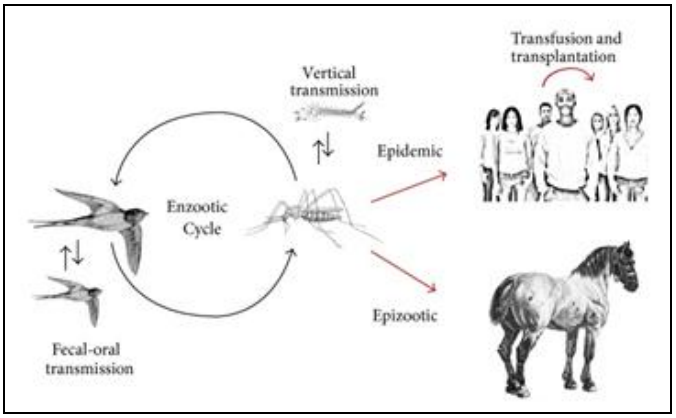

FIG. 2: WNV TRANSMISSION CYCLE

Enzootic amplification of WNV by birds and mosquitoes supplemented by bird-to-bird trans-mission and transmission between cofeeding mosquitoes. Vertical transmission by mosquitoes provides the mechanism of virus overwintering. Humans and horses are counted as incidental dead-end hosts. Human-to-human transmission may come through blood transfusion, organ transplantation, and breastfeeding and in utero [19-25].

2.2. Hantaan Virus: The genus *Hantavirus* is one of five genera in the family *Bunyaviridae*, which is a zoonosis endemic in eastern Asia, especially in China. Hantaan virus is transmitted to humans from persistently infected mice (*Apodemus agrarius*), which serve as the primary reservoir [26].

The virus particle is oval or spherical in shape with a diameter ranging from 80 to 120 nm. The genome of HTNV-RNA consists of three segments designated S [small: 1700–2100 nucleotides(nt)], M(medium: 3600–3700 nt), and L(large: ~6500 nt). The S segment encodes the nucleocapsid protein; the M segment encodes envelope glycoproteins (G1 and G2); L segment encodes the RNA-dependent polymerase protein [27-28]. HTNV is very stable and can remain infective for 2 weeks at room temperature and presumably for more time at a lower temperature. Hantaan virus induces toll-like receptor 4 expression, leading to enhanced production of beta interferon, interleukin-6, and tumor necrosis factor-alpha.

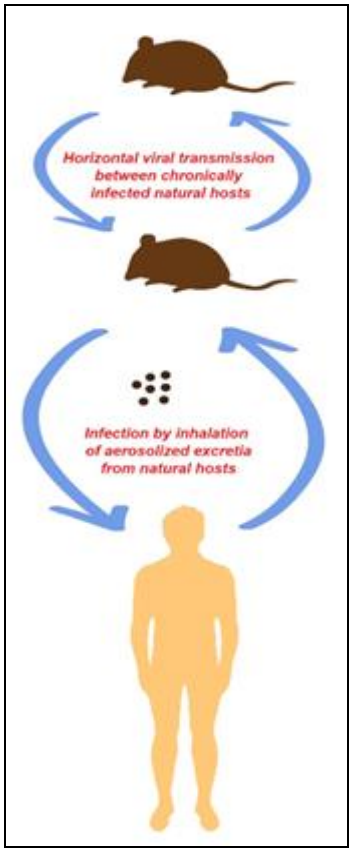

FIG. 3: HANTAVIRUS LIFE CYCLE AND SPILLOVER INFECTION TO HUMANS

The main transmission pathway from rodents to humans is aerosolized excreta inhalation and contact infection. Person-to-person transmission has not been found. Rural areas, with poor housing conditions and high rodent density, accounts for more than 70% of HFRS cases, and the majority of infected cases are local farmers [29]. Forest workers, shepherds, woodcutters, and military personnel also have high occupational hazards from HTNV infection in that epidemiologic investigations have linked virus exposure to such activities as heavy farm work, threshing, sleeping on the ground, and military exercises [30] **Fig. 3**.

In nature, hantaviruses are circulating via horizontal transmission between chronically infected natural host reservoirs (mice, rats, voles). Most human infections occur when contaminated aerosolized rodent excreta are inhaled [31].

Hantaviruses primarily affect blood vessels and lead to variable degrees of generalized capillary dilatation and edema. By activating complement and by triggering mediator release from platelets and immune effector cells, immune complexes may be involved in vascular injury [32]. Increased vascular permeability leads to plasma exosmosis and even hemorrhage, which is associated with lots of clinical features, such as hemoconcentration, hypotension, shock, and abdominal pains [33, 34].

The clinical symptoms of hantavirus person are primarily characterized by fever, circulatory collapse with hypotension, hemorrhage, and acute kidney injury (AKI). The disease typically progresses through five phases: febrile, hypotensive shock, oliguric, polyuric, and convalescent. Laboratory findings during acute stage of the disease are anemia, leukocytosis, thrombocytopenia, elevated liver enzymes, and serum creatinine (renal dysfunction), as well as proteinuria and hematuria. Most of the cases can recover completely, while some severe cases still have some sequelaes, including headache, insomnia, hyperhidrosis, hemorrhage, and hyperdiuresis [35-38].

Laboratory diagnosis of acute hantavirus infections is based on serology as virtually all patients have IgM and usually also IgG antibodies present in serum at the onset of symptoms [39]. The hantavirus infection can also be confirmed by the detection of the hantavirus genome in blood or serum samples by RT-PCR. Both traditional and quantitative RT-PCR is used to detect viraemia [40-42].

The earlier detection and admission to ICU then supportive treatment, causes a greater reduction of mortality rate [43]. Maintaining fluid and electrolyte balance is a crucial and fundamental treatment method. In addition to rectifying kidney dysfunction, blood pressure and oxygenation also need to be maintained; several antiviral drugs, including IFN-α, steroids, and cyclophosphamide, have been used in clinical for various effects.

Ribavirin (1-beta-D-ribofuranosy 11,2,4-triazole- 3-carboxamide) has been used in the treatment of HCPS and HFRS [44] Favipiravir (T-705, 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) was reported to have a high activity against a panel of Bunya-viruses (La crosse, Punta Toro, Rift Valley fever, sandfly fever viruses, SNV, Andes virus) by cytopathic effect and virus yield reduction[48]. MAbs against HTNV have been developed. In China, a single-dose intravenous injection of a murine MAb against HTNV was developed and applied in healthy volunteers[45].

2.3. Ebola Virus: Ebola virus is one of the most virulent pathogens known to infect humans [46]. The first recognized Ebola outbreak occurred in 1976, near the Ebola River in Zaire (now Democratic Republic of Congo, DRC). Over the past 40 years, more than 20 outbreaks have occurred in Africa, with most of the known outbreaks occurring in the past 20 years [47, 48]. Ebola virus becomes not only a public health problem to Africa but also a worldwide bio-threat.

EBOV belongs to the order Mononegavirale (single-stranded, non-segmented, negative-sense RNA virus) of the family Filoviridae, genus Ebolavirus. The genus Ebolavirus consists of five species *viz*., (1) Zaire ebolavirus (Zaire virus – ZEBOV), (2) Sudan ebolavirus (Sudan virus – SUDV), (3) Reston ebolavirus (Reston virus – RESTV), (4) Taï Forest ebolavirus (Taï Forest virus – TAFV), and (5) Bundibugyo ebolavirus (Bundibugyo virus – BDBV) and Côte d'Ivoire ebolavirus (CIEBOV) [49-51].

EBOV is a non-segmented negative-sense single-stranded RNA virus with filamentous particles, a morphological characteristic of all Filoviruses [52]. EBOV particles are the same in width (80 nm) but vary in length (up to 1400 nm), which can be coiled, toroid, or branched. The EBOV genome fig. 4 is approximately 1.5 kb in length and contains seven genes encoding nucleoprotein, virion protein (VP) 35, VP40, glycoprotein (GP), VP30, VP24, and RNA-dependent polymerase [53].

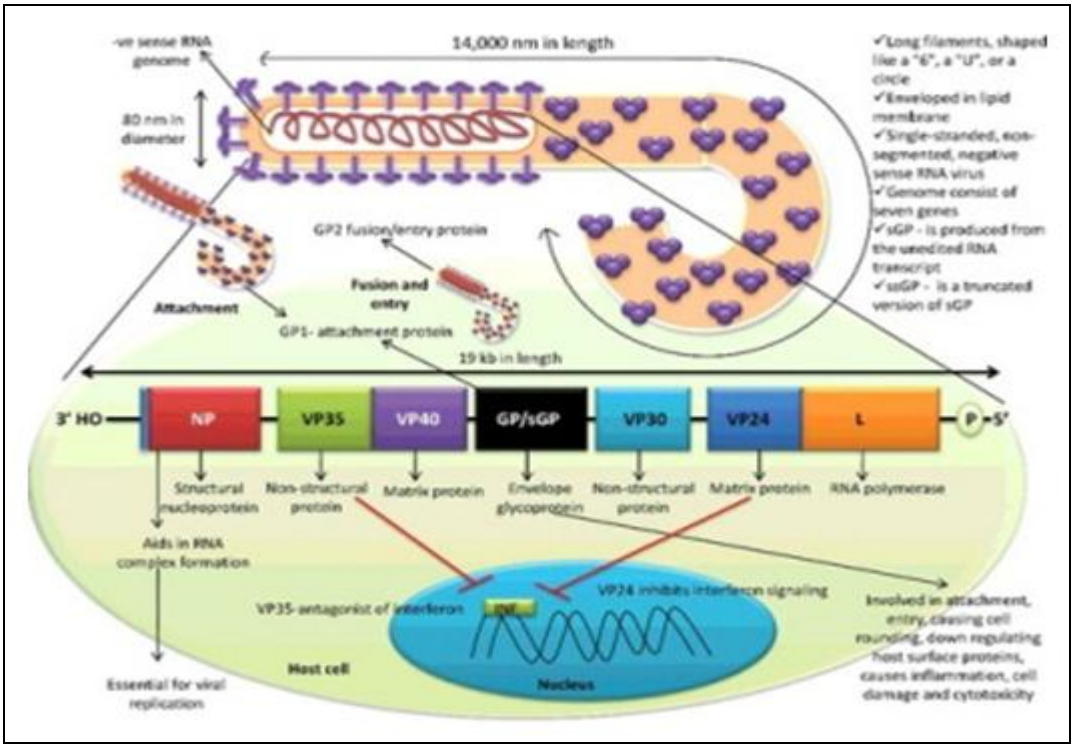

FIG. 4: STRUCTURE OF EBOLA VIRUS AND ITS GENOME. EBOLA VIRUS POSSESSES NEGATIVE-SENSE RNA GENOME WITH EXCEPTIONALLY 14000 nm LENGTH WITH 3' NUCLEOPROTEIN AND 5' RNA POLYMERASE END

The high viral mutation rate of the 2014 EVD outbreak strains implied the potential of rapid evolution. The mutant strains of EBOV can be generated with different virulence, infectivity, tissue tropism, and the capability of immuno-suppression.

EVD is a typical zoonotic disease, but the wild reservoir of EBOV is still unclear. Non-human primates, like apes or monkeys, have long been considered as important sources of infection to humans. Patients at the contagious stage are the main sources of human-to-human transmission. The viruses can exist in body fluids such as blood, semen, and genital secretions as well as the skin of contagious patients[54, 55]. The incubation period is up to 21 days, which is the epidemiological basis for quarantine.

Fever and other EVD symptoms such as headache, fatigue, and diarrhea often appear at the earlier contagious stages [56]. Presence of thrombocytopenia and leukopenia with elevated transaminase levels is characteristic of filovirus disease as well as some other viral hemorrhagic fevers, but a severe progressive course with abdominal pain and diarrhea should lead to suspicion of a filovirus.

Significant alterations of the laboratory indexes, allowing for timely identification of infected patients Polymerase-chain-reaction (PCR) test for EBOV nucleic acid and the detection for the viral antigen in the blood can become reliably positive from 2 to 16 days after the onset of symptoms. Immunoglobulin M (IgM) can be detected as early as 2 days after the onset, and immunoglobulin G (IgG) usually appears between 6 and 18 days after the appearance of the clinical signs [57].

Even though there are no approved therapies for patients with EVD, experimental therapies are in development. A cocktail of 3 monoclonal antibodies directed against the Ebola viral glycoprotein (ZMapp) prevented the death of Ebola-infected macaques, even when initiated after the animals had developed full clinical symptoms [58].

This cocktail has been administered to 4 healthcare workers during the 2014 outbreak, 2 of whom survived and recovered [59, 60]. Controlled studies are needed to evaluate this and other novel treatments [61].

2.4. HIV/AIDS Virus: Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV) [62-64]. HIV is a member of the group of viruses known as retroviruses [65]. The HIV epidemic arose after zoonotic infections with simian immunodeficiency viruses from African primates; bushmeat hunters were probably the first group to be infected with HIV. HIV-1 was transmitted from apes and HIV-2 from sooty mangabey monkeys. Four groups of HIV-1 exist and represent three separate transmission events from chimpanzees (M, N, and O), and one from gorillas (P). Groups N, O, and P are restricted to West Africa. Group M, which is the cause of the global HIV pandemic, started about 100 years ago and consisted of nine subtypes: A–D, F–H, J, and K.

HIV is a member of the genus Lentivirus [66], part of the family Retroviridae [67]. Lentiviruses share many morphological and biological characteristics. Many species of mammals are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period [68]. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle **Fig. 5**. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors [69]. Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system [70]. Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew [71].

HIV is spread primarily by unprotected sex (including anal and oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breast-feeding. Some bodily fluids, such as saliva, sweat, and tears, do not transmit the virus.

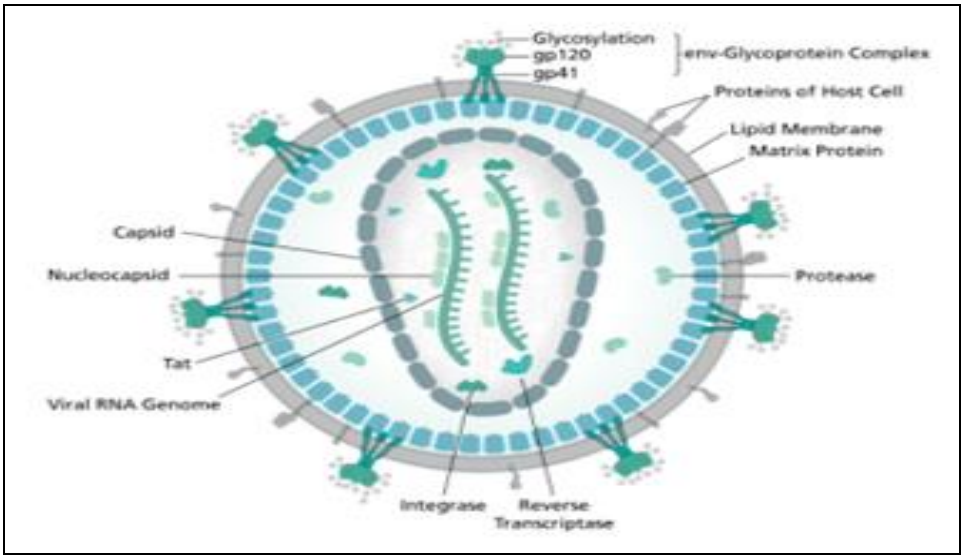

FIG. 5: DIAGRAM OF THE HIV VIRION

HIV is a retrovirus that primarily infects components of the human immune system such as $CD4^+$ T cells, macrophages, and dendritic cells. It, directly and indirectly, destroys $CD4^+$ T cells [72].

The period from infection to the primary seroconversion illness is usually 1 to 4 weeks. The period from infection to development of anti-HIV antibodies is usually less than 1 month but maybe up to 3 months; newer tests have a shorter window period, where a false negative result may be obtained early in infection.

The interval from HIV infection to the diagnosis of AIDS ranges from about 9 months to 20 years or longer, with a median of 12 years. There is a group of people with a more rapid onset of disease who develop AIDS within 3–5 years of infection and another smaller group who do not seem to progress to AIDS [73].

Most people infected with HIV develop specific antibodies (*i.e.* seroconvert) within three to twelve weeks after the initial infection. Diagnosis of primary HIV before seroconversion is done by measuring HIV-RNA or p24 antigen [74]. Positive results obtained by antibody or PCR testing are confirmed either by a different antibody or by PCR.

The most common symptoms are similar to a flu-like or mononucleosis-like illness within several days to weeks after exposure to the virus, including fever, headache, open sores or ulcers in the mouth (like canker sores, also known as aphthous ulcers), fatigue, weight loss, sweating or night sweats, appetite loss, rash that may come and go quickly sore throat; and swollen lymph nodes (glands) in the neck and groin. These HIV-associated symptoms usually disappear within a few weeks

During the latent period, the virus continues to multiply actively. It infects and kills critical infection-fighting cells, a type of white blood cell called CD4 cells or T helper cells (T cells). Even though the person has no symptoms, he or she is contagious and can pass HIV to others through the routes described above. At the end of this phase, as the virus overwhelms the CD4 cells, the HIV viral load starts to rise, and the CD4 count begins to drop.

AIDS is the later stage of HIV infection when the body is losing T cells and its ability to fight infections. The infections that occur with AIDS are called opportunistic infections because they take advantage of the opportunity to infect a weakened host. A person diagnosed with AIDS may need to be on antibiotic prophylaxis to prevent certain opportunistic infections from occurring. The AIDS-defining infections include (but are not limited to) the following:

- Pneumonia caused by Pneumocystis jiroveci, which causes severe shortness of breath and dry cough.
- Toxoplasmosis, a brain infection which can cause problems with thinking, headache, or symptoms that mimic a stroke.

- Widespread (disseminated) infection with a bacteria called *Mycobacterium avium* complex (MAC), which can cause fever, diarrhea, and weight loss.
- Yeast (Candida) infection of the mouth and swallowing tube (esophagus), which causes pain with swallowing.
- Disseminated diseases with certain fungi: Cryptococcus neoformans is a typical example and causes slowly progressing meningitis.
- Polyomavirus or JC virus can cause progressive multifocal leukoencephalopathy, an incurable brain infection that leads to death.

A weakened immune system can also lead to other unusual conditions:

- Lymphoma (a form of cancer of the lymphoid tissue) can cause fever and swollen lymph nodes throughout the body.
- Cancer of the soft tissues called Kaposi's sarcoma causes brown, reddish, or purple lumps that develop on the skin or in the mouth.

Antiretroviral drug therapy is used to treat established HIV infection. Typical NRTIs include zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC) 75. As of 2019, dolutegravir/lamivudine/tenofovir is listed by the World Health Organization as the first-line treatment for adults, with tenofovir/lamivudine/ efavirenz as an alternative [76]. Combinations of agents that include protease inhibitors (PI) are used if the above regimen loses effectiveness.

2.5. Avian Influenza Viruses (AIVs): Influenza viruses fall into the Orthomyxoviridae family, which consists of six genera, Influenzavirus A, Influenzavirus B, Influenzavirus C, Thogotovirus, Isavirus, and Quarajavirus, classified by serological cross-reactivity to the nucleoprotein and matrix proteins. Of the three types of influenza viruses, Influenza A has the most genetic variation and the broadest host rangem[77].

- Influenza viruses infect humans and many different animals. The emergence of a new and very different influenza A virus with the ability to infect people and have sustained human to human transmission can cause an influenza pandemic.
- Influenza B viruses circulate among humans and cause seasonal epidemics. Recent data showed seals also could be infected.
- Influenza C viruses can infect both humans and pigs, but infections are generally mild and are rarely reported.
- Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

Depending on the origin host, influenza A viruses can be classified as avian influenza, swine influenza, or other types of animal influenza viruses. Examples include avian influenza "bird flu" virus subtypes A (H5N1) and A(H9N2) or swine influenza "swine flu" virus subtypes A(H1N1) and A(H3N2). All of this animal influenza type A viruses are distinct from human influenza viruses and do not easily transmit among humans.

Influenza viruses are further categorized into subtypes by their hemagglutinin (HA) and neuraminidase (NA) genes: as of now, there are 18 HA and 11 NA types. Influenza A viruses contain negative-sense, single-stranded segmented genomes that encode for 10 viral proteins: HA, NA, M1, M2, NP, NS1, NEP, PB1, PB2, and PA [78]. The 10 viral proteins are encoded by 8 segmented genomic strands [79], which are coated with NP, have a double-helical hairpin structure, and carry one polymerase heterotrimer consisting of PB1, PB2, and PA (viral ribonucleoprotein particles [vRNPs]) [80, 81].

Upon entry into a cell, the HA protein on the surface of the virion recognizes and binds to sialic acid on the surface of host cells (**Fig. 6** Steps 1-8). After binding, the virus enters the cell through receptor-mediated endocytosis [82].

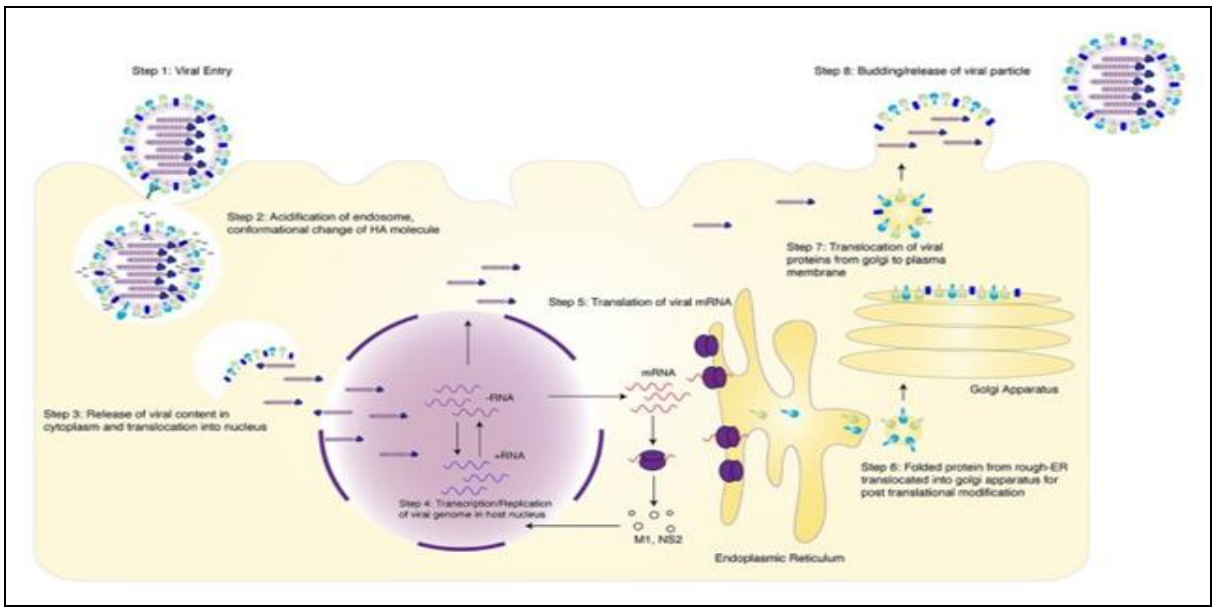

FIG. 6: REPLICATION CYCLE OF INFLUENZA VIRUSES

Note: (Step 1) Viral entry into the host cell. (Step 2) Virus endocytosis into host endosome and acidification, leading to a conformational change of the HA molecule exposing fusion peptide and fusion of viral and host membrane. M2 protein pumps H+ atoms into the viral core, causing the dissociation of M1 and the release of vRNP. (Step 3) Release of vRNP into the cytoplasm and translocation into the nucleus. (Step 4) vRNP replication and transcription, and cap-snatching mechanisms occur in the nucleus. Viral proteins such as M1 and NS2 chaperone vRNP out of the nucleus and into the cytoplasm to be packaged into viral particles. (Step 5) Structural proteins are translated by host ribosomes and are transported to the endoplasmic reticulum for proper folding. (Step 6) Properly folded viral proteins are released from the endoplasmic reticulum and are directed towards the plasma membrane or to the Golgi for modifications prior to release. (Step 7) Movement of modified proteins from the Golgi network to the plasma membrane for viral budding. (Step 8) Release of infectious viral progeny [83].

The A/goose/Guangdong/1/96 virus was initially detected in wild birds in Southeast Asia, but shortly thereafter was detected in several areas in Asia, Europe, Africa, and recently North America [84]. There are nine different types of H5 viruses in wild-bird populations (H5N1, H5N2, H5N3, H5N4, H5N5, H5N6, H5N7, H5N8, and H5N9). These H5 subtypes can present considerable risk to the human population [85].

HPAIV H5 virus infection in humans can initially present as an uncomplicated seasonal influenza infection with clinical signs of fever, body aches, and upper respiratory tract symptoms [86-88]. However, the infection eventually progresses into a lower respiratory tract infection. The infection can progress to become severe pneumonia, multi-organ failure, encephalitis, and septic shock. The incubation period for H5N1 virus infection is estimated to be seven days but is more commonly 2–5 days after exposure. In the rare cases where human-to-human transmission occurred, the incubation period varied from 3–4 days to 2–10 days.

The options for diagnosing influenza virus in clinical specimens include virus culture, antigen detection, detection of viral nucleic acids by RT-PCR, and detection of rising titers of antibodies [89]. The adamantanes (amantadine and rimantadine) and the NA inhibitors (oseltamivir and zanamivir) are the two currently available classes of drugs that are specifically active against influenza viruses [90].

Passive immunotherapy using convalescent-phase serum is believed to have conferred clinical benefit in the 1918 pandemic [91], and neutralizing monoclonal antibodies have shown therapeutic efficacy in influenza A virus infection in mice with severe combined immunodeficiency [92]. Thus, passive immunotherapy also remains a possible consideration for the management of human H5N1 disease [93].

2.6. Sin Nombre Virus (SNV): Sin Nombre virus (SNV), a member of the *Hantavirus*genus, causes acute viral pneumonia in humans and is thought to persistently infect mice. The deer mouse, *Peromyscus maniculatus*, has been identified as the primary reservoir host for SNV [94].

It is an enveloped, negative-sense, single-stranded RNA virus **Fig. 6**. Sin Nombre replicates exclusively in the host cell cytoplasm, with entry thought to occur by receptor-mediated endocytosis. It was first isolated in the Four Corners Region of the United States [95].

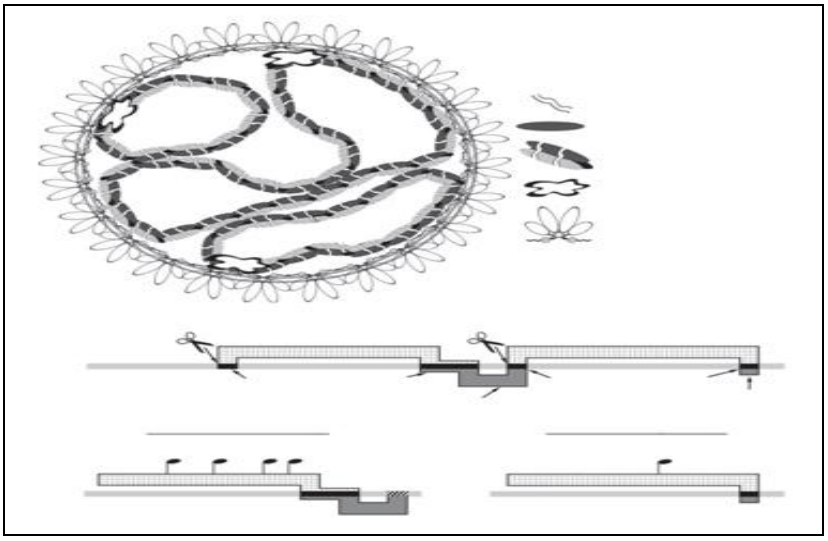

FIG. 7: SIN NOMBRE VIRUS (SNV) PARTICLE

(a) Schematic representation of the virion. (b) The GPC (ORF of M segment) is shown above, and mature Gn and Gc are shown below. The scissors in GPC indicate the cleavage sites of signal peptides, transmembrane (TM) helices are shown in black, the cytoplasmic tails (Gn-CT and Gc-CT) in dark grey, and the membrane in light grey. In mature proteins, the N-glycosylation sites are numbered based on HTNV GPC, and an underlined label indicates a conserved Nglycosylation site. The signal sequence of Gc is included in the mature Gn; however, the faith of this TM helix is unknown. ER, Endoplasmic reticulum **Fig. 7**.

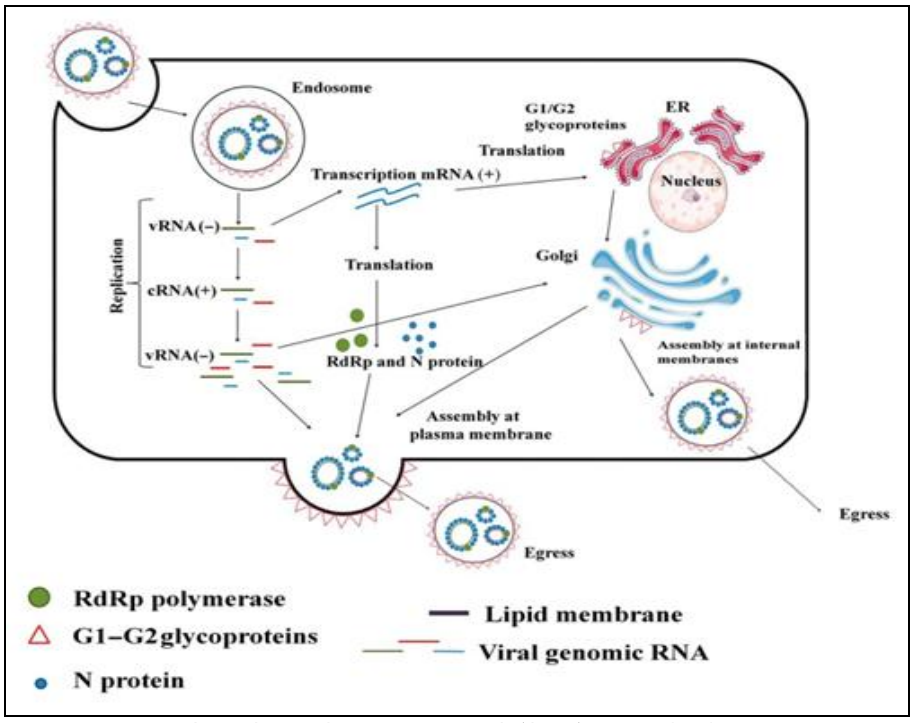

FIG. 7: SIN NOMBRE VIRUS (SNV) LIFE CYCLE

Virion binds to the cell surface membrane receptor and enters the cell via endocytosis. Once inside the cell, RNPs are released from the late endosome via pH-mediated membrane fusion. Virion-supplied RdRp is driving initial mRNA transcription, which takes place in cytoplasm. Viral genomic (minus sense) RNA serves as a template for the generation of mRNA utilized for protein synthesis. When sufficient amounts of the viral proteins are produced, RdRp switches to the replication mode synthesizing full-length anti-genomic (plus sense) RNA, which in turn serves as a template for producing a large amount of the new full length minus sense viral RNA molecules. Newly synthesized vRNA becomes encapsidated with N protein forming ribonucleoprotein and transported into the perinuclear membrane system, from where they will be transported to Golgi for initiation of virion formation. Egress takes place at the plasma membrane.

The main mode of transmission is through the aerosol spread of infected excreta (urine and possibly feces) and less frequently by bites of infected rodents. HCPS is an explosive febrile illness accompanied by myalgias and sometimes abdominal pain. In 4-5 days, respiratory symptoms appear and rapidly progress to severe noncardiogenic pulmonary edema with subsequent hypoxia and shock within hours. Cardiac dysfunction also occurs.

A fever precedes other symptoms of myalgia, chills, headache, dizziness, cough, nausea, shortness of breath, and a cough. The patient's fluid eventually shifts from the circulation to the lungs, causing a high white blood count and a low platelet count. The prodromal period exists for 3-5 days from time of infection.

Unfortunately, hantavirus infections can lead to HPS. According to the CDC, hantavirus infections according have a mortality rate of about 38%. At this time, there is no definitive treatment for HPS other than early recognition of HPS and subsequent medical support (usually consisting of symptomatic medical treatment and respiratory support or mechanical ventilation). Experimentally, doctors have administered the antiviral medication ribavirin (Rebetol, Copegus), but there are no clear data currently that establish that the drug is effective against HPS; however, its use against HFRS early in the disease suggests ribavirin can decrease illness and deaths. There is no vaccine available to protect against any hantaviruses to date.

2.7. Nipah Virus (NiV): Nipah virus (NiV) is an RNA virus belonging to the family *Paramyxoviridae*. It belongs to the genus *Henipavirus* which also contains Hendra virus (HeV) and the recently described Cedar virus. Bats are the natural reservoir of Henipaviruses [96].

NiV is highly pathogenic to a broad range of mammals and is considered to have pandemic potential due to its zoonotic as well as person to person transmission [97]. The reservoir of infection, *Pteropus* bats, has a worldwide distribution.

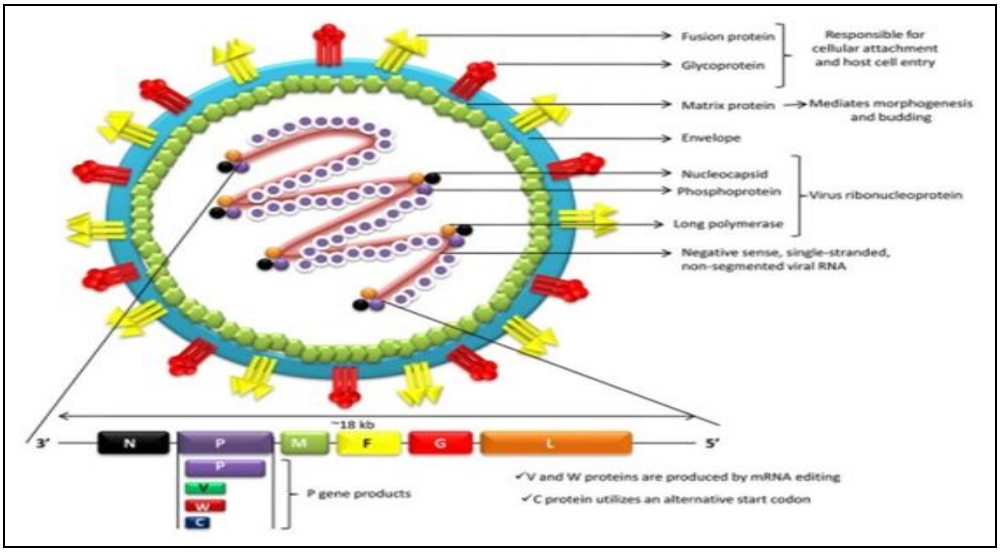

FIG. 8: STRUCTURE OF NIPAH VIRUS

Human NiV infection was first identified in Malaysia from 1998 to 1999 [98]. The name 'Nipah' comes from Sungai Nipah (Nipah River village). In India, there was a large outbreak (66 probable cases and 45 deaths) in Siliguri, West Bengal in 2001, and another smaller outbreak (five cases, 100% fatality) in 2007 in Nadia district, West Bengal [99].

They have a nonsegmented negative-stranded RNA genome consisting of helical nucleocapsids encased in an envelope forming spherical to filamentous, pleomorphic virus particles. Both HeV and NiV have a significantly larger genome than other paramyxoviruses [100]. **Fig. 8** show the genome encodes six structural proteins, the nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G), and large protein (L) or RNA polymerase, in the order 3′-N-P-M-F-G-L-5′. There are three predicted non-structural proteins, C, V, and W, which are all encoded by the P gene [101].

The incubation period of NiV varies from 4 to 21 days. NiV primarily causes acute encephalitis and respiratory illness and is highly fatal. A small percentage of infected people are asymptomatic [102].

Case-control study of risk factors for human infection with a new zoonotic paramyxovirus as in **Fig. 9**.

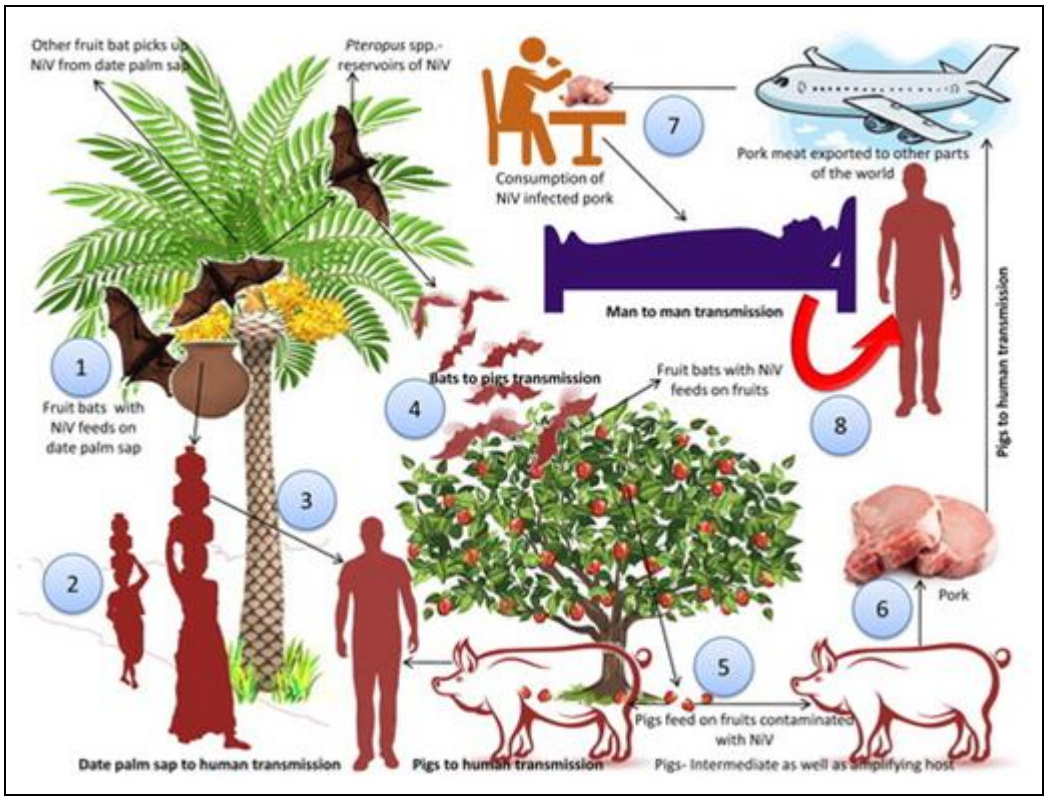

FIG. 9: TRANSMISSION OF THE NIPAH VIRUS

1. Fruit bats act as a natural reservoir of Nipah viruses. Fruit bats with NiV feed on date palm sap. The virus can survive in solutions that are rich in sugar, *viz*., fruit pulp. 2. The virus is transmitted to humans through the consumption of date palm sap. 3. Fruit bats of *Pteropus* spp. Which are NiV reservoirs visited such fruit trees and got the opportunity to naturally spill the drop containing the virus in the farm to contaminate the farm soil and fruits. 4. Contaminated fruits are consumed by pigs and other animals. Pigs act as intermediate as well as amplifying hosts. Combination of close surroundings of fruiting trees, fruits-like date palm, fruit bats, pigs, and human altogether form the basis of the emergence and spread of new deadly zoonotic virus infection like Nipah. 5. Pork meat infected with NiV is exported to other parts. 6. Consumption of infected pork can act as a source of infection to humans. 7. Close contact with NiV affected humans can lead to the spread of NiV to other persons.

A short incubation period is followed by prodromal signs and symptoms such as a fever, headache, and

myalgia [103]. Features of encephalitis develop within a week, with the most common symptoms being altered mental status, areflexia, hypotonia, segmental myoclonus, gaze palsy, and limb weakness. Patients deteriorate rapidly, and coma and death follow within a few days.

The NCDC, India, recommends throat swabs (in a viral transport medium), urine, blood and/or CSF for diagnosis. The best test for direct detection is polymerase chain reaction (PCR) due to its high sensitivity, specificity, and rapidity. NiV RNA can be identified by Real-Time PCR (RT-PCR) from respiratory secretions, urine or cerebrospinal fluid [104]. IgM antibody in serum or CSF is used for diagnosis. Detection of IgG antibodies is a good test for surveillance in humans and for the identification in reservoir animals during epidemiological investigations. ELISAs for the detection of IgG and IgM developed by the CDC were used in the confirmation of the diagnosis in Malaysia. It has since been used for surveillance in Bangladesh during NiV outbreaks[105].

Ribavirin, which is effective against other Paramyxoviruses (such as Respiratory Syncytial Virus) was used to treat infected patients in Malaysia. Acyclovir was used in Singapore but whether it was effective is unclear [106]. Favipiravir, a drug licensed in Japan for treatment of Influenza, has been shown to be effective in a hamster model[107]. Neutralizing human monoclonal antibody has been found to be effective in a non-human primate model [108]. The use of anti-G and anti-F monoclonal antibodies in an emergency setting is approved in India.

2.8. Zika Virus: The viruses of the *Flaviviridae* family found in arthropods (primarily in ticks and mosquitoes) can occasionally infect humans [109,110]. Members of this family belong to a single genus.

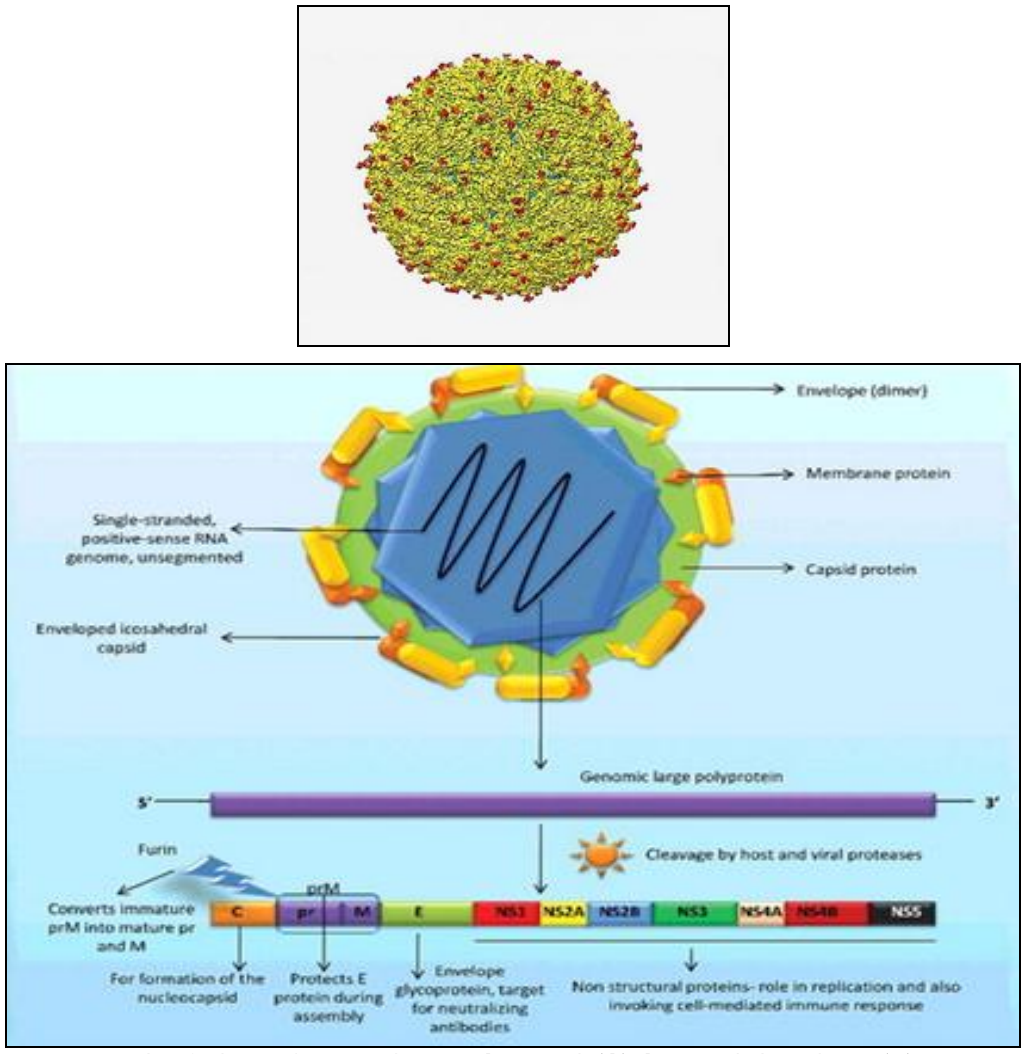

FIG. 10: STRUCTURE OF ZIKA VIRUS (A) AND ITS GENOME (B)

Zika virus is being transmitted by the mosquitoes [111]. Zika virus possesses an un-segmented, single-stranded, positive-sense RNA genome of approximately 11 kb and its single open reading frame (ORF) (10272 bp) encodes a polyprotein which includes three structural proteins *viz*., capsid, pre-membrane, and envelope and seven non-structural (NS) proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). Hitherto studies elucidate the phylogenetic relationship among Zika virus strains targeting selected genes (*e.g.*, envelope, NS3, NS5, *etc*.) from a few strains/ isolates. Still, we are falling short of a broad spectrum picture of Zika virus evolution **Fig. 10** (A) & (B).

Zika possess+ve sense RNA which has seven non-structural genes and three structural genes (C, M, E). M exists as prM (immature form), which gets cleaved to pr and M with the aid of furin enzyme.

The first Zika virus isolation was done in 1947, [112]. Since the Zika disease outbreak in Brazil during early 2015 [113], the disease is spreading rapidly across South and Central America, and Mexico [114].

As of 30th March 2016, locally transmitted (autochthonous) cases of Zika virus infection have been reported from 61 countries or territories worldwide [115] **Fig. 11**.

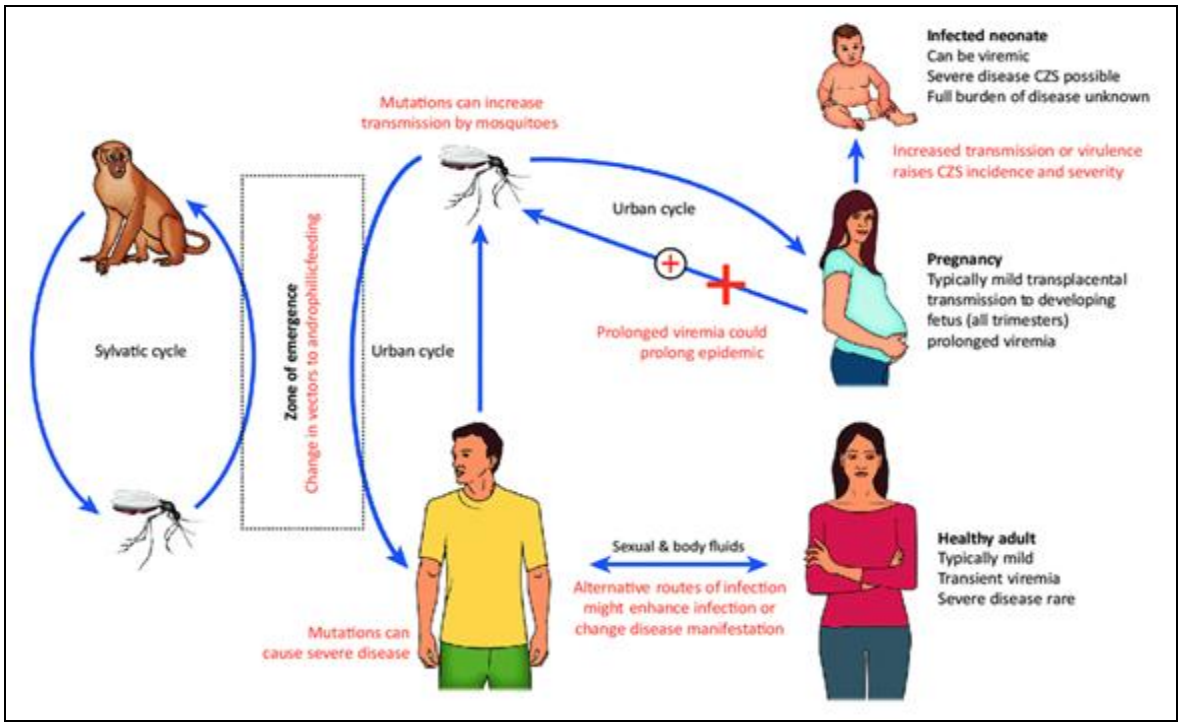

FIG. 11: TRANSMISSION OF ZIKA VIRUS

The family *Flaviviridae* comprises four genera *viz*., 1. *Flavivirus* (53 Species), *Hepacivirus* (one Species), *Pegivirus* (two Species), and *Pestivirus* (four Species). Based on virus transmission, the genus *Flavivirus* has further divided into three major groups *viz*., (1) tick-borne viruses (mammalian tick-borne virus group, seabird tick-borne virus group), (2) mosquito-borne viruses (Aroa virus group, Dengue virus group, Japanese encephalitis virus group, Kokobera virus group, Ntaya virus group, Spondweni virus group, and Yellow Fever virus group), and (3) viruses with no known arthropod vector (Entebbe bat virus group, Modoc virus group, and Rio Bravo virus group).

Zika virus has an incubation period of 3–12 days [116]. Clinical signs include acute fever, macula-papular skin rashes, non-purulent conjunctivitis, arthralgia, headache, myalgia, asthenia, edema of hand and feet, and less evident signs like anorexia, abdominal pain, vomiting, diarrhea, vertigo, burning sensation of sole and palm and at times there may be a pain in the retro-orbital region, and pruritis [117, 118]. Aedes mosquito injects the Zika virus while feeding on man, and the virus enters the cells through receptors like AXL, DC-SIGN, Tyro3, and Tim-1 (lesser extent) that are found on the surface of both skin and nerve cells [119]. Inside the cells, they use host machinery and finally cause

apoptosis and autophagy of the cells, thereby entering other cells.

In earlier reports, the Zika virus had been shown to have an affinity towards the brain that Zika virus can cross the blood-brain barrier Neurons and glial cells were infected by virus-producing intracytoplasmic inclusions called viral factories having their origin from the endoplasmic reticulum and also from mitochondria and nucleus [120].

Haemagglutination inhibition test, serum neutralization test and complement fixation tests have been employed for the diagnosis of Zika virus disease. The serological diagnosis involves the detection of IgG and IgM antibodies. For detecting antibodies against Zika virus in serum of patients, IgM antibodies can be monitored by ELISA [121].

Molecular diagnosis involves detecting RNA of Zika virus by RT-PCR. In the initial phase of the disease (first seven days) viral nucleic acids can be detected in the serum [122].

Advances in diagnostic techniques need to be applied for Zika virus detection *viz*., multiplex PCR, LAMP, recombinant diagnostics, gene sequencing, and phylogenetic analysis, biosensors, biochips, microarrays, and nanotechnology-based diagnostics [123].

Mechanical control methods involve the removal of any objects that can aid in unwanted storage of water in the premises that serve as a breeding point for female mosquitoes. Removal of those objects like plastic bags, unused tyres, unused containers, bottles, and also closing water tanks with lids can prevent breeding areas of the mosquitoes [124]. Chemical control of insects and vectors is an age-old technique and can be used with caution as it can cause toxicity to animals [125]. Recently, chemicals like pyrethroids, organochloride, and organo-phosphorus, which acts on the nervous system of the vectors, are being used to prevent mosquitoes.

Currently, there is no antiviral drug that can save the human population against potential pandemic threats of Zika virus. Only supportive treatment is in use for Zika virus disease like rest, use of fluids, and analgesics to reduce pain and antipyretics to reduce fever [126].

Antipyretics-like acetaminophen or dipyrone can be used to reduce fever; Xiyanping is a semi-synthetic component extracted from *Andrographis paniculata*, a Chinese herb [127] is used in treatment.

Vaccines are not yet available to counter the Zika virus infection. The development of the Zika virus vaccine requires a long timeline process.

2.9. Severe Acute Respiratory Syndrome (SARS): Severe acute respiratory syndrome (SARS) first emerged in China's Guangdong Province in November 2002. This virus (SARS-CoV) belongs to a family of large, positive, single-stranded RNA viruses. Nevertheless, genomic characterization showed that the SARS-CoV is only moderately related to other known corona-viruses [128].

The coronavirus genome is about 30 kb in size and generally encodes three broad protein classes [129] **Fig. 12**. Virions are roughly 90 to 120 nm in diameter and contain a lipid bilayer surrounding a helical nucleocapsid structure that protects the genome. Several structural proteins are encoded within the intact virion, and these include the 180/90-kDa spike (S) protein, a ~50- to 60-kDa nucleocapsid (N) protein, an 8-kDa envelope (E) protein, and the ~23-kDa membrane (M) protein.

These pathological events and cascade of changes form the basis for clinical symptoms and pathological findings at different stages of SARS. A correct understanding of the pathogenesis will provide guidance to the prevention, diagnosis, and treatment of this new disease. MIP-1α, macrophage inflammatory protein-1α; RANTES, regulated on activation normal T cell expressed and secreted; TNF-α, tumor necrosis factor-α; TGF-β1, transforming growth factor-β1; MCP-1, monocyte chemoattractant protein-1.

Most respiratory illnesses, including SARS, spread through droplets that enter the air when someone with the disease coughs, sneezes, or talks. Most experts think SARS spreads mainly through close personal contact, such as caring for someone with SARS. The virus may also be spread on contaminated objects - such as doorknobs, telephones, and elevator buttons [130, 131].

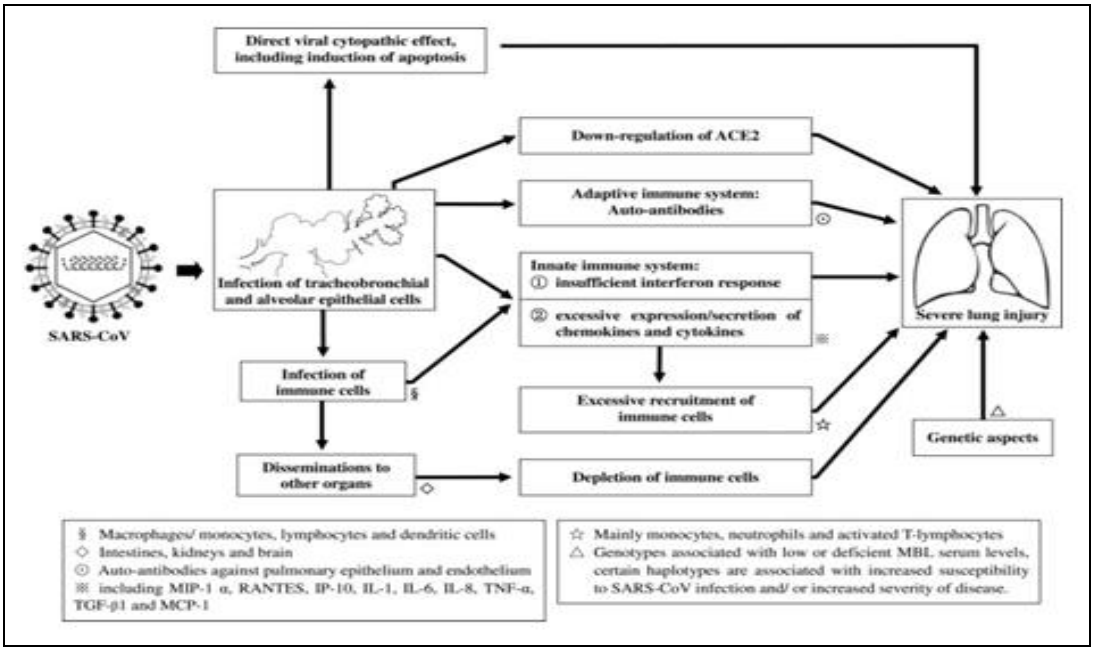

FIG. 12: MAJOR MECHANISMS CONTRIBUTING TO THE PATHOGENESIS OF SARS

Symptoms normally appear within 3 to 5 days after exposure to the SARS virus, but they can develop after 2 to 7 days. During the incubation period, before symptoms appear, the disease is not contagious.

Symptoms begin two to seven days after acquiring the virus. Initially, the illness resembles influenza and lasts for up to one week. Symptoms include fever, chills, headache, aches or pain in the muscles, a general feeling of weakness (malaise), and poor appetite. Nausea, vomiting, and diarrhea are less common. This period is followed by a syndrome suggesting atypical pneumonia, including dry cough and progressively worsening to severe shortness of breath (dyspnea) and inability to maintain oxygenation (hypoxia).

Progression may be rapid or it may take several days. Severely affected people develop a potentially fatal form of respiratory failure, known as adult respiratory distress syndrome (ARD or ARDS) [132-135].

Laboratory tests can help identify SARS-CoV.

Reverse transcription-polymerase chain reaction (RT-PCR) testing can detect the virus in the blood, stool, and nasal secretions.

Serologic testing can detect SARS-CoV antibodies in the blood. If a person has antibodies, they are also likely to have the infection.

Doctors may also use a viral culture. This involves putting a small same of body tissue or fluid into a container with some cells in which the virus can grow. If the virus grows, the cells will change.

Good personal hygiene practices can help restrict the spread of the virus.

These include:

- Frequent handwashing
- Avoiding touching the eyes, mouth or nose with unclean hands
- Covering the mouth and nose with a tissue when coughing or sneezing
- Encouraging others to do the same

Patients with SARS often require oxygen therapy, and severe cases require tracheal intubation and mechanical ventilation to support life until recovery begins. Severely ill patients should be admitted to the intensive-care unit. No medication has been proven to treat SARS effectively, and treatment is supportive and directed by the patient's clinical condition. Medical caregivers need to follow strict policies on gloves, masks, gowns, and other protocols to avoid becoming infected.

2.10. MERS-CoV: Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a novel human coronavirus that was previously called “novel human coronavirus Erasmus Medical

Center" (HCoV-EMC). The virus was discovered for the first time in Saudi Arabia in 2012 [136].

MERS-CoV belongs to the family *Coronaviridae*, order *Nidovirales*. It is one of the recently reported zoonotic viruses. The family *Coronaviridae* is classified into four genera (α, β, γ, and δ). Each genus is divided into linage subgroups. MERS-CoV belongs to lineage-C of the β coronaviruses. Although bats are the main reservoir for most coronaviruses, dromedary camels are considered the only known reservoir for MERS-CoV to date. Additionally, MERS-CoV isolated from dromedary camels is relatively closely related to some bat coronaviruses [137-139].

MERS-CoV belongs to the family *Coronaviridae* and has a large RNA viral genome of approximately 26-33 kb and G+C contents varying from 32 to 43% [140, 141]. The functional receptor of MERS-CoV is dipeptidyl peptidase 4 (DPP4) and its expression induces the infection. The DPP4 protein expresses large quantity conversion of amino acid sequences in various species [142]. MERS-CoV has the capability of infecting multiple human cell lines [143].

The fusion of S protein to the plasma membrane of host cell, formation of a double membrane vesicle in the host cell, eventually releasing the RNA enclosed in the nucleocapsid followed by genome transcription. The viral RNA undergoes replication and transcription followed by the 4, 5, and 6 RNA synthesis and translation; the endoplasmic reticulum aids the assembly and packaging of virus particle, forming a complete double-membrane vesicle and lastly through exocytosis and MERS-CoV is released out of the host cell **Fig. 13**.

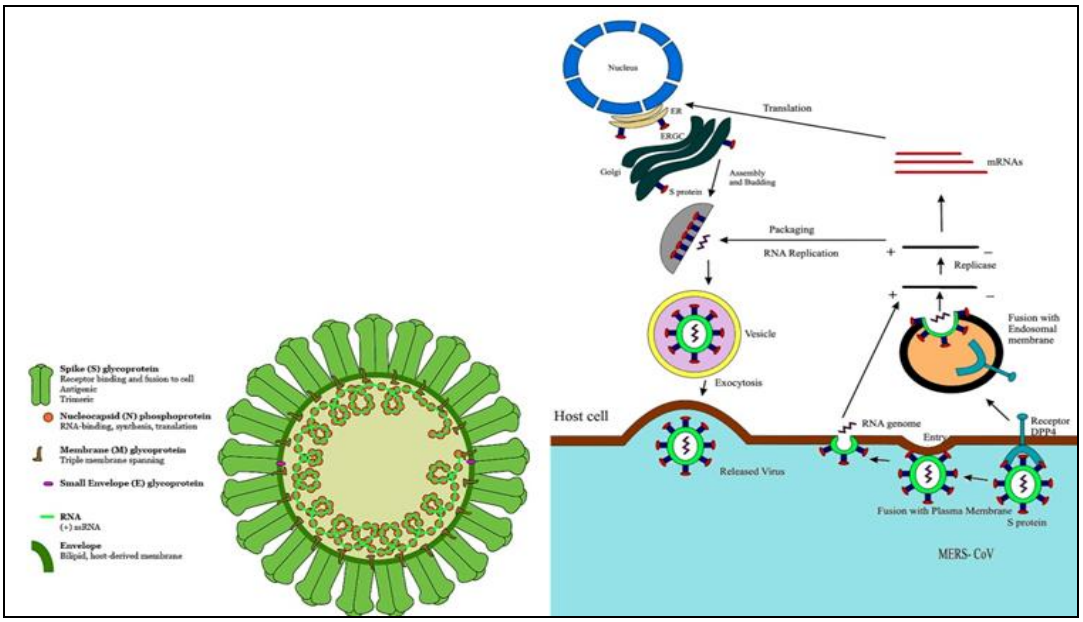

FIG. 13: LIFE CYCLE OF MERS-CoV DISPLAYING FUSION WITH PLASMA MEMBRANE

The genome of the coronavirus consists of 6 and 7 open reading frames (ORFs). The ORF 1a and 1b encompass two-third of the viral genome, which encodes the non-structural poly-proteins and the other four ORFs on the downstream side encode for the structural proteins such as envelope protein (E), Spike protein (S), nucleocapsid protein (N), and membrane protein (M). In some coronaviruses, the hemagglutinin-esterase (HE) gene is present in the region between ORF 1b and S [144]. These structural proteins are folded and entered into the endoplasmic reticulum (ER) and transported to the ER-Golgi transitional slot [145]. During the replication of coronavirus, substantial amounts of structural proteins are synthesized in order to assemble the progeny virions [146]. They occupy the RNA genome, which encodes structural proteins such as S protein, M protein, and N protein [147].

MERS-CoV can infect non-human primate, porcine, bat, civet, rabbit, as well as horse cell lines [148]. Infected patients often indicate the presence of hemoptysis, sore throat, fever, cough, shortness of breath, and other gastrointestinal symptoms such as

diarrhea and vomiting [149]. MERS-CoV causes disease of the lower respiratory tract and can be found in tracheal aspirates, sputum, or broncho-alveolar lavage fluid of symptomatic patients.

The primary diagnosis of MERS-CoV infection was performed by molecular techniques such as real-time reverse transcriptase PCR (RT-PCR) [150], reverses transcription–loop-mediated isothermal amplification (RT-RTPA) [151,] and reverses trans-cription-recombinase polymerase amplification (RT-LAMP) [152]. Numerous serological assays were used to detect MERS-CoV or closely related viruses in seropositive camels; these tests were protein microarrays like indirect enzyme-linked immunosorbent assay (ELISA), recombinant spike immunofluorescent assay, spike pseudoparticle neutralization, and microneutralization assay [153 154].

Administration of both ribavirin and interferon-α2b may decrease viral load, as they decrease the multiplication of MERS-CoV in Vero as well as LLC-MK2 cells [155]. It is hypothesized that DPP4 inhibitors may restrain viral replication; this yet requires further study. Further, the development of vaccination targeting receptor binding subdomain (RBSD) of MERS-CoV is under investigation. Recently, a candidate DNA vaccine developed from the MERS-Cov spike protein subunit 1 (S1) is under study.

No vaccination or treatment is currently available for MERS-CoV. A great challenge exists in developing MERS-CoV infection models for several reasons. For one, small and larger animal models that aid in initial screening do not express the DPP4 receptor [156].

2.11. SARS – COV-2 (COVID-19): The 2019-nCoV is officially called SARS-CoV-2, and the disease is named COVID-19. The Novel corona-virus (SARS-CoV-2) caused pneumonia in Wuhan, China in December 2019 is a highly contagious disease[157]. The origin of SARS-CoV-2 was thought to be wild animals in the Huanan Seafood Market in Wuhan. However, not all cases have an apparent connection with the Wuhan Huanan Seafood Wholesale Market. It is evident now that SARS-CoV-2 is capable of person-person transmission.

As the largest known RNA viruses, CoVs are further divided into four generations: alpha-coronavirus, beta- coronavirus, gamma-coronavirus and delta-coronavirus [158]. Nowadays, there are six human coronaviruses (HCoVs) that have been identified, including the alpha-CoVs HCoVs-NL63 and HCoVs-229E and the beta-CoVs HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV) [159], and Middle East respiratory syndrome-CoV (MERS-CoV) [160].

All coronavirus genomes are arranged similarly with the replicase locus encoded within the 5’ end and the structural proteins encoded in the 3’ third of the genome arranged in the order hemagglutinin esterase (HE), if present (HE is only present in some beta coronaviruses), spike (S), small membrane (E), membrane (M)and nucleocapsid (N) and internal (I) protein, encoded within the N gene. The nucleocapsid protein complexes with the genome RNA to form a helical capsid structure found within the viral envelope. Trimers of the spike protein form the peplomers embedded in the envelope giving the virion its corona or crown-like morphology. In some coronavirus virions, the HE protein forms smaller spikes on the membrane. M and E are also transmembrane proteins involved in virus assembly [161] **Fig. 14**.

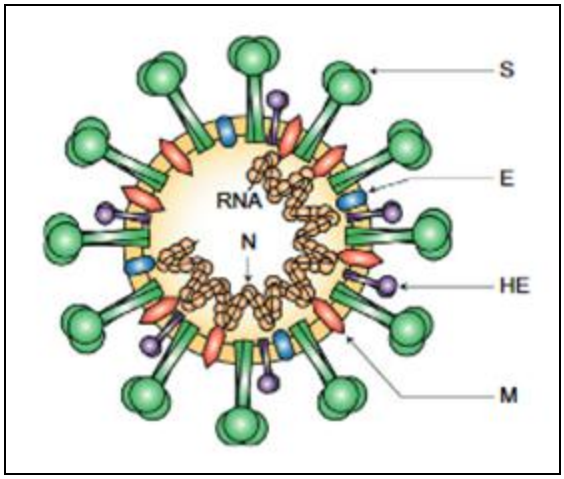

FIG. 14: CORONAVIRUS VIRION STRUCTURE

The various CoVs of animal origin undergo evolution and genetic recombination, thereby resulting in mutated CoVs that may be highly pathogenic and potentially be more deadly to humans [162].

SARS-CoV originated from bats of the Hipposideridae family before dissemination to humans [163]. CoVs can transmit across species barriers. The earliest patients infected with SARS-

CoV-2 in Wuhan ultimately caused the epidemic known as CoronaVirus Disease 2019 (COVID-2019) [164]. Some of these patients had a history of contact with a wholesale seafood market in the early stages, suggesting animal-to-person spread. Subsequently, a large number of patients reportedly did not have exposure to the markets, suggesting the development of person-to-person [165-168].

There are three ways to transmit the virus, including [169-171]:

1. Close person-to-person contact
2. Aerosol transmission
3. Transmission by touch

The mean incubation period of CoVID-19 is 2 to 14 days. A symptom of CoVID-19 can range from no symptoms (asymptomatic) to severe pneumonia and death. The patients were initially diagnosed with the outbreak found that the most common symptoms were fever, cough, myalgia or fatigue, and atypical symptoms included sputum, headache, hemoptysis, and diarrhea. About half of the patients had dyspnea (the median from onset to dyspnea was 8 days). Lymphocytopenia and pneumonia were observed in all patients [172].

The identification of CoVID-19 mainly includes virus isolation and viral nucleic acid detection. A variety of specimens (such as swabs, nasal swabs, nasopharynx or trachea extracts, sputum or lung tissue, blood, and feces) were used for testing in a timely manner, which gives a higher rate of positive detection of lower respiratory tract specimens [173]. The Patients suspected SARS-CoV-2 infection for diagnosis by real-time RT-PCR method [174].

There's currently no treatment specifically approved for COVID-19, and no cure for an infection, although treatments and vaccines are currently under study. Instead, treatment focuses on managing symptoms as the virus runs its course. The general strategies include bed rest and supportive treatment, including antiviral therapy [175] (Lopinavir/ritonavir [176] Darunavir/ritonavir (possibly in combination with umifenovir), Remdesivir [177]), antibiotics (Chloroquine) application, immunomodulating therapy [178] (Tocilizumab), organ function support, respiratory support, bronchoalveolar lavage (BAL), blood purification and extra-corporeal membrane oxygenation (ECMO) [179]. convalescent plasma therapy could be an effective way to alleviate the course of disease for severely infected patients [180]. Corticosteroid therapy is not recommended for viral pneumonia; however, use may be considered for patients with refractory shock or acute respiratory distress syndrome. At present, unfortunately, there is no FDA approved vaccine against SARS [181].

Apart from antiviral treatment, public health management includes personal protective measures like:

- Regular hand washing with proper drying of the hands.
- Good respiratory hygiene – covering mouth and nose when coughing or sneezing, using tissues and disposing of them correctly.
- Early self-isolation of those feeling unwell, feverish and having other symptoms of influenza.
- Avoiding close contact with sick people.
- Avoiding touching one's eyes, nose, or mouth.

Health care workers performing aerosol-generating procedures should use airborne precautions. Standard contact and droplet precautions and appropriate personal protective equipment (PPE) should be made available and used during epidemics.

Travelers to countries and people living in countries with known outbreaks of avian influenza should, if possible, avoid poultry farms, contact with animals in live poultry markets, entering areas where poultry may be slaughtered, and contact with any surfaces that appear to be contaminated with faeces from poultry or other animals. Good food safety and food hygiene practices *e.g.*, hands washing with soap and water, should be followed. Travelers returning from affected regions should report to local health services if respiratory symptoms suspecting zoonotic influenza virus infection.

Pre-exposure or post-exposure prophylaxis with antivirals is possible but depends on several factors *e.g.*, individual factors, type of exposure, and risk associated with the exposure.

3. Pandemic Potential: Large proportion of the world affect due to a novel virus. Pandemics are unpredictable due to zoonotic viruses, but recurring events can cause health, economic, and social consequences worldwide. A pandemic occurs when a novel virus emerges with the ability to cause sustained animal-to-human or human to human transmission, and the human population has little to no immunity against the virus. With the growth of global travel, a pandemic can spread rapidly globally with little time to prepare a public health response.

Ongoing circulation of some zoonosis viruses in poultry, such as A(H5) and A(H7) viruses, swine, monkey, bat, dog, fish, is of a public health concern as these viruses cause severe disease in humans and the viruses have the potential to mutate to increase transmissibility among humans. Whether currently-circulating avian, swine, and other zoonotic influenza viruses will result in a future pandemic is unknown. Several infectious viral agents (DNA and RNA viral families) have emerged as zoonotic agents. They are associated with flu-like signs (Alkhumra virus infection, influenza A) to respiratory (SARS), pox lesions mostly localized distributed over hairless parts of body namely udder, teats, ears and tail (in buffaloes) and fingers and hands (in humans) due to buffalopox and Orf virus infections in affected goats, hepatitis (hepatitis E virus), haemorrhagic fevers (Ebola, Marburg and hanta virus infections) and encephalitis (Henipa virus complex). Treatment/prophylaxis is not available to many of these infections. But some of the antiviral compounds, which are under trial, are found to be effective.

4. Future Perspectives of Rare Viral Zoonosis: The complex interaction between environment/ ecology, social, health care, human demographics and behavior influences the emergence and re-emergence of zoonotic viral diseases. Periodic discovery of new zoonoses suggests that the known viruses are only a fraction of the total number that exists in nature. The RNA viruses are capable of adapting to changing environmental conditions rapidly and are among the most prominent emerging pathogens. Mutations are more common in RNA viruses (Influenza) than DNA viruses (Pox). The common mutations are point (insertion/ deletion), drift (minor), and shift (major).

In addition to these, movement of population, birds, vectors, pathogens, and trade contribute to the global spread of emerging infectious diseases (influenza, severe acute respiratory syndrome). Other factors *viz*., human migration, change in land use pattern, mining (disturbance of ecosystem), coastal land degradation, wetland modification, construction of buildings, habitat fragmentation, deforestation, expansion of agents host range, human intervention in wildlife resources like hiking, camping, and hunting also influence on acquiring zoonotic infections from wildlife.

Despite successful eradication of some viral diseases (smallpox and almost polio in humans and rinderpest in cattle) due to intensive research and dedicated coordinated efforts, modern medicine has failed to control many infectious diseases resulting from emerging and re-emerging viruses. Some infectious agents already known to be pathogenic have gained increasing importance in recent decades due to change in disease patterns. Several previously unknown infectious agents with high pathogenic potential have also been identified.

Several viral infections cause a nonspecific febrile illness in humans and occur rarely. Many of them are animal pathogens, but often they produce nonspecific febrile illnesses in humans, though humans are not the primary hosts. However, there is an increasing trend of occurrence of such infections in recent times. Transmission of these infections have been reported upon direct contact of human objects with an infected animal (FMD, particularly serotypes O followed by C and rarely A, buffalo pox, Orf), handling of such organisms in the laboratory (bluetongue, Newcastle disease), sexual contact (simian immunodeficiency (SID) virus), bite/ scratch (monkey B virus), vectors (semliki forest virus, African horse sickness and louping ill) and food and water (calici viruses such as swine vesicular exanthema, feline calicivirus and rabbit haemorrhagic disease virus causing vomition and diarrohoea. Recently, animal rotaviruses and Eyach virus related to Colorado tick fever virus and Oropouche fever virus, an arbovirus to dengue fever in Trinidad are reported to cause mild infections in humans.

Prion diseases are caused by scrapie associated prion protein (PrP^{sc}), which are pertinacious

infectious agents common in animals and humans. Some of the animal prion diseases are scrapie of sheep, Bovine Spongiform Encephalopathy (BSE) and goats, and mink spongiform encephalopathy. Human prion diseases are Creutzfeldt-Jakob Disease (CJD), Kuru, Gertsmann Straussler Schienker Syndrome (GSS) and fatal familial insomnia. The human disease variant (vCJD) is believed to be a zoonotic disease caused by BSE agent and recently an emerging disease as well. Transmission of infectious agents between species through xenotransplantation called xenosis is another way of introducing viruses from animal to human (porcine endogenous retroviruses).

5. Recommendation: Over the past few decades, the understanding and recognition of the Zoonosis virus have greatly improved worldwide. Both the amplitude and the magnitude of Zoonosis virus outbreaks have been increasing. This could be explained by better clinical awareness, development of sensitive diagnostic tests, intensive research on the reservoir, and changing climatic conditions. Although some are newly detected, viruses are old viruses, but environmental changes may affect the geographic distribution, abundance, and the dynamic of the carrier rodent species, and hence the epidemiology of virus disease. Although, today, we can only speculate how extensive environmental and climatic changes will be responsible for viral infection. Therefore, further research on zoonotic virus pathogenesis, diagnostics, antiviral, and vaccine development are needed.

This could be accomplished through the development and implementation of uniform data collection forms on patient and disease characteristics for those treated from Zoonosis virus infection, through the collaboration of local ministries of health and international relief organizations. Information on the length of viral shedding in different secretions (including saliva, breast milk, and genital secretions) and their potential to transmit disease is also needed to help inform guidance on preventing secondary transmission of pathogenic viruses.

More studies are needed to confirm the pathophysiology of the infection in order to identify new targets for medical intervention. Although it is necessary to speed up the pace of developing effective vaccines and therapeutics for the prevention and treatment of Zoonosis virus, public health prophylaxis is the most important issue at present to control the spread of this disease cost-effectively. The ability to predict which viruses are capable of spreading among humans, and therefore have the potential to cause human epidemics has practical implications.

6. Prevention, Control Measures and Perspectives: Effective prevention and control measures can be achieved through proper diagnostics and prophylactic aids to curtail further spread in most of the zoonotic viral diseases. Improved sanitary conditions such as proper treatment and disposal of human waste, higher standards for public water supplies, improved personal hygiene procedures, and sanitary food preparation are vital to strengthening the control measures. A clear understanding of the epidemiology of the diseases with wildlife as a reservoir, namely the virulence and transmissibility of many diseases (human monkeypox, Tana pox, and Yaba pox) could help in understanding the severity and thereby to take appropriate measures in the eradication of such dreadful diseases. Research should focus on the molecular biology of these viruses so as to develop diagnostics and prophylactics in a modern way to combat these infections in a short time. To safeguard the public health from pathogens of zoonotic infections, the application of skills, knowledge, and resources of veterinary public health is essential. It is time to combat viral zoonoses with a combined effort of veterinary and public health specialists. A better understanding of avian migration patterns and their infectious diseases would be useful to forecast disease outbreaks due to emerging zoonotic infections like avian influenza.

Further, the control measures for emerging and re-emerging viral pathogens are demanding, as there is a population explosion. Novel, highly sensitive, and specific techniques comprising genomics and proteomics along with conventional methods would be useful in the identification of emerging and re-emerging viruses; thereby, therapeutic/prophylactic / preventive measures would be applied on time. The first line of measure to control any disease is surveillance. Control and prevention strategies

should be designed based on the transmission pattern and characteristics of the virus, the involvement of vectors, the environment, and the epidemiology of the disease.

CONCLUSION: Strong antiviral treatment has improved the prognosis of many kinds of viral diseases. Therefore, new potent antiviral drugs against the novel virus should be developed. It should be emphasized that more and more studies are now focusing on the pathogenesis of increased capillary leakage. This research direction may provide great inspiration for the searches on effective therapies and exploring potential therapeutic targets. Further important questions mainly refer to the identification of risk factors, preventive measures, and vaccination.

However, the diversity of zoonotic influenza viruses that have caused human infections is alarming and necessitates strengthened surveillance in both animal and human populations, a thorough investigation of every zoonotic infection, and pandemic preparedness planning.

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