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A COMPREHENSIVE REVIEW ON EMERGENCE, TRANSMISSION, DIAGNOSIS AND TREATMENT OF NIPAH VIRUS

Diptee Gupta [*1], Sudhir Kumar [2] and Anchal Srivastava [3]

Krishna Institute of Pharmacy & Sciences [1], Kanpur - 208001, Uttar Pradesh, India.
Seth Vishambhar Nath Institute of Pharmaceutical Sciences [2], Deva Road, Lucknow - 225003, Uttar Pradesh, India.
Maharishi University of Information & Technology [3], Lucknow - 226013, Uttar Pradesh, India.

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Correspondence to Author:
Diptee Gupta

Research Scholar,
Krishna Institute of Pharmacy & Sciences, Kanpur - 208001, Uttar Pradesh, India.

E-mail: gdiptee98@gmail.com

ABSTRACT: Currently, COVID-19 pandemic is a major zoonotic disease that has killed millions of people all over the world. Similarly, Nipah virus (NiV), causes severe acute respiratory syndrome (SARS) along with febrile encephalitis. NiV belongs to the class of paramyxovirus of the genus Henipavirus is a deadly virus that has caused several outbreaks in recent years. Despite the fact that NiV causes a small number of infections, the severity of the disease results in a higher death rate unlike COVID-19 infection. Many research studies termed bats as a natural host for NiV. Recently two NiV strains were identified *i.e.* NiV-MY (Malaysian strain) and NiV-BD (Bangladesh strain), is the major cause of epidemic in various geographical areas. Various techniques like ELISA, immunohistochemistry and polymerase chain based reaction have been developed for diagnostic purposes. Currently, there is no approved treatment or vaccine available for either people or animals, and treatment is limited to supportive care. In context with current COVID-19 pandemic, health infrastructure in many countries will be incompetent to manage such sudden viral outbreaks. Therefore, in this review we have discussed the outbreak of NiV, mode of transmission, pathogenesis, diagnostic methods, and available treatment strategies for NiV infected individuals.

INTRODUCTION: Nipah virus (NiV) is recently recognized as a class of paramyxovirus of the genus Henipavirus. It is a zoonotic virus and can also be transmitted through contaminated food or person to person. In infected people, it causes a wide range of diseases from asymptomatic infection to severe acute respiratory illness and fatal encephalitis in humans. It has many physical attributes to serve as a potential agent of bioterrorism [1].

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A major NiV outbreak occurred in pigs and humans from September 1998 to April 1999 in Malaysia & Singapore [2]. Three years later, a genetically distinct NiV independently emerged in India as well as in Bangladesh [3]. NiV also caused an outbreak of a disease in horses and people in the Philippines in 2014 [3]. The case-fatality ratio is 38%–75% in Malaysia and Singapore.

Its name originated from Sungai Nipah, a village in the Malaysian Peninsula where pig farmers became ill with encephalitis. NiV is closely related to Hendravirus (HeV), which recently was discovered in Australia as a cause of disease in horses and humans [4] but flying foxes of the genus *Pteropus* were subsequently identified as the reservoir for NiV [3]. Laboratory investigations by Dr. K. B. Chua at the University of Malaysia, uncovered the

culprit, the newly discovered NiV [4]. The virus is found in the urine and saliva of infected flying foxes, and pigs consuming foodstuffs contaminated by these secretions can be infected [5]. Nipah virus infection causes a high mortality rate in humans. NiV can survive in the environment for long periods in favorable conditions; it survives for days in fruit bat urine and contaminated fruit juice. Antibodies to NiV antigen were detected into *Pteropus giganteus* adult females from Bangladesh [6]. Recently, antibodies to NiV and virus isolation were successfully demonstrated in *Pteropus lylei* from Cambodia [6].

It is considered that NiV is a biosafety level-4 pathogen [4]. Due to its high mortality rate in people and the lack of effective vaccines, NiV is listed as a selective agent with high risk for public health and security [7]. Diagnosis of NiV infection is done with clinical history during the acute and convalescent phase of the disease. Although NiV has caused only a few known outbreaks in Asia, it infects a wide range of animals and causes severe disease and death in people, making it a public health concern. W.H.O. has identified Nipah as a priority disease for the W.H.O. Research and Development Blueprint.

Outbreak of Nipah Virus: Nipah Virus is a highly fatal emerging disease that causes severe febrile encephalitis resulting in death in 40% to 75% of human cases which has been shown in **Fig. 1**. NiV was first recognized in Peninsula Malaysia during a 1998 outbreak [7]. It spread due to close contact with infected pigs. Dr. K. B. Chua has presented a detailed account of the initial Nipah outbreak in Malaysia [2]. In Malaysia, a total of 265 cases were reported in which 105 died.

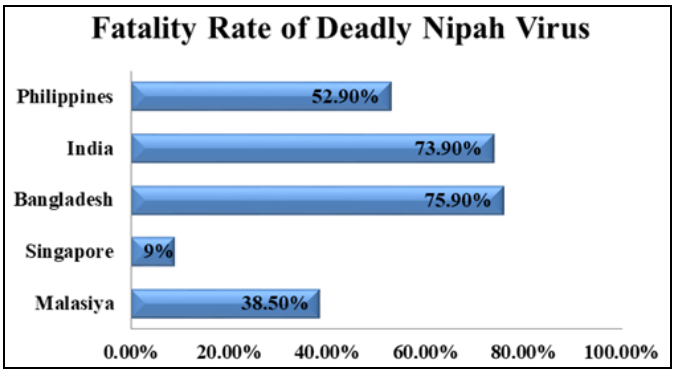

FIG. 1: FATALITY RATE OF INDIVIDUALS INFECTED BY NIPAH VIRUS (ADAPTED FROM HAUSER *ET AL*, 2021)

Nipah virus is similar to the HeV that was discovered in Australia in 1994 where it caused severe illness and death among the people. In March 1999 after handling imported pigs from Malaysia 11, abattoir workers in Singapore became infected. An outbreak in Singapore ended when the importation of pigs from Malaysia was prohibited, and the outbreak in Malaysia ceased when more than one million pigs were euthanized which caused a high social economy loss. Since 1999, no new outbreak has been reported in Malaysia & Singapore [8].

In 2001, in India, at Siliguri, West Bengal the first recorded outbreak of NiV infection occurred, affecting 66 persons with a mortality rate of 68% [9]. In Nadia, West Bengal, in 2007 it affected 5 individuals with a 100% mortality rate.

In Bangladesh during the winters of 2001, 2003, and 2004 NiV like virus was identified as the cause of the outbreaks of fatal, febrile encephalitis in humans [10]. Two outbreaks consisting of 48 cases of NiV were detected in 2004 in 2 adjacent districts (30 km apart) of central Bangladesh (Rajbari and Faridpur) with a case-fatality rate of nearly 75% [10, 11]. During May-June 2018 an outbreak occurred in Kerala in which 23 cases were identified, only 2 cases survived with a 91% fatality rate.

Malaysia and Singapore: In 1997 an outbreak of an encephalitic illness among pig-farm workers was reported from the Kinta District in the state of Perak in Malaysia; one patient died [12]. The region is endemic for Japanese encephalitis virus infections and, despite some uncharacteristic clinical features, the cases were assumed to have been caused by this virus. In September 1998, again in Perak, the numbers of adults presenting with a high fever and an encephalopathic illness rose sharply. All these patients either were pig farmers or directly associated with the pig industry [13].

In 1998-1999 Nipah virus emerged in Malaysia and Singapore as a porcine respiratory and neurologic disease. Two major strains of the NiV were isolated from pigs in Malaysia. In May 1999, the Malaysian Ministry of Health, in association with the Centers for Disease Control and Prevention (CDC), Atlanta, reported a total of 258 cases of encephalitis in

adults, with a case fatality rate of almost 40%. The predominant symptoms in Malaysian patients were fever, headache, altered mental state, vomiting, and loss of consciousness Myoclonus, areflexia, and tachycardia were among the signs that indicated brain stem dysfunction and central nervous system (CNS) involvement [14].

Bangladesh: In Bangladesh between 2001 and 2005, five outbreaks of NiV infection have been recognized; transmission to humans by direct contact with bats or indirectly by contact with material contaminated by bats. Person-to-person spread was also noted during the 2004 NiV outbreak in Faridpur, Bangladesh [2, 13]. 102 human cases of Nipah infection have been reported; 75% of those were fatal. Genetic characterization of the Nipah virus isolated from humans in Bangladesh in 2004 is distinct from the Malaysian strain, with the two viruses having approximately 92% nucleotide sequence homology [7].

Siliguri, India: An outbreak of the first NiV attack in India occurred in Siliguri (West Bengal) between January 31 and February 23, 2001 [2, 15]. A total of 66 probable human cases and 45 deaths were reported. NiV strains associated with the outbreak in Siliguri were more closely related to NiV isolated in Bangladesh [15]. After 2001, the second NiV outbreak was reported in Nadia district, West Bengal, India in 2007 [8]. The cases presented mainly with fever, headache and body ache with a few cases having episodes of vomiting, disorientation and respiratory distress [2, 16].

Philippines: In Philippines, the outbreak was reported in 2014 that included 17 cases of NiV infection & case fatality rate of 80%. The infection occurs due to consumption of horse meat i.e infected by fruit bats. The strain responsible for transmission is closely related to NiV-BD strain [17].

Kerala, India: It was the first NiV outbreak in South India that lasted for approximately 1 month (2–29 May 2018) and resulted in 23 cases and a case-fatality rate of 91% [9]. It occurred as direct zoonotic transmission from fruit bats, particularly *P. giganteus* (Indian flying fox), which is abundant in the area. All remaining cases were due to nosocomial transmission in 3 different hospitals. Recently in 2019, one patient tested positive for Nipah virus infection was reported in the Ernakulam district of Kerala. Approximately 300 people came in contact with an infected patient; all of these have acquired symptoms of NiV infection [18]. These were all kept in a strictly isolated environment and monitored for every response. Kerala government's farsighted approach tackled these conditions rapidly and prevented the spread of the infection at a huge level [19]. In the era of Covid-19 pandemic, a NiV case was also confirmed in a 12 year old boy at Kerala's Kozhikode hospital and his death was reported in September, 2021. As per report, Rambutan fruit infected via bat saliva was consumed by the boy, a few days before the death [20].

Identification of NiV: On 11th of March 1998, after 3 days of inoculated and inactivated Vero cells infected with the virus were ready for viewing under an electron microscope, Dr. Chau took ultra-thin sections of electron microscopy slides prepared by Ms. Elsie Wong of the Department of Pathology [21]. On the 14th of March, Dr. Chau met Dr. Nick, the Centers of Disease Control Prevention (CDC), USA and they recognized a "concrete ring-like" structure of paramyxovirus nucleocapsids.

Structure: Nipah virus is the newly originated Henipavirus genus with the closely related Hendra and Cedar virus. NiV is classified under the subfamily Paramyxovirinae in the family Paramyxoviridae that comprises the five genera *Respiro-*, *Morbilli-*, *Rubula-*, *Avula-* and *Henipavirus* [22]. The genus Henipavirus contains two of the most pathogenic viruses known in humans, HeV and NiV virus. NiV contains 18.6 kb-long negative-sense single-stranded RNA (ss-RNA). The genome consists of six genes yielding nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), glycoprotein (G) and large RNA polymerase (L) described [23] in **Fig. 2.** The genome of Henipa group of viruses is large, around 18, 250 nucleotides as compared to other members of paramyxoviruses. The G and F proteins of NiV are required in mediating the viral entry into the cell as well as for inducing neutralizing antibodies [1]. The M proteins of NiV are essential for morphogenesis and budding [24]. The N, P and L proteins together form virus ribonucleoproteins (vRNP) that are attached to viral RNA [25].

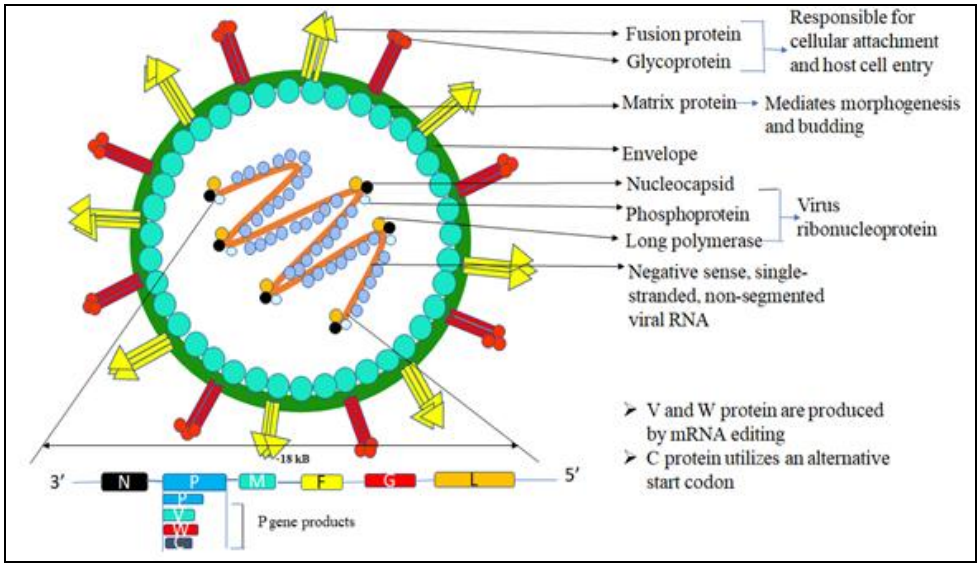

FIG. 2: STRUCTURE OF NIPAH VIRUS GENOME

Genetic Lineages of NiV: The NCBI database has a collection of various strains of NiV submitted by various countries including Malaysia, Cambodia, Bangladesh, Thailand and India during 2001-2018. These strains taken from a database and a phylogenetic analysis are done by using the maximum likelihood method (1000 bootstrap replicates) in MEGA 6 software (v 6.06).

These studies revealed two major strains of NiV *i.e.* NiV BD and NiV MY. The genome of NiV BD is six nucleotides longer as compared to NiV MY thereby NiV B have a high fatality rate [26]. The outbreak in Malaysia and Cambodia was likely caused due to NiV MY while the outbreak in India and Bangladesh due to NiV BD strains [27]. The NiV BD cases mainly have lethal encephalitis problems while NiV MY have encephalitis with some common respiratory symptoms [28].

Ephrin B_2 is Entry Receptor for NiV: Due to their BSL4 categorization, research on the NiV has been restricted, however, recent studies using HeV proteins expressed from cloned genes elaborates the unique properties of particular HeV proteins [29]. Recent research revealed that G protein of both HeV and NiV binds to a cell surface-bound receptor Ephrin B_2, a class of receptor tyrosine kinases (RTKs), which specifically binds to G-glycoprotein (G) of NiV. The study data suggest that ephrin B_2 is a functional receptor for NiV entry *in-vivo*. This study was performed using human microvascular endothelial cells (HMVECs) and primary rat neurons [30]. Ephrin B_2 is expressed on neurons, endothelial cells, and smooth muscle cells surrounding small arteries [31]. Ephrin B2 is a critical gene involved in embryogenic development and has established roles in vasculogenesis and axonal guidance.

Transmission: Due to the similarity between NiV and HeV, it is considered that flying foxes (fruit bats) are a natural host of the Nipah virus [2]. In the Malaysian outbreak, infected pigs were the source of infection in the farm workers. But preliminary data suggested pigs are effective "dead-end" hosts. NiV is present in urine, saliva, pharyngeal and respiratory secretions of infected pigs and bats. The outbreak of NiV among abattoir workers in Singapore also showed the associatedness of infected pig urine and exposure to the workers. No occurrence of person-to-person transmission was reported in Malaysia and Singapore outbreak [32, 33]. Different possible routes of transmitting NiV are illustrated in **Fig. 3**.

Two outbreaks in India and several outbreaks of NiV have been reported in human beings in Bangladesh from 2001 to 2013 but none had shown any involvement of pigs [2, 34]. According to an investigation, various routes were involved in the transmission of NiV in Bangladesh such as infected date palm sap with the bat, contact with infected persons, and contact with infected animals. Ingestion of fresh date palm sap is the most frequently implicated route in the first outbreak of Bangladesh. Infrared camera studies confirm that *P. giganteus* bats frequently visit date palm sap

trees and lick the sap during collection [35]. Date palm sap is a national delicacy that is enjoyed by millions of Bangladeshis each winter [12]. It is processed at high temperatures to make molasses. But some people prefer to drink raw juice. The first exposure in Bangladesh was significantly associated with drinking raw date palm sap.

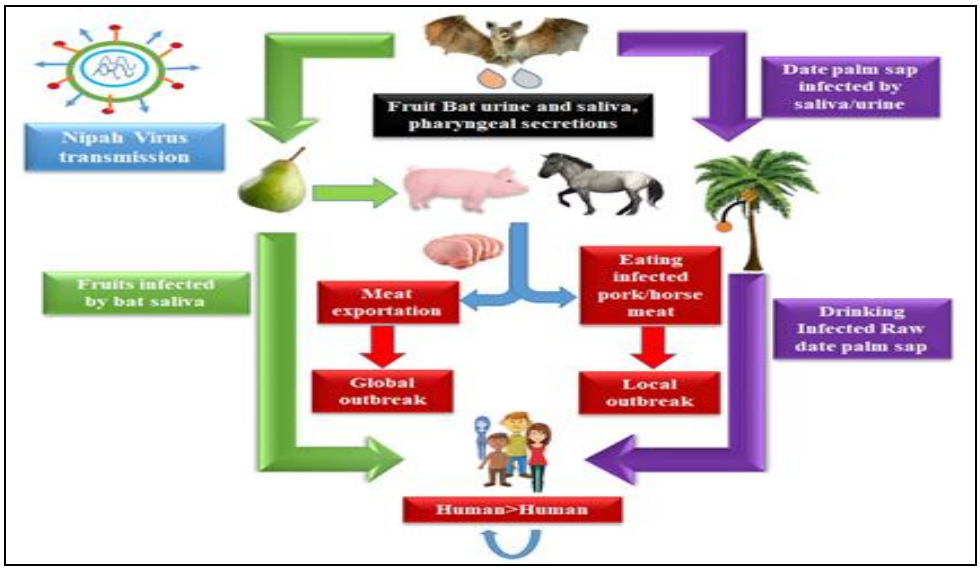

FIG. 3: POSSIBLE ROUTE OF TRANSMISSION OF NIV FROM NATURAL HOST (FRUIT BATS) TO OTHER FARM ANIMALS INCLUDING HUMAN

The second exposure of the NiV occurred due to chain transmission that was from fruit bats to domestic animals to humans. Fruit bats commonly drop partially eaten saliva-laden fruit which was occasionally fed by domestic animals and they shed the virus to other animals including humans [3, 35]. This type of transmission was observed in Meherpur, Bangladesh in 2001.

The third exposure of the NiV was due to person to person transmission, which was observed in Faridpur, Bangladesh, 2004. Respiratory secretions appear to be particularly important for person-to-person transmission of NiV. NiV RNA is readily identified in the saliva of the infected patient [35]. In Siliguri, India, the transmission of the virus was also reported within a health-care setting, where 75 % of cases occurred among hospital staff or visitors [36]. In this exposure, no samples were obtained from local wildlife or domestic animals. It is observed that only adults were affected by NiV, supporting the nosocomial transmission theory, as the number of children on the wards of hospitals was minimal [36]. NiV outbreak in Kerala (Kozhikode District hospital) lasted for approximately 1 month (2–29 May 2018) [9]. The clinical manifestations and high fatality rate were similar to those of earlier NiV outbreaks in India [10, 37]and Bangladesh. In Kerala, there was no evidence in the environmental samples like, in bat eaten fruit or urine or saliva of fruit bats. All nosocomial transmissions to the primary cases happened when the index case had a persistent cough and was nearing the terminal stage of illness [9]. However, two bat species, *Rousettus leschenaultii* and *Pipistrellus pipistrellus*, were recently discovered with presence of NiV RNA and anti-NiV IgG antibodies in the Mahabaleshwar cave in Pune, India, in March 2020. These findings were done by Indian Council of Medical Research-National Institute of Virology (ICMR-NIV), Pune by collecting the blood, throat & rectal swab samples of anesthetized bats [38].

Signs and Symptoms: Infection with NiV arises with rapid and severe illness associated with respiratory system and encephalitis. It has an incubation period of 5-14 days and symptoms start to appear initially 3-14 days. Common symptoms include fever, headache, vomiting, drowsiness, sore throat along with disorientation & mental confusion [32]. At the initial stage, coughing, sore throat is relevant in all patients. But in severe cases, development of encephalitis eventually leads to coma within 24-48 hrs. Patients who have difficulty in breathing are at more risk for NiV infection [39].

Pathogenesis: The first line defense in the prevention of NiV infection is respiratory epithelium. In the initial stage, the NiV infection is detected in epithelial cells of bronchioles. Necrotizing alveolitis with bleeding, pulmonary edema, and aspiration pneumonia are all histological abnormalities observed in the lungs of NiV patients [40].

In the last stage, the NiV replicates very fast & enters into endothelial cells of lungs and affects the small vessels & capillaries causing endothelial syncytium and mural necrosis. Due to homologous fusion of infected endothelial cells, multinucleated giant cells developed i.e a specific characteristics in the progression of severe infection. After that it enters into the bloodstream via dispersion either freely or in host leukocyte bound form [41].

After infecting and disrupting the endothelial cells, NiV enters into the immune cells of secondary lymphoid organs (Mucosal Associated Lymphoid Tissues [MALT], Gut Associated Lymphoid Tissues [GALT]). However, it inhibits the synthesis of IFN α/β & reduces the expression of cytokines such as CCL4, CCL5 and TNF-α. These all factors impair the antiviral activity of the immune system [42].

The entry of viral into CNS occurs *via* two major routes *i.e.* haematogenous route (through choroid plexus or blood vessels of the cerebrum) and anterogradely via olfactory nerves. In addition to lung, spleen and kidneys, the brain may serve as target organs, contributing to multiple organ failure [43]. Due to this blood brain barrier is damaged and IL-1β is expressed along with TNF-α due to CNS infection which eventually contributes to neurological sign production by the virus [44].

Diagnosis: In humans and animals, infections by NiV are confirmed by various laboratory tests. Laboratory tests are performed by using various virus isolation, nucleic acid amplification tests, and serologic tests [32]. It is a biosafety level 4 pathogen so diagnosis is performed under high-level facilities. For the diagnosis of the virus, the sample is collected from throat swabs, cerebrospinal fluid, and urine, blood analysis during acute and convalescent stages of the disease. NiV can also be isolated from the saliva of infected people. A primary case of virus detection is performed under the BSL-3 facilities. If the virus is confirmed by immunofluorescent detection in acetone fixed infected cells, it is transferred to the BSL-4 lab [2, 35].

Antibodies against NiV were detected in *P. hypomelanus*, *P. vampyrus, P. lylei*, and *H. larvatus*. Antibodies to NiV antigen were detected in Thailand; immunoglobulin G (IgG) antibodies to NiV were assayed by indirect ELISA. Serum samples were heated to 56°C and titrated at 4 dilutions of the 1,054 serum specimens tested, 82 were NiV IgG antibody–positive [6]. In the Malaysian outbreak NiV infection was confirmed by immunohistochemical examination of one dead dog [45].

In the infected animals NiV can also be confirmed by ELISA serological test method. Infected cell lysate antigens were used for coating the plates and were used in BSL-4 laboratories. Because of many limitations of this method and to overcome this problem, recombinant proteins have been developed and used as an alternative antigen for serological detections of HeV and NiV [46, 47].

Nipah virus nucleocapsids (NiV-N) protein was expressed in *Escherichia coli* and purified by histidine tag-based affinity chromatography. One hundred thirty-three suspected patient sera and 16 swine sera were used to evaluate the newly established ELISA systems in comparison with the CDC inactivated-virus-based ELISA systems. For the human sera, the NiV-N protein-based indirect IgG ELISA had a sensitivity of 98.6% and a specificity of 98.4%, and the NiV-N protein-based IgM capture ELISA had a sensitivity of 91.7% and a specificity of 91.8%, with reference to the CDC ELISA systems [47].

These infections can also be detected by RT-PCR *i.e.* Reverse transcriptase- Polymerase Chain reaction. It is one of the most sensitive diagnostic tests for viral infections. Some other techniques are also used like Real time RT-PCR and Duplex Nested RT-PCR in which sequencing of amplified products is done. Immunohistochemistry is also one of the safest methods for detecting NiV as it uses formalin tissue fixed samples [48]. Multiple research studies in the nanomedicine area have been conducted to combat the NiV effect.

Nanoparticles found to be an effective technique for dealing with NiV. According to a recent study, nanoparticles that can bind to NiV surface glycoproteins G & F which acts as viral entry inhibitors for NiV pathogenesis [49].

Treatment: Currently, there is no approved treatment or vaccine available for either people or animals, and treatment is limited to supportive care. NiV is one of the pathogens in the WHO Research & Development (R&D) blueprint of epidemic threats needing urgent R&D action [18]. Over the period of time, different treatment strategies like monoclonal antibodies, antiviral drugs and vaccines have been evaluated in humans, animal models and *in-vitro*.

Monoclonal Antibodies: At present, monoclonal antibody (mAb) m102.4 is surely the most promising therapeutic for both NiV and HeV infection. Antibody m102.4 blocks the entry of NiV infection in host cells by inhibiting the complex of attachment protein G (glycoprotein) and Ephrin B2/B3 host cell receptor [39, 50, 51]. In 2020, m102.4 mAb was under phase-I human trial and demonstrated positive response [52]. Its neutralization activities were observed against various isolates likeNiV Malaysia, HeV-1994, HeV-Redlands and NiV-Bangladesh [39]. Administration of m102.4 mAb in American Green monkey (AGM) and Ferret model post-infection provided full protection against NiV [53, 54, 55].

Another promising antibody therapy under research is humanized, cross-reactive, and neutralizing anti-F mAb (h5B3.1). The mAb h5B3.1 targets fusion glycoprotein F of NiV/HeV and inhibits the conformational change in fusion protein necessary for membrane fusion and viral infection. Antibody h5B3.1 was administered in ferrets post NiV and HeV infection, and found that all subjects injected with mAb were protected but controls died. Protective effects of anti-F mAb was also demonstrated in Hamsters against NiV and HeV challenge which suggests to improvise the use of anti-F mAb (h5B3.1) as a potential treatment for human use. Combined doses of h5B3.1 and m102.4 antibodies could simultaneously target both F and G glycoprotein and could be more effective [56, 57]. However more research is needed before administering these mAb's in humans either single or combined doses. Monoclonal antibodies may not be the most practical for use in field outbreaks due to the need for cold chain storage and intravenous administration.

Antiviral Drugs: Till date, different active substances have been evaluated to explore a drug that inhibits NiV entry or proliferations. One of them is ribavirin; a broad spectrum nucleoside analogue has undergone several clinical trials in 1998-99 in Malaysian outbreak [58, 59]. During the initial outbreak in Malaysia ribavirin reduced mortality rate by 36% and less neurological problems in survivors [18, 59]. Ribavirin may have a role in reducing mortality among patients infected with Nipah virus disease. In May 2018, NiV disease outbreak was seen in Kozhikode and patients were administered with ribavirin therapy, even though the case fatality rate was more [60]. Moreover in the hamster model, ribavirin in combination with chloroquine showed inconclusive evidence in treating NiV disease [61]. However, antimalarial drug chloroquine was effective in disrupting NiV in cell cultures, but not in animal models [62].

In a Syrian hamster model, a purine derived antiviral Favipiravir (T 705) showed effective action up to 14 days with a lethal dose of Nipah virus [63]. Remdesivir (GS-5734) is a broad spectrum antiviral, nucleotide analogous prodrug and is effective against COVID-19 virus, filovirus, ebola virus and paramyxovirus replication [64]. Recently, Remdesivir (GS-5734) in four African green monkeys provides full protection with a lethal dose of NiV-BD strain [65]. Earlier, in-vitro study concluded that Remdesivir is highly effective against both NiV-BD and NiV-MY strains which validated further testing of remdesivir against NiV infection *in-vivo*.

Remdesivir can be only administered intravenously, so its usage becomes limited to hospitals. Therefore, another variant of Remdesivir *i.e.* ODBG-P-RVn is an orally available, broad spectrum, lipid-modified prodrug of the remdesivir parent nucleoside (GS-441524) is having 20 times more antiviral activity than remdesivir nucleoside (GS-441524) in human small airways epithelial cells. *In-vitro* analysis of orally available remdesivir variant (ODBG-P-RVn) in different

virus families including NiV and Coronavirus is effective. Therefore in-vivo evaluation of a lipid modified analogue ODBG-P-RVn should be encouraged for its effective use in several viral infections [66].

Griffithsin (GRFT), is a 121 amino acid sequence, homodimeric oligosaccharide binding lectin isolated from red algae, *Griffithsia* [67]. Due to three identical carbohydrate binding sites, griffithsin protein is capable to bind oligosaccharides present on surface viral glycoproteins which marks GRFT as a potential antiviral agent in preventing the entry of viral particles into the host cell and its transmission [68]. GRFT shows broad spectrum activity in binding to glycoproteins of other viruses, such as coronavirus, HIV, HSV (Herpes simplex virus), HCV (Hepatitis C virus), Ebola virus as well as NiV [69, 70]. Recently, Lo *et al.,* evaluated *in-vitro* antiviral properties of GRFT and its synthetic trimeric tandemer (3mG) and found that 3mG has significantly higher potency than GRFT against NiV infected cell culture. Earlier in vivo evaluation of Q-GRFT (oxidation resistant GRFT) showed protection against Syrian golden hamsters challenged by NiV infection [70]. Apart from monoclonal antibodies, antiviral drug therapy potentially adds to the improved preparedness in case of sudden outbreak of NiV.

Defective Interfering Particles: Defective interfering particles (DIP's) or genome are a type of virion which consist of important viral proteins needed for cellular entry. Subsequently, these DIP's are also known as incomplete viruses that can interfere with standard virus replication. Several research studies suggest that DIP's may alter the dynamics, reduce disease severity *in-vitro* and inclusion in vaccines development improves immunity [71, 72]. Recently, *in-vivo* analysis demonstrated that DIP's treatment reduced clinical signs and provided protection in Hamsters from Lethal NiV infection. Active DIPs were able to directly inhibit viral replication and transcription [73].

In-vitro assays showcased that naturally occurring as well as *in-silico* DIPs reduced viral titration 100 times and reduced structural changes in Vero cells[73]. DIPs should be administered in different animal models in future to reveal its antiviral properties.

Vaccines: Injectable vaccines against NiV infection in humans or livestocks (pigs and horses) could be effective in preventing the transmission of the virus [74]. Clinical trials with vaccines against NiV infection are limited in number because of no recent viral break-out. Hence most of the research has tested the vaccine preparations in animal models. Although there is no approved vaccine, more than 10 vaccine preparations have been reported based on viral vector, mRNA, r-protein subunits or virus like particles [74, 75]. Different vector based vaccines such as canarypox virus, vesicular stomatitis virus glycoprotein (VSVDG) and rhabdovirus have been evaluated [76]. A recombinant measles virus (rMV) vaccine expressing NiV's glycoprotein envelope has been considered to be effective for human use [77].

In recent yearsa recombinant vaccine based on vesicular stomatitis virus (replication competent) has been developed encoding a glycoprotein of NiV which showed their effectiveness in hamster model [78]. In African green monkeys, a single IM dose of this vaccine is administered which provides a protective immunity [79]. Health care workers and family members of infected patients were also administered with this vaccine dose which generated a strong immune response and inhibited shedding and replication of virus. Thus it proved effective in the prevention of human to human transmission.

Nipah virus-like particles (NiV-VLPs) were developed and validated as a vaccine in BALB mice composed of three NiV proteins G, F and M derived from mammalian cells. It reported good immunogenicity. In golden Syrian hamster these vaccines were tested which provided full prevention against viral challenge [80].

Advancement in immunoinformatics has been used by prediction and simulation of T cell epitopes of NiV antigenic proteins for the production of peptide based NiV vaccines. Specific epitopes such as VPATNSPEL, NPTAVPFTL and LLFVFGPNL potentially stimulate T cell mediated immunity [81].

Prevention: Prevention towards the NiV is very important because no licensed drug or approved vaccines are available. Only limited work has been done to develop medications against NiV infection.

The following precautions are necessary to prevent the spread of NiV infection such as [40]

- Avoid close contact with infected patients.
- Avoid eating partially consumed fruits by bats.
- Avoid drinking raw palm sap contaminated by bats.
- Cover the container properly for collecting raw date palm sap.
- Avoid consuming undercooked meats of infected animals.
- Before consuming, wash, and peel fruits and vegetables properly.
- Maintain personal hygiene and properly cover households.

Awareness among the public can be done by using posters, public broadcasting, flyers, and social media services. Only proper awareness and hygienic habits could break the risk of this infection [82].

CONCLUSION: NiV outbreaks in various countries cause a high rate of morbidity and mortality. The economies of various countries are also affected by this global pandemic. The ability of its changing reservoirs from bat to pigs, pigs to humans, or bat to humans by contaminated date palm sap targeted human beings. Proper awareness and surveillance is only one way to tackle this infection as no approved medicine is available. There is a requirement of cooperativeness between the institute as well as scientist and ecologist for better understanding of its mechanism in the transmission of this virus. For preventing future outbreaks, the government and authorities related to the health sector should provide various preventive measures and spread awareness among the public. A new international center i.e. Coalition for Epidemic Preparedness Innovations (CEPI) is also set up to develop safe, effective, and easily available vaccines for infection like NiV.

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CONFLICTS OF INTEREST: Nil

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